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Asymmetric Synthesis XVII[1] : Facile Generation of a Chiral Azomethine Ylide via the CN(R,S) Method[2]

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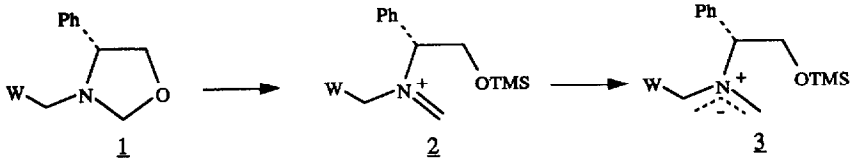
Abstract : (-)-N-cyanomethyl-4-phenyl-1,3-oxazolidine, prepared in one step from R-(-)-phenylglycinol, gives a chiral azomethine ylide on treatment with TMSOTf and $(iPr)_2NEt$. This ylide undergoes 1,3-dipolar cycloaddition reactions with activated olefins under very mild conditions giving optically active functionalized pyrrolidines.

Within the context of asymmetric synthesis based on the use of the N-cyanomethyl-4-phenyl-1,3-oxazolidine system[1,3] according to the CN(R,S) method[1,3b], we now report a facile formation of a chiral azomethine ylide **3** from **1a** and **1b** (scheme 1).



a : W = CN; b : W = CO_2Me

Scheme 1

Although 1,3-dipolar cycloadditions of azomethine ylides represent one of the most powerful methods for pyrrolidine synthesis, no general methodology for generation of differently substituted dipoles exists ; development of new methods is therefore attractive. The thermolysis or photolysis of aziridines[4], the deprotonation[4,5] or desilylation[6] of imines or iminium ions are among the most employed methods. Furthermore, nonstabilized nonsubstituted azomethine ylides may be obtained[6b,7], whereas stable ylides have been also isolated[8].

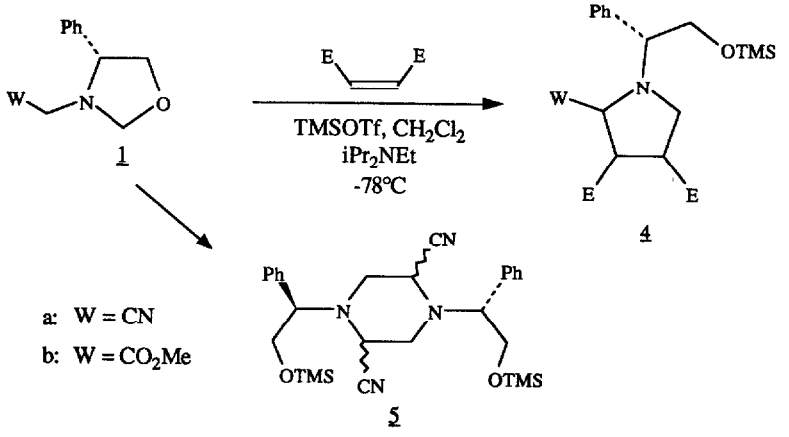
Contrasting with 1,3-dipolar cycloaddition to chiral nitrones[9], only one attempt has been described to perform a cycloaddition with a chiral azomethine ylide, and no enantiomerically pure pyrrolidine was isolated by this method[10].

We have shown that selective functionalization of either the α-aminonitrile or α-aminoether centers of chiral synthon of type **1** can be achieved. In particular, it was found that electrophilic substitution of the aminonitrile anion proceeded in good yields and in a diastereoselective manner.

Moreover, nucleophilic addition could be performed via an intermediate iminium ion derived from opening of the oxazolidine ring[3]. Synthons 1 thus integrate the potential of a 1,3-dipolar system corresponding to the azomethine ylide 3 (Scheme 1). It was thus necessary to generate selectively the iminium ion corresponding to 2 from two potential functions (α-aminonitrile and α-aminoether). Trimethylsilyl triflate appeared to be suitable for opening the oxazolidine ring irreversibly, due to concomitant protection of the primary hydroxyl group.

