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Preparation of β- and γ-lactams from carbamoyl radicals derived from oxime oxalate amides†

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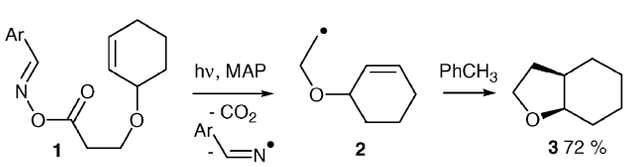
A general synthetic route to oxime oxalate amides was developed and applied to the preparation of molecules incorporating *N*-benzyl-*N*-alkenyl amides linked with acetone oxime or benzaldoxime units. In addition, 2-substituted-thiazolidine-4-carboxylic acid methyl ester amides of oxalyl benzaldoxime were also prepared. It was shown by EPR spectroscopy that the oxalyl benzaldoxime amides dissociated to produce benziminyl and carbamoyl (aminoacyl) radicals when photolysed with 4-methoxyacetophenone as a photosensitizer. Carbamoyl radicals derived from *N*-alk-3-enyl oxime oxalate amides underwent ring closure to afford pyrrolidin-2-ones. The analogous *N*-alk-2-enyl precursors afforded azetidin-2-ones. Reactions of the cyclohexenyl and cinnamyl oxime oxalate amides afforded a bicyclic β-lactam and a 3-benzyl-substituted β-lactam respectively. Interestingly, both products were isolated as hydroxylated compounds. A thiazolidine-derived oxime oxalate amide containing an isobutenyl side chain also dissociated with production of the corresponding thiazolidinyl-carbamoyl radical, as shown by EPR spectroscopy. GC-MS evidence indicated that this radical cyclised to afford some of the corresponding penicillin derivative

Introduction

The advantages of free-radical based synthetic methods have been ably described in several recent books[1] and reviews.[2] Many free radical chain syntheses rely on organotin compounds but, because of their toxicity, alternative reagents are very desirable.[3] Oxime esters [$R^1R^2C{=}NOC(O)R$] contain weak N–O bonds and were shown to release C-centred radicals under certain circumstances. Hasebe and co-workers used benzophenone oxime esters as photochemical sources of alkyl radicals in preparations of alkyl aromatics,[4a,b] alkyl chlorides[4c,d] and alkanes.[4c,d] In our group we used EPR spectroscopy to show that the efficiency of radical release from oxime esters could be improved by using *p*-methoxyacetophenone (MAP) as a photosensitiser and by incorporating methoxy substituents into an aromatic group R^1. In this way good yields of cyclized products (*e.g.* **3**) were obtained from suitably unsaturated di- and tri-methoxy-substituted aldoxime esters such as **1** (Scheme 1).[5]



Scheme 1 Cyclization of a C-centred radical derived from an oxime ester.

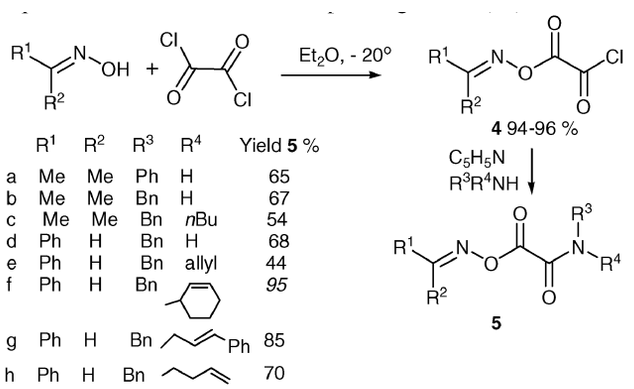
Interference from the iminyl radicals ($R^1R^2C{=}N^{\bullet}$) produced was minimal. They simply abstracted a hydrogen atom from the solvent and the resulting imine hydrolysed during work-up to afford the corresponding aldehyde or ketone. It was evident that there was wide scope for radical generation from this class of compounds. These results suggested that other oxime derivatives could be useful as 'clean' sources of various radical types. Oxime oxalate amides **5** (OOAs) retain the weak N–O bond of **1**. The acyloxyl radical generated on fission of this bond was expected to extrude CO_2 very easily. Thus **5** appeared promising as a precursor type for aminoacyl radicals (carbamoyl radicals). In this paper we report the synthesis of a range of oxime oxalate amides, a study of radical generation by EPR spectroscopy and some applications of these compounds to the preparation of β- and γ-lactams. Part of this research was published in a preliminary communication.[6]

Results and discussion

Preparation and characterisation of oxime oxalate amides

In the only previous synthesis of an oxime oxalate amide, Jochims *et al*. treated acetone *O*-(chlorooxalyl)oxime **4** ($R^1{=}R^2{=}$ Me) with 2 eq. of aniline to afford the corresponding amide (**5a**).[7]

Not only did this method 'waste' one eq. of amine, but we also found that it failed for other amines. We attempted to make mono-amides of oxalyl chloride with *N*-benzyl-*N*-*n*-butylamine, for subsequent condensation with oximes, but without success. However, when **4** was treated with 1 eq. of a primary or secondary amine, in the presence of 1 eq. of pyridine at 0 °C, good yields of the corresponding oxime oxalate amides were obtained. As Scheme 2 shows, the method worked well for benzaldehyde oxalyl oximes as well as the acetone analogues. The oxime oxalate amides derived from benzaldehyde, **5d**–**h**, are



	R^1	R^2	R^3	R^4	Yield **5** %
a	Me	Me	Ph	H	65
b	Me	Me	Bn	H	67
c	Me	Me	Bn	*n*Bu	54
d	Ph	H	Bn	H	68
e	Ph	H	Bn	allyl	44
f	Ph	H	Bn		*95*
g	Ph	H	Bn		85
h	Ph	H	Bn		70

Scheme 2 Preparation of oxime oxalate amides.

† Electronic supplementary information (ESI) available: Gaussian98 ARC files for model carbamoyl radicals. See http://www.rsc.org/suppdata/ob/b3/b315223e/

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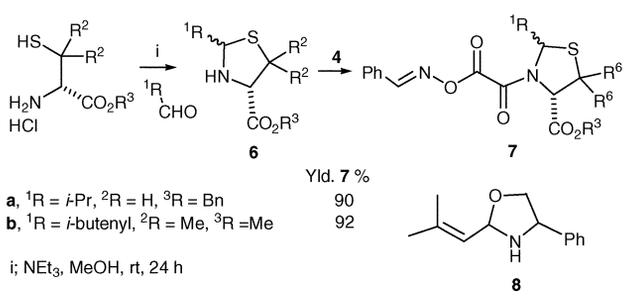
believed to be the *syn* isomers (*i.e.* *E*-isomers). The synthesis of benzaldoxime was specific to the *syn* isomer.[8] Reported chemical shifts of the oximyl hydrogen of various substituted benzaldoximes were dramatically different for the *syn* and *anti* isomers.[9] All the *syn* isomers had protons with $\delta > 8$, while the *anti* isomers (*Z*-isomers) had $\delta < 7.5$. The δ values for **5d**–**h** were all in the range 8.38–8.50 ppm, *i.e.* as expected for *syn* isomers. This was confirmed for **7b** by an X-ray structure determination (see below). However, the ^{1}H NMR spectra of **5e**,**f** showed two resonances for the oximyl and other H-atoms. This probably indicated the presence of two isomers due to restricted rotation about the N–C(O) amide bond. The isomer proportions were close to 1 : 1 in each case.

