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A NEW ROUTE TO HEXAHYDROPYRROLIZINES DERIVATIVES <u>VIA</u> NONSTABILIZED YLIDE GENERATED FROM N-METHYLPYRROLIDINE N-OXIDE

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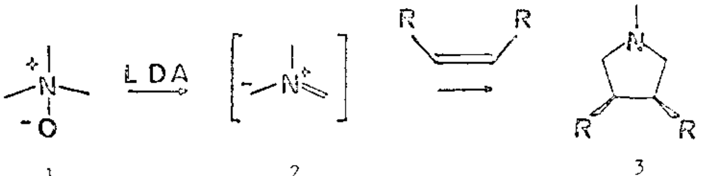
<u>Abstract</u> — N-Methylpyrrolidine N-oxide treated with lithium diisopropylamide in the presence of various olefins, leads to the corresponding hexahydropyrrolizines(6) <u>via</u> the ylide intermediate (5).

We have recently shown that the non stabilized ylide (2) can be generated by treating trimethylamine N-oxide (1) with lithium diisopropylamide (LDA). This intermediate is a highly reactive specie since it is trapped by simple alkenes to give good yields of the corresponding N-methylpyrrolidines (3).[1]



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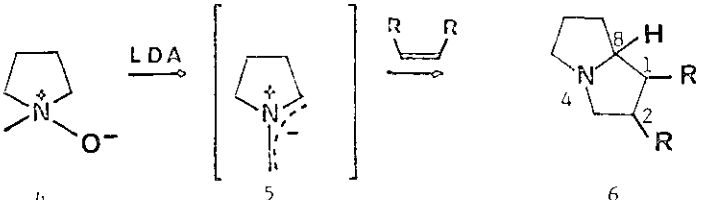
It appears to us worthwhile to exploit this new reaction in building pyrrolizidine skeleton (6), by condensing N-methylpyrrolidine N-oxide (4) with various olefins in the presence of LDA. This skeleton is encountered in a rather



4 5 6

large group of alkaloids with wide range of biological activities that makes them a particularly attractive synthetic target.[2]

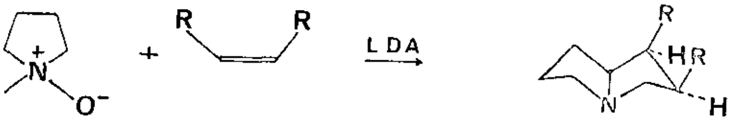
Results and Discussion

The N-oxide (4) (1 eq.) in THF is treated (0°C) with LDA (4 eq.) in the presence of various olefins. The reaction is followed by GLC. After 4 h a usual workup provides the pyrrolizidines 6. Most of these products are quite unstable and their purification has not been always possible in our hands. In the experiments leading to inseparable isomers the analyses were performed on the mixtures. The *cis* ring junction of compounds (8a), (10a) and (13b) has been determined on the basis of their ^{1}H NMR (400 MHz) spectra which display single proton multiplets in the 3.7-4.1 ppm region for H_8, and/or by the ^{13}C NMR spectra in which the C_8 signal appears at 69.3 ppm, consistent with chemical shift reported for *cis* ring junction in this system.[3]

In addition, no Bohlmann band could be assigned in the infrared spectra.[4] The shielding of H_8 proton and the deshielding of the C_8 carbon atom in (8b) may be justified by conformational variation and increased strain in the *cis* ring junction due to the presence of the cyclopentane ring.

The nuclear magnetic resonance data reveal the stereochemistry of the substitution patterns, downfield signals indicative of hydrogens on a same side of the ring system as the nitrogen lone pair.[3]

The reaction between 4 and symmetrical *cis* olefins (7a,b) provides respectively 43 and 79% of the single *cis* (2Z,8Z) 1,2-disubstituted hexahydropyrrolizines 8a,b



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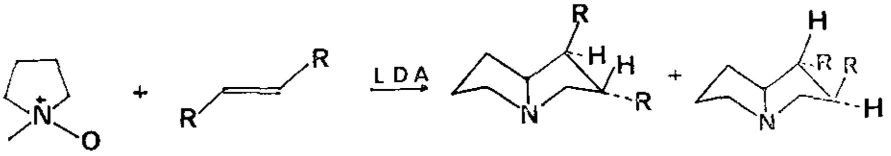
7 a) R = Ph
b) R,R = $(CH_2)_3$

8 a) 43%
b) 79%

whilst with *trans* stilbene (9a) and 1,1,4,4-tetramethoxy 2-butene (9b) a mixture of (2E,8Z)-10 and (2E,8E)-(11) are formed (in 1/0.16 and 1/0.1 ratios) in 32 and 67% yields respectively.



