

A 3+2 CYCLOADDITION ROUTE TO N-H PYRROLIDINES DEVOID OF ELECTRON-WITHDRAWING GROUPS

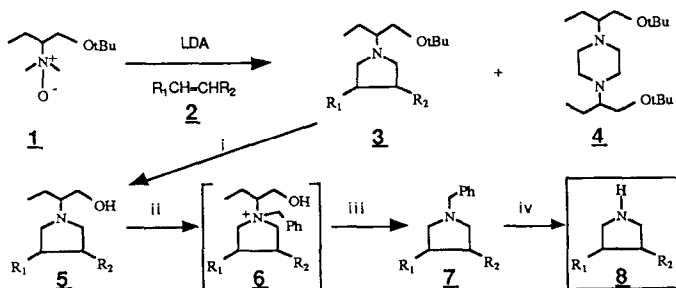
Georges Roussi* and Jidong Zhang

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

Abstract. - N-H pyrrolidines are obtained from intermolecular 3+2 cycloaddition reactions between nonactivated olefins and ylide generated from amine N-oxide 1 structurally designed in such a way as to allow easy dealkylation of the cycloadduct.

Among the recently proposed ways for generating nonstabilized azomethine ylides, ^{1a,c} only tertiary amine N-oxides base deprotonation allows the formation of entities reactive enough for undergoing intermolecular 3+2 cycloaddition with nonactivated olefins to yield N-alkylated pyrrolidines. ^{2a,b} A route to N-H pyrrolidines of interest in the field of natural products ³ could be derived and implies i) an amine N-oxide (CH₃)₂NR from which an highly reactive ylide could be selectively generated, ii) an efficient 3+2 cycloaddition reaction of this ylide with nonactivated olefins leading to N-R alkylated pyrrolidines from which R could easily be removed. Benzyldimethyl amine N-oxide deprotonation does not generate the proper ylide leading to N-CH₂Ph pyrrolidines, ^{2a} whereas the ylide generated from trimethylamine N-oxide efficiently gave N-CH₃ pyrrolidines; however, attempted dealkylation by methods known to be operative on tertiary amines or N-CH₃ piperidines were unsuccessful. ^{4a,b}

We report now a route to N-H pyrrolidines devoid of electron-withdrawing groups, starting from the amine N-oxide 1 structurally designed ⁵ in such a way as to allow the substituent R to be easily removed from the N-R pyrrolidines (Scheme).



Reagents : i) Me₃SiI/CCl₄ (M.E. Jung and M.A. Lyster, *J. Org. Chem.*, 1977, 42, 3761);
 ii-iii) PhCH₂Cl, NaHCO₃/MeOH followed by tBuOK/tBuOH in a one-pot sequence (A. Cope and
 E.R. Trumbull in *Organic Reactions*, 1960, 11, 385); iv) HCOONH₄, 10% Pd-C/MeOH (S. Ram
 and L.D. Spicer, *Tetrahedron Lett.*, 1987, 28, 515).

The 3+2 cycloaddition reaction leading to 3a-f took place with yields ranging from 35 to 63%, while the yields of the next steps i-iv were almost quantitative. As observed in previous investigations with other amine N-oxides^{2a,b}, the ylide derived from 1 underwent a competitive dimerization leading to various amounts of piperazine 4 when opposed to dipolarophiles less efficient than 2a,b,e. We are currently applying this sequence in the field of natural product synthesis.

Table. Cycloaddition Products 3, 5, 7 and N-H Pyrrolidines 8 Yields (%)

<u>2</u>	Dipolarophiles	Cycloadducts ⁷ ; Yields (%)			
		<u>3</u>	<u>5</u>	<u>7</u>	<u>8</u> ^a
a	R ₁ = Ph ; R ₂ = Ph ^b	63	100	96	60
b	H Ph	48	99	90	39
c	(CH ₂) ₃	52 ^c	97	85	42
d	(CH ₂) ₆	52 ^c	98	85	41
e	H Butyl	60 ^d	-	-	-
f	H CH ₂ OH	35 ^e	94	89	29

(a): Overall yield of pure N-H pyrrolidines calculated on 1. (b) trans stilbene. (c): Piperazine 4 was formed together with 3c, 3a, 3f and was isolated in 21%, 21%, 35% yield respectively. (d) Not deprotected.

References

1. a) E. Vedejs and F.G. West, *Chem. Rev.*, 1986, 86, 941; b) R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 180; c) M. Joucla and J. Mortier, *J. Chem. Soc., Chem. Commun.*, 1985, 1566.
2. a) R. Beugelmans, L. Benadjila-Iguertsira, J. Chastanet, G. Negron and G. Roussi, *Can. J. Chem.*, 1984, 63, 725; b) J. Chastanet and G. Roussi, *J. Org. Chem.*, 1985, 80, 2910.
3. G. Massiot and C. Delaude in "The Alkaloids", A. Brossi Ed., 1986, 27, 270.
4. We have tried methods reported by a) I. Moukovic, H. Wong and C. Bachand, *Synthesis*, 1985, 770. b) O. Achmatowicz Jr., Y. Tsuda and L. Marion, *Canad. J. Chem.*, 1965, 43, 2336 whereas our colleagues C. Mioskowski and coworkers (Strasbourg) have tried methods a). c) R.A. Olofson, J.T. Martz, J.P. Senet, M. Piteau and T. Malfroot, *J. Org. Chem.*, 1984, 49, 2081; d) M. Lounasmaa and A. Koskinen, *Heterocycles*, 1984, 22, 1591. e) L. Bernardi and G. Bosisio, *J. Chem. Soc., Chem. Comm.*, 1974, 690. f) D. Herlem, Y. Hubert-Briere and F. Khuong-Huu, *Tetrahedron Lett.*, 1973, 4173.
5. Protection of the hydroxyl group appeared necessary to avoid the intramolecular trapping of the initially formed imonium salt by oxygen.
6. C. Mioskowski, personal communication.
7. Reactions were run on a small scale (0.2 mMole) and the yields were not optimized. Purification of products (oils) 3, 7, 8 was achieved by preparative thin layer chromatography. No attempt was made for separating isomeric compounds 3 or 5. All products had spectral data (M.S., N.M.R. 200 MHz) in agreement with the proposed structure and are new except 8b and 8c.
8b m.p. 156-157 (picrate); lit.⁸ m.p. 155; 8c is reported in the lit.⁹ as the hydrochlorid salt, but we were unable to prepare this salt from the small sample of 8c.
8. G. Bettoni, C. Cellucci and V. Tortorella, *J. Heterocyclic Chem.*, 1976, 13, 1053.
9. R. Griot, *Helv. Chim. Acta*, 1959, 42, 67.

(Received in France 21 May 1988)