Pergamon

Tetrahedron Letters, Vol. 37, No. 23, pp. 3993-3996, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00741-1

Selective Reduction of 2-(ß-Cyanoalkyl)oxazolines into Cyclic Amidines

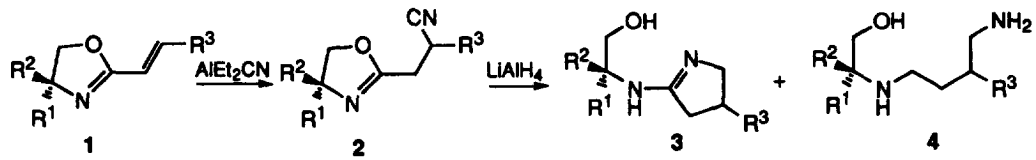
Nicole Langlois* and Nathalie Dahuron

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

Abstract : *The selective reduction of 2-(2-cyanopropyl)-4,5-dihydrooxazoles into heterocyclic amidines has been achieved with LAH in carefully controlled conditions. This reaction was applied to the enantioselective synthesis of (S)-4-methylpyrrolidin-2-one, starting from (R)-phenylglycinol derived oxazoline 1b.*

2-(β–Cyanoalkyl)oxazolines have been prepared through conjugate addition of cyanide to 2-alkenyl-4,5-dihydrooxazoles as **1**, using diethylaluminum cyanide and diastereoselectivity up to 56% was observed with the optically pure oxazoline **1b**.[1] In order to apply these results to the synthesis of enantiomerically enriched β-substituted GABA,[2] we planned to study the chemoselective reduction of 2-(ß-cyanoalkyl)oxazolines **2**.

The selective reduction of the cyano group of **2a** to primary amine was anticipated to be carried out using excess LAH, since the oxazoline ring has been reported to be inert towards this reducing agent.[3] However, the addition of an ether solution of LAH in excess to one mole of the nitrile **2a** in ether led rapidly to two reduction products **3a** and **4a** in a ratio of 3 : 1. Several conditions were checked to improve the yield of **3a** and the main results are summarized in the Table.



a $R^1 = R^2 = R^3 = CH_3$
b $R^1 = Ph$, $R^2 = H$, $R^3 = CH_3$
c $R^1 = R^3 = Ph$, $R^2 = H$

The structures of **3a**[4] and **4a**[5] were deduced from NMR data. In ^1H and ^{13}C NMR spectra the relatively low chemical shifts of the methylene OCH_2 (**3a** : ^1H at 3.49 ppm, ^{13}C at 71.23 ppm, **4a** : 3.31 and 68.20 ppm), compared with those of **2a** (^1H at 3.93, ^{13}C at 79.33 ppm) are characteristic of the opening of the oxazoline ring. Furthermore, the ^{13}C NMR spectrum of the diaminoalcohol **4a** showed the presence of four methylenes and the absence of a N=C quaternary carbon (164.81 ppm in **3a**). The endo- or exocyclic position

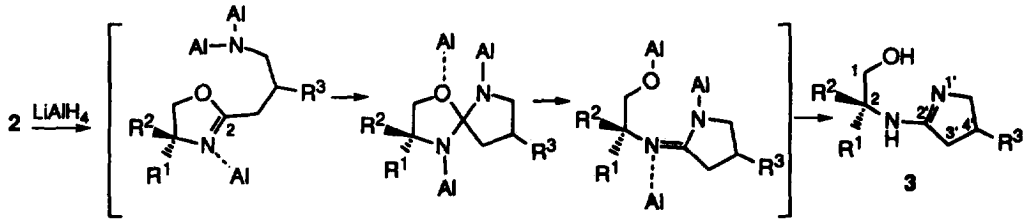
of the double bond could not be deduced from the spectra of **3a** and no evidence of tautomerism of the amidine function could be observed.

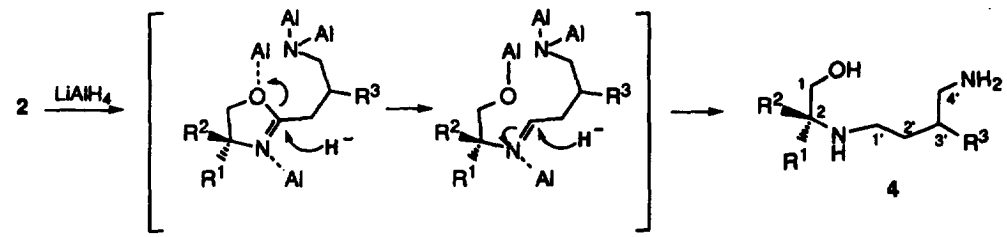
The ratio **3a** : **4a** increased with the use of THF as solvent at higher concentration Thus, minimization of over-reduction to **4a** could be obtained by direct addition of a THF solution of **2a** to a LAH solution in THF[6,7] (entry 2). The formation of by-products from a possible partial reduction of the nitrile function, or from α-deprotonation and self-condensation leading to 1,3-diamines,[6] was not observed. The over-reduction to the diaminoalcohol **4a** could be avoided by using very short reaction times at 18°C (entry 3) ; in these conditions the amidine **3a** was isolated in 92% yield.