We also investigated if the radical methodology developed for the preparation of simple bicyclic lactams could be applied to the preparation of penicillins. The general synthetic strategy envisaged preparation of penicillins *via* 4-*exo* cyclisations of thiazolidine-containing OOAs **7**. Thus, thiazolidines with double bonds suitably placed for ring closure, *e.g.* **6b**, were required. Only one thiazolidine of this type had previously been prepared.[10] The synthetic strategy we employed was based on the well known condensation reaction of penicillamine esters with appropriate aldehydes.[11] This condensation reaction had never been applied to the preparation of a vinylic thiazolidine and it was anticipated that there might be a mixture of products arising from the competing Michael addition, whereby nucleophilic attack would occur at the "softer" Michael centre of the double bond rather than at the desired aldehyde carbon. To bias the equilibrium towards the desired thiazolidine condensation product, the Michael addition site was hindered by using the dimethyl-substituted double bond of 3-methylbut-2-enal. In this way functionalised thiazolidines **6** were prepared from condensation of L-cysteine, D,L-penicillamine and L-penicillamine with aldehydes (Scheme 3). Because the yields of **6b** were low (25–28%) we tried to circumvent this poor step, *via* condensations with glyoxal, and protected glyoxal. The thiazolidine could then have been elaborated *via* a Wittig reaction. However, condensation of penicillamine with glyoxal failed and, although condensation with $OCHCH(OMe)_2$ succeeded, deprotection failed.



Scheme 3 Preparation of oxime oxalate amides from thiazolidines.

Secondary amines **6a**,**b** were converted to the corresponding oxime oxalate amides **7** in high yields on treatment with **4** in the presence of pyridine. An analogous oxazolidine **8** was also prepared, but this failed to give an oxime oxalate amide; probably because of steric hindrance from the phenyl group adjacent to the amine group.

The oxime oxalate amide derived from D,L-penicillamine *i.e.* **7b** was a crystalline solid and hence its structure was obtained by X-ray diffraction (Fig. 1). As might be expected, the two oxalyl carbonyl groups were *trans* to one another. As a consequence, the molecule exists in an *all-trans* extended conformation and, except for the substituents in the thiazolidine ring, is almost planar. The N–O bond length of 1.453 Å is long for an oxime, the usual range being[12] 1.38–1.43 Å. This supported our premise that N–O homolysis would be comparatively facile.

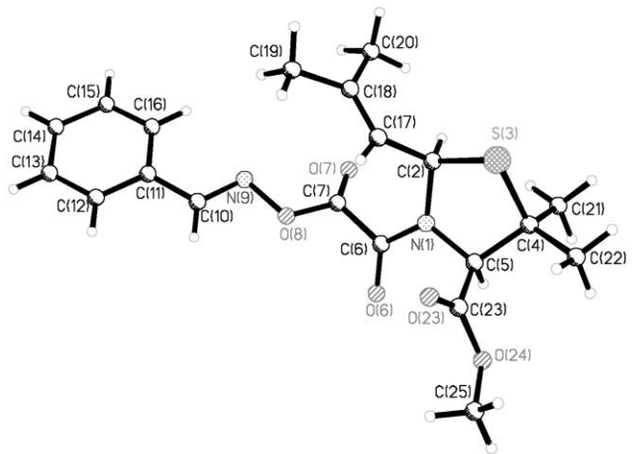


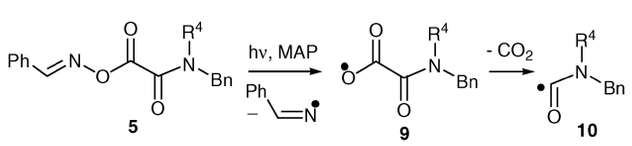
Fig. 1 X-Ray structure of oxime oxalate amide **7b** in the crystal.

EPR spectroscopic study of radical generation and cyclisation

Photolyses (500 W Hg arc, unfiltered) of deoxygenated *tert*-butylbenzene solutions of acetone ketoxime oxalate ester amides **5a**–**c** in the resonant cavity of a 9 GHz EPR spectrometer gave rise to spectra of the propan-2-iminyl radical ($Me_2C{=}N^{\bullet}$) with EPR parameters identical to those reported in the literature.[13]

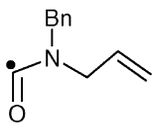
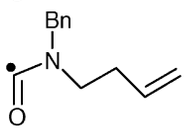
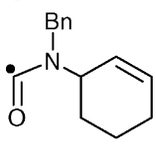
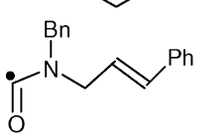
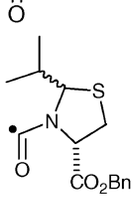
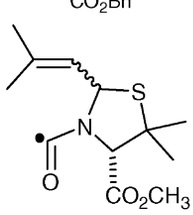
Addition of one or more eq. of 4-methoxyacetophenone (MAP) as photosensitiser[14] to samples prior to degassing, dramatically improved the spectral intensity. No signals from the corresponding carbamoyl radicals were observed for any of these acetone–oxime derived precursors. However, MAP photosensitised reactions of the benzaldoxime oxalate ester amides **5c**–**h** and **7a**,**b** gave spectra containing signals from the iminyl radical $PhCH{=}N^{\bullet}$ [$g = 2.0034$, $a(N) = 9.9$, $a(1H) = 79.9$ G at 220 K][15] accompanied by 3-line spectra having $a(N)$ values of 22 ± 1 G (Table 1 and Fig. 2). A few archetype carbamoyl radicals have previously been characterised by EPR spectroscopy,[16,17] and comparison with this data supported identification of our 3-line spectra as carbamoyl radicals **10**. Similarly, DFT computations[18] of the hyperfine splittings (hfs) of several model radicals (UB3LYP with a 6-311+G(d,p) basis set, Table 1) gave N- and H-atom hfs satisfyingly close to the experimentally measured data. These aminoacyl radicals are all capable of existing as *E*- and *Z*-isomers. Separate spectra for the two forms were not, however, observed in any case. Individual components of the aminoacyl N-triplets were often rather broad ($\Delta H_{pp} \sim 2$ G) and this might be a consequence of overlap of *E*- and *Z*-species with similar $a(N)$ values. In the case of the thiazolidinyl containing radicals a small doublet hfs, probably from one of the thiazolidine ring H-atoms, was resolved (Fig. 2). Judging by the EPR spectra, **10** are σ-radicals with high barriers to rotation about their N–C(O) amide bonds.

The results indicated that oxime ester amides **5** underwent homolysis of their weak N–O bonds on direct and photosensitised UV photolysis to afford mixtures of iminyl and acyloxyl radicals **9**. The latter rapidly lost CO_2 to release the corresponding carbamoyl radicals **10** (Scheme 4). The ratio of the concentrations of the iminyl and aminoacyl radicals depended on temperature and on the nature of R^4. Scission of a N–O bond in **5** should initially produce equal amounts of an iminyl and an acyloxyl radical **9** (Scheme 4). However, the experimental ratio of aminoacyl to iminyl radicals [**10**]/[Im] (Table 1)



Scheme 4 Photodissociation of oxime oxalate amides.

Table 1 EPR parameters for carbamoyl radicals at 220 K in PhBu-*t* solution[a]

Carbamoyl radical		*g*-factor/theoretical method	hfs/G	[**10**]/[Im][b]
	**10e**	2.0018	*a*(N) = 22.3	0.8
	**10h**	2.0017	*a*(N) = 21.7 *a*(1H) = 0.8	0.8[c]
	**10f**	2.0016	*a*(N) = 21.2	0.7[d]
	**10g**	2.0017	*a*(N) = 21.9	0.2
		2.0016	*a*(N) = 21.5 *a*(1H) = 1.5	1.0
	**16**	2.0018	*a*(N) = 21.0 *a*(1H) = 1.6	1.2
(O)C$^{\bullet}$NMe$_2$		UB3LYP 6-311+G(d,p)	*a*(N) = 24.2	
(O)C$^{\bullet}$NHCH$_2$Ph		UB3LYP 6-311+G(d,p)	*a*(N) = 26.5 *a*(1H) = 24.0 *a*(2H) = −0.7	
(O)C$^{\bullet}$NMeCH$_2$Ph		UB3LYP 6-311+G(d,p)	*a*(N) = 23.4 *a*(3H) = −0.7 *a*(2H) = −0.7	

[a] In each case the iminyl radical PhCH=N$^{\bullet}$ (Im) with *g* = 2.0034, *a*(N) = 9.9, *a*(1H) = 79.9 G at 220 K was also detected. [b] Ratio of the concentrations of the carbamoyl and iminyl radicals determined by double integration of suitable EPR lines. [c] The ring closed radical **11h** [*g* = 2.0025, *a*(2H) = 22.3, *a*(1H) = 31.6 G at 220 K] was also detected. [d] The bicyclic radical **11f** was also detected and is included with **10** in the ratio.

will depend on the completeness of decarboxylation of **9** as well as the radical termination efficiencies. For most of the oxime oxalate amides the observed ratio was within a factor of two or three of unity. Decarboxylations of **9** were, therefore, rapid and the observed differences can be attributed to minor variations in the rates of their termination reactions.

