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UV promoted phenanthridine syntheses from oxime carbonate derived iminyl radicals†

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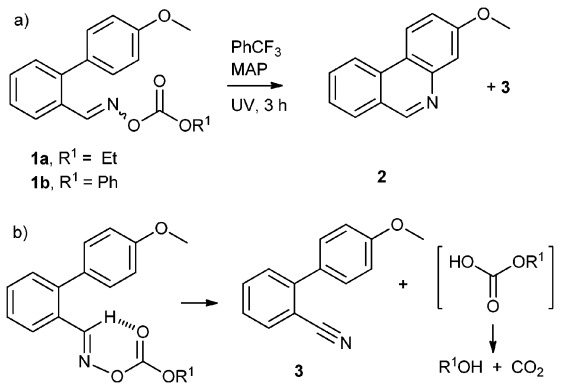
Oxime carbonates were found to be excellent precursors for the clean and direct generation of iminyl radicals under UV irradiation. Suitably functionalised iminyls underwent cyclisations yielding various phenanthridines and also substituted quinolines and isoquinolines. EPR and X-ray analyses of oxime carbonates provided insight into the mechanism.

Our group has long been interested in the clean and direct generation, and subsequent synthetic use, of organic radicals.[1] Iminyl radical cyclisations to form various *N*-heterocyclic products have been well investigated.[2,3] Whilst most methods use the toxic and explosive stalwarts of radical chemistry, *i.e.* tin hydrides, AIBN, peroxides, *etc*., some reports are of "greener" alternatives.[4] Methods to generate iminyl radicals can be neutral and mild,[2,3] attracting those seeking to develop 'clean' synthetic procedures. We reported the direct generation of iminyl radicals *via* microwave irradiation of oxime ethers[5] and UV irradiation of oxime esters,[6] oxime oxalate amides[7] and dioxime oxalates.[8] Also of note are thermal routes for iminyl radicals through cascade processes[9,10] and from iminoxyperacetates *en route* to benzoisothiazoles.[11] Herein, we report the use of oxime carbonates for radical mediated synthesis of *N*-heterocycles, where the only by-products produced are innocuous.

Surprisingly, despite possessing weak N–O bonds similar to those of other oxime esters, oxime carbonates have not yet been used as precursors for the generation of iminyl radicals. Our synthetic route to the oxime carbonates (see ESI†) was relatively inexpensive. A second advantage of oxime carbonates is their long-term stability *cf*. dioxime oxalates which readily decomposed.[8] Previous studies demonstrated that UV promoted cyclisations proceeded best when oxime-derived radical precursors possessed an aryl group adjacent to the C=N bond.[8] Therefore, initial exploratory UV cyclisations were performed on 4′-methoxybiphenyl-2-carbaldehyde *O*-ethoxycarbonyl oxime **1a** (Scheme 1a). UV reactions were carried out in deaerated benzotrifluoride solutions with 1 equiv. *wt*/*wt* of 4-methoxyacetophenone (MAP) as a photosensitiser. UV irradiation was supplied by an unfiltered 400 W medium pressure Hg lamp situated 6–8 cm from quartz tubes containing the oxime carbonates. After irradiation for 3 h 6-methoxyphenanthridine **2** was isolated in a low 30% yield, also obtained was nitrile **3** in a comparable yield (27%). In addition, an aldehyde produced by hydrolysis of the corresponding imine (generated by the iminyl radical undergoing hydrogen abstraction) was observed.

We reasoned that a resonance stabilised oxygen centred radical might improve the efficacy of this reaction, thus *O*-phenoxycarbonyl oxime derivative **1b** was synthesised and tested. Whilst the yield of phenanthridine **2** improved (40%), the yield of nitrile **3** also increased (41%) and aldehyde by-product was still observed. We postulated that nitrile **3** is produced by a competing pericyclic mechanism, where a degree of pre-organisation is required such that an intramolecular hydrogen bond is formed (Scheme 1b). In order to disrupt the H-bonding, to favour production of phenanthridine over nitrile, a brief set of solvent screening reactions was undertaken employing acetonitrile, *N*,*N*-dimethylformamide and *tert*-butanol (*t*-BuOH) (see ESI†). Pleasingly, performing the UV photolysis reaction on **1b** in *t*-BuOH resulted in a greater yield of phenanthridine **2** (75%) with only 20% of nitrile **3** isolated. Although the reaction selectivity had been altered to



Scheme 1 (a) UV photolysis of carbaldehyde oxime carbonate derivatives; (b) proposed intramolecular mechanism of nitrile formation.

