Aerobic oxidation of NHC-catalysed aldehyde esterifications with alcohols: benzoin, not the Breslow intermediate, undergoes oxidation†

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Benzoin (and neither the Breslow intermediate nor the NHC–aldehyde tetrahedral adduct) has been unambiguously identified as the oxidised species in aerobic NHC-catalysed aldehyde esterifications.

In the previous communication,1 the first examples of broad scope, efficient, N-heterocyclic carbene (NHC)-catalysed aerobic oxidative methyl esterifications of aromatic aldehydes in the absence of allylating agents, solid stoichiometric oxidants or co-oxidation catalysts were reported. Previously these reactions (when O2/air had been used as the oxidant) had been postulated to proceed either through the oxidation of the Breslow intermediate or its immediate precursor. We wished to ascertain the nature of the oxidised intermediates that were involved in these aerobic oxidative esterifications, and began by examining the scope of the process with respect to the alcohol component. If the reaction proceeds through a highly electrophilic acyl triazolium 14 (Fig. 1), one would not expect to observe significant differences between esterifications using different alcohols (Scheme 1).

Experiments were carried out using two sets of conditions (Scheme 1): a 1:1 THF–alcohol solvent mixture (condition set A) and use of 3.0 equivalents of alcohol in THF solvent (condition set B). We commenced our study with a series of alcohols which form esters 3 (amenable to different deprotection methodologies). Both benzylic and allylic alcohols were suitable substrates; providing the corresponding products 4 and 5 in good (condition set B) to excellent yields (condition set A) yields. The formation of the trichloroethanol-derived 6 proceeded in ca. 60% yield irrespective of the conditions employed. Interestingly, the synthesis of the corresponding trifluoro-analogue 7 was limited by the volatility of the alcohol, and could only be formed under condition set B. Similar difficulties were encountered with the more hindered hexafluoroisopropanol – resulting in the formation of 8 in low yield. The more hindered and less acidic isopropanol proved resistant to esterification: ester 9 could not be generated.

Using precatalyst 2 and DBU, 1 could also be cleanly oxidised to the acid 10 in THF/H2O (10:1 v/v) in excellent isolated yield (eqn (1)). Recently disclosed examples of imidazolium ion derived carbene-mediated aerobic oxidations of aromatic aldehydes to carboxylic acids in the presence of water2 either require significantly elevated temperatures (60 °C) and reaction times >36 h (ref. 2a) or are only efficacious with highly activated aldehyde substrates (e.g. formation of 10 with <10% yield).2b
With the breadth of the reaction scope and the intriguing dependency on steric effects established, we attempted to divine some information regarding the reaction mechanism.

The results of our studies (outlined in Scheme 1) are not readily reconciled with either ‘oxidative’ or ‘oxygenative’ mechanisms (Fig. 1). For instance, the ‘oxidative’ esterification reaction requires alkyl transfer from an electrophile (such as an alkyl halide). The ‘oxidative’ esterification mechanism is also unsatisfactory here, as the sensitivity of the process described in this work to the steric bulk of both the nucleophilic and electrophilic reaction components is not consistent with that we observed in a previous study involving the use of azobenzene as a stoichiometric reactant (e.g. in esterifications involving azobenzene as an oxidant, o-tolualdehyde and isopropanol served as excellent coupling partners, while in the current study both are poor substrates). This strongly indicates that our aerobic oxidative esterifications outlined above do not proceed via acyl azolium ion intermediates.

Since the esterifications do not proceed in the absence of O₂, we were forced to consider alternative species which are oxidised in these reactions. The most likely candidate appeared to be benzoin (16) – the slow, base-catalysed aerobic oxidation of which to benzil (17) by O₂ is known. While we never isolated/observed 17 in any of the reactions outlined above, it is a highly electrophilic species: therefore its rapid destruction in the presence of the relatively unhindered carbene derived from 2 and methanol would not be implausible. In addition, while the sensitivity of the esterifications to steric factors did not match that of known processes involving acyl azolium ions, it was consistent with the influence of steric bulk on the benzoil condensation, which encouraged us to further investigate in the direction of this hypothesis.

We began by subjecting benzaldehyde (1) to the esterification conditions in the absence of methanol. To our delight, we observed the formation of both 16 and 17 after just 5 min reaction time (Scheme 2). After 20 min, both these species have been replaced by a hydroacylation product 18 (in good yield) and the acid 10 (presumably formed due to the presence of adventitious water).

