THE [3+2] INTRAMOLECULAR CYCLOADDITION REACTION OF AZOMETHINE YLIDES GENERATED FROM BENZYLIC N-OXIDES

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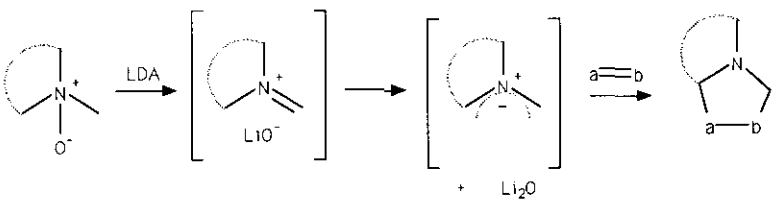
Abstract - Benzylic azomethine ylides (Y) generated by deprotonation of the corresponding tertiary amine N-oxides (1a, 1b, 4) react intramolecularly with the suitably positioned unactivated double bond to yield the corresponding fused membered pyrrolidines (2a, 2b, 5). A competitive evolution of the ylide is observed at low temperature leading to the corresponding head to head piperazines (3, 6, 8).

We have proposed a new access to various unstabilized azomethine ylides (Y) by base deprotonation of the corresponding tertiary amine N-oxides.[1a] The mechanism involves an initial iminium salt formation which is deprotonated in its turn (Scheme 1).



Y

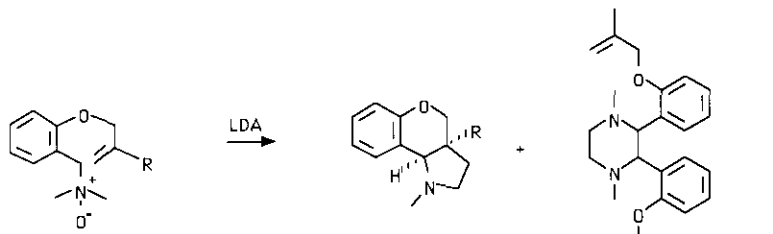
Scheme 1

These entities are highly reactive since they are able to cycloadd with various non-activated dipolarophiles to yield the corresponding five membered heterocycles.[1b] Some limitations have been observed with the gem disubstituted double

bonds which cannot be trapped by the formed ylides, and with the benzylic N-oxides which give piperazines instead of cycloadducts with dipolarophiles.[1b]

For a planned synthetic application of our method it was of importance to know if the energetic gain of intramolecular reaction could allow the cycloaddition between a benzylic ylide derived from N-oxide (1a) and conveniently situated double bond, resulting in the formation of the tricyclic compound (2a). Moreover, it appeared interesting to study the possibility of generating the tricyclic compound (2b) bearing a quaternary carbon center by trapping the gem disubstituted double bond by the N-oxide (1b) derived ylide. Finally, the chain length influence to the cycloaddition efficiency was studied in the case of the N-oxides (4 and 7). We report here the preliminary results obtained by treating the N-oxides (1a, 1b , 4 and 7) with LDA at various temperatures.

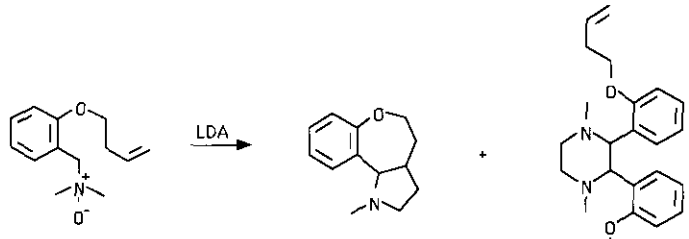
The N-oxide (1a), slowly added to LDA in THF at low temperature (-78°C), led quantitatively[2] and stereospecifically to the cis ring junction tricyclic compound (2a).[3]



1 a	R=H	-78° C	2 a	100%	3
b	R=Me	-78° C	b	13%	11%
		0° C		44%	30%

Under the same conditions, the N-oxide (1b) bearing a gem disubstituted double bond gave poor yields of the expected pyrrolidine (2b) (13%). A mixture of trans and cis piperazines (3t+3c) is formed competitively (11%) (3t/3c = 1.6). However, when the reaction was run at 0°C, 44% of the quaternary carbon cycloadduct was obtained as a single cis ring junction product, besides 30% of a mixture of piperazines (3t+3c). When the chain length between the dipole and the olefin was increased, the cyclisation rate slowed as illustrated with N-oxides (4 and 7). In the former case, only 8% of the seven membered tricyclic compounds (5) (5t/5c = 16) were formed at low temperature, while 26% of dimerization occurred leading to the trans and cis piperazines (6) (6t/6c = 1.2). When the reaction temperature was reached to 0°C, 48% of the isomeric pyrrolidines (5) (5t/5c = 7) formed.