4

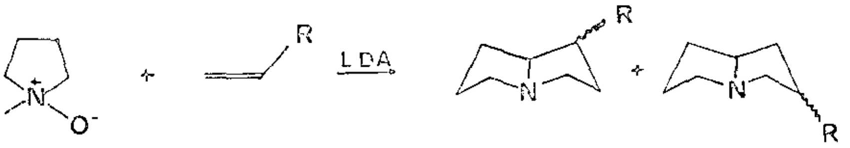
9 a) R = Ph
b) R = $CH(OMe)_2$

10 a) 28%

10 b) + 11 b) 67%

11 a) 4%

Monosubstituted olefins, styrene (12a) and 2-propen-1-ol (12b) provide the four possible isomers of (13a) and (13b) (in 1/0.8/0.3/0.06 and 1/0.5/0.2/0.1 ratios) in 70 and 26% yields respectively.



4

12 a) R = Ph
b) R = CH_2OH

13 a) 71%
b) 26%

The yields of the pyrrolizidines obtained in the course of the reaction between non-activated olefins 7, 9 and 12 and N-methylpyrrolidine N-oxide 4, are smaller than those obtained with N-methylpiperidine N-oxide.[6] This difference seems to be due in part to its slight solubility in solvents compatible with LDA.

The reaction is of 1,3-dipolar cycloaddition type[7] as shows the retention of the cis stilbene configuration and non polymerization with styrene. It generates stereospecifically β-disubstituted hexahydropyrrolizine 8a,b via endo transition state. Theoretical interpretations have been recently proposed to explain the 1,3-dipolar cycloaddition regioselectivity.[8] The lack of data concerning the orbital coefficients of the ylide (5) carbons atoms exclude here any quantitative interpretation of our results. However, it is noteworthy that selectivity is markedly less important than with other ylides like nitrones[9] or diazoalkanes[8a] since a mixture of 1- and 2-substituted isomers is formed with monosubstituted olefins 12a,b. This fact may be due to the ambivalence of the terminii of the 1,3-dipole leading to close value for orbital atomic coefficients of 5.

In conclusion, we have shown that it is possible to generate the nonstabilized cyclic ylide 5, by treating N-methylpyrrolidine N-oxide with LDA. Trapped with various simple olefins, it easily provides the corresponding hexahydropyrrolizines.

EXPERIMENTAL

Melting points are uncorrected. Analytical gas liquid chromatography analyses (GLC) were executed on a Girdel 75 chromatograph. Mass spectra (MS) were obtained with MS 50 spectrograph and with a Hewlett Packard 5992 A equipped with vapor phase chromatograph. High resolution mass spectrometry (HRMS) was conducted with a Kratos MS 80 RF instrument. ^1H NMR spectra were obtained using a Brüker WM 400 (400 MHz) and Perkin-Elmer R12 (60 MHz). Carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Brüker HX 90E. Chemical shifts are reported in δ units downfield from internal Me_4Si and the J values are given in Hertz.

General procedure

In a typical experiment, a suspension in anhydrous THF (50 ml) of the highly hygroscopic N-oxide (4) (1 eq.) dried under vacuum in the reaction flask, and the olefin (1.1 eq.) are cooled to 0°C. The LDA (3.5 eq.) is then added. The reaction progress is followed by GLC. After 3-4 h, hydrolysis, extraction with CH_2Cl_2 and usual workup lead to expected products.

Reaction between (4) and cis stilbene (7a). Preparation of cis (2Z,8Z) 1,2-diphenylhexahydropyrrolizine (8a): N-Oxide (4) (305 mg, 3 mmoles) in THF (100 ml) and cis stilbene (7a) (600 μl, 3.3 mmoles) are treated with LDA (10.5 mmoles) for 3 h. Usual workup gives pyrrolizidine 8a (337 mg, 1.28 mmoles, 43%)