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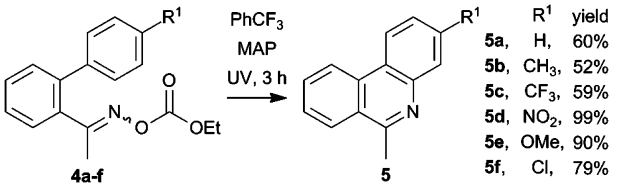
† Electronic supplementary information (ESI) available: General methods, characterising data for oxime carbonates and *N*-heterocyclic products including ^{1}H & ^{13}C NMR spectra. CCDC 824855–824858. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12720a



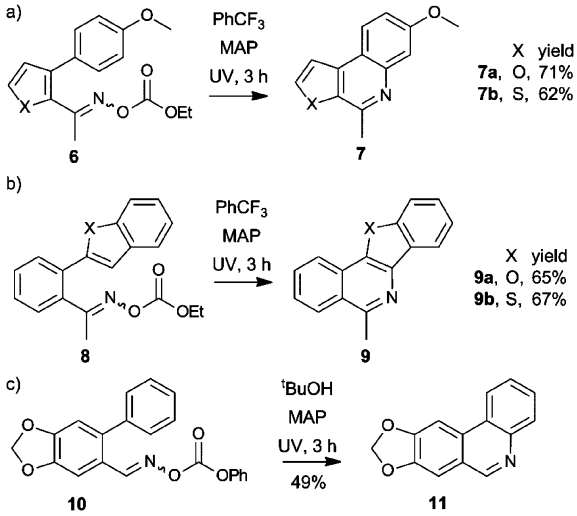
Scheme 2 Phenanthridine preparations from UV photolyses of acetophenone *O*-ethoxycarbonyl oxime derivatives at RT.

favour our desired phenanthridine product (~4 : 1), the electrocyclic mechanism was still in play. To avert nitrile production, we chose to replace the iminyl hydrogen with a methyl group, thus blocking the electrocyclic pathway. Incorporation of a methyl group adjacent to the C=N bond was achieved by starting the synthesis of oxime carbonate **4a** from 2′-bromoacetophenone and phenyl boronic acid. UV photolysis of **4a** (R^1 = H) under our reaction conditions, 1 equiv. of MAP, $PhCF_3$ as solvent, 3 h UV irradiation at ambient temperature, gave 6-methylphenanthridine **5a** in 60% yield (Scheme 2).[12]

A set of substituted biphenyl *O*-ethoxycarbonyl oxime derivatives **4b–f** was prepared to probe the toleration of the process for substituents in the *para* position of the aromatic ring on to which the iminyl radical cyclised. Under our standard photolysis conditions, we isolated 3-substituted 6-methylphenanthridines **5b–f** in good to quantitative yields (52%–99%, Scheme 2) irrespective of the electron-withdrawing or -releasing character of the substituent. *Para*-nitro substituted oxime carbonate **4d** gave rise to a welcome surprise after UV irradiation. Crystals suitable for X-ray crystallographic analysis had grown from a nucleation site on the wall of the quartz tube closest to the UV source! ^{1}H NMR and X-ray analysis of the crystals confirmed the structure as that of **5d** (see ESI†). Filtration of the crude reaction mixture gave **5d** in quantitative yield, which is probably a result of a kinetic effect arising from the crystallisation of **5d** out of the reaction solution. The yield of 3-methoxy-6-methyl-phenanthridine (**5e**) was also high (90%) so we further examined this reaction to see if shorter UV irradiation times resulted in better yields. Sadly, after 1 h irradiation just 56% of **5e** was isolated. Interestingly, in the absence of MAP, UV irradiation for 3 h produced **5e** in 74% yield. We attribute these high yields to the structural similarity of **4e** to MAP, facilitating effective harvesting of UV light without the need for a photosensitiser.

