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Preparation of oxime oxalate amides and their use in free-radical mediated syntheses of lactams

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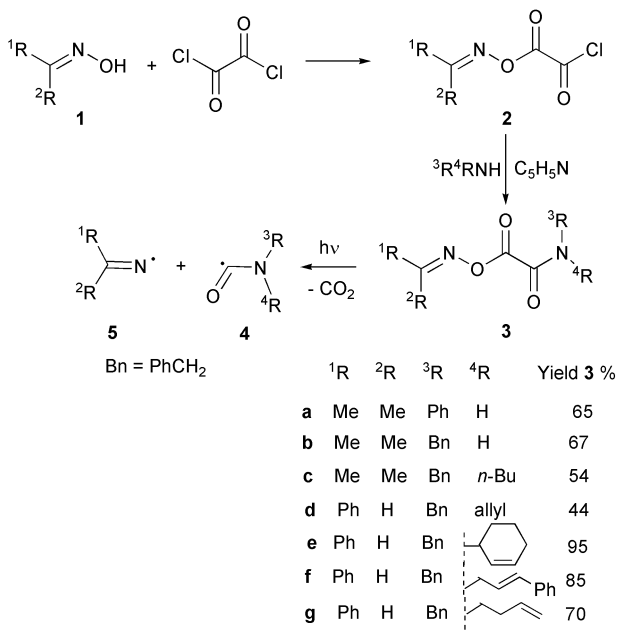
Photosensitised decomposition of oxime oxalate amides is a useful new route to carbamoyl radicals that may cyclise to afford β- or γ-lactams.

Mild 'clean' free radical precursors, as alternatives to organotin hydrides, for large and small scale organic syntheses are very desirable. Other group 14 element hydrides, xanthates, hypophosphorous acid derivatives and cyclohexadienyl derivatives are prominent among the new alternatives.[1,2] It was known[3,4] that C-centred radicals R· could be obtained by photolyses of oxime esters $R^1R^2C{=}NOC(O)R$. Furthermore, suitably unsaturated radicals generated in this way cyclised in yields of over 70%.[5] By analogy, the structural features of oxime oxalate amides **3** hinted that they might function as novel, clean sources of aminoacyl radicals (carbamoyl radicals) **4**. Suitably unsaturated aminoacyl radicals could then ring close, so that the final outcome would be the establishment of a new synthetic route from secondary amines to lactams.

The only previous synthesis of an oxalate of type **3** utilised acetone *O*-(chlorooxalyl)oxime (**2** $R^1 = R^2 = Me$) together with 2 equiv. of aniline to afford the corresponding amide.[6] However, we found that this method failed for most other amines. Attempts to make mono-amides of oxalyl chloride and condense these with oximes also failed. However, when **2** was treated with 1 equiv. of a primary or secondary amine, in the presence of 1 equiv. of pyridine at 0 °C good yields of the corresponding oxime oxalate amides were obtained (Scheme 1).

Solutions of individual oxime oxalate amides in *tert*-butylbenzene (*ca*. 0.05 mol dm^{-3}) were deaerated and photolysed with UV light from a 500 W Hg arc in the resonant cavity of a 9 GHz EPR spectrometer. For all of **3a**–**g** spectra were observed in the temperature range 200–320 K. Considerable enhancement of signal intensity was achieved on addition of 1 or more equiv. of 4-methoxyacetophenone (MAP) as a photosensitiser. Fig. 1 shows the remarkable spectrum obtained on MAP sensitised photolysis of **3g**. A clear 'snapshot' of all three radicals was captured, that proved their intermediacy, and enabled them to be characterised.



	^1R	^2R	^3R	^4R	Yield **3** %
a	Me	Me	Ph	H	65
b	Me	Me	Bn	H	67
c	Me	Me	Bn	*n*-Bu	54
d	Ph	H	Bn	allyl	44
e	Ph	H	Bn		95
f	Ph	H	Bn	Ph	85
g	Ph	H	Bn		70

Scheme 1 Synthesis and photodissociation of oxime oxalate amides.