Previous spectroscopic work showed that oxime esters of type **1** were susceptible to addition by C- and O-centred radicals to produce alkoxyaminyl radicals PhCH(X)N$^{\bullet}$OC(O)R.[5] When **5d**, containing benzyl and H-atom substituents on the amide N-atom, was photolysed with MAP at T > 320 K a second spectrum accompanied that of the iminyl radical. The EPR parameters of this species [*g* = 2.0046, *a*(N) = 14.6, *a*(1H) = 19.7 G at 320 K] were very similar to those reported for the oxyaminyl radicals referred to above and it is probable that this spectrum belongs to an adduct radical of similar type. Oxyaminyl adducts were not detected for any other oxime oxalate amides, probably because other reaction pathways supervened.

EPR spectra from photosensitised reactions of **5e**–**h** and **7a**,**b** containing benzyl and unsaturated substituents, or thiazolidine-2-alkenyl substituents, displayed iminyl and aminoacyl radicals (see Fig. 2 and Table 1). These aminoacyl radicals **10** can potentially undergo *5-exo*-cyclisations to produce 2-oxopyrrolidinylmethyl radicals **11h** or *4-exo*-cyclisations to produce 2-oxoazetidinylalkyl radicals **11f**. A noteworthy spectrum containing three radicals, the iminyl, aminoacyl **10h** and the ring-closed 2-oxopyrrolidinylmethyl radical **11h** was described previously.[6] The EPR spectra from **5e** and **5g** showed minor signals that might have been due to cyclised radicals, in addition to those of the iminyl and aminoacyl radicals, but they were not intense enough for definitive analysis.

Preparations of β- and γ-lactams

Preparative scale photolyses were carried out for oxime oxalate amides **5e**–**h**. A short series of experiments with **5h** established that the γ-lactam, *N*-benzyl-3-methylpyrrolidin-2-one (**12h**), could be obtained in >80% yield from photolyses of dilute solutions in toluene with a three-fold excess of MAP. Similar conditions were used for the other substrates. GC-MS analysis showed that the *N*-formyl compound **13**, resulting from direct H-atom transfer to the aminoacyl radical, was negligible (<1%) (Scheme 5). β-Lactam formation was expected to be more difficult because of the disfavoured 4-*exo*-ring closures [**C^{4x}**]. Photosensitised reaction of the allyl OOA-precursor **5e** yielded 40% of *N*-benzyl-3-methylazetidin-2-one (**12e**). Although this is a modest yield it compares favourably with previous radical

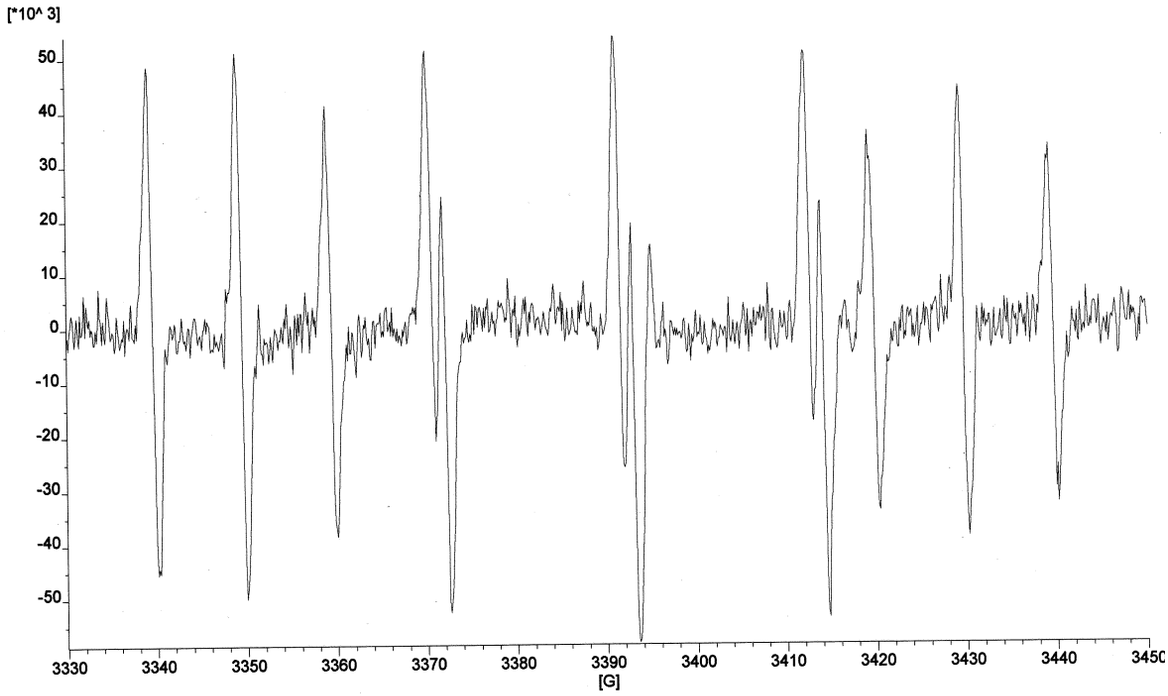
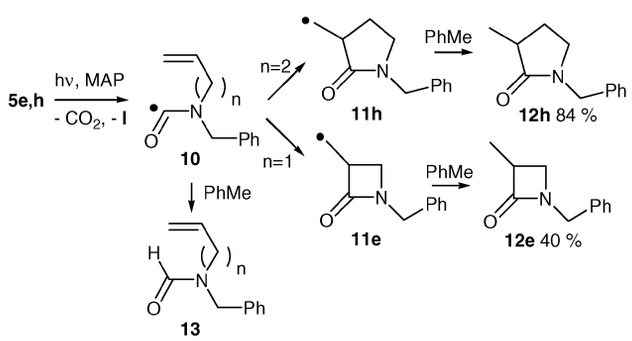


Fig. 2 EPR spectrum obtained on photolysis of **7b** and MAP in PhBu-*t* at 220 K. The carbamoyl radical appears as a triplet of doublets in the central region. The two N-triplets from PhCH=N$^{\bullet}$ appear in the wings.

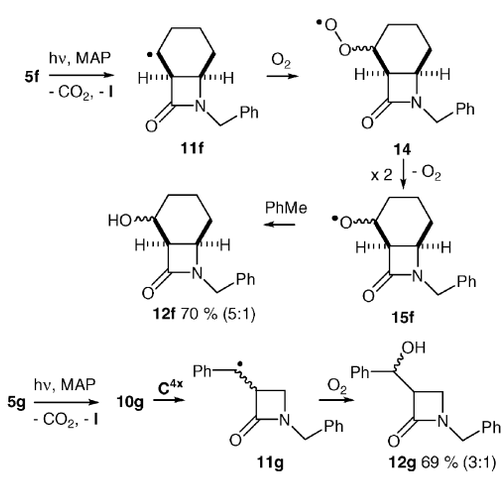


Scheme 5 Preparation of β- and γ-lactams.

routes to azetidin-2-ones involving aminoacyl radicals generated from Co-salophens[19] or amidocyclohexadienes.[20]

Reactions of the cyclohexenyl (**5f**) and cinnamyl (**5g**) precursors afforded the bicyclic β-lactam **12f** and the 3-benzyl-substituted β-lactam **12g** respectively. In both cases the ring-closed radicals were more stabilised (one was secondary and the other benzylic) than primary radicals **11e**,**h** and this favoured cyclisation; as was attested by the good yields of β-lactams. Interestingly, however, for both **5f** and **5g** the products isolated were the hydroxylated compounds **12f** (5 : 1 mixture of diastereomers) and **12g** (3 : 1 mixture of enantiomers). A plausible mechanistic interpretation is outlined in Scheme 6. Because the cyclised radicals **11f** and **11g** are thermodynamically stabilised they couple with dissolved dioxygen more rapidly than they abstract hydrogen from the solvent. The resulting peroxyl radicals, (**14f**,**g**) couple in pairs, extrude dioxygen, and generate alkoxyl radicals **15f**,**g** that are very good H-atom abstractors and hence afford the hydroxylated products. Analogous hydroxylation sequences are well known.[21]

