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STUDIES ON THE SYNTHESIS AND REACTIVITY OF 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID

by

José Luis Garrido Solís

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

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"Success is a state of mind.
If you want success, start thinking of yourself as a success"

- ANONYMOUS

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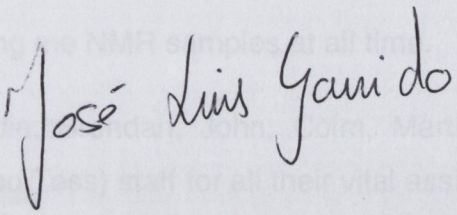

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Thanks a lot

SUMMARY

This thesis is about studies carried out on the synthesis and reactivity of 2-cyanoacrylic acid and 2-cyanoacrylate esters, and is divided into four chapters.

Chapter 1 provides an introduction and includes a complete survey of approaches to these compounds (2-cyanoacrylic acid and 2-cyanoacrylate esters) and studies on the reactivity of alkyl (methyl and ethyl) 2-cyanoacrylates reported in the literature.

Chapter 2 discusses the attempted synthesis of some of these 2-cyanoacrylate compounds using condensation reactions. For this purpose, the syntheses of *tert*-butyl and of benzyl 2-cyanoacrylates were attempted using the reactions of *tert*-butyl and of benzyl 2-cyanoacetate with paraformaldehyde. The synthesis of 2-cyanoacrylic acid from different precursors was also attempted using either protonolysis or oxidation reactions.

Chapter 3 describes attempts to use the readily available ethyl 2-cyanoacrylate for the synthesis of 2-cyanoacrylic acid and 2-cyanoacrylate esters. A three-step process was carried out which involves the protection of the double bond of ethyl 2-cyanoacrylate, hydrolysis or transesterification and regeneration of the double bond. The protection of the double bond of ethyl 2-cyanoacrylate is required in order to prevent polymerisation when either hydrolysis or transesterification of the ethyl ester is tried.

Chapter 4 describes three completely novel approaches to 2-cyanoacrylic acid. The first approach involves the attempted opening with cyanide ion of the episulfide ring of thiirancarboxylic acid to afford a precursor to 2-cyanoacrylic acid. The second approach deals with the attempted palladium-catalyzed cyanation reaction of *tert*-butyl 2-bromoacrylate. The third approach describes preliminary investigations into the use of solid phase supports for the synthesis of these compounds

TABLE OF CONTENTS

GLOSSARY AND ABBREVIATIONS 1

CHAPTER 1. *INTRODUCTION* 4

1. 1. Synthesis of Esters of 2-Cyanoacrylic Acid 7

1. 2. Reactivity of the Alkyl 2-Cyanoacrylates 13

1. 2. 1. Nucleophilic additions 13

1. 2. 1. i. Sulfur compounds as nucleophiles 15

1. 2. 1. ii. Alcohols as nucleophiles 18

1. 2. 1. iii. Phosphorus compounds as nucleophiles 19

1. 2. 1. iii. a. Reactions of alkyl 2-cyanoacrylates with trivalent phosphorus compounds 19

1. 2. 1. iii. b. Reactions of alkyl 2-cyanoacrylates with pentavalent phosphorus compounds 25

1. 2. 1. iv. Carbanions as nucleophiles 27

1. 2. 2. Cycloaddition reactions 28

1. 2. 3. Reduction reactions 30

1. 2. 4. Dihalogenation reactions 30

1. 3. Conclusions 31

1. 4. References 32

CHAPTER 2. *APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID FROM CONDENSATION REACTIONS* 36

2. 1. Attempted Preparation of *t*-Butyl and Benzyl 2-Cyanoacrylate from Condensation Reactions 38

2. 2. Attempted Preparation of 2-Cyanoacrylic acid from Different Precursors Obtained by Condensation Reactions 42

2. 2. 1. Preparation of 2-cyanoacrylic acid from dicyclohexylammonium 2-cyanoacrylate 42

2. 2. 1. i. Cation exchange of dicyclohexylammonium 2-cyanoacrylate using non-aqueous conditions 43

2. 2. 1. ii. Cation exchange of dicyclohexylammonium 2-cyanoacrylate using aqueous conditions 44

2. 2. 2. Preparation of 2-cyanoacrylic acid from 2-(chloromethyl)acrylonitrile 47

2. 2. 3. Preparation of 2-cyanoacrylic acid from 2-(hydroxymethyl)acrylonitrile 49

2. 3. Experimental Part 55

2. 4. References 62

CHAPTER 3. *APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID FROM ETHYL 2-CYANOACRYLATE (ECA)* 64

3. 1. Protection of the Double Bond of ECA 65

3. 1. 1. Protection of the double bond using Diels-Alder reactions 65

3. 1. 2. Protection of the double bond using Michael addition reactions 74

3. 1. 2. i. Alcohols as nucleophiles 75

3. 1. 2. ii. Sulfur compounds as nucleophiles 81

3. 1. 2. iii. Phosphorous acid as nucleophile 87

3. 2. Hydrolysis and Transesterification of ECA-adducts 92

3. 2. 1. Hydrolysis of ethyl 2-cyano-3-(2'-methylfuryl)propanoate 92

3. 2. 2. Attempted hydrolysis and transesterification of ethyl 2-cyano-3-methoxypropanoate 93

3. 2. 3. Hydrolysis of ethyl 2-bromo-2-cyano-3-methoxypropanoate 94

3. 2. 4. Attempted hydrolysis of ethyl 2-cyano-3-(4'-toluenesulfonyl)propanoate 94

3. 2. 5. Hydrolysis of ethyl 2-cyano-3-(4'-toluenesulfanyl)propanoate and ethyl 3-(*n*-butylsulfanyl)-2-cyanopropanoate 95

3. 2. 6. Hydrolysis of ethyl 2-cyano-3-benzoylthiopropanoate 96

3. 3. Regeneration of the double bond from ECA-adducts 97

3. 3. 1. Attempted regeneration of the double bond from 2-cyano-3-(2'-methylfuryl)propanoic acid using trifluoroacetic acid 97

3. 3. 2. Regeneration of the double bond from 2-bromo-2-cyano-3-methoxypropanoic acid using zinc metal 98

3. 3. 3. Regeneration of the double bond from 2-cyano-3-(4'-toluenesulfanyl)propionic acid and 3-(*n*-butylsulfanyl)-2-cyanopropionic acid using *tert*-butyl hydroperoxide 102

3. 3. 4. Attempted regeneration of the double bond from 2-cyano-3-(4'-toluenesulfanyl)propionic acid and 3-(*n*-butylsulfanyl)-2-cyanopropionic acid using other approaches 106

3. 4. Experimental Section 108

3. 5. References 135

CHAPTER 4. *OTHER APPROACHES TO 2-CYANOACRYLIC ACID* 138

4. 1. Approaches from Thiirancarboxylic Acid 138

4. 1. 1. Synthesis of thiirancarboxylic acid 138

4. 1. 2. Attempted ring-opening of thiirancarboxylic acid 142

4. 1. 2. i Attempted ring-opening reaction of thiirancarboxylic acid by cyanide under aqueous conditions 143

4. 1. 2. ii. Attempted ring-opening reaction of thiirancarboxylic acid by cyanide under non-aqueous conditions 146

4. 2. Approaches Utilising Palladium-Assisted Coupling Reactions 149

4. 2. 1. Palladium-assisted coupling reactions of iodobenzene with cyanide anion 149

4. 2. 2. Attempted palladium-assisted coupling reactions of *t*-butyl 2-bromo-2-propenoate with cyanide anion 150

4. 3. Approaches *via* Solid-Phase Organic Synthesis 154

4. 4. Experimental Part 166

4. 5. References 180

APPENDIX

GLOSSARY AND ABBREVIATIONS

AcOH	acetic acid
Ac	acetyl
Ar	aryl
b.p	boiling point
bs	broad singlet
CAA	2-cyanoacrylic acid
$CDCl_3$	deuterated chloroform
Cq	quaternary carbon
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	dicyclohexylcarbodiimide
DIPC	diisopropylcarbodiimide
D_2O	deuterated water
DMSO-d_6	deuterated dimethylsulfoxide
Δ	heat
ECA	ethyl 2-cyanoacrylate
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate

EtOH	ethanol
ES+	electron-spray positive
FT-IR	Fourier transform
[H^+]	protonolysis reaction
***i*-Bu**	*iso*butyl
***i*-Pr**	*iso*propyl
LDA	lithium diisopropylamide
LiTMP	lithium 2, 2, 6, 6-tetramethylpiperidide
***m*-CPBA**	*meta*-chloroperbenzoic acid
Me	methyl
MS	mass spectra
***n*-Bu**	*n*-butyl
NBS	*n*-bromosuccinimide
NMR	nuclear magnetic resonace
[O]	oxidation reaction
Ph	phenyl
***p*-TsOH**	*para*-toluenesulfonic acid
ppm	part per million
PS	polymeric support
PVP	*poly*(4-vinylpyridine)

S_Ni	unimolecular or bimolecular nucleophilic substitution
R_f	retention factor
r.t.	room temperature
***t*-Bu**	*tert*-butyl
TBACN	tetrabutylammonium cyanide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tol	tolyl
s	singlet
q	quartet

CHAPTER 1.

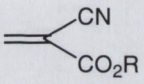
INTRODUCTION

CHAPTER 1.

INTRODUCTION

The discovery of the adhesive properties of the alkyl 2-cyanoacrylates **1** [Figure 1] in the 1950s was followed by their introduction as rapid-setting industrial sealants.[1]

Figure 1

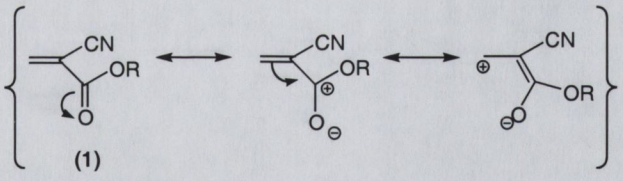


(1)

The adhesive effect of these compounds originates from their polymerisation. However, this effect only takes place between two surfaces because the polymer prepared separately does not possess adhesive properties.

The carbon–carbon double bonds of these compounds are greatly polarised [Figure 2], so they are quite reactive and consequently susceptible to suffer Michael addition of nucleophiles such as alcohols, thiols and traces of water. Importantly, water can be present on the surface of metals, rubbers and plastics, and consequently, induce their polymerisation.

Figure 2

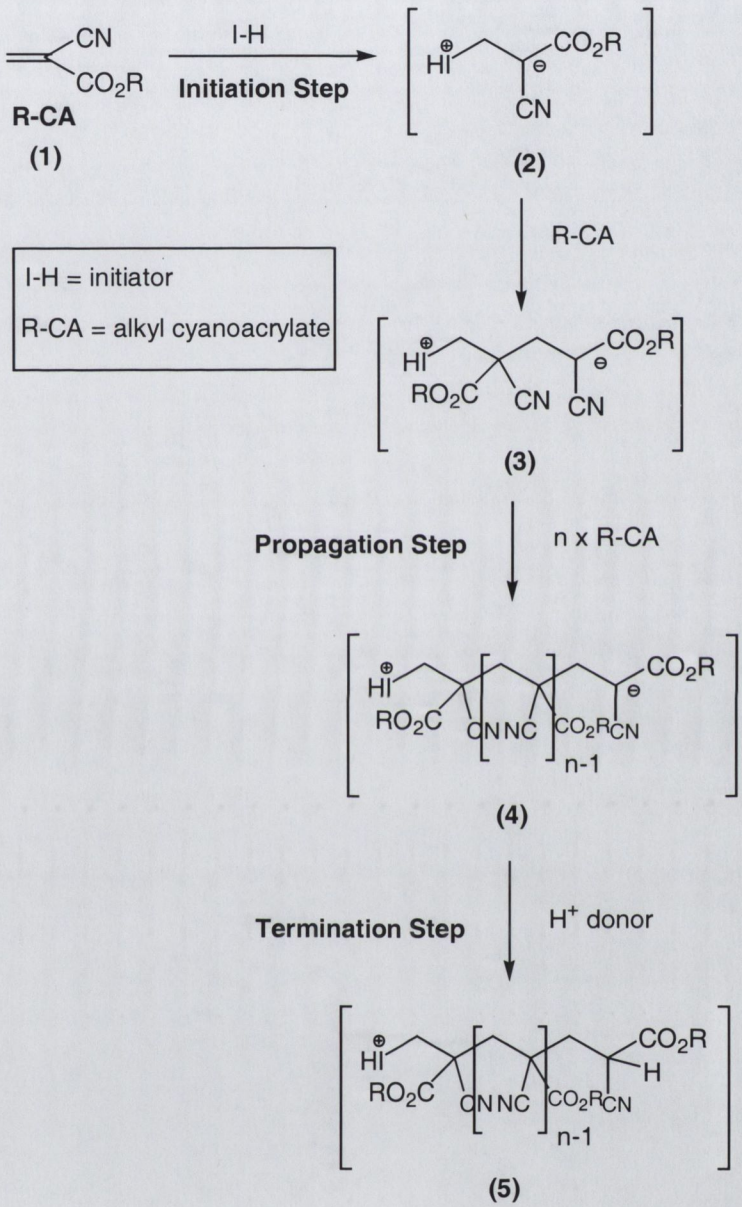


(1)

This great electrophilic character at the β-carbon of the double bond forms the basis of the polymerisation process, which occurs easily through an anionic mechanism and causes the low-viscosity monomeric compounds to be converted into the derived solid polymer [Scheme 1].

Scheme 1

Polymerization Via Anionic Mechanism



Many potential applications of interest have arisen from these alkyl 2-cyanoacrylates **1** such as their use in surgical and dental procedures and applications associated with the automobile and electronics industries.

In the surgical field the alkyl 2-cyanoacrylates **1** have been tested for the sutureless closure of wounds and incisions because of their ability to undergo an almost instantaneous polymerisation on skin surfaces and in the presence of blood.[2]

In the dental field the alkyl 2-cyanoacrylates (for instance, the methyl **1a**, ethyl **1b**, *n*-butyl **1c** and isobutyl esters **1d**) have been investigated as pit and fissure sealants for the prevention of caries, the cementing of dental pins to retain restorations, periodontal surgery and the direct bonding of orthodontic brackets.[3]

In the electronic field the alkyl 2-cyanoacrylates **1** have been used as adhesives, coatings and sealants.[4]

In the automotive industry alkyl 2-cyanoacrylates **1** have been successfully used to seal difficult parts, such as engine blocks, cylinder heads, valves, pump housings, gear boxes, fittings, vehicle brake components and high pressure systems.[5]

Others applications are those related to the formation of Langmuir-Blodgett monomolecular layers[6]. Thus, alkyl 2-cyanoacrylates **1** with alkyl moeties of more than six units have been used for the formation of monolayers. These monolayers come from the polymerisation of the monomeric alkyl 2-cyanoacrylate **1** on water surfaces. Since the interaction of the polymer with water is low, the monolayer can be easily transferred to a solid support.

2-Cyanoacrylate esters **1** are soluble in liquid carbon dioxide and consequently can be packed in aerosol bottles. Thus, vapours rich in 2-cyanoacrylate esters **1** can be deposited on surfaces and fix any traces left there, such as fingerprints.[6]

Despite the rapid-setting characteristics of the 2-cyanoacrylates **1**, their major handicap is the degradation of the adhesive bond in the presence of moisture. This fact was checked when the bond strengths of joints made using methyl **1a**, ethyl **1b** and *n*-butyl 2-cyanoacrylates **1c** were tested in either the presence or

the absence of water. Thus, the initially good dry bond strengths deteriorated rapidly when exposed to 1 M aqueous saline solution for 24 hours.[7]

Other disadvantages are the low thermal and impact resistances shown by the polymerised alkyl 2-cyanoacrylates **5**. Thus, several procedures, which involve either the use of cross-linked monomers or the addition of non-reactive rubbers, have been employed in order to circumvent these problems.[8]

Further disadvantages are the unpleasant odours and irritating vapours released by the monomeric 2-cyanoacrylate esters **1**, and problems with photodegradation of the polymerised 2-cyanoacrylate esters **5**.

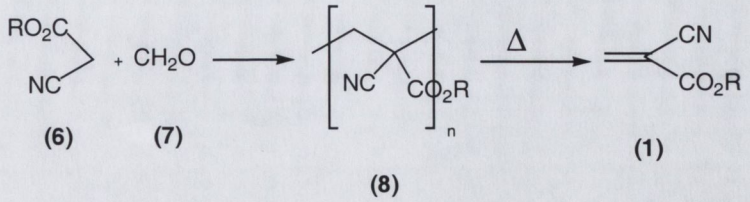
Apparently, the 2-cyanoacrylate esters **1** do not exhibit adhesive properties with some types of polymer such as silicone rubbers or Teflon. However, these polymers can be cemented together with 2-cyanoacrylate esters **1** after treating their surfaces with special activators, such as amines or phosphines.[9]

The manufacture of 2-cyanoacrylate esters **1** is carried out by a variety of firms in several countries, such as the United States, Ireland (**Loctite**), Germany and Japan. The commercial adhesives are low molecular weight alkyl esters of cyanoacrylic acid, generally ethyl - butyl esters and these are usually sold in a stabilised formulation.

1. 1. SYNTHESIS OF 2-CYANOACRYLATE ESTERS AND OF 2-CYANOACRYLIC ACID

To date, the main manufacturing processes for 2-cyanoacrylate esters **1** have been based on the Knoevenagel reaction between 2-cyanoacetic acid esters **6** and paraformaldehyde **7** under the influence of different basic catalysts (amines, sodium ethoxide or sodium hydroxide).[10] The reaction proceeds readily under reflux to give high yields of oligomeric 2-cyanoacrylates **8**. Finally, the oligomers are thermally converted into the corresponding monomeric esters **1** by distillation and are then stabilised by the controlled addition of a suitable acid [Scheme 2].

Scheme 2



(6) (7) (8) (1)

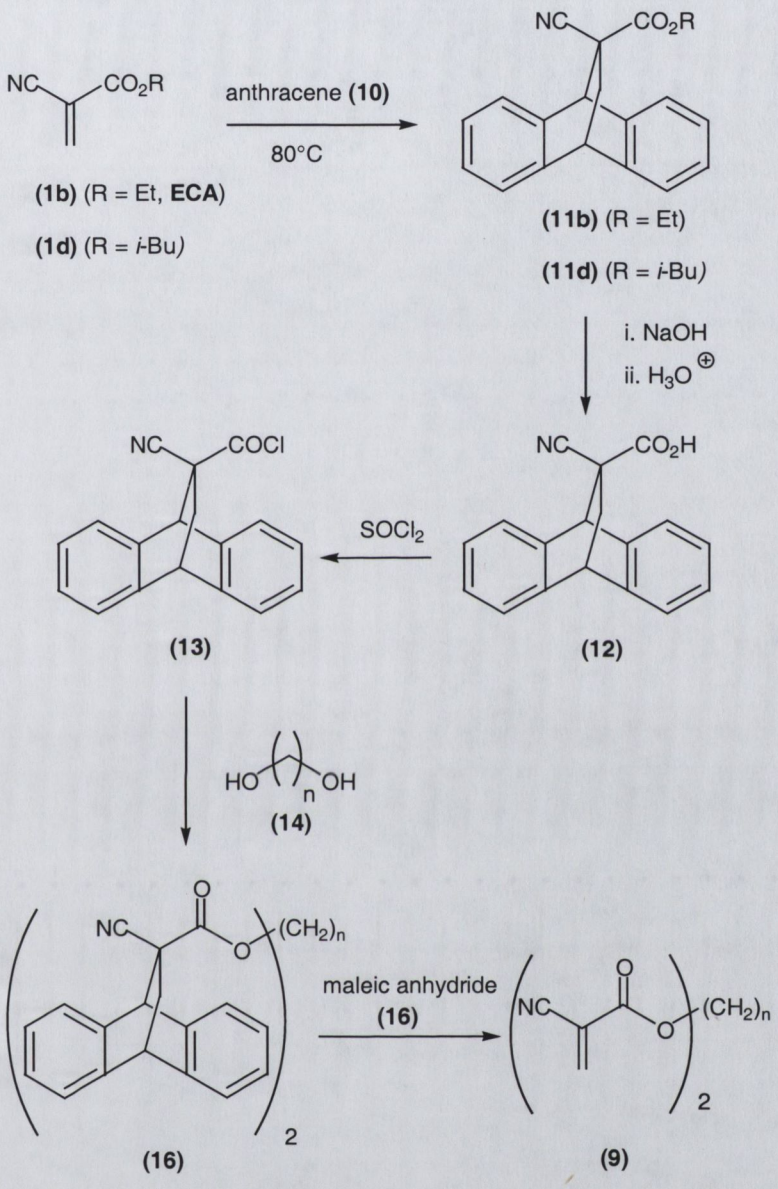
The Knoevenagel methodology is essentially limited to the synthesis of alkyl cyanoacrylates in which the alkyl moiety contains less than eight carbon atoms because the boiling points of higher esters are such that they cannot be distilled without decomposition.[11]

In the same way, multifunctional 2-cyanoacrylates, such as *bis*-2-cyanoacrylates **9**, cannot be synthesised *via* the Knoevenagel approach because they are not distillable below their thermal destruction temperatures.

Thus, an alternative approach to compounds such as *bis*-2-cyanoacrylate esters **9**, which are actually quite resistant to high temperatures and moisture, has been devised. This involves a sequence of five steps.[12]

Thus, in this five-step method [Scheme 3], ethyl 2-cyanoacrylate **(ECA) 1b** or *iso*butyl 2-cyanoacrylate **1d** are reacted with anthracene **10** to afford their stable Diels-Alder adducts **11b** or **11d**. The adducts **11b** and **11b** can be saponified to give the carboxylic acid **12** which is converted into its acid chloride **13** with thionyl chloride. The acid chloride **13** is reacted with a diol **14** to afford the *bis*-anthracene diester adduct **15**. Then, the adduct **15** is reacted with the dienophile maleic anhydride in order to form the anthracene-maleic anhydride Diels-Alder adduct and liberate the *bis*-cyanoacrylate **9.**

Scheme 3

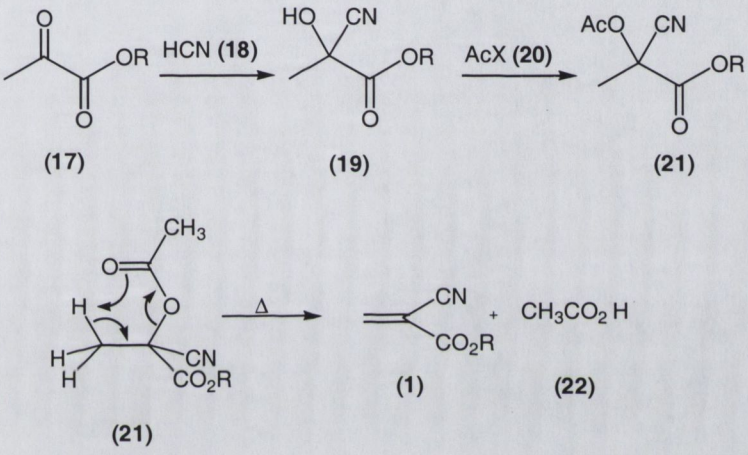


However, this multi-step synthesis is a purely laboratory method and scaling up to an industrial process has not been satisfactorily carried out.

Other approaches to the synthesis of alkyl 2-cyanoacrylates involve the use of pyruvic acid esters **17** as precursors. Thus, these esters are reacted with hydrogen cyanide **18** to afford the corresponding cyanohydrins **19**.

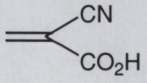
The cyanohydrins **19** are then acylated with an acetate halide **20** to afford the corresponding 2-acetoxy-2-cyanopropionate esters **21**, which are thermally converted into cyanoacrylate esters **1** by *syn*-elimination of a molecule of acetic acid **22** [Scheme 4].[13]

Scheme 4



2-Cyanoacrylic acid **(CAA) 23** can be considered as a more obvious and interesting precursor to alkyl 2-cyanoacrylates **1** because of the possibility of its direct conversion to these esters, and its acidic character which implies its self-stabilisation and, consequently, the possibility of long-term storage [Figure 3].

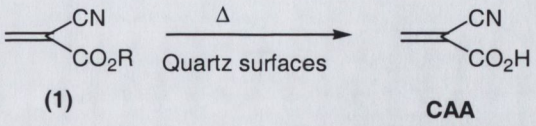
Figure 3



CAA (23)

Thus, a patent publication describes the first synthesis of **CAA** from the pyrolysis reactions of cyanoacrylate esters **1** carried out on silicate-type surfaces, such as quartz surfaces [Scheme 5].[14]

Scheme 5

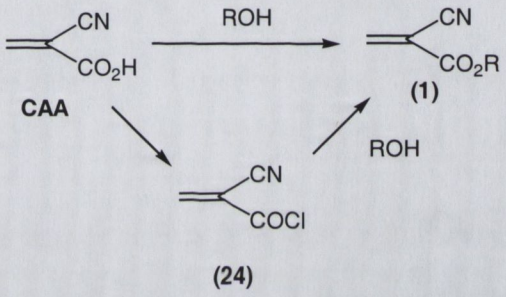


(1) **CAA**

This methodology for obtaining **CAA** was exploited later by forming the derived acyl chloride **24** and using it to synthesise various esters.[8]

Thus, the esterification of **CAA** can be carried out either directly or *via* 2-cyanoacryloyl chloride **24** [Scheme 6].

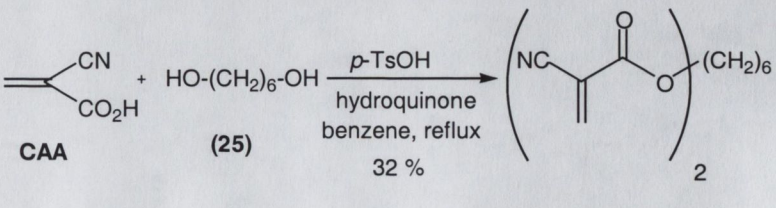
Scheme 6



(24)

In both cases, the removal of water or hydrohalic acid, as appropiate, forces the reaction to go to completion, particularly if the reactions are carried out at elevated temperatures. Gololobov *et al.* prepared the *bis*-cyanoacrylate **9a** by the esterification reaction of **CAA** with hexane-1,6-diol **25** in benzene at reflux The reaction was catalyzed by *p*-toluenesulfonic acid (*p*-TsOH) and hydroquinone was added in order to prevent polymerisation *via* radical mechanism [Scheme 7].[15]

Scheme 7

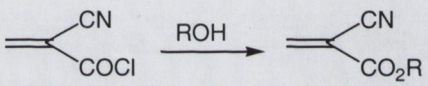


CAA **(25)** **(9a)**

However, the low yield obtained (32 %) suggested carrying out the esterification reaction using the more reactive derived acyl chloride **24** . The acid chloride 2-cyanoacryloyl chloride **13** was first reported by Kandror *et al.* by reaction of **CAA** with phosphorus pentachloride.[16]

The patent literature has described the synthesis of esters which are not available from condensation reactions by reaction of 2-cyanoacryloyl chloride **13** with the alcohol of interest [Scheme 8].[8]

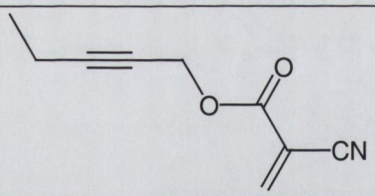
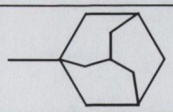
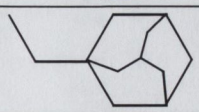
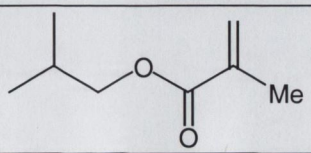
Scheme 8



(24) **(1)**

The alkyl group **R** can be varied widely to include saturated, unsaturated, linear, branched, mono-, or polysubstituted chains [Table 1].

Table 1

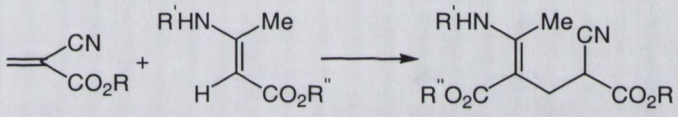
-R	Number	Reference
$-(CH_2)_{14}CH_3$	**1e**	8
	**9d**	17
	**1f**	18
	**1g**	19
	**1h**	8

1. 2. REACTIVITY OF THE ALKYL 2-CYANOACRYLATES

For more than 40 years the study of the reactivity of the monomeric compounds was neglected because of the high polarisation of their double bonds [Figure 1] and consequently their high susceptibility towards polymerisation [Scheme 1].

The only antecedents found in the literature were the use of either ethyl 2-cyanoacrylate **(ECA) 1b** or *iso*-butyl 2-cyanoacrylate **1d** as dienes in the previously described Diels-Alder reaction with anthracene **10**[12] [Scheme 4], and Michael addition of β-aminocrotonates to 2-cyanoacrylate esters **1** which were carried out in the late 1970s [Scheme 9].[20]

Scheme 9



(1) (26) (27)

The first studies of the reactivity of alkyl 2-cyanoacrylates **1** were reported in the late 1980s by Gololobov *et al.*, overcoming the then existing idea of rejecting the use of these compounds in organic and heteroaromatic synthesis.[21]

To date, the most interesting results which have been obtained are connected with reacting the highly electrophilic double bond with different nucleophiles, although [4+2]-cycloaddition, reduction and dihalogenation reactions of the double bond have also been reported.

1. 2. 1. Nucleophilic additions

Gololobov *et al.* postulated two conditions[21] in order to successfully execute nucleophilic additions to these compounds and at the same time avoid their polymerisation:

- a minimal amount of a free alkyl 2-cyanoacrylate acid ester must be present in the reaction mixture at any moment.

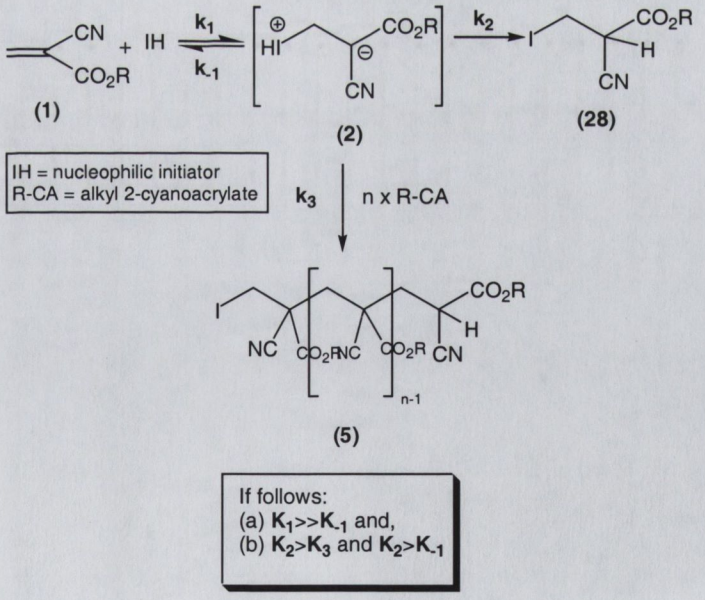
- a primary addition product must be formed, and it either must be rather stable or conditions for its stabilisation must be created. The latter means in a practical sense that an anionic center at the α-carbon of the primary reaction product must be trapped instantly.

In other words these two previous statements imply two observations [Scheme 10]:

(a) a rapid addition of the nucleophile to the highly electrophilic β-carbon must occur.

(b) the protonation of the newly-created anionic center must occur faster than either its nucleophilic addition to other molecule of an 2-cyanoacrylate or its intramolecular reverse reaction displacing the recently incorporated nucleophile.

Scheme 10



The literature describes the incorporation of several nucleophiles into these compounds, including sulfur compounds, alcohols, phosphorus compounds and soft nucleophiles such as carbanions originating from β-keto esters, β-nitroesters, 1,3-diketones,...etc.

1. 2. 1. i. Sulfur compounds as nucleophiles

The Michael additions of several sulfur compounds to ethyl 2-cyanoacrylate **(ECA) 1b** have been reported in the literature. In most cases good yields (over 60%) were obtained.

Highly nucleophilic mercaptans have a rather active hydrogen atom[22] [Table 2] and easily and quantitatively add to the double bond of alkyl 2-cyanoacrylates.[21]

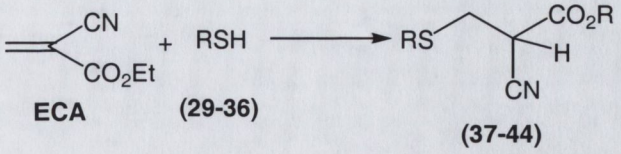
Table 2

Acid / Conjugated Base	Pka (H_2O)
SH_2 / SH^-	7.00
n-BuSH / *n*-BuS^-	10-11
PhSH / PhS^-	7

The adducts obtained using thiols as nucleophiles are liquids under neutral conditions at room temperature, and to obtain these compounds a slow addition of the corresponding alkyl 2-cyanoacrylate to the mercaptan is required. Thus, a rapid addition of the mercaptan to the β-position of the double bond takes place with instantaneous protonation of the α-carbanion which is generated. The conditions employed mean that there is no excess of the alkyl 2-cyanoacrylate present at anytime.

Some examples of this nucleophilic addition reaction are listed next [Table 3].

Table 3

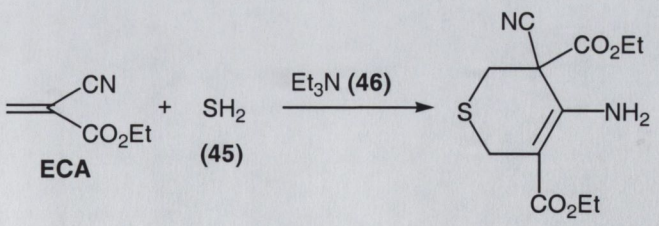


ECA **(29-36)** **(37-44)**

R-	Thiol	Product	Reference
n-Bu-	**29**	**37**	23
t-Bu-	**30**	**38**	23
Ph-	**31**	**39**	23
$HO(CH_2)_2$-	**32**	**40**	23
$HS(CH_2)_2$-	**33**	**41**	24
$-(CH_2)_2NH_3^+ Cl^-$	**34**	**42**	24
$-CH_2CO_2H$	**35**	**43**	24
$-CH_2CO_2H(NH_3^+) Cl^-$	**36**	**44**	24

A particular case, which deserves special discussion, was found when **ECA** was reacted with hydrogen sulfide **45** in the presence of catalytic triethylamine **46** to yield **47** [Scheme 11].[24]

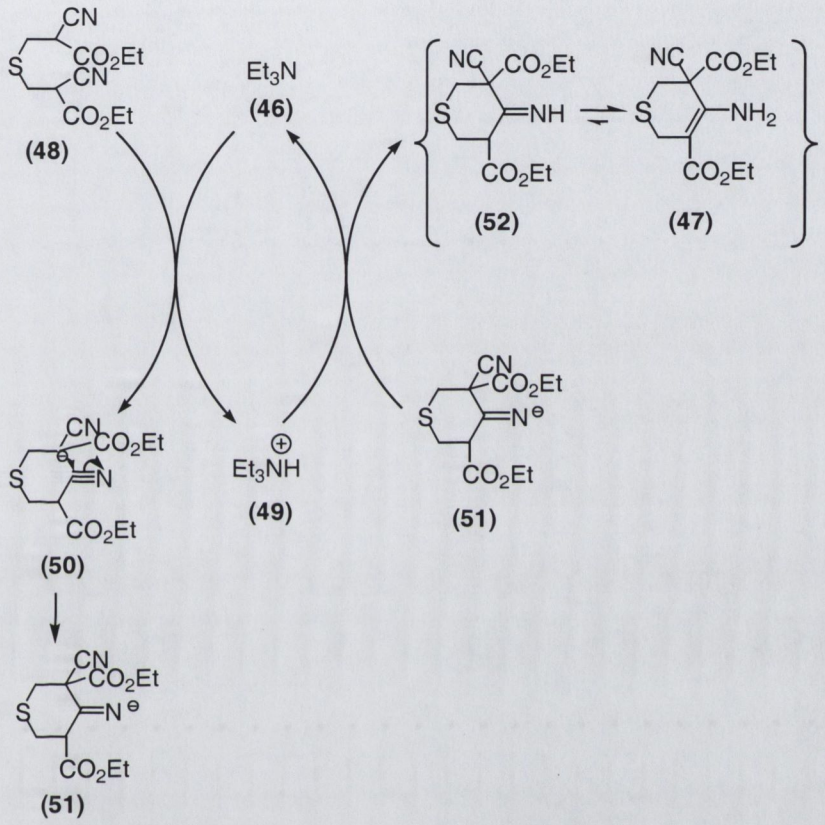
Scheme 11



ECA **(45)** **(47)**

Gololobov *et al.* postulated the role of triethylamine **46** in this reaction. Thus, its presence was assumed to catalyse the Thorpe-Ziegler cyclization in a second reaction step, after formation of the sulfide **48** [Scheme 12].

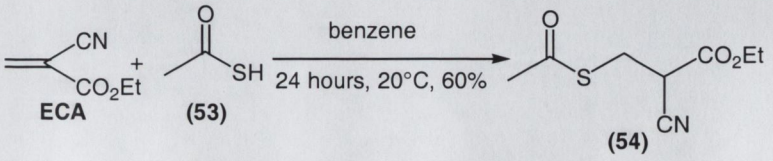
Scheme 12



These authors suggested that triethylamine **46** could also promote the transformation of hydrogen sulfide **45** into its thiolate-anionic form in the initial step of the reaction.[21]

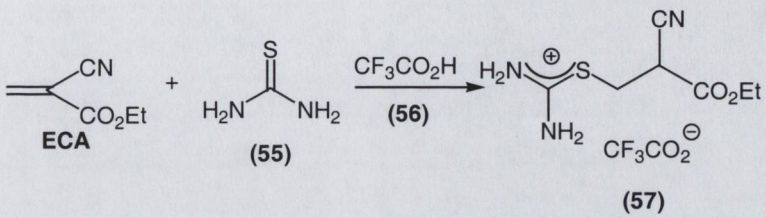
Thioacetic acid **53** can also be added to **ECA** to yield the corresponding adduct **54** [Scheme 13].[23]

Scheme 13



Thiourea **55** has been added to **ECA** in the presence of stochiometric trifluoroacetic acid **56** to give the corresponding saturated *S*-alkylthiouronium trifluoroacetate **57** [Scheme 14].[25]

Scheme 14

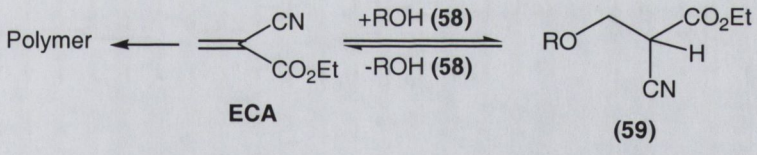


1. 2. 1. ii. Alcohols as nucleophiles

Unlike their sulfur-analogues, obtained from mercaptans or hydrogen sulfide, no reports of stable adducts **59** where low-molecular weight alcohols or water are the Michael-donors have been found in the literature, although their presence has been detected spectroscopically.[21]

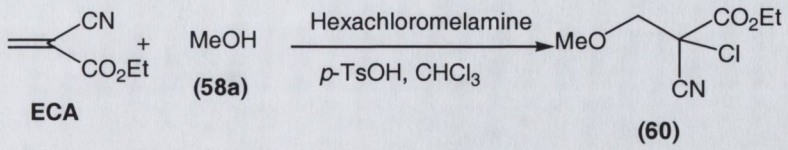
Thus, ethyl *poly*(2-cyanoacrylate) is eventually observed when alcohol or water are used as Michael donors [Scheme 15].

Scheme 15



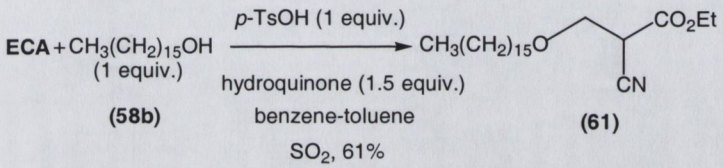
However, the addition of methanol **58a** to **ECA** has been carried out successfully under conditions where the labile methine hydrogen of the Michael product is replaced by chlorine, to yield **60** [Scheme 16].[26]

Scheme 16



The addition of high-molecular weight alcohols to **ECA** has been reported. Thus, the addition of hexadecyl alcohol **58b** to **ECA** affords the adduct **61** in 61% yield [Scheme 17].[27]

Scheme 17



The conditions employed in this reaction are complex and inconvenient from a technical point of view in industrial processes.

1. 2. 1. iii. Phosphorus compounds as nucleophiles.

Several examples of stable phosphorus-containing adducts have been reported in the literature. Thus, in these adducts the phosphorus atom can be found in different oxidation states, forming trivalent or pentavalent compounds.

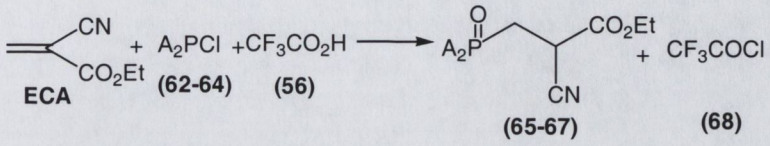
1. 2. 1. iii. a. Reactions of alkyl 2-cyanoacrylates with trivalent phosphorus compounds.

Trivalent phosphorus compounds can be divided into three groups with respect to their reactivity towards 2-cyanoacrylate esters.

Thus, the first group includes phosphorus halides (PX_3) and their derivatives, such as dialkyl halophosphites ($(RO)_2PX$) and halodiarylphosphines ($(Ar)_2PX$), which do not exhibit affinity towards 2-cyanoacrylate esters at room temperature.

However, the phosphorus halide derivatives **(62-64)** react with **ECA** to afford either the phosphonates **65** and **66** or the phosphine oxide **67**, in the presence of stochiometric amounts of trifluoroacetic acid **56** [Table 4].[25]

Table 4

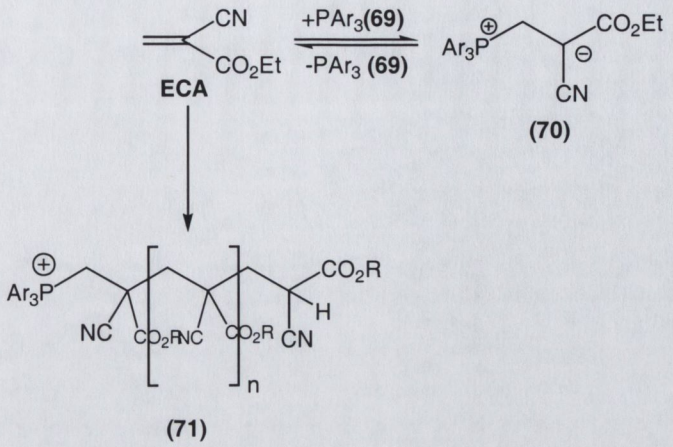


Phosphorus Halide Derivative			Product
-X	**-A**	**Number**	
-Cl	-OEt	**62**	**65**
-Cl	*ortho*(-O-C_6H_4-O-)	**63**	**66**
-Cl	-Ph	**64**	**67**

Thus, the reactions shown in Table 3 were the first examples of conjugate additions of weak nucleophiles to a cyanoacrylate under the influence of an acid.

The second group of trivalent phosphorus compounds includes weak nucleophiles such as triarylphosphines (PAr_3) **69**, which add reversibly to **ECA**. Here, the equilibrium is so shifted to the left that it is not possible to create a deficit of the cyanoacrylate in the reaction mixture. Accordingly, polymerisation is unavoidable, involving the phosphonium center as the head group of the polymer [Scheme 18].[21]

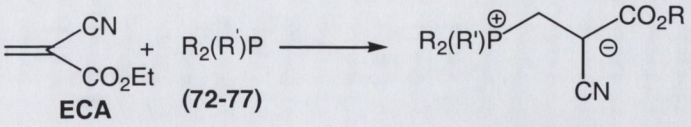
Scheme 18



The third group of trivalent phosphorus compounds includes those which are strong nucleophiles, such as trialkylphosphines (PR_3), trialkylphosphites ($P(OR)_3$) and their derivatives, which rapidly add to **ECA** to afford zwitterions. So, the concentration of free **ECA** is minimal when the addition takes place. However, it is necessary to point out that when these zwitterions are placed in an **ECA** solution instant polymerisation is observed.[21]

Thus, trialkylphosphines and their derivatives react with **ECA** to afford stable zwitterionic adducts **78-83** [Table 5].