We have already shown that compound **1a** is easily prepared on a large scale (currently 20 - 50 g) in a one pot procedure from (R)-(-)-phenylglycinol, formaldehyde and KCN (Y : 94%)[3c]. Treatment of a CH_2Cl_2 solution of **1a** at - 78°C with trimethylsilyl triflate and a tertiary amine[11] allowed the generation of ylide **3a**[12] as proved by cycloaddition with activated olefins, leading to substituted pyrrolidines **4a** (Scheme 2) in high yield (dimethylmaleate 75%, N-phenylmaleimide 95%, methylacrylate 71%).

However, non activated olefins and benzaldehyde did not react and only dimerization products 5 were observed (scheme 2).



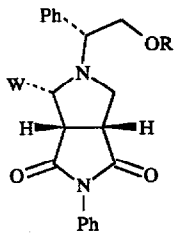
Scheme 2

An important aspect of this cycloaddition is related to the issue of its regio- and stereoselectivities or at least facile separation of diastereomeric products.

As a prelude, we have carefully examined the simpler case of N-phenyl maleimide[13]. Four adducts **6a**, **7a**, **8a** and **9a**[14] (Figure) were isolated in a ratio 44:32:16:8 respectively. The major stereoisomer **6a** was obtained in 41% overall yield from phenylglycinol.

The relative stereochemistry of each compound was determined by ^1H NMR spectra and their absolute configurations were unequivocally proved from X-ray analysis[15] of **6a**.

Synthon **1b**, the ester analog of **1a**, led with N-phenylmaleimide to the formation of two major adducts **6b** and **7b** in nearly equal amounts (Y : 85%) and only traces of adducts **8b** and **9b**. The two major components were isolated and characterized as their acetate derivatives **6c** and **7c**.

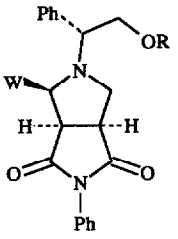


6a mp 172°C

$[\alpha]_D^{20}$ -113° (c 1.0, $CHCl_3$)

6c mp 124°C

$[\alpha]_D^{20}$ -17° (c 1.0, $CHCl_3$)

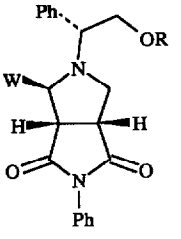


7a mp 175°C

$[\alpha]_D^{20}$ -118° (c 1.0, $CHCl_3$)

7c mp 153°C

$[\alpha]_D^{20}$ -96° (c 1.2, $CHCl_3$)



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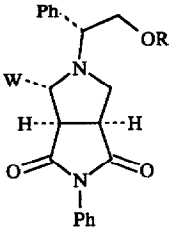
a) R = TMS

b) R = TMS

c) R = $COCH_3$



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W = CN

W = $COOCH_3$

W = $COOCH_3$

Despite the lack of selectivity of the above-mentioned cycloadditions, the results described here provide a novel example of azomethine ylide formation in very mild conditions and also furnish an efficient and simple procedure for the preparation of enantiomerically pure highly substituted pyrrolidines, serving as precursors of natural products of pharmacological interest (e.g. : kainic acid and its analogs[16]).

Further work is in progress to determine the factors governing the selectivity of this cycloaddition.

References and Notes

1. For Part XVI see : Aitken, D.J.; Royer, J.; Husson, H.-P. Tetrahedron Lett. **1988**, 29, 3315.
2. Preliminary communication at the 7th IUPAC Conference on Organic Synthesis. Nancy, France, 4-7 July, **1988**.
3. a) Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. J. Am. Chem. Soc. **1983**, 105, 7754. Royer, J.; Husson, H.-P. J. Org. Chem., **1985**, 50, 670. Guerrier, L.; Grierson, D.S.; Royer, J.; Husson, H.-P. J. Org. Chem. **1986**, 51, 4475.
   b) Arseniyadis, S.; Huang, P.Q.; Husson, H.-P. Tetrahedron Lett. **1988**, 29, 1391.
   c) Marco, J.-L.; Royer, J.; Husson, H.-P. Tetrahedron Lett. **1985**, 26, 3567 and 6345.
4. Lown, J.M. "1,3-Dipolar Cycloaddition Chemistry" ; Padwa, A., Ed.; J. Wiley, New York **1984** ; vol 1, p. 653.