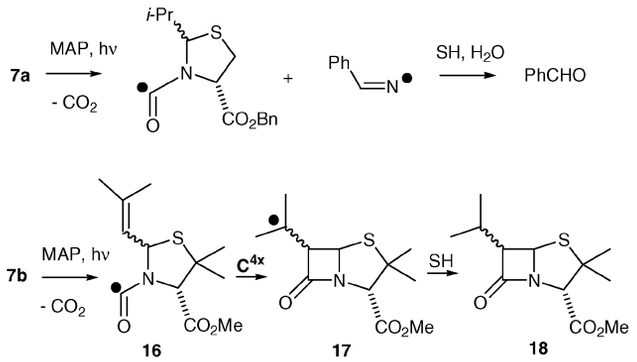
Iminyl radicals (PhC(H)=N$^{\bullet}$) were produced as co-intermediates with the aminoacyls **10**. The major product derived from this species was benzaldehyde. It is probable that the iminyl radicals abstract hydrogen from the solvent to afford the corresponding imine which was hydrolysed to benzaldehyde during work-up. In a few instances traces (<1%) of the azine (PhCH=NN=CHPh), formed by combination of two iminyls, was detected by GC-MS.



Scheme 6 Formation of hydroxylated β-lactams.

We also studied the thiazolidine-based OOAs as radical precursors. The photolysis of oxime oxalate amides **7a**,**b** were first investigated using EPR spectroscopy. Fig. 2 shows the EPR spectrum obtained at 220 K for MAP sensitised photolysis of **7b**. The EPR parameters of the carbamoyl radicals **10** obtained from **7a** and **7b** are in Table 1. The ratios of iminyl to carbamoyl were close to 1.0, as expected. The ring closed azetidinylalkyl radical **17** was not, however, observed in the accessible temperature range.

A product study was also carried out in order to determine if a simple penicillin could be prepared *via* oxime oxalate amide methodology (Scheme 7). OOA **7b** in the presence of MAP (3 M eq.) was photolysed with light from a 400 W UV lamp at 80 °C in toluene for 8 h. GC-MS analysis showed a peak having the correct molecular ion (257) for the cyclised penicillin derivative **18**. This was, in fact, the sole product derived from **7b** because all the other components in the chromatogram stemmed from the solvent or from the MAP. The fragmentation pattern was consistant with that of the expected penicillin. The formula weight of the formamide that would be obtained from H-transfer to carbamoyl radical **16** is also 257. However, the MS did not show the $(M - H)^+$ ion expected for a formamide.



Scheme 7 Photosensitised reactions of thiazolidine-containing precursors.

Furthermore, negligible amounts of formamides were obtained from other OOAs. Several attempts were made to isolate the penicillin by column chromatography and by preparative HPLC but without success. Column chromatography gave only MAP and benzaldehyde and HPLC produced a large collection of minor unidentified components. We conclude that some **18** was formed but that it degraded during photolysis and work-up.

Conclusions

Benzaldoxime oxalate amides and acetone oxime oxalate amides can be prepared in high yields from both primary and secondary amines. The former dissociate efficiently on sensitised photolysis to generate carbamoyl radicals, accompanied by iminyl radicals. In toluene solution the iminyl radicals abstract H-atoms to afford, after hydrolysis, benzaldehyde and hence do not interfere. Carbamoyl radicals with *N*-alkenyl substituents ring-closed efficiently to afford substituted pyrrolidin-2-one or azetidin-2-one derivatives, depending on the position of the double bond. An interesting feature of the process was that when the cyclised azetidinylalkyl radicals were secondary or benzylic [**11f**, **11g**] the corresponding β-lactams contained hydroxyl groups at the site of the original radical centre. We explained this hydroxylation by a mechanism involving peroxyl and alkoxyl radicals (Scheme 6). Good yields of the α-hydroxy-β-lactams were obtained. Of course, such hydroxy substituents are an advantage for further functional group elaboration. The 7-benzyl-2-hydroxy-7-azabicyclo[4.2.0]octan-2-one (**12f**) had previously been obtained, as a mixture with the 6- and 7-hydroxylated analogues, by biohydroxylation of the parent azabicycle with *Beauveria sulfurescens*.[22]

2-Substituted-thiazolidine-4-carboxylic acid methyl ester amides of benzaldehyde oxalyl oxime were also prepared. It was shown by EPR spectroscopy that they also dissociated to produce carbamoyl and iminyl radicals when photolysed with MAP. A thiazolidine-derived oxime oxalate amide containing an isobutenyl side chain released the corresponding thiazolidinyl-carbamoyl radical, (confirmed by EPR spectroscopy). GC-MS evidence indicated that this radical cyclised to afford some of the corresponding penicillin derivative **18**. However, none of this product could be isolated and it seems probable that the cyclisation step was inhibited by the 5-member thiazolidine ring and that the sulfur-containing bicyclic β-lactam degraded during photolysis and work-up.

Experimental

^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz, in $CDCl_3$ solutions with tetramethylsilane as reference. Coupling constants are expressed in Hz. EI mass spectra were obtained with 70 eV electron impact ionisation and CI spectra were obtained with isobutane as target gas on a VG Autospec spectrometer. Ultra Violet irradiation was carried out in quartz apparatus using a 400 W medium pressure Hg lamp.

Ether refers to diethyl ether. THF was distilled under nitrogen from sodium benzophenone ketyl prior to use. Where dry DCM was used, it was distilled over CaH_2. DMSO was dried, distilled from CaH_2, and stored over 4 Å molecular sieves. Other organic compounds were used as received. TLC was carried out using either Polygram silica plates (0.2 mm with 254 nm fluorescent dye) or Fluka alumina plates (0.2 mm with 254 nm fluorescent dye). Fisher silica gel and Fisher neutral alumina were used for column chromatography. Nitrogen gas was dried (NaOH, $CaCl_2$, 4 Å molecular sieves) prior to use. *N*-Benzylformamide, *N*-benzyl-3-buten-1-ylamine,[23] *N*-benzyl-prop-2-enylamine, *N*-cinnamylbenzylamine, *N*-benzyl-2-cyclohexenylamine[24] and penicillamine methyl ester hydrochloride[25] were made by literature methods.

EPR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 kHz modulation. Samples of the substrate (0.3 to 40 mg) and MAP (1 eq.), in *tert*-butylbenzene (up to 0.5 cm^3), in 4 mm od quartz tubes, were de-aerated by bubbling nitrogen for 20 min, and photolysed in the resonant cavity by light from a 500 W super pressure mercury arc lamp. For reactions performed in cyclopropane, the solution was degassed on a vacuum line using the freeze–pump–thaw technique, and the tube was flame sealed. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker Simfonia software package. For quantitative measurements signals were double integrated using the Bruker WinEPR software.

Acetone *O*-(chlorooxalyl)oxime[7] 4a

A solution of acetone oxime (2.92 g; 40 mmol) in diethyl ether (10 cm^3) was added dropwise under stirring to a cold (−20 °C) solution of oxalyl chloride (7.60 g; 60 mmol) in diethyl ether (10 cm^3). The mixture was stirred at −20 °C for 30 min followed by 10 min at 23 °C (after which time the initial ppt had completely dissolved). The solvent was removed at 23 °C/13 torr to yield a colourless volatile oil, which started to turn yellow on standing at rt (6.07 g; 94%); δ_H (2 isomers) 2.11, 2.12 (3H, s, CH_3).