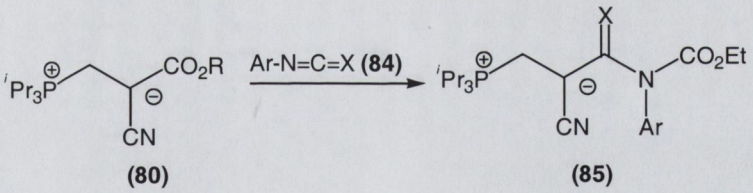
Table 5



R-	R-	R'-	Phosphorus compound	Product	Reference
Et-	Et-	Et-	**72**	**78**	28
Pr-	Pr-	Pr-	**73**	**79**	29
i-Pr-	*i*-Pr-	*i*-Pr-	**74**	**80**	30
Bu-	Bu-	Bu-	**75**	**81**	29
-$(CH_2)_4$-		Et_2N-	**76**	**82**	29
Et_2N-	Et_2N-	*t*-BuNH-	**77**	**83**	29

The reaction of the zwitterions **80** with either aryl isocyanates or aryl isothiocyanates **84** leads to the stable zwitterions **85** [Scheme 19].[31]

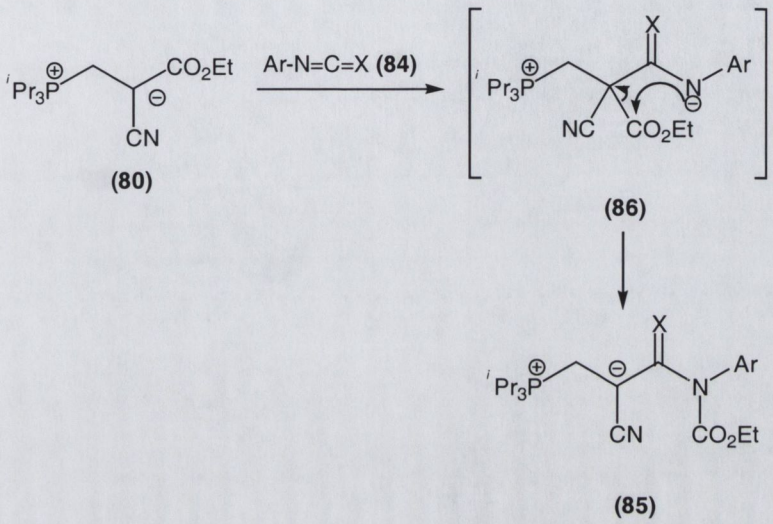
Scheme 19



Gololobov *et al.*[31] speculated that the formation of these zwitterions **85** takes place as a result of initial electrophilic attack by the zwitterions **80** on an isocyanate or isothiocyanate to give an intermediate **86**. Subsequent migration of

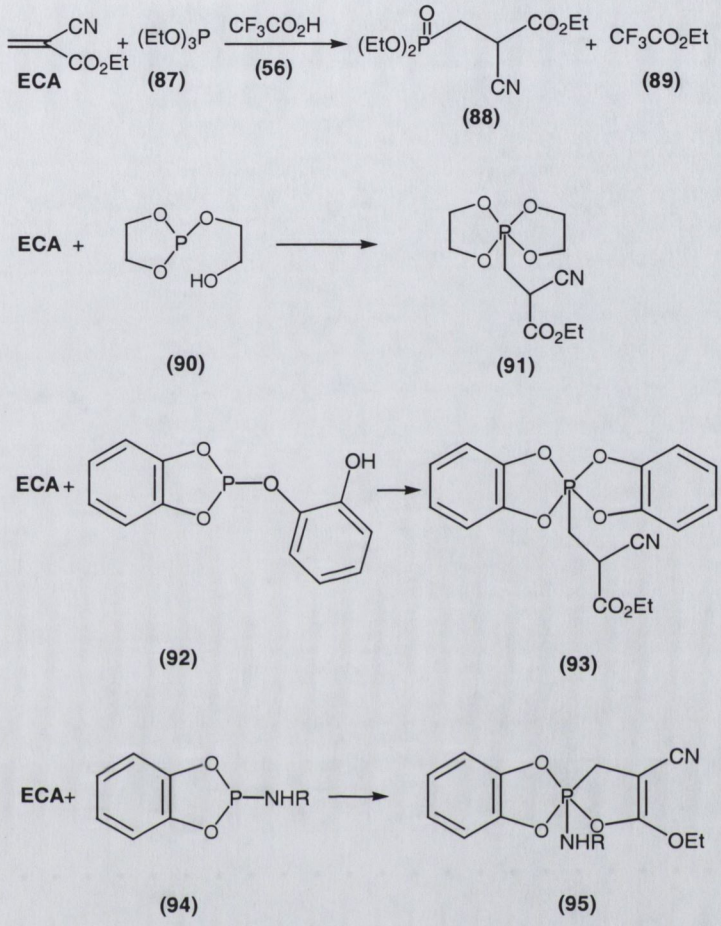
the ethoxycarbonyl substituent of **86** from carbon to nitrogen affords the observed product **85** [Scheme 20].

Scheme 20



The reaction of phosphites ($P(OR)_3$) and their analogues with **ECA** affords neutral products **88, 91, 93** and **95** [Scheme 21].

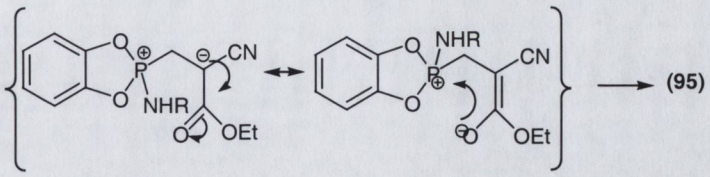
Scheme 21



The formation of **88** takes place *via* an Arbusov reaction in the presence of stoichiometric trifluoroacetic acid **56**.[25]

The formation of the cyclization products **91** and **93** can be rationalised in terms of trapping the cationic phosphorus atom by the oxygroups of the starting phosphites to give the spirophosphoranes **91** and **93**.[29] In the case of **95,** the cationic phosphorus atom of the zwitterionic intermediate **96** is intramolecular trapped by its terminal ester enolate[29] [Scheme 22].

Scheme 22



(96)

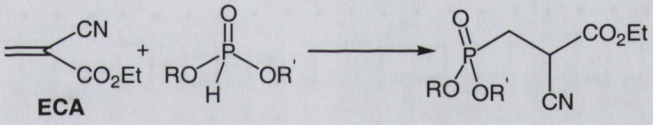
1. 2. 1. iii. b. Reactions of alkyl 2-cyanoacrylates with pentavalent phosphorus compounds.

Some examples of nucleophilic additions of pentavalent phosphorus compounds with **ECA** have been reported in the literature, and these can be separated into two different sets: those which involve reaction at the phosphorus atom, and those which do not.

Reactions which involve the phosphorus atom.

Dialkyl ($(RO)_2HP{=}O$) and diaryl ($(ArO)_2HP{=}O$) esters of phosphorous acid have been used as nucleophiles to effect conjugate addition reactions [Table 6].[32]

Table 6



(97-100)

(66), (88) and (101-102)

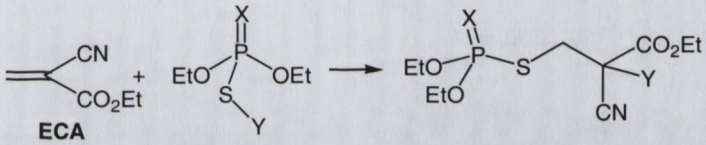
R	R'	Phosphorus Compound	Product
Et	Et	**97**	**88**
i-Pr	*i*-Pr	**98**	**101**
Ph	Ph	**99**	**102**
ortho(-C_6H_4-)		**100**	**66**

These reactions proceed straightforwardly and do not require the use of either active metals (most commonly sodium) or strong bases (sodium ethoxide, sodium hydride, sodium amide ...etc) to remove the proton on the phosphorus atom of these ester derivatives and create an anion that then acts as the nucleophile.

Reactions which do not involve a central phosphorus atom.

In this type of reaction, the hydrogen atom of ester derivatives of phosphorous and thiophosphorous acid is replaced by a more electronegative atom than phosphorus, such as sulfur. Thus, the Michael addition to **ECA** proceeds from the sulfur atom of **103** and **104** to yield stable adducts **105-106** respectively [Table 7].

Table 7



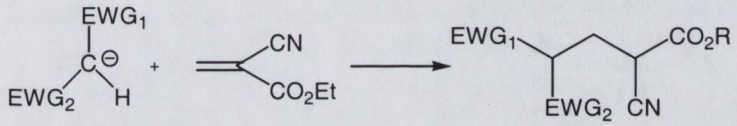
X	Y	Phosphorus compound	Product	Reference
S	H	**103**	**105**	23
O	Cl	**104**	**106**	33

These reactions, as for the previous examples of Table 5, proceed easily and do not require the use of any base to create an anion which then acts as the nucleophile.

1. 2. 1. iv. Carbanions as nucleophiles

Other examples of Michael additions to alkyl 2-cyanoacrylates involve the use of carbanions originating from the deprotonation of compounds with a rather acidic hydrogen atom, such as β-ketoesters, β-nitroesters and diphosphonates [Scheme 23].

Scheme 23



(107) **ECA** **(108)**

EWG = Electron-withdrawing Group

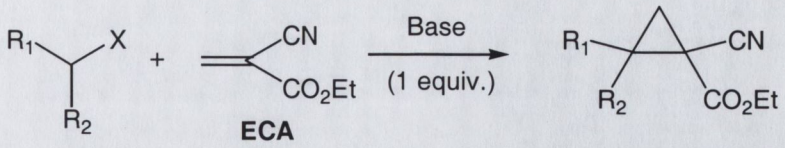
Thus, Gololobov *et al.*[34] managed to carry out the Michael addition of some of these compounds to **ECA** in the presence of piperidine as catalyst [Table 8].

Table 8

EWG_1	EWG_2	Product
CO_2Et	COMe	**108 a**
CO_2Me	NO_2	**108 b**

Other examples from the literature include the addition of carbanions bearing a leaving group to **ECA** to afford cyclopropanation products [Table 9].

Table 9



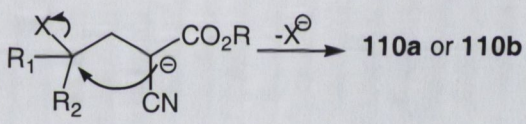
ECA

(109a,b) **(110a,b))**

R_1	R_2	X	Compound	Base	Product	Reference
CO_2Et	CN	Br	**109a**	NaH	**110a**	35
$PO(OEt)_2$	$PO(OEt)_2$	Br	**109b**	TlOEt	**110b**	36

Thus, the anionic center of **111 a** and **111 b**, created after the addition of the carbanion, are trapped *via* intramolecular displacement of bromide ion to yield the cyclopropanation products **110a** or **110b** [Scheme 24].

Scheme 24



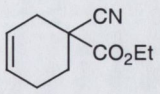
(111a,b)

1. 2. 2. Cycloaddition reactions

Alkyl 2-cyanoacrylates are excellent dienophiles in the Diels-Alder reaction because, in general, the greater the number of electron–attracting substituents on the double bond the more reactive is the dienophile.Thus, some [4+2] cycloaddition reactions of alkyl 2-cyanoacrylates have been described in the literature.

The first of these dates back to the late 1940s and involves the [4+2] cycloaddition reaction of **ECA** with 1, 3-butadiene **112** to afford the Diels-Alder adduct **113** [Figure 4].[37]

Figure 4

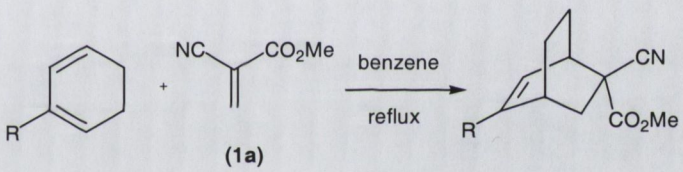


(113)

In the late 1970s the [4+2] cycloaddition reaction of 2-cyanoacrylate esters with anthracene was carried out by Buck[12] [Scheme 3].

Later on, further investigations related to regioselective [4+2] cycloadditions were reported. Thus, the Diels-Alder reaction of methyl 2-cyanoacrylate **1a** with 1,3-cyclohexadiene **114a** and 2-methyl-1,3-cyclohexadiene **114b** afford the bicyclic compound **115a** and the regioisomer bicyclic compound **115b** respectively [Scheme 25].[38]

Scheme 25



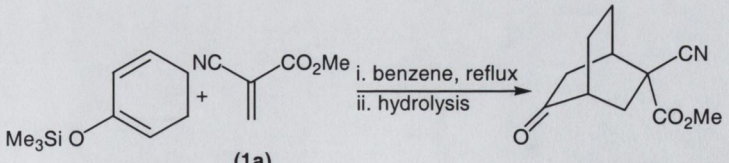
(1a)

(114a) (R = H)
(114b) (R = Me)

endo-**(115a)**
endo-**(115b)**

Additionally, the reaction of methyl 2-cyanoacrylate **1a** with 2-(trimethylsilyloxy)-1,3-cyclohexadiene took place regiospecifically to afford, after hydrolysis, the bicyclic compound **117** [Scheme 26].[38]

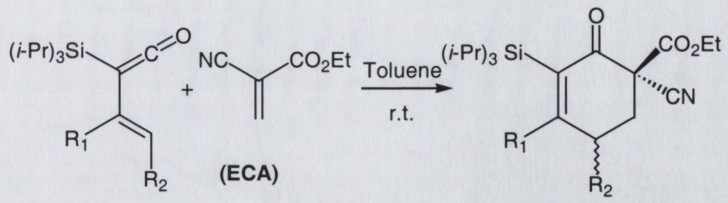
Scheme 26



(116) **(1a)** *endo*-**(117)**

When the different (triisoproylsilyl)vinylketenes **118** or **119** were reacted with **ECA** the highly functionalized six-membered rings **120** or **121** were obtained [Table 10].[39]

Table 10



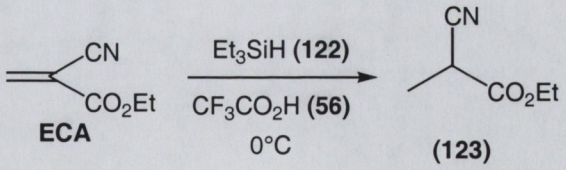
(118-119) (120-121)

Diene			Reaction Time (hours)	Adduct		
R_1	R_2				*Trans/cis*	Yield (%)
Me	Me	**118**	24	**120**	2/1	98
H	2, 6, 6-trimethylcyclohex-1-enyl	**119**	93	**121**	4/1	43

1. 2. 3 Reduction reactions

The reduction of the highly-polarised double bond of **ECA** has been reported using triethylsilane **122** in the presence of trifluoroacetic acid **56** to afford **123** [Scheme 27].[40]

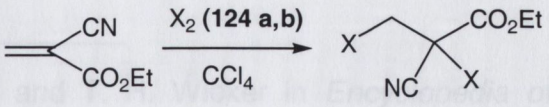
Scheme 27



1. 2. 4 Dihalogenation reactions.

The dihalogenation of the double bond of **ECA** has been reported using either bromine **124 a** or chlorine **124 b** in an inert solvent, such as carbon tetrachloride to yield dihalogenated adducts **125 a** and **126 b** [Scheme 28].[26]

Scheme 28



ECA

(125 a) (X = Cl)

(125 b) (X = Br)

1. 3. CONCLUSIONS.

In this Chapter different approaches to the synthesis of alkyl 2-cyanoacrylates, 2-cyanoacrylic acid **(CAA)** and 2-cyanoacryloyl chloride have been reviewed. Furthemore, a comprehensive survey of the reactivity of the double bond of 2-cyanoacrylate esters has been outlined which includes Michael additions of nucleophiles such as sulfur compounds, alcohols, phosphorus compounds and carbanions, Diels-Alder cycloadditions, reduction and dihalogenation reactions.

To date, none of the compounds obtained from the different reactions of alkyl 2-cyanoacrylates have been used for the reversible protection of the carbon-carbon double bond and that implies the possibility of opening a new field of investigation into the synthesis of novel cyanoacrylate esters and new routes of synthesis to known cyanoacrylate esters and cyanoacrylic acid **(CAA)**.

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CHAPTER 2.

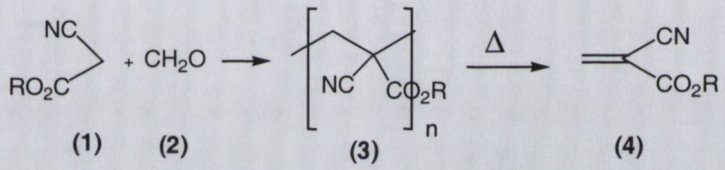
APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID FROM CONDENSATION REACTIONS

CHAPTER 2.

APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID USING CONDENSATION REACTIONS

To date, and as mentioned in Chapter 1, most approaches to cyanoacrylate compounds involve Knoevenagel reactions of an alkyll cyanoacetate **1** with paraformaldehyde **2** in the presence of a basic catalyst. Homopolymerization of the Knoevenagel product under these conditions is inevitable, so thermal conditions ("cracking") are required to obtain the monomer **4** [Scheme 1].[1]

Scheme 1



This condensation can be carried out in aqueous or in non-aqueous media. Thus, an aqueous solution of formaldehyde can be used in aqueous media and anhydrous formaldehyde, such as paraformaldehyde, is desirably employed in non-aqueous media.[2]

This condensation is catalysed by means of basic catalysts such as piperidine, trimethylamine, alkali alcoholates and sodium hydroxide. Piperidine and trimethylamine are the preferred catalysts for aqueous conditions.[2] Piperidine, trimethylamine and alkali alcoholates, which are produced from the reaction a metal with the desired alcohol, are the main catalysts employed in non-aqueous media.[2]

Although the condensation can be effected in both media it is preferred to carry it out in non-aqueous media in order to facilitate the preparation of anhydrous polymers (it is desirable to bring the polymer to a moisture content below about

0.4%)[2] which can be readily depolymerised to form the targeted monomer. Thus, a solvent capable of forming an azeotrope with the water evolved in the condensation reaction is required, for instance benzene or toluene.

The depolymerisation can be effected by heating the anhydrous crude polymeric product at an elevated temperature under reduced pressure in order to evolve monomeric vapours. Then, these monomeric vapours can be condensed and collected in a suitable receiver.

The best results obtained in the depolymerisation process are those where tertiary esters of phosphoric acid such as triphenyl phosphate, tricresyl phosphate, trihexyl phosphate, or similar high boiling esters are employed as heat-transfer agents in the depolymerisation medium because with the use of these phosphate esters the depolymerization conditions are less stringent than those in which the depolymerizaton is effected on the molten polymer itself.[2]

Additionally, it is advisable to carry out the depolymerisation process in the presence of inhibitors such as phosphoric anhydride, polyphosphoric acid or *para*-toluenesulfonic acid. These acidic inhibitors prevent anionic polymerisation.[2]

Free radicals inhibitors can also be included in the depolymerisation process to prevent radical polymerisation. Polyhydric phenols such as hydroquinone or catechol, nitrophenols such as *para*-nitrophenol or picric acid and aromatic nitro compounds such as trinitrobenzene can be employed for this purpose.[2]

Optimum results can be attained by introducing an acidic gaseous inhibitor into the depolymerisation system in order to entrain it with the gaseous monomer which evolves from the polymer. The preferred gaseous inhibitors are sulfur dioxide and nitric oxide[2].

ABSTRACT

Alkyl 2-cyanoacrylates are compounds of great importance to the adhesives industry. 2-Cyanoacrylic acid represents an important intermediate to these compounds. Investigations into routes to novel 2-cyanoacrylate esters and to 2-cyanoacrylic acid using several approaches are described.

The first approach involves condensation reactions to give either 2-cyanoacylate esters or precursors to 2-cyanoacrylic acid. Thus, Knoevenagel reactions between *tert*-butyl and benzyl cyanoacetate and paraformaldehyde afforded the derived *oligo*(2-cyanoacrylate) esters, but these were not amenable to thermal cracking to give monomers. Mannich and Wittig-Horner reactions were used to synthesise other potential precursors to 2-cyanoacrylic acid. Protonolysis (of an ammonium salt) and oxidation (of allylic compounds) were unsuccessfully tried for the conversion of these precursors to 2-cyanoacrylic acid.

The second approach involves the use of ethyl 2-cyanoacrylate as starting material. A strategy utilising the synthesis of a stable intermediate by protection of the double bond of ethyl 2-cyanoacrylate, hydrolysis or esterification of this intermediate and the regeneration of the double bond to afford either a 2-cyanoacrylate ester or 2-cyanoacrylic acid was devised and attempted.

The third approach involves the use of 2-thiirancarboxylic acid as a possible precursor to 2-cyanoacrylic acid. Several unsuccessful attempts to open the episulfide ring with cyanide ion were carried out.

The fourth approach involves attempted palladium-catalysed coupling reactions of *tert*-butyl 2-bromoacrylate with a cyanide source.

The fifth approach involves the use of solid-phase supports for the synthesis of cyanoacrylates in order to circumvent problems associated with polymerisation and with purification which held back progress when conventional methods were used.

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The fifth approach involves the use of solid-phase supports for the synthesis of cyanoacrylates in order to circumvent problems associated with polymerisation and with purification which held back progress when conventional methods were used.

And finally, it is advisable to store the monomeric material collected from the depolymerisation process in the presence of an acidic stablizer such as methanesulfonic or *para*-toluenesulfonic acids.

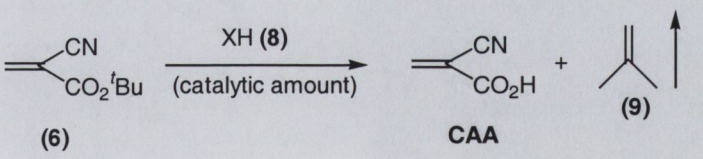
In the present work it was intended to synthesise 2-cyanoacrylate esters **4** and 2-cyanoacrylic acid (**CAA**) **5** using condensation reactions. Knoevenagel, Mannich and Wittig-Horner condensation reactions were tried for this purpose in order to obtain either 2-cyanoacrylate esters **4** or precursors of **CAA**. These precursors might then be easily converted into **CAA** from straightforward reactions such as hydrolysis, oxidation or cation-exchange.

2. 1. ATTEMPTED PREPARATION OF *t*-BUTYL AND BENZYL 2-CYANOACRYLATE BY CONDENSATION REACTIONS.

The synthesis of *tert*-butyl 2-cyanoacrylate **6** and of benzyl 2-cyanoacrylate **7** was considered because both esters could be transformed to **CAA** via straightforward cleavage reactions.

Initially, it was intended to prepare *tert*-butyl 2-cyanoacrylate **6** using the Knoevenagel methodology because the *tert*-butyl function could be easily hydrolysed using the well-established acid-catalysed cleavage of *tert*-butyl esters, which is so frequently used in peptide synthesis [Scheme 2].[3]

Scheme 2

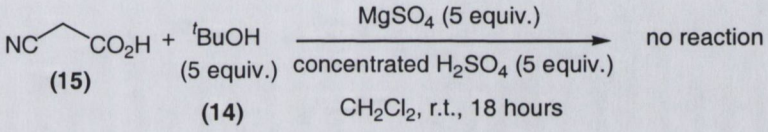


(6) **CAA**

The preferred reagent acid will be trifluoroacetic acid (TFA) **10** which posses a non-nucleophilic counterion, thus avoiding conjugate addition to the **CAA**-product. Additionally, the tertiary alkyl moiety of the *tert*-butyl ester will be largely converted into isobutene **9**, and only catalytic amounts of TFA will be required.

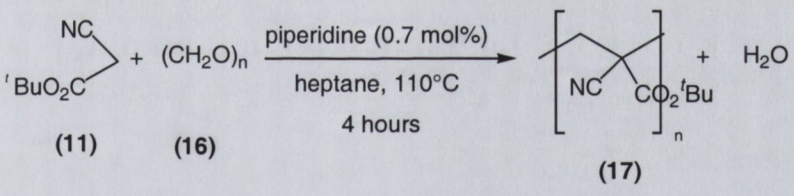
tert-Butyl 2-cyanoacetate **11** was readily prepared from *tert*-butyl 2-chloroacetate **12** and cyanide ion **13** in a mixture (95:5) of ethanol and water. Another attempt to synthesise **11** was made using the methodology reported by Wright *et al.*[4] This describes the esterification in good yield of several carboxylic acids with *tert*-butanol **14** in the presence of anhydrous magnesium sulfate and catalytic sulfuric acid as additional reagents. Thus, the esterification of 2-cyanoacetic acid **15** with *tert*-butanol **14** using the same methodology was attempted but no reaction was observed [Scheme 3].

Scheme 3



With *tert*-butyl 2-cyanoacetate **11** in hand its condensation with paraformaldehyde **16** under Knoevenagel conditions was carried out to give a gummy material which was assumed to be *oligo*(*tert*-butyl 2-cyanoacrylate) **17** [Scheme 4].

Scheme 4



Initial attempts to effect thermal cracking of the oligomer **17** to monomeric *tert*-butyl 2-cyanoacrylate **6** were unsuccessful, even when reaction conditions recommended by Loctite were used. Here, water was removed from the reaction mixture using a Dean and Stark apparatus, heptane was stripped off with simultaneous addition of hydroquinone (3 mol%) to prevent radical polymerization and of tritolylphosphate (3 mol%) to transfer heat more efficiently during the distillation process, and then the residual amount of piperidine was neutralised

with *p*-toluenesulfonic acid (*p*-TsOH) (0.3 mol%). Pyrolysis of the residual oligomer **17** gave only a carbonaceous residue.

It would seem that *p*-TsOH, which is added to neutralise the piperidine, could have mediated cleavage of the *tert*-butyl ester function to give either **CAA** or its oligomer which then suffered decomposition under the reaction conditions.

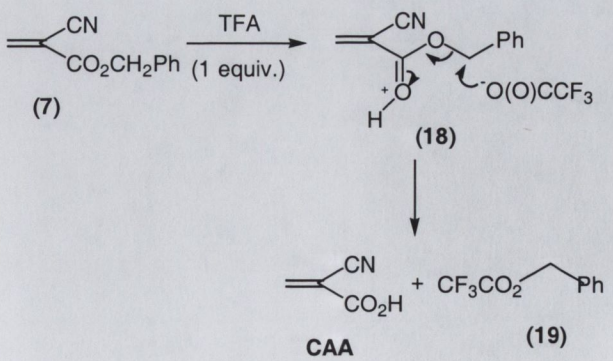
Consequently, it was thought advisable to neutralise the piperidine by stirring a solution of oligomer **17** in an organic solvent (for instance EtOAc) with the strongly acidic ion-exchanger Amberlite sulfonic acid resin. Then, the insoluble resin could be filtered off and the remaining solution would remain neutral avoiding possible cleavage of the *tert*-butyl ester group on thermal cracking of the oligomer.

However, when this was attempted using IR-120 (H^+) resin the same carbonaceous residue was observed after attempted cracking.

It was concluded that it would be impossible to obtain the monomeric compound **6** from a depolymerisation process without decomposition.

The next objective was the synthesis of benzyl 2-cyanoacrylate **7** because **CAA** could, in principle, be easily obtained by the cleavage reaction of the benzyl function of **7** with TFA [Scheme 5].

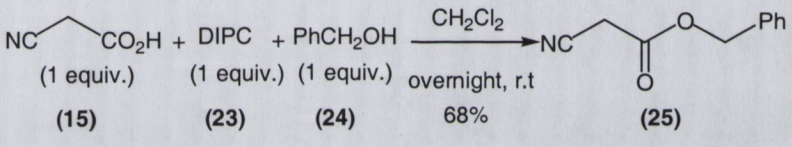
Scheme 5



Initially, the synthesis of benzyl 2-cyanoacetate **20** was tried using the reaction of benzyl 2-chloroacetate **21** with sodium cyanide **22** which unexpectedly afforded 2-cyanoacetic acid **15**. Thus, displacement of chloride anion with further hydrolysis of the benzyl function took place. The hydrolysis of the ester could be mainly due to the basic conditions employed in this process.

Kuo *et al.* reported the synthesis of 2-cyanoacetamides from the reaction of 2-cyanoacetic acid **15** with amines mediated by diisopropylcarbodiimide (DIPC) **23**.[5] The same methodology was therefore applied for the esterification reaction of 2-cyanoacetic acid **15** with benzyl alcohol **24** to afford the desired benzyl ester **25** [Scheme 6].

Scheme 6



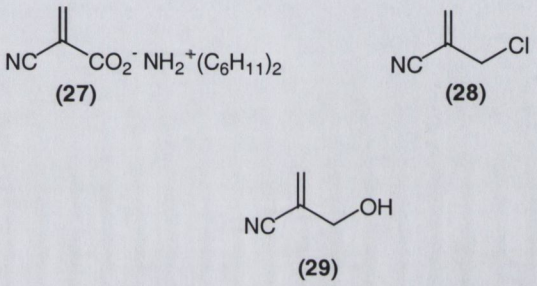
The Knoevenagel condensation of **20** with paraformaldehyde **16** was carried out to give a gummy material which was assumed to be *oligo*(benzyl 2-cyanoacrylate) **26**. Attempts to depolymerise **26** were unsuccessful, affording the same carbonaceous residue as had been observed for the *tert*-butyl case discussed above. These attempts were made using the same procedures as were employed for the attempted depolymerisation of **17**.

The conclusion that can be drawn from the above results is that preparing the 2-cyanoacrylate esters **6** and **7** using Knoevenagel condensations followed by depolymerisation of oligomer is not a practical route to these compounds.

2. 2. ATTEMPTED PREPARATION OF 2-CYANOACRYLiC ACID FROM DIFFERENT PRECURSORS OBTAINED BY CONDENSATION REACTIONS.

The synthesis of **CAA** from different precursors which can be synthesised using condensation reactions was considered next. Thus, the compounds **27-29** were chosen as possible precursors [Figure 1].

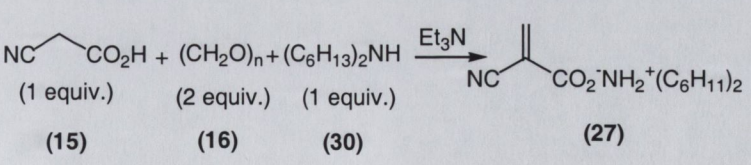
Figure 1



2. 2. 1. Preparation of 2-cyanoacrylic acid from dicyclohexylammonium 2-cyanoacrylate

The synthesis of the compound **27** has been reported by Krawczyk[6], and involves the Mannich condensation of 2-cyanoacetic acid **15** with paraformaldehyde **16** in the presence of dicyclohexylamine **30** and triethylamine **31** [Scheme 7].

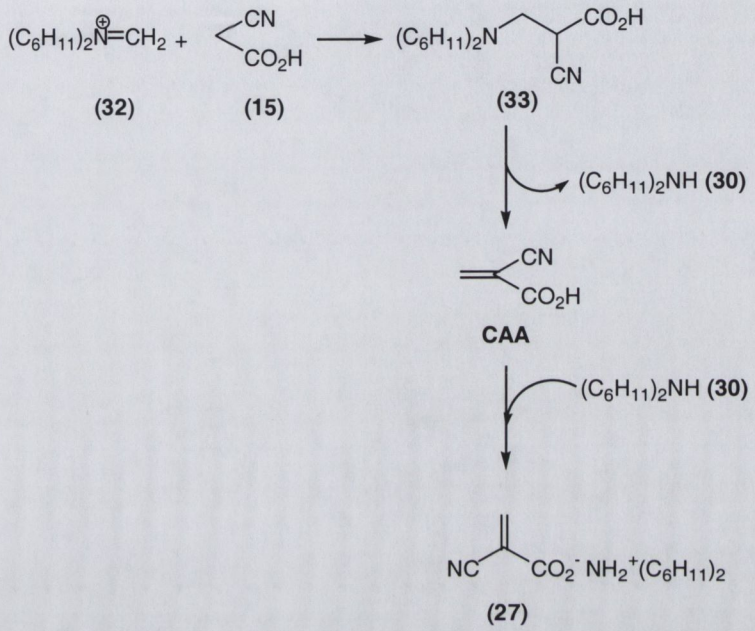
Scheme 7



Presumably, the secondary amine dicyclohexylamine **30** acts with a double role in this reaction. Initially, dicyclohexylamine **30** will form with paraformaldehyde **16** the Mannich adduct **32** which will react with 2-cyanoacetic acid **15** to afford **33**.

β-Elimination of the dicyclohexylamine **30** in **33** yields **CAA** which reacts with dicyclohexylamine **30** to form the salt **27** [Scheme 8].

Scheme 8



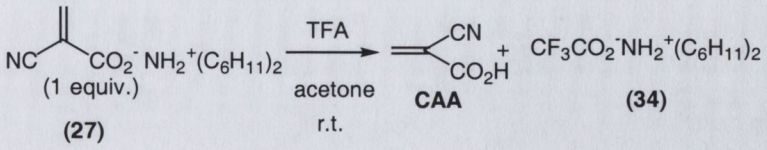
With the salt **27** in hand exchange of its ammonium cation by a proton was attempted in order to obtain **CAA**.

For this purpose, two different methods were tried. The first involved cation exchange by proton in non-aqueous media. The second pathway involved cation exchange under aqueous conditions.

2. 2. 1. i. Cation exchange of dicyclohexylammonium 2-cyanoacrylate using non-aqueous conditions.

TFA was initially tried as a reagent for the protonation of the ammonium salt **27**. Thus, 1 equivalent of TFA was reacted with the ammonium salt **27** in acetone to afford a solid which was identified as dicyclohexylammonium trifluoroacetate **34**, and a solution containing both the desired **CAA** and dicyclohexylammonium trifluoroacetate **34** [Scheme 9].

Scheme 9



The solution was concentrated and checked by ^{1}H-NMR which showed two singlets at δ 7.11 and 6.70 ppm and several multiplets at δ 3.16 and 1.90-1.19 ppm. The two singlets were assigned to the olefinic protons of **CAA** and the multiplets were assigned to dicyclohexylammonium trifluoroacetate. These multiplets match with those given in the ^{1}H-NMR spectrum of authentic dicyclohexylammonium trifluoroacetate **34**.

The impossibility of separating **CAA** from the dicyclohexylammonium salt by differences of solubility in acetone led to trial of another solvent (*iso*-butylmethyl ketone) but no significant differences in the solubilities of **CAA** and dicyclohexylammonium trifluoroacetate **34** were seen.

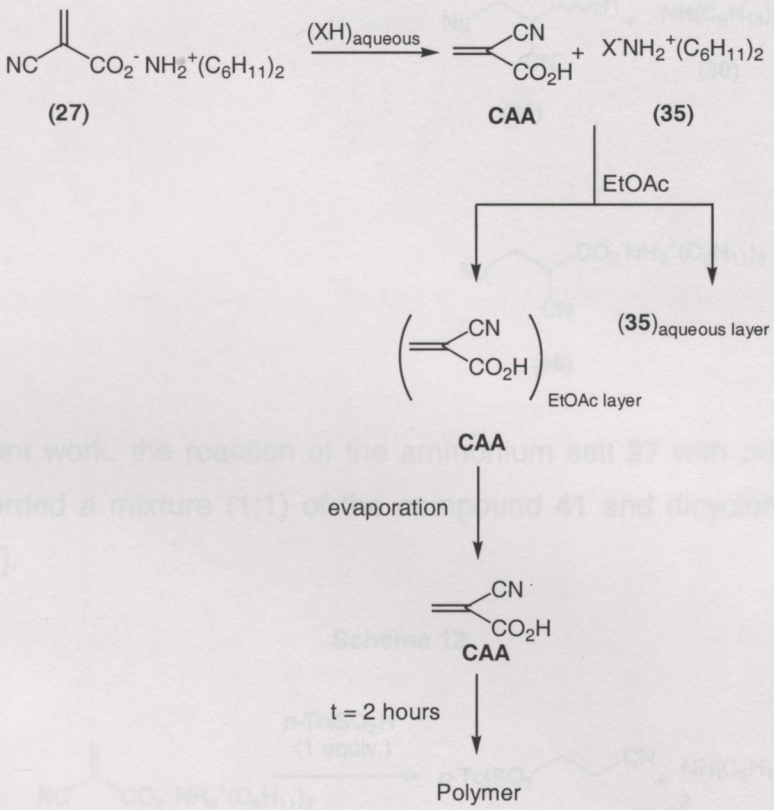
In order to circumvent this problem it was decided to use a strongly acidic cation exchange resin because then **CAA** could be easily separated from the resin by filtration. Thus, Amberlite IR-120 (H^+), previously dried by azeotroping with toluene, was suspended in a solution of **27** in CH_2Cl_2. However, after filtration of the Amberlite, the ammonium salt **27** was recovered. This result implies that the proton transfer needed to liberate **27** from its salt does not take place in non-aqueous solution.

2. 2. 1. ii. Cation exchange of dicyclohexylammonium 2-cyanoacrylate using aqueous conditions.

Titration of the ammonium salt **27** with aqueous acidic solutions and extraction of the liberated **CAA** into an organic solvent was considered despite the fact that this procedure meant exposing **CAA** to aqueous conditions. Thus, treatment of **27** with either 10% HCl or 1M H_2SO_4 solutions afforded, after extraction with EtOAc, **CAA.** The presence of **CAA** was confirmed by ^{1}H-NMR

spectroscopy, showing two singlets at δ 7.00 and 6.60 ppm assigned to its olefinic protons. However, **CAA** eventually suffered polymerisation when the organic layer was evaporated to dryness [Scheme 10].

Scheme 10

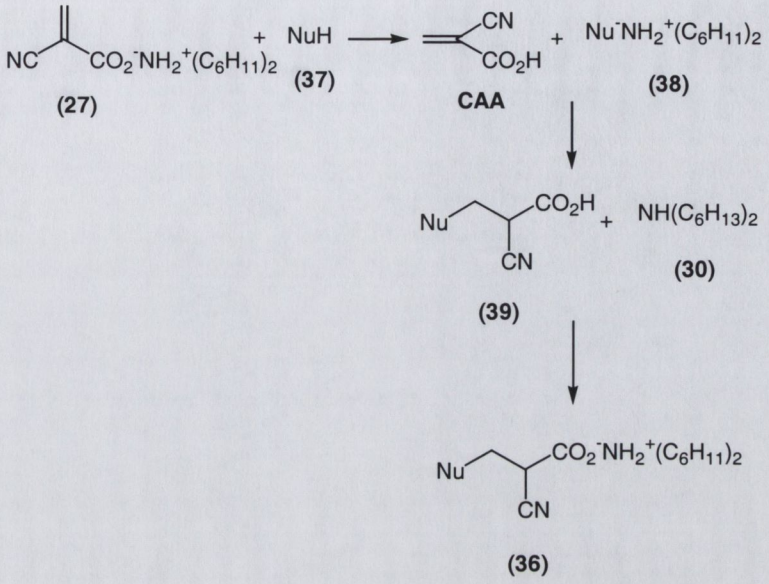


Polymerisation was observed even when a stabilizer, such as methanesulfonic acid, was added to the organic layer.

The conclusion that can be drawn from the above results is that the titration of the ammonium salt **27** must be carried out in non-aqueous media because the polymerisation of **CAA** is caused by the presence of even traces of water.

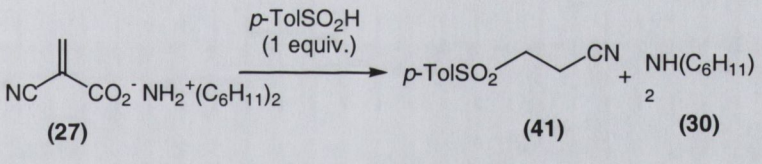
Krawczyk reported the Michael addition of 1,3-dicarbonyl compounds to dicyclohexylammonium 2-cyanoacrylate **27** mediated by the "internal" catalyst to afford the corresponding dicyclohexylammonium 2-cyanopropanoate adduct **36** [Scheme 11].[6]

Scheme 11



In the present work, the reaction of the ammonium salt **27** with *p*-toluenesulfinic acid **40** afforded a mixture (1:1) of the compound **41** and dicyclohexylamine **30** [Scheme 12].

Scheme 12

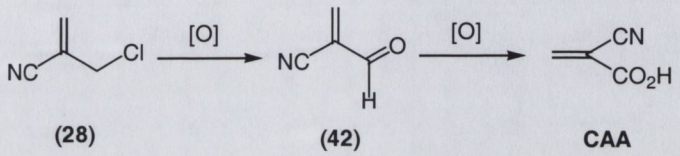


The compound **41** could be detected in the ^{1}H-NMR spectrum of the crude product by the presence of a set of two triplets centered at 3.55 and 2.82 ppm, with the same integration and the same coupling constant (*J* 7.5 Hz). Additionally, the presence of free base dicyclohexylamine **30** in the ^{1}H-NMR spectrum supported the fact of a decarboxylation process to afford **41**.

2. 2. 2. Preparation of 2-cyanoacrylic acid from 2-(chloromethyl)acrylonitrile

The compound 2-(chloromethyl)acrylonitrile **28** seemed to be an interesting intermediate because of its possible conversion into either 2-cyanopropenal **42** or **CAA** by oxidation reactions [Scheme 13].

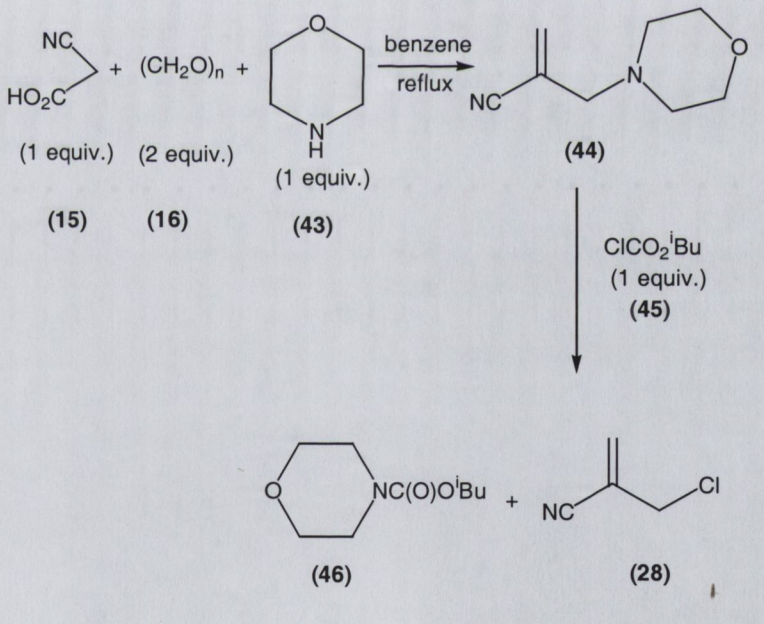
Scheme 13



(28) **(42)** **CAA**

Krawczyk reported the synthesis of **28** using a convenient two-step route from 2-cyanoacetic acid **15** [Scheme 14].[7]

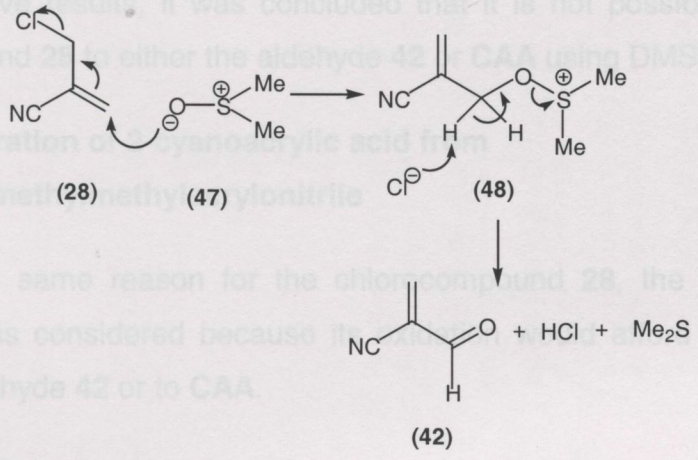
Scheme 14



This two-step synthesis involves the double Mannich reaction of 2-cyanoacetic acid **15** with paraformaldehyde **16** and morpholine **43** followed by decarboxylation and the by a dialkylamino-chloride exchange utilising an *iso*-butyl chloroformate **45** as reagent.

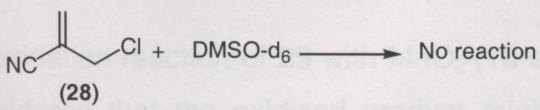
In the present work, it was intended to synthesise 2-cyanopropenal **42** by oxidising 2-(chloromethyl)acrylonitrile **28** *via* Kornblum reaction with dimethylsulphoxide (DMSO) **43**. Thus, the mechanism below was expected to take place [Scheme 15].

Scheme 15



Several attempts to oxidise **28** [Table 1] with DMSO-d_6 were carried out in order to monitor the oxidation reaction with respect to time using NMR but the expected aldehyde **42** or **CAA** was never detected. This observation was based on the absence of a signal for either an aldehyde or a carboxylic acid function in the carbon spectrum.

Table 1. Attempted Kornblum oxidation reaction of 2-(chloromethyl)acrylonitrile (9) with DMSO-d_6



Temperature (°C)	Reaction time (hours)
25	48
100	10

It was thought that the presence of a base during the oxidation reaction of **28** would assist the deprotonation of the intermediate **48** and consequently would force the reaction to the desired aldehyde **42**.[8] Thus, one equivalent of either sodium bicarbonate or triethylamine was added to the reaction mixture but no reaction was again observed.

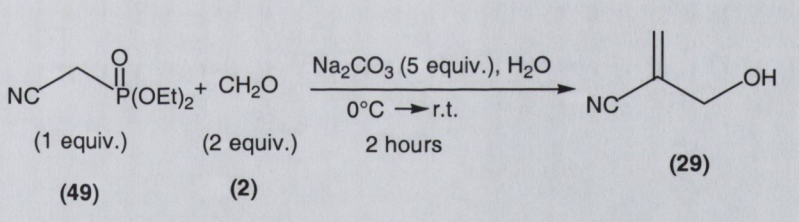
From the above results, it was concluded that it is not possible to oxidise the chlorocompound **28** to either the aldehyde **42** or **CAA** using DMSO as reagent.

2. 2. 3. Preparation of 2-cyanoacrylic acid from 2-hydromethylmethylacrylonitrile

For the same reason for the chlorocompound **28**, the synthesis of the alcohol **29** was considered because its oxidation would afford direct access to either the aldehyde **42** or to **CAA**.

