Preferential Oxygenation of 4-Cycloalkylideneoxazol-5(4*H*)-ones: Synthesis of *N*-Acylcycloalk-1-enecarboxamides

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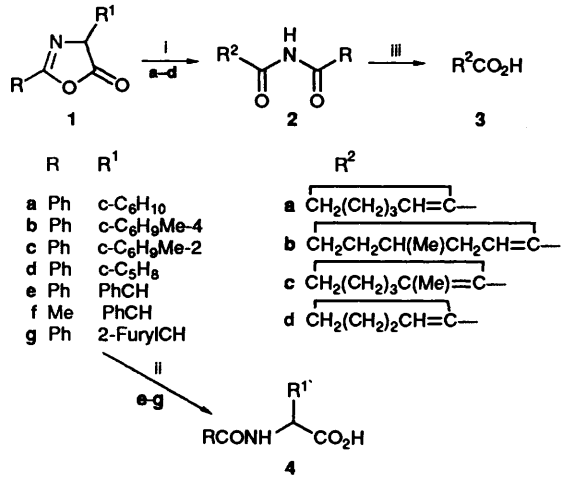
The addition of oxygen, in the presence of base, to 4-cycloalkylideneoxazol-5(4*H*)-ones led to new substituted *N*-acylcycloalkenecarboxamides in high yield, *via* base-catalysed isomerisation, oxygenation and subsequent fragmentation of a hydro- or endo-peroxide intermediate.

The 4-ylideneoxazol-5(4*H*)-ones **1**, commonly known as azlactones, are highly versatile synthons for several biologically active compounds.[1-3] The stereospecific cyclopropanations and Michael additions of azlactones are well documented in the literature,[4,5] however, there have been no reports of the oxygenation of unsaturated azlactones. In continuation of our interest in the chemistry of azlactones, we have carried out reactions of various azlactones with molecular oxygen. It was observed that the 4-cycloalkylideneoxazol-5(4*H*)-ones **1a–d** interacted with oxygen in the presence of base to give *N*-acylcycloalkenecarboxamides **2a–d** in high yields. However, 4-arylideneoxazol-5(4*H*)-ones[1e-g] did not undergo autoxidation under the same reaction conditions, but gave the usual hydrolysis product, *N*-benzoyl derivatives **4e–g**,[6] along with a small amount of the starting material.

Treatment of 4-cyclohexylideneoxazol-5(4*H*)-one[7] **1a** with solid potassium hydroxide and triethylbenzylammonium chloride (TEBA) in benzene with a slow stream of oxygen for 5 h gave a colourless crystalline solid, *N*-benzoylcyclohex-1-enecarboxamide **2a**, Scheme 1 (see Experimental section); further



Scheme 1 *Reagents and conditions:* i, DMSO, 28 °C, O_2, KOBu^t, 1 h; ii, benzene, TEBA (1 mol%), KOH, 5 h, O_2; iii, aq. KOH (40%), reflux 2–5 h

chemical transformation to acid **3a** substantiated the structure of **2a**. The compounds **2a–d** prepared by this reaction are listed in Table 1.

It was established that base, oxygen and a phase transfer catalyst were required for the formation of the carboxamides **2**; the reaction also proceeded smoothly in the presence of triethylamine. When the reaction was carried out under nitrogen, no imide was formed, but the acylamino acid hydrolysis product was obtained.

Table 1 Formation of carboxamides **2** and **4**

	Method[a]	*t*/h	Yield (%)
2a	A	1	90
	B	5	90
2b	A	1	80
	B	4	88
2c	A	1	80
	B	4.5	75
2d	A	2	75
	B	8	70
4e	A	3	*b*
	B	5	*b*
4f	A	3	*b*
	B	5	*b*
4g	A	3	*b*
	B	5	*b*

[a] See Experimental section for method. [b] The corresponding acylamino acids and starting azlactones were obtained.

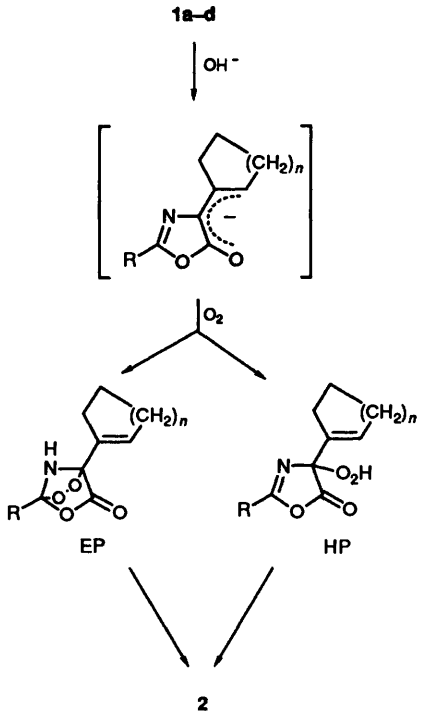
Mechanistically, the formation of compounds **2** may be envisioned as the initial base-induced isomerisation of the cyclohexylidene moiety to the cyclohexenyl anion (Scheme 2). Interaction of this resonance-stabilised anion with molecular oxygen can result in a hydroperoxide (HP) or an endoperoxide (EP) intermediate.[8] Fragmentation of HP or EP would lead to imide **2** and carbon dioxide (isolated stoichiometrically as potassium carbonate). No chemiluminescence was observed. The involvement of the anion is evidenced by the ready exchange of an α-methylene hydrogen of **1** in acetonitrile containing triethylamine under nitrogen.

