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The Synthesis of Oxazoles by Thermolysis or Photolysis of 2-Acylisoxazol-5-ones

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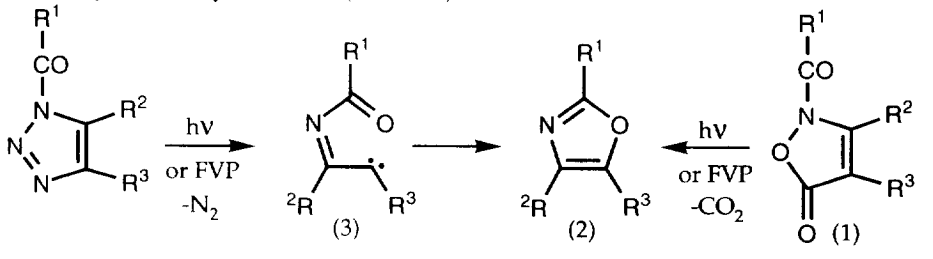
Abstract: N-acylisoxazol-5-ones are converted into the corresponding 2-substituted oxazoles by photolysis at 300 or 254nm, or by flash vacuum pyrolysis. The former procedure is favoured for isoxazolones with electron withdrawing groups at C-4, and pyrolysis for all others.

The recent isolation of a number of marine derived cytotoxic agents containing the oxazole[1], bis-oxazole[2] or tris-oxazole[3] system has revived interest in the development of new synthetic methods for this ring system. Most recent methods have utilised a biosynthetic modelled approach, involving oxidation[4,5] of a peptide derived oxazoline, but rhodium catalysed carbenoid cyclisations have also played a major role[6]. We have previously pointed out the possibility of similar modes of photochemical or thermal loss of nitrogen and carbon dioxide from triazoles and isoxazol-5-ones respectively[7](Scheme 1), and have pyrolysed[8] or photolysed[9] the latter to produce a variety of heterocycles including imidazoles and pyrimidines.

The photolysis[10] or pyrolysis[11,12] of 1-acyltriazoles leads to low yields of oxazoles as well as other products. However, Williams[13] has recently reported a new procedure for the thermal rearrangement of a number of acyltriazoles to oxazoles in good yields, although the procedure appears to be capable of variation only in the substituent at C-2.

Isoxazol-5-ones are readily acylated on nitrogen[14], and we herein report that pyrolysis or photolysis of these compounds gives oxazoles in yields that invariably are superior to those obtained from the corresponding acyltriazoles. Furthermore, we have shown the process is capable of simple iteration, leading to polyoxazoles similar to those synthesised by Pattenden[15](Scheme 2).



Scheme 1

The yields of isolated oxazoles, shown in Table 1, are significantly better than those obtained from triazoles where such information is available. In addition, the reaction of triazoles with R^2=EWG frequently leads to rearrangement of the intermediate iminocarbene, suggested to occur via the corresponding 1H-azirine[29,30], but only one example[24] of such a rearrangement has been observed during pyrolysis of

Table 1. Synthesis of Oxazoles(2) from 2-Acylisoxazol-ones(1)

R^1	R^2	R^3	Procedure ; Yield %	m.p. (b.p)
CH_3	CO_2Et	CH_3	A 95 ; B 40	117 /0.1mm[16]
Ph	CO_2Et	CH_3	A 95 ; B 60 ; C 20	130 /0.01mm[17]
CH_3	Ph	H	A 95 ; C 29	45[18]
Ph	CH_3	H	A 95 ; C 24	92-95 /5mm[19]
CH_3	CH_3	H	A 95	108 /760mm[20]
CH_3			A 95 ; B 0 ; D 24[21]	59 /12mm[22]
CH_3	Ph	Ph	A 95	210 /18mm[23]
Ph	Ph	Ph	A 70 ; D 30[10]	116[23]
Ph	Ph	H	A70[24] ; C 24	102-103[18]
Ph			A 95 ; D 35[21]	104-105[21]
Ph	H	H	A 80	100 /12mm[25]
CF_3	Ph	H	A 50	46-48
CH_3	H	CO_2Et	A 10 ; B 85	75-80 /0.1mm[26]
$(CH_3)_2CH$	H	CO_2Et	C 81	40 /0.05mm
Ph	H	CO_2Et	C 70	58-60[26]

(A) Flash vacuum pyrolysis, 540-600° / 0.01mm[27]; (B) Photolysis, 254nm in CH_3CN, silica ; (C) Photolysis, 300nm in acetone, pyrex [28]; (D) % Yield from corresponding triazole.

isoxazolones. We believe the lack of rearrangement is due to the lower pyrolysis temperatures, or longer irradiation wavelengths necessary to achieve formation of the carbene (3) from the isoxazolones compared to the corresponding triazoles.