The alcohol **29** is readily available from the Horner-Wittig reaction of diethyl 2-cyanomethylphosphonate **49** with formaldehyde **2** in the presence of potassium carbonate [Scheme 16].[9]

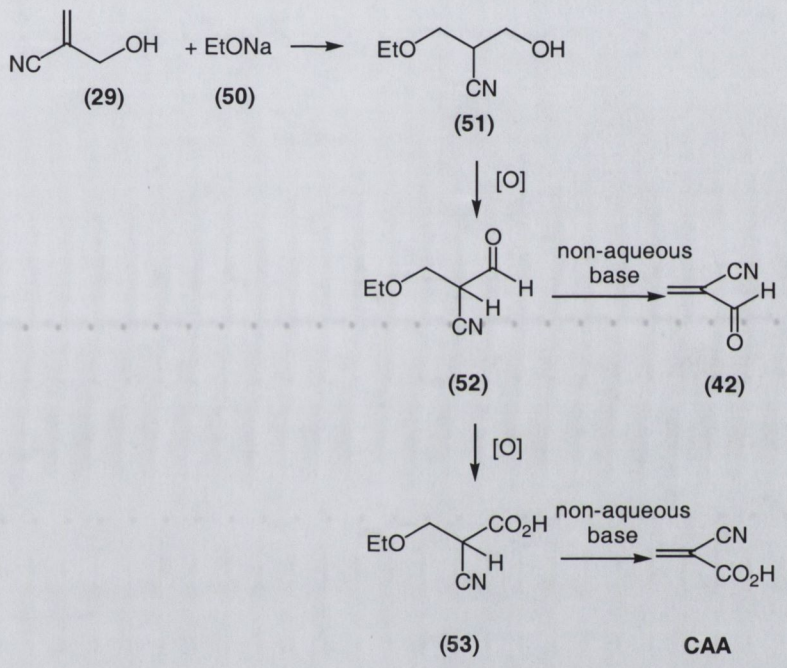
Scheme 16



The heterogeneous oxidation reaction of **29** with MnO_2 (16 equiv.) was attempted because it was considered that the oxidised product might be easily obtained after reaction by filtration of the solid MnO_2.[10] Only a very small amount (< 5%) of the starting allyl alcohol **29** was recovered after filtration and evaporation of the reaction mixture. The conclusion that can be drawn is that an oxidation-polymerisation process of **29** took place to afford an insoluble polymer of the oxidation product of **29** (aldehyde or, possibly acid).

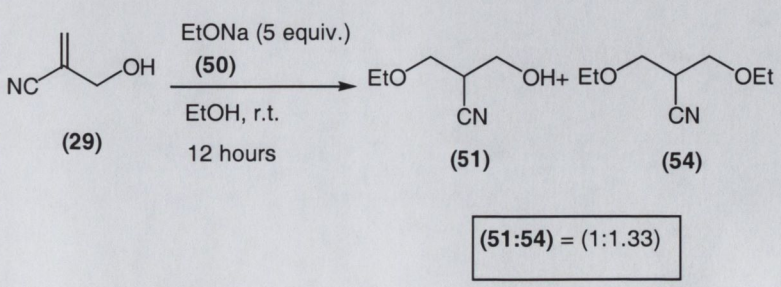
In order to avoid polymerisation it was thought to protect the double bond of **29** before trying the oxidation of the alcohol function. Reaction of **29** with sodium ethoxide would afford the Michael addition product **51** which could be oxidised without risk of polymerisation reactions. Regeneration of the double bond of the oxidised product with a non-aqueous base would afford either the aldehyde **42** or **CAA** [Scheme 17].

Scheme 17



The Michael addition reaction of the allyl alcohol **29** with sodium ethoxide **50** at r.t. for 24 hours afforded a mixture (1:1.3) of **51** and **54** [Scheme 18].

Scheme 18



Structures of **51** and **54** were unequivocally determined by NMR (proton and carbon spectra and C-H and H-H COSY experiments). Thus, the structure of **51** can be elucidated from the presence of two different doublets centred at 3.91 and 3.73 ppm with the same integration value and the presence of a quintet centred at 3.00 ppm with the half integration value with respect to the above doublets in the ^{1}H-NMR. The H-H COSY experiment showed correlation between the quintet with the two other doublets and the C-H COSY experiment showed a correlation of each doublet with a methylene carbon and a correlation of the quintet with a methine carbon. The structure of **54** was determined from the presence of a doublet (centred at 3.65 ppm and integration value of 4 in the ^{1}H-NMR) and correlated with a quintet (centred at 2.98 ppm and integration value of 1 in the ^{1}H-NMR) in the H-H COSY experiment. The C-H experiment showed correlation of the doublet with a methylene carbon and correlation of the quintet with a methine carbon.

In order to avoid formation of the compound **54**, which possibly originated from **51** by the elimination-addition displacement of its hydroxy function by ethoxide nucleophile, the same reaction was attempted at 0 °C for 5 hours to afford a mixture (8:1) of **51** and **54**.

Attempts to purify **51** and **54** by distillation were unsuccessful because of the impossibility of separating each compound as an individual fraction.

Additionally, the same Michael addition reaction of ethoxide to **29** was attempted but at this time one equivalent of sodium ethoxide **50** was used at r.t. and only 10% conversion to Michael addition product was observed.

Finally, reaction of the allyl alcohol **29** with boiling ethanol was attempted without success.

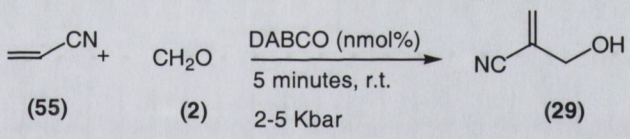
Consequently, it was decided to abandon this approach towards either the aldehyde **42** or **CAA** because of the impossibility of obtaining the intermediate **51** in good yield. A good yield of **51** is demanded because this approach towards either the aldehyde **42** or **CAA** requires two further steps.

Other approaches for the oxidation of the allyl alcohol **29** such as the Pfitzner oxidation reaction were considered.[11] Thus, the alcohol **29** was dissolved with DIPC and phosphorous acid in DMSO-d_6 and heated at 100 °C for 5 hours but no reaction was observed.

From the above unsuccessful attempts for the oxidation of **29** it was concluded that it is not possible to oxidise the hydroxy function of **29** using conventional methods and obtain a monomeric product.

The synthesis of **29** has been reported in the literature using the Baylis-Hillman reaction [Scheme 19].[12]

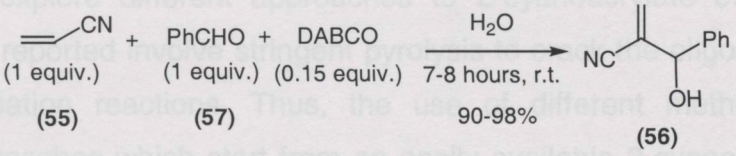
Scheme 19



(55) (2) (29)

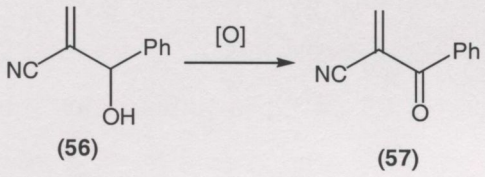
The high pressures needed to carry out this reaction did not allow to us to perform it with our facilities. However it was thought to use the Baylis-Hillman methodology in order to obtain other allyl alcohols which required less stringent conditions in their synthesis than the alcohol **29**. For this purpose, it was found in the literature that the synthesis of the allyl alcohol **56** using the DABCO-catalyzed coupling reaction of benzaldehyde **57** with acrylonitrile **55** in water at atmospheric pressure had been reported [Scheme 20].[13]

Scheme 20



The allyl alcohol **56** seemed to be an interesting intermediate because of its potential for straightforward conversion to the corresponding ketone **57** by oxidation [Scheme 21].

Scheme 21



Thus, oxidation should be easy because the alcohol is benzylic as well as allylic, and the ketone **57** should be more stable than the easily-polymerised aldehyde **42**.

The presence of two electron-withdrawing groups on the same carbon atom of **57** might confer similar adhesive properties to those observed for the 2-cyanoacrylate esters. Thus, the oxidation of the alcohol **56** was attempted by stirring a solution in CH_2Cl_2 with MnO_2 (16 equiv.) to afford, after filtration and evaporation, a small amount of the starting alcohol. It must be assumed that an oxidation-polymerisation process again took place as was observed for the oxidation of the allyl alcohol **29**.

The conclusion that can be drawn from all of the above results is that there is a challenge to explore different approaches to 2-cyanoacrylate esters because those already reported involve stringent pyrolysis to crack the oligomers obtained from condensation reactions. Thus, the use of different methodologies (for instance, approaches which start from an easily available 2-cyanoacrylate ester) or modifications to those methodologies already mentioned (for instance, by conducting Knoevenagel condensation reactions on solid phase supports in order to prevent polymerisation) will be discussed in depth in further Chapters.

2. 3. EXPERIMENTAL PART

^{1}H-NMR (400.13 MHz) and ^{13}C-NMR (100.62 MHz) spectra were recorded in $CDCl_3$ using a Bruker Avance DPX-400 spectrometer. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are quoted in Hz and obtained by first-order analysis of spin patterns. FT-IR spectra were recorded using a Mattson FT-IR spectrometer and measured in cm^{-1}. All solvents were dried using standard techniques.

_t_-Butyl 2-cyanoacetate (11)

Sodium cyanide **22** (10.78 g, 0.22 mmol) was added to a solution of *t*-butyl 2-chloroacetate **12** (30 g, 0.20 mmol) in a mixture (95:5) of ethanol:H_2O (286 ml) at r.t. The reaction mixture was heated at 80 °C for 5 hours. Then, the reaction mixture was quenched with sodium bicarbonate solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to afford 16.10 g (57 %) of **11**.

^{1}H-NMR ($CDCl_3$) δ: 3.39 (2 H, s, $CNC\underline{H}_2CO_2{}^{t}Bu$) and 1.53 (9 H, s, $(C\underline{H}_3)_3C$-).

Attempted preparation of _t_-butyl 2-cyanoacetate (11) from 2-cyanoacetic acid (15) and _t_-butanol (14)

t-Butanol **14** (11.23 mL, 117.5 mmol) was added to a suspension of 2-cyanoacetic acid **15** (2 g, 23.5 mmol), concentrated sulphuric acid (1.29 mL, 23.5 mmol), anhydrous magnesium sulphate (11.30 g, 94 mmol) in CH_2Cl_2 (94 mL). The suspension was stirred at r.t. for 18 hours. Then, the reaction mixture was washed with sodium bicarbonate solution, extracted with EtOAc, washed with saturated sodium chloride solution, dried over $MgSO_4$, filtered and concentrated to afford 150 mg of *t*-butanol **14**.

Benzyl 2-cyanoacetate (20)[5]

Diisopropylcarbodiimide (DIPC) **23** (4.32 g, 5.25 mL, 34.31 mmol) was added to a solution of 2-cyanoacetic acid **15** (2.91 g, 34.31 mmol) and benzyl alcohol **24** (3.1 mL, 34.31 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to reach r.t. and stirred at that temperature for 12 hours. Then, the reaction mixture was filtered and concentrated to afford 4.1 g (68%) of **20** as yellow liquid.

^{1}H-NMR ($CDCl_3$) δ: 7.39 (5 H, s, $C_6\underline{H}_5CH_2O$-), 5.25 (2 H, s, $C_6H_5C\underline{H}_2O$-) and 3.50 (2 H, s, $C\underline{H}_2CNCO_2Bn$).

Attempted preparation of benzyl 2-cyanoacetate (20) from benzyl 2-chloroacetate (21)

Sodium cyanide **22** (3.99 g, 0.08 mmol) was added to a solution of benzyl 2-chloroacetate **21** (13.31 g, 0.07 mmol) in a mixture (95:5) of ethanol:H_2O (100 mL) at r.t. The reaction mixture was heated at 80 °C for 5 hours. Then, the reaction mixture was quenched with sodium bicarbonate solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to afford 2.13 g of 2-cyanoacetic acid **15**.

Attempted preparation of *t*-butyl (6) and benzyl 2-cyanoacrylate (7) from Knoevenagel condensation

Paraformaldehyde **16** (1 equiv.) was added to a stirred solution of the corresponding 2-cyanoacetate ester **11** or **20** (1 equiv.) and piperidine (0.07 equiv.) in heptane (14 M). The reaction mixture was heated at 110 °C until the stoichiometric amount of water was collected using a Dean-Stark apparatus. Then, hydroquinone (0.02 equiv.), tritolphosphate (0.02 equiv.) and *p*-TsOH (0.008 equiv.) were added to the reaction mixture. This crude mixture was unsuccessfully distilled under reduced pressure to give black carbonaceous residue in both cases.

The same procedure above described was followed but at this time the crude mixture was dissolved in EtOAc and stirred in amberlite IR-120 (H^+) resin before the cracking process. The same carbonaceous residue was observed again after filtration of the amberlite and heating under reduced pressure.

Dicyclohexylammonium 2-cyanoacrylate (27)[6]

A suspension of 2-cyanoacetic acid **15** (4.25 g, 50 mmol), paraformaldehyde **16** (3 g, 100 mmol), dicyclohexylammonium **30** (9.05 g, 50 mmol) and triethylamine **31** (3.79 g, 37.5 mmol) in benzene (150 mL) was stirred at 120 °C for 30 minutes. Then, the reaction mixture was filtrated and the filtrate was evaporated to afford a white solid. The white solid was suspended in hexane, filtered and dried. The recrystallization of the white solid was carried out from benzene to yield **27** (4.25 g, 32 %).

^{1}H-NMR ($CDCl_3$) δ: 6.79 (1 H, d, *J* 1.0 Hz, HHC=), 6.33 (1 H, s, *J* 1.0 Hz, HHC=), 3.15-3.09 (2 H, m, 2 x (N-CH)), 2.09-2.06 (4 H, m), 1.85-1.82 (4 H, m), 1.69-1.66 (2 H, m), 1.53-1.45 (4 H, m) and 1.34-1.15 (6 H, m).

^{13}C-NMR ($CDCl_3$) δ: 164.1 (CO_2Et), 117.9 (CN), 52.6 (CH), 29.1 (CH_2), 24.7 (CH_2) and 24.3 (CH_2).

2-(Morphylin-4'-ylmethyl)acrylonitrile (44)[7]

Morpholine **43** (26.1 g, 0.3 mmol) was added to a suspension of 2-cyanoacetic **15** (25.5 g, 0.3 mmol) and paraformaldehyde **16** (0.72 mmol, 21.6 g) in benzene (150 ml). The suspension was stirred and heated at reflux for 6 hours using a Dean-Stark water apparatus. Then, the reaction mixture was concentrated and the residue was extracted with chloroform, washed with water, dried over $MgSO_4$ and concentrated to afford **44** (29.3 g, 64 %).

^{1}H-NMR ($CDCl_3$) δ: 5.92 (1 H, s, HHC=), 5.84 (1 H, s, HHC=), 3.62-3.59 (4 H, m, 2 x (NCH_2CH_2O)), 3.02 (2 H, s, =C(CN)CH_2N) and 2.37-2.43 (4 H, m, 2 x (NCH_2CH_2O)).

2-(Chloromethyl)acrylonitrile (28)[7]

i-Butyl chloroformate **45** (9.26 mL, 0.07 mmol) was added to a solution of **44** (10 g, 0.06 mmol) in benzene (29 mL) at r.t. The mixture was stirred at r.t. for 2 hours. Then, the reaction mixture was concentrated to give a residue which was distilled (55 °C, 1 mm Hg) to give **28** (3.28 g, 50 %).

^{1}H-NMR ($CDCl_3$) δ: 6.08 (1 H, s, HHC=), 6.05 (1 H, s, HHC=) and 4.13 (2 H, s, CH_2).

IR: 3114.9, 3022.1, 2965, 2360.4, 2228.4 (CN), 1918.1, 1695.9, 1624.1, 1441.9, 1401.3, 1266.9, 958.5, 774.0 and 602.9 cm^{-1}.

Attempted oxidation of 2-(chloromethyl)acrylonitrile (28) with DMSO-d_6

In the absence of base

A solution of **28** (0.2 g, 1.98 mmol) in DMSO-d_6 (2 mL) was heated at 100 °C for 10 hours. The reaction was monitored at different times from NMR but reaction was never observed. The ^{13}C-NMR never showed either an aldehyde signal or an acid signal.

In the presence of base

A solution of **28** (0.2 g, 1.98 mmol) and triethylamine **31**(1mL) in DMSO-d_6 (2 ml) was heated at 100 °C for 10 hours. The reaction was monitored at different times from NMR but reaction was never observed. The ^{13}C-NMR never showed either an aldehyde signal or an acid signal.

Cyanomethylphosphonate (49)[14]

Triethylphosphate (9.52 mL, 55.5 mmol) was added to chloroacetonitrile (3.51 mL, 55.5 mmol). The reaction mixture was heated at 145 °C for 11 hours. Then, the crude mixture was heated smoothly under reduced pressure (0.5 mm /

85 °C) in order to remove the unreacted material to afford 5.54 g (56 %) of cyanomethylphosphonate **49**.

^{1}H-NMR ($CDCl_3$) δ: 4.20 (4 H, qd, J_{H-H} 7.5 Hz and $^3J_{H-P}$ 15.6 Hz, 2 x ((O)POC$\underline{H}_2$CH$_3$), 2.86 (2 H, d, $^2J_{H-P}$ 21.1 Hz, POC$\underline{H}_2$CN) and 1.35 (6 H, t, *J* 7.5 Hz, 2 x (OCH$_2$C$\underline{H}_3$)).

^{13}C-NMR ($CDCl_3$) δ: 112.3 ($\underline{C}$N), 63.34 (O$\underline{C}$H$_2$), 16.6 ($\underline{C}$H$_3$), 15.8 ($\underline{C}$H$_2$) and 15.2 ($\underline{C}$H$_3$).

IR: 3480.9, 2987.2, 2912.0, 2341.2, 2256.3 (CN), 1639.2, 1394.3, 1267.0, 1022.1, 977.7, 844.7 and 804.2 cm^{-1}.

2-(Hydroxymethyl)acrylonitrile (29)[9]

A solution of sodium carbonate (15 g, 141 mmol) in H_2O (15 mL) was added to a solution of cyanomethylphosphonate **49** (5g, 28.3 mmol) and 35% aqueous solution of formaldehyde (14.8 mL). The reaction was left at r.t. for 2 hours. Then, a saturated ammonium chloride solution was added and the crude mixture was extracted with ether. The ethereal layers were combined, dried over $MgSO_4$, filtered and concentrated to afford 1.26 g of yellow residue. The residue was chromatographied using hexane: EtOAc (9:1) as eluent to afford 0.48 g (20 %) of **10** (R_f 0.30 in Hexane: EtOAc 1: 1) as a colourless liquid.

^{1}H-NMR ($CDCl_3$) δ: 6.03 (1 H, s, H$\underline{H}$C=), 6.00 (1 H, s, $\underline{H}$HC=) and 4.20-4.19 (2 H, m, CH_2) and 3.33 (1 H, bs, -O$\underline{H}$).

^{13}C-NMR ($CDCl_3$) δ: 130.2 ($\underline{C}_q$), 122.3 (=$\underline{C}$H$_2$), 116.8 ($\underline{C}$N) and 62.0 ($\underline{C}$H$_2$).

Preparation of MnO_2[15]

A solution of tetrahydrate manganese sulphate (11.10 g, 49.8 mmol) in H_2O (15 mL) and a solution of NaOH (40%, 11.70 mL) were simultaneously added to a hot stirred solution of potassium permanganate (9.6 g, 60.7 mmol) in water (60 mL). MnO_2 was precipitated soon after the start as a fine brown solid.

Stirring was continued for a further hour and then the solid was collected with a centrifuge and washed with water until the washings were colourless. The solid was dried in the oven and ground to a fine powder before use.

Attempted oxidation of 2-(hydroxymethyl)acrylonitrile (29) using MnO_2

MnO_2 (0.84 g, 9.64 mmol) was added to a solution of **29** (0.05 g, 0.60 mmol) in CH_2Cl_2 (2 mL) at r.t. The suspension was stirred at that temperature for 12 hours. Then, MnO_2 was filtered and the filtrate was evaporated to afford 0.003 g of **29**.

^{1}H-NMR ($CDCl_3$) δ: 6.03 (1 H, s, H$\underline{H}$C=), 6.00 (1 H, s, H$\underline{H}$C=) and 4.20-4.19 (2 H, m, CH_2) and 3.33 (1 H, bs, -O$\underline{H}$).

Michael addition reaction of sodium ethoxide to 2-(hydroxymethyl)acrylonitrile (29)

10 mL of 1M EtONa solution in ethanol was added to **29** (0.17 g, 2.04 mmol) at 0 °C. The solution was allowed to reach r.t. and kept at that temperature for 12 hours. Then the reaction was quenched with sodium chloride and extracted with EtOAc to afford 0.2 g of a mixture (1:1.33) of 3-ethoxy-2-(hydroxymethyl)propionitrile **51** and 3-ethoxy-2-(ethoxymethyl)propionitrile **54**.

^{1}H-NMR ($CDCl_3$) δ: 3.91 (2 H, d, *J* 5.4 Hz, HOC$\underline{H}_2$CH(CN)-, **51**), 3.72 (2 H, d, *J* 5.4 Hz, EtOC$\underline{H}_2$CH(CN)-, **51**), 3.65 (4 H, d, *J* 6.0 Hz, 2 x (EtOC$\underline{H}_2$CH(CN)-), **54**), 3.58 (2H, q, *J* 7.0 Hz, -OC$\underline{H}_2$CH$_3$, **51**), 3.56 (4 H, q, *J* 7.0 Hz, 2 x (-OC$\underline{H}_2$CH$_3$), **54**), 3.00 (1H, q, *J* 6.0 Hz, EtOCH$_2$C$\underline{H}$CH$_2$OEt, **54**), 2.98 (1 H, q, *J* 6.0 Hz, EtOCH$_2$C$\underline{H}$CH$_2$OH, **51**), 1.23 (3 H, t, *J* 7.0 Hz, -OCH$_2$C$\underline{H}_3$, **51**) and 1.22 (6 H, t, *J* 7.0 Hz, 2 x (-OCH$_2$C$\underline{H}_3$), **54**).

^{13}C-NMR ($CDCl_3$) δ: 118.8 (C$\underline{N}$, **54**), 118.4 (C$\underline{N}$, **51**), 67.3 (EtO$\underline{C}H_2$, **51**), 66.7 ($\underline{C}H_2$), 66.6 ($\underline{C}H_2$), 66.5 ($\underline{C}H_2$), 60.4 (HO$\underline{C}H_2$, **51**), 34.6 ($\underline{C}$H, **51**), 33.0 ($\underline{C}$H, **51**) and 14.4 ($\underline{C}H_3$).

Attempted Pfitzner oxidation reaction of 2-(hydroxymethyl)acrylonitrile (29)

The compound **29** (0.37 g, 4.44 mmol) was added to a solution of diisopropylcarbodiimide **23** (0.55 g, 4.44 mmol) and phosphorous acid (0.36 g, 4.44 mmol) in DMSO-d_6 (2 mL) at 100 °C for 5 hours. The reaction was monitored at different times from ^{1}H-NMR but reaction was never observed.

2-(Hydroxybenzyl)acrylonitrile (56)[13]

Acrylonitrile **55** (6.4 mL, 0.17 mmol) was added to a suspension of benzaldehyde **57** (17.8 g, 0.17 mmol) and DABCO (2.82 g, 0.025 mmol) in H_2O (84 mL) at r.t. The suspension was stirred for 12 hours at that r.t. Then, 10% HCl was added and the reaction mixture was extracted with ether. The ethereal layers were combined, washed with NaCl solution, dried over $MgSO_4$, filtered and evaporated to afford 19.08 g (71 %) of **56** as a black residue. The residue was distilled under reduced pressure to give **56** (19.08 g, 71%) as brown liquid.

^{1}H-NMR ($CDCl_3$) δ: 7.48-7.35 (5 H, m, $C_6\underline{H}_5$-), 6.09 (1 H, s, $\underline{H}HC$=), 6.00 (1 H, s, $H\underline{H}C$=) and 5.28 (1 H, s, $C\underline{H}$).

^{13}C-NMR ($CDCl_3$) δ: 143.8 ($\underline{C}_q$), 138.9 ($\underline{C}_q$), 129.4 ($H_2\underline{C}$=), 128.3 (-$\underline{C}H$=), 126.1 (-$\underline{C}H$=), 116.6 ($\underline{C}N$) and 73.6 (-$\underline{C}H$).

Attempted oxidation of 2-(Hydroxybenzyl)acrylonitrile (56) using MnO_2

MnO_2 (1.75 g, 20.12 mmol) was added to a solution of **56** (0.2 g, 1.26 mmol) in CH_2Cl_2 (4 mL) at r.t. The suspension was stirred at that temperature for 12 hours. Then, MnO_2 was filtered and the filtrate was evaporated to afford 0.06 g of **56**.

^{1}H-NMR ($CDCl_3$) δ: 7.48-7.35 (5 H, m, $C_6\underline{H}_5$-), 6.09 (1 H, s, $\underline{H}HC$=), 6.00 (1 H, s, $H\underline{H}C$=) and 5.28 (1 H, s, $C\underline{H}$).

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CHAPTER 3.

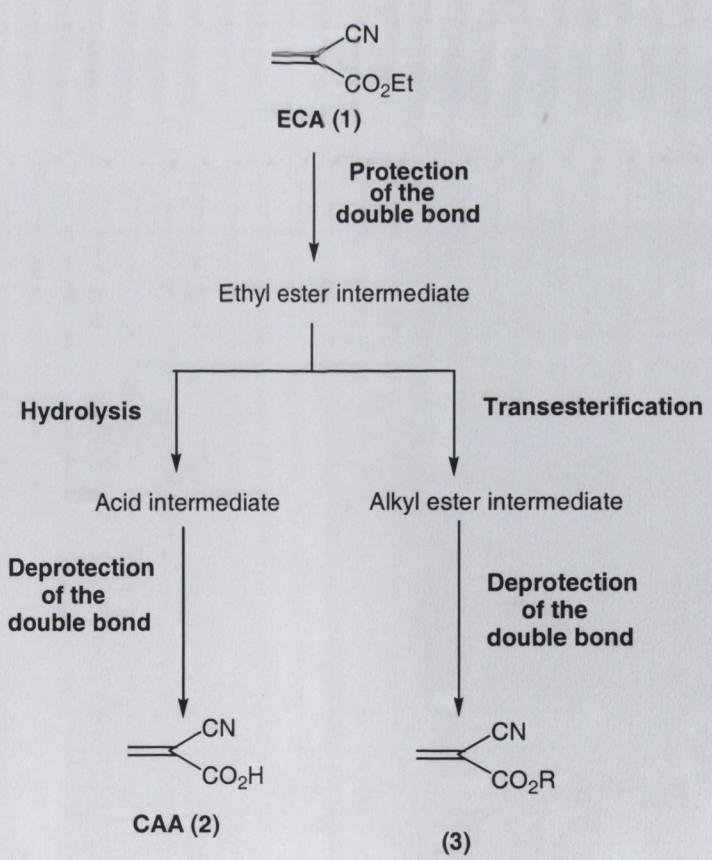
APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID FROM ETHYL 2-CYANOACRYLATE (ECA)

CHAPTER 3.

APPROACHES TO 2-CYANOACRYLATE ESTERS AND 2-CYANOACRYLIC ACID FROM ETHYL 2-CYANOACRYLATE (ECA)

A considerable amount of ethyl 2-cyanoacrylate (**ECA**) **1** was supplied by Loctite.Thus, it was considered useful to examine other approaches to 2-cyanoacrylic acid (**CAA**) **2** and 2-cyanoacrylate esters **3** utilising **ECA** as the starting material. Due the high polarizibility of the double bond of **ECA** and consequently its high reactivity as a Michael acceptor, it is impossible to avoid side reactions when either hydrolysis or transesterification reactions are tried with **ECA**. For instance, Michael additions eventually lead to the polymerisation of **ECA**. Hence, the following strategy was considered in order to circumvent the polymerisation process [Scheme 1].

Scheme 1



This strategy would imply the protection of the double bond to give a saturated ester intermediate derived from **ECA** in order to avoid facile polymerisation. This protection could potentially be carried out *via* Michael additions. Hydrolysis and transesterification reactions of the derived saturated intermediate would afford either a carboxylic acid or a new alkyl ester. Deprotection of the double bonds of these intermediates would give either **CAA** or a new 2-cyanoacrylate ester.

3. 1. PROTECTION OF THE DOUBLE BOND OF ECA.

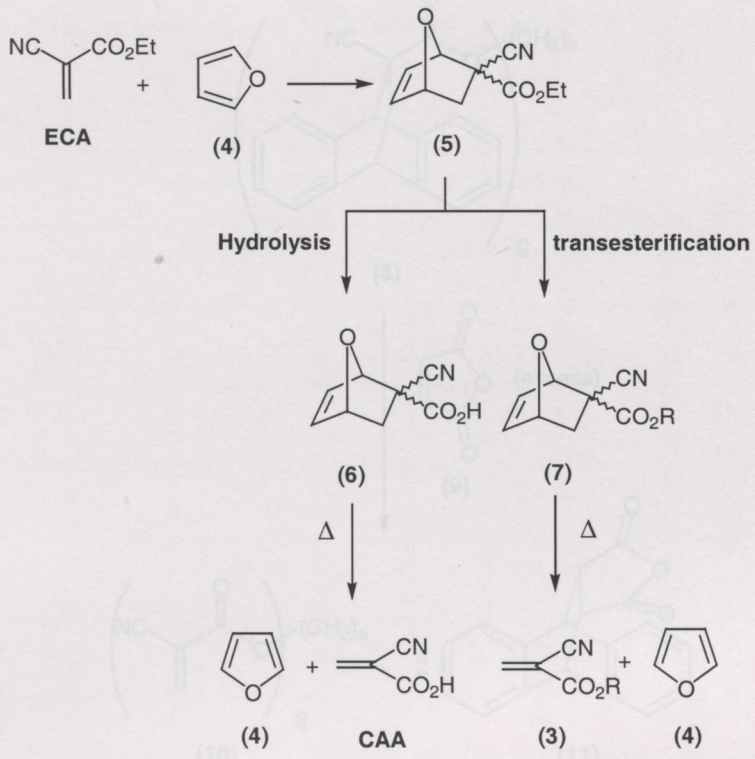
In the literature many methods have been reported for the protection of double bonds such as cycloadditions, Michael additions and hydroxylations.[1]

3. 1. 1. Protection of the double bond using Diels-Alder reactions.

Initially, it was decided to start to work with Diels-Alder reactions using furan as diene, hoping to exploit the ready reversibilityof the furan [4+2]-cycloaddition for deprotection of the double bond.[2]

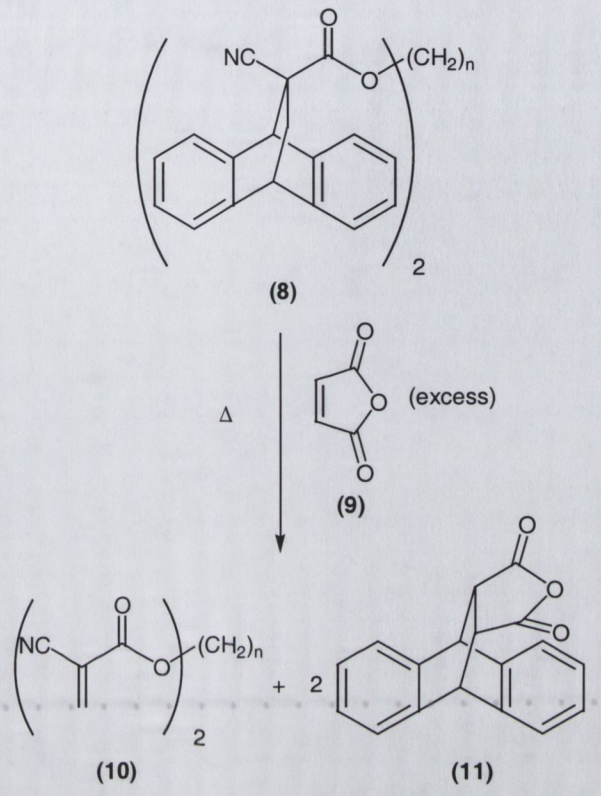
Reaction of furan **4** with **ECA** should yield an adduct **5** which could be either hydrolysed under basic conditions to give a bicyclic cyano-acid **6** or transesterified with any alcohol of interest to give the bicyclic cyano-ester **7**. Eventually, gentle heating (at temperatures below 100 °C) should yield either 2-cyanoacrylic acid **2** or the corresponding cyanoacrylate ester **3** together with volatile furan, which could be recycled [Scheme 2].

Scheme 2



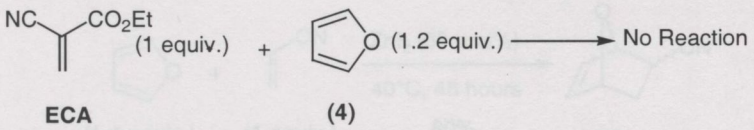
It should be noted that this process, if successful, would provide far superior methodology to that already reported in the literature by Buck[3] and previously mentioned in Chapter 1 (Introduction). Thus, Buck reported the reaction between the Diels-Alder bis-adduct **8** with the dienophile maleic anhydride **9** in order to release the monomer diester **9** together with the anthracene-maleic anhydride Diels-Alder adduct **11** [Scheme 3].

Scheme 3



The Diels-Alder reaction of **ECA** with furan **4** was tried in both the presence and the absence of various Lewis acids but the expected Diels-Alder adduct was never obtained [Table 1].

Table 1. Attempted Diels-Alder reaction between ECA and furan.



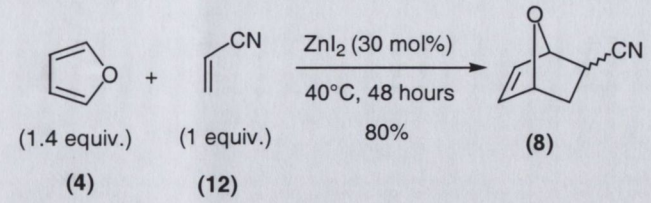
ECA **(4)**

Lewis Acid (5 mol%)	Temperature	Solvent	Reaction time
———	r.t.	CH_2Cl_2	6 hours
$BF_3.Et_2O$	r.t.	CH_2Cl_2	12 hours
$BF_3.Et_2O$	r.t.	$PhCH_3$	12 hours
$TiCl_4$	r.t.	$PhCH_3$	12 hours
ZnI_2	40 °C	CH_2Cl_2	3 hours
$TiCl_4$	r.t.	$CDCl_3$	17 hours

This result was interpreted as meaning either that the reaction did not proceed at all, or that the anticipated [2 + 4π] adducts were unstable at ambient temperatures and reverted to the starting materials furan and **ECA** *via* a very facile retro Diels-Alder proccess.[2]

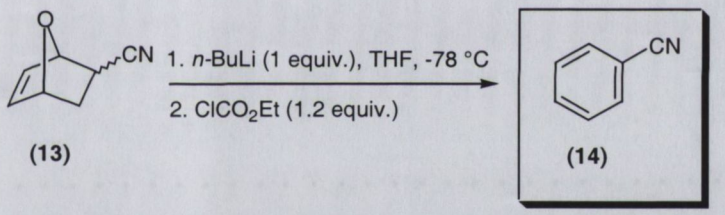
In order to test the instability hypothesis it was decided to try to perform a rational synthesis of the furan-ethyl cyanoacrylate adduct **5**. Thus, furan **4** was reacted with acrylonitrile **12** in the presence of zinc iodide to yield a isomeric mixture of Diels-Alder adducts **13**, which are thermally stable (b.p 100-110 °C at 0.5 mm Hg) [Scheme 4].[4]

Scheme 4



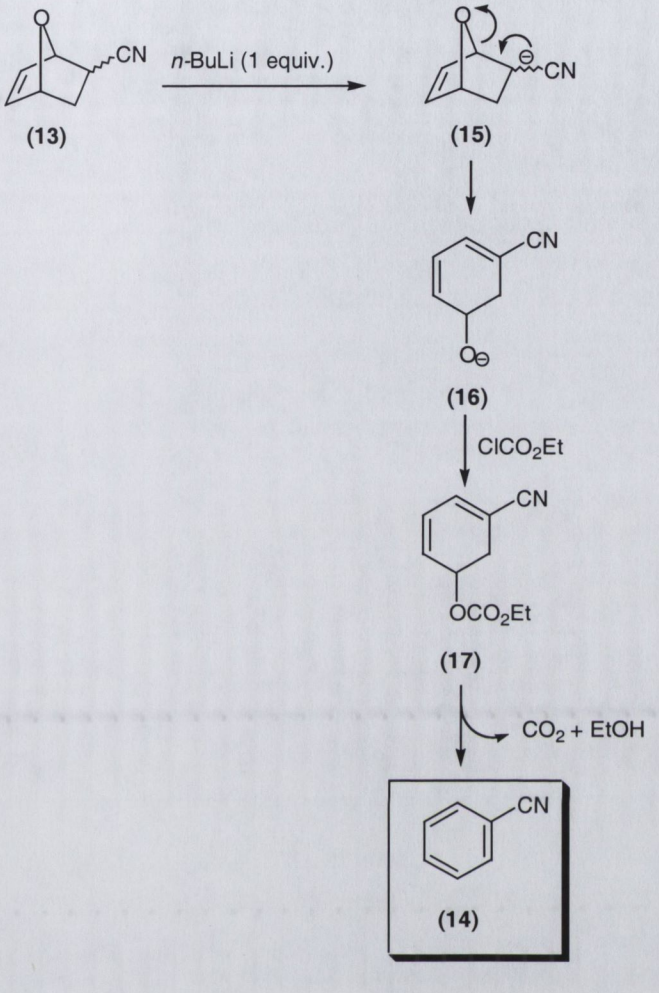
Deprotonation of these adducts **13** using a strong non-aqueous base followed by reaction with ethyl chloroformate was expected to yield the diastereoisomeric ethyl cyanoacrylate-furan adducts **5**, whose thermal stability (or otherwise) could easily be checked. In the event, deprotonation of an *exo-endo* mixture of the acrylonitrile-furan adducts **13** using *n*-butyllithium at –78 °C, followed by addition of ethyl chloroformate yielded only benzonitrile as the principal product [Scheme 5].

Scheme 5



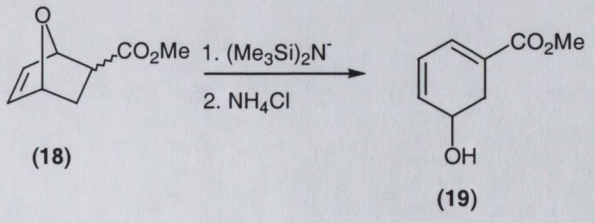
This result can be rationalised as follows. Reaction of the adduct **13** with *n*-butyllithium leads to a rapid ring-opening reaction to give a cyclohexadienyl alkoxide **16**. This then reacts with ethyl chloroformate to yield a mixed carbonate **17**. β-Elimination - fragmentation of the carbonate group of **17** then takes place to give benzonitrile **14** [Scheme 6].

Scheme 6



Brion[4] reported the base-promoted β-elimination of the heteroatom bridge of the Diels-Alder adduct **18** which leads to the cyclohexadienol **19** [Scheme 7].

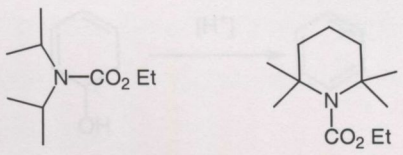
Scheme 7



The reaction of **13** with ethyl chloroformate was repeated again and this time lithium diisopropylamide (LDA) was used as base and ethyl chloroformate was present at the outset. So, the possibility of trapping the anion **15** prior to the opening of the bicyclic adduct **13** was maximised. In this instance, the LDA reacted with ethyl chloroformate to give the carbamate ester **20** and benzonitrile [Figure 1].

Substitution of the very hindered lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as base[5] also afforded the derived carbamate ester **21** together with some benzonitrile **14** [Figure 1].

Figure 1



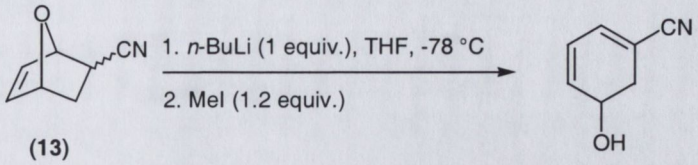
(20) **(21)**

It is clear from the above results that two practical problems arise: the rapid ring-opening of the adduct **13** to give the cyclohexadienyl systems **16** and the competing reaction of the acylating agent ethyl chloroformate with the lithium amide bases present.

In order to maximise the trapping of the anion of **13** with an electrophile, iodomethane was used because it is an electrophile which is very reactive towards nucleophilic substitution but which does not react with *n*-butyllithium.

In the event, the cyclohexadiene **22** was obtained *via* competing ring-opening of the adduct **13** [Scheme 8].

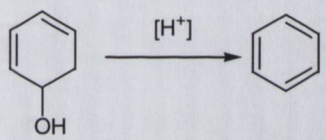
Scheme 8



(13) **(22)**

Surprisingly, the compound **22** (previously reported by Fang *et al.*[6]) was able to survive passage through silica gel when the crude mixture was purified by column chromatography because it is known that 2,4-cyclohexadiene-1-ol **23** decomposes to benzene when it is treated under acid conditions [Scheme 9].[7]

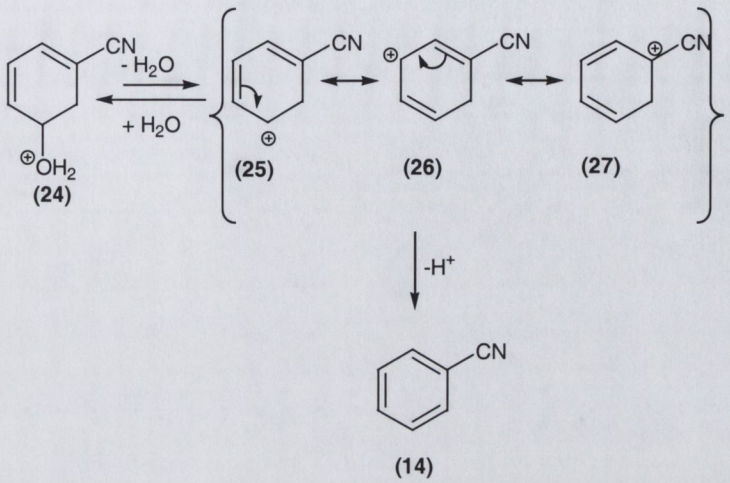
Scheme 9



(23)

A plausible explanation for the relative stability of **22** in the presence of silica can be understood in terms of an E_1 mechanism. Thus, in the rate-determining step, elimination of the hydroxyl group would take place to give a carbocation intermediate **24**. This would not be favorable thermodynamically due the presence of some unstable canonical forms **25** and **26** in the carbocationic intermediate [Scheme 10].

Scheme 10

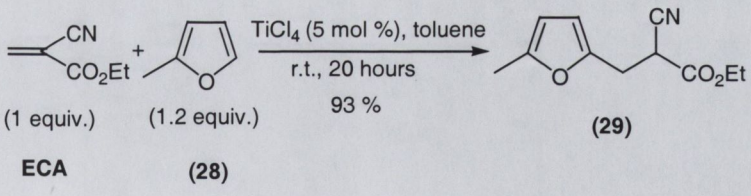


The stability of **22** also provides supporting evidence that the carbonate **17** is an intermediate in the formation of benzonitrile when **13** is reacted with BuLi and ethyl chloroformate [Scheme 6].

From all of these results, it was concluded that it would not be possible to prepare the Diels-Alder adduct **5** by either of the approaches outlined above.

A catalysed Diels-Alder reaction was attempted using 2-methylfuran **28** as diene and **ECA** as dienophile. Unexpectedly, the disubstituted furan **29** was obtained *via* electrophilic substitution of the furan ring with **ECA** [Scheme 11].

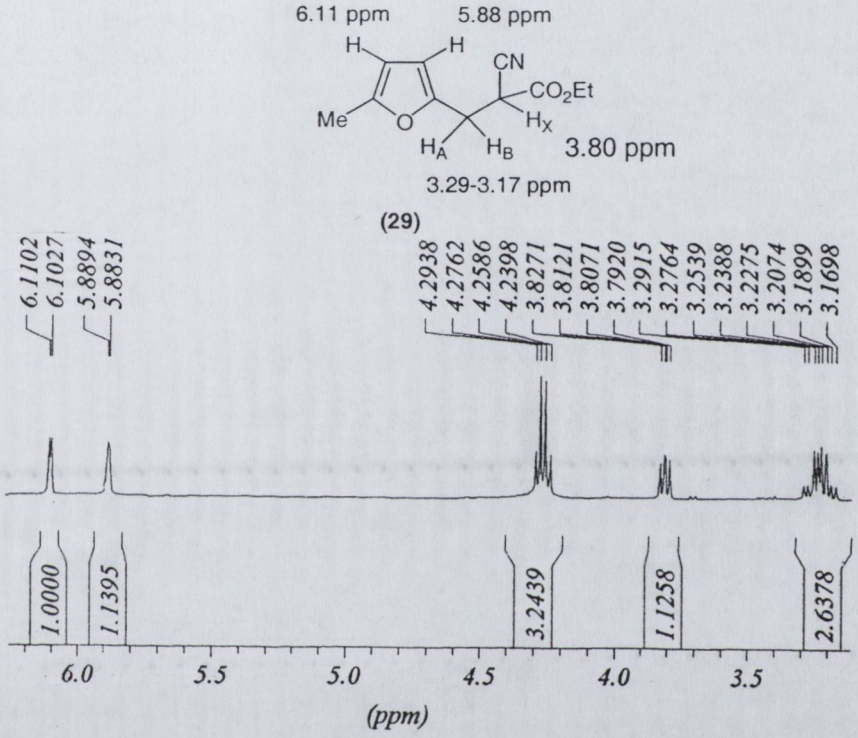
Scheme 11



The structure of **29** was identified by NMR spectroscopy. Thus, the appearance of two singlets at 6.11 and 5.89 ppm confirmed the disubstitution in the furan ring. Additionally, the appearance of an ABX system of three protons was clearly characteristic of methylene and methine groups of **29**. The proton H_X resonates as a doublet of doublets centered at 3.80 ppm with coupling constants 6.0 and

8.0 Hz. The proton H_A resonates as a doublet of doublets centered at 3.29 ppm with coupling constants 6.0 and 15.1 Hz. And finally, the proton H_B resonates as a doublet of doublets centered at 3.22 ppm with coupling constants 8.0 and 15.1 Hz. [Figure 2].