The two groups of three lines at the left and right ends of the spectrum (marked I in Fig. 1) are due to the iminyl radical PhC(H)=N·. The well-spaced N-triplet (marked A) is due to the aminoacyl radical **4g**. This latter radical contains a vinyl group suitably placed for a 5-*exo*-trig [$\mathbf{C^{5x}}$][7] cyclisation and indeed the doublet of triplets (marked C) is due to the cyclised 2-oxopyrrolidinylmethyl radical **7g** (n = 2).[8] The spectra from most of the other oxime oxalate amides showed iminyl **5** and aminoacyl radicals **6**. In no case was an iminoxyl radical $^1R^2RC{=}NO$· observed. The EPR spectra demonstrated, therefore, that scission of the N–O bonds of **3** occurred cleanly and that this was followed by rapid CO_2 loss to afford radicals **4** that could subsequently cyclise.

The best conditions for preparations of lactams (**9**–**11**) were established by means of a series of photolyses with compound **3g**. Dilute solutions in toluene, with a three-fold excess of MAP, were found to afford *N*-benzyl-3-methylpyrrolidin-2-one (**9g**) in > 80% yield.[9] GC–MS analysis showed that the *N*-formyl by-product (**8g**) was negligible (< 1%). It was expected that β-lactam formation would be more difficult because this would involve disfavoured 4-*exo*-ring closures [$\mathbf{C^{4x}}$]. Although the 40% yield of *N*-benzyl-3-methylazetidin-2-one (**9d**) was certainly modest, it compared favourably with previous radical routes to azetidin-2-ones involving aminoacyl radicals generated from Co–salophens[10] or amidocyclohexadienes.[11]

Ring closures of the aminoacyl radicals (**4e**, **4f**) derived from the cyclohexenyl- and phenyl-substituted materials **3e** and **3f** afforded the bicyclic β-lactam **10** and 3-benzyl-substituted β-lactam **11** respectively. In both cases the cyclised radicals were more stabilised (one was secondary and the other secondary-benzylic) and this favoured 4-*exo*-ring closure. Yields of **10** and **11** were good and compared very favourably with those of β-

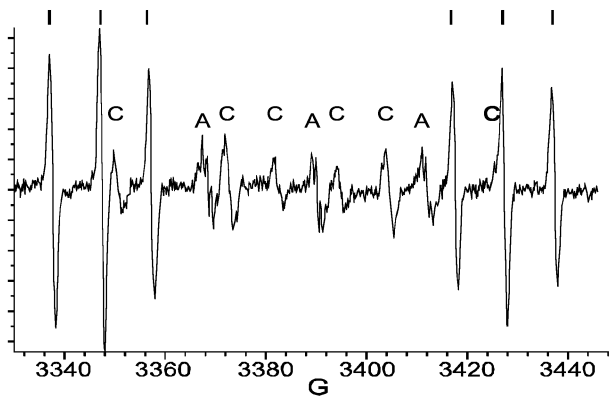


Fig. 1 9.4 GHz EPR spectrum obtained on photolysis of a solution of **3g** and MAP in *tert*-butylbenzene at 220 K. I; iminyl **5g**, A; aminoacyl **4g**, C; *N*-benzyl-2-oxopyrrolidinylmethyl radical **7g**.

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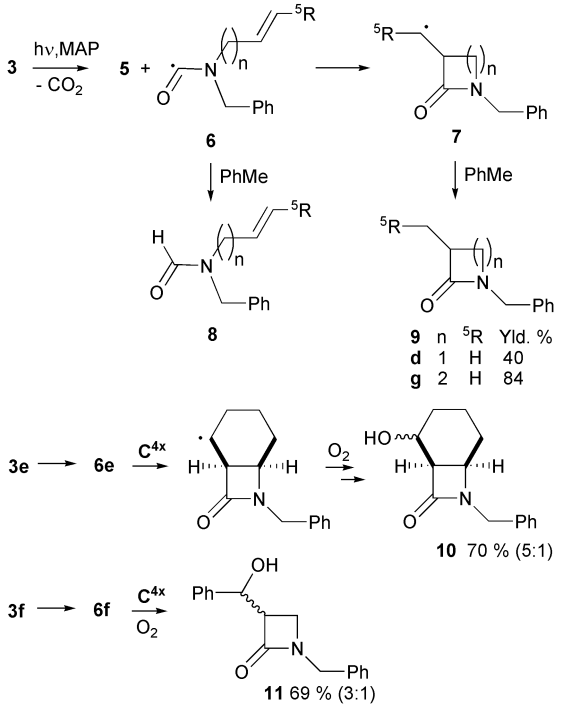
lactams prepared by organotin hydride mediated cyclisations of 1-amidoalkyl radicals.[12–14]