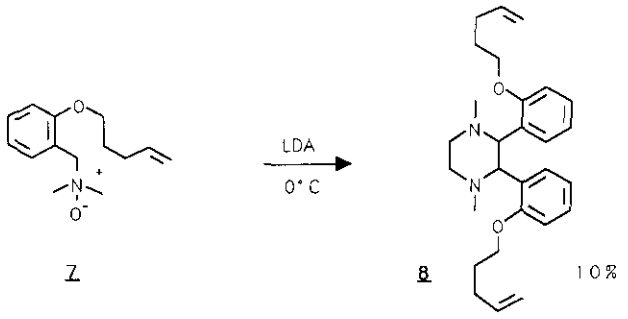
At 25°C, the formation of (5) decreased to 30% and the ratio (5t/5c) to 5. The stereochemistry of the major isomer (5t) was assigned to be trans on the basis of the nmr spectra. The benzylic methine proton exhibited a doublet with a coupling constant of 10 Hz a typical diaxal value for a trans fused adduct while the minor isomer cis coupling constant was 7 Hz.



4 5 6

	5	6
-78° C	6%	28%
0° C	48%	
25° C	30%	

In the case of the N-oxide (7), the reaction was run only at 0°C and afforded the unstable dimeric products (8) in poor yields.



7 8 10%

The results obtained in the course of this work are in agreement with the exceptional reactivity of the ylides generated by N-oxides deprotonation. The quantitative formation of (2a), the creation of a quaternary carbon center in (2b), and the cyclisation of (4) in good yield into the seven membered system (5) are the best illustration of this reactivity. When the temperature reaction is too low, or the chain length too long as in (7), dimerization into crowdy unstable piperazines (3, 6 and 8) is observed.

EXPERIMENTAL

Proton (^{1}H nmr) or carbon (^{13}C nmr) spectra were recorded in Brucker WP 200-S4 (200 MHz), chemical shifts from tetramethylsilane are given in δ. Low resolution mass spectra (ms) were obtained on a AEI MS 50 spectrometer. Purification were achieved on Silica gel by column chromatography (elution) and preparative thin layer chromatography (tlc, elution).

Materials. The N-oxides (1, 4, 7) were prepared by H_2O_2 oxidation of the corresponding tertiary amines.[4]

General procedure. The amine oxides (1 mmol) were dried, just before using by heating under vacuum at 40°C in a three-necked flask for 4 h. Anhydrous THF (50 ml) was added with a syringe through a rubber septum and the solution was siphonated in LDA (15 mmol) in THF (50 ml). The reaction was monitored by vapor phase chromatography (vpc) and thin layer chromatography (tlc, elution).

N,N-Dimethyl-2-(2-propenyloxy)benzylamine N-oxide (1a).
Obtained by H_2O_2 oxidation of the corresponding tertiary amine; ^{1}H nmr (60 MHz) δ 3.12 (s, 6H), 4.50-4.85 (m, 4H), 5.15-5.60 (m, 2H), 5.65-6.50 (m, 1H), 6.80-8.10 (m, 4H); ms m/z 191, 147, 91.

N,N-Dimethyl-2-(2-methyl-2-propenyloxy)benzylamine N-oxide (1b).
Obtained by H_2O_2 oxidation of the corresponding tertiary amine; ^{1}H nmr (60 MHz) δ 1.52 (s, 3H), 2.78 (s, 6H), 4.05 (s, 2H), 4.12 (s, 2H), 4.75-4.90 (br s, 2H), 6.25-7.30 (m, 4H).

