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REDUCTION OF 5,6-DIHYDRO-2*H*-1,3-OXAZINES. A SIMPLE APPROACH TO 1,3-AMINOALCOHOLS FROM 2-AZA-1,3-DIENES

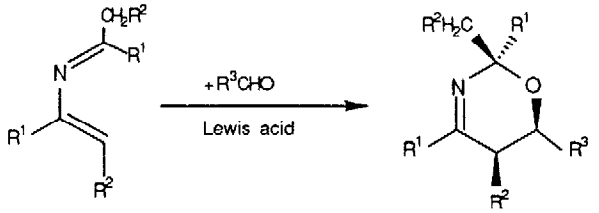
José Barluenga,* Jesús Joglar, Francisco J. González, and Santos Fustero
Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

Summary: The reduction of 5,6-dihydro-2*H*-1,3-oxazines **2** is described for the first time.This reaction allows the diastereoselective synthesis of 1,3-amino alcohols **3** and **4** with three and four chiral centers.

1,3-Difunctionalized compounds, particularly those having the 1,3-amino alcohol structural unit, have attracted a great deal of attention because of their pharmacological properties and their utility as synthons in natural products synthesis.[1]

Simple 1,3-amino alcohols are in most cases prepared either from 1,3-amino carbonyl [2]-or 1,3-oxy imino [3]- compounds, or from alkenes via isoxazolines [1,4] or isoxazolidines.[1,5] In this context, we have recently described a diastereo- and enantioselective synthesis of 1,3-amino alcohols by reduction of 4-amino-1-azadienes, via 1,3-amino ketones.[6] Other strategies [7], *e.g.* opening of oxetanes with trimethylsilyl cyanide and intramolecular amido mercuration of homoallylic alcohols have been also recently described.

On the other hand, we have described a simple procedure for the preparation of 5,6-dihydro-2*H*-1,3-oxazines **2** from 2-aza-1,3-dienes **1** by [4+2]-cycloaddition processes [8](Scheme I).



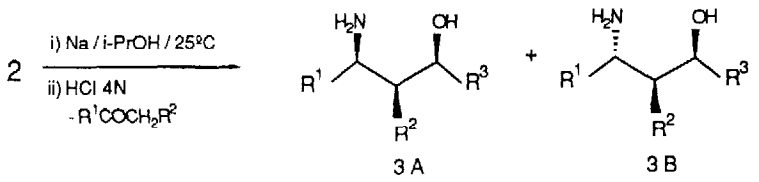
1 2

Scheme I

While the reduction of isoxazolines and isoxazolidines has been studied in detail,[1,4-5] the reduction of 5,6-dihydro-2*H*- 1,3-oxazines **2** has not yet been reported.We wish to report here our results on the stereoselective synthesis of 1,3-amino alcohols having three and four chiral centers by reduction of **2**.[8] Dissolved metals (Na / *i*-PrOH) and complex metal hydrides ($LiAlH_4$) were

used as reducing agents.

Thus, the treatment of **2** with Na / *i*-PrOH in THF at 25 ºC for several hours, followed by acid hydrolysis (4N HCl) of the crude mixture, led in nearly quantitative yields to 1,3-amino alcohols **3** as a mixture of **A**, and **B** diastereoisomers [9] (Scheme II, Table 1). Although the change of co-solvent from *i*-PrOH to EtOH or *t*-BuOH did not lead to appreciable variations in the selectivity, from Table 1 it can be seen that the temperature does influence the diastereoisomer ratio.A lowering in the temperature increases slightly the relative amount of **3A**. Finally, it is worth noting that this procedure complements the one previously reported, [6] in which the **3A** isomer was not formed at all.



Scheme II

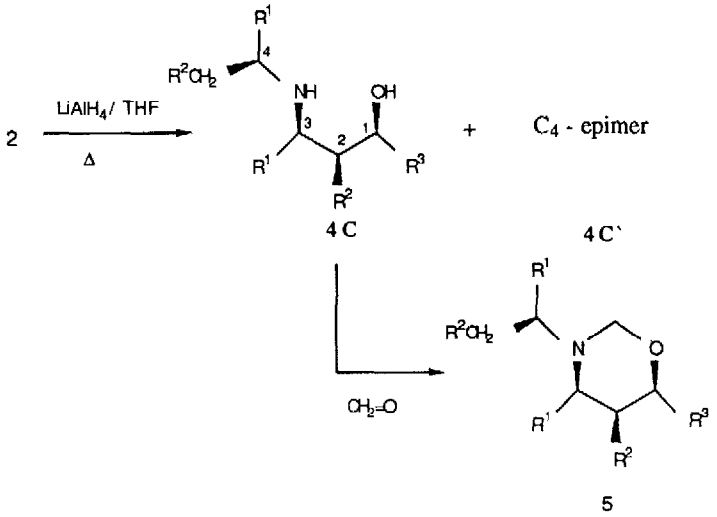
Table 1. 1,3-Amino Alcohols **3** and **4** obtained by reduction of 5,6-dihydro-2*H*- 1,3-oxazines **2**.

