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From dioxime oxalates to dihydropyrroles and phenanthridines *via* iminyl radicals†

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Received (in Cambridge, UK) 21st May 2008, Accepted 7th July 2008
First published as an Advance Article on the web 1st August 2008
DOI: 10.1039/b808625g

Published on 01 August 2008. Downloaded by Trinity College Dublin on 01/05/2014 08:30:44.

Dioxime oxalates are useful precursors for the clean generation of iminyl radicals by sensitised UV photolysis and can be adapted for serviceable preparations of 3,4-dihydro-2*H*-pyrroles and phenanthridines.

The rate constant for iminyl radical ($R_2C{=}N^{\bullet}$) cyclisation is only about a factor of 20 less than that of the archetype hex-5-enyl radical,[1] so it is not surprising the reaction is useful for N-heterocycle preparations.[2] An important objective is to find ways of generating iminyls that are simple, "clean" and flexible. Zard *et al.* made significant progress towards this goal with *N*-hydroxypyridine-2-thione and ketoxime xanthate precursors.[3] A somewhat specialised thermal route involves addition of imidoyl radicals onto cyanoalkyl groups.[4] A direct thermal route, with promise of flexibility, employs microwave irradiation of *O*-phenyl oxime ethers.[5] Oxime esters have been enlisted for release of iminyl radicals[6] and acyl types are good precursors for photochemical syntheses of phenanthridines and isoquinolines.[7] Anion radicals generated by one-electron transfer to *O*-aryl oxime ethers and acyl oximes act as iminyl radical equivalents in N-heterocycle preparations.[8]

We already knew that oxime oxalate amides [$R_2C{=}NOC(O)C(O)NR'_2$] were good photochemical precursors for iminyl and carbamoyl radicals.[9] It seemed possible, therefore, that the structurally related dioxime oxalates **1** could function as particularly clean and atom-efficient sources of iminyl radicals because the only by-product would be CO_2:

$$R_2C{=}NOC(O)C(O)ON{=}CR_2 \rightarrow 2\ R_2C{=}N^{\bullet} + 2CO_2$$

1, **a**; R = Me, **b**; R = Ph

The only previous attempt to generate radicals from dioxime oxalates was described in a couple of brief mentions in papers from Forrester *et al.*[10] They concluded that both iminyl and iminoxyl radicals [$R_2C{=}NO^{\bullet}$] were formed during UV photolyses. In this *communication* we report our study of the preparation and photochemical reactions of a range of symmetrical and unsymmetrical dioxime oxalates.

Jochims and co-workers made dioxime oxalates by condensation of an oxime with oxalyl chloride to give an oxime oxalyl chloride which was then reacted with a second mole of the oxime to afford the dioxime oxalate in good yield.[11] We used this method to prepare both symmetrical and unsymmetrical dioxime oxalates. Purification was usually impracticable because most dioxime oxalates hydrolysed and degraded rapidly on exposure to air and during chromatography (SiO_2 or Al_2O_3). By using fresh oxalyl chloride, and by careful control of the reactant quantities, almost pure dioxime oxalates could be made quantitatively and used immediately without further purification. In a few cases solid dioxime oxalates resulted which were purified by low temperature recrystallisation. Most of the dioxime oxalates were obtained as mixtures of *E*/*Z* stereoisomers about their C=N bonds.[12]