after chromatography on silica gel (CH_2Cl_2-MeOH 98/2 - 80/20). MS: m/e 263, 83; ^{1}H NMR (400 MHz) δ: 1.60 (m, 1H, $H_{7\beta}$), 2.0 (m, 3H, $H_{6\alpha}$, $H_{6\beta}$, H_7), 2.80 (m, 1H, $H_{5\beta}$), 3.10 (m, 1H, $H_{3\beta}$), 3.20 (m, 1H, $J_{1\alpha,8\alpha}$ = 7 Hz, $J_{1\alpha,2\alpha}$ = 7 Hz, $H_{1\alpha}$), 3.40 (m, 1H, $H_{5\alpha}$), 3.70 (m, 2H, $H_{3\alpha}$, $H_{2\alpha}$), 4.0 (dd, 1H, $H_{8\alpha}$), 6.85 (m, 2H, aromatic protons), 6.95 (m, 2H, aromatic protons), 7.10 (m, 6H, aromatic protons); ^{13}C NMR δ: 26.19 (C_7), 31.57 (C_6), 50.47 (C_2), 56.02 (C_1), 56.76, (C_5), 59.11 (C_3), 69.27 (C_8), 126.46, 127.84, 128.61, 128.66 (aromatic CH), 138.25, 138.41 (aromatic C).

Picrate, mp 133°C (EtOH). Anal.calcd for $C_{25}H_{24}N_4O_7$: C, 60.98; H, 4.88; N, 11.38; O, 22.76. *Found:* C, 60.71; H, 4.91; N, 11.20; O, 22.99.

Reaction between (4) and cyclopentene (7b): Preparation of (2Z,8Z)[1,2-a] cyclopentanohexahydropyrrolizine (8b): A suspension of N-oxide (4) (370 mg, 3.66 mmoles) in THF (100 ml) and cyclopentene (270 mg, 4.02 mmoles) are treated with LDA (12.8 mmoles) for 4 h. Usual workup gives pyrrolizidine 8b (440 mg, 2.92 mmoles, 79%) after chromatography on alumina. MS: m/e 151, 123, 122, 83; ^{1}H NMR (400 MHz) δ: 2.30 (m, 1H, $H_{5\beta}$), 2.65 (m, 1H, $H_{3\beta}$),2.7 (m, 1H, $H_{1\beta}$), 2.85 (m, 1H, $H_{2\beta}$), 2.95 (m, 1H),3.05 (dd, 1H, $H_{8\alpha}$); ^{13}C NMR δ: 24.93, 26.00, 31.29, 32.33, 32.69 (cyclopentane CH_2, C_6, and C_7), 44.02 (C_2), 50.48 (C_1), 53.58 - 60. 60,49 (C_3 - C_5), 73.07 (C_8).

Picrate, mp 183°C (EtOH). Anal.Calcd for $C_{16}H_{20}N_4O_7$: C, 50.53; H, 5.26; N, 14.74; O, 29.47. Found: C, 50.28; H, 5.41; N, 14.50; O, 29.68.

Reaction between (4) and trans stilbene (9a): Preparation of (2E,8Z) 1,2-diphenylhexahydropyrrolizine (10a): A suspension of N-oxide (4) (225 mg, 2.23 mmoles) in THF (100 ml) and trans stilbene (9a) (441 mg, 2.4 mmoles) are treated with LDA (7.80 mmoles) for 3 h. Usual workup provides a crude mixture (662 mg). GLC analysis indicates the presence of three products in a 1/1.1/0.16 ratio. Chromatography on silica gel (CH_2Cl_2-MeOH 90/10) affords a pure isomeric unknown compound (107 mg, 1.04 mmole, 17%), an intermediate fraction (40 mg) containing a mixture of (10a) and (11a) (CH_2Cl_2-MeOH 20%), and pure isomer 10a (154 mg, 0.58 mmole, 26%). MS m/e 263, 83; ^{1}H NMR (400 MHz): δ 1.9 (m, 1H), 2.65 (m, 1H, $H_{5\beta}$), 3.20 (m, 2H, $H_{3\beta}$, $H_{5\alpha}$), 3.40 (m, 1H, $H_{3\alpha}$),3.6 (m, 1H, $H_{2\beta}$), 3.95 (dd, 1H, $J_{1\alpha,2\beta}$ = 11 Hz, $H_{1\alpha}$), 4.05 (m, 1H, $J_{1\alpha,8\alpha}$ = 8 Hz, $H_{8\alpha}$); 7.1 - 7.3 (m, 10H, aromatic protons).