1-Methyl-4H-2,3,3a,9b-tetrahydropyrrolo[2,3-d]benzo[b]pyran (2a).
The N-oxide (1a) (0.39 g, 1.85 mmol) was slowly added at -78°C to LDA (6.4 mmol) in THF (60 ml). At the end of the addition, tlc analysis (CH_2Cl_2-MeOH 90:10) revealed the complete disapearance of (1a), and vpc showed the exclusive formation of (2a) as a single isomer. Usual workup yielded crude product (2a). Preparative tlc on silica gel (CH_2Cl_2-MeOH 99:1) gave the pure product[3] (0.20 g, 57%). ^{1}H Nmr (200 MHz) δ 1.39-1.72 (m, 1H), 2.02-2.28 (m, 1H), 2.31 (q, J = 9 Hz, 1H), 2.38-2.45 (m, 1H), 2.43 (s, 3H), 2.93 (d, J = 6 Hz, 1H), 3.18 (dt,

J = 2, 9 Hz, 1H), 3.88 (t, J = 11 Hz, 1H), 4.03 (dd, J = 5, 11 Hz, 1H), 6.82-7.10 (m, 2H), 7.10-7.50 (m, 2H); ^{13}C Nmr 24.97, 35.15, 40.06, 54.93, 62.77, 67.84, 117, 129, 121, 123, 131, 155; *ms m/z* 189, 188, 145, 131.

1-Methyl-3a-methyl-2,3,3a,9b-tetrahydropyrrolo[2,3-d]benzo[b]pyran (2b) and N,N-dimethyl-2,3-di[2-(2-methyl-2-propenyloxy)phenyl]piperazine (3t+3c). The N-oxide (1b) (0.298 g, 1.35 mmol) was slowly added to LDA (5.2 mmol) in THF (50 ml) at -78°C. Usual workup yielded a crude mixture containing (2b) and (3t + 3c). Preparative tlc on silica gel (CH_2Cl_2-MeOH 99:1) afforded (2b) (0.035 g) and (3t + 3c) (3t/3c = 1.6, 0.031 g, 11%). 3c ^{1}H Nmr (200 MHz) δ 1.77 (s, 1H), 2.17 (s, 6H), 2.20-2.70 (m, 4H), 4.27 (d, J = 8 Hz, 4H), 4.67 (br s, 2H), 4.97 (d, J = 13 Hz, 2H), 6.60-7.60 (m, 8H); *ms m/z* 406, 391, 351, 320, 202, 162, 146.

The N-oxide (1b) (0.636 g, 2.8 mmol) was slowly added to LDA (9.1 mmol) in THF (100 ml) at 0°C. Usual workup yielded a crude mixture containing (2b and 3t+3c) in a ratio (3t/3c = 3). Column chromatography on silica gel (CH_2Cl_2) afforded 2b (0.247 g, 44%). ^{1}H Nmr (200 MHz) δ 1.07 (3H, s), 1.45-1.80 (m, 2H), 2.27-2.51 (m, 1H), 2.43 (s, 3H), 2.56 (s, 1H), 3.23 (dt, J = 4, 9 Hz, 1H), 3.72 (d, J = 10 Hz, 1H), 4.09 (d, J = 10 Hz, 1H), 6.90-7.60 (m, 4H); ^{13}C nmr δ 21.47, 33.46, 38.33, 40.14, 54.16, 69.63, 72.19, 117.01, 119.89, 128.96, 132.08, 154.43; *ms m/z* 203, 202, 188, 170, 145.

N,N-Dimethyl-2-(3-butenyloxy)benzylamine N-oxide (4).

Obtained by H_2O_2 oxidation of the corresponding tertiary amine. ^{1}H Nmr (60 MHz) δ 2.21-2.89 (m, 2H), 3.18 (s, 6H), 3.93-4.28 (m, 2H), 4.53 (s, 2H), 4.88-5.44 (2H), 5.46-6.22 (1H), 6.77-7.77 (m, 4H); ms m/z 205, 161, 150, 107, 55. Picrate mp (EtOH) 120°C. Anal. Calcd for $C_{19}H_{22}N_4O_9$: C, 50.67; H, 4.89; N, 12.44; O, 32.00. Found: C, 50.19; H, 5.09; N, 12.41; O, 32.14.

