Pergamon

Tetrahedron, Vol. 52, No. 6, pp. 2097-2102, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01025-4

Stereoselective Ring Transformation of *N*-Alkyl Aziridines into Oxazolidin-2-ones

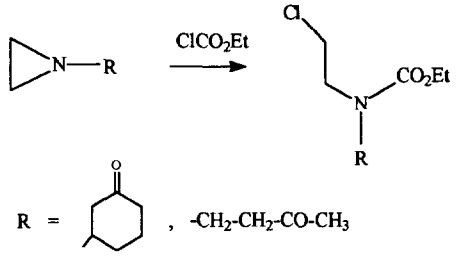
José Sepúlveda-Arques,*[a] Trinidad Armero-Alarte,[a] Alberto Acero-Alarcón,[a]
Elena Zaballos-García,[a] Belén Yruretagoyena Solesio,[b] and Jesús Ezquerra Carrera[b]

a. Department of Organic Chemistry, University of Valencia, Valencia, Burjassot, Spain
b. Lilly Research Center , 28130- Valdeolmos, Madrid, Spain

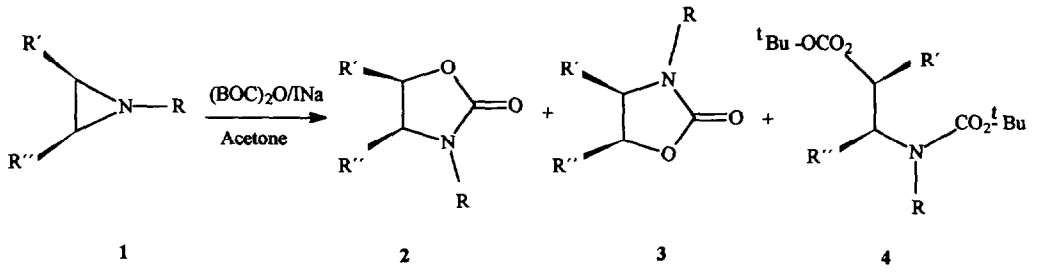
Abstract : N-Alkyl aziridines react stereoselectively with di-*tert*-butyl dicarbonate and sodium iodide in acetone to give oxazolidin-2-ones in excellent yields.

As a consequence of the ring strain present in aziridines, ring opening reactions are a dominant feature of their reactivity. With "nonactivated" aziridines (H, alkyl, or aryl on N) these reactions usually occur only after protonation, quaternization or formation of a Lewis acid adduct.[1]

In this context it has been reported that the reaction of N-alkylaziridines with ethyl chloroformate, results in cleavage of the aziridine ring and formation of *N*-alkyl, *N*-(2-chloroethyl)-urethanes.[2,3]



When a similar reaction was attempted with the N-alkylaziridines **1a-h** using di-*tert*-butyl dicarbonate and sodium iodide in acetone, oxazolidin-2-ones **2a-h** were obtained in excellent yields (84-97%). The transformation of the aziridines into the oxazolidinones **2** took place at room temperature, or in the case of the aziridines **1f** and **1h** at reflux in acetone. Mixtures of regioisomers **2** + **3** were obtained with unsymetrically substituted aziridines **1b** and **1d**. Small amounts (2-5%) of the Boc-derivatives **4** were detected in the reactions of **1a** and **1c**. (Table 1)



1 2 3 4

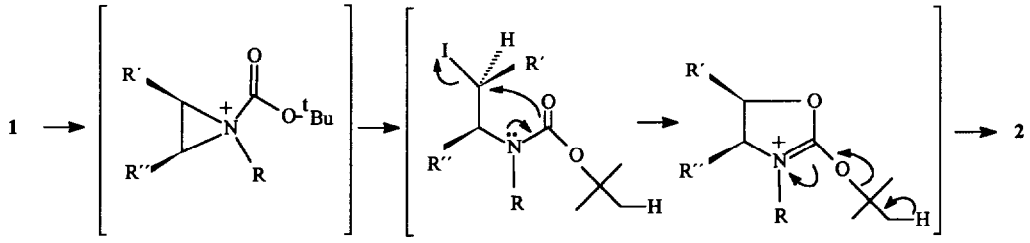
Table 1.- Oxazolidin-2-ones (**2** , **3**) and Boc derivatives (**4**) obtained by reaction of aziridines (**1**) with di-*tert*-butyl dicarbonate.