Acetone *O*-(anilinooxalyl)oxime[7] 5a

A solution of aniline (1.86 g; 20 mmol) in $CHCl_3$ was added dropwise under stirring to a cold (−40 °C) solution of **4a** (1.62 g, 10 mmol) in $CHCl_3$ (20 cm^3). After stirring for 1 h at 23 °C, anilinium chloride was filtered off. Evaporation of the filtrate yielded a colourless powder which was purified *via* recrystallisation from $CHCl_3$ (25 cm^3) at −20 °C (1.42 g; 65%, lit.[7] = 69%), mp = 175–178 °C; ν_{max}(NaCl)/cm^{-1} 1746, 1703 (C=O); δ_H 2.16, 2.21 (6H, s, CH_3), 7.28–7.69 (5H, m, ArH), 8.95 (1H, br, N–H), δ_C 17.5, 21.9 (CH_3), 136.3, 125.6, 129.2, 119.8 (ArC), 153.3, 158.8, 167.6 (C=N, C=O).

Acetone *O*-(benzylaminooxalyl)oxime 5b

A solution of benzylamine (2.14 g; 20 mmol) in $CHCl_3$ (10 cm^3) was added dropwise under stirring to a cold (−40 °C) solution of **4a** (1.63 g; 10 mmol). After stirring for 1 h at rt the reaction mixture was left standing overnight. The mixture was filtered, and the filtrate evaporated to yield a colourless powder. The product was then washed with hexane–diethyl ether and ethyl acetate, and the solution was filtered to furnish **5b** as a colourless powder (3.14 g; 67%); mp. 198–202 °C; δ_H 2.11, 2.12 (3H, s, CH_3), 4.55 (2H, d, Ar–CH_2), 7.35 (5H, s, Ar–H), 7.52–7.68 (1H, br, NH), 2.11, 2.14 (6H, s, CH_3-dioxime); δ_C 17.9, 22.4 (CH_3), 44.4 (CH_2), 158.7, 167.9 (C=N), (C=O), 137.1, 128.5, 128.4, 129.3 (ArC); CIMS *m/z* (%), 235 (MH^+, 50), 180 (100); found: 235.1092, $C_{12}H_{15}N_2O_3$ requires 235.1086.

Acetone *O*-(*N*-benzyl-*N*-butylaminooxalyl)oxime 5c

A solution of *N*-benzyl-*N*-butylamine (1.86 g; 11.3 mmol) was added dropwise to a cold (−40 °C) solution of **4a** (1.63 g; 10 mmol) in $CHCl_3$ (20 cm^3). After stirring for 1 h at −20 °C, the solvent was removed at 0 °C to yield a colourless solid (1.57 g; 54%). The product was then recrystallised from dry $CHCl_3$; δ_H 0.96 (3H, t, *J* 7, CH_3), 1.33 (2H, m, CH_2), 1.55 (2H, m, CH_2), 2.01 (6H, s, 2 CH_3), 3.22 (2H, t *J* 7, NCH_2), 4.49 (2H, s, NCH_2Ph), 7.23–7.64 (5H, m, ArH); δ_C 16.9 (CH_3), 21.5 (2 × CH_3). 19.7 (CH_2), 29.7 (CH_2), 47.3 (NCH_2), 51.1 (NCH_2Ph), 127.9, 128.5, 127.4, 135.5 (ArC), 161.5, 165.5, 165.7 (C=O, C=N); CIMS *m*/*z* (%), 291 (MH^+ 89), 164 (100).

Benzaldehyde *O*-(chlorooxalyl)oxime 4d[7]

A solution of benzaldoxime (1.21 g; 10 mmol) in diethyl ether (10 cm^3) was added dropwise to a cold (−40 °C) solution of oxalyl chloride (1.90 g; 15 mmol) in diethyl ether (10 cm^3). After stirring for 1 h at −20 °C the solvent was evaporated at −10 °C/13 torr to leave a colourless temperature sensitive powder which was dried under vacuum for 2 h to remove residual diethyl ether. (2.01 g; 96%, lit.[7] = 97%); ν_{max}(NaCl)/cm^{-1} 1791 (C=O); δ_H 7.2–7.49 (5H, m, ArH), 8.55 (1H, s, CH); δ_C 128.2, 128.8, 129.2, 132.9 (Ar) 159.4, 160.4 (C=N, C=O); *m*/*z* (%) 211 (M^+, 20%).

Benzaldehyde *O*-(*N*-benzylaminooxalyl)oxime 5d

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (1.2 g; 6 mmol) in DCM (10 cm^3) at 0 °C was added a solution of pyridine (0.5 g; 6 mmol) in DCM (5 cm^3), followed by a solution of benzylamine (0.64 g; 6 mmol) in DCM (5 cm^3). The mixture was stirred at −10 °C for 10 min and then at rt for 3 h. After this time the ppt which had formed was filtered off and the solvent was removed. The product was filtered through a pad of silica and was recrystallised from DCM–hexane at −20 °C to give **5d** as colourless platelets (1.38 g; 82%) mp 20–22 °C; δ_H 4.57 (2H, d, *J* 6, $ArCH_2$), 7.31–7.40 (5H, m, ArH), 7.43–7.55 (3H, m, ArH), 7.75–7.78 (2H, m, ArH), 8.62 (1H, s, HC=N); δ_C 44.7 ($ArCH_2$), 128.3, 128.4, 128.5, 129.1, 129.2, 129.3, 129.4, 132.8 (ArC), 156.0, 158.7, 159.5 (C=O, C=O, C=N); CIMS *m*/*z* (%), 283 (MH^+, 29%), 180 (100); found: MH^+ 283.1082, $C_{16}H_{15}N_2O_3$ requires MH^+ 283.1083).

Benzaldehyde *O*-(*N*-benzyl-prop-2-enylaminooxalyl)oxime 5e

To a stirred solution of **4d** (2.11 g; 10 mmol) in DCM (25 cm^3) at 0 °C was added pyridine (1.0 g; 13 mmol) in DCM (5 cm^3) followed by *N*-benzylprop-2-enylamine (1.5 g; 10 mmol) in DCM (10 cm^3). The mixture was allowed to reach rt and then stirred at rt for 2 h. After this time pentane (*ca*. 3 cm^3) was added to promote formation of the pyridine hydrochloride ppt. The ppt was filtered off and the filtrate was evaporated to dryness to give a yellow oil. The oil was further purified *via* flash column chromatography to give the pure target molecule as a colourless oil which solidified on cooling (1.40 g; 44%) mp = 0–5 °C; ν_{max}(NaCl)/cm^{-1} 1744 (C=O), 1656 (C=N); δ_H (2 isomers) 3.83 (1H, d, *J* 7, CH_2), 3.88 (1H, d, *J* 7, CH_2), 4.46 (1H, s, $ArCH_2$), 4.64 (1H, s, $ArCH_2$), 5.18–5.27 (2H, m, $=CH_2$), 5.66–5.84 (1H, m, =CH), 7.22–7.68 (10H, m, ArH), 8.41 (1/2H, s), 8.44 (1/2H, s); δ_C (2 isomers) 47.8, 48.8, 50.3, 51.1 (CH_2), 119.2 ($=CH_2$), 127.9, 128.0, 128.1, 128.3, 128.6, 128.8, 128.9, 129.0, 129.1, 130.4, 130.6, 132.1 (ArC), 132.7 (=CH), 157.7, 157.9 (C=O), 163.3 (C=N); CIMS *m*/*z* (relative intensity), (CI), 323 (MH^+, 36%), 220 (100); found: MH^+ 323.1392, $C_{19}H_{19}N_2O_3$ requires MH^+ 323.1396.