5. Deyrup, J.A.; Szabo, W.A. J. Org. Chem. **1975**, 40, 2048. Deyrup, J.A.; Kuta, G.S. J. Org. Chem. **1978**, 43, 501. Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. J. Chem. Soc. Chem. Commun. **1978**, 109.

6. a) Vedejs, E.; West, F.G. Chem. Rev. **1986**, 89, 941.
b) Vedejs, E.; Martinez, G.R. J. Am. Chem. Soc. **1979**, 101, 6452.
c) Padwa, A.; Eisenbarth, P.; Venkatramanan, M.K.; Wong, G.S.K. J. Org. Chem. **1987**, 52, 2427.

7. Beugelmans, R.; Negron, G.; Roussi, G. J. Chem. Soc. Chem. Commun. **1983**, 31.

8. a) Huisgen, R.; Nicklas, K. Heterocycles, **1984**, 22, 21 and references cited therein.
b) Tsuge, O.; Kanemasa, S.; Sakamoto, K.; Takenaka, S. Bull. Chem. Soc. Jpn **1988**, 61, 2513.

9. See for e.g.: Vasella, A.; Voeffray, R. Helv. Chim. Acta **1982**, 65, 1134. Wovkulich, P.M.; Uskokovic, M.R. J. Am. Chem. Soc. **1981**, 103, 3956.

10. Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. Tetrahedron, **1985**, 41, 3529.

11. iPr_2NEt appeared to be the best tested base, in contrast with Et_3N more commonly used for deprotonation (i.e. cycloaddition to N-phenylmaleimide in the presence of Et_3N is obtained with a modest yield of 35%).

12. A similar non-chiral ylide has been recently obtained[6c] in a less straightforward manner.

13. A typical experiment is as follows : compound **1a** (1.05 g ; 5.5 mmol) was dissolved into CH_2Cl_2 (50 ml) and iPr_2NEt (1.95 mL ; 11 mmol) and olefin (2.9 mmol ; 1.5 eq.) were added before the solution was cooled to - 78°C. TMSOTf (1.3 mL ; 6.7 mmol ; 1.2 eq.) was added very slowly via syringe and the solution was allowed to stir at -78°C for 4 h. The mixture was warmed to room temperature and then washed with brine, dried (Na_2SO_4) and evaporated to dryness before flash-chromatography.

14. The spectral data for all compounds were in accord with their proposed structures. Satisfactory microanalyses and/or high-resolution mass spectra were obtained for these products.
6a : mp 172°C (CH_2Cl_2-hexane) ; $[\alpha]_D^{20}$ - 113° (c 1.0, $CHCl_3$).
^1H NMR ($CDCl_3$, 200 MHz) δ : 0.13 (s, 9H) ; 2.71 (dd, J = 10 Hz, J' = 8 Hz, 1H) ; 3.25 (t, J = 10 Hz, 1H) ; 3.5 (m, 1H); 3.90 (m, 3H) ; 5.06 (d, J = 8 Hz, 1H) ; 7.5 (m, 10 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: - 0.9 (q) ; 42.4 (d) ; 48.6 (d) ; 52.1 (t) ; 55.2 (d) ; 66.8 (t); 67.1 (d) ; 114.2 (s) ; 126.6 (d) ; 127.4 (d) ; 128.2 (d) ; 128.7 (d); 128.8 (d) ; 129.1 (d) ; 131.3 (s) ; 138.3 (s) ; 173.0 (s); 175.3 (s).

15. The X-Ray analysis has been performed at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette) by Drs. A. Chiaroni and C. Riche who are gratefully thanked.

16. See for e.g.: Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. J. Am. Chem. Soc. **1988**, 110, 4807.

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