Photochemical dissociations of **1a** and **1b** were studied by 9 GHz EPR spectroscopy. Deaerated solutions of each dioxime oxalate in *tert*-butylbenzene were photolysed with unfiltered light from a 500 W Hg lamp directly in the EPR resonant cavity. Signals were weak unless 4-methoxyacetophenone (MAP) (1 or 2 equiv.) was included as a photosensitiser. In that case good spectra of dimethyl- and diphenyliminyl radicals ($Me_2C{=}N^{\bullet}$ and $Ph_2C{=}N^{\bullet}$), with EPR parameters identical to those reported in the literature,[13] were observed. In initial experiments with **1a**,**b**, and with some of the dioxime oxalates reported below, spectra of iminoxyl radicals ($R_2C{=}NO^{\bullet}$) accompanied the iminyl radical spectra. However, iminoxyls were not observed when a completely pure dioxime oxalate was employed. We believe, therefore, that the iminoxyl spectra result from H-atom abstraction from traces of oxime impurities and are not due to UV induced scission of the O–C bonds in **1**.[14] The EPR spectra established that iminyl radicals are cleanly released from dioxime oxalates on photolysis, although the signal intensities suggested this process was more efficient for dioxime oxalates with phenyl substituents on their C=N bonds.

A set of dioxime oxalates containing pent-4-enyl chains **4a–d** was prepared to assess the usefulness of these precursors in preparations of dihydropyrroles. Individual dioxime oxalates were dissolved in toluene along with 2 equivalents of MAP and the solutions were photolysed for 4 h in quartz tubes with light from a 400 W medium pressure Hg lamp. After removal of MAP by chromatography the products were shown to be 5-aryl-3,4-dihydro-2*H*-pyrroles **7a–d**.[15] A plausible mechanism

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† Electronic supplementary information (ESI) available: Preparations of a model ketone, oxime and dioxime oxalate; also dihydropyrroles and phenanthridines with NMR spectra of new compounds. EPR spectra of iminyl and iminoxyl radicals. See DOI: 10.1039/b808625g

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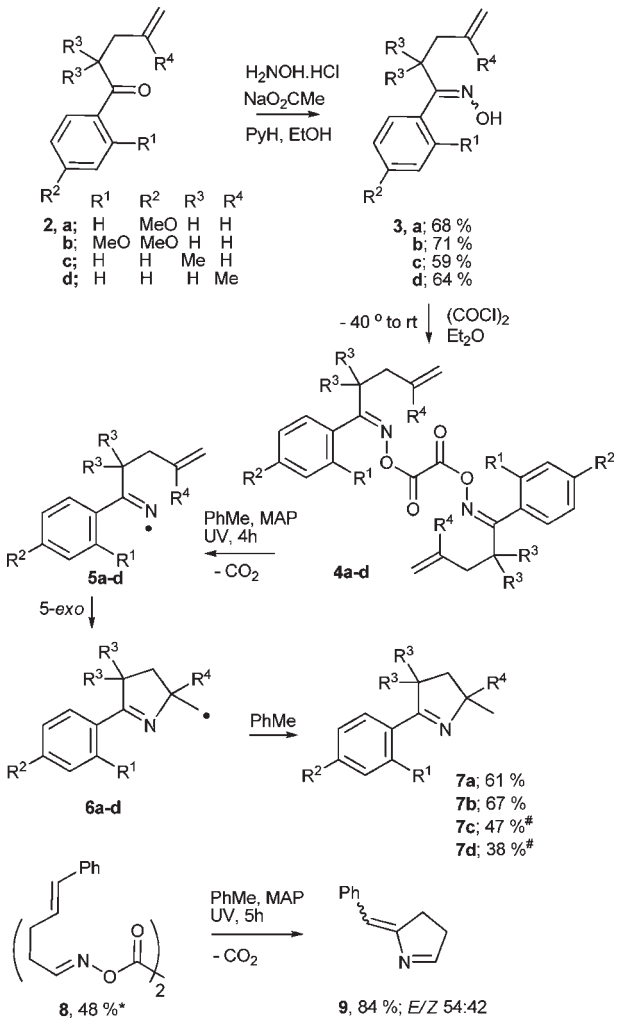
is outlined in Scheme 1. By analogy with mono-oxime esters, the weak N–O bond of the dioxime oxalate should break first, yielding an iminyl radical **5** and an acyloxyl radical. Rapid dissociation of the latter is expected to release a second iminyl radical along with two CO_2 molecules. The iminyl radicals **5** then undergo ring closure in the favoured 5-*exo*-*trig* mode to afford dihydropyrrolomethyl radicals **6** that abstract a hydrogen atom from the toluene solvent with production of the heterocycles **7**. The imines (or their ketone hydrolysis products) resulting from H-atom abstraction by uncyclised radicals **5**, were at most minor by-products, so the iminyl cyclisations must be fast in comparison with this process. The yield of **7d** was lower than that of **7a**, in agreement with the expected slower ring closure at the more substituted –C(Me)= atom. The yield of **7c** was also comparatively low, *i.e.* no support was forthcoming for *gem*-dimethyl enhancement of aryliminyl cyclisation.