Benzaldehyde *O*-(*N*-benzyl-2-cyclohexenylaminooxalyl)oxime 5f

To a stirred solution of **4d** (1.13 g; 5.3 mmol) in DCM (20 cm^3) at 0 °C was added pyridine (0.42 g; 5.3 mmol) in DCM (5 cm^3) and *N*-benzyl-2-cyclohexenylamine (0.98 g; 5.3 mmol) in DCM (5 cm^3). The mixture was allowed to reach rt and then stirred at rt for 3 h. After this time, pentane (*ca*. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride ppt. The solution was filtered and then evaporated to dryness. The crude product was purified *via* flash column chromatography to give a colourless oil (1.80 g; 95%); ν_{max}(NaCl)/cm^{-1} 1744 (C=O), 1612 (C=N); δ_H 1.56 (1H, m, CH), 1.63 (1H, m, CH), 1.74 (1H, m, CH), 1.97 (3H, m, CH), 4.43 (1H, d, *J* 15, ArCH), 4.77 (1H, d, *J* 15, ArCH), 5.50 (1H, m, =CH), 5.94 (1H, m, =CH), 7.24–7.76 (10H, m, ArH), 8.49 (1H, s, HC=N); δ_C 21.7 (CH_2), 24.7 (CH_2), 28.9 (CH_2), 45.5 ($ArCH_2$), 56.8 (CH), 126.9, 127.5, 127.8, 127.9, 128.9, 129.0, 129.4, 129.5, 132.6, 133.8, (ArC, =CH, =CH), 157.9, 158.0, 158.9 (C=O, C=O, C=N); CIMS *m*/*z* (relative intensity), 363 (MH^+, 11%), 104 (100); found: MH^+ 363.1713, $C_{22}H_{23}N_2O_3$ requires MH^+ 363.1710.

Benzaldehyde *O*-(*N*-cinnamyl-benzylaminooxalyl)oxime 5g

To a stirred solution of **4d** (1.3 g; 6.0 mmol) in DCM (20 cm^3) was added dropwise a solution of pyridine (0.62 g; 6 mmol) in DCM (5 cm^3) followed by *N*-cinnamylbenzylamine (1.34 g; 6 mmol) in DCM (5 cm^3). The solution was allowed to reach rt and then stirred at rt for 3 h. After this time a small amount of pentane (*ca*. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride salt. The ppt was filtered off and the filtrate collected. The filtrate was evaporated to dryness to give the crude product as a colourless oil. The product was purified *via* flash column chromatography to give **5g** as a colourless oil (2.0 g; 85%); ν_{max}(NaCl)/cm^{-1} 1764 (C=O), 1665 (C=N); δ_H 3.92 (1H, d, *J* 6, N–CH_2), 4.03 (1H, d, *J* 6, N–CH_2), 4.46 (1H, s, $ArCH_2$), 4.62 (1H, s, $ArCH_2$), 5.98–6.14 (1H, m, =CH), 6.41 (1H, d, *J* 15, =CH), 7.16–7.60 (15H, m, ArH), 8.38 (1H, s); δ_C 45.7, 47.1, 49.6, 51.1 (CH_2), 127.4, 128.3, 128.5, 128.7, 128.9, 129.0, 129.1, 129.3, 129.4, 129.5 (ArC), 135.3 (CH=CH), 158.1 (C=O), 161.9 (C=N).

Benzaldehyde *O*-(*N*-benzyl-3-buten-1-ylaminooxalyl)oxime 5h

To a stirred solution of **4d** (1.43 g; 0.8 mmol) in DCM (15 cm^3) at 0 °C was added pyridine (0.54 g; 6.8 mmol) in DCM (8 cm^3) followed by *N*-benzyl-3-buten-1-ylamine (1.1 g; 6.8 mmol) in DCM (8 cm^3). The mixture was allowed to reach rt and then stirred at rt for 2 h. After this time pentane (*ca*. 3 cm^3) was added to promote formation of the pyridine hydrochloride ppt. The ppt was filtered off and the filtrate was evaporated to dryness. The resulting oil was purified *via* flash column chromatography to give the product as a white solid (1.60 g; 70%) mp 0–5 °C; ν_{max}(NaCl)/cm^{-1} 1739 (C=O), 1636 (C=N); δ_H (2 isomers) 2.34 (1H, q, *J* 7), 2.40 (1H, q, *J* 7) (apparent sextet), 2.32 (1H, t, *J* 7, N–CH_2), 2.42 (1H, t, *J* 7, N–CH_2), 4.55 (1H, s, Ar–CH_2), 4.69 (1H, s, Ar–CH_2), 5.00–5.13 (2H, m, $=CH_2$), 5.63–5.82 (1H, m, =CH), 7.30–7.70 (10H, m, ArH), 8.42 (1/2H, s), 8.50 (1/2H, s); δ_C (2 isomers) 31.1, 32.5, 43.4, 46.5, 47.1, 51.8 (CH_2), 117.3 ($=CH_2$), 127.9, 128.3, 128.3, 128.6, 128.6, 128.8, 128.9, 132.3, (ArC), 134.9, 135.7 (=CH), 157.7, 157.9 (C=O), 160.9, 161.2 (C=N); CIMS *m*/*z* (%) MH^+ (337, 24%), 234 (92), 190 (25), 104 (77), 57 (100); found: MH^+ 337.1562, $C_{20}H_{21}N_2O_3$ requires MH^+ 337.1552.

1-Benzyl-3-methylazetidin-2-one[26] 12e

A solution of benzaldehyde *O*-(*N*-benzylprop-2-enylaminooxalyl)oxime **5e** (800 mg; 2.5 mmol) and MAP (1.13 g; 7.5 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was evaporated to dryness and purified *via* column chromatography (DCM; MeOH) to give the pure product as a colourless oil (173 mg; 40%); δ_H 1.27 (3H, d *J* 7, Me), 2.73 (1H, dd *J* 5 and 2, CH), 3.15 (1H, m, CH), 3.26 (1H, m, CH),

4.30 (1H, d, *J* 15, CH), 4.35 (1H, d, *J* 15, CH), 7.30 (5H, m, ArH); δ_C 13.7 (CH_3), 44.5 (CH), 45.8 (CH_2), 46.7 (CH_2–Ph), 127.7, 128.3, 128.8, 135.9 (Ar), 171.4 (C=O).

7-Benzyl-2-hydroxy-7-aza-bicyclo[4.2.0]octan-2-one 12f

A solution of **5f** (800 mg; 2.2 mmol) and MAP (1.0 g; 6.6 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified *via* column chromatography (DCM; MeOH) to give a mixture of isomers as a colourless oil (330 mg, 70%). The product exists as a mixture of *anti* and *syn* isomers (5 : 1) and these were separated by column chromatography (EtOAc; hexane) (35 : 65); *anti* δ_H 1.21–1.80 (5H, m), 1.95 (1H, m), 3.23 (1H, m), 3.78 (1H, dd), 4.13 and 4.53 (2H, d, *J* 15), 4.27 (1H, m, HC–OH), 7.29 (5H, m, Ar); δ_C 15.0 (C-7), 22.9 (C-8), 28.8 (C-6), 44.4 (CH_2–Ar), 50.8 (C-1), 54.9 (C-4), 65.5 (C-OH), 127.7, 128.3, 128.8, 135.8 (Ar), 168.6 (C=O); CIMS *m*/*z* (relative intensity), 232 (MH^+, 100%), found MH^+ 232.1344, $C_{14}H_{18}NO_2$ requires MH^+ 232.1338. *Syn* δ_H 1.15–2.12 (5H, m), 2.53 (1H, m), 3.81 (1H, d, *J* 4), 3.95 (1H, m), 4.03 (1H, m, HC-OH), 4.09 and 4.53 (2H, d, *J* 15, CH_2Ar), 7.22 (5H, m, Ar); δ_C ($CDCl_3$) 15.9 (C-7), 24.4(C-8), 40.2 (C-6), 45.0 (CH_2–Ar, C-9), 51.1 (C-1), 61.7 (C-4), 77.2 (C-OH), 128.1, 128.4, 129.0, 135.0 (Ar), 160.7 (C=O).