	R	R′, R″	Time (hours)	Temperature (°C)	Yield **2**, **3**, **4** (%)
a		H, H	72	20	**2** (87), **4** (2)
b		CH_3 , H	96	20	**2** (85) + **3** (traces)
c	$-CH_2-CH_2-CO-CH_3$	H, H	72	20	**2** (86), **4** (5)
d	$-CH_2-CH_2-CO-CH_3$	CH_3 , H	72	20	**2** + **3**, (85) (ratio **2**:**3** was 3:2)
e	$-CH_2-CH_2-CO-CH_2$	$(CH_2)_3$	48	20	**2** (97)
f	$-CH_2-CH_2-CO-CH_3$	$(CH_2)_4$	16	58	**2** (95)
g	$-CH_2-Ph$	$(CH_2)_3$	24	20	**2** (92)
h	$-CH_2-Ph$	$(CH_2)_4$	30	58	**2** (91)

The Boc-derivative **4a** was obtained as a major product in experiments carried out with **1a** at room temperature in benzene or when sodium bromide or chloride were used instead of sodium iodide.

Solvent	XNa	Time (Days)	**2a** (%)	**4a** (%)
acetone	INa	3	85	3
benzene	INa	3	37	44
acetone	BrNa	3	46	35
benzene	BrNa	7	17	63
acetone	ClNa	7	-	87
benzene	ClNa	8	-	81
benzene	-	6	-	94

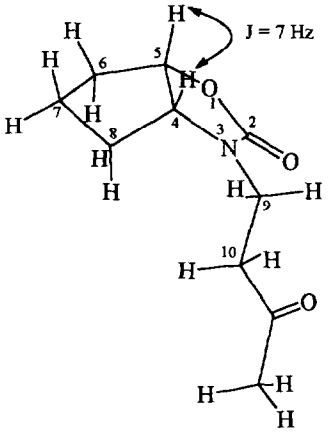
The formation of the Boc-derivatives **4** or the oxazolidinones **2,3** can be explained by an initial acylation of the tertiary nitrogen atom, followed by nucleophilic attack and ring opening either by the *tert*-butyl carbonate or by the iodide. In this latter case the intermediates, *tert*-butyl N-alkyl-β-iodocarbamates, rearrange to oxazolidinones at the temperature of the reaction. The cyclization takes place via backside attack by the carbonyl oxygen of the carbamate on the halogenated carbon, followed by carbonylation of the *tert*-butoxy group and elimination of 2-methylpropene (Scheme 1 show the formation of oxazolidinones **2**).



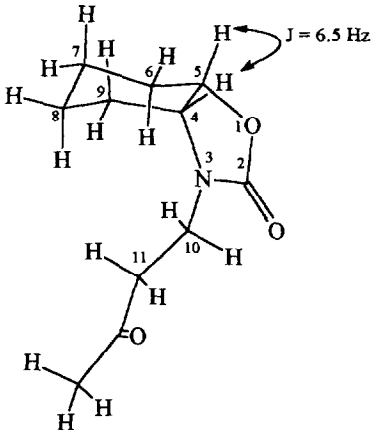
Scheme 1

The results obtained in the reaction of the aziridines **1b** and **1d**, showed that bond breaking is facilitated by stabilization of the incipient carbocation (R′-CH$^+$-CHR′′-N) in the opening of the aziridinium intermediate, although steric factors would promote attack at the methylene carbon, and favours formation of one of the regioisomers. (Trace amounts of **3b** were detected; the ratio **2d:3d** was 3:2). In the case of **2b** the major compound was obtained as a mixture of diastereoisomers (65:35) which were perfectly distinguishable by NMR.

Cis stereochemistry for the bicyclic compounds, 4,5-trimethyleneoxazolidin-2-one **2e**, and 4,5-tetramethyleneoxazolidin-2-one **2f**, was stablished by NOE experiments. When either of the bridge hydrogens in compounds **2e** and **2f** was irradiated, positive NOE effects (**2e**, 13.5 % H-5 to H-4, 13.2 % H-4 to H-5; **2f**, 3.4 % H-5 to H-4, 6.3 % H-4 to H-5), were observed in the other hydrogen. COSY NMR allowed assignement of some hydrogens signals in bicyclic compound **2f**, specially those coupled with the bridge hydrogens H-4 and H-5. Coupling constants of 7.0 Hz for H-4 to H-5 in compounds **2e** and **2g**, and 6.5 Hz for compounds **2f** and **2h**, assigned for the first time in bicyclic oxazolidin-2-ones, were very close to theoretical values calculated from dihedral angles of optimized structures obtained by molecular mechanics calculations[13] and supported *cis* stereochemistry (**2e** 5.1 degrees, J = 7.7 Hz; **2f** 29.3 degrees, J = 6.6 Hz).