Table : Reduction of cyanoalkyloxazolines **2a** and **2b** with LAH

Entry	[Nitrile] (mol/l)	[LAH] (mol/l)	Solvent	T (°C)	t (min.)	Amidine **3** (%)	Ratio **3** : **4**
1	**2a** (0.09)	0.08	Et_2O	35	60	36	75:25
2	**2a** (0.18)	0.14	THF	35	30	75	90:10
3	**2a** (0.18)	0.14	THF	18	5	92	100:0
4	**2b** (0.08)	0.07	THF	18	5	100	100:0

The cyanoalkyloxazolines **2b**, obtained from (*R*)-phenylglycinol derived oxazoline **1b** as a mixture of diastereomers (d.e. : 48%, determined by ^1H NMR)[8] gave similar results and could be quantitatively converted into the amidines **3b**[9] (entry 4).

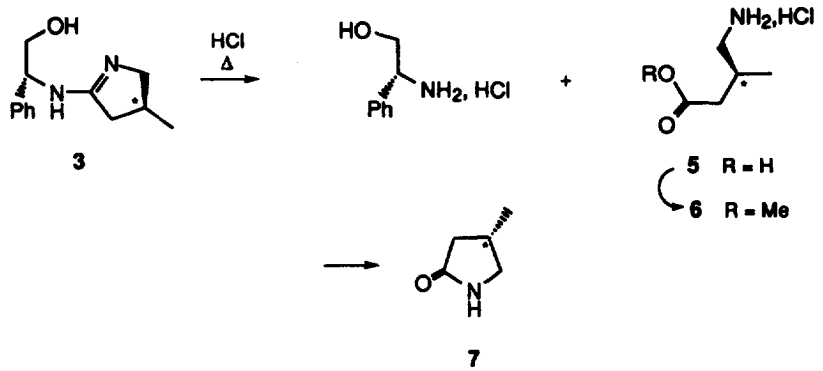




The formation of amidines **3** and diaminoalcohols **4** could be rationalized by a scheme involving a complexation of the nitrogen and oxygen of the oxazoline moiety by aluminum reagent. The position 2 of the

oxazoline ring was made electrophilic by this complexation, allowing the cyclization to the five-membered ring of **3**, or further reduction to **4**.

Acid hydrolysis of the heterocyclic amidines **3b** with 6N HCl at reflux led to the hydrochloride of 4-amino-3-methylbutanoic acid **5** (β-methyl GABA)[10], which could be separated from (*R*)-phenylglycinol hydrochloride or directly converted into its methyl ester (**6**) by treatment with $SOCl_2$ in anhydrous methanol. Purification by chromatography on silicagel of the crude products obtained after basification afforded the 4-methylpyrrolidin-2-one **7** in 57% yield from the cyanoalkyloxazoline **2b**. Optical rotation of **7** confirmed the absolute configuration of the major enantiomer as (*S*) and indicated 50% of enantiomeric excess,[11,12] a value in good agreement with the diastereomeric excess of starting nitrile **2b** (48%).



3 **7**

The reduction of (ß-phenyl-ß-cyanoethyl)oxazoline **2c** was more difficult to control. With LAH, the best results were obtained in ether instead of THF : the amidine **3c** was isolated in 44% yield along with small amount of starting cyanoalkyloxazoline **2c** (13%). It is interesting to note that the diastereomeric excess of the recovered nitrile was very low (4%) as compared with that of the starting cyanoalkyloxazoline **2c** (d.e. 50%). Another general method to reduce nitriles into the corresponding primary amines uses sodium borohydride in the presence of $CoCl_2$[13-15] but this system was unsuccessful, since low conversion (ca. 50%) was observed at room temperature. Improvement of the preparation of **3c** is now under investigation in our laboratory, as well as applications of the over-reduction of cyanoalkyloxazolines into chiral diaminoalcohols such as **4** or related 1,4-diamines.

Acknowledgement : We thank the "Ministère de l'Enseignement et de la Recherche" for a grant (N. D.)