An interesting contrast was provided by dioxime oxalate **8** obtained from 5-phenylpent-4-en-1-al. After photolysis under similar conditions, the product isolated was 2-benzylidene-3,4-dihydro-2*H*-pyrrole **9**, instead of the expected benzyldihydropyrrole. In this case cyclisation of the intermediate iminyl radical will afford a resonance-stabilised benzyl type radical for which H-atom abstraction from solvent will be much slower. Instead, the pyrrolobenzyl radical loses an H-atom to produce **9**. Possibly the mechanism involves electron transfer from the pyrrolobenzyl radical to MAP with production of the pyrrolobenzyl cation which then transfers a proton (see below).



Scheme 1 Preparation of dihydropyrroles. Yields are mol% isolated product except those marked # which were determined by NMR spectra of the total product mixtures. * Yield over 3 steps from 5-phenylpent-4-en-1-ol.

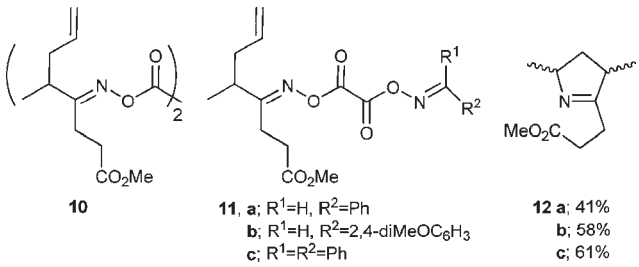
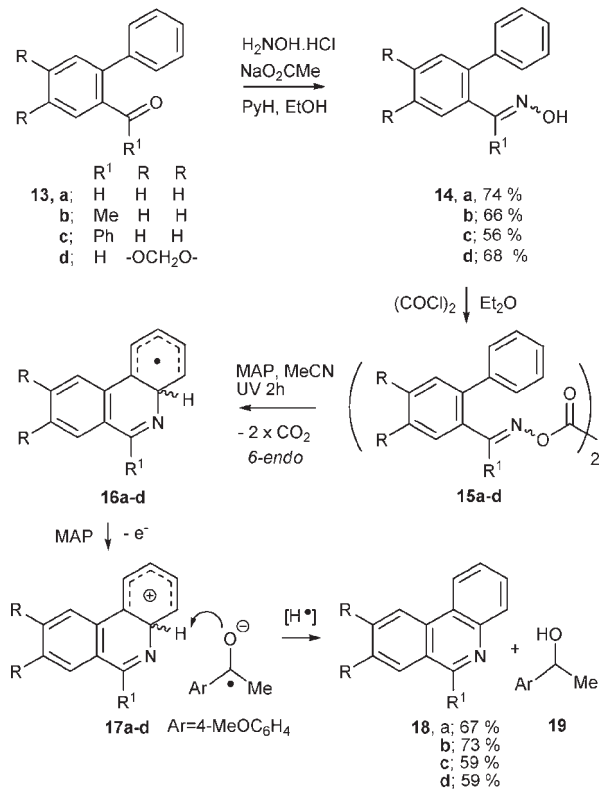


Fig. 1 Symmetrical and unsymmetrical dioxime oxalates from ester-containing precursors. Yields are mol% isolated product.