2e



2f

Although the cyclization step has certain similarities with other reported methods of preparation of oxazolidin-2-ones, starting from olefins,[4,5,6] amino alcohols,[7] and N-acylaziridines,[8,9] it involves different intermediates and takes place under mild reaction conditions.

The reported reaction constitutes a new synthetic procedure for the stereoselective preparation of N-substituted oxazolidin-2-ones with excellent yields and under mild reaction conditions. In addition it provides an access to *cis*-amino alcohols by hydrolysis with alcoholic base of the oxazolidinones.

EXPERIMENTAL SECTION

The IR spectra were determined with a Perkin Elmer 843 (neat or KBr). ^{1}H-NMR and ^{13}C-NMR spectra were run on a Bruker 250 in $CDCl_3$. High Resolution Mass Spectra (HRMS) were recorded on a VG-Autospec, Trio 1000 Fisons. Aziridine was prepared from 2-chloroethylamine.[10] 7-Azabicyclo [4,1,0] heptane and 6-aza-

bicyclo [3,1,0] hexane were obtained from the corresponding iodoazides.[11] 2-Methylaziridine was comercially available. N-alkylaziridines were prepared by Michael additions of the aziridines to 2-cyclohexenone and methyl vinyl ketone[2] or by alkylation with benzyl bromide.[12]

General procedure for the reaction of N-alkylaziridines with di-tert-butyl dicarbonate.

Di-*tert*-butyl dicarbonate (0.02 mol) in acetone (10 ml) was added to a mixture of the corresponding N-alkylaziridine (0.02 mol) and INa (0.02 mol) in acetone (20 ml) and stirred at room or reflux temperature until complete reaction of the aziridine (TLC). Experiments with **1a** were also carried out with NaBr, NaCl and benzene as a solvent.

After removal of the solvent, the residue was chromatographed on silica gel column with increasing ratios of hexane-ethyl acetate. The following compounds have been isolated using this procedure:

3-(3-Oxocyclohexyl) oxazolidin-2-one (2a). Obtained in 87% yield. Mp. 112-113°C (dichloromethane-hexane); ν_{max}/cm^{-1} (KBr) : 1720, 1740; ^1H NMR ($CDCl_3$) δ 1.50 (m, 1H), 1.70 (m, 1H), 1.90 (m, 2H), 2.15 (m, 2H), 2.40 (d, J =12.5Hz, 2H), 3.45 (t, J = 7Hz, 2H), 3.80 (m, 1H), 4.20 (t, J = 7Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.6 (t), 28.3 (t), 40.1 (t), 40.5 (t), 44.8 (t), 51.9 (d), 61.8 (t), 157.1 (s), 207.6 (s). Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.01; H, 7.10; N, 7.65. Found: C, 58.89; H, 7.18; N, 7.58.

N,O-di (*tert*-butoxycarbonyl)-N-(3-oxocyclohexyl)-2-aminoethanol (4a). Obtained in 2 % yield. Mp. 67-69°C (hexane); ^1H NMR ($CDCl_3$) δ 1.21 (s, 9H), 1.24 (s, 9H), 1.6-2.5 (m, 8H), 3.1 (m, 2H), 3.7 (m, 1H), 3.88 (t, J = 6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 22.1 (t), 27.6 (q), 28.2 (q), 29.2 (t), 40.4 (t), 43.1 (t), 46.0 (t), 55.6 (d), 65.0 (t), 80.4 (s), 82.1 (s), 153.2 (s), 154.5 (s), 208.6 (s). HRMS : $(M+1)^+$ 358.2236. $C_{18}H_{32}NO_6$, requires $(M+1)^+$ 358.2229.

5-Methyl-3-(3-oxocyclohexyl) oxazolidin-2-one (2b). Obtained in 85% yield; ν_{max}/cm^{-1}(neat): 1720, 1760; ^1H NMR ($CDCl_3$) Diastereoisomeric mixture (65:35) δ 1.35 and 1.37 (2xd, J = 6.2 Hz, 3H), 1.60 (m, 1H), 1.76 (m, 1H), 1.99 (m, 1H), 2.19 (m, 1H), 2.36 (m, 2H), 2.46 (m, 2H), 3.13 (m, 1H), 3.6 (m, 1H), 3.95 (m, 1H), 4.59 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.4 and 20.4 (q), 21,7 (t), 28.4 and 28.6 (t), 40.2 (t), 44.8 and 45.1 (t), 47.5 (t), 51.9 (d), 70.2 (d), 156.8 (s), 207.8 (s). *Anal.* Calcd. for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.10. Found : C, 60.80; H, 7.58; N, 7.13.