In conclusion, since isoxazol-5-ones are readily prepared from β-ketoesters and their equivalents[31], the procedures described herein should represent a useful additional method for the preparation of oxazoles. We have found it applicable in the synthesis of some naturally occurring derivatives.

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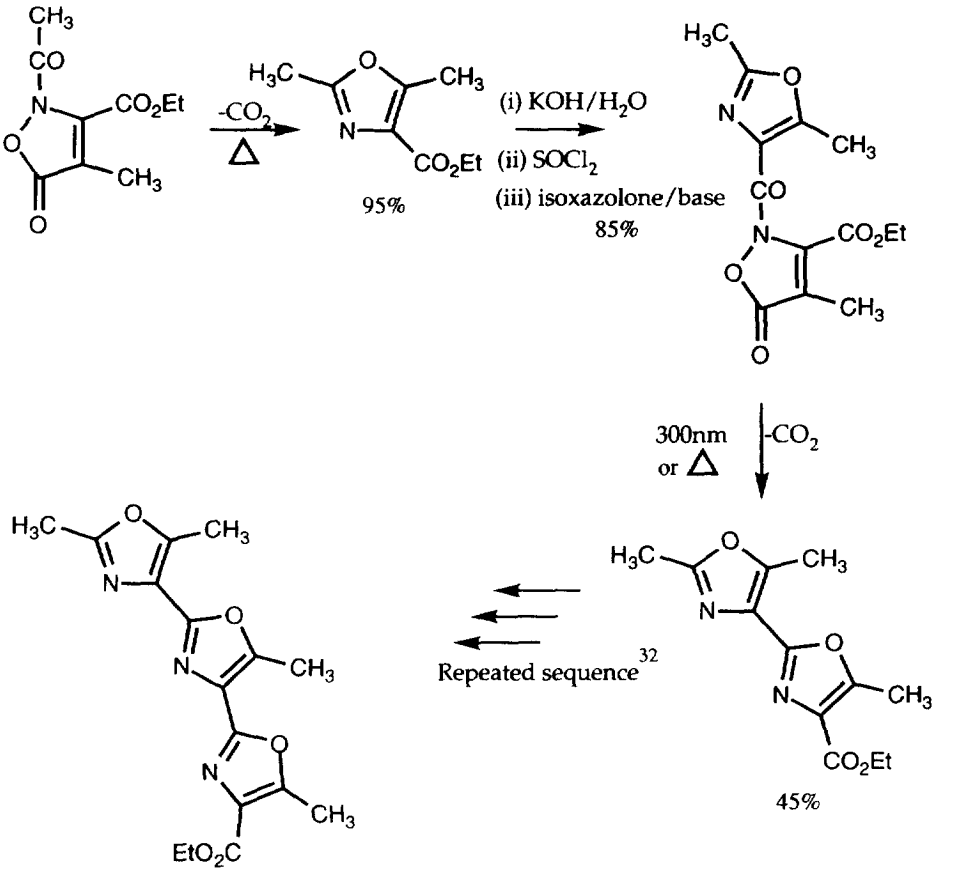

Scheme 2

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14. Posnor, T., *Ber. Dtsch. Chem. Ges.* , **1906**, *39*, 3515. General acylation procedure. 3-Methyl isoxazol-5-one (2.0g, 20mmol), benzoyl chloride (3.0g, 21mmol) and triethylamine (2.1g, 21mmol) were stirred in dichloromethane (50 ml) at 25° for 14h. The solution was washed with a solution of K_2CO_3, dried and evaporated to give an oil. The two products were separated by radial chromatography on silica with dichloromethane/light petroleum (1:1). The first fraction was identified as 3-methylisoxazol-5-yl benzoate, m.p. 43-45° (40%). The second fraction was identified as 2-benzoyl-3-methylisoxazol-5-one (1, R^1=Ph R^2=CH_3, R^3=H) m.p. 74-75° (60%).
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28. General photolysis procedure. Ethyl 2-benzoyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (1, R^1=Ph, R^2=H, R^3=CO_2Et) (100mg) was dissolved in anhydrous acetone (40 ml) and irradiated at 300nm (pyrex). On completion of reaction, the solvent was removed and the residue was recrystallised (ether / light petroleum) to give ethyl 2-phenyloxazole-5-carboxylate(2, R^1=Ph, R^2=H, R^3=CO_2Et)(70%) as white crystals, m.p. 58-60° (lit[26] 56°).
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32. This process has not yet been optimised : the overall yield of tris oxazole in preliminary experiments is of the order of 10%.

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