Compd.[a]	R^2	R^3	Yield (% **3**)[b]	**3A /3B** [c]	Yield (% **4**)[d]	**4C / 4C'** [c]
a	Me	Ph	99	61 / 39 (76 / 24)[e]	95	90 / 10
b	Me	2-Thienyl	100	59 / 41	93	87 / 13
c	Me	PhCH(Me)[f]	98	60 / 40	90	81 / 19
d	Et	Ph	97	65 / 35	98	89 / 11

[a] R^1=Ph; [b] Reduction with Na / *i*-PrOH / THF / 25 ºC; [c] By ^1H and ^{13}C NMR of the crude residue (estimated error ≤ ±2); [d] Reduction $LiAlH_4$ / THF / reflux; [e] Reduction with Na / *i*-PrOH / THF / -30 ºC; [f] Only a single diastereomer (Cram adduct) was isolated in the preparation of **2c** (see ref. 8).

On the other hand, $LiAlH_4$ reduction of **2** in THF at reflux for several hours (24-48 h) resulted in the formation of *N*-alkylated 1,3-amino alcohols **4** in nearly quantitative yields (Scheme III, Table 1). Among the four possible diastereoisomers, only the epimers **4C** and **4C'**-ratio **4C** / **4C'**: ~9 / 1, table 1- could be detected in the crude mixture.

Isolation and purification of the major isomer **4C**[10] was usually achieved by crystallization of either the aminoalcohol mixture or the tetrahydro-1,3-oxazines **5** [9] obtained by condensation with CH_2O (Scheme III).



Scheme III

The stereochemical relationship between C-1, C-2, and C-3 on **4C** and **4C'** was based on ^1H and ^{13}C NMR data.[9] On the other hand, the relative configuration of C-4 was confirmed by an X-Ray structural analysis of **5a** (R^1=R^3= Ph; R^2= Me).[11]

The stereochemical results shown for the $LiAlH_4$-reduction of **2** can be explained by initial addition of hydride to the carbon of carbon-nitrogen double bond from the less hindered face (Fig. 1), which in fact led to a degree of stereoselectivity higher than 98%; further hydride transfer, presumably from a ring-open tautomer, would take place through the rigid, cyclic alkoxyaluminate transition state depicted in Fig. 2.

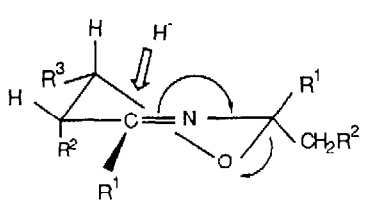


Fig. 1

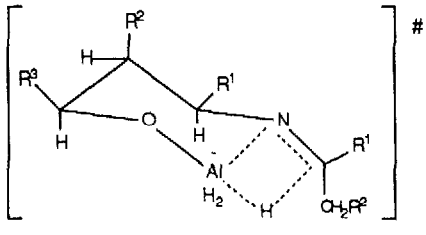


Fig. 2

In conclusion, the reduction of 5,6-dihydro-2*H*-1,3-oxazines **2** has been studied for the first time. The process allows the diastereoselective, high-yield preparation of 1,3-amino alcohols with three **3**, and four **4** chiral centers.