Figure 2. ^{1}H-NMR (400 MHz, $CDCl_3$) of ethyl 2-cyano-3-(2-methylfuryl)propanoate (29)



Here protection of the double bond of **ECA** has been carried as a result of electrophilic substitution into the furan ring instead of the initially intended Diels-Alder reaction. Attempts to conduct the reverse (deprotection) process are discussed in Section 3.3 below.

3. 1. 2. Protection of the double bond using Michael addition reactions

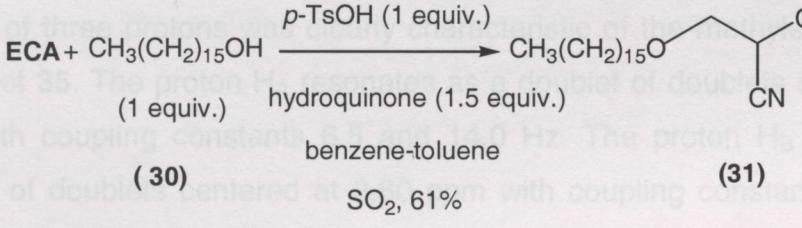
A second line of approach for protecting the double bond of **ECA** is the Michael addition of nucleophiles to yield β-substituted ethyl 2-cyanopropanoates. For this purpose several nucleophiles such as alcohols, sulfur compounds and phosphorous acid were investigated.

3. 1. 2. i. Alcohols as nucleophiles.

As mentioned in Chapter 1, no reports of stable adducts from the reaction of **ECA** with low-molecular weight alcohols or water, as Michael donors, have been found in the literature, although their presence has been detected spectroscopically.[8]

The patent literature had indicated conditions for the nucleophilic addition of various high-molecular weight alcohols, e.g. hexadecyl alcohol to **ECA**, to afford the adduct **31** in 61% yield [Scheme 12].[9]

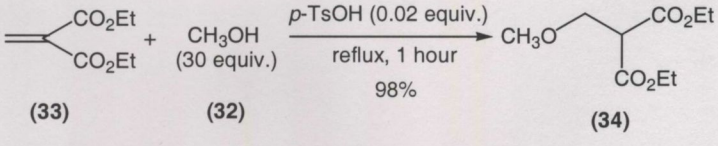
Scheme 12



However, the conditions employed in this reaction are complex and inconvenient from a technical point of view in industrial processes and so they are not likely to be easily applicable in large-scale work.

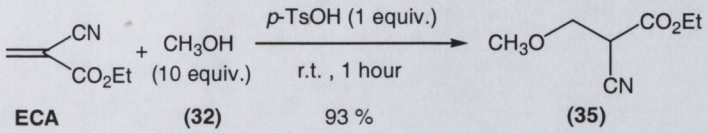
Delépine *et al.*[10] reported the Michael addition of methanol **32** to diethyl methylenemalonate **33** in the presence of catalytic amounts of *p*-TsOH to afford the adduct **34** in 98 % yield after purification [Scheme 13].

Scheme 13



Thus, in the present work, the Michael addition of methanol to **ECA** was carried out in the presence of *p*-TsOH (0.02 equiv.) to afford a mixture (7:93) of **ECA** and the methanol-**ECA** adduct **35** in 93% yield [Scheme 14].

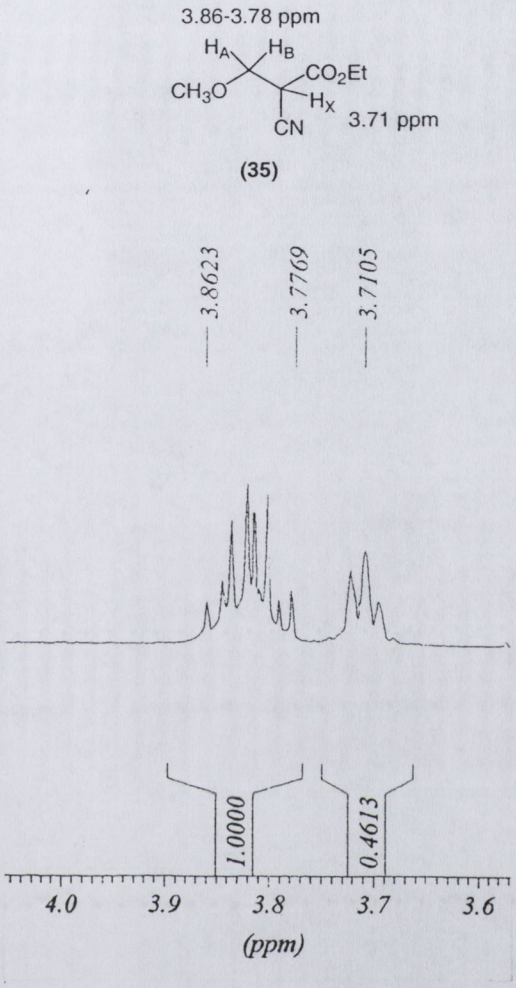
Scheme 14



ECA **(32)** 93 % **(35)**

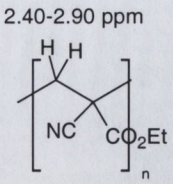
The compound **35**, whose synthesis in 6% yield was reported by Foldi *et al.*[11] in 1942 from the reaction of sodio ethyl cyanoacetate with methoxymethylchloride, was easily identified by ^{1}H-NMR spectroscopy. Thus, the appearance of an ABX system of three protons was clearly characteristic of the methylene and methine groups of **35**. The proton H_A resonates as a doublet of doublets centered at 3.84 ppm with coupling constants 6.5 and 14.0 Hz. The proton H_B resonates as a doublet of doublets centered at 3.80 ppm with coupling constants 7.0 and 14.0 Hz. And finally, the proton H_x resonates as a doublet of doublets centered at 3.71 ppm with coupling constants 6.5 and 7.0 Hz. [Figure 3].

Figure 3. ^{1}H-NMR (400 MHz, $CDCl_3$) of ethyl 2-cyano-3-methoxypropanoate (35)



In the reaction mixture, the amount of the methanol adduct **35** slowly decreased to eventually afford ethyl *oligo*(2-cyanoacrylate). The presence of this oligomer was detected by ^{1}H-NMR from the appearance of new multiplets between 2.40-2.90 ppm which were assigned to the methylene groups of the oligomer [Figure 4].

Figure 4

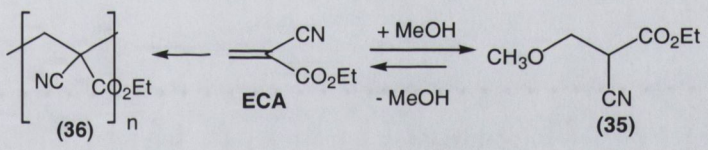


(36)

Additionally, the presence of ethyl *oligo*(2-cyanoacrylate) **36** could be also determined by mass spectroscopy (positive ion spectroscopy) which revealed a series of peaks with a difference of 125 mass units between them. The number 125 corresponds to the molecular sub-unit of **ECA**.

Thus, the nucleophilic addition of methanol to **ECA** is a reversible process and the free **ECA** which is present eventually oligomerises, disturbing the equilibrium between **ECA** and product **35**, so that, eventually, the oligomer **36** is the major product [Scheme 15].

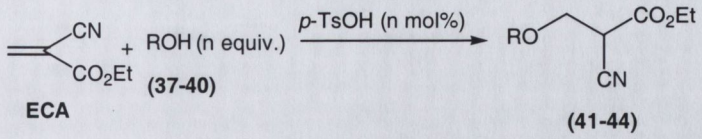
Scheme 15



Surprisingly, the oligomerisation of **ECA** was observed in the presence of *p*-TsOH despite its assumed role as stabilizer.

The Michael additions of other low-molecular weight alcohols to **ECA** were attempted in the presence of *p*-TsOH to afford the following results of conversion to the corresponding adducts [Table 2].

Table 2. Michael Addition of low-molecular weight alcohols to ECA

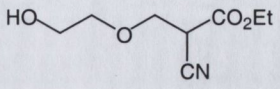


ROH (n equiv.)	Number	*p*-TsOH (n mol%)	Temperature (°C)	Time (hours)	Adduct	Yield (%)
^{i}PrOH (100 equiv.)	**37**	4.5	r.t.	24	**41**	88
^{t}BuOH (50 equiv.)	**38**	4.5	r.t.	24	**42**	50
BnOH (5 equiv.)	**39**	4.5	60	5	**43**	80
$HO(CH_2)_2OH$ (1 equiv.)	**40**	4.5	r.t.	6	**44**	40
$HO(CH_2)_2OH$ (0.5 equiv.)	**40**	4.5	r.t.	6	**44**	7

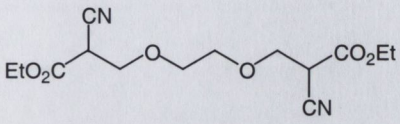
The low-molecular weight alcohols-**ECA** adducts **41-44** showed the same pattern of ABX signals in their ^{1}H-NMR spectra as those exhibited by the methanol-adduct **35**. Additionally, the adducts **41-44** showed the same tendency to give ethyl *oligo*(2-cyanoacrylate) **36** with time *via* retro-Michael reactions.

Additionally, the formation of the adduct **44** from **ECA** and ethylene glycol **40** is remarkable in that none of the *bis*-adduct **45** could be detected [Figure 5].

Figure 5



(44)



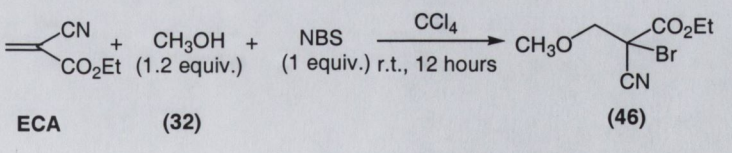
(45)

The structure of **44** followed from its NMR spectrum which showed *three* different non-ester methylene groups and the structure of **45** requires only *two* such resonances.

It was concluded that it was impossible to work with the adducts obtained from the Michael addition reactions of low-molecular weight alcohols with **ECA** because of their instability with respect to time based on the ease of removing their labile methine hydrogen.

In order to circumvent the instability of these adducts it was intended to replace the easily removed methine hydrogen by another atom, for instance a halogen. Thus, the synthesis of the bromocompound **46**, reported by Aronovich *et al.*[12], was carried out by the reaction of **ECA** with methanol **32** and *N*-bromosuccinimide (NBS) **47** in CCl_4 [Scheme 16].

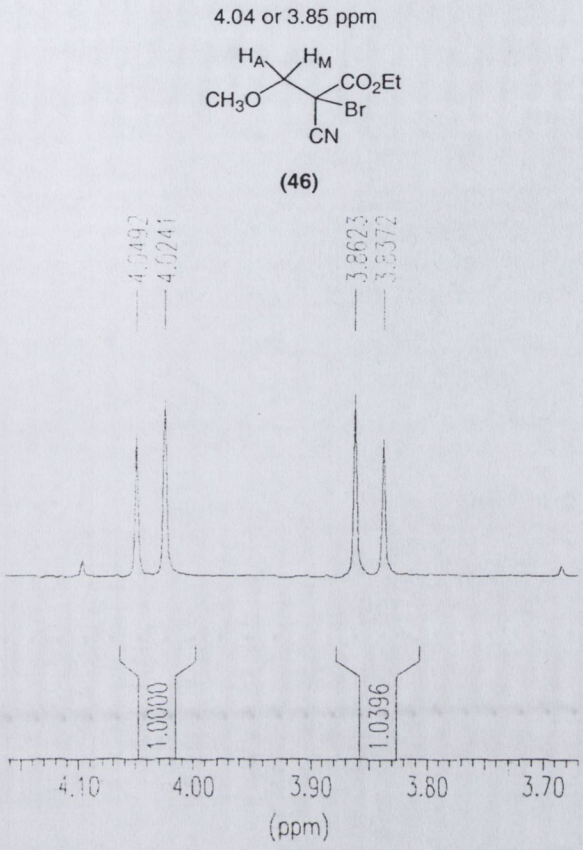
Scheme 16



ECA **(32)** **(46)**

The appearance of an AM system in the ^{1}H-NMR was characteristic of the methylene group of **46**. The protons H_A and H_M resonate as doublets centered at 4.04 and 3.85 ppm with a geminal coupling constant 10.0 Hz [Figure 6].

Figure 6. ^{1}H-NMR (400 MHz, $CDCl_3$) of ethyl 2-bromo-2-cyano-3-methoxypropanoate (46)



Thus, the replacement of the labile methine hydrogen by another atom, such as halogen, is required in order to obtain stable alcohol-**ECA** adducts

3. 1. 2. ii. Sulfur compounds as nucleophiles

In parallel, the conjugate addition of sulfur-based nucleophiles to **ECA** was examined.

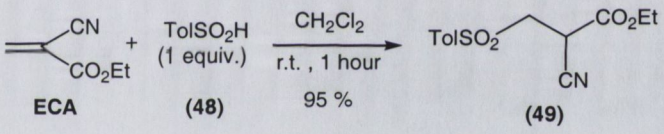
Sulfinic acids, highly nucleophilic mercaptans and thiocarboxylic acids have a rather active hydrogen atom.[13] So they should easily add to the double bond of **ECA**, even in the absence of acidic catalysts or stablizers such as *p*-TsOH [Table 3].

Table 3. pK_a of some Sulfur Compounds

Acid / Conjugated Base	pK_a	
	H_2O	DMSO
SH_2 / SH^-	7.00	—
n-BuSH / *n*-BuS^-	10-11	17
PhSH / PhS^-	7	10.3

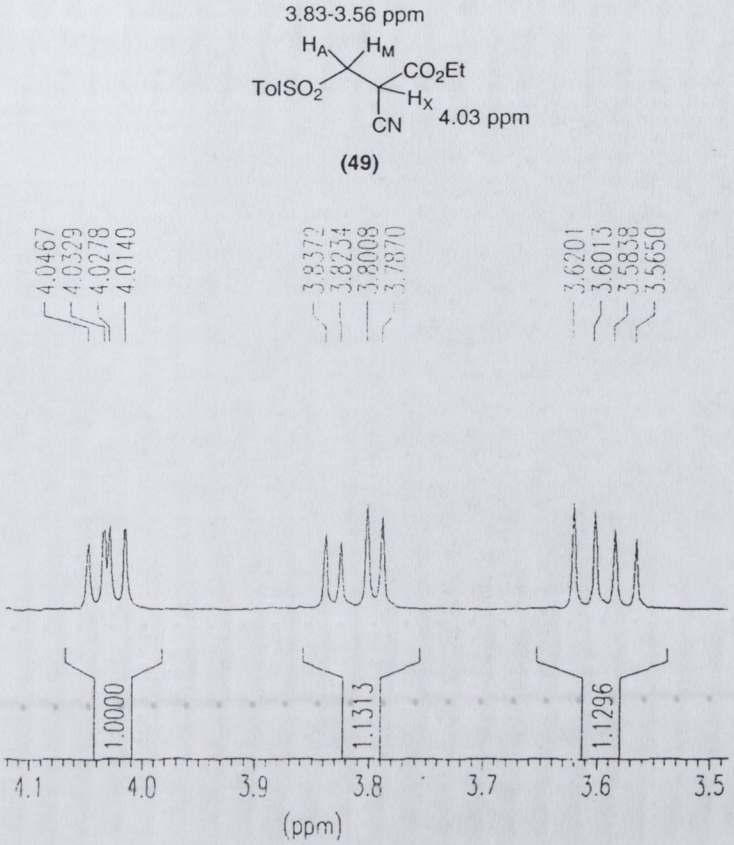
The reaction of **ECA** with the commercially available *p*-toluenesulfinic acid **48** afforded the crystalline sulfone **49** quantitatively. No evidence for competing formation of oligomeric cyanoacrylates was observed in this reaction [Scheme 17].

Scheme 17



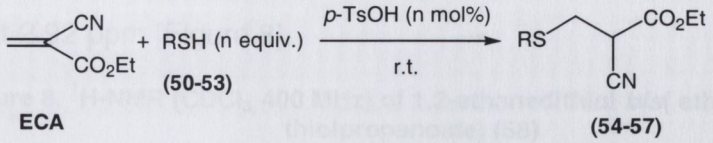
The adduct **49** exhibited an AMX system in its ^{1}H-NMR spectrum. Remarkably, the methine hydrogen resonates at lower field than the methylene hydrogens. These resonate at lower field than the methine hydrogen in the alcohol adducts **35, 41, 42, 43, 44** and **45** [Figure 7].

Figure 7. ^{1}H-NMR (400 MHz, $CDCl_3$) of ethyl 2-cyano-3-(4'-toluenesulfonyl)propanoate (49)



Similarly, **ECA** was reacted with several mercaptans **50-53** to afford the oily thioether adducts **54-57** in good yields and without any evidence of competing oligomer formation. The same AMX pattern as that observed for the crystalline sulfone **49** was detected again in their ^{1}H-NMR spectra [Table 4].

Table 4. Michael Addition of Mercaptans to ECA

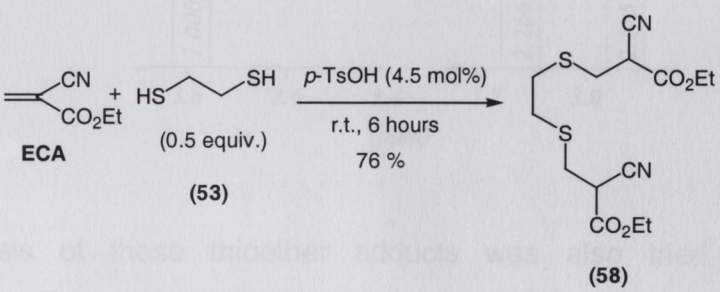


ECA **(54-57)**

RSH (n equiv.)	Number	*p*-TsOH (n mol%)	Time (hours)	Adduct	Yield (%)
TolSH (1 equiv.)	**50**	———	1	**54**	85
n-BuSH (1 equiv.)	**51**	———	3	**55**[14]	88
$HO(CH_2)_2SH$ (1 equiv.)	**52**	4.5	6	**56**[14]	83
$HO(CH_2)_2SH$ (0.5 equiv.)	**52**	4.5	6	**56**	60
$HS(CH_2)_2SH$ (1 equiv.)	**53**	4.5	6	**57**[15]	78

The reaction of **ECA** with 0.5 equivalents of 1,2-ethanedithiol **53** afforded the crystalline dithioether adduct **58** in 76 % yield [Scheme 18].

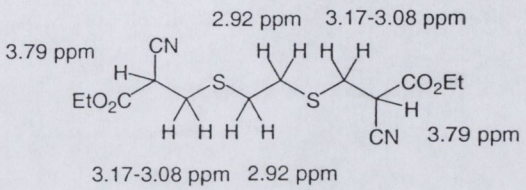
Scheme 18



ECA **(53)** **(58)**

The structure of **58** was determined by its NMR spectrum which showed *two* different non-ester methylene groups which resonated at the interval 3.17-3.08 ppm and at 2.92 ppm [Figure 8].

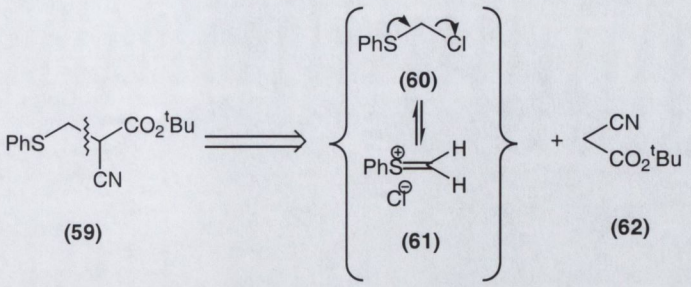
Figure 8. ^{1}H-NMR ($CDCl_3$, 400 MHz) of 1,2-ethanedithiol *bis*(ethyl 2-cyano-3-thiolpropanoate) (58)



(58)

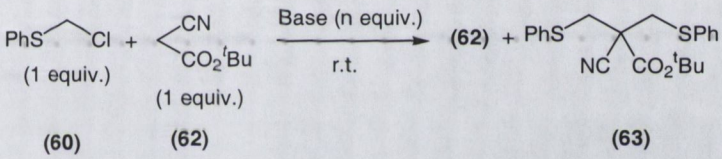
The synthesis of these thioether adducts was also tried using different methodology. Thus, it was intended to synthesise *tert*-butyl 2-cyano-3-(phenylthio)propanoate **59** from the reaction of chloromethylphenyl sulfide **60** with *tert*-butyl cyanoacetate **62** [Scheme 19].

Scheme 19



Initially, basic conditions were tried in order to create the anion of **62** required to displace chloride anion from chloromethylphenyl sulfide. Several bases were tried but in all cases the dithioether **63** originating from the double alkylation of *tert*-butyl cyanoacetate **62** was obtained [Table 5].

Table 5. Attempted preparation of *tert*-butyl 2-cyano-3-(phenylthio)propanoate (59) using basic conditions

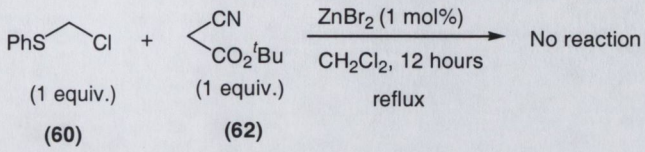


Base (n equiv.)	Solvent	Time (hours)	%Conversion (62:63)
NaOEt (1 equiv.)	EtOH	20	(38:62)
Na_2CO_3 (0.5 equiv.)	Acetone:H_20 (1:1)	20	(82:18))
KO^{t}Bu (1 equiv.)	THF	12	(56:44))

Many alkylations of ketones and esters have been proven to be more efficient by changing the basic conditions of enolate chemistry to acidic conditions.[16]

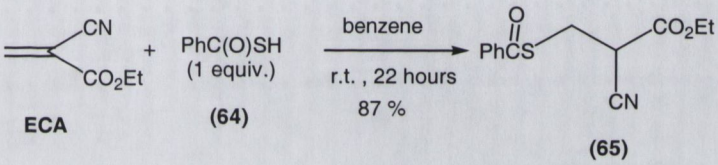
Thus, the synthesis of the thioether adduct **59** was attempted by the reaction of chloromethylphenyl sulfide **60** with *tert*-butyl cyanoacetate **62** in the presence of zinc bromide (1 mol%) but no reaction was observed [Scheme 20].

Scheme 20



ECA was also reacted with thiobenzoic acid **64** to afford the thioester adduct **65** in 87 % yield, also without any evidence for competing oligomer formation [Scheme 21].

Scheme 21



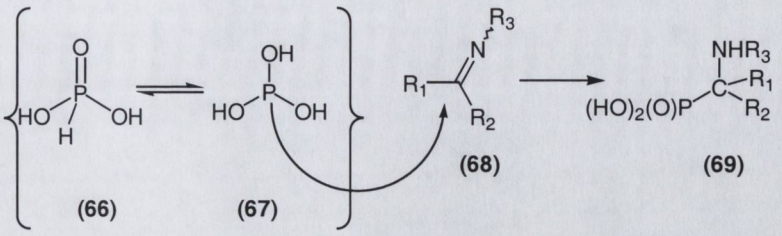
The same AMX system as that previously observed for the sulfone and thioether adducts was observed again in the ^{1}H-NMR spectrum of the thioester adduct **65**.

In conclusion, the conjugate addition of sulfur nucleophiles to **ECA** affords stable Michael adducts. These reactions proceed straightforwardly (at r.t.) and in good yields (60-95 %).

3. 1. 2. iii. Phosphorous acid as nucleophile

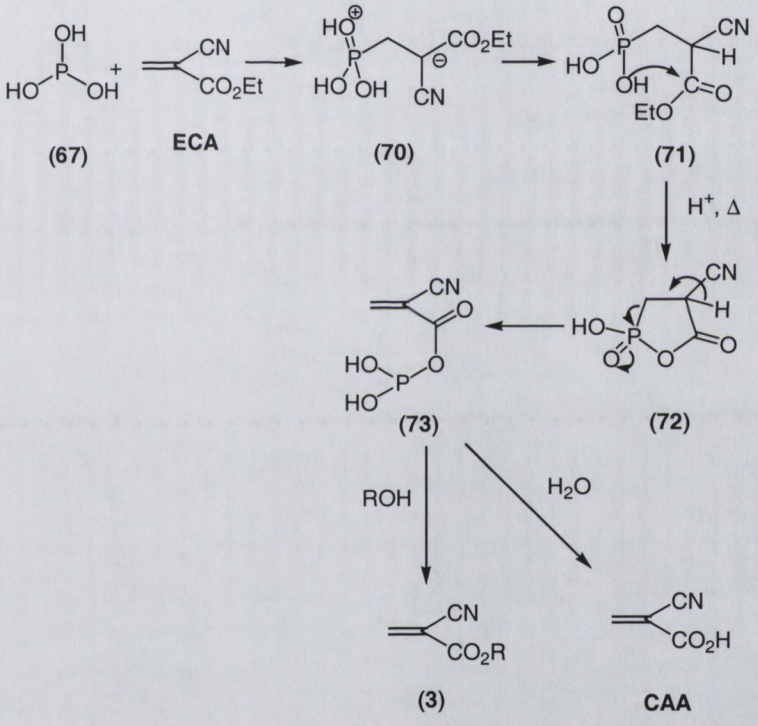
Phosphorous acid **66** is well known to be a good nucleophile, adding efficiently to double bonds of, e.g, imine systems [Scheme 22].[17]

Scheme 22



Thus, it was considered that the chemistry described below might take place [Scheme 23].

Scheme 23

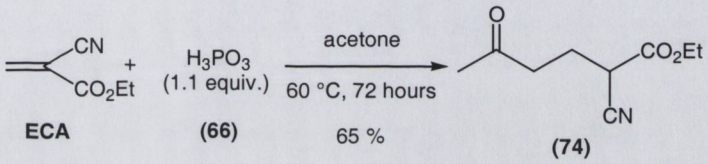


Here, the conjugate addition of inexpensive phosphorous acid to **ECA** would give the Michael adduct **71** which, under the influence of an acidic catalyst (which could be phosphorous acid itself), would be expected to undergo intramolecular ring-closure with elimination of ethanol under heating to give **72**. β-Elimination of **72** should then provide a mixed anhydride species **73** which should react with water to give **CAA** (together with recyclable phosphorous acid), or with an alcohol to give a 2-cyanoacrylate ester **3**.

For this purpose, one equivalent of each of phosphorous acid **66** and **ECA** were reacted together for 12 hours in dry acetone at r.t. but no reaction was observed.

However, if **ECA** and a slight (15%) molar excess of phosphorous acid were reacted together in acetone at 60 °C during 70 hours the compound **74** was unexpectedly obtained. This result can be explained by means of the conjugate addition of the enol of acetone to **ECA** [Scheme 24].

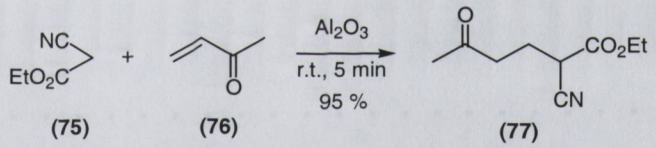
Scheme 24



ECA **(66)** **(74)**

Ranu *et al.* reported the reaction of ethyl 2-cyanoacetate **75** with methyl vinyl ketone **76** on alumina surface without any solvent to give **77** [Scheme 25].[18]

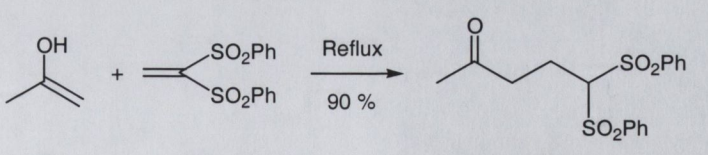
Scheme 25



(75) **(76)** **(77)**

Additionally, de Lucchi *et al.* reported the conjugate addition under neutral conditions of the enol of acetone **78** to 1,1-bis(phenylsulfonyl)ethylene **79** to give the adduct **80** [Scheme 26].[19]

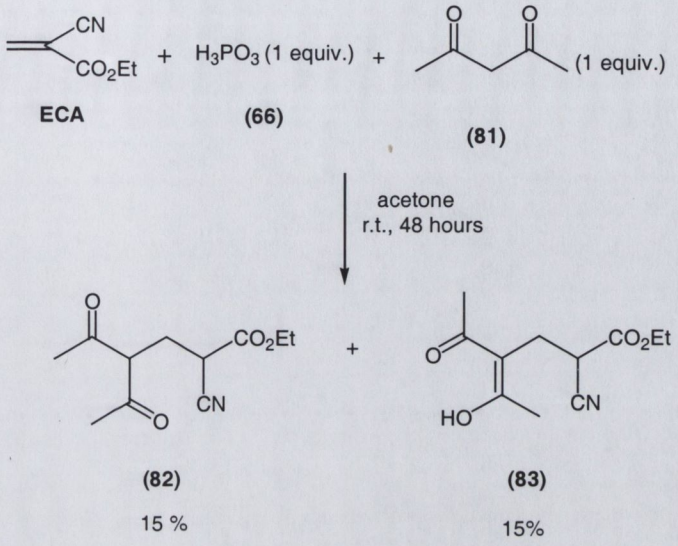
Scheme 26



(78) **(79)** **(80)**

In the present work, **ECA** was reacted with the more easily enolizable ketone acetylacetone **81** to yield a 50:50 mixture of the tautomers **82** and **83** [Scheme 27].

Scheme 27

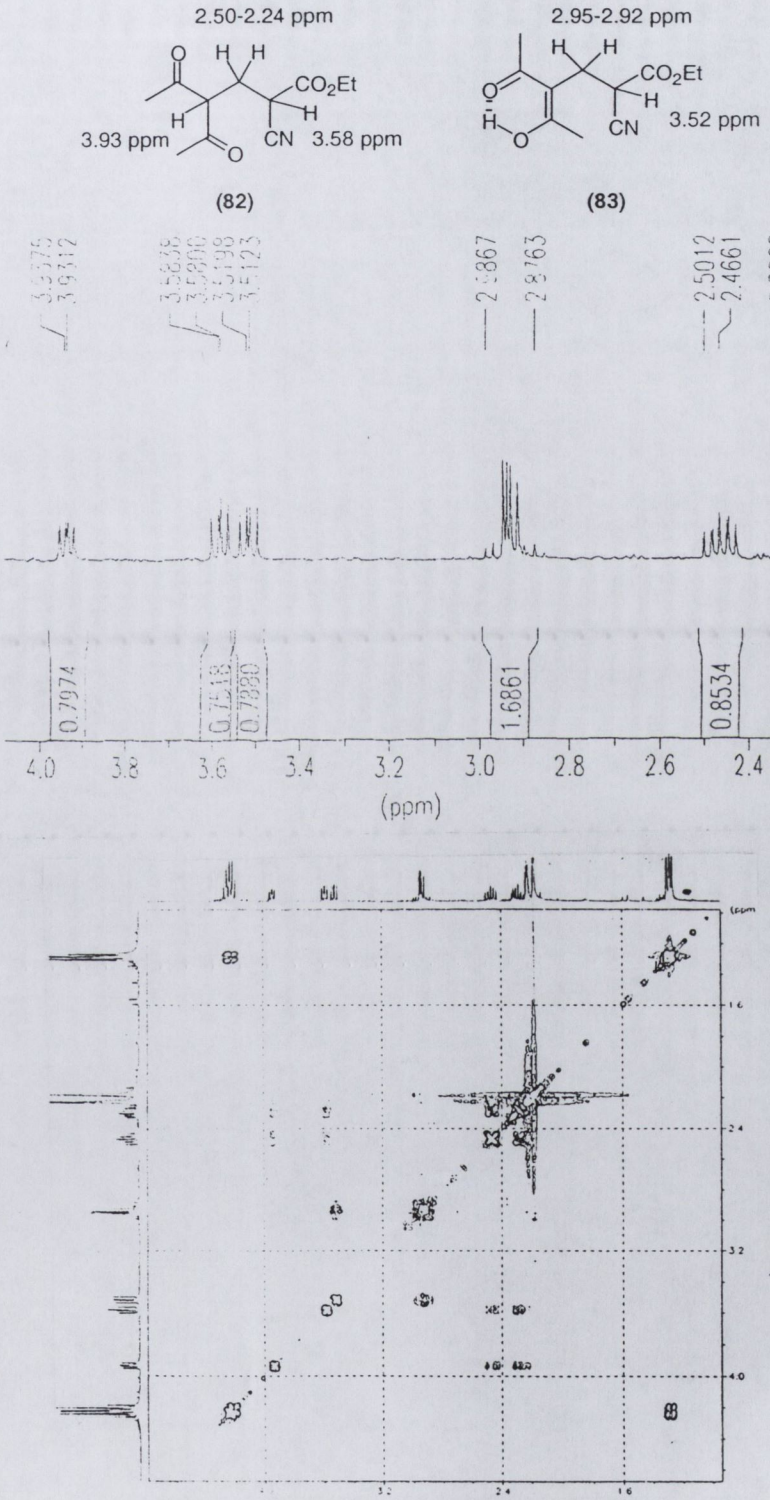


(82) 15 %

(83) 15%

Structures of **82** and **83** could be elucidated from ^{1}H-NMR, H-H COSY and C-H COSY spectroscopy. Thus, the compound **82** shows resonances at 3.93, 3.58, 2.47 and at 2.33-2.25 ppm. The proton at 3.93 ppm resonates as a doublet of doublets with coupling constants 5.5 and 8.0 Hz and is characteristic of the α-methine group of **82**. The proton at 3.58 ppm resonates as a doublet of doublets with coupling constants 7.0 and 8.5 Hz and is characteristic of the other methine group of **82**. The proton at 2.47 ppm resonates as ddd with coupling constants 7.0, 8.0 and 14.6 Hz and is characteristic of the methylene group in **82**. The other proton of the methylene group resonates at 2.33-2.25 ppm as a multiplet. The tautomer **83** shows resonances at 3.52, 2.96 and 2.91 ppm. The proton at 3.52 ppm resonates as a doublet of doublets with coupling constants 6.5 and 9.5 Hz and is characteristic of the α-methine group of **83**. The proton at 2.96 ppm resonates as a doublet of doublets with coupling constants 6.5 and 15.6 Hz and is characteristic of the methylene group of **83**. The other proton of the methylene group resonates at 2.91 ppm as a doublet of doublets with coupling constants 9.5 and 15.6 Hz [Figure 9].

Figure 9. ^{1}H-NMR ($CDCl_3$, 400 MHz), H-H cosy of the mixture of tautomers of ethyl 4-acetyl-2-cyano-5-oxohexanoate (82) and ethyl 2-cyano-4-(hydroxymethylmethylene)-5-oxohexanoate (83)



Clearly, the conjugate addition of a ketone to **ECA** could be avoided by not using an enolizable ketone as solvent. Thus, phosphorous acid **66** was melted at 80 °C and added to **ECA** to observe, after 3 hours at that temperature, no reaction.

In conclusion and from the above results, it seems to be clear that the role of phosphorous acid in these attempted Michael additions to **ECA** was never as a nucleophile and that it assumed the role of an acidic catalyst.

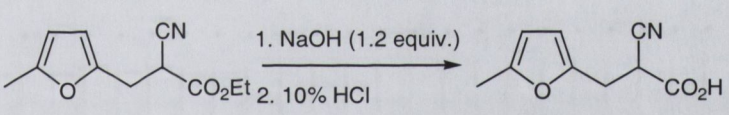
3. 2. HYDROLYSIS AND TRANSESTERIFICATION OF ECA-ADDUCTS

With a number of **ECA** Michael adducts in hand, it was decided to investigate either their hydrolysis or transesterification in order to obtain precursors to **CAA** or to 2-cyanoacrylate esters.

3. 2. 1. Hydrolysis of ethyl 2-cyano-3-(2-methylfuryl)propanoate

The ester **29** could be saponified to afford, after acidification, the corresponding carboxylic acid **84** [Scheme 28].

Scheme 28



(29) **(84)**

55%

The structure of **84** was confirmed using NMR by the absence of the ethoxycarbonyl signals of **29** (a quartet centred at 4.29 ppm and a triplet centred at 1.33 ppm) and from the presence of a broad signal at 8.33 ppm characteristic of a carboxylic hydroxyl group.

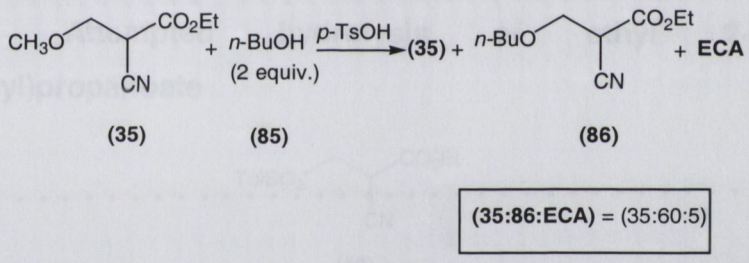
3. 2. 2. Attempted hydrolysis and transesterification of ethyl 2-cyano-3-methoxypropanoate

Despite the short-term stability of **35** its hydrolysis and transesterification was attempted.

Thus, the hydrolysis of **35** led to substantial amount of oligomeric compounds together with a small amount of **CAA**. The oligomeric compound was detected from ^{1}H-NMR by the presence of a broad signal centered at 2.60 ppm.

In the literature the transesterification of methyl acrylate with *n*-butanol in the presence of *p*-TsOH has been reported.[20] Thus, the same transesterification was tried with the ethyl ester **35** to yield a mixture of the methanol-**ECA** adduct **35**, the *n*-butanol-**ECA** adduct **86** and **ECA** [Scheme 29].

Scheme 29



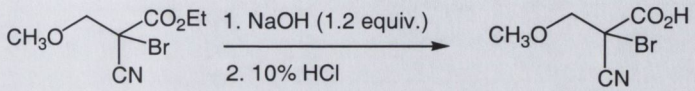
The butanol-**ECA** adduct **86** shows by ^{1}H-NMR spectroscopy the same ABX system of signals as those usually observed for the alcohol-**ECA** adducts.

It was concluded that it would be impossible to hydrolyse and transesterify alcohol-**ECA** adducts due their short-term stability.

3. 2. 3. Hydrolysis of ethyl 2-bromo-2-cyano-3-methoxypropanoate

The α-bromoester **46** could be successfully saponified to afford, after acidification, the α-bromoacid **87** [Scheme 30].

Scheme 30

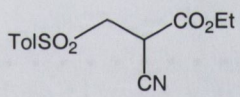


(46) **(87)**

50%

The structure of **87** was confirmed by NMR from the absence of the ethoxycarbonyl signals of **46** (a quartet centred at 4.34 ppm and a triplet centred at 1.34 ppm) and from the presence of a broad signal at 10.62 ppm characteristic of the acid function.

3. 2. 4. Attempted hydrolysis of ethyl 2-cyano-3-(4'-toluenesulfonyl)propanoate



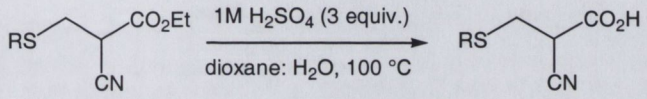
(49)

When the sulfonyl adduct **49** was treated either with $NaHCO_3$ solution or diluted HCl solution the sulfonyl function was eliminated and *oligo*-cyanoacrylic acid was formed. It is not clear if hydrolysis of the ester group takes place before or after elimination of the sulfonyl function but the latter seems more likely because it is easier to hydrolyse a monomeric unit than the corresponding oligomer.

3. 2. 5. Hydrolysis of ethyl 2-cyano-3-(4'-toluenesulfanyl)propanoate and ethyl 3-(*n*-butylsulfanyl)-2-cyanopropanoate

The thioethers adducts **54** and **55** decomposed under basic conditions but both could be successfully hydrolysed using sulfuric acid in a water-dioxane mixture at elevated temperature to give the carboxylic acids **88** and **89** [Table 6].

Table 6. Hydrolysis of ethyl 2-cyano-3-(4'-toluenesulfanyl)propanoate (54) and ethyl 3-(*n*-butylsulfanyl)-2-cyanopropanoate (55).



(54-55) **(88-89)**

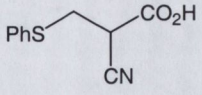
Ester adduct	R	(dioxane: H_2O)	Acid adduct	Yield (%)*
54	Tol	(1: 2)	**88**	58
55	*n*-Bu	(1: 3)	**89**	36

**Both yields were determined from the crude mixture by NMR*

The hydrolysis of the ester adducts **54** and **55** was easily checked by NMR from the absence of the ethoxycarbonyl signals (quartets centred at 4.24 ppm and 4.31 ppm and triplets centred at 1.32 ppm and 1.35 ppm for **54** and **55** respectively) and from the presence of broad signals centred at 6.80 ppm and 8.72 ppm for **88** and **89** respectively and characteristic of carboxylic functions.

The direct synthesis of 2-cyano-3-(benzenesulfanyl)propanoic acid **90** [Figure 10] was tried using the same methodology as had been employed for the corresponding *tert*-butyl ester **62** (above), and was carried out by the reaction of chloromethylphenyl sulfide **60** with 2-cyanoacetic acid **91**.

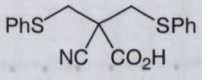
Figure 10



(90)

For this purpose, both acidic and basic conditions were employed. In the acidic conditions, zinc bromide (1 mol%) was used as Lewis acid but no reaction was observed. In the basic conditions, sodium ethoxide (2 equiv.) or sodium carbonate (1 equiv.) were employed as bases when either no reaction or the presence of the double alkylated compound **92** were observed, respectively [Figure 11].

Figure 11

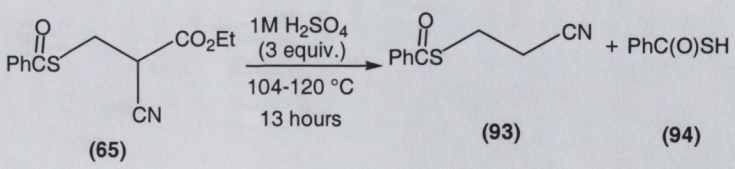


(92)

3. 2. 6. Hydrolysis of ethyl 2-cyano-3-benzoylthiopropanoate

When the adduct **65** was treated with sulfuric acid in a water-dioxane mixture at elevated temperature a mixture of **93** and thiobenzoic acid was observed [Scheme 31].

Scheme 31



(65) **(93)** **(94)**

(93:94) = (1:2)

The structure of compound **93** was unequivocally determined by exhibiting the same proton spectrum as the product obtained from the Michael addition reaction of thiobenzoic acid with acrylonitrile. Thus, a hydrolysis - decarboxylation process

could take place to yield **93**, which partially decomposes in the presence of acid to afford the low-boiling point acrylonitrile and thiobenzoic acid.

From all of the above results it was concluded that the 2-methylfuran-**ECA** adduct **29**, the α-bromoester **46** and the thiol-**ECA** adducts **54** and **55** were the only compounds, which could be successfully hydrolysed to afford stable **CAA**-adducts.

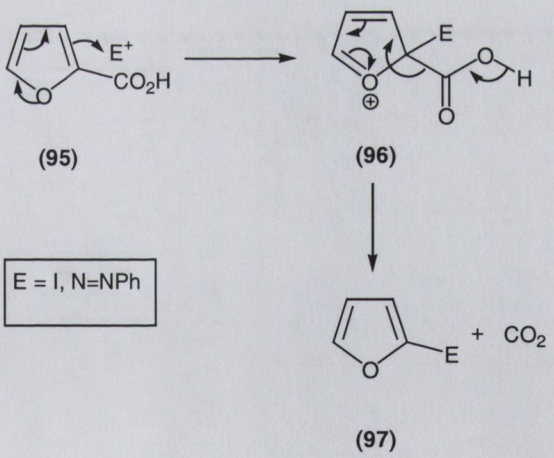
3. 3. REGENERATION OF THE DOUBLE BOND FROM CAA-ADDUCTS.

With the stable **CAA**-adducts **84, 87, 88** and **89** in hand the next objective was to find approaches for regenerating the double bond to give **CAA**.

3. 3. 1. Attempted regeneration of the double bond from 2-cyano-3-(2-methylfuryl)propanoic acid using trifluoroacetic acid

Katritzky reported the electrophilic substitution of 2-furoic acid **95** in a process which presumably follows the mechanism shown below [Scheme 32].[21]

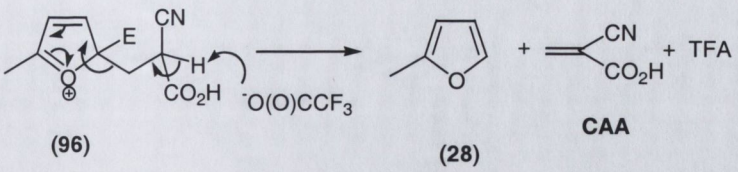
Scheme 32



(95) **(96)** **(97)**

By extension, it was thought that the **CAA**-adduct **84** could undergo the electrophilic substitution reaction with trifluoroacetic acid (TFA) to afford **CAA**, the low-boiling point 2-methylfuran **28** and TFA [Scheme 33].