Chan and Scheidt have previously reported the formation of 18 in the NHC-mediated reaction between 1 and 17. They rationalised this in terms of a hydride transfer process between the carbene–aldehyde adduct and 17, which generates an acyl azolium ion and benzoin (Scheme 2, inset). To the best of our knowledge the reaction outlined in Scheme 2 is the first example of the efficient NHC-mediated formation of a hydroacylation product from an aldehyde alone in the presence of air. Next, we attempted to establish if 17 is a catalytically relevant intermediate in the presence of alcohol. Accordingly, benzil was exposed to methanol and the carbene under an argon atmosphere.

Under these conditions we observed rapid conversion of 17 to methyl benzoate (19), 16 and aldehyde 1 at ambient temperature (Scheme 3). Similarly, the carbene-catalysed reaction of 16 with an equivalent amount of 17 in the absence of both air and MeOH generated the hydroacylation product 18 as the major constituent of the crude reaction mixture (Scheme 4), indicating that benzoin may also be able to play the role of the nucleophilic alcohol in these reactions.

The hydroacylation product 18 is conspicuously absent in the ¹H NMR spectra of reactions involving methanol or other smaller alcohols. Therefore we next assessed the stability of 18 under anaerobic reaction conditions; whereupon smooth acyl transfer to afford methyl benzoate (19) in excellent yield was observed (eqn (2)).

Finally, to gain some insight regarding the origins of the influence of the alcohol structure on reaction efficiency, benzil (17) was reacted in the presence of the NHC under anaerobic conditions in a competition experiment using alcohol and water solvent mixtures (yielding either an ester or acid resp., Scheme 5). We expected products derived from nucleophilic attack of the less hindered water molecule to dominate over the ester analogues stemming from the more hindered alcohols. Surprisingly, the 1:1-solvent mixture of methanol and water generated the methyl ester 19 as the major product.
The formation of benzoin (16) from benzil (17) in the absence of O₂ (but presence of CH₃OH) also requires explanation: we would suggest that – by analogy with a recent proposal in a distinct but related transformation – attack by the enamino 23 on diketone 17 would yield 27 (isolated by Massi et al.). In the presence of excess base and methanol, the cleavage of 27 to yield ester 19 and 16 via hemiacetal 28 is conceivable. This model was supported by the inefficiency of the corresponding amidation chemistry (Scheme 6) involving pyrrolidine – a more nucleophilic but less acidic reagent than MeOH.

We suggest that this may be related to the attack of the more hindered amine on the very bulky ketone 25. This reaction would also be hampered by considerably less efficient general base catalysis of the attack on the ketone involving the considerably less acidic amine.

In summary these reactions have been shown to be mechanistically distinct from other either NHC-catalysed ‘oxidative’ or ‘oxygenative’ esterifications in that the species which reacts with oxygen in the air is not the Breslow intermediate, but the arylin (or more accurately, its enolate). In aqueous solvent benzoic acid (10) is accessible from aldehyde 1 in excellent yield. Investigations to further develop the scope and utility of these reactions are underway. Financial support from the IRCSET, Science Foundation Ireland and the DFG is gratefully acknowledged.

Notes and references

7. Quoted yields within the figures are determined by 1H NMR spectroscopy with an internal standard. See the ESI for details.
9. This process features a comparison of reactions of different molecular complexity; therefore (to avoid confusion), we have quote the yields as mmol of product.
10. It is noteworthy that Massi et al. have recently observed the benzoylation of PEG₄₀₀ on treatment of benzil with a thiazolium ion-derived NHC, see: O. Bortolini, G. Fantin, M. Fogagnolo, P. P. Giovannini, V. Venturi, S. Pacifico and A. Massi, Tetrahedron, 2011, 67, 8110.
11. It must be acknowledged that reversion of 16 to 1, followed by a hydroacylation reaction as proposed by Scheidt (see Scheme 2) cannot be ruled out at this juncture.
12. For use of an unsymmetrical benzil, see the ESI.
13. It is noteworthy that in mixtures with MeCN, MeOH has been found to be more nucleophilic than EtOH: (a) S. Minegishi, S. Kobayashi and H. Mayr, J. Am. Chem. Soc., 2004, 126, 5174; (b) T. B. Phan and H. Mayr, Can. J. Chem., 2005, 83, 1554.
14. In a control experiment under standard aerobic conditions in the absence of 2, 16 (1.0 mmol) was converted to 17 (0.19 mmol) after just one 1 h reaction time.
15. We note that a similar intermediate has been suggested (in a different process) by Massi et al., see ref. 10.
16. This process occurs in both the presence and absence of 2.