References and notes

1. (a) W. Schwab and V. Jäger, *Angew. Chem., Int. Ed. Engl.*, **1981**,*20*, 603; (b) P.M. Wovkulich and M.R. Uskokovic, *J. Am. Chem. Soc.*, **1981**, *103*, 3956; (c) P.N. Confalone, E.D. Lollar, G. Pizzolato, and M.R. Uskokovic, *J. Am. Chem. Soc.*, **1978**, *100*, 6291; (d) P.N. Confalone, G. Pizzolato, and M.R. Uskokovic *J. Am. Chem. Soc.*, **1980**, *102*, 1954; (e) Y-F. Wang, T. Izawa, S. Kobayashi, and M. Ohno, *J. Am. Chem. Soc.*, **1982**, *104*, 6465; (f) M. Ohno, S. Kobayashi, T. Izawa, and Y-F. Wang, *J. Chem. Soc., Chem. & Ind. Chem.*, **1983**,*12*, 99; (g) H. Hahn, H. Heitsch, R. Rathmann, G. Zimmermann, Ch. Bormann, H. Zähner, and W.A. König, *Liebigs Ann. Chem.*, **1987**, 803 and references cited therein.
2. M. Tramontini, *Synthesis*,**1982**, 605.
3. (a) K. Narasaka and Y. Ukaji, *Chem. Lett.*, **1984**,147; (b) Y. Yamamoto, T. Komatsu and K. Maruyama, *J. Chem. Soc. Chem. Commun.*, **1985**, 814.
4. (a) V. Jäger and V. Buss, *Liebigs Ann. Chem.*, **1980**, 101; (b) V. Jäger, V. Buss and W. Schwab, *ibid.*, **1980**, 122 and references cited therein.
5. J. Mulzer, *Nach. Chem. Tech. Lab.*, **1984**, *32*, 882.
6. (a) J. Barluenga, B. Olano and S. Fustero, *J. Org. Chem.*, **1985**, *50*, 4052; (b) J. Barluenga, B. Olano, S. Fustero, Mª C. Foces-Foces, F. Hernández, *J. Chem. Soc. Chem. Commun.*, **1988**, 410.
7. (a) P.G. Gassman and L.M. Haberman, *Tetrahedron Lett.*, **1985**, *26*, 4971; (b) K.E. Harding, T.H. Marman, and D. Nam, *Tetrahedron*, **1988**, *44*, 5605.
8. J. Barluenga, J. Joglar, S. Fustero, V. Gotor, C. Krüger, and M.J. Romão, *Chem. Ber.*, **1985**, *118*, 3652.
9. Satisfactory ^1H , ^{13}C NMR and Mass Spectra were obtained for all new 1,3-amino alcohols **3** and **4**. For example, **3Aa** and **3Ab** (see ref. 6a). **3Ad** (Data taken of crude mixture): ^1H NMR ($DCCl_3$) δ 0.10 (t, 3H), 1.10 (m,1H), 1.30 (m, 1H), 1,90 (m, 1H), 3.20 (m, 2H, exchangeable with D_2O), 4.31 (d, 1H,*J*=3.2 Hz), 5.13 (d, 1H, *J*=2.2 Hz), 7.1-7.6 (m, 10H); ^{13}C NMR ($DCCl_3$) δ 144.9 (s), 143.7 (s) ,128.5 -125.4(m), 77.5 (d), 59.7 (d), 52.8 (d), 14.4 (q), 13.7 (t); MS *m/z* 237 (M^+-18). **3Bd** (Data taken of crude mixture) : ^1H NMR ($DCCl_3$) δ 0.80 (t, 3H), 1.40 (m, 1H), 1.50 (m, 1H), 1.70 (m, 1H), 3.20 (m, 2H, exchangeable with D_2O), 4.30 (d, 1H, *J*=8 Hz), 4.83 (d, 1H, *J*=2.21 Hz), 7.1- 7.6 (m, 10H); ^{13}C NMR ($DCCl_3$) δ 143.8 (s), 143.2 (s), 128.5- 125.4 (s), 72.6 (d), 55.9 (d), 51.9 (d), 17.4 (t), 12.0 (q).
4Ca (oil): ^1H NMR ($DCCl_3$) δ 0.51 (d, 3H), 0.67 (t, 3H), 1.70-1.85 and 1.97-2.12 (m, 3H), 3.40 (dd, 1H, *J*= 3.9 and 9.6 Hz), 4.53 (d, 1H, *J*= 2.7 Hz), 5.37 (d, 1H, *J*= 2.0 Hz), 6.80-7.90 (m, 15H); ^{13}C NMR ($DCCl_3$) δ 3.0 (q), 8.5 (q), 27.4 (t), 46.0 (d), 61.8 (d), 64.2 (d), 78.0 (d), 123.5-129.7 (m), 140.5 (s), 143.2 (s), 143.8 (s); MS *m/z* 359 (M^+). **4Cb** (m.p. 105-7°C): ^1H NMR ($DCCl_3$) δ 0.64 (d, 3H), 0.65 (t, 3H), 1.70-1.90 and 1.97-2.20 (m, 3H), 3.37 (dd, 1H, *J*= 3.7 and 9.5 Hz), 4.49 (d, 1H, *J*= 2.5 Hz), 5.62 (dd, 1H, *J*= 1.2 and 2.0 Hz), 6.80-7.40 (m, 13H); ^{13}C NMR ($DCCl_3$) δ 4.3 (q), 9.8 (q), 27.7 (t), 46.3 (d), 61.3 (d), 64.2 (d), 75.5 (d), 121.5-128.2 (m), 140.5 (s), 142.8 (s), 147.8 (s); MS *m/z* 365 (M^+). **5a** (m.p.120-2°C): ^1H NMR ($DCCl_3$) δ 1.13 (t, 3H), 1.20 (d, 3H), 2.17-2.67 (m, 3H), 4.40 (dd, 1H), 4.80 (d, 1H, *J*= 3.0 Hz), 4.90 (d, 1H, *J*= 10.0 Hz), 5.20 (d, 1H, *J*= 10.0 Hz), 5.33 (d, 1H, *J*= 3.0 Hz), 7.67-8.17 (m, 15H); ^{13}C NMR ($DCCl_3$) δ 7.7 (q), 12.4 (q), 17.1 (t), 41.6 (d), 60.9 (d), 68.7 (d), 81.1 (t), 83.1 (d), 125.3-129.1 (m), 140.6 (s), 141.1 (s), 141.4 (s); MS *m/z* 371 (M^+).
10. The minor isomer **4C'** was never isolated.
11. The X-Ray analysis was performed by: C. Krüger and Y.-H. Tsay, Max-Planck-Institut für Kohlenforschung, Mülheim a.d. Ruhr, West Germany. Further details will be published elsewhere.

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