Scheme 34



(96) (28)

$E^+ = H^+$

Thus, the **CAA**-adduct **84** was boiled in TFA for 18 hours to afford, after evaporation, a gummy material insoluble in $CHCl_3$ and presumably identified as polymer. Assuming that the mechanism described in Scheme 33 takes place, only catalytic amount of TFA would be required to successfully regenerate of the double bond. Thus, the electrophilic substitution reaction of **84** catalyzed by TFA was tried but no reaction was observed.[Table 7].

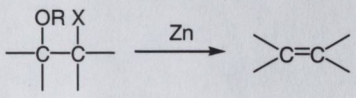
Table 7. Attempted retro-Michael addition reaction of 2-cyano-3-(2-methylfuryl)propanoic acid (84) catalyzed by TFA

TFA (n mol%)	Solvent	Temperature (°C)	time (hours)
20	$PhCH_3$	25.	24
10	$CHCl_3$	60	5

3. 3. 2. Regeneration of the double bond from 2-bromo-2-cyano-3-methoxypropanoic acid using zinc metal

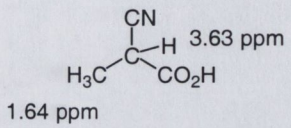
The reductive elimination of α-halo-β-ethers using zinc metal is a reliable reaction frequently reported in the literature which leads a carbon-carbon double bond [Scheme 34].[22]

Scheme 34



The regeneration of the double bond from **87** using zinc powder in acetic acid was attempted.[23] Initially, 15 equivalents of zinc powder were stirred in an acetic acid solution of **87** at r.t. for 22 hours to afford, after quenching with NH_4Cl solution, the compound **98** [Figure 12].

Figure 12

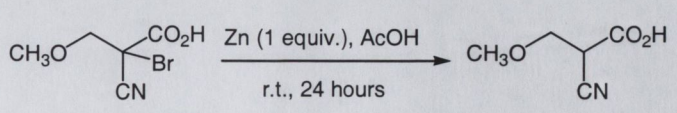


(98)

The structure of **98** was elucidated using ^{1}H-NMR spectroscopy. The presence of a quartet and a doublet at 3.63 and 1.64 ppm were clearly characteristic of a methyl group and methine group respectively in **98**. Additionally, the same pattern of signals (quartet and doublet) at similar chemical shifts was found for the methyl, *iso*-propyl and *tert*-butyl esters of the acid **98** reported in the literature.[24]

The compound **98** was obtained again when an acetic acid solution of **87** was stirred with 5 equivalents of zinc powder at r.t for 6 hours. However, a mixture (13:87) of **CAA** and **98** could be detected by NMR spectroscopy after 2 hours. Thus, it was speculated that the compound **98** could arise from the reduction of the double bond of **CAA** by electron-transfer from zinc. This further reduction could be avoided with the use of one equivalent of zinc metal. The reaction of **87** with one equivalent of zinc powder in acetic acid at r.t for 24 hours afforded, after quenching with NaCl solution, the compound **99** [Scheme 35].

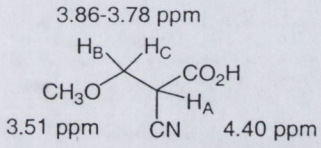
Scheme 35



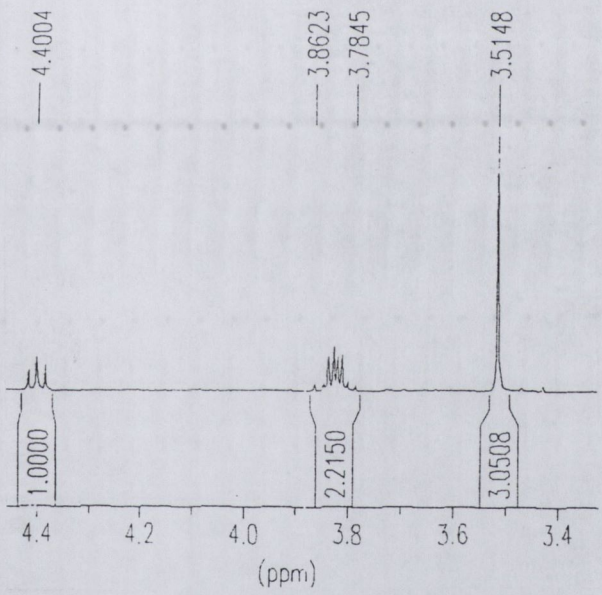
(87) **(99)**

The MeOH-**CAA** adduct **99** showed the same pattern of ABX system of signals (a triplet at 4.40 ppm, a doublet of doublet at 3.84 and other doublet of doublet at 3.80) in its ^{1}H-NMR spectroscopy than the observed for the MeOH-**ECA** adduct **35**. However, the triplet resonates at lower field than the two doublet of doublets resonate in **99** and this spectroscopic observation is contrary to that observed for all alcohol-**ECA** adducts. Additionally, the presence of a methoxy function at 3.51 was also detected in the ^{1}H-NMR of **99** [Figure 13].

Figure 13



(99)

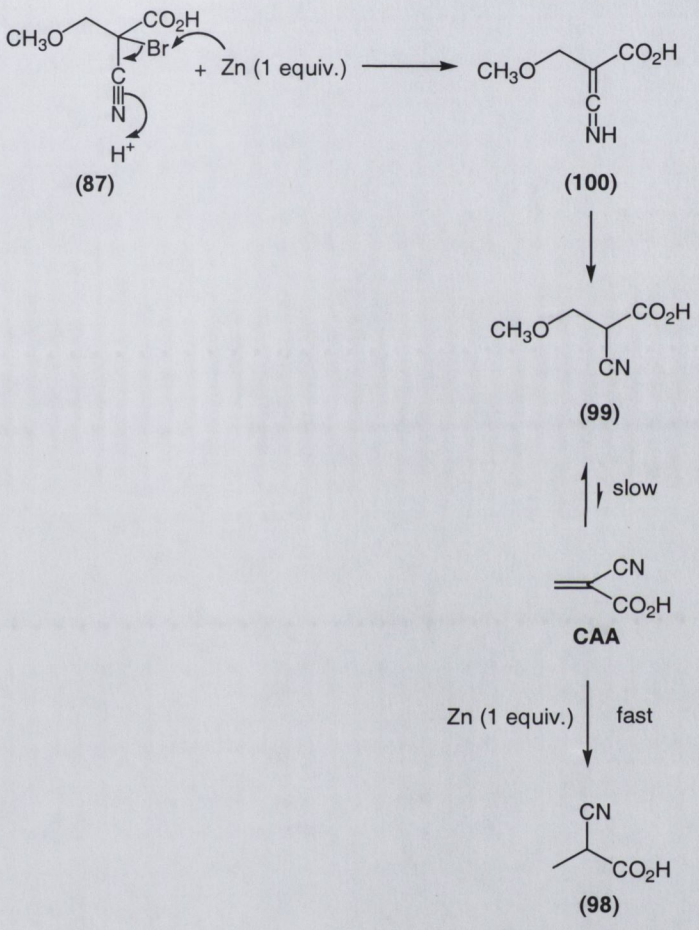


Other spectroscopic observations which support the structure of **99** includes the presence of a signal at 115.5 ppm in its ^{13}C-NMR spectrum which is assigned to its cyano function. A band at 3259.12 cm^{-1} and an intense band at 1711.52 cm^{-1} were observed in its IR spectrum, and are characteristic of its carboxylic function. Also, the presence of a band at 2248.60 cm^{-1} in its IR spectrum provides more evidences for the presence of its cyano function.

The reaction of an acetic acid solution of **87** with two equivalents of zinc powder at r.t. afforded, after 24 hours, a mixture (55:45) of **98** and **99**.

From the above results, the sequence of reaction steps below can be speculated [Scheme 36].

Scheme 36



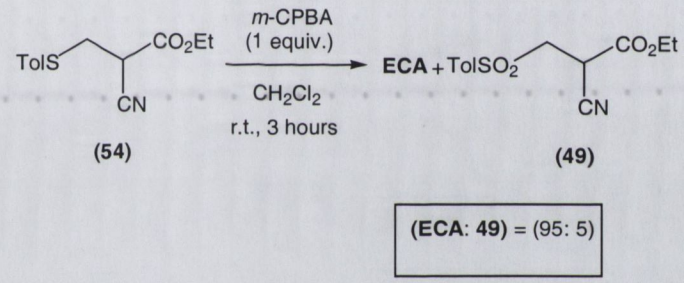
Thus, the reaction of **87** with one equivalent of zinc powder in acetic acid would afford the intermediate **100** which rapidly tautomerises to **99.** The MeOH-**CAA** adduct **99** coexists with **CAA** in an equilibrium mostly shifted towards **99**. The presence of more zinc disturbs the equilibrium towards **CAA** because it is irreversibly reduced to **98**.

The conclusion that can be drawn from the attempted regeneration of the double bond from 2-bromo-2-cyano-3-methoxypropanoic acid **87** using zinc powder is the impossibility of obtaining **CAA** in pure form by this route although the equilibrium mixture MeOH-**CAA** adduct **99** / **CAA** can be obtained as described above.

3. 3. 3. Regeneration of the double bond from 2-cyano-3-(4'-toluenesulfanyl)propanoic acid and 3-(*n*-butylsulfanyl)-2-cyanopropanoic acid using *tert*-butyl hydroperoxide.

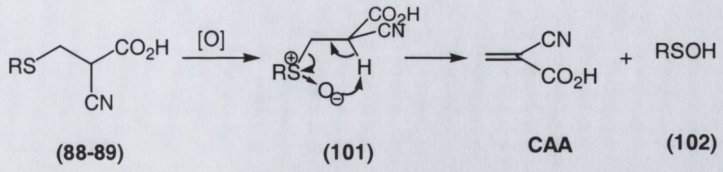
Initially, the oxidation of the thioether **54** was attempted with *m*-CPBA to afford traces of the sulfone adduct **49** together with **ECA** [Scheme 37].

Scheme 37



The presence of **ECA** can be explained by an intramolecular elimination reaction of the sulfoxide group initially obtained by oxidation of the sulfide function of **54**. Thus, it was thought to turn this property of very easy elimination to practical advantage because in principle **CAA** could be obtained directly from the acids **88** and **89** [Scheme 38].

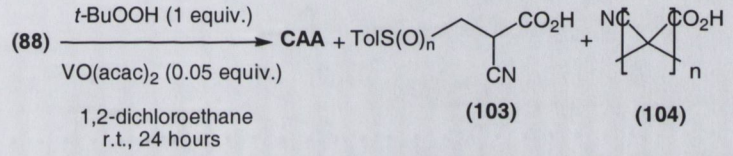
Scheme 38



(88-89) (101) **CAA** (102)

Thus, oxidation of the thioether **88** to its sulfoxide with *tert*-butylhydroperoxide in the presence of a vanadium catalyst[25] was attempted to give, after 24 hours, a mixture of **CAA**, different thiocompounds originating from Michael addition of sulfenic and sulfinic acids to **CAA**, and oligomeric compounds [Scheme 39].

Scheme 39



(103) (104)

In the light of this encouraging result, it was intended to control the evolution of this oxidation reaction with respect to time. For this purpose, two different sets of experiments were carried out and monitored by NMR, utilising $CDCl_3$ as solvent in both cases.

In the first set, vanadium catalyst was used to afford the following conversions to **CAA** presented below [Table 8].

Table 8. Monitored oxidation reaction with respect to time of 2-cyano-3-(4'-toluenesulfanyl)propanoic acid (88) using *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate ($VO(acac)_2$).

Time	% Conversion to CAA
10 minutes	58
3 hours	48
6 hours	40
24 hours	25

In this experiment, the % conversion to **CAA** was calculated by ^{1}H-NMR from the ratio of **88** and **CAA** with respect to the signal for residual $CHCl_3$ in the $CDCl_3$. For this purpose, the formula below was used

$$\left(\frac{(\text{Integr } \mathbf{CAA}/\ \text{Integr } CDCl_3)}{(\text{Integr } 88/\ \text{Integr } CDCl_3)} \right) \times 100$$

wherein

Integr **CAA** is the integration value of one proton of **CAA** in the ^{1}H-NMR spectrum at anytime.

Integr 88 is the integration value of one proton of **88** in the ^{1}H-NMR spectrum before adding the oxidizing agent.

Integr $CDCl_3$ is the constant integration value of the residual $CHCl_3$ in $CDCl_3$ in the ^{1}H-NMR spectrum.

Initially, the ratio **88**/ $CDCl_3$ was calculated before adding the oxidizing agent (*tert*-butyl hydroperoxide/ $VO(acac)_2$). After adding the oxidizing agent, the ratio **CAA**/ $CDCl_3$ was calculated at different times and thus the % conversion to **CAA** could be determined.

In the second set of experiments, the same oxidation reaction was tried again but in the absence of vanadium catalyst, to afford the following results of % conversion to **CAA** [Table 9].

Table 9. Monitored oxidation reaction with respect to time of 2-cyano-3-(4'-toluenesulfanyl)propanoic acid (88) using *tert*-butyl hydroperoxide.

Time	% Conversion to CAA
10 minutes	<1
3 hours	66
6 hours	75
24 hours	72

Surprisingly and from the above results, the best **% conversion to CAA** was 75 % after 6 hours in the absence of a vanadium catalyst. Thus, the presence of the vanadium catalyst could have catalysed the oxidation of the sulfide to afford **CAA** in a first stage and then the same vanadium catalyst could have mediated its polymerisation and consequently decreases its yield. This observation is supported when the **% conversion to CAA** at times 10 minutes and 24 hours are compared in the presence and the absence of the vanadium catalyst.

The purification of the product **CAA** could not be achieved because of the impossibility of separating it from other byproducts, such as tolylsulfenic acid, tolylsulfinic acid and sulfur compounds originating from the Michael addition of these acids to **CAA**.

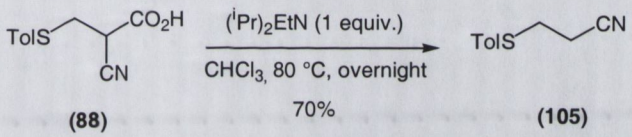
Accordingly, it was speculated that if the oxidation reaction of 3-(*n*-butylsulfanyl)-2-cyanopropanoic acid **89** was carried out the unavoidable sulfur by-products (*n*-butylsulfenic acid and *n*-butylsulfinic acid) might be separated from **CAA** by vacuum distillation because of their lower molecular weights and, presumably, greater volatility. Unfortunately, these by-products could not be separated from **CAA** by this means.

3. 3. 4. Attempted regeneration of the double bond from 2-cyano-3-(4'-toluenesulfanyl)propanoic acid and 3-(*n*-butylsulfanyl)-2-cyanopropanoic acid using other approaches

Other approaches, such as basic conditions and the use of methyl iodide to form sulfonium salts, were attempted for regeneration of the double bond from the thioethers **88** and **89.**

Basic conditions were tried in order to capture the labile methine hydrogen of the thioether **88** and retrieve the double bond. Surprisingly, a decarboxylation process which afforded **105**, took place when the thioether **88** was reacted with one equivalent of diisopropylethylamine at 80 °C [Scheme 40].

Scheme 40

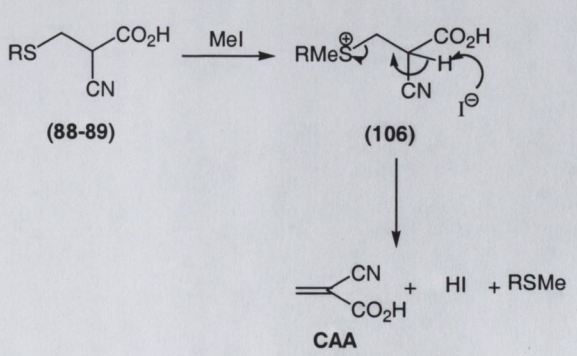


(88) **(105)**

The compound **105** showed two different triplets at 3.08 and 2.57 ppm in its ^{1}H-NMR spectrum. These triplets were characteristic of the methylene functions in **105**.

The other approach for regenerating a double bond from the thioethers **88** and **89** involved the use of methyl iodide. The following pathway was speculated [Scheme 41].

Scheme 41



(88-89) **(106)** **CAA**

However, when the thioether **88** was reacted with methyl iodide no reaction was observed, even when no solvent and elevated temperatures were employed.

In conclusion, from the above results the only successful reactions for the regeneration of the double bond of **CAA** are those in which the reductive elimination reaction of the α-bromo-β-methoxy acid **87** and oxidation reactions of the thioethers **88** and **89** are carried out. However, the impossibility of separating **CAA** from other byproducts from the oxidation reactions make these approaches not as interesting as were initially expected. An alternative to this methodology could be the use of polymeric supports in order to separate easily **CAA** from insoluble byproducts. This possibility will be described in depth in Chapter 4.

3. 5. EXPERIMENTAL SECTION.

The same spectroscopic and purification techniques mentioned at the beginning of the experimental part of Chapter 2 were followed in this section. Additionally, mass spectra was conducted using a LCT spectrometer and recorded using ES^+ technique. Mass data are reported in mass units (*m/z*) and the values in brackets refer the relative intensity from the base peak (as 100%). Analytical Thin-Layer Chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates and column chromatography was performed under gravity using 70-230 mesh silica gel. Melting points were obtained using a Griffin apparatus and are uncorrected.

PROTECTION OF THE DOUBLE BOND OF ECA USING DIELS-ALDER REACTIONS

Attempted Preparation of 2-Ethoxycarbonyl-7-oxabicyclohept[2.2.1]-5-ene-2-carbonitrile (5)

i. Diels-Alder reactions between ECA and furan (4).

1st Attempt. In the absence of Lewis Acid.

ECA (1 g, 8 mmol) was added to a solution of furan **4** (0.69 ml, 9.6 mmol) in CH_2Cl_2 (20 ml) at r.t.. Stirring was continued at r.t. for 6 hours. Then, the reaction mixture was washed with brine and the organic layer was taken up, dried over $MgSO_4$ and concentrated to afford 1.23 g of a colourless oil which was identified as *oligo*(ethyl 2-cyanoacrylate) **36**.

^{1}H-NMR ($CDCl_3$) δ: 4.32 (bs, *oligo*($OC\underline{H}_2CH_3$)), 2.60 (bs, *oligo*(-$C\underline{H}_2C(CN)CO_2Et$-)) and 1.35 (bs, *oligo*($OCH_2C\underline{H}_3$)).

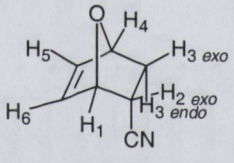
2nd Attempt. In the presence of Lewis Acid.

ECA (1 g, 8 mmol) was added to a solution of furan **4** (0.69 ml, 9.6 mmol) and $BF_3.Et_2O$ (0.48 mmol, 0.07 g) in CH_2Cl_2 (2 ml) at r.t. Stirring was continued at r.t. for 24 hours. Then, the reaction mixture was washed with brine and the organic layer was taken up, dried over $MgSO_4$ and concentrated to afford **ECA**.

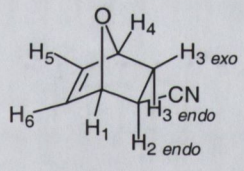
^{1}H-NMR ($CDCl_3$) δ: 7.00 (1 H, s, $\underline{H}HC$=), 6.60 (1 H, s, $H\underline{H}C$=), 4.29 (2 H, q, *J* 7.0 Hz, -$OC\underline{H}_2CH_3$) and 1.32 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$).

ii. From 7-oxabicyclo[2.2.1]hept-5-en-2-carbonitrile (13)[4]

A mixture containing acrylonitrile **12** (0.53 g, 0.66 mL, 10 mmol), furan **4** (0.95 g, 1.02 mL, 14 mmol) and zinc iodide (0.96 g, 3 mmol) was stirred in a closed system at 40 °C for 48 hours. Then, the reaction mixture was washed with 0.1M $Na_2S_2O_3$ aqueous solution (20 mL), extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$ and concentrated to afford 0.68 g (56 %) of **13** as yellow oil. The *endo*/*exo* ratio found was (34:66).



endo-**(13)**



exo-**(13)**

^{1}H-NMR ($CDCl_3$) δ: 6.56 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.47 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.42 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 6.30 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 5.24 (1 H, d, *J* 4.0 Hz, H_1, *exo*-**(13)**), 5.22 (1 H, d, *J* 4.5 Hz, H_1, *endo*-**(13)**), 5.18 (1 H, d, *J* 4.0 Hz, H_4, *exo*-**(13)**), 5.13 (1 H, d, *J* 4.5 Hz, H_4, *endo*-**(13)**), 2.95 (1 H, td, *J* 4.3 and 9.5 Hz, $H_{2\ exo}$, *endo*-**(13)**), 2.44 (1 H, dd, *J* 4.0 and 8.5 Hz, $H_{2\ endo}$, *exo*-**(13)**), 2.29 (1 H, ddd, *J* 3.5, 10.0 and 13.1 Hz, $H_{3\ exo}$, *endo*-**(13)**), 2.17-2.02 (1 H, m, $H_{3\ exo}$, *exo*-**(13)**), 1.76 (1 H, dd, *J* 8.5 and 11.5 Hz, $H_{3\ endo}$, *exo*-**(13)**) and 1.53 (1 H, ddd, *J* 1.5, 3.5 and 13.1 Hz, $H_{3\ endo}$, *endo*-**(13)**).

^{13}C-NMR ($CDCl_3$) δ: 137.3 ($\underline{C}_6$, *endo*-**(13)**), 137.0 ($\underline{C}_6$, *exo*-**(13)**), 133.1 ($\underline{C}_5$, *endo*-**(13)**), 132.3 ($\underline{C}_5$, *exo*-**(13)**), 121.6 (CN), 80.8 ($\underline{C}_1$, *exo*-**(13)**), 78.5 ($\underline{C}_1$, *endo*-**(13)**), 78.3 ($\underline{C}_4$, *endo*-**(13)**), 77.6 ($\underline{C}_4$, *exo*-**(13)**), 31.0 ($\underline{C}_3$, *endo* and *exo*-**(13)**), 27.2 (C_2, *exo*-**(13)**) and 25.7 (C_2, *endo*-**(13)**).

1st Attempt

To a mixture of *exo/endo* diastereoisomers **13** (1g, 8.33 mmol) in THF (4 mL) was added 2.3 M *n*-BuLi solution (3.95 mL, 9.16 mmol) at –78 °C. Then, ethyl chloroformate (0.8 mL, 8.33 mmol) was added to this solution. Stirring was continued at that temperature for 5 hours. Then, the reaction was allowed to reach r.t., washed with NH_4Cl solution and extracted with ether. The ethereal layers were combined, dried over $MgSO_4$ and concentrated to afford 1.53 g of a mixture which contained *endo/exo* diastereoisomers **13** and benzonitrile **14**.

^{1}H-NMR ($CDCl_3$) δ: 7.67 (2 H, d, *J* 7.5 Hz, 2 x (*o*-C_6H_5-), **14**), 7.62 (1 H, t, *J* 7.5 Hz, *p*-C_6H_5-, **14**), 7.49 (2 H, t, *J* 7.5 Hz, 2 x (*m*-C_6H_5-), **14**), 6.56 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.47 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.42 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 6.30 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 5.24 (1 H, d, *J* 4.0 Hz, H_1, *exo*-**(13)**), 5.22 (1 H, d, *J* 4.5 Hz, H_1, *endo*-**(13)**), 5.18 (1 H, d, *J* 4.0 Hz, H_4, *exo*-**(13)**), 5.13 (1 H, d, *J* 4.5 Hz, H_4, *endo*-**(13)**), 2.95 (1 H, td, *J* 4.3 and 9.5 Hz, $H_{2\ exo}$, *endo*-**(13)**), 2.44 (1 H, dd, *J* 4.0 and 8.5 Hz, $H_{2\ endo}$, *exo*-**(13)**), 2.29 (1 H, ddd, *J* 3.5, 10.0 and 13.1 Hz, $H_{3\ exo}$, *endo*-**(13)**), 2.17-2.02 (1 H, m, $H_{3\ exo}$, *exo*-**(13)**), 1.76 (1 H, dd, *J* 8.5 and 11.5 Hz, $H_{3\ endo}$, *exo*-**(13)**) and 1.53 (1 H, ddd, *J* 1.5, 3.5 and 13.1 Hz, $H_{3\ endo}$, *endo*-**(13)**).

2nd Attempt

Firstly, LDA was prepared by dripping 2.3 M n-BuLi solution (3.95 mL, 9.16 mmol) in a solution of diisopropylamine (1.2 mL, 9.16 mmol) in THF (2 mL) at –78 °C. Then, a solution of a mixture of *exo/endo* diastereoisomers **13** (1g, 8.33 mmol) and ethyl chloroformate (0.8 mL, 8.33 mmol) in THF (2 mL) was added to the LDA solution at –78 °C. Stirring was continued at that temperature for 5

hours. Then, the reaction was allowed to reach r.t., washed with NH_4Cl solution and extracted with ether. The ethereal layers were combined, dried over $MgSO_4$ and concentrated to afford a mixture which contained *endo/exo* diastereoisomers **13,** benzonitrile **14** and **20**.

^{1}H-NMR ($CDCl_3$) δ: 7.67 (2 H, d, *J* 7.5 Hz, 2 x (*o*-C_6H_5-), **14**), 7.62 (1 H, t, *J* 7.5 Hz, *p*-C_6H_5-, **14**), 7.49 (2 H, t, *J* 7.5 Hz, 2 x (*m*-C_6H_5-), **14**), 6.56 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.47 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.42 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 6.30 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 5.24 (1 H, d, *J* 4.0 Hz, H_1, *exo*-**(13)**), 5.22 (1 H, d, *J* 4.5 Hz, H_1, *endo*-**(13)**), 5.18 (1 H, d, *J* 4.0 Hz, H_4, *exo*-**(13)**), 5.13 (1 H, d, *J* 4.5 Hz, H_4, *endo*-**(13)**), 4.15 (2 H, q, *J* 7.2, -OC$\underline{H}_2$$CH_3$, **20**), 2.95 (1 H, td, *J* 4.3 and 9.5 Hz, $H_{2\ exo}$, *endo*-**(13)**), 2.44 (1 H, dd, *J* 4.0 and 8.5 Hz, $H_{2\ endo}$, *exo*-**(13)**), 2.29 (1 H, ddd, *J* 3.5, 10.0 and 13.1 Hz, $H_{3\ exo}$, *endo*-**(13)**), 2.17-2.02 (1 H, m, $H_{3\ exo}$, *exo*-**(13)**), 1.76 (1 H, dd, *J* 8.5 and 11.5 Hz, $H_{3\ endo}$, *exo*-**(13)**), 1.53 (1 H, ddd, *J* 1.5, 3.5 and 13.1 Hz, $H_{3\ endo}$, *endo*-**(13)**), 1.32 (3 H, t, *J* 7.2, -$OCH_2C\underline{H}_3$, **20**) and 1.20 (12 H, d, *J* 7.0, 2 x ($C\underline{H}_3$)$_2$CH, **20**).

3rd Attempt

Firstly, LiTMP was prepared by dripping 2.3 M n-BuLi solution (1.97 mL, 4.58 mmol) in a solution of tetramethylpiperidine (0.78 mL, 4.58 mmol) in THF (1 mL) at –78 °C. Then, a solution of a mixture of *exo/endo* diastereoisomers **13** (0.5 g, 4.16 mmol) and ethyl chloroformate (0.55 mL, 4.58 mmol) in THF (1 mL) was added to the LiTMP solution at –78 °C. Stirring was continued at that temperature for 5 hours. Then, the reaction was allowed to reach r.t., washed with NH_4Cl solution and extracted with ether. The ethereal layers were combined, dried over $MgSO_4$ and concentrated to afford a mixture which contained *exo/endo* diastereoisomers **13,** benzonitrile **14** and **21**.

^{1}H-NMR ($CDCl_3$) δ: 7.67 (2 H, d, *J* 7.5 Hz, 2 x (*o*-C_6H_5-), **14**), 7.62 (1 H, t, *J* 7.5 Hz, *p*-C_6H_5-, **14**), 7.49 (2 H, t, *J* 7.5 Hz, 2 x (*m*-C_6H_5-), **14**), 6.56 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.47 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *endo*-**(13)**), 6.42 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 6.30 (1 H, d, *J* 6.0 Hz, $H_{5\ or\ 6}$, *exo*-**(13)**), 5.24 (1 H, d, *J* 4.0 Hz, H_1, *exo*-**(13)**), 5.22 (1 H, d, *J* 4.5 Hz, H_1, *endo*-**(13)**), 5.18 (1 H, d, *J* 4.0 Hz, H_4, *exo*-**(13)**), 5.13 (1 H, d, *J* 4.5 Hz, H_4, *endo*-**(13)**), 4.15 (2 H, q, *J* 7.2 Hz, -$OC\underline{H}_2CH_3$, **21**), 2.95 (1 H, td, *J* 4.3 and 9.5 Hz, $H_{2\ exo}$, *endo*-**(13)**), 2.44 (1 H, dd, *J* 4.0 and 8.5 Hz, $H_{2\ endo}$, *exo*-**(13)**), 2.29 (1 H, ddd, *J* 3.5, 10.0 and 13.1 Hz, $H_{3\ exo}$, *endo*-**(13)**), 2.17-2.02 (1 H, m, $H_{3\ exo}$, *exo*-**(13)**), 1.76 (1 H, dd, *J* 8.5 and 11.5 Hz, $H_{3\ endo}$, *exo*-**(13)**), 1.53 (1 H, ddd, *J* 1.5, 3.5 and 13.1 Hz, $H_{3\ endo}$, *endo*-**(13)**), 1.45 (12 H, s, 2 x (($C\underline{H}_3)_2C$), **21**) and 1.30 (3 H, t, *J* 7.2, -$OCH_2C\underline{H}_3$, **21**).

4th Attempt

Firstly, LDA was prepared by dripping 2.3 M n-BuLi solution (1.97 mL, 4.58 mmol) in a solution of diisopropylamine (0.6 mL, 4.58 mmol) in THF (1 mL) at –78 °C. Then, a solution of a mixture of *exo/ endo* diastereoisomers **13** (0.5 g, 4.16 mmol) and methyl iodide (0.26 mL, 4.16 mmol) in THF (1 mL) was added to the LDA solution at –78 °C. Stirring was continued at that temperature for 5 hours. Then, the reaction was allowed to reach r.t., washed with NH_4Cl solution and extracted with ether. The ethereal layers were combined, dried over anhydrous $MgSO_4$ and concentrated to afford a mixture which contained *exo/endo* diastereoisomers **13** and 5-hydroxycyclohexan-1,3-diene-1-carbonitrile **22**[7]. The crude mixture was purified by column chromatography using a mixture of EtOAc: Hexane (1:1) as eluent to afford **22** (R_f 0.29) in 16% yield.

^{1}H-NMR ($CDCl_3$) δ: 6.75 (1 H, d, *J* 5.5 Hz, -CH-C$\underline{H}$=C(CN)-), 6.26 (1 H, dd, *J* 4.5 and 9.5 Hz, =CH-C$\underline{H}$=CH-), 6.16 (1 H, dd, *J* 5.5 and 9.5 Hz, -CH=C$\underline{H}$-CH-), 4.36 (1 H, ddd, *J* 4.5, 6.0 and 11.5 Hz, =CH-C$\underline{H}$-OH) and 2.73-2.38 (3 H, m, -$C\underline{H}_2$- and -O$\underline{H}$).

^{13}C-NMR ($CDCl_3$). δ:136.7, 133.1, 123.6, 119.0 (<u>C</u>N), 107.6, 32.9 (<u>C</u>H) and 20.0 (<u>C</u>H_2).

IR : 3384.1 (OH), 3049.4, 2924.9, 2209.0 (CN), 1638.2, 1566.3, 1406.4, 1147.6, 1075.0, 1022.2, 825.1, 753.2 and 692.0 cm^{-1}.

Ethyl 2-cyano-3-(2-methylfuryl)propanoate (29)

ECA (1 g, 8 mmol) was added to a stirred solution of 2-methylfuran **28** (0.87 mL, 9.6 mmol) and $TiCl_4$ (0.4 mmol, 0.8 mL of 1M $TiCl_4$ solution in toluene) in toluene (2 mL) at r.t. Stirring was continued at that temperature for 20 hours. Then, the reaction mixture was washed with water, taken up in CH_2Cl_2, dried over $MgSO_4$ and concentrated to yield 1.54 g (93 %) of **29** as red oil.

^{1}H-NMR ($CDCl_3$) δ: 6.13 (1 H, d, *J* 3.0 Hz, -CH-C<u>H</u>=C-(CH_2-)-), 5.91 (1 H, d, *J* 3.0 Hz, -CH-C<u>H</u>=C-CH_3), 4.29 (2 H, q, *J* 7.0 Hz, -OC<u>H_2</u>CH_3), 3.82 (1 H, dd, *J* 6.0 and 8.0 Hz, -CH_2C<u>H</u>(CN)CO_2Et), 3.29 (1 H, dd, *J* 6.0 and 15.1 Hz, -C<u>H</u>HCH(CN)CO_2Et), 3.22 (1 H, dd, *J* 8.0 and 15.1 Hz, -CH<u>H</u>CH(CN)CO_2Et), 2.27 (3 H, s, C<u>H_3</u>-C=) and 1.33 (3 H, t, *J* 7.0 Hz, -OCH_2C<u>H_3</u>).

^{13}C-NMR ($CDCl_3$). δ: 165.2 (<u>C</u>O_2Et), 155.5 (<u>C_q</u>), 147.2 (<u>C_q</u>), 115.8 (<u>C</u>N), 109.2 (-<u>C</u>H=), 106.2 (-<u>C</u>H=), 62.9 (O<u>C</u>$H_2$$CH_3$), 37.5 (<u>C</u>H(CN)$CO_2$Et), 29.6 (Ar-<u>C</u>$H_2$), 13.9 (<u>C</u>$H_3$) and 13.4 (<u>C</u>$H_3$).

IR : 2982.5, 2923.8, 2360.0, 2250.5 (CN), 1745.4 (CO_2Et), 1617.6, 1566.1, 1447.3, 1369.7, 1217.5, 1097.0, 1025.6, 962.9, 875.2 and 787.9 cm^{-1}.

MS (ES+) required: 208.23 (M+), Found: 182.21, 288.24, 290.13, 371.17, 396.23, 419.34, 463.37, 507.39, 551.42, 578.34, 595.48, 633.26 and 707.26.

General Procedure for the Preparation of Alcohol-ECA Adducts

ECA was added to a stirred solution of *p*-TsOH (2 or 4.5 mol %) and the corresponding alcohol (0.5, 1, 5, 10, 50 or 100 equiv.) at r.t. Stirring was continued at rt or 60 °C for 1, 5, 6 or 24 hours. Then, the reaction mixture was concentrated to give a mixture of the corresponding alcohol-adduct and **ECA**.

Ethyl 2-cyano-3-methoxypropanoate (35)[11]

Alcohol: MeOH **(32)**, ***p*-TsOH**: 2 mol%, **Temperature:** r.t., **Reaction Time:** 1 hour, **Yield:** 93 %

^{1}H-NMR ($CDCl_3$) δ: 7.00 (1 H, s, HHC=, **ECA**), 6.60 (1 H, s, HHC=, **ECA**), 4.38 (2 H, q, *J* 7.0 Hz, -OCH_2CH_3, **35**), 4.29 (2 H, q, *J* 7.0 Hz, -OCH_2CH_3, **ECA**), 3.84 (1 H, dd, *J* 6.5 and 14.0 Hz, -OCHHCH(CN)CO_2Et, **35**), 3.80 (1 H, dd, *J* 7.0 and 14.0 Hz, -OCHHCH(CN)CO_2Et, **35**), 3.71 (1 H, dd, *J* 6.5 and 7.0 Hz, -OCHHCH(CN)CO_2Et, **35**), 3.48 (3 H, s, CH_3O, **35**), 1.35 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3, **35**) and 1.32 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3, **ECA**).

^{13}C-NMR ($CDCl_3$). δ:163.8 (CO_2Et), 114.7 (CN), 69.2 (OCH_2CH), 62.5 (OCH_2CH_3), 58.8 (CH_3O), 38.2 (CH) and 13.4 (OCH_2CH_3).

IR : 2987.2, 2937.1, 2834.9, 2256.3 (CN), 1745.3 (-CO_2Et), 1463.7, 1369.2, 1193.7, 1120.4, 1018.2 and 836.9 cm^{-1}

MS (ES+) required: 158.23 (M+), Found: 305.11, 430.17 and 555.26.

Ethyl 2-cyano-3-*i*-propoxypropanoate (41)

Alcohol: *i*-propanol **(37)**, ***p*-TsOH**: 4.5 mol%, **Temperature:** r.t., **Reaction Time:** 24 hours, **Yield:** 88 %

^{1}H-NMR ($CDCl_3$). δ: 7.00 (1 H, s, HHC=, **ECA**), 6.60 (1 H, s, HHC=, **ECA**), 4.38 (2 H, q, *J* 7.0 Hz, -OCH_2CH_3, **ECA**), 4.31 (2 H, q, *J* 7.5 Hz, -OCH_2CH_3, **41**), 3.89 (2 H, d, *J* 5.5 Hz, -OCH_2CH(CN)CO_2Et, **41**), 3.69 (1 H, sept, *J* 6.0 Hz,

$(CH_3)_2C\underline{H}O$-, **41**), 3.68 (1 H, t, *J* 5.5 Hz, $-OCH_2C\underline{H}(CN)CO_2Et$, **41**), 1.35 (3 H, t, *J* 7.5 Hz, $-OCH_2C\underline{H}_3$, **41**), 1.32 (3 H, t, *J* 7.5 Hz, $-OCH_2C\underline{H}_3$, **ECA**) and 1.19 (6 H, d, *J* 6.0 Hz, $(C\underline{H}_3)_2CH$-, **41**).

^{13}C-NMR ($CDCl_3$). δ: 164.0 ($\underline{C}O_2Et$), 114.9 ($\underline{C}N$), 72.5 ($O\underline{C}H_2CH(CN)CO_2Et$), 65.2 ($(Me)_2C\underline{H}O$-), 62.4 ($O\underline{C}H_2CH_3$), 38.7 ($OCH_2\underline{C}H$), 21.3 ($(\underline{C}H_3)_2CH$) and 13.5 ($OCH_2\underline{C}H_3$)

IR : 2977.6, 2937.1, 2881.1, 2256.3 (CN), 1747.2 (CO_2Et), 1467.6, 1371.1, 1238.1, 1191.8, 1126.2, 1097.3, 1024.0, 916.0 and 734.7.

Ethyl 2-cyano-3-*t*-butoxypropanoate (42)

Alcohol: *t*-butanol **(38)**, ***p*-TsOH**: 4.5 mol%, **Temperature:** r.t., **Reaction Time:** 24 hours, **Yield:** 50 %

^{1}H-NMR ($CDCl_3$). δ: 7.00 (1 H, s, $\underline{H}HC$=, **ECA**), 6.60 (1 H, s, $H\underline{H}C$=, **ECA**), 4.38 (2 H, q, *J* 7.0 Hz, $-OC\underline{H}_2CH_3$, **ECA**), 4.30 (2 H, q, *J* 7.0 Hz, $-OC\underline{H}_2CH_3$, **42**), 3.74 (1 H, dd, *J* 6.3 and 14.0 Hz, $-OC\underline{H}HCH(CN)CO_2Et$, **42**), 3.73 (1 H, dd, *J* 6.8 and 14.0 Hz, $-OC\underline{H}HCH(CN)CO_2Et$, **42**), 3.65 (1 H, dd, *J* 6.3 and 6.5 Hz, $-OCHHC\underline{H}(CN)CO_2Et$, **42**), 1.35 (3 H, t, *J* 7.0 Hz,$-OCH_2C\underline{H}_3$, **42**), 1.32 (3 H, t, *J* 7.0 Hz, $-OCH_2C\underline{H}_3$, **ECA**) and 1.15 (9 H, s, $(C\underline{H}_3)_3C$-, **42**).

Ethyl 3-benzoxy-2-cyanopropanoate (43)

Alcohol: benzyl alcohol **(39)**, ***p*-TsOH**: 4.5 mol%, **Temperature:** 60 °C, **Reaction Time:** 5 hours, **Yield:** 80 %

^{1}H-NMR ($CDCl_3$). δ: 7.37-7.28 (5 H, m, C_6H_5-, **43**), 7.00 (1 H, s, $\underline{H}HC$=, **ECA**), 6.60 (1 H, s, $H\underline{H}C$=, **ECA**), 4.64 (2 H, $C_6H_5C\underline{H}_2O$-, **43**), 4.38 (2 H, q, *J* 7.0 Hz, $-OC\underline{H}_2CH_3$, **ECA**), 4.30 (2 H, q, *J* 7.0 Hz, $-OC\underline{H}_2CH_3$, **43**), 3.94 (1 H, dd, *J* 6.0 and 14.0 Hz, $-OC\underline{H}HCH(CN)CO_2Et$, **43**), 3.94 (1 H, dd, *J* 5.2 and 14.0 Hz, $-OCH\underline{H}CH(CN)CO_2Et$, **43**), 3.72 (1 H, t, *J* 6 Hz, $-OCHHC\underline{H}(CN)CO_2Et$, **43**), 1.34 (3 H, t, *J* 7.0 Hz, $-OCH_2C\underline{H}_3$, **43**) and 1.32 (3 H, t, *J* 7.0 Hz, $-OCH_2C\underline{H}_3$, **ECA**).

Ethyl 2-cyano-(2'-hydroxyethoxy)propanoate (44)

Alcohol: ethylenglycol **(40)**, ***p*-TsOH**: 4.5 mol%, **Temperature:** r.t., **Reaction Time:** 6 hours, **Yield:** 40% for 1 equivalent of ethylenglycol **(40)** and 3% for 0.5 equivalent of ethylenglycol **(40)**.

^{1}H-NMR ($CDCl_3$). δ: 7.00 (1 H, s, HHC=, **ECA**), 6.60 (1 H, s, HHC=, **ECA**), 4.38 (2 H, q, *J* 7.0 Hz, -OCH_2CH_3, **ECA**), 4.25 (2 H, q, *J* 7.0 Hz, -OCH_2CH_3, **44**), 4.00 (1 H, bs, -OH, **44**), 3.91 (1 H, dd, *J* 6.0 and 10.0 Hz, -OCHHCH(CN)CO_2Et, **44**), 3.88 (1 H, dd, *J* 4.5 and 9.5 Hz, -OCHHCH(CN)CO_2Et, **44**), 3.77 (1 H, dd, *J* 5 and 6 Hz, -OCHHCH(CN)CO_2Et, **44**), 3.66-3.63 (2 H, m, **44**), 3.60-3.56 (2 H, m, **44**), 1.32 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3, **ECA**) and 1.27 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3, **44**).

IR : 3394.6, 2937.9 (OH), 2238.8 (CN), 1740.0 (CO_2Et), 1614.8, 1466.6, 1389.0, 1291.4, 1193.0, 1089.0, 1023.0, 865.0 and 804.0 cm^{-1}

Ethyl 2-bromo-2-cyano-3-methoxypropanoate (46)[12]

ECA (2 g, 16 mmol) was added to a stirred suspension of methanol **(32)** (0.8 mL, 19.76 mmol), NBS (2.85 g, 16 mmol) and *p*-TsOH (0.085 g, 0.48 mmol) in CCl_4 (5 mL) at r.t. Stirring was maintained at that temperature overnight. Then, the reaction mixture was suspended in hexane, filtered and the filtrate was concentrated to afford 2.45 g (65 %) of **46** as brown oil.

^{1}H-NMR ($CDCl_3$) δ: 4.34 (2 H, dq, *J* 2.0 and 7.0 Hz, -OCH_2CH_3), 4.04 (1 H, d, *J* 10.0 Hz, CH_3OCHHC(Br)(CN)CO_2Et), 3.85 (1 H, d, *J* 10.0 Hz, MeOCHHC(Br)(CN)CO_2Et), 3.47 (3 H, s, CH_3O-) and 1.34 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3).

^{13}C-NMR ($CDCl_3$). δ:162.6 (CO_2Et), 114.6 (CN), 75.1 (CH_2), 64.1 (OCH_2CH_3), 59.6 (CH_3O-) and 13.4 (OCH_2CH_3).

Ethyl 2-cyano-3-(4'-toluenesulfonyl)propanoate (49)

ECA (1.25 g, 10 mmol) was added to a stirred solution of *p*-tolylsulfinic acid (1.56 g, 10 mmol) in acetone (20 ml) at r.t. Stirring was continued at r.t. for a hour and then the solvent was removed to afford 2.6 g (95%) of **49** as yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.85 (2 H, d, *J* 8.5 Hz, 2 x (*o*-C_6H_4-)), 7.43 (2 H, d, *J* 8.5 Hz, 2 x (*m*-C_6H_4-)), 4.31 (2 H, q, *J* 7.5 Hz, -$OC\underline{H}_2CH_3$), 4.03 (1 H, dd, *J* 5.5 and 7.5 Hz, -$CH_2C\underline{H}(CN)CO_2Et$), 3.82 (1 H, dd, *J* 5.5 and 14.5 Hz, -$SO_2C\underline{H}HCH(CN)CO_2Et$), 3.59 (1 H, dd, *J* 7.5 and 14.6 Hz, -$SO_2C\underline{H}HCH(CN)CO_2Et$), 2.49 (3 H, s, $C\underline{H}_3C_6H_4$-) and 1.35 (3 H, t, *J* 7.5 Hz, -$OCH_2C\underline{H}_3$).