1-Benzyl-3-(hydroxy-phenyl-methyl)-azetidin-2-one 12g

A solution of **5g** (400 mg; 0.97 mmol) and MAP (452 mg; 3.0 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified *via* column chromatography (DCM; MeOH) to give a mixture of isomers (3 : 1; *anti* : *syn*) as a colourless oil (169 mg; 69%). The isomers were separated by further column chromatography (EtOAc; hexane) *anti* δ_H 3.04 (1H, t, *J* 5, N–CH), 3.20 (1H, dd, *J* 5 and 3, N–CH), 3.59 (1H, m, COCH), 3.81 (1H, br, OH), 4.39 (2H, AB, $ArCH_2$), 5.24 (1H, d, *J* 3, ArCH), 7.14–7.38 (10H, m, ArH); δ_C ($CDCl_3$) 40.2 (N–CH_2), 45.9 ($ArCH_2$), 56.7 (CH), 69.6 (CHOH), 127.6, 127.7, 127.9, 128.3, 128.4, 128.5, 128.7, 128.8 (ArC), 168.3 (C=O); EIMS *m*/*z* (relative intensity) 267 (M^+, 10%), 176 (17), 133 (38), 105 (62), 91 (100), 84 (62), 77 (55); found M^+ 267.1267, $C_{17}H_{17}NO_2$ requires M^+ 267.1259; *syn* δ_H 2.99 (1H, dd, *J* 2 and 6, N–CH), 3.14 (1H, t, *J* 6, N–CH), 3.61 (1H, m, COCH), 3.81 (1H, br, OH), 4.35 (2H, AB, $ArCH_2$), 5.02 (1H, d, *J* 7, $ArCH_2$), 7.03–7.44 (10H, m, ArH); δ_C 41.6 (N–CH_2), 45.8 ($ArCH_2$), 56.1 (CH), 73.0 (CHOH), 127.6, 127.8, 127.9, 128.1, 128.2, 128.6, 128.8, 128.9 (ArC), 168.3 (C=O); EIMS *m*/*z* (relative intensity) 267 (M^+, 11%), 176 (37), 133 (59), 105 (47), 91 (100), 77 (41); found M^+ 267.1259, $C_{17}H_{17}NO_2$ requires M^+ 267.1259.

1-Benzyl-3-methylpyrrolidin-2-one 12h

A solution of **5h** (800 mg; 2.38 mmol) and MAP (1.07 g; 7.14 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified *via* column chromatography (DCM; MeOH) to give the product **12h** as a colourless oil (378 mg; 84%); δ_H 1.25 (3H, d, *J* 17, CH_3), 1.6 (1H, m, CH), 2.25 (1H, m, CH_2), 4.42 (1H, AB, CH), 4.48 (1H, AB), 7.21–7.37 (5H, m, ArH); δ_C 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). EIMS *m*/*z* (relative intensity) 189 (100, M^+), 174 (11), 161 (12), 91(90); found M^+ 189.1153, $C_{12}H_{15}NO$ requires M^+ 189.1154.

2-Isopropyl thiazolidine-4-carboxylic acid benzyl ester 6a

To a stirred solution of the benzyl ester of cysteine (2.0 g; 10 mmol) in pentane (50 cm^3) was added triethylamine (2.0 g; 20 mmol) and isobutyraldehyde (1.44 g; 20 mmol). The mixture was refluxed under Dean–Stark conditions for 24 h. After this time the pentane was removed and the thiazolidine was isolated as a colourless oil *via* column chromatography (hexane : EtOAc, 8 : 2),(2.43 g, 92%). The amine was further purified by recystallisation from hexane and the thiazolidine was isolated as colourless platelets (mp 18–20 °C). The thiazolidine was isolated as a mixture of isomers in a ratio of 2 : 1. Major isomer: δ_H 1.06 (3H, d, *J* 7, $CHCH_3$), 1.11 (3H, d, *J* 7, $CHCH_3$), 1.99 (1H, m, $CH(CH_3)_2$), 2.24 (1H, br, NH), 2.76 (1H, t, *J* 10, 5-HCH), 3.30 (1H, dd, *J* 7, 10, 5-HCH), 3.87 (1H, dd, *J* 7 and 10, 4-CH), 4.36 (1H, d, *J* 7, 2-CH), 5.21 (2H, AB, CH_2–Ph), 7.36 (5H, s, ArH); δ_C 20.9, 21.1 (CH_3), 34.0 (=CH), 38.0 (C-5), 65.9 (C-4), 67.6 (CH_2–Ph),78.5 (C-2), 128.7, 128.8, 129.0, 129.1 (ArC), 171.7 (C=O); minor isomer: δ_H 0.98 (3H, d, *J* 7, $CHCH_3$), 1.04 (3H, d, *J* 7, $CHCH_3$), 1.79 (1H, m, $CH(CH_3)_2$), 2.24 (1H, br, NH), 3.02 (1H, dd, *J* 7 and 10, 5-HCH), 3.20 (1H, dd, *J* 7 and 10, 5-HCH), 4.13 (1H, t, *J* 7, 4-CH), 4.44 (1H, d, *J* 7, 2-CH), 5.21 (2H, AB, CH_2–Ph), 7.36 (5H, s, ArH); δ_C 20.2, 20.8 (CH_3), 35.5 (=CH), 37.7 (C-5), 64.8 (C-4), 67.5 (CH_2–Ph),77.0 (C-2), 128.7, 128.8, 129.0, 129.1 (ArC), 171.7 (C=O); *m*/*z* (relative intensity)(ElectroSpray) 288 (100, M^+ + Na); found M^+ 266.1219, $C_{14}H_{20}NO_2S$ requires M^+ 266.1215.

5,5–Dimethyl-2-(2-methylpropenyl)-thiazolidine-4-carboxylic acid methyl ester 6b

To a stirred solution of the methyl ester of D,L-penicillamine hydrochloride (4.5 g; 22.5 mmol) in MeOH (40 cm^3) at 0 °C was added a solution of triethylamine (2.3 g; 22.5 mmol) in MeOH (10 cm^3) and a solution of 3-methylbut-2-enal (1.9 g; 22.5 mmol) in MeOH (10 cm^3). The mixture was allowed to reach rt and then stirred at rt for 24 h. The solvent was removed and the crude product was purified *via* column chromatography (hexane; EtOAc) (8 : 1). The product was recrystallised from hexane at −20 °C to give colourless needles mp = 52–54 °C (1.3 g; 25%); δ_H 1.24 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.74 (3H, s, CH_3), 2.91 (1H, br, NH), 3.63 (1H, s, 3-H), 3.77 (1H, s, OMe), 5.24 (1H, m, =CH), 5.39 (1H, m, =CH); δ_C 18.9 (CH_3), 26.0 (CH_3), 28.9 (CH_3), 29.5 (CH_3), 52.5 (OMe), 60.0 (q, C3), 65.0 (C2), 74.8 (C1), 123.7 (=CH), 137.9 (=MeMe), 170.2 (C=O); *m*/*z* (relative intensity) 229 (52, M^+), 214 (11), 196 (15), 170 (20), 155 (86), 95 (100); EIMS found M^+ 229.1137, $C_{11}H_{19}NO_2S$ requires 229.1129. X-Ray diffraction showed this to be the 4*S* stereoisomer.

Attempted preparation of 2-formyl-5,5-dimethylthiazolidine-4-carboxylic acid methyl ester

To a stirred solution of the methyl ester of D,L-penicillamine hydrochloride (2 g; 10 mmol) in MeOH (20 cm^3) at 0 °C was added a solution of triethylamine (1.0 g; 10 mol) in MeOH (5 cm^3) and dimethoxyacetaldehyde (1.17 g; 10 mmol). The mixture was stirred at room temperature for 24 h and after this time the mixture was filtered and the solvent removed. The yellow oil which resulted was separated by column chromatography and the thiazolidine was isolated as a mixture of isomers in 81% yield. The dimethoxythiazolidine was dissolved in MeOH and treated with solutions of 0.1 M, 1.0 M, 5 M and 6 M HCl. Each solution was heated to reflux for up to 3 h but the expected thiazolidine was never observed

Benzaldehyde *O*-(2-isopropyl thiazolidine-4-carboxylic acid benzyl ester oxalyl) oxime 7a