Dihydropyrroles of type **12** were of interest because they can serve as precursors for biologically active pyrrolizines.[16] The symmetrical dioxime oxalate **10** was therefore prepared and photolysed in toluene. However, no **12** was obtained on photolysis. Instead, the starting material and its hydrolysis products were recovered.

Compound **10** contains no aryl ring and, in agreement with the conclusion mentioned above, iminyl generation was much less efficient. To overcome this problem unsymmetrical dioxime oxalates **11a–c**, with one half containing an aromatic oxime, were examined. They were prepared by reacting the oxime oxalyl chloride from methyl 5-methyl-4-oxooct-7-enoate with the oximes of benzaldehyde, 2,4-dimethoxybenzaldehyde and benzophenone respectively. Photolyses of these precursors with MAP



Scheme 2 Preparation of phenanthridines.

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did indeed afford **12** along with the aryl-imines (plus ketones from hydrolysis) produced by hydrogen transfer to the aryl-iminyl radicals. The somewhat greater yields of **12** from **11b** and **11c** (Fig. 1) suggested there was an advantage in using di-methoxy-substitution of the aromatic part or in employing benzophenone. We conclude that dihydropyrroles like **12**, with no aryl substituents, can be made in good yields by employing unsymmetrical dioxime oxalates but, of course, this reduces the atom-efficiency of the method.

We also prepared dioxime oxalates **15a–d** from 2-formylbiphenyl derivatives **13a–d** as shown in Scheme 2. After UV irradiation in acetonitrile, phenanthridine derivatives **18a–d** were obtained. In this case, the iminyl radicals released on photolysis of **15** preferentially underwent 6-*endo* cyclisation onto the phenyl acceptors because this yielded the resonance-stabilised cyclohexadienyl type radicals **16**. The latter are too thermodynamically stabilised to abstract H-atoms from the solvent. Instead they lost an H-atom, re-aromatised and afforded phenanthridines **18** (Scheme 2). The reaction was tolerant of Me and Ph substituents on the iminyl radical and a methylenedioxy substituent in the base aryl ring.

The mechanism of the final oxidation may involve electron transfer from the cyclohexadienyl radical **16** to MAP yielding the corresponding delocalised cation, together with $MAP^{-\bullet}$ radical anion. Proton transfer from **16** to $MAP^{-\bullet}$ would then yield the phenanthridine **18** together with $MAPH^{\bullet}$ which would pick up hydrogen in solution to give 1-(4-methoxyphenyl)ethanol **19**. This alcohol was detected by NMR spectroscopy and MS in several reactions.

Dioxime oxalates are easily and efficiently prepared from a wide variety of oximes and can be used immediately without purification for UV generation of iminyl radicals. The process works best with precursors having aryl substituents attached to their C=N bonds. The advantage over other precursors is that the symmetrical variety cleanly release just one type of iminyl radical. The method is useful for spectroscopic work and can also be adapted for serviceable preparations of 3,4-dihydro-2*H*-pyrroles and phenanthridines.

We thank GSK and EaStChem for financial support.

Notes and references

1 M.-H. Le Tadic-Biadatti, A.-C. Callier-Dublanchlet, J. H. Horner, B. Quiclet-Sire, S. Z. Zard and M. Newcomb, *J. Org. Chem.*, 1997, **62**, 559.

2 A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543.

3 J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron Lett.*, 1991, **32**, 4299; J. Boivin, A.-M. Schiano and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 7849.

4 D. Nanni, P. Pareschi, C. Rizzoli, P. Sgarabotto and A. Tundo, *Tetrahedron*, 1995, **51**, 9045; R. Leardini, H. McNab, M. Minozzi and D. Nanni, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1072.

5 (*a*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun.*, 2007, 4041.