^{13}C-NMR ($CDCl_3$) δ: 163.2 ($\underline{C}O_2Et$), 146.1 ($\underline{C}_q$), 135.0 (=$\underline{C}$H-), 130.3 (=$\underline{C}$H-), 128.4 ($\underline{C}_q$), 113.8 ($\underline{C}N$), 64.1 ($O\underline{C}H_2CH_3$), 54.3 ($\underline{C}H_2CH(CN)CO_2Et$), 32.1 ($CH_2\underline{C}H(CN)CO_2Et$), 21.7 ($\underline{C}H_3$) and 13.8 (.$OCH_2\underline{C}H_3$).

IR (Nujol): 2923.0, 2854,4, 2360.9 (CN), 1735.7 (CO_2Et), 1597.5, 1461.3, 1376.7, 1262.9, 1147.3 , 1073.6 and 722.1 cm^{-1}

MS (ES+) required: 282.32 (M+), Found: 299.10, 424.16, 580.19, 705.21 and 830.27

$C_{13}H_{15}NO_4S$, required C 48.82 %, H 5.85 %, N 8.13 %, found C 48.62 %, H 5.70 %, N 8.05 %

M.P: 79 °C (recrystallised in EtOH).

Ethyl 2-cyano-3-(4'-toluenesulfanyl)propanoate (54)

ECA (11.61 g, 92.88 mmol) was added to a solution of *p*-thiocresol **50** (11.61 g, 92.88 mmoles) in CH_2Cl_2 (100 mL) at r.t. Stirring was continued at that temperature during 1 hour and then the crude mixture was concentrated to afford 19.74 g (85 %) of **54** as yellow oil.

^{1}H-NMR ($CDCl_3$). δ: 7.39 (2 H, d, *J* 8.0 Hz, 2 x (*o*-C_6H_4-)), 7.17 (2 H, d, *J* 8.0 Hz, 2 x (*m*-C_6H_4-)), 4.24 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$$CH_3$), 3.61 (1 H, dd, *J* 6.5 and 8.0 Hz, -$SCH_2C\underline{H}$(CN)CO_2Et), 3.41 (1 H, dd, *J* 6.5 and 14.0 Hz, -SC$\underline{H}$HCH(CN)CO_2Et), 3.27 (1 H, dd, *J* 8.0 and 14.0 Hz, -SCH$\underline{H}$CH(CN)CO_2Et), 2.36 (3 H, s, C$\underline{H}_3$Ph) and 1.32 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 164.2 ($\underline{C}O_2$Et), 138.1 ($\underline{C}_q$), 132.3 (=$\underline{C}$H-), 129.7 (=$\underline{C}$H-), 128.9 ($\underline{C}_q$), 114.9 ($\underline{C}$N), 62.7 (O$\underline{C}H_2CH_3$), 37.7 ($CH_2\underline{C}$H(CN)CO_2Et), 34.6 ($\underline{C}H_2$CH(CN)CO_2Et), 20.6 ($\underline{C}H_3$) and 13.4 (.$OCH_2\underline{C}H_3$).

IR: 2982.9, 2924.2, 2251.9 (CN), 1745.7 (C=O), 1493.0, 1445.8, 1369.1, 1250.7, 1205.9, 1019.2 and 809.4 cm^{-1}

Ethyl 3-(*n*-butylsulfanyl)-2-cyanopropanoate (55)[14]

ECA (2.64 g, 21.15 mmol) was added to a solution of *n*-butanethiol **51** (1.71 mL, 16 mmol) in CH_2Cl_2 (16 mL) at r.t. Stirring was continued at that temperature during 3 hours and then the crude mixture was concentrated to afford 3.03 g (95 %) of **55** as colourless liquid.

^{1}H-NMR ($CDCl_3$). δ: 4.31 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$$CH_3$), 3.72 (1 H, dd, *J* 6.0 and 7.5 Hz, -$SCH_2C\underline{H}$(CN)CO_2Et)), 3.09 (1 H, dd, *J* 6.0 and 14.0 Hz, -SC$\underline{H}$HCH(CN)CO_2Et), 3.04 (1 H, dd, *J* 7.5 and 14.0 Hz, -SCH$\underline{H}$CH(CN)CO_2Et), 2.67 (2 H, t, *J* 7.5 Hz, -SC$\underline{H}_2$$CH_2$), 1.64-1.57 (2 H, m, -$SCH_2C\underline{H}_2CH_2$), 1.46-1.40 (2 H, m, -$SCH_2CH_2C\underline{H}_2CH_3$), 1.35 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$) and 0.94 (3 H, t, *J* 7.5 Hz, -$SCH_2CH_2CH_2C\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 164.4 ($\underline{C}O_2Et$), 115.4 ($\underline{C}N$), 62.6 ($O\underline{C}H_2CH_3$), 38.6 ($CH_2\underline{C}H(CN)CO_2Et$), 32.0 ($\underline{C}H_2$), 31.0 ($\underline{C}H_2$), 30.9 ($\underline{C}H_2$), 21.3 ($\underline{C}H_2$), 13.4 ($\underline{C}H_3$) and 13.1 ($\underline{C}H_3$).

IR: 2958.3, 2929.3, 2873.4, 2250.5 (CN), 1745.2 (C=O), 1465.6, 1369.2, 1292.1, 1251.6, 1201.4, 1022.1 and 854.3 cm^{-1}

Ethyl 2-cyano-3-(2'-hydroxythioethyl)propanoate (56)[14]

ECA was added to a solution of 2-mercaptoethanol **52** (1 or 0.5 equiv.) and *p*-TsOH (4.5 mol%) in CH_2Cl_2 (1 mL/ mmol) at r.t. Stirring was continued at that temperature during 6 hours and then the crude mixture was filtered and concentrated to afford **56** as a colourless liquid. The yield obtained for 1 equivalent of 2-mercaptoethanol was 83 % and for 0.5 equivalent of 2-mercaptoethanol was 60 %.

^{1}H-NMR ($CDCl_3$). δ: 4.23 (2 H, q, *J* 7.0 Hz, $-OC\underline{H}_2CH_3$), 3.85 (1 H, dd, *J* 6.0 and 7.0 Hz, $-SCH_2C\underline{H}(CN)CO_2Et$), 3.74 (2 H, t, *J* 6.0 Hz, $HOC\underline{H}_2CH_2$), 3.09 (1 H, dd, *J* 6.0 and 14.0 Hz, $-SC\underline{H}HCH(CN)CO_2Et$), 3.03 (1 H, dd, *J* 7.0 and 14.0 Hz, $-SCH\underline{H}CH(CN)CO_2Et$), 2.77 (2 H, t, *J* 6.0 Hz, $-SC\underline{H}_2CH_2OH$) and 1.27 (3 H, t, *J* 7.0 Hz, $-OCH_2C\underline{H}_3$).

IR: 3473.23, 2925.32 (OH), 2253.42 (CN), 1743.47 ($-CO_2Et$), 1464.04, 1371.87, 1296.88, 1254.91, 1207.34, 1022.80, 855.31 and 484.67 cm^{-1}.

Ethyl 2-cyano-3-(2-mercaptothioethyl)propanoate (57)[15]

ECA (1.97 g, 15.8 mmol) was added to a solution of 1,2-ethanethiol **53** (1.49 g, 15.8 mmol) and *p*-toluenesulfonic acid (0.71 mmol, 0.13 g) in CH_2Cl_2 (16 mL) at r.t. Stirring was continued at that temperature during 6 hours and then the crude mixture was filtered and concentrated to afford 2.73 g (78 %) of **57** as white solid.

^{1}H-NMR ($CDCl_3$). δ: 4.32 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 3.76 (1 H, dd, *J* 6.0 and 7.0 Hz, -SCH$_2$C$\underline{H}$(CN)CO$_2$Et), 3.14 (1 H, dd, *J* 6.0 and 14.0 Hz, -SC$\underline{H}$HCH(CN)CO$_2$Et), 3.08 (1 H, dd, *J* 7.0 and 14.0 Hz, -SCH$\underline{H}$CH(CN)CO$_2$Et), 2.94-2.90 (2 H, m), 2.80-2.74 (2 H, m) and 1.36 (3 H, t, *J* 7.0 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 164.2 ($\underline{C}$O$_2$Et), 115.3 ($\underline{C}$N), 63.0 (O$\underline{C}$H$_2$CH$_3$), 38.7 (CH$_2\underline{C}$H(CN)CO$_2$Et), 36.4 ($\underline{C}$H$_2$), 31.0 ($\underline{C}$H$_2$), 24.2 ($\underline{C}$H$_2$) and 13.6 ($\underline{C}$H$_3$).

IR: 3546.5, 2929.35, 2566.8, 2254.4 (CN), 1733.7 (CO$_2$Et), 1467.6, 1371.1, 1272.8, 1213.0, 1024.0, 933.4, 860.1 and 682.7 cm^{-1}.

Diethyl 2, 9-dicyano-4, 7-dithiadecandioate (58)

ECA (3.58 g, 28.70 mmol) was added to a solution of 1,2-ethanethiol (1.35 g, 14.33 mmol) and *p*-toluenesulfonic acid (1.29 mmol, 0.25 g) in CH_2Cl_2 (29 mL) at r.t. Stirring was continued at that temperature during 6 hours and then the crude mixture was filtered and concentrated to afford 5.31 g (76 %) of **58** as white solid.

^{1}H-NMR ($CDCl_3$). δ: 4.31 (4 H, q, *J* 7.0 Hz, 2 x (-OC$\underline{H}_2$CH$_3$)), 3.79 (2 H, dd, *J* 6.0 and 7.0 Hz, 2 x (-SCH$_2$C$\underline{H}$(CN)CO$_2$Et)), 3.15 (2 H, dd, *J* 6.0 and 14.1 Hz, 2 x (-SC$\underline{H}$HCH(CN)CO$_2$Et)), 3.10 (2 H, dd, *J* 7.0 and 14.1 Hz, 2 x (-SCH$\underline{H}$CH(CN)CO$_2$Et)), 2.92 (4 H, s, 2 x (-SC$\underline{H}_2$-)) and 1.35 (6 H, t, *J* 7.0 Hz, 2 x (-OCH$_2$C$\underline{H}_3$)).

^{13}C-NMR ($CDCl_3$). δ: 164.2 (-$\underline{C}$O$_2$Et), 115.3 (-$\underline{C}$N), 62.9 (-O$\underline{C}$H$_2$CH$_3$), 38.7 (-CH$_2\underline{C}$H(CN)(CO$_2$Et)), 32.4 ($\underline{C}$H$_2$), 31.10 ($\underline{C}$H$_2$) and 13.5 ($\underline{C}$H$_3$).

IR (Nujol): 2918.99, 2854.87, 2255.05 (CN), 1731.48 (CO$_2$Et), 14645.13, 1376.62, 1301.17, 1279.55, 1205.54, 1026.24, 860.81, 796.24, 723.08 and 681.72 cm^{-1}.

MS (ES+) required: 367.43 ($M+Na^+$), 383.54 ($M+K^+$). Found: 367.5 ($M+Na^+$), 383.5 ($M+K^+$).

$C_{14}H_{20}N_2O_4S_2$, required C 48.82 %, H 5.85 %, N 8.13 %, found C 48.62 %, H 5.70 %, N 8.05 %

MP (recrystallised in EtOH) = 88-90 °C

Attempted Preparation of *tert*-butyl 2-cyano-3-(phenylsulfanyl)propanoate (57) from chloromethylphenyl sulfide (60)

1st Attempt. General Procedure using Basic Conditions.

The corresponding base (n equiv.) was added to a stirred solution of *tert*-butyl cyanoacetate **62** (1 equiv.) in the corresponding solvent (1 mL/ 1mmol of **62**) at r.t. After 30 minutes chloromethylphenyl sulfide **60** (1 equiv.) was added at r.t and the reaction mixture was left at that temperature for n hours. Then, the reaction mixture was washed with brine and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to afford a mixture of *tert*-butyl 2, 2-di(benzenesulfanylmethyl)-2-cyanoacetate **63** and *t*-butyl cyanoacetate **62**.

^{1}H-NMR ($CDCl_3$). δ: 7.45-7.12 (10 H, m, 2 x (C_6H_5S-), **63**), 4.62 (2 H, s, $C\underline{H}_2(CN)CO_2{}^tBu$, **62**), 3.35 (4 H, s, 2 x ($C_6H_5SC\underline{H}_2$-), **63**), 1.63 (9 H, s, ($C\underline{H}_3)_3C$-, **62**) and 1.54 (9 H, s, ($C\underline{H}_3)_3C$-, **63**).

- **Base (n equiv):** NaEtO (1 equiv.), **Solvent:** EtOH, **Time (hours):** 20, **% Conversion (62:63):** (38:62)

- **Base (n equiv):** Na_2CO_3 (0.5 equiv.), **Solvent:** Acetone: H_2O (1:1), **Time (hours):** 20, **% Conversion (62:63):** (82:18)

- **Base (n equiv):** KO^tBu (1 equiv.), **Solvent:** THF, **Time (hours):** 12, **% Conversion (62:63):** (56:44).

2nd Attempt. General Procedure using Acidic Conditions.

Chloromethylphenyl sulfide (0.5 g, 3.15 mmol) was added to a mixture of *t*-butyl 2-cyanoacetate **62** (0.44 g, 3.15 mmol) and zinc bromide (7.09 mg, 0.03 mmol) in CH_2Cl_2 at r.t. The reaction mixture was stirred at r.t. for 16 hours. Then, the crude mixture was filtered and concentrated to observe a mixture of starting materials.

Ethyl 2-cyano-3-benzoylthiopropanoate (65)

ECA (1.86 g, 14.9 mmol) was added to a solution of thiobenzoic acid **64** (2.06 g, 14.9 mmol) in benzene (15 ml) at r.t. The stirring was continued at r.t. for 22 hours and then the solvent was removed to afford 3.98 g (87%) of **65** as yellow liquid.

^{1}H-NMR ($CDCl_3$). δ: 7.98 (2 H, d, *J* 7.5 Hz, 2 x (*o*-C_6H_5-)), 7.63 (1 H, t, *J* 7.5 Hz, *p*-C_6H_5-), 7.49 (2 H, t, *J* 7.5 Hz, 2 x (*m*-C_6H_5-)), 4.33 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$$CH_3$), 3.95 (1 H, dd, *J* 7.0 and 8.0 Hz, -SCHHC$\underline{H}$(CN)CO_2Et), 3.71 (1 H, dd, *J* 7.0 and 14.0 Hz, -SC$\underline{H}$HCH(CN)CO_2Et), 3.51 (1 H, dd, *J* 8.0 and 14.0 Hz, -SC$\underline{H}$HCH(CN)CO_2Et) and 1.36 (3 H, t, *J* 7.0 Hz, -OCH_2C$\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 189.5 ($C_6H_5\underline{C}$(O)S-), 164.1 (-$\underline{C}O_2$Et), 135.5 ($\underline{C}_q$), 133.7 ($\underline{C}$H), 128.4 ($\underline{C}$H), 126.9 ($\underline{C}$H), 114.9 (-$\underline{C}$N), 62.9 (-O$\underline{C}H_2CH_3$), 37.6 (-$CH_2\underline{C}$H(CN)(CO_2Et)), 27.9 ($\underline{C}H_2$-S) and 13.5 ($\underline{C}H_3$).

IR: 2984.53, 2926.72, 2252.65 (CN), 1746.07 (CO_2Et), 1670.49 (C_6H_5C(S)O), 1581.35, 1448.69, 1295.03, 1251.64, 1208.46, 1022.71, 908.84, 774.34, 688.09 and 647.81 cm^{-1}.

MS (ES+) required: 264.31 (M+), Found: 327.08, 411.10, 452.12, 578.26 and 799.20.

Attempted preparation of ethyl 2-cyano-3-phosphonopropanoate (71)

1st Attempt. In the presence of solvent.

ECA (2 g, 16 mmol) was added to a stirred solution of H_3PO_3 (1.51 g, 18.4 mmol) in acetone (16 mL) at r.t. Then, the reaction mixture was heated at 60 °C and the stirring was maintained at that temperature during 72 hours. The solvent was removed under reduced pressure and the crude mixture was chromatographied using hexane:EtOAc (3:7) to yield 1.90 g (10.4 mmol, 65 %) of ethyl 2-cyano-5-oxohexanoate **74**.[19]

R_f: 0.25 in EtOAc:Hexane (5:3)

^{1}H-NMR ($CDCl_3$). δ: 4.27 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$CH$_3$), 3.70 (1 H, dd, *J* 6.0 and 8.0 Hz, -CH$_2$C$\underline{H}$(CN)CO$_2$ Et), 2.72 (2H, t, *J* 7.0 Hz, -COC$\underline{H}_2$CH$_2$-), 2.32-2.23 (1 H, m, -CH$_2$C$\underline{H}$HCH$_2$-), 2.20 (3 H, s, C$\underline{H}_3$CO-), 2.18-2.09 (1 H, m, -CH$_2$CH$\underline{H}$CH$_2$-) and 1.33 (3 H, t, *J* 7.0 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 205.7 ($\underline{C}$=O), 165.3 (-$\underline{C}$O$_2$Et), 115.7 (-$\underline{C}$N), 62.4 (-O$\underline{C}$H$_2$), 39.0 ($\underline{C}$H$_2$), 35.8 ($\underline{C}$H), 29.5 ($\underline{C}$H$_2$), 23.0 ($\underline{C}$H$_3$CO) and 13.5 (-OCH$_2\underline{C}$H$_3$).

2nd Attempt. In the absence of solvent.

ECA (1g, 8 mmol) was added to H_3PO_3 (0.7 g, 8.5 mmol) previously melted at 80 °C. The reaction mixture was stirred at that temperature for 2 hours to observe no reaction.

^{1}H-NMR ($CDCl_3$): δ: 7.00 (1 H, s, $\underline{H}$HC=), 6.60 (1 H, s, $\underline{H}$HC=), 4.29 (2 H, q, *J* 7.0 Hz, -OC$\underline{H}_2$CH$_3$).and 1.32 (3 H, t, *J* 7.0 Hz).

Ethyl 4-acetyl-2-cyano-5-oxohexanoate (82) and ethyl 2-cyano-4-(hydroxymethylmethylen)-5-oxohexanoate (83)

ECA (2 g, 16 mmol) was added to a stirred solution of acetylacetone **81** (1.64 ml, 16 mmol) and H_3PO_3 (1.32g, 16 mmol) in acetone (1 mL) at r.t. The stirring was kept at that temperature for 48 hours. Then. the reaction mixture was washed with water and taken up in ether. The ethereal layer was dried over $MgSO_4$, filtered off, concentrated and subject to chromatography (eluent:: (hexane:EtOAc) (3:1)) to yield 1.10 g of a mixture of **82** (15%) and **83** (15%) as a yellow oil. The unequivocal assignment of this mixture was determined from H-H COSY, C-H COSY and DEPT 135.

R.f = 0.4 in hexane:EtOAc (1:1)

^{1}H-NMR ($CDCl_3$). δ: 4.26-4.19 (4 H, q, *J* 7.0 Hz, 2 x (-$OC\underline{H}_2CH_3$)), 3.93 (1 H, dd, *J* 5.5 and 8.0 Hz, $(CH_3C(O))_2C\underline{H}CH_2$-, **82**), 3.58 (1 H, dd, *J* 7.0 and 8.5Hz, $CO_2Et(CN)C\underline{H}CH_2$-, **82**), 3.52 (1 H, dd, *J* 6.5 and 9.5 Hz, $CO_2Et(CN)C\underline{H}CH_2$-, **83**), 2.96 (1H, dd, *J* 6.5 and 15.6 Hz, =C-C$\underline{H}$H-CH, **83**), 2.91(1 H, dd, *J* 9.5 and 15.6 Hz, =C-C$\underline{H}$H-CH, **83**), 2.47 (1 H, ddd, *J* 7.0, 8.0 and 14.6 Hz, $(COMe)_2CHC\underline{H}HCH(CN)CO_2Et$, **82**), 2.33-2.25 (1 H, m, $(COMe)_2CHC\underline{H}HCH(CN)CO_2Et$, **82**), 2.23 (3H, s,), 2.22 (3 H, s), 2.18 (6 H, s, 2X($C\underline{H}_3$)) and 1.30-1.26 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$).

^{13}C-NMR ($CDCl_3$). δ: 201.4 ($\underline{C}$(O), **82**), 191.9 (=C-$\underline{C}$(O), **83**), 165.0 (-$\underline{C}O_2Et$), 164.8 (-$\underline{C}O_2Et$), 115.7 (-$\underline{C}N$), 115.3 (-$\underline{C}N$), 63.9 ($(CH_3C(O))_2\underline{C}H$, **82**), 62.7 (-$O\underline{C}H_2$), 38.0 ($CO_2Et(CN)\underline{C}H$, **83**), 34.8 ($CO_2Et(CN)\underline{C}H$, **82**), 29.2 ($\underline{C}H_3CO$), 29.0 ($\underline{C}H_3CO$), 27.9 ($\underline{C}H_2$, **83**), 26.5 ($\underline{C}H_2$, **82**), 22.7 ($\underline{C}H_3$) and 13.4 ($OCH_2\underline{C}H_3$).

IR: 2986.3, 2941.1, 2251.1 (CN), 1744.5 (C=O), 1705.7 (C=C-C=O), 1596.0, 1252.5 and 1022.3 cm^{-1}

MS (ES+) required: 248.23 ($M+Na^+$), Found: 248.16 ($M+Na^+$)

HYDROLYSIS AND TRANSESTERIFICATION OF ECA-ADDUCTS

Hydrolysis of ethyl 2-cyano-3-(2-methylfuryl)propanoate (29)

1M NaOH solution (9.9 mL, 9.9 mmol) was added to a solution of **29** (1.71 g, 8.26 mmol) in EtOH (3 mL) at r.t. The reaction mixture was stirred at that temperature for 12 hours. Then, the reaction mixture was washed with EtOAc, acidified with 10% HCl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to afford 2-cyano-3-(2-methylfuryl)propionic acid **84** (0.94 g, 4.55 mmol, 55 %) as purple liquid.

^{1}H-NMR ($CDCl_3$) δ: 8.33 (1 H, bs, -CO_2H), 6.15 (1 H, d, *J* 3.0 Hz, -CH-CH=C(CH_2-)-), 5.91 (1 H, d, *J* 3.0 Hz, -CH-CH=C-CH_3), 3.88 (1 H, dd, *J* 6.0 and 8.5 Hz, -CH_2CH(CN)CO_2H), 3.31 (1 H, dd, *J* 8.0 and 15.1 Hz, -CHHCH(CN)CO_2H), 3.23 (1 H, dd, *J* 8.0 and 15.1 Hz, -CHHCH(CN)CO_2H) and 2.27 (3 H, s, CH_3C=).

^{13}C-NMR ($CDCl_3$). δ: 168.9 (-$C_q$$O_2$H), 152.5 ($C_q$), 147.8 ($C_q$), 116.0 (-CN), 114.9 (-CH=), 110.2 (-CH=), 36.2 (-CH(CN)(CO_2H)), 26.8 (Ar-CH_2-) and 13.7 (CH_3).

IR : 3482.0 (OH), 2922.9, 2598.3, 2256.2 (CN), 1740.2 (CO_2H), 1569.5, 1437.5, 1384.8, 1217.0, 1024.0, 962.5, 791.1 and 732.9 cm^{-1}.

Attempted hydrolysis of ethyl 2-cyano-3-methoxypropanoate (35)

1M H_2SO_4 solution (1.5 mL, 1.5 mmol) was added to **35** (0.2 g, 2.0 mmol) at r.t. The reaction mixture was stirred at r.t for 72 hours. Then, the reaction mixture was concentrated to afford a mixture (2:10:88) of **ECA**, **CAA** and *oligo*(ethyl 2-cyanoacrylate) **36**.

^{1}H-NMR ($CDCl_3$) δ: 9.19 (1 H, bs, -CO_2H), 7.16 (1 H, s, HHC=, **CAA**), 7.00 (1 H, s, HHC=, **ECA**), 6.77 (1 H, s, HHC=, **CAA**), 6.60 (1 H, s, HHC=, **ECA**), 4.32 (bs, *oligo*(O$CH_2$$CH_3$), **36**), 4.29 (2 H, q, *J* 7.0 Hz, -O$CH_2$$CH_3$, **ECA**), 2.60 (bs, *oligo*(-

$C\underline{H}_2$-C(CN)(CO_2Et)-), **36**), 1.35 (bs, *oligo*($OCH_2C\underline{H}_3$), **36**).and 1.32 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$, **ECA**).

Attempted transesterification of ethyl 2-cyano-3-methoxypropanoate (35) with *n*-butanol (85)

n-Butanol **85**(1.16 mL, 12.7 mmol) was added to a mixture of **35** (1 g, 6.4 mmol) and *p*-TsOH (0.06 g, 0.32 mmol) at r.t. The reaction mixture was stirred at 80 °C for 5 hours. Then, the reaction mixture was concentrated to afford a mixture (35: 60: 5) of **35,** ethyl 3-*n*-butoxy-2-cyanopropanoate **86** and **ECA**.

^{1}H-NMR ($CDCl_3$) δ: 7.00 (1 H, s, $\underline{H}HC$=, **ECA**), 6.60 (1 H, s, $H\underline{H}C$=, **ECA**), 4.38 (2 H, q, *J* 7.0 Hz, -$OC\underline{H}_2CH_3$, **35**), 4.29 (2 H, q, *J* 7.0 Hz, -$OC\underline{H}_2CH_3$, **ECA**), 4.19 (2 H, q, *J* 7.0 Hz, -$OC\underline{H}_2CH_3$, **86**), 3.91 (1 H, dd, *J* 6.5 and 14.0 Hz, -$OC\underline{H}HCH(CN)CO_2Et$, **35**), 3.89 (1 H, dd, *J* 7.0 and 14.0 H, -$OCH\underline{H}CH(CN)CO_2Et$, **35**), 3.81 (1 H, dd, *J* 6.0 and 9.5 Hz, -$OC\underline{H}HCH(CN)CO_2Et$, **86**), 3.77 (1 H, dd, *J* 4.5 and 9.5 Hz, -$OCH\underline{H}CH(CN)CO_2Et$, **86**), 3.70 (1 H, dd, *J* 6.5 and 7.0 Hz, -$OCHHC\underline{H}(CN)CO_2Et$, **35**), 3.68 (1 H, dd, *J* 4.5 and 6.0 Hz, **86**), 3.50 (3 H, s, $C\underline{H}_3O$, **35**), 3.48-3.39 (2 H, m, -$OC\underline{H}_2CH_3$, **86**), 1.50-1.41 (4 H, m, **86**), 1.35 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$, **35**), 1.32 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$, **ECA**), 1.23 (3 H, t, *J* 7.0 Hz, -$OCH_2C\underline{H}_3$, **86**) and 0.82 (3 H, t, *J* 7.52 Hz, $C\underline{H}_3CH_2$, **86**).

Hydrolysis of ethyl 2-bromo-2-cyano-3-methoxypropanoate (46)

1M NaOH solution (16.27 mL, 916.27 mmol) was added to a solution of **46** (3.20 g, 13.55 mmol) in EtOH (3 mL) at r.t. The reaction mixture was stirred at that temperature for 2 hours. Then, the reaction mixture was washed with EtOAc, acidified with 10% HCl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The reaction mixture was dissolved in acetone (1 mL) and a solution of Na_2CO_3 (500 mg) in H_2O (5 mL) was added at r.t. Then, the reaction mixture was washed with EtOAc, acidified with 10% HCl solution, extracted with

EtOAc, dried over $MgSO_4$, filtered and concentrated to afford 1.33 g (50%) of 2-bromo-2-cyano-3-methoxypropionic acid **87** as brown oil.

^{1}H-NMR ($CDCl_3$) δ: 9.65 (1 H, bs, -CO_2H), 4.11 (1 H, d, *J* 10.0 Hz, $CH_3OCHHC(Br)(CN)CO_2H$), 3.91 (1 H, d, *J* 10.0 Hz, $MeOCHHC(Br)(CN)CO_2H$) and 3.55 (3 H, s, CH_3O-).

^{13}C-NMR ($CDCl_3$). δ: 1625.2 (CO_2H), 114.5 (CN), 75.0 (CH_2) and 59.6 (CH_3O).

MS (ES+) required: 193.01 (M+), Found: 182.19, 288.20, 454.29, 578.25 and 803.54.

General Procedure for the Hydrolysis of (54) and (55)

1M H_2SO_4 solution (3 equiv.) was added to a stirred solution of the corresponding thioester **54** and **55** in 1,4-dioxane at r.t. The reaction mixture was heated at 100 °C for 24 hours. Then, the reaction mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated. The %conversion (acid:ester) was determined and the crude mixture was dissolved in acetone. Then, the crude mixture was titrated with 0.5 equivalents of Na_2CO_3 with respect the amount of acid, washed with EtOAc, acidified with 10% HCl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to yield the corresponding acid **88** and **89**.

2-cyano-3-(4'-toluenesulfanyl)propanoic acid (88)

(dioxane: H_2O) = (1:2), **Yield:** 58*

^{1}H-NMR ($CDCl_3$). δ: 7.41 (2 H, d, *J* 8.0 Hz, 2 x (*o*-C_6H_4-S-)), 7.19 (2 H, d, *J* 8.0 Hz, 2 x (*m*-C_6H_4-S-)),6.80 (1 H, bd, -CO_2H), 3.66 (1 H, dd, *J* 6.5 and 8.0 Hz, -$SCH_2CH(CN)CO_2H$), 3.43 (1 H, dd, *J* 6.5 and 14.0 Hz, -$SCHHCH(CN)CO_2H$), 3.30 (1 H, dd, *J* 8.0 and 14.0 Hz, -$SCHHCH(CN)CO_2H$) and 2.37 (3 H, s, CH_3 C_6H_4-).

^{13}C-NMR ($CDCl_3$). δ: 168.8 ($\underline{C}O_2H$), 138.4 ($\underline{C}_q$), 132.4 (=$\underline{C}$H-), 129.8 (=$\underline{C}$H-), 128.2 ($\underline{C}_q$), 114.3 ($\underline{C}N$), 62.7, 37.7 (-$CH_2\underline{C}H(CN)CO_2H$), 34.5 (-$\underline{C}H_2CH(CN)CO_2H$) and 20.6 ($\underline{C}H_3$).

IR: 2923.0, 2853.6, 2257.6 (CN), 1712.3 (C=O), 1462.3, 1376.5, 928.7, 810.9 and 722.3 cm^{-1}

3-(*n*-butylsulfanyl)-2-cyanopropanoic acid (89)

(dioxane:H_2O) = (1:3), **Yield:** 36*

^{1}H-NMR ($CDCl_3$). δ: 8.75(1 H, bd, -$CO_2\underline{H}$), 3.80 (1 H, dd, *J* 6.0 and 7.5 Hz, -$SCH_2C\underline{H}(CN)CO_2H$), 3.12 (1 H, dd, *J* 6.0 and 14.0 Hz, -$SC\underline{H}HCH(CN)CO_2H$), 3.07 (1 H, dd, *J* 7.5 and 14.0 Hz, -$SCH\underline{H}CH(CN)CO_2H$), 2.70 (t, 2 H, *J* 7.0 Hz, -$CH_2C\underline{H}_2S$-), 1.65-1.57 (m, 2 Hz, -$CH_2C\underline{H}_2CH_2S$-), 1.48-1.37 (m, 2 H, $CH_3C\underline{H}_2CH_2C\underline{H}_2S$-) and 0.94 (t, 3 H, $C\underline{H}_3CH_2CH_2C\underline{H}_2S$-).

^{13}C-NMR ($CDCl_3$). δ: 167.4 ($\underline{C}O_2H$), 115.7 ($\underline{C}N$), 38.8 ($CH_2\underline{C}H(CN)CO_2H$), 32.1 (-$\underline{C}H_2CH(CN)CO_2H$), 30.1 ($\underline{C}H_2$), 30.8 ($\underline{C}H_2$), 21.3 ($\underline{C}H_2$) and 13.1 ($\underline{C}H_3$).

**Yield was determined from the crude mixture by NMR*

IR: 3480.9, 2960.2, 2931.3, 2871.5, 2589.9, 2256.3 (CN), 1726.0 (C=O), 1421.3, 1378.9, 1226.5, 912.2 and 734.7 cm^{-1}

Attempted preparation of 2-cyano-3-(benzenesulfanyl)propanoic acid (90)

1st Attempt. Using Lewis acid conditions

Chloromethylphenyl sulfide **60** (0.27 g, 3.15 mmol) was added to a mixture of 2-cyanoacetate acid **91** (0.44 g, 3.15 mmol) and zinc bromide (7.09 mg, 0.03 mmol) in CH_2Cl_2 at r.t. The reaction mixture was stirred at r.t. for 16 hours. Then, the crude mixture was filtered and concentrated to observe a mixture of starting materials.

2nd Attempt. Using Basic Conditions.

The corresponding base (1 equiv.) was added to a stirred solution of 2-cyanoacetic acid **91** (1 equiv.) in the corresponding solvent (1 mL/ 1mmol of **91**) at r.t. After 30 minutes chloromethylphenyl sulfide **60** (1 equiv.) was added at r.t and the reaction mixture was left at that temperature for 20 hours. Then, the reaction mixture was washed with brine and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to observe no reaction when sodium ethoxide was employed as base and a mixture (50:50) of 2, 2-(dibenzenesulfanylmethyl)-2-cyanoacetic acid **92** and chloromethylphenyl sulfide **60** when sodium carbonate was employed as base.

- **Base:** NaEtO, **Solvent:** EtOH.

^{1}H-NMR ($CDCl_3$). δ: 7.65-7.55 (2 H, m, 2 x (*o*-C_6H_5S-)), 7.45-7.35 (3 H, *m* and *p*-(C_6H_5)S) and 5.05 (2 H, s, $C_6H_5SC\underline{H}_2Cl$).

- **Base:** Na_2CO_3, **Solvent:** Acetone: H_2O (1:1)

^{1}H-NMR ($CDCl_3$). δ: 7.60-7.30 (15 H, m,), 5.05 (2H, s, $C_6H_5SC\underline{H}_2Cl$) and 4.38 (2 H, s, 2 x ($C_6H_5SC\underline{H}_2$-).

Hydrolysis of ethyl 2-cyano-3-benzoylthiopropanoate (65)

1M H_2SO_4 solution (21.10 mL) was added to a stirred solution of **65** in 1,4-dioxane (3 mL) at r.t. The reaction mixture was heated between 104-120 °C for 13 hours. Then, the reaction mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford a mixture (65:35) of thiobenzoic acid **64** and 3-(benzoylthio)propionitrile **93**.

^{1}H-NMR ($CDCl_3$). δ: 7.91 (2 H, d, *J* 8.5 Hz, 2 x (*o*-C_6H_5), **64**), 7.89 (2 H, d, *J* 8.5 Hz, 2 x (*o*-$C_6H_5C(O)SH$), **93**), 7.65-7.60 (3 H, t, m, **93**), 7.59 (1 H, t, *J* 8.5 Hz, (*p*-C_6H_5), **64**), 7.46 (2 H, t, *J* 8.5 Hz, 2 x (*m*-C_6H_5), **64**), 3.53 (2 H, t, *J* 7.0 Hz, $C_6H_5C(O)SC\underline{H}_2CH_2$-, **93**) and 3.02 (2 H, t, *J* 7.0 Hz, $(NC)C\underline{H}_2CH_2$-, **93**).

REGENERATION OF THE DOUBLE BOND FROM CAA-ADDUCTS

Attempted retro-Michael addition of 2-cyano-3-(2'-methylfuryl)propanoic acid (84)

(a) A solution of **84** (0.3 g, 1.67 mmol) in TFA (3 ml) was heated at 65 °C under reflux for 18 hours. Then, the reaction mixture was evaporated to afford a black gummy material insoluble in $CHCl_3$.

(b) TFA (n mol%) was added to a solution of **84** in the corresponding solvent (1 ml/ 1 mmol) at r.t. The reaction mixture was left at r.t. or 60 °C for 24 or 5 hours. Then, the reaction mixture was concentrated to observe no reaction in all the attempts.

1st Attempt

TFA (n mol%): 20, **Solvent:** $PhCH_3$, **Temperature (°C):** 25, **Time (hours):** 24

2nd Attempt

TFA (n mol%): 10, **Solvent:** chloroform, **Temperature (°C):** 60, **Time (hours):** 5

Reductive elimination of 2-bromo-2-cyano-3-methoxypropionic acid (87) using zinc metal

The compound **87** (1 equiv.) was added to a suspension of zinc powder (n equiv.) in AcOH (10 mL/ 1 mmol of **87**) at r.t. The crude mixture was stirred at that temperature for 24 hours. Then, the reaction mixture was washed with concentrated NaCl solution, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated.

1st Attempt

Zn powder (n equiv.): 15, **Product:** 2-cyanopropionic acid **(98)**.

^{1}H-NMR ($CDCl_3$). δ: 3.63 (1 H, q, *J* 7.5 Hz, $CH_3CH(CN)CO_2H$) and 1.64 (3 H, d, *J* 7.5 Hz, $CH_3CH(CN)CO_2H$).

2nd Attempt

Zn powder (n equiv.): 5, **Product:** 2-cyanopropionic acid **(98)**.

3rd Attempt

Zn powder (n equiv.): 1, **Product:** 2-cyano-3-methoxypropionic acid **(99)**

^{1}H-NMR ($CDCl_3$). δ: 4.40 (1 H, dd, *J* 6.0 and 7.0 Hz, $-CH_2CH(CN)CO_2H$), 3.84 (dd, 1 H, *J* 7.0 and 10.6 Hz, $-CHHCH(CN)CO_2H$), 3.80 (1 H, dd, *J* 6.0 and 10.6 Hz, $-CHHCH(CN)CO_2H$) and 3.51 (3 H, s, CH_3O-).

^{13}C-NMR ($CDCl_3$). δ:165.6 ($-CO_2H$), 115.5 (-CN), 72.7 ($-OCH_2CH$), 59.1 (CH_3O-), and 24.54 (CH).

IR: 3259.12 (CO_2H), 2940.93, 2833.90, 2248.60 (CN), 1711.52 (C=O), 1457.93, 1400.07, 1378.9, 1201.44, 1120.4, 916.02 and 715.46 cm^{-1}

4th Attempt

Zn powder (n equiv.): 2, **Product:** mixture (27:73) of **98** and **99**.

^{1}H-NMR ($CDCl_3$). δ: 4.40 (1 H, dd, *J* 6.0 and 7.0 Hz, $-CH_2CH(CN)CO_2H$, **99**), 3.84 (dd, 1 H, *J* 7.0 and 10.6 Hz, $-CHHCH(CN)CO_2H$, **99**), 3.80 (1 H, dd, *J* 6.0 and 10.6 Hz, $-CHHCH(CN)CO_2H$, **99**), 3.63 (1 H, q, *J* 7.5 Hz, $CH_3CH(CN)CO_2H$, **98**), 3.51 (3 H, s, CH_3O-, **99**) and 1.64 (3 H, d, *J* 7.5 Hz, $CH_3CH(CN)CO_2H$, **98**).

Oxidation of ethyl 2-cyano-3-(4'-toluenesulfanyl)propanoate (54) with *m*-CPBA

A 70 % solution of *m*-CPBA (0.65 g, 2.61 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of **54** (0.59 g, 2.20 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was stirred at that temperature for 3 hours, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated to afford a mixture (95:5) of **ECA** and ethyl 2-cyano-3-(4'-toluenesulfonyl)propanoate **49**.

^{1}H-NMR ($CDCl_3$). δ: 7.83 (2 H, d, *J* 8.0 Hz, 2 x (*o*-C_6H_4-), **49**), 7.64 (2 H, d, *J* 8.0 Hz, 2 x (*m*-C_6H_4-), **49**), 7.00 (1 H, s, H̲HC=, **ECA**), 6.60 (1 H, s, H̲HC=, **ECA**), 4.31 (2 H, q, *J* 7.0 Hz, -OCH_2CH$_3$, **ECA**), 4.03 (1 H, dd, *J* 6.0 and 7.0 Hz, -SO_2CH_2CHCNCO_2Et, **49**), 3.83 (1 H, dd, *J* 6.0 and 14.5 Hz, -SO_2CHHCHCNCO_2Et, **49**), 3.59 (1 H, dd, *J* 7.0 and 14.5 Hz, -SO_2CHHCHCNCO_2Et, **49**), 2.44 (3 H, s, C$H_3C_6H_4$-, **49**) and 1.32 (3 H, t, *J* 7.0 Hz, -OCH_2CH_3, **ECA**).

Monitored oxidation of 2-cyano-3-(4'-toluenesulfanyl)propanoic acid (88) with *tert*-butyl hydroperoxide

In the presence of catalytic amount of vanadyl acetylacetonate ($VO(acac)_2$)

2.17M *tert*-butyl hydroperoxide (0.11 mL, 0.23 mmol) in 1,2-dichloroethane was added to a suspension of **88** (0.05 g, 0.22 mmol), $VO(acac)_2$ (0.003 g, 0.01 mmol) in $CDCl_3$ (2.2 mL) at r.t. The reaction was monitored by ^{1}H-NMR at different times until 24 hours after the starting.

Thus, the **% Conversion to CAA** at 3 hours was 48%.

(Integr **88**/ Integr $CDCl_3)_{to}$ = (3.03/ 1.00) = 3.03

^{1}H-NMR δ: 7.41 (2 H, integration = 6.31, *J* 8.0 Hz, 2 x (*o*-Ar-S-), **88**), 7.28 (1 H, integration = 1.00, s, $CDCl_3$), 7.17 (2 H, integration = 6.06, d, *J* 8.0 Hz, 2 x (*meta* (Ar-S-), **88**), 6.80 (1 H, bd, -CO_2H̲, **88**), 3.66 (1 H, integration = 2.53,

dd, *J* 6.5 and 8.0 Hz, -$SCH_2C\underline{H}(CN)CO_2H$, **88**), 3.43 (1 H, integration = 2.90, dd, *J* 6.5 and 14.0 Hz, -$SC\underline{H}HCH(CN)CO_2H$, **88**), 3.30 (1 H, integration = 2.90, dd, *J* 8.0 and 14.0 Hz, -$SCH\underline{H}CH(CN)CO_2H$, **88**) and 2.37 (3 H, integration = 10.80, s, $C\underline{H}_3Ph$, **88**).

Integr 88 = Average integration of 1 H in **88**

$$\text{Integr 88} = \frac{(6.31/2) + (6.06/2) + 2.53 + 2.90 + 2.90 + (10.80/2)}{6} = 3.03$$

(Integr **CAA**/ Integr $CDCl_3)_{3h}$ = (1.44/ 1.00) = 1.44

^{1}H-NMR δ: 7.28 (1 H, Integration = 1.00, s, $CDCl_3$), 7.19 (1 H, integration = 1.40, s, $\underline{H}HC=C(CN)CO_2H$, **CAA**) and 7.17 (1 H, integration = 1.49, s, $H\underline{H}C=C(CN)CO_2H$, **CAA**)

Integr **CAA** = Average integration of 1 H in **CAA**

$$\text{Integr } \mathbf{CAA} = \frac{1.40 + 1.49}{2} = 1.44$$

$$\textbf{(\% Conversion to CAA)}_{3h} = \frac{(\text{Integr } \mathbf{CAA}/ \text{Integr } CDCl_3)_{3h}}{(\text{Integr } \mathbf{88}/ \text{Integr } CDCl_3)_{to}} \times 100 = \frac{1.47}{3.03} \times 100 = 48\%$$

In the absence of vanadyl acetylacetonate ($VO(acac)_2$)

2.17M *tert*-butyl hydroperoxide (0.90 mL, 0.20 mmol) in 1,2-dichloroethane was added to a solution of **88** (0.04 g, 0.20 mmol) in $CDCl_3$ (2.2 mL) at r.t. The reaction was monitored by ^{1}H-NMR at different times until 24 hours after the starting.

Attempted regeneration of the double bond from 2-cyano-3-(4'-toluenesulfanyl)propanoic acid (88) using basic conditions

Diisopropylethyl amine (0.1 mL, 0.58 mmol) was added to a solution of **88** (0.13 g, 0.58 mmol) in $CHCl_3$ at r.t. The reaction was heated at 80 °C for 12 hours. Then, the reaction mixture was evaporated to afford 3-(benzoylthio)propionitrile **105**.

^{1}H-NMR δ: 7.38 (2 H, *J* 8.0 Hz, 2 x (*o*-C_6H_5S-)), 7.17 (2 H, d, *J* 8.0 Hz, 2 x (*m*-C_6H_5S-)), 3.08 (2 H, t, *J* 7.5 and 8.0 Hz, -$SC\underline{H}_2CH_2(CN)$), 2.57 (2 H, t, *J* 7.5 and 14.0 Hz, -$SCH_2C\underline{H}_2(CN)$) and 2.35 (3 H, s, $C\underline{H}_3Ph$).

Attempted regeneration of the double bond from 3-(*n*-butylsulfanyl)-2-cyanopropanoic acid (89) using methyl iodide

Methyl iodide (0.1 mL, 1.89) was added to **89** (0.3 g, 1.57 mmol) at r.t. The raction mixture was heated at 30 for 12 hours. Then, the reaction mixture was concentrated to observe no reaction.

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CHAPTER 4.