3-(3-Oxobutyl) oxazolidin-2-one (2c). Obtained in 86% yield; ν_{max}/cm^{-1}(neat): 1710, 1730; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H), 2.78 (t, J =6Hz, 2H), 3.48 (t, J =6Hz, 2H), 3.61 (t, J =8Hz, 2H), 4.29 (t, J =8Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 29.3 (q), 38.2 (t), 40.6 (t), 44.6 (t), 61.4 (t), 157.8 (s), 206.4 (s). HRMS $(M)^+$ 157.0739. $C_7H_{11}NO_3$ requires 157.0738.

N,O-di (*tert*-butoxycarbonyl)-N-(3-oxobutyl)-2-aminoethanol (4c). Obtained in 5% yield; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 148 (s, 9H), 2.15 (s, 3H), 2.75 (m, 2H), 3.46 (m, 4H), 4.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 28.2 (q), 27.7 (q), 30.0 (q), 43.6 (t), 42.4 (t), 47.2 (t), 64.9 (t), 80.0 (s), 82.1 (s), 155.1 (s), 153.2 (s), 207.1 (s). HRMS $(M-C_4H_8)^+$ 275.1369. $C_{12}H_{21}NO_6$ requires 275.1368.

5-methyl-3-(3-oxobutyl) oxazolidin-2-one and **4-methyl-3-(3-oxobutyl) oxazolidin-2-one (2d and 3d).** Obtained in 85% yield as an inseparable mixture of two isomers (**2d**:**3d** = 3:2). ν_{max}/cm^{-1}(neat): 1740, 1725. Major isomer **2d** ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 6.22 Hz, 3H), 2.12 (s, 3H), 2.71 (m, 2H), 3.12 (dd, J = 8.4 and 6.9 Hz, 1H), 3.4 (m, 2H), 3.63 (t, J = 8.4 Hz, 1H), 4.52 (m, 1H). **3d** (Minor isomer) ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 5.8 Hz, 3H), 2.11 (s, 3H), 2.7 (m, 2H), 3.4 (m, 2H), 3.7 (dd, J = 7.6 and 6.8 Hz, 1H), 3.8 (m, 1H), 4.3 (dd, J = 7.6 and 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ (2d+2d') : 17.9 (q), 20.2 (q), 29.7 (q), 29.8 (q), 36.1 (t), 38.6 (t), 41.3 (t), 51.4 (d), 52.0 (t), 68.8 (t), 70.0 (d), 157.7 (s), 206.6 (s). HRMS $(M)^+$ 171.0894. $C_8H_{13}NO_3$ requires 171.0895.

3-(3-Oxobutyl)-*cis*-4,5-trimethyleneoxazolidin-2-one (2e). Obtained in 97% yield. Mp. 62-64 °C (hexane); ν_{max}/ cm^{-1}(KBr): 1720, 1750; ^{1}H NMR ($CDCl_3$) δ 1.45-1.61 (m, 4H), 1.70-1.95 (m, 2H), 2.11 (s, 3H), 2.69 (dt, J = 17.5, 7.1 1H, H-10), 2.81 (dt, J = 17.5, 7.1, H-10, 1H), 3.23 (dt, J = 14.4, 7.1, 1H, H-9), 3.51 (dt, J = 14.4, 7.1 Hz, 1H, H-9), 4.10 (dd, J = 7.0, 5.8 Hz, 1H, H-4), 4.81 (dd, 7.0, 6.6, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 21.6 (t), 29.7 (q), 30.7 (t), 33.54 (t), 36.9 (t), 41.1 (t), 60.5 (d), 78.7 (d), 157.7 (s), 206.5 (s). *Anal.* Calcd. for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.10. Found : 60.77; H, 7.81; N, 7.19.