An interesting feature was that both **10** and **11** were obtained as hydroxyl derivatives, the former as a 5:1 mixture of *anti*- and *syn*-isomers[15] and the latter as a pair of diastereoisomers (3:1) (Scheme 2). Probably hydrogen abstraction from the toluene solvent was slower for the secondary precursor radical for **10** and the benzylic precursor radical for **11**, so that addition of dissolved dioxygen supervened. The peroxyl radicals formed in this way would be converted to more reactive oxyl radicals (by self-coupling and O_2 loss)[16] that did abstract hydrogen, hence affording the hydroxyl derivatives.



Scheme 2 Preparation of β- and γ-lactams via photosensitised reactions of oxime oxalate amides.

Iminyl radicals **5** are inevitably formed as co-intermediates with the desired aminoacyls **4**. However, the only significant product derived in each case from **5** (**d**–**g**) was benzaldehyde. Evidently **5** abstracts hydrogen from the solvent to give PhC(H)=NH that is hydrolysed on work-up. Under the experimental conditions described above, hydrogen abstraction prior to cyclisation was unimportant and negligible amounts of formamides **8** were produced. In practice, therefore, interference from undesired by-products was unproblematic.

We conclude that photosensitised decompositions of oxime amide oxalates provide an efficient and general route to aminoacyl radicals. Good yields of γ-lactams can be obtained from ring closures of 4-unsaturated aminoacyl radicals. Similarly, β-lactams can be obtained from secondary amines with alk-2-enyl substituents, and related amines, in a two-step process. If the unsaturated bond is functionalised with an aryl or alkyl group at the 3-position in the amine, the cyclised azetidinylalkyl radical is stabilised and consequently a hydroxybenzyl or hydroxyalkyl side chain is introduced with potential for additional functional group manipulation.

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8 EPR parameters for the radicals derived from **3g** in *tert*-butylbenzene at 220 K were: iminyl (I) g = 2.0034, a(N) = 9.9, a(H) = 79.9 G; aminoacyl (A) g = 2.0017, a(N) = 21.7 G; cyclised radical **7g** (C) g = 2.0025, a(2H) = 22.3, a(1H) = 31.6 G (1G = 10 mT).
9 A solution of oxime oxalate amide **3g** (0.8 g, 2.38 mmol), and MAP (1.0 g, 7.14 mmol) in toluene 400 cm^3 was heated to 100 °C and photolysed with a 400 W UV lamp in a quartz cold finger immersed in the solution for 5 h. The mixture was allowed to cool to room temperature and then evaporated to dryness to give the crude lactam. Column chromatography (DCM: 1.0% MeOH) gave the pure cyclised product, 1-benzyl-3-methyl-pyrrolidin-2-one (**9g**) as a colourless oil (378 mg; 84%); δ_H (300 MHz, $CDCl_3$) 1.25 (3 H, *d*, J = 7.2 Hz, CH_3), 1.60 (1 H, m, CH), 2.25 (1 H, m, CH), 2.52 (1 H, m, J = 7.2 Hz), 3.19 (2 H, m, CH_2) 3.19 (2 H, m, CH_2), 4.42 (1 H, AB, CH), 4.48 (1 H, AB, CH), 7.21–7.37 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 27.1 (CH_2), 36.8 (CH), 44.7 (CH_2), 46.8 (CH_2), 127.5, 128.1, 128.6 (5 × CH), 136.7 (C), 177.4 (C=O); *m*/*z* (relative intensity) 189 (100, M^+), 174 (11), 161 (12), 91 (90); found M^+ 189.1153, $C_{12}H_{15}NO$ requires 189.1154.
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