To expand the scope of our methodology we synthesised *O*-ethoxycarbonyl oximes based on furan and thiophene derivatives, Scheme 3a. The *para*-methoxy substituent was retained due to the high yields achieved for the synthesis of **5e**. Under our standard conditions furanyl oxime carbonate **6a** and thiophenyl oxime carbonate **6b** gave quinolines **7a** and **7b** in 71% and 62% yields respectively. The ground state iminyl SOMO and the attacked aromatic ring orbital, in the radicals derived from **6a,b**, will be further apart than in the radicals derived from **4a–f**, because of the larger angles associated with 5-membered rings (72°) compared to 6-membered rings (60°). However, our results demonstrate that this did not significantly affect the yields of cyclised heterocycles **7a,b**.

Benzo[b]furan (**8a**) and benzo[b]thiophene (**8b**) oxime carbonates were next investigated, Scheme 3b. Comparable yields



Scheme 3 (a) and (b) UV photolysis of heterocyclic *O*-ethoxycarbonyl oxime derivatives, and (c) synthesis of trispheridine.

were observed for both isoquinolines **9a** (65%) and **9b** (67%). To complete our synthetic exploration we turned to the pharmacologically active alkaloid trispheridine. An *O*-phenoxycarbonyl oxime was synthesised as our earlier results had demonstrated that aldehyde-*O*-phenoxy-carbonates gave better yields than aldehyde-*O*-ethoxy-carbonates. Precursor **10** was subjected to UV irradiation in *t*-BuOH, to disrupt any preorganised H-bonding that would favour nitrile formation, and produced trispheridine **11** in 49% yield. Extended UV irradiation times (5 h) led to photo-degradation of the natural product, reducing the yield to only 22%.

Here, our oxime carbonates were stable over a period $\geq$ 1 year. Indeed, a year-old neat sample of oxime carbonate **4f** had developed crystals suitable for X-ray crystallographic analysis which revealed two independent molecules within the asymmetric unit (Fig. 1a).[13] Furthermore, **1b** and **10** also crystallised out from neat samples (Fig. 1b and 1c).[13] The oxime carbonate units were found to be close to planar and in extended all-*trans* conformations;[14] as observed previously for dioxime oxalates.[8]

We studied all of the oxime carbonates by 9 GHz EPR spectroscopy. Deaerated samples of the each oxime carbonate plus 1 equiv. *wt*/*wt* of MAP in PhBu-*t* were photolysed directly in the resonant cavity by a 500 W unfiltered Hg lamp. The spectrum (Fig. 2a) obtained from **1b** showed an iminyl radical (1 : 1 : 1 triplets at either wing) with EPR parameters [*g*-factor = 2.0029, *a*(1H) = 80.00, *a*(1N) = 9.91 G] similar to those reported for other iminyls.[15,16]

The spectrum in the central region [*g* = 2.0049, *a*(2H) = 2.02, *a*(2H) = 6.85, *a*(1H) = 9.87 G] was clearly that of the phenoxyl radical.[17] Similar iminyl radical spectra were observed for all our oxime carbonates.[18] In our proposed mechanism (Scheme 4) the weak N–O bond homolytically cleaves to generate the iminyl radical **12**, as observed in the EPR spectra, plus acyloxyl radical **13**. The EPR spectrum from **1b** showed equal amounts of **12** and PhO$^\bullet$ (49.7% : 50.3%) and hence dissociation of **13** to CO_2 and phenoxyl (ethoxyl for other precursors) must have been essentially instantaneous even at 240 K. An intramolecular ring closure of iminyl radical **12**

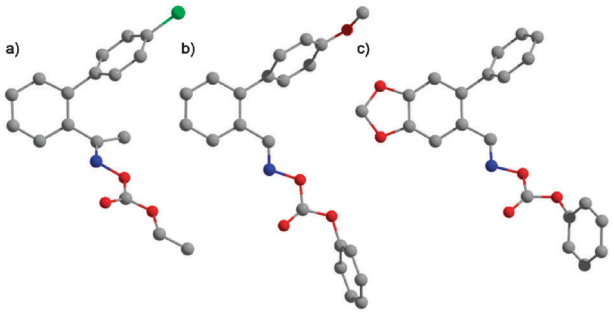


Fig. 1 The X-ray crystal structures[13] of oxime carbonates (a) **4f** (showing just one of the two independent molecules present in the asymmetric unit), (b) **1b**, and (c) **10**.