OTHER APPROACHES TO 2-CYANOACRYLIC ACID

CHAPTER 4.

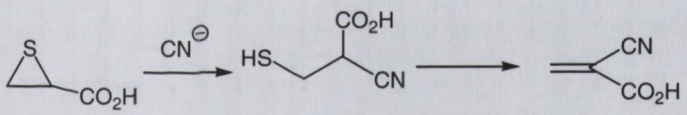
OTHER APPROACHES TO 2-CYANOACRYLIC ACID

In this chapter, three different groups of approaches to cyanoacrylate esters and 2-cyanoacrylic acid **1** are described. The first group includes approaches from thiirancarboxylic acid **2**, the second group includes approaches using palladium-assisted coupling reactions of alkyl α-haloacrylates and the third group includes approaches which involve the use of solid-phase organic synthesis.

4. 1. APPROACHES FROM THIIRANCARBOXYLIC ACID

Thiirancarboxylic acid **2** was investigated as an interesting precursor of cyanoacrylic acid **1** because of its possible conversion into 2-cyano-3-mercaptopropionic acid **3** by means of the opening of its episulfide ring with cyanide ion to give the intermediate **3**, followed by conversion of **3** into cyanoacrylic acid (**CAA**) **1** [Scheme 1].

Scheme 1

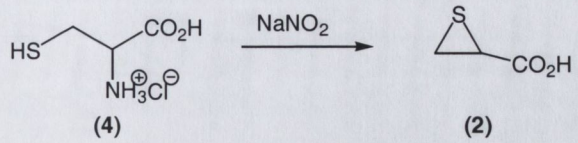


(2) (3) **CAA (1)**

4. 1. 1. Synthesis of thiirancarboxylic acid

Thiirancarboxylic acid **2** was synthesised followed a straightforward procedure which involved the reaction of cysteine hydrochloride **4** with sodium nitrite in the presence of glacial acetic acid [Scheme 2].[1]

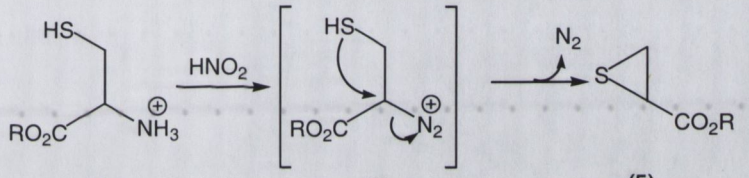
Scheme 2



(4) (2)

Stoodley *et al.* reported the first examples of optically active thiirancarboxylic acid derivatives **5** in the late 1970s.[1] The conversion in question was described by these authors as a matter of diazotization of the amino group of the cysteine ester **6**, followed by S_Ni expulsion of nitrogen from the diazotised thiol **7** [Scheme 3].

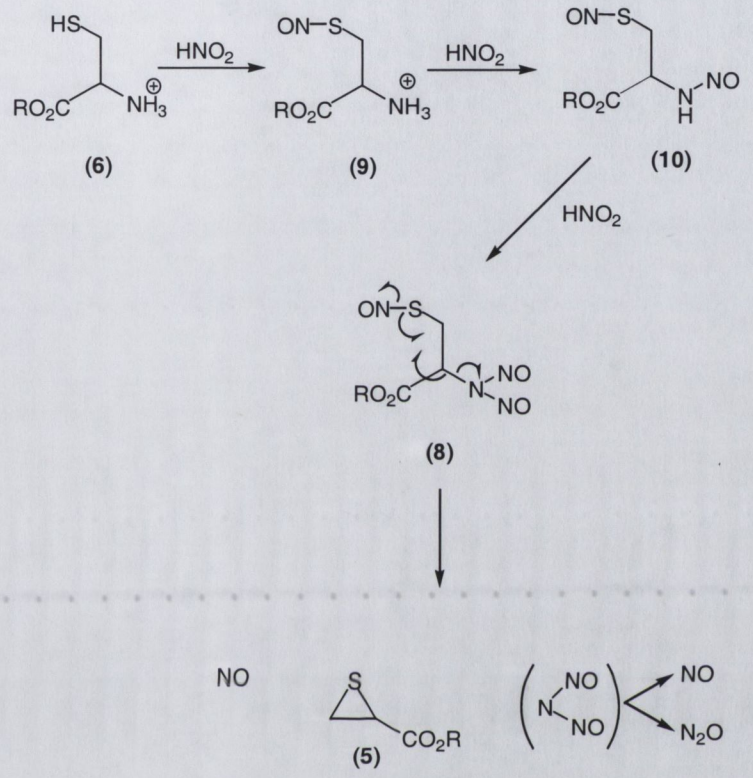
Scheme 3



(6) (7) (5)

However, the use of three moles of nitrite per mole of amine was required despite the fact that diazotization of the amine requires no more than 1 mole. In the early 1990s Owen *et al.* offered a plausible explanation for the use of a 3-fold excess of nitrite in the synthesis of thiirancarboxylic acid derivatives[2], speculating that formation of the dinitrosamine thionitrite **8** took place [Scheme 4].

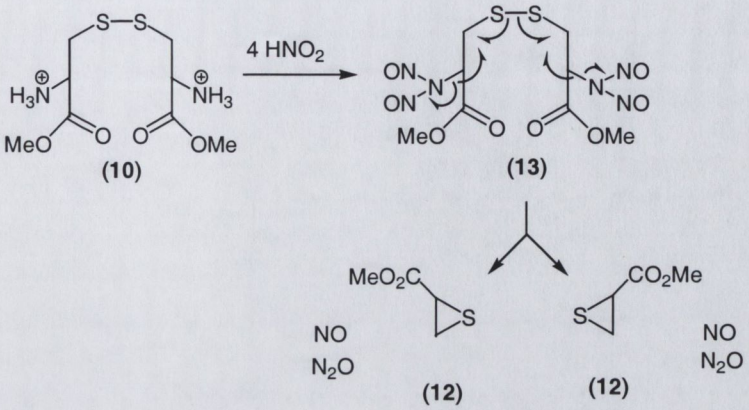
Scheme 4



Hence, the formation of the thionitrite **9** is followed by double nitrosation of the amino group to afford the compound **8**, which is ideally constructed for collapse by a intramolecular radical mechanism to yield one molecule of a thiirancarboxylic acid derivative **5,** two molecules of nitric oxide and one molecule of nitrous oxide.[2]

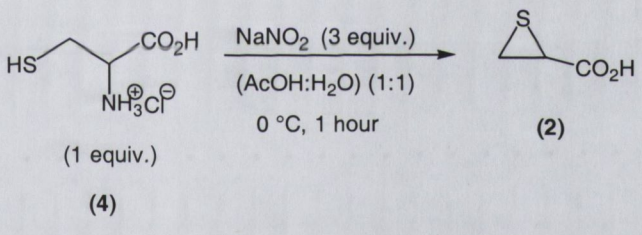
Owen *et al.* also reported the conversion of L-cystine dimethyl ester hydrochloride **11** into methyl thiirancarboxylate **12**, demonstrating that the thiol group is not essential for the formation of the episulfide and excluding pathways involving diazonium displacement.[2] The requirement for a 2-fold excess of nitrite can be explained in terms of the intermediate **13** [Scheme 5].

Scheme 5



The low yields obtained in the synthesis of thiirancarboxylic acid **2** were explained by Owen *et al.*[2] in terms of the polymerisation of **2**. In the present work similar results were obtained [Table 1].

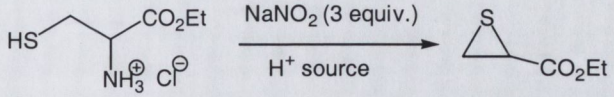
Table 1. Synthesis of thiirancarboxylic acid



Number of mmol of starting material (4)	Yield of 2 (%)
10	23
45	14

Owen *et al.* developed a procedure for the synthesis of ethyl thiirancarboxylate **14** involving anaerobic conditions[2] which raised the yield up to 80 % versus the recorded 40 % obtained under the usual aerobic conditions [Scheme 6].

Scheme 6



(1 equiv.)

(4)

(14)

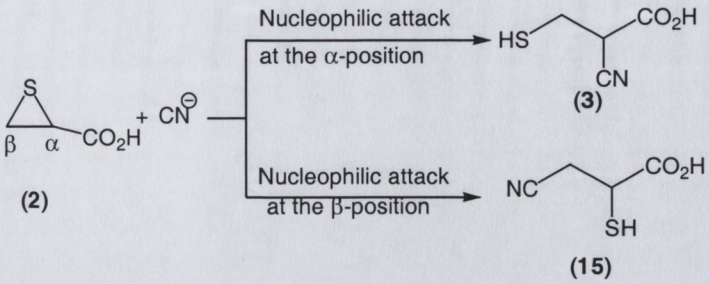
H^+ Source	Yield
deaerated HCl 1M	80
HCl 1M	40

Thus, Owen *et al.*[2] reasoned that a rapid polymerisation of thiirancarboxylic acid derivatives took place under the influence of nitrogen dioxide, a radical which is generally reactive toward electron-paired substrates[2], and which can be formed by the oxidation of the nitric oxide liberated in the deamination reaction. This assumption was proved by Owen *et al.*[2] when dissolved oxygen was inserted during the synthesis of **14** to result in the formation of much polymer.

4. 1. 2. Attempted ring-opening of thiirancarboxylic acid

The ring-opening of thiirancarboxylic acid **2** was intended using cyanide ion as nucleophile. Thus, the nucleophilic attack of cyanide on **2** depends on either electronic or steric factors. The regioisomer **3** will be the product obtained if nucleophilic attack takes place at the most electronically favoured α-position, and the regioisomer **15** will be the product obtained if the nucleophilic attack takes place at the less congested β-position [Scheme 7].

Scheme 7

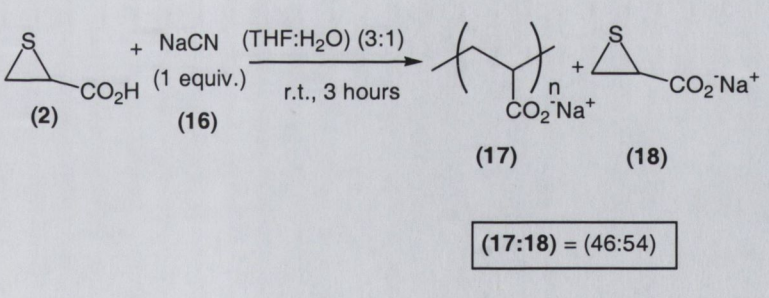


Hence, some studies on the ring-opening of thiirancarboxylic acid **2** with cyanide ion were carried out using both aqueous and non-aqueous conditions.

4. 1. 2. i. Attempted ring-opening reaction of thiirancarboxylic acid (2) by cyanide under aqueous conditions

Sodium cyanide was the reagent used as cyanide source for the ring-opening reaction in aqueous conditions. Hence, thiirancarboxylic acid **2** was reacted with sodium cyanide **16** (1 equiv.) in a 3:1 mixture of THF-H_2O to afford a mixture (46:54) of sodium *poly*(acrylate) **17** and sodium thiirancarboxylate **18** [Scheme 8]. Thiirancarboxylic acid **2** was recovered after acidification of the crude mixture and extraction with chloroform.

Scheme 8

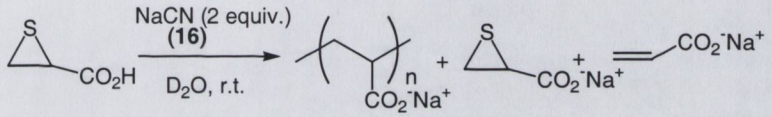


In fact, two equivalents of sodium cyanide **16** are required in order to execute the ring-opening reaction because the first equivalent is consumed to form sodium thiirancarboxylate **18**. This is insoluble in organic solvents (THF, ethyl acetate and chloroform). Hence, several tests were carried out in deuterated water (D_2O)

in order to dissolve the sodium salt **18** and to enable the use of NMR to monitor the opening reaction with respect to time.

The reaction of thiirancarboxylic acid **2** with sodium cyanide **16** (2 equiv.) in D_2O was carried out to eventually afford sodium *poly*(acrylate) **17** and traces of sodium acrylate **19** [Scheme 9].

Scheme 9

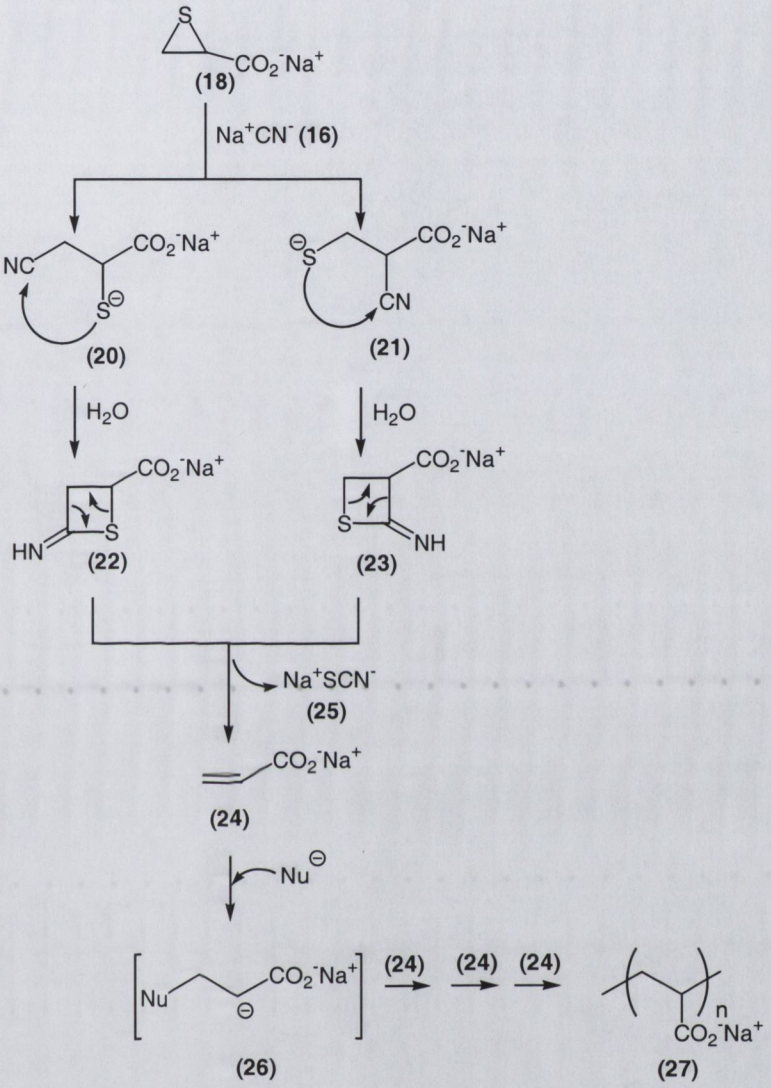


(2) **(17)** **(18)** **(19)**

Time (hours)	%conversion (17:18:19))
24	(68:26:6)
72	(94:0:6)

A possible mechanistic interpretation for the desulphuration process can be advanced in terms of the addition of sodium cyanide **16** to sodium thiirancarboxylate **18** to give the thiolate intermediates **20** or **21** . Reaction of thiolates with the cyano function of **20** and **21** could afford the four-membered ring intermediates **22** or **23**, which can eventually decompose to give sodium acrylate **24** and sodium isothiocyanate **25**. Then, the Michael addition of a nucleophile (for instance, water or sodium isothiocyanate itself) to the formed sodium acrylate **24** initiates its polymerisation *via* an anionic mechanism to afford sodium poly(acrylate) **27** [Scheme10].

Scheme 10



A test which supported the mechanism described in Scheme 10 was that carried out to prove the presence of sodium isothiocyanate in the reaction. Thus, a solution of Fe^{+3} was added to the reaction mixture in order to form the complex $[Fe(SCN)_n]^{3-n}$, whose presence is easily detected from the typical red colour of this complex in aqueous solution.[3]

When a 3% aqueous solution of Fe^{+3} in 0.2 M HCl solution was added to the crude mixture obtained by the reaction of thiirancarboxylic acid with 2 equivalents

of sodium cyanide after 24 hours to afford a black solid suspension in a red solution was observed.

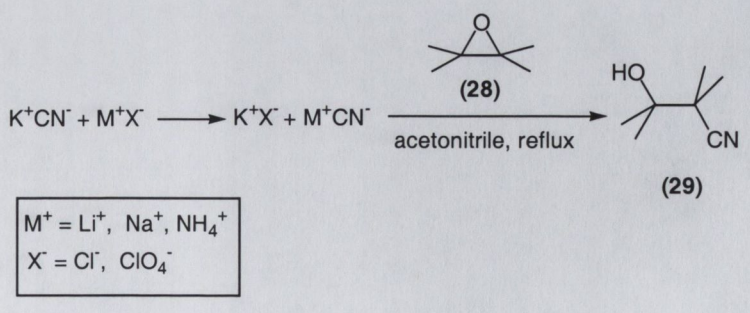
Another test which supports the intervention of cyanide ion in the desulphuration process is the reaction of thiirancarboxylic acid **2** with sodium bicarbonate (2 equiv.) which affords, after acidification and extraction of the crude mixture, the unchanged episulfide **2** quantitatively.

4. 1. 2. ii. Attempted ring-opening reaction of thiirancarboxylic acid using non-aqueous conditions

In view of the unsuccessful results obtained in the attempted opening of thiirancarboxylic acid **2** under aqueous conditions, attention was turned to non-aqueous conditions. These non-aqueous conditions imply the use of different cyanide sources because of the insolubility of alkaline-metal cyanides (NaCN, KCN) in most organic solvents.

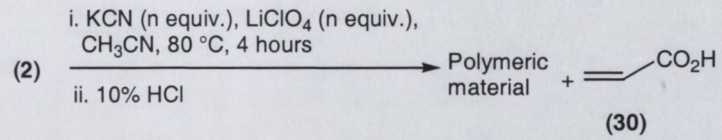
Chini *et al.*[4] reported the conversion of epoxides **28** into β-hydroxynitriles **29** under aprotic conditions using potassium cyanide with other metal salts under metathesis conditions in refluxing acetonitrile. The metal cyanides obtained from potassium cyanide in this way are presumably the reactive species because the addition of potassium cyanide to epoxides is ineffective in the absence of an appropriate salt [Scheme 11].

Scheme 11



Thus, in the present work, thiirancarboxylic acid **2** was reacted with potassium cyanide and lithium perchlorate in acetonitrile at reflux to afford polymeric material and traces of acrylic acid **30** [Scheme 12].

Scheme 12

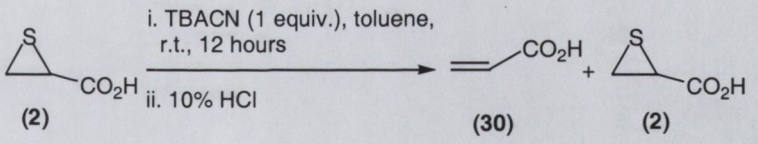


n = 1.5 or 3

Because solid suspensions were observed in these reactions, it was thought advisable to use cyanide sources more soluble in organic solvents. Therefore, tetrabutylammonium cyanide (TBACN) **31**, readily available from the reaction of tetrabutylammonium hydrogen sulfate with potassium cyanide[5], was used as a cyanide source.

Thiirancarboxylic acid **2** was reacted with TBACN (1 equiv.) in toluene at r.t. for 12 hours to afford, after aqueous work-up, a mixture (58:42) of acrylic acid **30** and unreacted thiirancarboxylic acid **2**, together with polymeric material left in the aqueous layer [Scheme 13].[6]

Scheme 13



n = 1.5 or 3

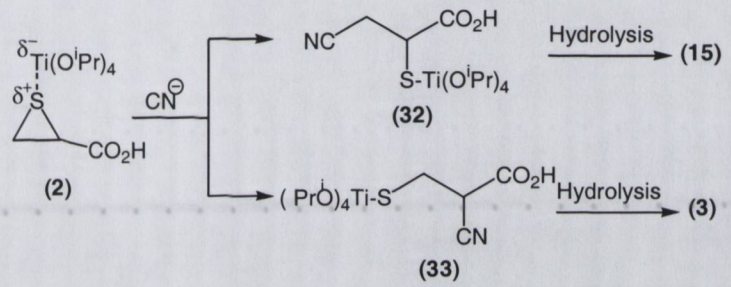
% Conversion (30:2) = (58:42)

Complete conversion of **2** to acrylic acid **30** and polymeric material took place when the reaction was carried out at 92 °C and left for 12 hours. Thus, the intramolecular participation of the cyano group in the desulphuration process is

speculated again to afford acrylic acid **30** which undergoes polymerisation [Scheme 10].

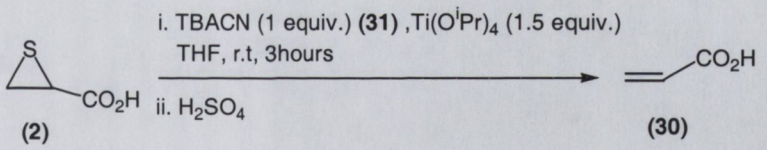
In order to circumvent the desulphuration process, the ring-opening reaction of thiirancarboxylic acid **2** in the presence of stochiometric titanium isopropoxide was attempted. Thus, it was anticipated that formation of **32** and **33** would prevent the intramolecular reaction of thiolate anion with the cyano group. These complexes **32** and **33** could later be hydrolysed and converted into the desired **3** and **15** [Scheme 14].

Scheme 14



However, the reaction of thiirancarboxylic acid **2** with TBACN (2 equiv.) and titanium isopropoxide (1.5 equiv.) in anhydrous THF again afforded acrylic acid **22** [Scheme 15].[7]

Scheme 15



From the above results it was concluded that it was impossible to obtain intermediates **3** or **15** because in all cases (those involving either aqueous or non-aqueous conditions) a desulphuration-polymerisation process was observed when the ring-opening of thiirancarboxylic acid **2** by cyanide anion was attempted.

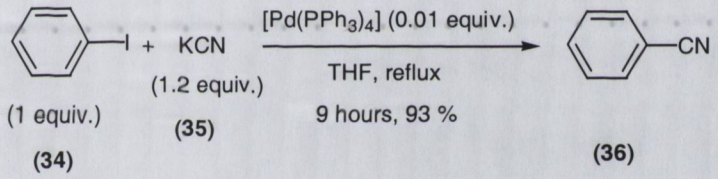
4. 2. APPROACHES UTILISING PALLADIUM-ASSISTED COUPLING REACTIONS

Palladium(0) catalyses the replacement of vinylic and aromatic halides by cyanide, sulfide, carboxylate and phosphonate ions.[8]

4. 2. 1. Palladium-assisted coupling reactions of iodobenzene with cyanide anion

The palladium-catalysed reaction of iodobenzene **34** and potassium cyanide **35** using palladium *tetrakis*(triphenylphosphine) [$Pd(PPh_3)_4$] as catalyst is reported in the literature[8] to give benzonitrile **36** in good yield (93 %) [Scheme 16].

Scheme 16

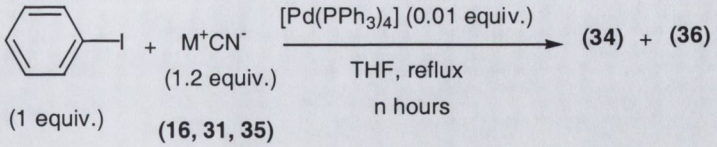


(1 equiv.)
(34)

(36)

This coupling reaction was repeated to check its reproducibility using sodium cyanide as nucleophile. There was no reaction. In a second attempt recrystallised potassium cyanide **16**[9] was used as nucleophile to afford a mixture (57:43) of iodobenzene **34** and benzonitrile **36**. The percentage of conversion to benzonitrile **36** (43 %) was small compared to the yield (93 % after purification) reported in the literature.[8] As incomplete solubilities were observed in these cyanation reactions, other cyanide sources were considered in order to improve the solubility in organic solvents. However, when TBACN was used as nucleophile only unchanged iodobenzene **34** was observed [Table 2].

Table 2. Cyanation reaction of iodobenzene assisted by palladium



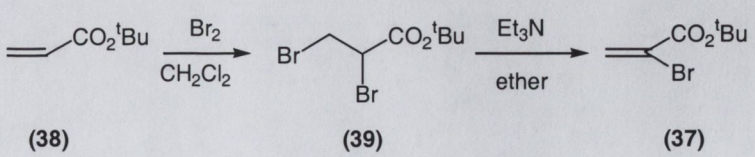
M^+CN^- (n equiv.)	Number	Time (n hours)	%Conversion (34:36)
Na^+CN^- (1.2 equiv.)	**16**	9	(100:0)
K^+CN^- (1.2 equiv.)	**35**	9	(57:43)
$(Bu)_4N^+CN^-$ (1 equiv.)	**31**	16	(100:0)

4. 2. 1. Attempted palladium-assisted coupling reaction of *tert*-butyl 2-bromo-2-propenoate

Despite the poor conversion of iodobenzene **34** to benzonitrile **36** (43%) using potassium cyanide **35** as cyanide source, the same methodology was tried for the coupling reaction of *tert*-butyl 2-bromo-2-propenoate **37** with potassium cyanide.

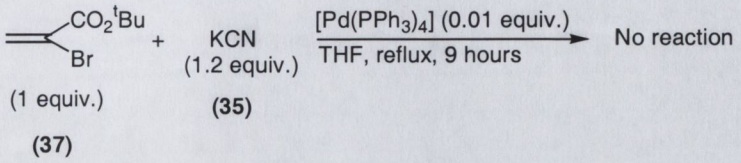
The compound **37** is readily available from a sequence of two steps which involves the bromination of the double bond of *t*-butyl acrylate **38** followed by dehydrobromination of **39** using triethylamine [Scheme 17].[10]

Scheme 17



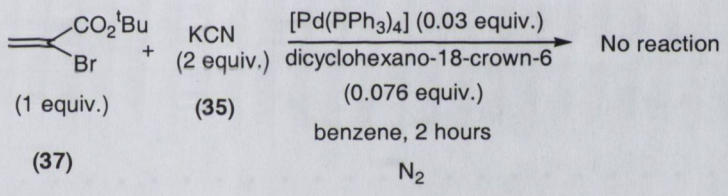
The compound **37** was reacted with recrystallised potassium cyanide **35** in the presence of the palladium catalyst but no reaction took place [Scheme 18].

Scheme 18



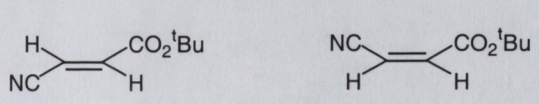
Yamamura *et al.*[11] reported the conversion of vinyl halides into the corresponding nitriles in the presence of catalytic amounts of the same palladium(0) complex and a crown ether. Thus, the compound **37** was reacted with potassium cyanide and palladium(0) catalyst in the presence of dicyclohexano-18-crown-6 but no reaction was again observed [Scheme 19].

Scheme 19



TBACN was used as another cyanide source, this time in the absence of crown ether, to give a mixture of mostly polymeric material, traces of unreacted **37** and the (*E*)- and (*Z*)-isomers of *t*-butyl 3-cyano-2-propenoate **40** and **41** [Figure 1].

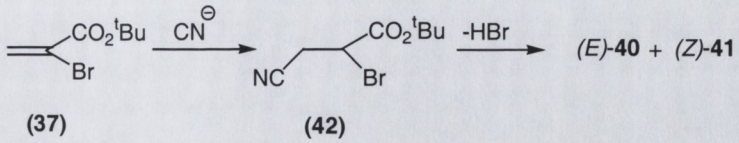
Figure 1



(40) **(41)**

The formation of **40** and **41** probably results from the initial Michael addition of cyanide to **37** to yield **42**. β-Elimination of hydrogen bromide from **42** would afford **40** and **41** [Scheme 20].

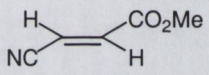
Scheme 20



(37) **(42)**

The synthesis of methyl (*E*)-3-cyanoacrylate **43** from the reaction of methyl α-chloroacrylate with sodium cyanide in a mixture of acetone and water has been reported in the literature [Figure 2].[12]

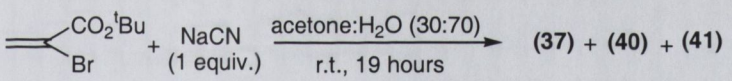
Figure 2



(43)

When *t*-butyl 2-bromo-2-propenoate **37** was reacted under the same conditions with sodium cyanide **16** in acetone-water there was obtained a mixture (65:20:15) of *t*-butyl (*E*)-3-cyano-2-propenoate **40,** *tert*-butyl (*Z*)-3-cyano-2-propenoate **41** and unreacted **37** [Scheme 21].

Scheme 21

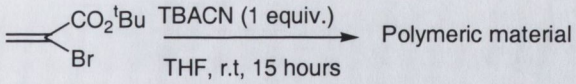


(37) **(16)**

(37:40:41) = (15:65:20)

The reaction of *t*-butyl 2-bromo-2-propenoate **37** with TBACN in THF was tried in the absence of palladium catalyst in order to determine if the polymerisation noted above took place from the Michael addition adduct or from the expected final product of a coupling reaction with cyanide. The same polymeric material as that previously observed in the catalysed reaction with palladium was obtained and thus, it may be concluded that a coupling reaction with cyanide does not take place and that only Michael addition is observed [Scheme 22].

Scheme 22



(37)

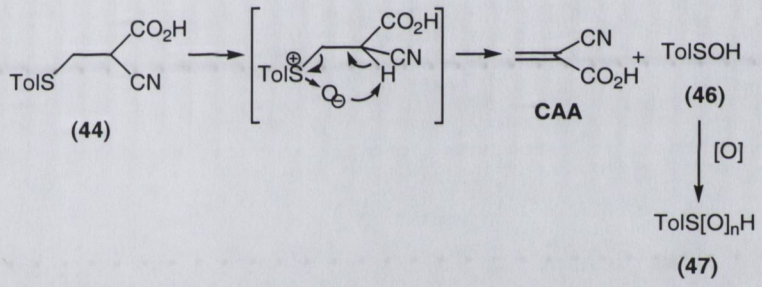
The conclusion that can be drawn from the above results is that the coupling of cyanide with *tert*-butyl 2-bromopropanoate **37** was never observed, and that either no reaction or the conjugate addition of cyanide ion to the compound **37** occurred.

4. 3. APPROACHES *VIA* SOLID-PHASE ORGANIC SYNTHESIS

Solid-phase organic synthesis refers to synthesis in which the starting material and synthetic intermediates are linked to an insoluble material (support), which enables the facile separation of the intermediates or products from reactants and solvents.

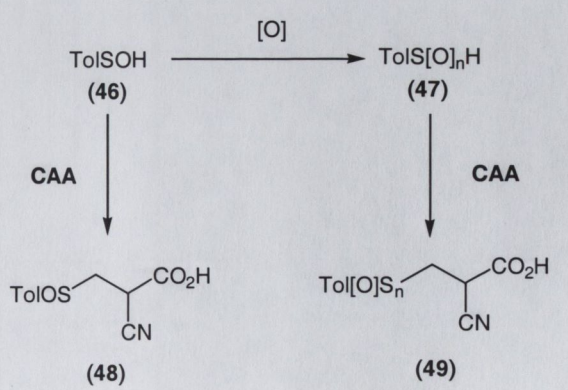
One of the problems found in this project (Chapter 3) has been the difficult separation of the reaction by-products obtained from deprotection reactions of the double bond of 2-cyanoacrylates. Thus, the oxidation-elimination reaction of the sulfide **44** afforded **CAA** and sulfur compounds **46-47** in different oxidation states [Scheme 23].

Scheme 23



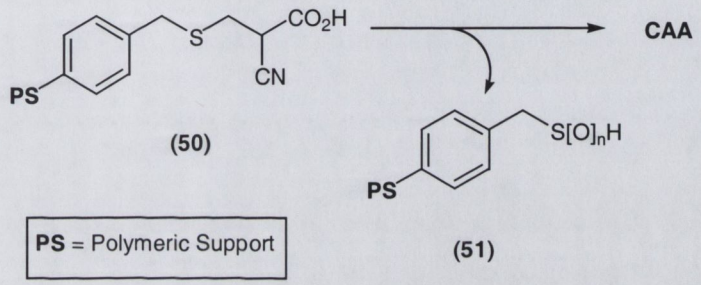
The impossibility of separating these reaction by-products eventually led to their Michael addition to the double bond of **CAA** [Scheme 24].

Scheme 24



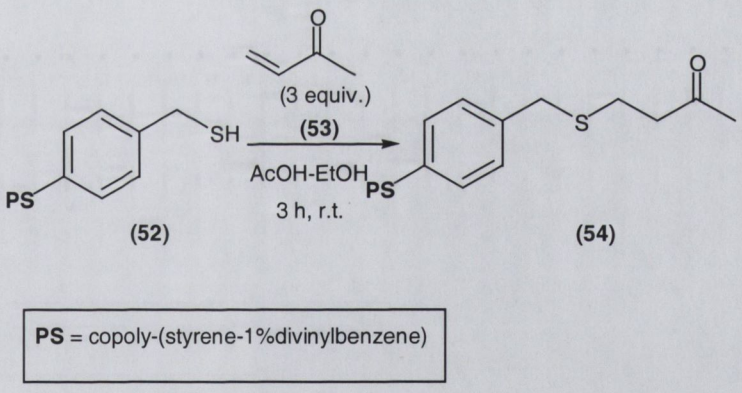
This problem might be circumvented if an alkyl 2-cyanoacrylate were attached to a thiol-functionalised resin to afford, after hydrolysis, the adduct **50**. Thus, an oxidative elimination reaction of **50** could be carried out to afford **CAA**, easily soluble in organic solvents, and the oxidised insoluble polymeric support **51**, which could be removed by filtration [Scheme 25].

Scheme 25



Barco *et al.*[13] have reported the Michael addition of the solid-anchored thiol **52** to 3-butenone **53** to afford the sulfide **54** [Scheme 26].

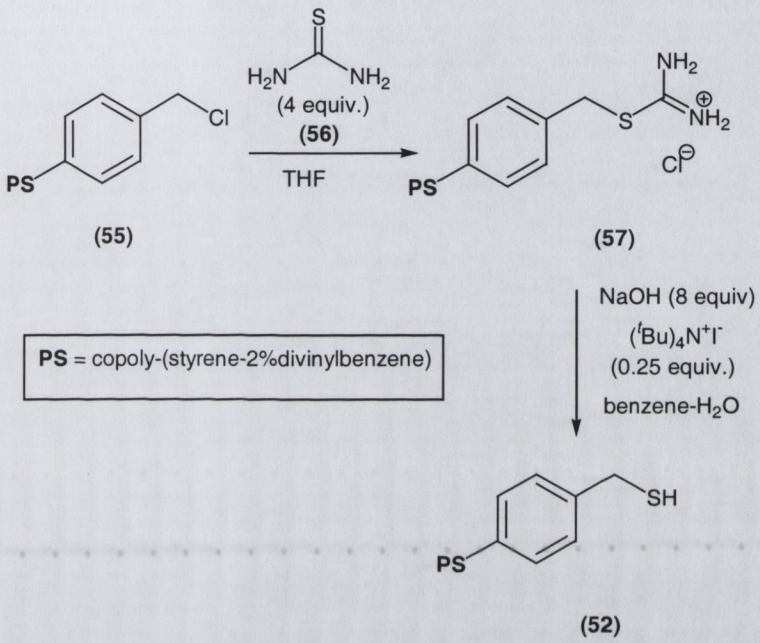
Scheme 26



In the present work the polymer-supported reagent **52** was prepared from Merrifield's (chloromethyl copoly-(styrene-2% divinylbenzene) resin **55** following a procedure reported by Fréchet *et al.*[14] Treatment of **55** with thiourea **56** gives the isothiouronium chloride **57**. Reaction of **57** with sodium hydroxide under an inert atmosphere led to the formation of **52** [Scheme 27]. Inert atmosphere is essential

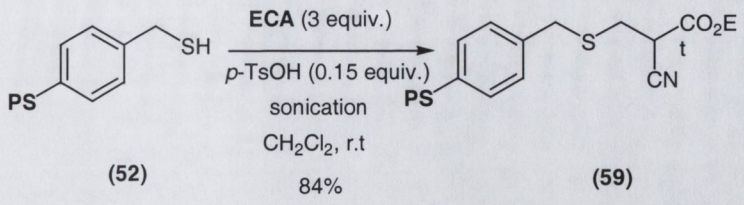
in the formation of **52** because it is easily oxidised to the derived disulfide in the presence of atmospheric oxygen.

Scheme 27



The resin **52** prepared from Fréchet's procedure was reacted with ethyl 2-cyanoacrylate (**ECA**) **58** to afford the resin **59** with a load of 1.67 mequiv. of **ECA**/g *versus* the potential load of 2 mequiv./g of the starting material resin **52**. This figure, which was obtained from combustion analysis, means an 84% yield for the coupling with **ECA** [Scheme 28].

Scheme 28



(52) (59)

PS = copoly-(styrene-1%divinylbenzene)

With the resin **59** in hand a hydrolysis - oxidative elimination process was attempted in order to obtain **CAA** and the oxidised insoluble polymeric support **51**, which could be removed by filtration [Scheme 25].

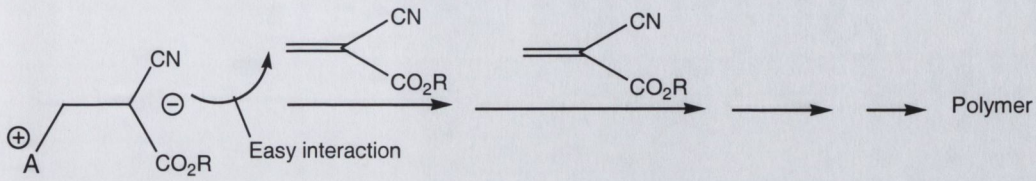
For this purpose, the resin **59** was stirred in 1M H_2SO_4 solution for 26 hours at 90 °C. Then, the resin was filtered, dried and stirred with 1 equivalent of *tert*-butylhydroperoxide in 1,2-dichloroethane to afford, after filtration of the resin and evaporation of the filtrate, **ECA** in 12% yield.

Due the unsuccessful hydrolysis of **59** and the low yield obtained (12 %) in the reductive elimination it was decided to abandon this methodology and explore other approaches which involve the use of solid phase methods.

Polymerisation is another problem which could be circumvented by the use of solid phase supports. Thus, the polymerisation of 2-cyanoacrylate esters, attached to a polymeric support by an ester-bond, would not be likely because of the non-linear arrangement of the 2-cyanoacrylate monomers linked to the spherical-shaped polymeric support. Additionally, the low "concentration" of reactive linkers in these polymeric supports imply long distances between the molecules attached individually to them, making intermolecular reactions difficult [Scheme 29].

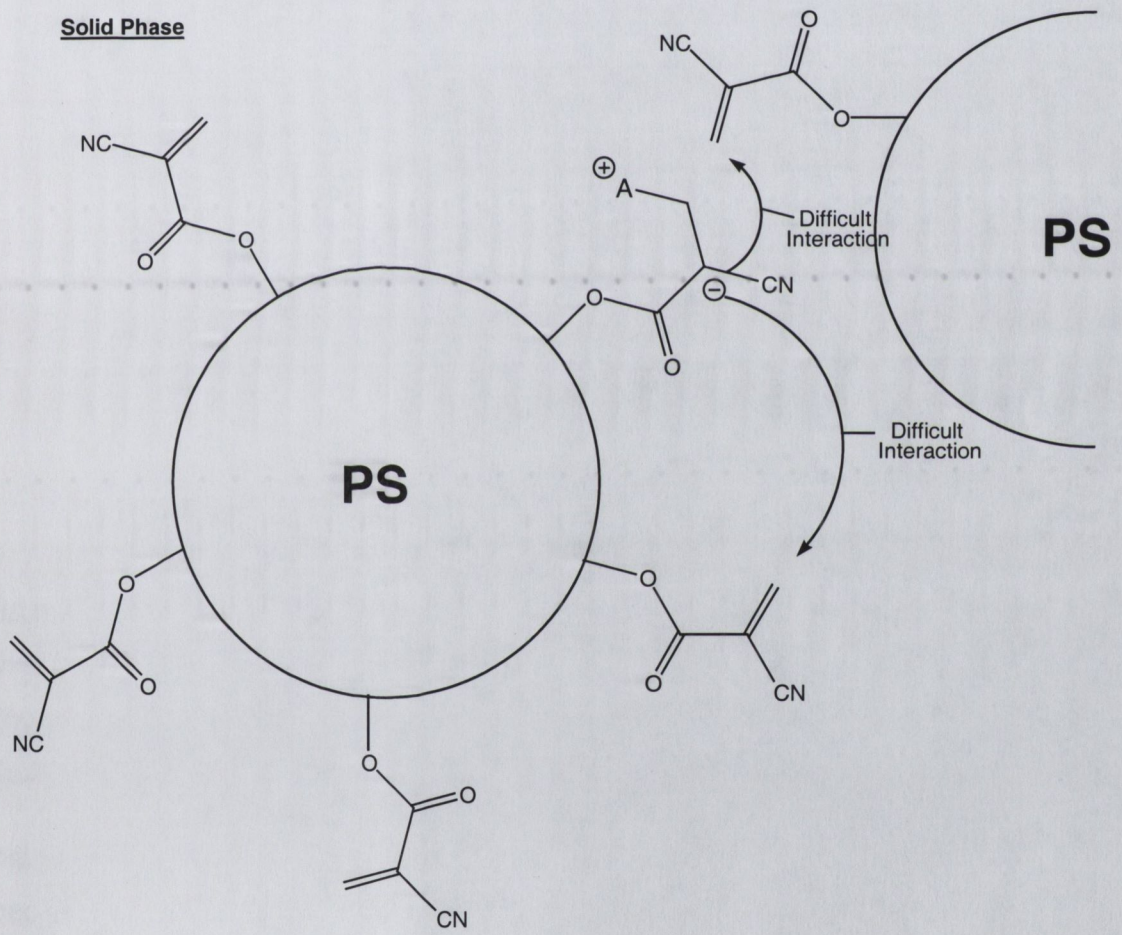
Scheme 29

Polymerisation under Homogenous Conditions



A = Initiator

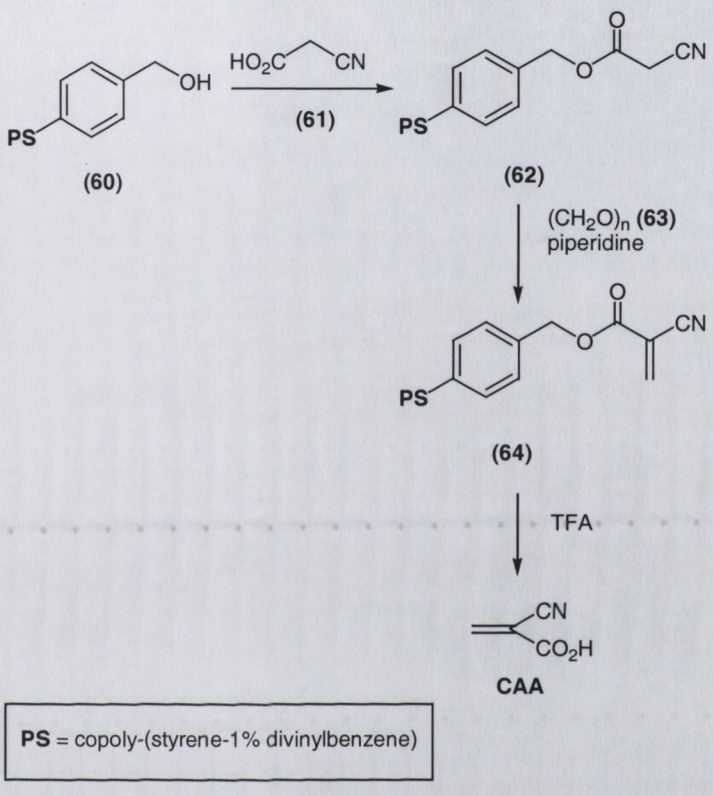
Solid Phase



A = Initiator

Thus, it was intended to synthesise monomeric 2-cyanoacrylates as benzylic esters with hydroxylic polymeric supports. Then, these monomeric units might be removed from the solid support *via* protonolysis to give **CAA** [Scheme 30].

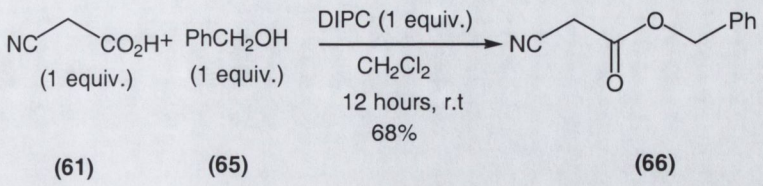
Scheme 30



Esterifying cyanoacetic acid **61** with (hydroxymethyl)polystyrene resin **60** would give the ester **62**. Treatment of **62** with paraformaldehyde **63** and piperidine in a Knoevenagel reaction would give the 2-cyanoacrylate ester **64**. This might be cleaved to give **CAA** using trifluoroacetic acid.

Initially, the model esterification of 2-cyanoacetic acid **61** with benzyl alcohol **65** mediated by diisopropylcarbodiimide (DIPC) was attempted, and afforded benzyl 2-cyanoacetate **66** in good yield (68 %)[15] [Scheme 31].