Picrate, mp 222°C (EtOH). Anal.calcd for $C_{25}H_{24}N_4O_7$: C, 60.98; H, 4.88; N, 11.38; O, 22.76. Found: C, 60.91; H, 4.90; N, 11.20; O, 22.99.

Reaction between (4) and 1,1,4,4-tetramethoxy-2-butene (9b). Preparation of 1,2-di(1',1'-dimethoxymethyl)hexahydropyrrolizine (10b) and (11b): A suspension of N-oxide 4 (320 mg, 3.16 mmoles) in THF (100 ml) and olefin (9b) (611 mg, 3.47 mmoles) are treated with LDA (11 mmoles) for 4 h. GLC analyses indicate the presence of 2 products in a 1/0.1 ratio. Elimination, under vacuum of the starting olefin, and flash chromatography on basical alumina affords the mixture of unstable pyrrolizidines 10b-11b (550 mg, 2.1 mmoles, 67%). HRMS calcd for $C_{13}H_{25}NO_4$: 259.1783, found 259.1775. MS m/e 259, 258, 228, 214, 198, 184, 83; 1H NMR (60 MHz) δ : 3.4 (m, 13H), 4.35 (d, 2H).

Reaction between (4) and styrene (12a). Preparation of phenylpyrrolizidines (13a): A suspension of N-oxide (4) (470 mg, 4.65 mmoles) in THF (100 ml) and styrene (12a) (580 mg, 5.5 mmoles) are treated with LDA (16.27 mmoles) for 3 h. Usual workup provides a crude mixture (800 mg). Flash chromatography on alumina affords pyrrolizidines 13a (620 mg, 3.31 mmoles, 71%). GLC analysis indicates the presence of 4 peaks in 1/0.8/0.3/0.06 ratios. The mass spectra of each isomer obtained with a spectrometer equipped with GLC apparatus are identical MS m/e 187, 83.

Reaction between (4) and 2-propen-1-ol (12b). Preparation of (1'-hydroxymethyl)hexahydropyrrolizine (13b): A suspension of N-oxide (4) (370 mg, 3.66 mmoles) in THF (100 ml) and 2-propen-1-ol (12b) (273 μl, 4.02 mmoles) are treated with LDA (16.47 mmoles) for 3 h. Usual workup provides a crude product (350 mg). GLC analysis shows the presence of 4 peaks in 1/0.5/0.2/0.1 ratios. Chromatography on neutral alumina (CH_2Cl_2-MeOH 90/10) provides pyrrolizidines 13b (135 mg, 0.96 mmole, 26%). Ms m/e 141, 110, 83; HRMS, calcd for $C_8H_{15}NO$: 141.1153, found 141.1144; ^1H NMR (200 MHz) δ: 1.5-2.1 (m, 6H), 2.2-3.2 (m, 6H), 3.3-3.8 (m, 3H), 3.8-4.2 (m, 1H).

REFERENCES AND NOTES

1. R. Beugelmans, G. Negron and G. Roussi, *J.Chem.Soc., Chem.Commun.*, 1983, 31.
2. T. Shono, Y. Matsumura, K. Uchida, K. Tsubata and A. Makino, *J.Org.Chem.*, 1984, **49**, 300 and ref. cited herein.
3. a) T.H. Jones, M.S. Blum, H.M. Fales, and C.R. Thompson, *J.Org.Chem.*, 1980, **45**, 4778.
   b) B. Lüning and H. Tränkner, *Acta Chem.Scand.*, 1968, **22**, 2324.
4. F. Bohlmann, *Chem.Ber.*, 1958, **91**, 2157.
5. This nomenclature system is used to describe the configurational isomers of 3-butyl-5-methylindolizidine from the Pharaoh ant, *Monomorium pharaonis*. P.E. Sonnett, D.A. Netzel and R. Mendoza, *J.Het.Chem.*, 1979, **16**, 1041.
6. R. Beugelmans, J. Chastanet, G. Negron and G. Roussi, submitted for publication.
7. R. Huisgen, *J.Org.Chem.*, 1976, **41**, 403.
8. a) J. Bastide, N. El Ghandour and O. Henri-Rousseau, *Tetrahedron Lett.*, 1972, **41**, 4225.
   b) K.N. Houk, *Acc.Chem.Res.*, 1975, **8**, 361.
9. A. Padwa, L. Fisera, K.F. Koehler, A. Rodriguez and G.S.K. Wong, *J.Org.Chem.*, 1984, **49**, 276 and ref. cited herein.

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