The present results provide a simple and direct method for the preparation of *N*-acyl substituted cycloalk-1-enecarboxamides starting from cycloalkanones *via* azlactones. Preliminary screening results have shown promising antibacterial and insecticidal activities.*

Experimental

General Methods.—M.p.s were determined on a Metler FP 51 capillary melting apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer Model 710 B spectrophotometer. ^{1}H NMR spectra were recorded with deuteriochloroform as solvent on a Bruker AM 300 spectrometer with $SiMe_4$ as internal standard. Mass spectra were determined on a micromass 7070 H model spectrometer with ionisation energy maintained at 70 eV.

* Compounds **2a–d** have shown insecticidal activity against 4–5 day old *Musca domestica* and toxicity determination was made by topical method of application. They have also shown significant antibacterial activity against *Bacillus subtilis*.



Scheme 2 Base-catalysed isomerisation and oxygenation of azlactone **1**

N-*Benzoylcyclohex*-1-*enecarboxamide* **2a**.—*Method A*. 4-Cyclohexylideneoxazol-5(4*H*)-one **1a** (2.41 g, 10 mmol) was mixed with powdered potassium hydroxide (0.56 g, 10 mmol) in benzene (80 cm^3) and TEBA (12 mg, 1 mol%) and stirred at 28 °C for 5 h by passing a stream of oxygen slowly through the mixture. The reaction was monitored by TLC using benzene as the eluent. At the end of the reaction, the contents were washed (water) and the benzene layer was concentrated under reduced pressure and passed through a column (silica gel, 200 mesh, eluent benzene) to give **2a** as a colourless solid (2.06 g, 90%), m.p. 125 °C (Found: C, 73.4; H, 6.6; N, 6.1. $C_{14}H_{15}NO_2$ requires C, 73.33; H, 6.59; N, 6.11%); δ_H(300 MHz; $CDCl_3$) 1.45–1.65 and 2.18–2.38 (both 4 H, m, c-C_6H_8), 6.7 (1 H, s, =CH), 7.4–7.8 (5 H, m, Ar) and 8.6 (1 H, br s, D_2O exch.); *m*/*z* 229.

Method B. Oxazol-5(4*H*)-one **1a** (2.41 g, 10 mmol) was mixed with powdered potassium *tert* butoxide (1.4 g, 10 mmol) in DMSO (200 cm^3) and stirred at 28 °C for 1 h by passing a stream of oxygen slowly through the mixture. The reaction was monitored by drawing aliquots from the mixture at intervals of 15 min; these were poured into chilled water and the solid obtained was filtered, dissolved in benzene and analysed by TLC using benzene as the eluent. At the end of the reaction, the contents were poured into crushed ice and washed (water). The solid obtained was passed through a column (silica gel, 200 mesh, eluent benzene) to give **2a** as a colourless solid (2.06 g, 90%), m.p. 125 °C; data as above.

N-*Benzoyl*-4-*methylcyclohex*-1-*enecarboxamide* **2b**.—*Method A*. Colourless solid (2.18 g, 90%), m.p. 110 °C (Found: C, 74.2; H, 6.95; N, 5.8. $C_{15}H_{17}NO_2$ requires C, 74.07; H, 6.99; N, 5.76%); δ_H(300 MHz; $CDCl_3$) 0.97 (3 H, d, Me), 1.65–2.28 (7 H, m, c-C_6H_7), 6.6 (1 H, s, =CH), 7.4–7.8 (5 H, m, Ar) and 8.7 (1 H, br s, D_2O exch.); *m*/*z* 243.

N-*Benzoyl*-2-*methylcyclohex*-1-*enecarboxamide* **2c**.—Colourless solid (2.185 g, 90% yield), m.p. 115 °C (Found: C, 74.2; H, 7.0; N, 5.75; $C_{15}H_{17}NO_2$ requires C, 74.07; H, 6.99; N, 5.76%); δ_H(300 MHz; $CDCl_3$) 1.1 (3 H, br, Me), 1.65–2.28 (8 H, m, c-C_6H_8), 7.3–7.8 (5 H, m, Ar) and 8.7 (1 H, br s, D_2O exch.); *m*/*z* 243.

Hydrolysis of the Carboxamides **2a–c**.—In a typical experiment, treatment of **2a** (2.29 g, 10 mmol) with 20% aqueous potassium hydroxide at 90 °C for 2 h gave a mixture of cyclohex-1-enecarboxylic acid and benzoic acid with the evolution of ammonia gas. The carboxylic acid was separated from benzoic acid by sublimation at 30–40 °C/20 mmHg). The carboxylic acid was obtained as colourless crystals (1.24 g, 99% yield) leaving the benzoic acid as a residue; the alkyl substituted acids were obtained by the above procedure and compared with authentic samples.

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References

1 R. F. Meyer and A. D. Essenberg, *J. Med. Chem.*, 1981, **24**, 964.
2 E. Etschenberg and S. Raddatz, BP 1570140/1980 (*Chem. Abstr.*, **94**, 17553z).
3 J. C. Cognacq, GP 2359796/1974 (*Chem. Abstr.*, **82**, P. 165725).
4 N. Lalitha, D. S. Iyengar and U. T. Bhalerao, *J. Org. Chem.*, 1989, **54**, 1771.
5 N. Lalitha, U. T. Bhalerao and D. S. Iyengar, *J. Chem. Soc., Chem. Commun.*, 1991, 897.
6 P. K. Tripathy and A. K. Mukerjee, *Synthesis*, 1984, 418.
7 V. Bockelheide and M. S. Lois, *J. Org. Chem.*, 1949, **14**, 298.
8 R. B. Bates, F. A. Fletcher, K. D. Janda and W. A. Miller, *J. Org. Chem.*, 1984, **49**, 3038.

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