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A new Synthesis of chiral Aminoalkyloxazolecarboxylate Esters from Isoxazol-5(2H)-ones: the Synthesis of Almazoles A and B

Jabbar Khalafy [a,b], Carina E. Svensson [a], Rolf H. Prager [a]* and Craig M. Williams [a]

[a]Chemistry Department, Flinders University, G. P. O. Box 2100, Adelaide, Australia, 5001

[b]Permanent address: Chemistry Department, Urmia University, Urmia 57154, Iran

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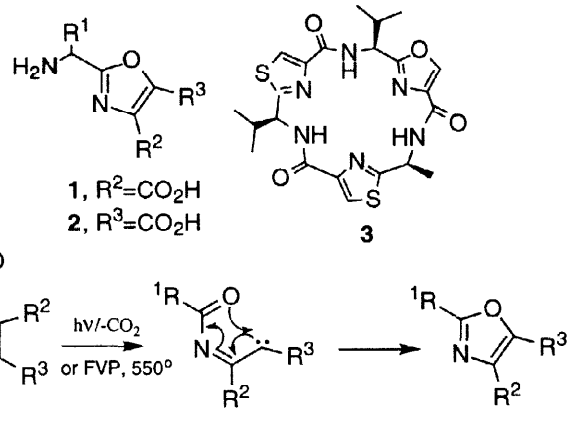
Abstract: 2-(1-Aminoalkyl)oxazole-4 and 5-carboxylates are available, without detectable racemisation, by a sequence involving N-acylation of isoxazol-5(2H)one carboxylates with phthalimidoamino acids, photolysis of the acylated product, and hydrazinolysis. An application of the procedure to the synthesis of almazole A and B is described. © 1998 Elsevier Science Ltd. All rights reserved.

As part of a programme to synthesise peptide mimetics incorporating non-natural amino acids, we required a general synthesis of 2-(1-aminoalkyl)oxazole-4 and 5-carboxylic acids, **1** and **2**. While a considerable number of marine-derived natural products, such as bistramide C [1], **3**, have been isolated and are based on the former amino acid, relatively few are based on the latter. Accordingly, recent work has developed a number of procedures for the synthesis of the former [2], generally based on biomimetic strategies. We have recently reported a new synthesis of oxazoles [3]and thiazoles [4], and in this communication we report the application of the former to the synthesis of some esters of 2-(1-aminoalkyl)oxazole-4 and 5-carboxylic acid, and the extension of this strategy to the synthesis of almazole A and B.

Our synthetic pathway involved the thermal or photochemical conversion of N-acylisoxazolones into the corresponding oxazoles (Scheme 1). While our previous work showed that pyrolysis was generally a higher yielding procedure, it was not a feasible option in the context of our desire to make small peptides.



Scheme 1

The required N-acylated isoxazol-5-ones were best prepared by reacting the N-protected amino acid with the corresponding isoxazol-5-one in the presence of DCC in dichloromethane at 0°. Benzyloxycarbonyl or t-butoxycarbonyl protected amino acids gave only poor yields, possibly due to azlactone formation, but

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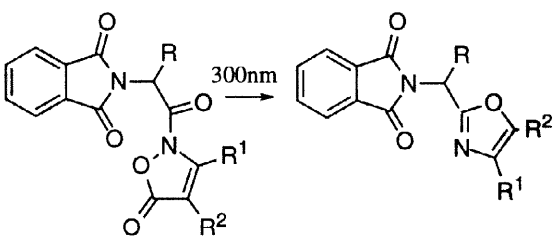
phthalimido protected acids were highly satisfactory. High N/O acylation ratios were achieved by maintaining low reaction temperatures, and this strategy also minimised the formation of N-acyl urea by-products[5] (Table 1). A second advantage arising from the presence of the phthalimido group now became apparent. Whereas photochemical conversion of N-acylated isoxazolones to oxazoles has generally been inefficient[3], the phthalimido derivatives **4-10** underwent facile conversion to oxazoles on photolysis in acetone at 300 nm. Apparently the protecting group was responsible for initial light absorption in this case. Yields of purified oxazoles are shown in Table 1. Hydrazinolysis was achieved without affecting the ethyl ester, which was readily hydrolysed by lithium hydroxide.