3-(3-Oxobutyl)-*cis*-4,5-tetramethyleneoxazolidin-2-one (2f). Obtained in 95% yield. ν_{max}/cm^{-1} (neat): 1720, 1740; ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 1H, H-8), 1.43 (m, 4H, H-7, H-8, H-9), 1.68 (m , 1H, H-6), 1.83 (m, 2H, H-6, H-9), 2.11 (s, 3H), 2.68 (dt, J = 17.5, 6.9 Hz, 1H, H-11), 2.77 (dt, J = 17.5, 6.9, 1H, H-11), 3.22 (dt, J = 14.2, 6.9 Hz, 1H, H-10), 3.47 (dt, J = 14.2, 6.9 Hz, 1H, H-10), 3.61 (dd,, J = 6.5 and 5.8 Hz, 1H, H-4) 4.37 (dt, J = 6.5 and 4.7 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 19.2 (t), 19.5 (t), 25.4 (t), 26.4 (t), 29.8 (q), 36.2 (t), 41.6 (t), 54.8 (d), 73.2 (d), 158.5 (s), 206.6 (s). HRMS $(M)^+$ 211.1213, $C_{11}H_{17}NO_3$ requires 211.1208.

3-benzyl-*cis*-4,5-trimethyleneoxazolidin-2-one (2g). Obtained in 92% yield. ν_{max}/cm^{-1}(neat): 3100-3000, 1750. ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 2H), 1.61 (m, 2H), 1.82 (m, 1H), 1.99 (m, 1H), 3.88 (dd, J = 7.0, 6.5 Hz, 1H, H-4), 3.98 (d, J = 15.3 Hz, 1H, H-9), 4.65 (d, J = 15.3 Hz, 1H, H-9), 4.77 (dd, J = 7.0, 5.1 Hz, 1H, H-5), 7.22 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.8 (t), 30.2 (t), 33.7 (t), 46.4 (t), 59.4 (d), 78.9 (d), 127.7 (d), 127.9 (d), 128.6 (d), 135.9 (s), 158.2 (s). Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 71.95; H, 6.97; N, 6.45. Found: C, 71.97; H, 6.93; N, 6.55.

3-benzyl-*cis*-4,5-tetramethyleneoxazolidin-2-one (2h). Obtained in 91% yield. ν_{max}/cm^{-1}(neat): 3100-3000, 1750. ^{1}H NMR ($CDCl_3$) δ 1.16 (m, 1H), 1.42 (m, 4H), 1.67 (m, 3H), 3.41 (q, J = 6.5 Hz, 1H, H-4), 3.96 (d, J = 15.1 Hz, 1H, H-10), 4.35 (dt, J = 6.5, 5.1 Hz, 1H, H-5), 4.66 (d, J = 15.1, 1H, H-10), 7.21 (bs, 5H). ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 19.4 (t), 25.1 (t), 26.7 (t), 45.6 (t), 53:3 (d), 73.2 (d), 127.5 (d), 127.9 (d), 128.5 (d), 136.1 (s), 158.7 (s). Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.05. Found C, 72.66; H, 7.46; N, 6.01.

Acknowledgements.- We thank M° Educación y Ciencia (DGICYT) for project PB91-0640.

References and notes

1 Tanner D., *Angew. Chem. Int. Ed.*, **1994**, 33, 599.
2 Dolfini, J.E.; Dolfini, D.M. *Tetrahedron Lett.*, **1965**, 25, 2953.
3 Rozing, G.P.; Moinat, T.J.H.; Koning, H.; Huisman, H.O. *Heterocycles*, **1976**, 4, 71
4 Hassner, A.; Lorber, M.E.; Heathcock, C. *J. Org. Chem.*, **1967**, 32, 540.
5 Hu, N.X.; Aso, Y.; Ogura, F. *J. Org. Chem.*, **1989**, 54, 4398.
6 Foglia, T.A.; Swern, D. *J. Org. Chem.*, **1967**, 32, 75.
7 Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron. Lett.*, **1993**, 34, 4509.
8 Heine, H.W.; Proctor, Z. *J. Org. Chem.*, **1958**, 23, 1554.
9 Banks, M.R.; Cadogan, J.I.G.; Gosney, I.; Hodgson, P.K.G.; Thompson, D.E. *J. Chem. Soc. Perkin Trans* I, **1991**, 1961.
10 Wystrach, V.P.; Kaiser, D.W.; Schaefer, F. *J. Am. Chem. Soc.*, **1955**, 77, 5915.
11 Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.*, **1969**, 51, 5046.
12 Ahman, J.; Somfai, P. *Synth. Commun.*, **1994**, 24, 1121.
13 PCMODEL v 3.1, Serena Software, Box 3076, Bloomington IN 47402.

(*Received in UK* 27 *July* 1995; *revised* 16 *November* 1995; *accepted* 23 *November* 1995)