6 A. J. McCarroll and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2399.

7 R. Alonso, P. J. Campos, B. Garcia and M. A. Rodriguez, *Org. Lett.*, 2006, **8**, 3521; R. Alonso, P. J. Campos, M. A. Rodrıguez and D. Sampedro, *J. Org. Chem.*, 2008, **73**, 2234.

8 T. Mikami and K. Narasaka, *Chem. Lett.*, 2000, 338; K. Narasaka, K. Uchiyama, A. Ono and Y. Hyashi, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2945; K. Narasaka, K. Uchiyama and Y. Hyashi, *Tetrahedron*, 1999, **55**, 8915; K. Narasaka and T. Mikami, *C. R. Acad. Sci., Ser. IIc: Chim.*, 2001, 477; K. Narasaka, M. Kitamura and M. Yoshida, *Chem. Lett.*, 2002, 144; M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 539.

9 E. M. Scanlan and J. C. Walton, *Helv. Chim. Acta*, 2006, **89** 2133; E. M. Scanlan and J. C. Walton, *Chem. Commun.*, 2002, 2086.

10 A. R. Forrester, M. Gill, C. J. Meyer, J. S. Sadd and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 2*, 1979, 606; A. R. Forrester, R. J. Napier and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 984.

11 J. C. Jochims, S. Hehl and S. Herzberger, *Synthesis*, 1990, 1128.

12 For our purpose this was not important because each *Z*/*E* isomer gave the same iminyl radical on fission of the N–O bond.

13 A. R. Forrester and F. A. Neugebauer, in *Landolt–Bornstein, Magnetic Properties of Free Radicals*, ed. H. Fischer and K.-H. Hellwege, Springer-Verlag, Berlin, vol. II9c1, 1979, p. 115.

14 Iminoxyl radicals are persistent and have much longer lifetimes than iminyls so their concentration can build up to levels detectable by EPR spectroscopy even when only minute traces of $R_2C{=}NOH$ are present. The observation of iminoxyls by Forrester *et al.*[10] was probably due to the same cause.

15 Experimental details for the preparation of 5-(2,4-dimethoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole (**7b**) are typical of the methodology. A solution of 1-(2,4-dimethoxyphenyl)pent-4-en-1-one oxime **2b** (500 mg, 2.1 mmol) in dry ether (10 cm^3) was added dropwise to a stirred solution of oxalyl chloride (133 mg, 1.05 mmol) in ether (10 cm^3) at −40 °C. The mixture was allowed to reach rt and then stirred at rt for 3 h. Evaporation of solvent yielded the dioxime oxalate as a red oil (96%). A solution of the dioxime oxalate (400 mg, 0.57 mmol) and 4-methoxyacetophenone (171 mg, 1.14 mmol) in toluene (25 cm^3) in a quartz tube was photolysed for 4 h at rt by light from a 400 W medium pressure UV lamp. After this time the toluene was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (10% EtOAc–hexane) giving **7b** as a red oil (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, d, J = 6.7 Hz, CH_3), 1.44 (1H, m, CH_2), 2.12 (1H, m, CH_2), 2.88 (1H, m, CH_2), 3.04 (1H, m, CH_2), 3.77 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.12 (1H, m, CH), 6.43 (2H, m , CH), 7.68 (1H, d, J = 8.5 Hz, CH); ^{13}C NMR δ_C 21.9 (CH_3), 30.1, 38.1 (CH_2), 55.5 (CH_3 × 2), 66.4 (CH), 98.6, 105.1 (CH), 116.6 (C), 131.7 (CH), 159.0, 165.8, 172.3 (C); IR 3018, 2964,1609 cm^{-1} HRMS (CI^+) calcd for $C_{13}H_{18}NO_2$ (MH^+); 220.1338. Found: 220.1337.

16 See for example: M. Vargas-Sanchez, F. Couty, G. Evano, D. Prim and J. Marrot, *Org. Lett.*, 2005, **7**, 5861.