Table 1. Yields of N-Acylated Isoxazol-5(2H)-ones and Oxazoles

	N-Acylisoxazol-5(2H)-one			
		N/O Ratio	Yield %	Oxazole %
4	25°, DCC	100:0	88	**11**, 66
5	0°, DCC	92:8	80	**12**, 61
	25°, DCC	79:21	68	
6	25°, DCC	100:0	89	**13**, 45
7	0°, DCC	100:0	80	**14**, 51
8	25°, DCC	100:0	96	**15**, 88
9	0°, DCC	100:0	77	**16**, 71
	25°, DCC	72:28	33	
10	acid chloride	100:0	90	**17**, 90

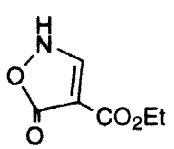


	R	R^1	R^2	
4	H	CO_2Et	Me	**11**
5	Me	CO_2Et	Me	**12**
6	H	Me	CO_2Et	**13**
7	Me	Me	CO_2Et	**14**
8	H	H	CO_2Et	**15**
9	Me	H	CO_2Et	**16**
10	Bz	H	CO_2Et	**17**

The optical integrity of the stereogenic centre in the chiral oxazoles was determined by conversion of the amines to their (R)-α-methoxy-α-(trifluoromethyl)phenylacetamides:[6] in all cases the two diastereoisomeric amides could be clearly differentiated by ^{19}F and ^{1}H nmr spectroscopy. No racemisation could be detected, showing that the N-acylation, oxazole formation and hydrazinolysis steps all proceeded with total retention of stereochemistry.

In 1994 Pietra[7] reported the isolation of almazole A, B and C, and of almazole D in 1996[8] from a red seaweed of the genus Heraldiophyllon. The unique feature of these oxazole derivatives is their 2,5 substitution

pattern, differing from the 2, 4-pattern commonly found in protein-derived oxazoles[9] and the synthesis of these natural products by the method outlined herein seemed appropriate. Although the acid chloride of N,N-dimethylphenylalanine and tetrachlorophthalimdophenylalanine decomposed under the reaction conditions necessary to alkylate the isoxazolone **18**, the acid chloride of (S)-phthalimido phenylalanine [10] gave the N-acylated isoxazolone **10** (90%), which gave the desired oxazole **17** (90%) on photolysis in acetone at 300nm. Deprotection with hydrazine, but not methylamine[11], smoothly gave the amine **19**, which was methylated either by formic acid/formaldehyde, or preferentially, hydrogenation in the presence of formalin. The resulting ester **20** was reacted at -80° with the dianion generated from 2-bromoformanilide[12], which generated a mixture of almazole A, **21** (10 %) and almazole B, **22** (24 %) which were separated by radial chromatography on silica. Reaction of the dianion with the corresponding Weinreb amide [13] or lithium carboxylate were unsatisfactory. When the reaction mixture was refluxed with ethyl formate for 2h, only almazole A was isolated. The spectral characteristics[14] were identical with those cited by Pietra[7].



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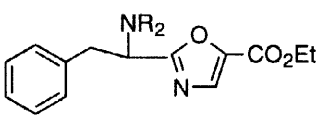
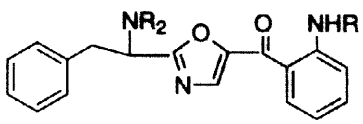


19, R=H
20, R=Me



21, R=CHO
22, R=H

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References and Notes

1. Foster, M.P., Concepcion, G.P., Caraan, G.B., Ireland, C.M., *J. Org. Chem.* **1992**, *57*, 6671.
2. Aguilar, E.; Meyers, A.I., *Tetrahedron Lett.*. **1994**, *35* , 2477; Turchi, I.J. ed., *Oxazoles*, Wiley-Interscience, NY, 1986; Evans, D. A.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I., *J. Org. Chem..*,**1979**, *44*, 497; Connel,R.; Scaro, F.; Helquist,P.; Akermark, B.,*Tetrahedron Lett.*, **1986**,*17,* 5559; Connel, R.; Tebbe, M.; Gangloff, A.; Helquist, P.; Akermark, B., *Tetrahedron*, **1993**, *49* , 5445; Evans, D. A.; Gage, J.R.; Leighton, J. L., *J. Am. Chem. Soc.* , **1992**, *114* , 9434; Wipf, P.; Miller, P., *J. Org. Chem.*, **1993**, *58* , 3604 ; Shapiro, R., *J. Org. Chem.* , **1993**, *58* , 5759 ; Wipf, P., *Chem. Rev.*, **1995**, *95* , 2115; Knight, D.W., Pattenden, G., Rippon, D.E., *Synlett*, **1990**, *1*, 36.
3. Prager, R.H.; Smith, J.A.; Weber, B.; Williams, C.M., *J.Chem. Soc., Perkin Trans.1*, **1997**, 2665.
4. Prager, R.H.; Taylor, M.R.; Williams, C.M., *J.Chem. Soc., Perkin Trans.1*, **1997**, 2673.
5. Klausner, Y.S.; Bodansky, M., *Synthesis*, **1972**, 453.
6. Dale, J.A.; Dull, D.L.; Mosher, H.S., *J.Org. Chem.*, **1969**, *34*, 2543..
7. N'Diaye, I.; Guella, G.; Chiasera, G.; Mancini, F.; Pietra, F., *Tetrahedron Lett.*, **1994**, *35*, 4827; Pietra, F.; Guella, G.; Mancini, I.; and N'Diaye, I., *Helv. Chim. Acta*, **1994**, *77*, 1999.