Cycloadducts (5t+5c) and piperazines (6t+6c).

The N-oxide (4) (0.209 g, 0.94 mmol) was slowly added to LDA (3.5 mmol) in THF (35 ml) at -78°C. Usual workup yielded a crude mixture containing (5t+5c) (5t/5c = 16) and piperazines (6t+6c) (6t/6c = 1.2) as determined by vpc analysis. Column chromatography on silica gel (CH_2Cl_2) afforded (6c) only (0.053 g, 28%): ^{1}H Nmr (200 MHz) δ 2.15 (s, 6H), 2.33-2.66 (m, 6H), 2.97-3.33 (m, 2H), 3.66-3.96 (m,

4H), 4.54 (br s, 2H), 4.98-5.21 (m, 4H), 5.76-6.09 (m, 2H), 6.66-6.76 (m, 4H), 6.80-7.13 (m, 2H), 7.52-7.72 (m, 2H); ms m/z 406, 390, 320, 245, 225.

The N-oxide (4) (0.110 g, 0.5 mmol) was slowly added to LDA (2 mmol) in THF (20 ml) at 0°C. Usual workup yielded a crude mixture containing (5t+5c) (5t/5c = 7) as determined by vpc analysis. Preparative tlc on silica gel (CH_2Cl_2-MeOH 95:5) afforded (5t+5c) (0.049 g, 48%). 5t: ^{1}H Nmr (200 MHz) δ 1.33-1.73 (m, 2H), 1.73-1.98 (m, 2H), 2.28-2.70 (m, 2H), 2.37 (s, 3H), 3.15 (dd, J = 6, 8 Hz, 1H), 3.56 (d, J = 10 Hz, 1H), 3.86-4.16 (m, 2H), 6.93-7.67 (m, 4H). ^{13}C Nmr δ 29.87, 37.48, 38.98, 42.19, 56.24, 69.0, 69.2, 121.71, 124.11, 128.29, 135.08, 153.99. The cis isomer (5c) was characterized by the benzylic proton which appeared as a doublet centered at 3.63 ppm with a 7 Hz coupling constant.

Piperazine (8). The N-oxide (7) (0.317 g, 1.35 mmol) was slowly added to LDA (5.4 mmol) in THF (50 ml) at 0°C. Usual workup yielded a crude mixture containing (8c+8t) among undefined compounds. Column chromatography on alumina (hexane-CH_2Cl_2 60:40) and preparative tlc on silica gel (CH_2Cl_2-MeOH 90:10) afforded (8t) (0.030 g, 10%). ^{1}H Nmr (400 MHz) δ 1.67-1.93 (m, 4H), 2.05 (s, 6H), 2.13-2.35 (m, 4H), 2.68 (d, J = 8 Hz, 2H), 3.08 (d, J = 8 Hz, 2H), 3.25-3.43 (m, 2H), 3.67-3.78 (m, 2H), 3.88 (s, 2H), 4.91-5.25 (m, 4H), 5.75-6.03 (m, 2H), 6.33-6.43 (d, J = 8 Hz, 2H), 6.74-6.86 (dd, J = 7, 8 Hz, 2H), 6.91-7.03 (dd, J = 7, 8 Hz, 2H), 7.55 (d, J = 7 Hz, 2H); Cl-ms m/z MH^+ 435.

REFERENCES

1 a) J. Chastanet and G. Roussi, J. Org. Chem., 1988, 53, 3808 and references cited herein. b) R. Beugelmans, L. Benadjiila-Iguertsira, J. Chastanet, G. Negron and G. Roussi, Can. J. Chem., 1985, 63, 725.

2 The formation of this compound is quantitative as shown by nmr analysis. The poor yield of the pure isolated product (58%) is due to tlc purification.

3 The same compound has been obtained, but with a lower selectivity, in the course of the intramolecular cycloaddition of imines of α-amino acid esters. P.N. Confalone and E.M. Huie, J. Amer. Chem. Soc., 1984, 106, 7175.

4 The tertiary amines had been obtained by etherification of salicylaldehyde with the corresponding alkenyl bromide and reductive alkylation of the carboxaldehyde group.

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