To a stirred solution of **4d** (633 mg; 3 mmol) at 0 °C in DCM (10 cm^3) was added pyridine (237 mg; 3 mmol) in DCM (5 cm^3) and **6a** (800 mg; 3 mmol) in DCM (5 cm^3). The mixture was allowed to stir at 0 °C for 10 min and then at rt for 3 h. After this time a small quantity of pentane was added in order to promote formation of the pyridine hydrochloride salt. The mixture was filtered and the solvent removed under vacuum. The oxime oxalate amide was purified by flash column chrom-

atography to give the product as a colourless oil (1.18 g; 90%); The compound was isolated as a mixture of isomers in a ratio of 2 : 1, ν_{max}(NaCl)/cm^{-1} 1747 (C=O), 1659 (C=N); δ_H 0.97–1.04 (6H, m, 2 × CH_3), 1.97 (1/3H m, $CH(CH_3)_2$), 2.15 (2/3H, m, $CH(CH_3)_2$), 3.23–3.42 (2H, m, 5-HCH), 5.07–5.37 (2H, m, 4-CH and 2-CH), 5.30 (2H, s, OCH_2), 7.26–7.53 (8H, m, ArH), 7.69–7.77 (2H, m, arH), 8.40 (1H, s, HC=N); δ_C 19.3, 19.5, 20.4, 20.5 (CH_3), 31.9, 33.4 (CH_2), 63.5, 64.5 (CH), 68.5, 68.8 (OCH_2), 71.9, 72.0 (CH), 128.9, 129.1, 129.1, 129.4, 132.7, 132.8 (ArC), 158.7, 165.6, 169.0 (C=O, C=N); CIMS found MH^+ 441.1489, $C_{23}H_{25}N_2O_5S$ requires MH^+ 441.1485.

Benzaldehyde *O*-(5,5–dimethyl-2-(2-methylpropenyl)-thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 7b

To a stirred solution of **4d** (700 mg; 3.2 mmol) in DCM (10 cm^3) was added dropwise a solution of pyridine (0.3 g; 3.2 mmol) in DCM (5 cm^3) followed by **6b** (0.8 g; 3.2 mmol) in DCM (5 cm^3). The solution was allowed to reach rt and then stirred at rt for 3 h. After this time a small amount of pentane (*ca*. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride salt. The ppt was filtered off and the filtrate collected. The filtrate was evaporated to dryness and the resulting oil was filtered through a pad of silica with DCM. The product was again evaporated to dryness and recrytallised from DCM–hexane at −20 °C to give the title compound as colourless platelets, (1.2 g; 92%); mp = 110–112 °C; (found C, 58.9; H, 6.4; N, 6.0%; $C_{20}H_{24}N_2O_5S$ requires C, 59.2; H 6.2; N, 6.9%); ν_{max}(NaCl)/cm^{-1} 1758 (C=O), 1739 (C=O), 1658 (C=N); δ_H 1.44 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.69 (3H, s, CH_3), 3.80 (1H, s), 3.83 (3H, s, OCH_3), 5.60 (1H, m, =CH), 6.08 (1H, m, =CH), 7.42–7.50 (3H, m, Ar), 7.71–7.75 (2H, m, Ar), 8.43 (1H, s, N=CH); δ_C 18.2 (CH_3), 23.9 (CH_3), 25.7 (CH_3), 32.1 (CH_3), 51.6 (Me_2), 52.4 (OCH_3), 60.1, 71.5, 121.5 (=CH), 128.5, 128.7, 129.0, 132.1 (ArC), 140.1 (=CMe_2), 157.3, 158.4 (C=O), 169.2 (C=N); CIMS found MH^+ 405.1488, $C_{20}H_{25}N_2O_5S$ requires MH^+ 405.1491.

Crystal data for **7b**‡: $C_{20}H_{24}N_2O_5S$, M = 404.47, colourless platelets, crystal dimensions 0.1 × 0.1 × 0.2 mm, monoclinic, space group $P2_1/c$, a = 8.9072(13), b = 18.141(3), c = 12.9956(19) Å, β = 99.949(3)°, V = 2092.1(5) Å^3, D_c = 1.284 Mg m^{-3}, T = 125(2) K, R = 0.0341, R_w 0.0831 for 2956 reflections with $I>2\sigma(I)$ and 259 variables. Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo–Ka radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined using full-matrix least squares methods. Atomic coordinates and bond lengths and coordinates are listed in the ESI and the structure is shown in Fig. 1.

Photolysis of benzaldehyde *O*-(2-isopropylthiazolidine-4-carboxylic acid benzyl ester oxalyl) oxime 7a

A stirred solution of **7a** (400 mg; 0.9 mmol) and MAP (137 mg; 0.91 mmol) in toluene (25 cm^3) was photolysed for 3 h at rt by light from a 400 W UV lamp. After this time the ppt which had formed was filtered off and the filtrate was evaporated to dryness to give a yellow oil. The oil was purified by column chromatography (EtOAc–hexane) to give only benzaldehyde and MAP. The ppt was found to be insoluble in all deuterated solvents and was probaly polymer.

Photolysis of benzaldehyde *O*-(5,5–dimethyl-2-(2-methylpropenyl)thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 7b

To a solution of **7b** (400 mg; 2 mmol) in toluene (400 cm^3) was added 3 M eq. of MAP (890 mg; 6 mmol). The mixture was photolysed by light from a 400 W medium pressure UV lamp at 100 °C for 8 h. After this time the mixture was allowed to cool and the solvent was removed. GC-MS: *peak no. 142*, PhCHNH (9%) *m/z* (%) 103 (M^+ 100), 76 (26), 50 (15), *peak no. 174*, (9%) $PhCH_2OH$ 108 (M^+ 87), 107 (66), 79 (100), 77 (56), *peak no. 217*, $OMeC_6H_4CHCH_2$ (8%) 134 (M^+ 100), 119 (32), 91 (28), *peak no. 332*, MAP (56%) *peak no. 373*, $PhCH_2CH_2Ph$ (52%), 182 (M^+ 26), 91 (100), 65 (12), *peak no. 435*, $PhCHOHCH_2Ph$ (25%), 198 (M^+ 3), 107 (82), 92 (100), 79 (60), 77(35), *peak no. 459*, penicillin derivative **17** (18%), 257 (M^+ 78), 242 (16), 228 (94), 225 (86), 214 (100), 198 (31), 187 (46), 170 (54), 155 (24), 142 (46), 115 (80), 114 (46), 95 (97), 84 (43), 67 (39) (several additional unidentified compounds derived from MAP were also present).

2-(2-Methylpropenyl)-4-phenyl-oxazolidine 8

To a stirred solution of (*S*)-β-aminophenethyl alcohol (1.37 g; 10 mmol), in DCM (15 cm^3) at 0 °C and in the presence of 4 Å molecular sieves was added a solution of 3-methylbut-2-enal (840 mg; 10 mmol) in DCM (5 cm^3). The mixture was stirred at rt for 3 h after which time the solution was filtered and concentrated to give a yellow solid. The solid was recrystallised from EtOAc–hexane at −20 °C to give the title compound as colourless needles (1.85 g; 91%) mp = 70–72 °C; δ_H 1.88 (3H, s, CH_3), 1.90 (1H, s, CH_3), 3.29 (1H, br, NH), 3.83 (1H, dd, *J* 11 and 4, CH), 3.96 (1H, dd, *J* 9 and 4, CH), 4.32 (1H, dd, *J* 9 and 4, CH), 6.08 (1H, d, *J* 9, CH), 7.21–7.37 (5H, m, ArH), 8.28 (1H, d, *J* 9, CH); δ_C 19.1 (CH_3), 27.1 (CH_3), 68.0 (CH_2),77.3 (C–Ph), 125.4, 127.6, 127.7, 129.0 (ArC), 149.0 (=C), 161.9 (=CH).

Attempted preparation of benzaldehyde O-(*N*-2-(2-methylpropenyl)-4-phenyloxazolidine)aminooxalayl oxime

To a stirred solution of **4d** (1.41 g; 6.7 mmol) in DCM (15 cm^3) at 0 °C was added a solution of pyridine (530 mg; 6.7 mmol) in DCM (5 cm^3) followed by a solution of 2-(2-methylpropenyl)-4-phenyl-oxazolidine (1.36 g; 6.7 mmol) in DCM (5 cm^3). The mixture was allowed to stir at 0 °C for 10 min and then at rt for 3 h. After this time the solvent was removed to give unreacted starting materials.

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