8. N'Diaye, I., Guella, G., Mancini, I., Pietra, K., *Tetrahedron Lett.*, **1996**, *37*, 3049.
9. Lewis, J.R., *Nat. Prod. Rep.*, **1995**, *12*, 135 and references therein to earlier parts.
10. Undheim, K.; Gacek, M., *Tetrahedron*, **1974**, *30*, 4233.
11. Wolfe, S.; Hasan, S. K., *Can. J. Chem.*, **1970**, *48*, 3572.
12. Fleming, I.; Loreto, A.M.; Wallace, I.H.M.; Michael, J.P., *J. Chem. Soc., Perkin Trans. 1*, **1986**, 349.
13. Weinreb, S.M.; Levin, J. I.; Turos, E., *Synth. Commun.*, **1982**, *12*, 989.
14. **10**, mp 165-167°C, $[\alpha]_D^{27}$-110°; **17**, mp 98-99°, $[\alpha]_D^{27}$-125.3° (*c* 1.5, $CHCl_3$); **20**, oil, $[\alpha]_D^{27}$ +49° (*c* 0.8, $CHCl_3$) ; **21**, almazole, A, colourless oil, $[\alpha]_D^{27}$ +95.5° (*c* 0.4, MeOH), HRMS for M-Bz: found 272.1033, calc. for $C_{14}H_{14}N_3O_3$ 272.1035, ^{1}H n.m.r. δ 2.44 (s,6H), 3.27 (dd, J 13.2, 5.6 Hz,1H), 3.38 (dd, J 13.2, 9.5 Hz 1H), 4.22 (dd, J 9.5, 5.6 Hz, 1H), 7.16-7.23 (m, 5H), 7.24 (ddd, J 7.8, 7.0,1.0 Hz, 1H), 7.64 (ddd, J 8.5, 7.0, 1.5 Hz, 1H), 7.70 (s, 1H), 7.76 (dd, J 7.8, 1.5 Hz, 1H), 8.46 (d, J 1.6 Hz, 1H), 8.64 (dd, J 8.5, 1.0 Hz, 1H), 10.43 (bs, 1H); ^{13}C n.m.r. δ 36.61,C2", 41.47,NMe_2, 64.44, C1", 122.48, C4, 122.78, C2', 123.47, C6', 126.89, C6", 128.65, C4", C8", 129.12, C5",C7",131.04, C7', 135.04, C5', 136.77, C4, 137.48, C3", 149.23, C5,159.60,CHO, 167.91,C2,183.24,C1' ; υ max (neat) 3326, 1699, 1635, 1583, 1507, 1450, 902 cm^{-1}; for minor (E) conformer ^{1}H n.m.r. δ 8.84 (bd,J 11.4 Hz,CHO,9.94 (bd,J 11.4 HZ NH. **22**, almazole B, yellow oil, $[\alpha]_D^{27}$ +82.2°, (*c* 0.56, MeOH), HRMS for M-Bz: found 244.1082, calc. for $C_{13}H_{14}N_3O_2$ 244.1086, ^{1}H n.m.r. δ 2.42 (s, 6H), 3.26 (dd, J= 13.5, 5.7Hz, 1H), 3.37 (dd, J 13.5, 9.6Hz,1H), 4.18 (dd, J 9.6,5.7Hz,1H), 6.02 (bs,2H), 6.68 (ddd, J 8.1, 7.2, 1.2 Hz,1H), 6.72 (dd,J 8.3,1.2 Hz,1H), 7.16-7.26 (m,5H), 7.32 (ddd, J 8.3,7.2,1.5 Hz,1H), 7.63 (s,1H), 7.72 (dd,J 8.1,1.5 Hz,1H); ^{13}C n.m.r. δ 36.84, C2", 41.55, NMe_2, 64.39, C1", 116.26, C6', 117.28, C4', 117.54, C2', 126.70, C6", 128.56, C4", C8", 129.13, C5", C7", 131.71, C7', 134.24, C4, 134.87, C5', 137.70, C3', 150.94, C5, 165.45, C2, 182.68, C1'. υ max (neat) 3331, 1622, 1588, 1508, 1457, 1309, 1256, 902 cm^{-1}.