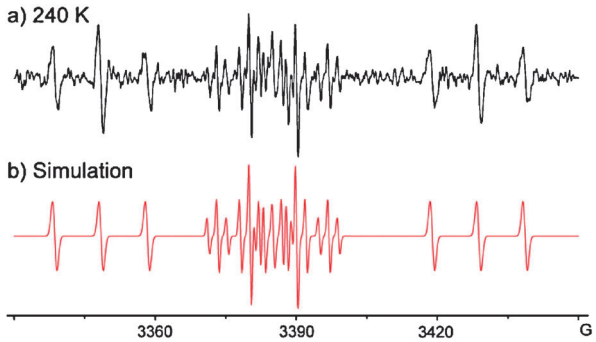
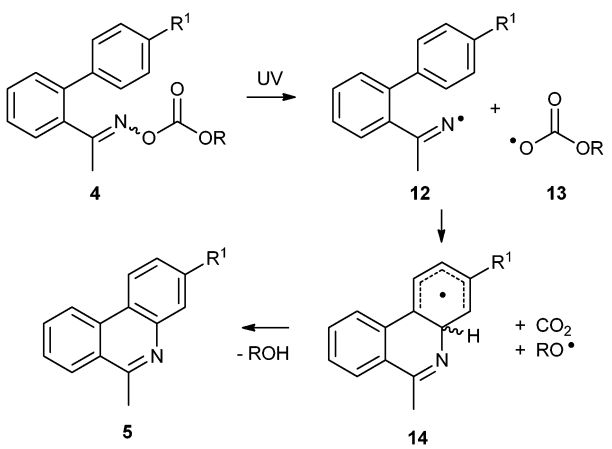


Fig. 2 (a) EPR spectrum from UV irradiation of **1b** in PhBu-*t* at 240 K; (b) computer simulated spectrum for both iminyl and phenoxyl radicals.

onto the phenyl acceptor produces a cyclohexadienyl radical **14** that undergoes H-atom transfer to an ethoxyl radical (or to phenoxyl) thus yielding the aromatic phenanthridine product and ethanol (or phenol).

Our investigations demonstrated that oxime carbonates are convenient and clean radical precursors. Benefiting from a cheap and facile synthesis from a large variety of carbonyl compounds, oxime carbonates also possess long shelf lives. They can be transformed into a variety of *N*-heterocycles



Scheme 4 Postulated radical mechanism for the formation of substituted phenanthridines.

including phenanthridines, furo- and thieno-quinolines, benzofuro- and benzothieno-isoquinolines by our mild radical-mediated procedure. The only by-products, CO_2 and either ethanol or phenol, are innocuous and easily removed. The process is evidently an attractive strategy for the development of target-oriented heterocycle syntheses.

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12 The cyclisations did not take place under thermal conditions (MW, 150 °C, 30 min) although nitrile formation from **1a,b** was efficient.
13 The crystal data and experimental details of the structural refinement for **1b**, **4f**, **5d** and **10** are provided in the ESI†. CCDC 824855, 824856, 824857 and 824858 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
14 The N–O bond lengths for **4f** were 1.425(9) Å and 1.431(10) Å. Replacing the iminyl methyl group with an H-atom did not appreciably affect the N–O bond lengths as shown by the crystal structures of **1b** at 1.4473(17) Å and **10** at 1.451(2) Å. The dihedral angle about the iminyl C=N bond was close to planar in each of the molecular structures: **4f** (−175.7(8)° and 177.5(8)°); **1b** (178.4(1)°); **10** (179.6(2)°).
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