References and Notes

1. Dahuron, N.; Langlois, N. *Synlett.* **1996**, 51-52.
2. a) Bowery, N.G.; Hill, D.R.; Hudson, A.L.; Doble, A.; Middlemiss, N.D.; Shaw, J.; Turnbull, M. *Nature*, **1980**, *283*, 92-94.
   b) Silverman, R.B.; Levy, M.A. *J. Biol. Chem.*, **1981**, *256*, 11565-11568.
3. Meyers, A.I.; Temple, D.L.; Haidukewych, D.; Mihelich, E.D. *J. Org. Chem.* **1974**, *39*, 2787-2793.

4. **3a** : HRMS (CI, isobutane) : $(MH)^+$ calcd for $C_9H_{19}N_2O$: 171.1497, found : 171.1517. IR : 3689, 3442, 2975, 1637, 1600, 1519 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3$, δ = 0 ppm : TMS, J(Hz)] : 3.74 (dd, 1H, J = 13, J' = 8, Ha-5'), 3.49 (s, 2H, H_2-1), 3.18 (dd, 1H, J = 13, J' =7, Hb-5'), 2.53 (dd, 1H, J = 15, J' = 9, Ha-3'), 2.39 (m, 1H, H-4'), 2.02 (dd, 1H, J = 15, J' = 6, Hb-3'), 1.24 (s, 6H, 2 x CH_3), 1.02 (d, 3H, J = 7, CH_3-C4'). ^{13}C NMR (75.0 MHz) : 164.81 (C-2'), 71.23 (C-1), 63.53 (C-5'), 55.87 (C-2), 41.74 (C-3'), 32.01 (C-4'), 25.15 (2 x CH_3), 19.59 (CH_3-C-4').
5. **4a** : MS (SI) : 175 (MH^+). IR : 3668, 2963, 2931, 2869, 1637 (sh), 1595, 1463. ^1H NMR (300 MHz) : 3.31 (s, 2H, H-1), 3.00 (m, 4H, NH, OH), 2.57 and 2.50 (2m, 4H, H_2-1' and H_2-4'), 1.57, 1.52 and 1.37 (3m, 3H, H_2-2' and H-3'), 1.07 (s, 6H, 2 x CH_3), 0.92 (d, 3H, J = 7, CH_3-3'). ^{13}C NMR (75 MHz) : 68.20 (C-1), 53.99 (C-2), 47.92 and 39.37 (C-1' and C-4'), 35.53 (C-2'), 34.34 (C-3'), 23.67 (2 x CH_3), 18.10 (CH_3-3').
6. Soffer, L.M.; Katz, M. *J. Am. Chem. Soc.*, **1956**, *78*, 1705-1709.
7. LAH solutions were titrated according to : Brown, E.; Lézé, A.; Touet, J. *Tetrahedron Lett.* **1991**, *32*, 4309-4310.
8. The diastereomeric excess was measured by examination of the distinct signals related to one of the proton of the oxazoline ring (H-5).
9. **3b** : MS (m/z) : 218 ($M^{+\cdot}$), 217, 201, 187 (100%), 106, 99, 77. HRMS : ($M^{+\cdot}$) calcd for $C_{13}H_{18}N_2O$: 218.1419, found : 218.1418. IR : 3435, 2970, 1696 (sh), 1636, 1509, 1460. ^1H NMR (300 MHz) : 7.33 (m, 5H, H-Ar), 4.67 (bd, 1H, J = 8, H-2), 3.89 (m, 1H, Ha-1), 3.76 (m, 2H, Hb-1, Ha-5'), 3.23, 3.14 (2dd, 1H, J = 12, J' = 6, Hb-5'), 2.63 (dd, 1H, J = 15.5, J' = 8.5, Ha-3'), 2.48 (m, 1H, H-4'), 2.11 (dd, 1H, J = 15.5, J' = 6, Hb-3'), 1.08, 1.06 (2d, J = 6.7, CH_3-4'). ^{13}C NMR (62.5 MHz) : 167.7 (C-2'), 140.3 (qC-Ar), 129.0, 127.9, 126.8 (CH-Ar), 68.5 (C-1), 62.3 (C-2), 60.2 (C-5'), 40.1 (C-3'), 31.8 (C-4'), 19.6 (CH_3).
10. Andruszkiewicz, R.; Barrett, A.G.M.; Silverman, R.B. *Synth. Commun.* **1990**, *20*, 159-166.
11. **7** : $[\alpha]_D^{30}$ = - 10 (c = 1.18, $CHCl_3$), lit. $[\alpha]_D$ = - 20 (c = 0.6, $CHCl_3$)[12].
12. Baggiolini, E.; Berscheid, H.G.; Bozzato, G.; Cavalieri, E.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1971**, *54*, 429-449.
13. Satoh, T.; Suzuki, S; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555-4558.
14. Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801-6802.
15. Ganem, B.; Osby, J.O. *Chem. Rev.* **1986**, *86*, 763-780.

(*Received in France* 22 *March* 1996; *accepted* 17 *April* 1996)