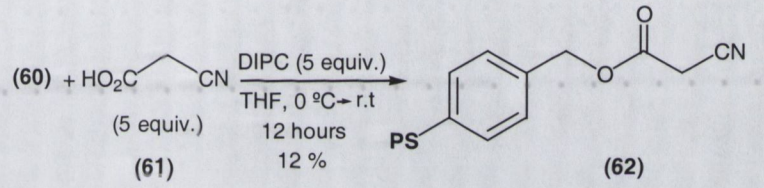
Scheme 31



(61) **(65)** **(66)**

DIPC was added to a mixture of (hydroxymethyl)polystyrene resin **60** and 2-cyanoacetic acid **61** in THF at 0 °C to afford, after several washings, the resin **62** with a load of 0.2 mequiv. cyanoacetic acid/g *versus* the potential load of 1.7 mequiv./g of the starting material resin **60**. These figures mean a 12 % yield for the coupling of cyanoacetic acid with the resin **60** [Scheme 32].

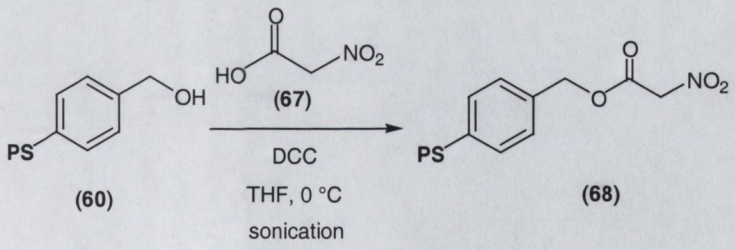
Scheme 32



(61) **(62)**

Sylvain *et al.*[16] had reported the attachment of nitroacetic acid **67** to hydroxylated Merrifield resin **60** using DCC (dicyclohexylcarbodiimide) as mediator in the presence of ultrasound to afford **68** [Scheme 33].

Scheme 33



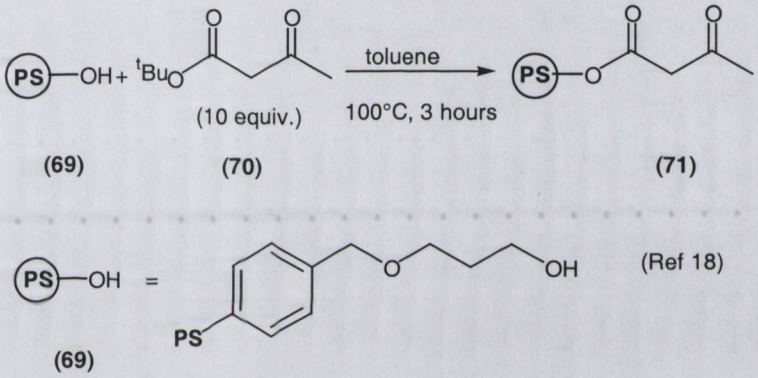
(60) **(68)**

PS = copoly-(styrene-2% divinylbenzene)

Accordingly, esterification of 2-cyanoacetic acid **61** with the resin **60** was tried again under sonication conditions to afford the resin **62** with a load of 1.67 mequiv. cyanoacetic acid./g *versus* the potential load of 1.7 mequiv./g of the starting material resin **60**. These figures mean a 98 % yield for the coupling of cyanoacetic acid with the resin **60**.

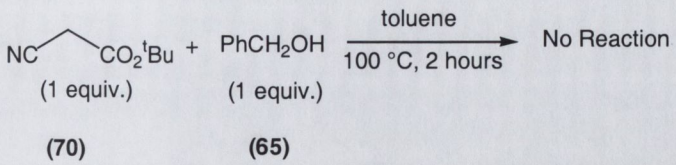
Tietze *et al.* reported the transacetoacetylation of the spacer-modified (toluene swollen) polystyrene-resin **69** with a 10-fold excess of *tert*-butyl acetoacetate **70** at 100 °C for 3 hours to afford the polymer-bound β-ketoester **71** [Scheme 34].[17]

Scheme 34



In the present work, the model transesterification of *t*-butyl cyanoacetate **70** with benzyl alcohol **65** was attempted following a method described by Witzeman *et al.*[19] This involves the preparation of either acetoacetates or acetoacetamides by heating at 100-105 °C a solution of *t*-butyl acetoacetate and the corresponding nucleophile (alcohol or amine) in a flask equipped with a distillation column and still head. When these conditions were applied to *tert*-butyl cyanoacetate and benzyl alcohol **65** only starting materials were detected after the reaction mixture had been heated at 100 °C for 20 hours [Scheme 35].

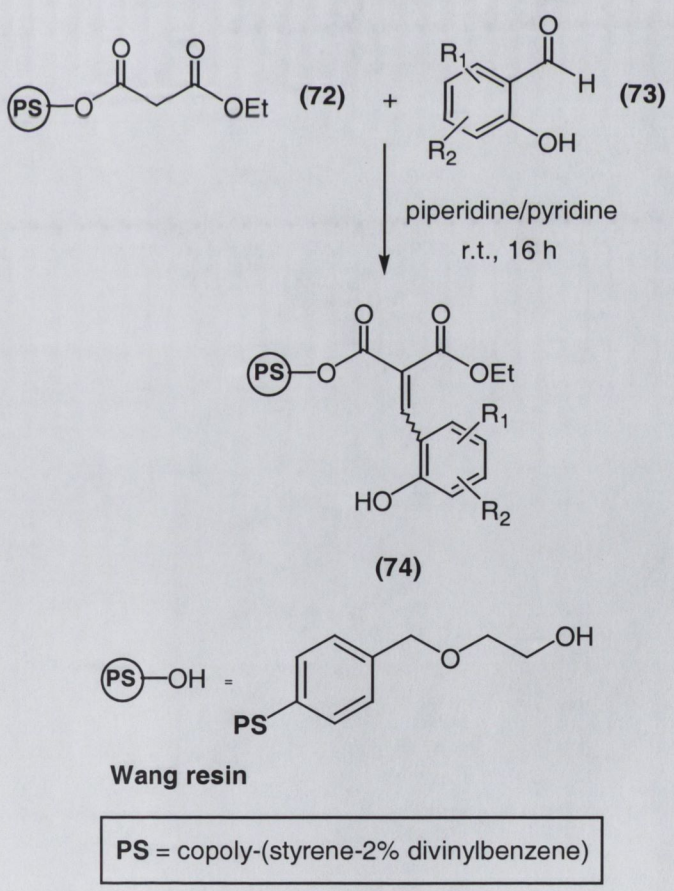
Scheme 35



Due the negative result obtained in the attempted transesterification in homogenous mixture it was decided not to carry out this reaction in the solid phase.

Watson *et al.* reported the Knoevenagel condensation reaction between Wang resin-bound ethyl malonate **72** with *o*-hydroxyarylaldehydes **73** catalysed by piperidine in pyridine to afford the resin **74** [Scheme 36].[20]

Scheme 36



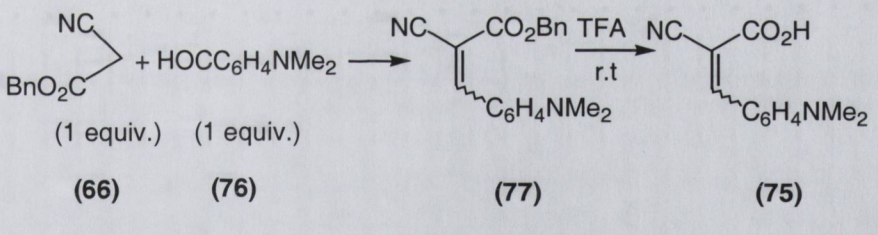
PS = copoly-(styrene-2% divinylbenzene)

In the present work the Knoevenagel condensation reaction between the hydroxylated Merrifield's resin-bound 2-cyanoacetic acid **62** and paraformaldehyde **63** was attempted using the methodology reported by Watson but no organic-soluble material was observed after cleavage with TFA.

As Watson's methodology uses the Wang resin for the Knoevenagel condensation reactions it was decided to check the feasibility of using the resin **62** in this reaction. For this purpose, it was necessary to choose a reliable two-step reaction which proceeds in homogenous conditions and which involves Knoevenagel condensation of benzyl 2-cyanoacetate **66** with an aldehyde of interest followed by the cleavage of the benzyl ester and then to attempt the same methodology with the resin **62.**

Thus, the synthesis of 2-cyano-3-(*p*-dimethylaminophenyl)propionic acid **75** was carried out using a straightforward procedure which involves Knoevenagel condensation of benzyl 2-cyanoacetate **66** with *p*-dimethylaminobenzaldehyde[22] followed by cleavage of the benzyl ester function of **77** with TFA[23] [Scheme 37].

Scheme 37



(1 equiv.) (1 equiv.)

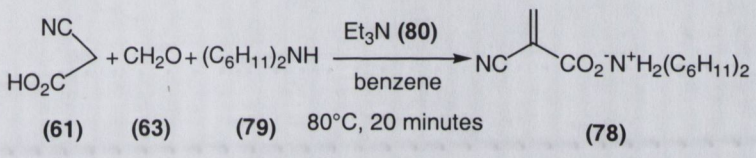
(66) **(76)** **(77)** **(75)**

The Knoevenagel condensation reaction of the hydroxylated Merrifield's resin-bound 2-cyanoacetic acid **62** with (*p*-dimethylamino)benzaldehyde **76** followed by cleavage of the benzyl ester function with TFA was attempted using the same conditions employed for the homogenous synthesis described above but no reaction was observed.

The conclusion that can be drawn from the above results is that it is difficult to carry out Knoevenagel condensation reactions with the resin **62**. To date, all successful Knoevenagel condensation reactions reported in the literature required the use of a resin with spacer such as the Wang resin. Accordingly, steric hindrance may be an important factor.

As previously described in Chapter 2 the synthesis of dicyclohexylammonium 2-cyanoacrylate **78** was reported by Krawczyk[24] who reacted 2-cyanoacetic acid **61** with paraformaldehyde **63**, dicyclohexylamine **79** and triethylamine **80** as catalyst [Scheme 38].

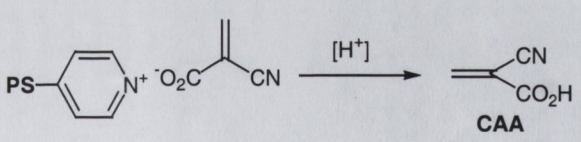
Scheme 38



(61) **(63)** **(79)** **(78)**

Thus, it was thought it might be possible to use the same methodology to synthesise **CAA** as its ammonium salt with *poly*(4-vinylpyiridine) **81**. The role of the *poly*(4-vinylpyridine) (PVP) **82** is to act as a polymeric amine which should afford a non-polymerisable salt **81**. The acid **CAA** might then be easily liberated from this salt by titration with a strong acid followed by removal of the insoluble pyridinium salt by filtration [Scheme 39].

Scheme 39

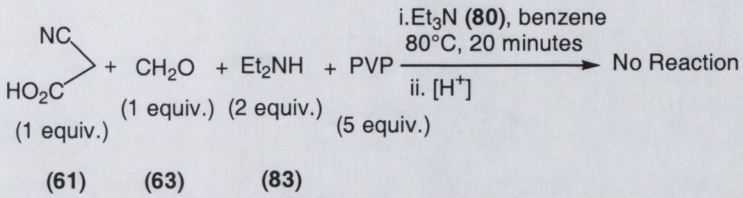


(81)

When PVP was reacted with 2-cyanoacetic acid **61**, paraformaldehyde **63**, diethylamine **83** and triethylamine **80** in benzene, cyanoacetic acid **61** and paraformaldehyde **63** were the only species observed after titrating the crude

insoluble polymer with acid (1M H_2SO_4 or 1M HCl) and extracting with EtOAc [Scheme 40]

Scheme 40



Although **CAA** was not obtained by the use of solid phase methods the conclusion that can be drawn is that this area is opened to more attempts for the synthesis of **CAA.** Thus, the development of a hydrolysis – oxidative elimination process and the use of resins with spacers in Knoevenagel condensation reactions are two routes should be further explored.

4. 4. EXPERIMENTAL PART

The same spectroscopic and purification techniques mentioned at the beginning of the experimental part of Chapter 2 were followed in this section.

APPROACHES FROM THIIRANCARBOXYLIC ACID (2)

Thiirancarboxylic acid (2)[1]

Sodium nitrite (2.07 g, 30 mmol) was added in one portion to a solution of the hydrochloride cysteine **4** (1.76 g, 10 mmol) in water (25 mL) and glacial acetic acid (25 mL) at 0 °C. The solution developed a deep red colour which gradually faded. After 1 hour, the pale red mixture was acidified with concentrated hydrochloric acid and extracted with chloroform (3 x 15 mL). Evaporation of the dried ($MgSO_4$) organic layer with several additions of benzene, in order to azeotrope the acetic acid, afforded a yellow syrup (0.24 g, 23 %) which was purified by distillation at 0.1 mm Hg to yield thiirancarboxylic acid **2** (0.02 g) as yellow viscous liquid.

^{1}H-NMR ($CDCl_3$) δ: 11.62 (1 H, bs, -CO_2H), 3.39 (1 H, dd, *J* 5.0 and 6.0 Hz, HO_2C-CHCH_2), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, -CHHCHCO_2H) and 2.69 (1 H, dd, *J* 1.0 and 6.0 Hz, -CHHCHCO_2H).

^{13}C-NMR ($CDCl_3$) δ: 177.9 (CO_2H), 27.8 (CH) and 23.1 (CH_2).

IR: 3089.3, 2635.9, 2552.2, 1714.3 (CO_2H), 1419.5, 1279.4, 1230.5, 1081.0, 1054.7, 922.8 and 847.4 cm^{-1}.

Attempted opening of thiirancarboxylic acid (2) using aqueous conditions

1st Attempt.

A solution of sodium cyanide **16** (0.33 g, 6.8 mmol) in water (2 mL) was added to a solution of thiirancarboxylic acid **2** (0.70 g, 6.8 mmol) in THF (6 mL) at r.t. The resulting mixture was left at r.t. for 3 hours and then it was concentrated to afford a colourless oil which was identified by ^{1}H-NMR as a mixture (46:54) of *poly*(sodium acrylate) **17** and sodium thiirancarboxylate **18**.

^{1}H-NMR (D_2O) δ: 3.49 (1 H, bd, *poly* (Na^+ ^-O_2C-C<u>H</u>CH_2), **17**), 3.29 (1H, dd, *J* 5.0 and 6.0 Hz, Na^+ ^-O_2C-C<u>H</u>CH_2, **18**), 2.95 (2 H, bd, *poly* (Na^+ ^-O_2C-CHC<u>H</u>$_2$), **17**) and 2.61 (2 H, t, *J* 5.5 Hz, Na^+ ^-O_2C-CHC<u>H</u>$_2$, **18**).

^{13}C-NMR (D_2O) δ: 177.7 (<u>C</u>$O_2^-Na^+$, **18**), 175.0 (*poly* (<u>C</u>$O_2^-Na^+$), **18**), 50.1 (*poly* (<u>C</u>H), **17**), 35.2 (*poly* (<u>C</u>H_2), **17**), 31.8 (<u>C</u>H, **18**) and 23.4 (<u>C</u>H_2, **18**).

Thiirancarboxylic acid **2** was recovered after acidification of the crude mixture with 1 M HCl solution and extraction with chloroform.

^{1}H-NMR ($CDCl_3$) δ: 11.62 (1 H, bs, -CO_2<u>H</u>), 3.39 (1 H, dd, *J* 5.0 and 6.0 Hz, HO_2C-C<u>H</u>CH_2), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, -C<u>H</u>HCH-CO_2H) and 2.69 (1 H, dd, *J* 1.0 and 6.0 Hz, -CH<u>H</u>CH-CO_2H).

2nd Attempt:

A solution of sodium cyanide **16** (0.18 g, 3.54 mmol) in D_2O (2.5 mL) was added to 0.18 g (1.77 mmol) of thiirancarboxylic acid **2** at r.t. After 24 hours, the reaction mixture was monitored by NMR to afford a mixture (68:26:6) of *poly*(sodium acrylate) **17**, sodium thiirancarboxylate **18** and sodium acrylate **19**.

^{1}H-NMR (D_2O) δ: 6.19 (1 H, dd, *J* 10.5 and 17.6 Hz, CH_2=C<u>H</u>-$CO_2^-Na^+$, **19**), 6.07 (1 H, d, *J* 17.6 Hz, *trans*-C<u>H</u>H=C$HCO_2^-Na^+$, **19**), 5.72 (1 H, dd, *J* 10.5 Hz, *cis*-CH<u>H</u>=C$HCO_2^-Na^+$, **19**), 3.49 (1 H, bd, *poly* (Na^+ ^-O_2C-C<u>H</u>CH_2), **17**), 3.29 (1H,

dd, *J* 5.0 and 6.0 Hz, Na^+ ^-O_2C-C<u>H</u>CH_2, **18**), 2.95 (2 H, bd, *poly* (Na^+ ^-O_2C-CHC<u>H</u>$_2$), **17**) and 2.61 (2 H, t, *J* 5.5 Hz, Na^+ ^-O_2C-CHC<u>H</u>$_2$, **18**).

A few drops of 0.3% Fe^{+3} aqueous solution in 0.2 M HCl solution were added to 0.5 mL of this crude mixture (0.5 mL) to afford a black solid suspension in red solution.

After 72 hours the reaction mixture was monitored again to afford a mixture (90: 10) of *poly*(sodium acrylate) **17** and sodium acrylate **19**.

^{1}H-NMR (D_2O) δ: 3.49 (1 H, bd, *poly* (Na^+ ^-O_2C-C<u>H</u>CH_2), **17**), 3.29 (1H, dd, *J* 5.0 and 6.0 Hz, Na^+ ^-O_2C-C<u>H</u>CH_2, **19**), 2.95 (2 H, bd, *poly* (Na^+ ^-O_2C-CHC<u>H</u>$_2$), **17**) and 2.61 (2 H, t, *J* 5.5 Hz, Na^+ ^-O_2C-CHC<u>H</u>$_2$, **19**).

3rd Attempt

A solution of sodium bicarbonate (0.13 g, 1.6 mmol) in D_2O (1 mL) was added to 0.08 g (0.8 mmol) of thiirancarboxylic acid **2** at r.t. After 5 minutes, the reaction mixture was monitored by NMR to afford quantitatively sodium thiirancarboxylate **18**.

^{1}H-NMR (D_2O) δ: 3.29 (1H, dd, *J* 5.0 and 6.0 Hz, Na^+ ^-O_2C-C<u>H</u>CH_2) and 2.61 (2 H, t, *J* 5.5 Hz, Na^+ ^-O_2C-CHC<u>H</u>$_2$).

Thiirancarboxylic acid **2** was recovered after acidification of the crude mixture with hydrochloric acid 1M and extraction with chloroform.

^{1}H-NMR ($CDCl_3$) δ: 11.62 (1 H, bs, -CO_2<u>H</u>), 3.39 (1 H, dd, *J* 5.0 and 6.0 Hz, HO_2C-C<u>H</u>CH_2), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, -C<u>H</u>HCH-CO_2H) and 2.69 (1 H, dd, *J* 1.0 and 6.0 Hz, -CH<u>H</u>CH-CO_2H).

Attempted opening of thiirancarboxylic acid using non-aqueous conditions

1st Attempt

Lithium perchlorate (0.4 g, 3.48 mmol) and sodium cyanide **16** (0.2 g, 3.48 mmol) were added consecutively to a solution of thiirancarboxylic acid **2** (0.24 g, 2.32 mmol) in acetonitrile (3 mL) at r.t. The resulting suspension was stirred at 70 °C for 5 hours. Then, the reaction mixture was diluted in water, acidified with 1M HCl solution and extracted with EtOAc, dried over $MgSO_4$ and concentrated to afford 15 mg of acrylic acid **30**. The remaining aqueous layer was concentrated to afford a white solid which was assumed to be polymeric material.

^{1}H-NMR ($CDCl_3$) δ: 6.51 (1 H, d, *J* 17.0 Hz, (*trans*)-C<u>H</u>H=CHCO$_2$H), 6.17 (1 H, dd, *J* 10.0 and 17.0 Hz, CHH=C<u>H</u>CO$_2$H),) and 5.95 (1 H, d, *J* 10.0 Hz, (*cis*)-C<u>H</u>H=CHCO$_2$H).

Preparation of tetrabutylammonium cyanide (TBACN) (31)[5]

The 97 % tetrabutylammonium hydrogensulfate (3.5 g, 10 mmol) was dissolved in CH_2Cl_2 (10 ml). After the addition of 10 M KOH solution (1 mL) and cooling the mixture at r.t. a solution of potassium cyanide (0.75 g, 11.5 mmol) in H_2O (1.5 mL) was added. The two-phase mixture was stirred at r.t. for 5 minutes and then the organic layer was taken up, dried over $MgSO_4$ and concentrated to afford 2.37 g (8.8 mmol, 88 %) of tetrabutylammonium cyanide (TBACN) as a red oil.

^{1}H-NMR ($CDCl_3$) δ: 3.29-3.15 (8 H, m, $^+$N(C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$)$_4$), 1.61-1.53 (8 H, m, $^+$N(CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$)$_4$), 1.40-1.31 (8 H, m, $^+$N(CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$)$_4$) and 0.90 (12 H, t, *J* 7.52 Hz, $^+$N(CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$)$_4$).

2nd Attempt

A solution of TBACN (0.6 g, 2.23 mmol) in toluene (10 ml) was added to thiirancarboxylic acid **2** (0.2 g, 2.23 mmol) at r.t. The solution was maintained at r.t. for 18 hours. Then, the crude mixture was partitioned between EtOAc and brine and the organic layer was taken up, dried over $MgSO_4$ and concentrated to afford a mixture (17:13:70) of acrylic acid **30**, unreacted thiirancarboxylic acid **2** and TBACN.

^{1}H-NMR ($CDCl_3$) δ: 6.51 (1 H, d, *J* 17.0 Hz, *trans*-C<u>H</u>H=CHCO$_2$H, **30**), 6.17 (1 H, dd, *J* 10.0 and 17.0 Hz, CHH=C<u>H</u>CO$_2$H, **30**), 5.95 (1 H, d, *J* 10.0 Hz, *cis*-C<u>H</u>H=CHCO$_2$H, **30**), 3.39 (1 H, dd, *J* = 5.0 and 6.0 Hz, HO$_2$CC<u>H</u>CH$_2$, **2**), 3.29-3.15 (8 H, m, $^+$N(C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$)$_4$, **31**), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, -C<u>H</u>HCHCO$_2$H, **2**) and 2.69 (1 H, dd, *J* 1.0 and 6.0 Hz, -CH<u>H</u>CHCO$_2$H, **2**)., 1.61-1.53 (8 H, m, $^+$N(CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$)$_4$, **31**), 1.40-1.31 (8 H, m, $^+$N(CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$)$_4$, **31**) and 0.90 (12 H, t, *J* 7.52 Hz, $^+$N(CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$)$_4$, **31**).

3rd Attempt

A solution of TBACN (1.5 g, 5.54 mmol) in THF (10 ml) was added to a solution of thiirancarboxylic acid **2** (0.2 g, 2.23 mmol), titanium isopropoxide (1.24 mL, 4.15 mmol) in THF (10 mL) under nitrogen atmosphere at r.t. The solution was maintained at r.t. for 3 hours. Then, the crude mixture was acidified with 9% H_2SO_4 solution, extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated to afford a mixture (65:35) of acrylic acid **30** and TBACN **31.**

^{1}H-NMR ($CDCl_3$) δ: 6.51 (1 H, d, *J* 17.0 Hz, *trans*-C<u>H</u>H=CHCO$_2$H, **30**), 6.17 (1 H, dd, *J* 10.0 and 17.0 Hz, CHH=C<u>H</u>CO$_2$H, **30**), 5.95 (1 H, d, *J* 10.0 Hz, *cis*-C<u>H</u>H=CHCO$_2$H, **30**), 3.39 (1 H, dd, *J* = 5.0 and 6.0 Hz, HO$_2$CC<u>H</u>CH$_2$, **2**), 3.29-3.15 (8 H, m, $^+$N(C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$)$_4$, **31**), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, -C<u>H</u>HCHCO$_2$H, **2**) 2.69 (1 H, dd, *J* 1.0 and 6.0 Hz, -CH<u>H</u>CHCO$_2$H, **2**)., 1.61-1.53

(8 H, m, $^{+}N(CH_2C\underline{H}_2CH_2CH_3)_4$, **31**), 1.40-1.31 (8 H, m, $^{+}N(CH_2CH_2C\underline{H}_2CH_3)_4$, **31**) and 0.90 (12 H, t, *J* 7.52 Hz, $^{+}N(CH_2CH_2CH_2C\underline{H}_3)_4$, **31**).

APPROACHES UTILISING PALLADIUM-ASSISTED COUPLING REACTIONS

Benzonitrile (36) from iodobenzene (34)[8]

1st Attempt

A suspension of $[Pd(PPh_3)_4]$ (0.04 g, 0.03 mmol), powdered sodium cyanide **16** (0.17 g, 3.6 mmol) and iodobenzene **34** (0.61 g, 0.34 mL, 3.0 mmol) in dry THF (3 mL) was stirred at reflux for 9 hours. After cooling, the insoluble salts were removed by filtration and the filtrate was concentrated to afford 0.6 g of unreacted iodobenzene **34**.

^{1}H-NMR ($CDCl_3$) δ: 7.75 (2 H, d, *J* 7.3 Hz, 2 x (*o*-C_6H_5-)), 7.38 (1 H, t, *J* 7.3 Hz, *p*-C_6H_5-) and 7.15 (2 H, t, *J* 7.3 Hz, 2 x (*m*-C_6H_5-)).

Recrystallization of potassium cyanide (35)[9]

Potassium cyanide **35** was dissolved in a hot solution (1:3) of H_2O-EtOH in order to obtain a saturated solution. Then, the solution was filtered off and cooled down at r.t. Ethanol was added to this solution in order to precipitate potassium cyanide from the solution as white solid. The suspension obtained was kept in the fridge for 30 minutes and then the white solid was filtered, washed with ethanol and dried at 65 °C for 4 hours and at 100 °C for another 4 hours to afford pure potassium cyanide **35** as white solid.

2nd Attempt

A suspension of $[Pd(PPh_3)_4]$ (0.03 g, 0.02 mmol), recrystallized powdered potassium cyanide **35** (0.20 g, 3.10 mmol) and iodobenzene **34** (0.52 g, 0.29 mL, 2.56 mmol) in dry THF (3 mL) was stirred at reflux for 9 hours. After cooling, the insoluble salts were removed by filtration and the filtrate was concentrated to

afford 0.51 g of a mixture (57:43) of unreacted iodobenzene **34** and benzonitrile **36**.

^{1}H-NMR ($CDCl_3$) δ: 7.75 (2 H, d, *J* 7.3 Hz, 2 x (*o*-C_6H_5-), **34**), 7.67 (2 H, d, *J* 7.5 Hz, 2 x (*o*-C_6H_5-), **36**), 7.62 (1 H, t, *J* 7.5 Hz, *p*-C_6H_5-, **36**), 7.49 (2 H, t, *J* 7.5 Hz, 2 x (*m*-C_6H_5-), **36**), 7.38 (1 H, t, *J* 7.3 Hz, *p*-C_6H_5-, **34**) and 7.15 (2 H, t, *J* 7.3 Hz, 2 x (*m*-C_6H_5-), **34**).

3rd Attempt

A solution of [$Pd(PPh_3)_4$] (0.02 g, 0.02 mmol), TBACN (0.46 g, 1.71 mmol) and iodobenzene **34** (0.35 g, 0.19 mL, 1.71 mmol) in dry THF (1 mL) was stirred at reflux for 16 hours. After cooling, the reaction mixture was filtered and the filtrate was concentrated to afford 0.89 g of a mixture (50:50) of unreacted iodobenzene **34** and TBACN **31**.

^{1}H-NMR ($CDCl_3$) δ: 7.75 (2 H, d, *J* 7.3 Hz, 2 x (*o*-C_6H_5-), **34**), 7.38 (1 H, t, *J* 7.3 Hz, *p*-C_6H_5-, **34**), 7.15 (2 H, t, *J* 7.3 Hz, 2 x (*m*-C_6H_5-), **34**), 3.29-3.15 (8 H, m, $(CH_3CH_2CH_2C\underline{H}_2)_4N^+$ CN^-, **31**), 1.61-1.53 (8 H, m, $(CH_3CH_2C\underline{H}_2CH_2)_4N^+CN^-$, **31**), 1.40-1.31 (8 H, m, $(CH_3C\underline{H}_2CH_2CH_3)_4N^+CN^-$, **31**) and 0.90 (12 H, t, *J* 7.52 Hz, $(C\underline{H}_3CH_2CH_2CH_2)_4N^+CN^-$, **31**).

<u>*t*-Butyl 2-bromoacrylate (37)</u>[10]

Bromine (6.36 g, 2.04 mL, 39.8 mmol) was added to a solution of *t*-butyl acrylate **38** (5.10 g, 39.8 mmol) in CH_2Cl_2 (40 mL) at r.t. The intense red colour of the reaction mixture ,developed after the addition of bromine, gradually faded to clear solution after 22 hours. Then, the reaction mixture was concentrated to afford 11.36 g (99%) of the dibromocompound **39**. This dibromocompound **39** (4.73 g, 16.4 mmol) was dissolved in ether (32 ml) and triethylamine (3.32 g, 4.57 mL, 32.85 mmol) was added under stirring at r.t. Stirring was continued at that temperature for 24 hours. Then, the reaction mixture was washed with water (10 mL) and extracted with ether (3 x 10 mL). The ethereal extracts were combined,

dried over $MgSO_4$, filtered off and concentrated to afford 1.59 g (47%) of **37** as orange liquid.

^{1}H-NMR ($CDCl_3$) δ: 6.84 (1 H, s, C<u>H</u>H=C$CO_2{}^t$Bu(Br)), 6.19 (1 H, s, CH<u>H</u>=C$CO_2{}^t$Bu(Br)) and 1.52 (9 H, s, -C(C<u>H</u>$_3$)$_3$).

^{13}C-NMR ($CDCl_3$) δ: 160.7 (-<u>C</u>$O_2{}^t$Bu), 129.2 (<u>C</u>H_2), 123.4 (=<u>C</u>-), 83.1 (-<u>C</u>(CH_3)$_3$) and 27.8 (<u>C</u>H_3).

<u>Attempted cyanation reaction of *t*-butyl 2-bromoacrylate (37)</u>

1st Attempt

A suspension of [Pd(PPh_3)$_4$] (0.03 g, 0.03 mmol), recrystallized powdered potassium cyanide **35** (0.24 g, 3.68 mmol) and *t*-butyl 2-bromoacrylate **37** (0.64 g, 3.07 mmol) in dry THF (4 mL) was stirred at reflux for 9 hours. After cooling, the insoluble salts were removed by filtration and the filtrate was concentrated to afford 0.53 g of *t*-butyl 2-bromoacrylate **37**.

2nd Attempt

A stirred suspension of *t*-butyl 2-bromoacrylate (0.34 g, 1.64 mmol) **37**, potassium cyanide (0.21 g, 3.28 mmol), [Pd(PPh_3)$_4$] (0.06 g, 0.05 mmol) and dicyclohexano-18-crown-6 (0.05 g, 0.12 mmol) in 2 mL of benzene (2 mL) was heated at 73 °C for 2 hours under nitrogen atmosphere. Then, 20 mL of (1: 1) mixture of acetone-water was poured into the reaction mixture. The organic layer was separated and concentrated and dried over anhydrous $MgSO_4$ to afford 0.39 g of brown liquid which was identified as a mixture of initial products.

3rd Attempt

A solution of TBACN (0.5 g, 1.86 mmol) in THF (1.5 ml) was added to a solution of *t*-butyl 2-bromoacrylate **37** (0.38 g, 1.86 mmol) in dry THF (0.5 mL) at r.t. Stirring was continued at r.t. for 1.5 hours. After cooling, the reaction mixture was filtrated and the filtrate was concentrated to afford 1.05 g of a mixture

(78:16:2:3:1) of polymeric material, TBACN **31**, *t*-butyl 2-bromoacrylate **37**, *t*-butyl (*E*) 3-cyanoacrylate **40** and *t*-butyl (*Z*) 3-cyanoacrylate **41**.

^{1}H-NMR ($CDCl_3$) δ: 6.84 (1 H, s, C<u>H</u>H=$CCO_2{}^t$Bu(Br), **37**), 6.65 (1 H, d, *J* 16.6 Hz, (*E*)-CNCH=$CHCO_2{}^t$Bu, **40**), 6.48 (1 H, d, *J* 11.5 Hz, (*Z*)-CNCH=$CHCO_2{}^t$Bu, **41**), 6.40 (1 H, d, *J* 16.6 Hz, (*E*)-CNCH=$CHCO_2{}^t$Bu, **40**), 6.19 (1 H, s, CH<u>H</u>=$CCO_2{}^t$Bu(Br), **37**), 5.87 (1 H, d, *J* 11.5 Hz, (*Z*)-CNCH=$CHCO_2{}^t$Bu, **41**), 3.28-3.24 (8H, m, $(CH_3CH_2CH_2C\underline{H}_2)_4N^+$, **31**), 1.74-1.71 (8 H, m, $(CH_3CH_2C\underline{H}_2CH_3)_4N^+$ **31**), 1.52-1.50 (36 H, m), 1.44-1.29 (8 H, m, $(CH_3C\underline{H}_2CH_2CH_3)_4N^+$, **31**), 1.38 (2 H, s, *poly*(*t*-butyl 2-bromoacrylate) and 0.90 (12 H, t, *J* 7.52 Hz, $(C\underline{H}_3CH_2CH_2CH_2)_4N^+$, **31**).

<u>*t*-Butyl (*E*)-(40) and (*Z*)-3-cyanoacrylate (41)</u>

A solution of sodium cyanide **16** (0.13 g, 2.60 mmol) in water (0.4 mL) was added to a solution of *t*-butyl 2-bromoacrylate **37** in acetone (1 mL) at r.t. Stirring was continued at r.t. for 19 hours. Then, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered off and concentrated to afford a mixture (15:65:20) of *t*-butyl 2-bromoacrylate **37**, *t*-butyl (*E*)-3-cyanoacrylate **40** and *t*-butyl (*Z*)-3-cyanoacrylate **41**.

^{1}H-NMR ($CDCl_3$) δ: 6.84 (1 H, s, C<u>H</u>H=$CCO_2{}^t$Bu(Br), **37**), 6.65 (1 H, d, *J* 16.6 Hz, (*E*)-CNCH=$CHCO_2{}^t$Bu, **40**), 6.48 (1 H, d, *J* 11.5 Hz, (*Z*)-CNCH=$CHCO_2{}^t$Bu, **41**), 6.40 (1 H, d, *J* 16.6 Hz, (*E*)-CNCH=$CHCO_2{}^t$Bu, **40**), 6.19 (1 H, s, CH<u>H</u>=$CCO_2{}^t$Bu(Br), **37**), 5.87 (1 H, d, *J* 11.5 Hz, (*Z*)-CNCH=$CHCO_2{}^t$Bu, **41**) and 1.52-1.50 (36 H, m).

APPROACHES *VIA* SOLID-PHASE ORGANIC SYNTHESIS

Thiomethyl copoly-(styrene-2%divinylbenzene) (52)[14]

A suspension of chloromethyl copoly-(styrene-2%divinylbenzene) **55** (2 g, 2 mequiv./g) and thiourea **56** (1.29 g, 17 mmol) in a mixture (3.5:1) of THF-EtOH was stirred and heated at 70 °C for 48 hours. The resin was washed with water followed by THF and benzene to remove all excess soluble reagents and by-products. Then, the polymer was suspended in benzene (25 mL) and a solution of *tetra*-butylammonium iodide (0.03 g, 0.09 mmol) and sodium hydroxide (1.25 g, 31 mmol) in distilled water was added at r.t. The third-phase mixture was stirred and heated at 85 °C for 48 hours under nitrogen atmosphere. After filtration the resin was washed with THF, water a mixture (3:1) of (THF:6 N HCl), water, THF, acetone, CH_2Cl_2 and MeOH. Then, the resin was dried under vacuum to afford the resin **52**, which showed, after combustion analysis, a load of 2 mequiv./g.

% S (required) = 6.4, **% S (found)** = 6.4.

The resin **52** showed a SH-band centred at 2362.3 cm^{-1} in its IR spectrum.

Michael addition of ECA with thiomethyl copoly-(styrene-2% divinylbenzene) (52)

ECA (1.07 g, 8.58 mmol) was added to a suspension of **52** (1.43 g, 2 mequiv./g) and *p*-toluenesulfonic acid (0.21 g, 1.23 mmol) in CH_2Cl_2 (25 ml) at r.t. The suspension was stirred under sonication conditions at that temperature for 12 hours. The resin was then thoroughly washed with water and CH_2Cl_2 and dried under vacuum to afford the resin **59** which showed, after combustion analysis, a load of 1.67 mequiv/ g.

% N (required) = 2.75, **% N (found)** = 2.30.

The resin **59** showed a CN band at 2249.48 cm^{-1} and an intense C=O band at 1745.69 cm^{-1} in its IR spectrum.

Attempted hydrolysis - reductive elimination process of the resin 59

A stirred suspension of **59** (1.77 g, 1.67 mequiv./g) in 1M H_2SO_4 solution (9 equiv.) solution was heated at 90 °C for 26 hours. Then, the resin was filtered, dried and suspended in 1, 2-dichloroethane (30 ml). The vanadium catalyst ($Vo(acac)_2$, 0.12 g, 0.44 mmol) and *t*-butyl hydroperoxide (0.26 g, 2.94 mmol) were added to the suspension at r.t and the stirring was continued for 24 hours. Then, the resin was filtered and the filtrate evaporated to afford 0.03 g (12 %) of **ECA**

Benzyl 2-cyanoacetate (66)

The compound DIPC (4.32 g, 5.25 mL, 34.31 mmol) was added to a solution of cyanoacetic acid **61** (2.91 g, 34.31 mmol) and benzyl alcohol **65** (3.1 mL, 34.31 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to reach r.t. and stirred at that temperature for 12 hours. Then, the reaction mixture was filtered and concentrated to afford 4.1 g (68%) of **66** as yellow liquid.

^{1}H-NMR ($CDCl_3$) δ: 7.39 (5 H, s, $C_6\underline{H}_5CH_2O$-), 5.25 (2 H, s, $C_6H_5C\underline{H}_2O$-) and 3.50 (2 H, s, $C\underline{H}_2(CN)CO_2Bn$).

Esterification of 2-cyanoacetic acid with hydroxymethyl copoly-(styrene-1% divinylbenzene) (60)

The compound DIPC (2.03 g, 2.47 mL, 16.15 mmol) was added to a suspension of **60** (1.9 g, 1.7 mequiv./g) and cyanoacetic acid **60** (1.40 g, 16.15 mmol) in THF (16 ml) at 0 °C. The suspension was allowed to reach r.t. and stirred at that temperature for 12 hours. The resin was then thoroughly washed with water, THF and EtOH and dried under vacuum to afford the resin **62** which showed, after combustion analysis, a load of 0.2 mequiv/ g.

% N (required) = 2.4, **% N (found) =** 0.27 - 0.34%

The same procedure above described was followed again but at this stage sonication conditions were employed to afford the resin **62** which showed, after combustion analysis, a load of 1.67 mequiv/ g.

% N (required) = 2.4, **% N (found)** = 2.32 - 2.39%

Attempted transacetoacetylation of *t*-butyl cyanoacetate (70) with benzyl alcohol (65)

A solution of *t*-butyl cyanoacetate **70** (2g, 14.18 mmol) and benzyl alcohol **65** (1.61 g, 1.54 mL, 14.89 mmol) in toluene (7 mL) was heated at reflux for 20 hours. Then, the reaction mixture was concentrated to afford a mixture of starting materials.

^{1}H-NMR ($CDCl_3$) δ: 7.39 (5 H, s, $C_6\underline{H}_5CH_2OH$), 4.27 (2 H, s, $C_6H_5C\underline{H}_2OH$) and 3.37 (2 H, s, $C\underline{H}_2(CN)CO_2{}^t\!Bu$) and 1.53 (9 H, s, $-CO_2C(C\underline{H}_3)_3$).

Attempted Knoevenagel condensation of the resin with paraformaldehyde (63)

Paraformaldehyde **63** (1.26 mmol, 0.04 g) was added to a stirred suspension of the resin **62** (0.38 g, 1.67 mequiv./g) and piperidine (0.063 mmol, 0.005 ml) in pyridine (7 mL) at r.t. The suspension was heated at 100 °C under stirring for 11 hours. Then, the resin was washed with DMF and CH_2Cl_2 and dried under vacuum. The resulting resin was suspended in a mixture (1:2) of TFA and CH_2Cl_2 and stirred at r.t. for one hour. Then the resin was filtered and the filtrate was concentrated to observe no material.

Benzyl 2-cyano-3-(*p*-dimethylaminophenyl)propenoate (77)[21]

A catalyst mixture made by dissolving piperidine (0.16 mL, 1.68 mmol) in glacial acetic acid (0.44 mL, 7.84 mmol) was added to a mixture of benzyl 2-cyanoacetate **66** (0.99 g, 5.6 mmol) and *p*-dimethylaminobenzaldehyde **76** (0.83

g, 5.6 mmol) in ethanol (10 mL) at r.t. The reaction mixture was heated at 80 °C for 2 hours. Then, the reaction mixture was cooled down and a red solid came up. The solid was filtered, washed with ethanol and identified as **77**.

^{1}H-NMR ($CDCl_3$) δ: 8.10 (1 H, s, -C<u>H</u>=), 7.95 (2 H, d, *J* 9.32, 2 x (*m*-$(CH_3)_2NC_6H_4$-), 7.48-7.46 (2 H, m, 2 x (*o*-C_6H_5-)), 7.42-7.33 (3 H, m, 2 x (*m*-C_6H_5-) and *p*-(C_6H_5-)), 6.70 (2 H, d, *J* 9.32, 2 x (*o*-$(CH_3)_2NC_6H_4$-)), 5.35 (2 H, s, -$CO_2C\underline{H}_2Ph$) and 3.12 (6 H, s, -$N(C\underline{H}_3)_2$).

^{13}C-NMR ($CDCl_3$) δ: 163.7 ($\underline{C}O_2Et$), 154.4 ($\underline{C}H$), 153.2 ($\underline{C}_q$), 135.2 ($\underline{C}_q$), 133.7 ($\underline{C}H$), 128.1 ($\underline{C}H$), 127.8 ($\underline{C}H$), 127.6 ($\underline{C}H$), 118.9 ($\underline{C}N$), 111.1 ($\underline{C}H$), 66.8 ($\underline{C}H_2$) and 39.5 ($\underline{C}H_3$).

2-cyano-3-(*p*-dimethylaminophenyl)propionic acid (75)[22]

A mixture of benzyl 2-cyano-3-(*p*-dimethylaminophenyl)propenoate **77** in THF (2 mL) was continued at r.t. for 3 hours. Then, the reaction mixture was concentrated to afford a mixture (51:49) of **75** and benzyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 9.23 (1 H, bs, -$CO_2\underline{H}$, **75**), 8.32 (1 H, s, -C<u>H</u>=, **75**), 8.13 (2 H, d, *J* 8.8, 2 x (*m*-$(CH_3)_2NC_6H_4$-), **75**), 7.69-7.67 (2 H, m, 2 x (*o*-C_6H_5-)), 7.46-7.37 (3 H, m, C_6H_5-), 7.39 (2 H, d, *J* 8.8, 2 x (*o*-$(CH_3)_2NC_6H_4$-), **75**), 5.39 (2 H, s, -$CO_2C\underline{H}_2Ph$) and 3.32 (6 H, s, -$N(C\underline{H}_3)_2$, **75**).

Attempted Knoevenagel condensation of the resin (62) with *p*-dimethylaminobenzaldehyde (76)

p-Dimethylaminobenzaldehyde **76** (1.03 mmol, 0.15 g) was added to a stirred suspension of the resin **62** (0.31 g, 1.67 mequiv./g), piperidine (0.31 mmol, 0.03 ml) and acetic acid (1.46 mmol, 0.08 mL) in EtOH (10 ml) at r.t. The suspension was stirred at 80 °C under stirring for 5 hours. Then, the resin was washed with CH_3Cl and dried under vacuum. The resulting resin was suspended in a mixture (1:2) of TFA and CH_2Cl_2 and stirred at r.t. for a hour. Then the resin was filtered and the filtrate was concentrated to observe no material.

Attempted preparation of *poly* (pyridinium 2-cyanoacrylatestyrene) (81)

A suspension of 2-cyanoacetic acid **61** (0.83 g, 9.75 mmol), paraformaldehyde **63** (0.58 g, 19.52 mmol), diethylamine **83** (1.97 g, 19.52 mmol), PVP (5.13 g, 48.82 mmol) and triethylamine **80** (0.27 mL, 7.32 mmol) in benzene (80 mL) was stirred and heated at 80 °C for 45 minutes. After filtration, the resin was washed thoroughly with water and THF and dried under vacuum. Then, the polymer was suspended in water and titrated with an excess of acid (1M HCl or 1M H_2SO_4). The aqueous solution was taken up, extracted with EtOAc, dried over $MgSO_4$ and concentrated to afford no material.

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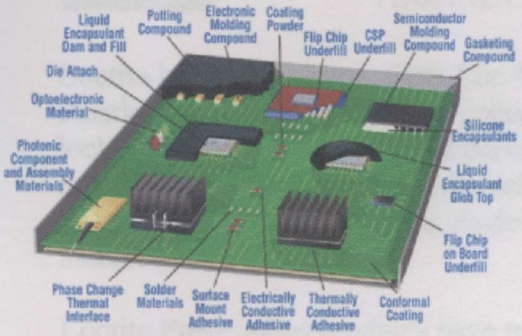

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