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THE [3 + 2] CYCLOADDITION REACTION OF NONSTABILIZED AZOMETHINE YLIDE GENERATED FROM TRIMETHYLAMINE N-OXIDE TO C≡C, C=N and C=S BONDS

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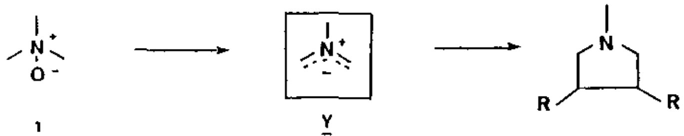
Abstract - The reported cycloaddition reactions between nonstabilized azomethine ylide Y generated from trimethylamine N-oxide 1 and unactivated C≡C 2 - 4, C=N 5 and C=S 6, 7 bonds constitute an attractive entry respectively to pyrrolines and pyrroles 10 - 13, imidazolidine 14 and thiazolidines 15, 16.

Since many years there is a permanent interest for [3 + 2] dipolar cycloaddition reactions involving azomethine ylides generated from various precursors bearing electron-withdrawing group(s).[1] Those stabilized ylides require activated dipolarophiles to react with conjugated double or triple bonds,[1] imines,[2] isothiocyanates.[1,3]

More recently, it appeared that unstabilized azomethine ylides generated either by α-silylonium salts desilylation[4] or amino-acids immonium salts decarboxylation[5] were surprisingly not more reactive as their stabilised counterparts. They undergo efficient intermolecular cycloaddition reactions to activated dipolarophiles only. Contrastingly, the corresponding nonstabilised ylides generated in our laboratory by strong base deprotonation of tertiary amine oxides appear to undergo intermolecular [3 + 2] cycloaddition, to unactivated olefins.[6]

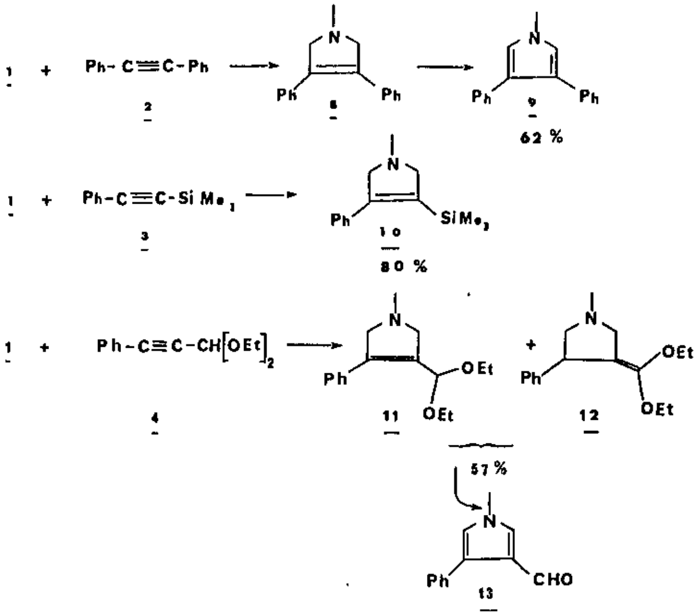


1　　Y

In this paper we report preliminary results concerning the extension of this reaction to acetylenic compounds devoid electron-withdrawing groups 2 - ,4, to the C=N bond of the benzalaniline 5 and C=S bond of the thiones 6 - 7 for which few reports are available on cycloaddition reaction.[7]

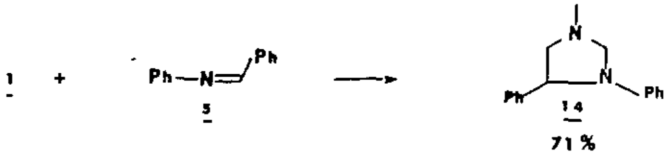
Trimethylamine N-oxide 1 treated at 0°C with lithium diisopropyl amide (LDA) in THF generates the ylide Y which undergoes cycloaddition with diphenylacetylene 2 to yield 3,4-diphenyl-1-methyl-pyrrole 9 62%) *via* the non-isolated pyrroline 8. In order to prevent the generation of a high energy LUMO anion unable to be trapped by azomethine ylide,[8] phenylacetylene was silylated prior reactions. The resulting protected alkyne 3 afforded the pyrroline 10 (80%), bearing a potential functionalization. 1,1-Diethoxy-3-phenyl-2-propyne 4 yielded a mixture of 11 and 12 (57%), 11/12 = 0.7) resulting from addition of the ylide respectively to the triple bond and to the monosubstituted isomeric allenic double bond.

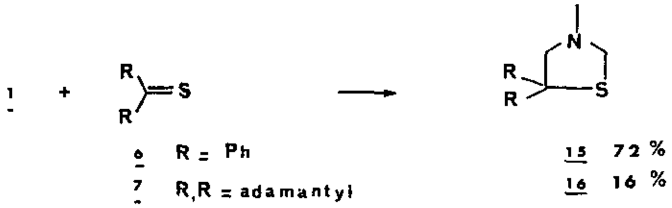
1-Methyl-3-formyl-4-phenylpyrrole 13 is obtained by refluxing the mixture in MeOH with Pd/C.



The reaction between trimethylamine N-oxide and benzalaniline 5 yields 3,4-diphenyl-1-methylimidazolidine 14 (71%).

The first example of addition of Y *generated from* tertiary amine oxide on terminal disubstituted double bond is observed with thioketones 6 and 7 in accord with the dipolarophilicity of the C=S derivatives. Benzothiophenone 6 and adamantanethione 7 yield respectively 15 (72%) and 16 (16%).*





Scope and limitations of the cycloaddition reactions between ylides generated from tertiary amine oxides and C≡C, C=N and C=S dipolarophiles which allow the synthesis of few documented five-membered ring heterocycles devoid of electro-withdrawing substituents in 2 and 5 positions are currently investigated in the laboratory.

EXPERIMENTAL

Melting points are uncorrected and were measured on a Reichert melting point apparatus. Low resolution mass spectra (ms) were obtained on an AEI M50 spectrometer, chemical ionisation mass spectra(cims) was obtained by using a AEI MS9 apparatus and exact masses (hrms) were determined by high resolution mass spectroscopy on a Kratos M50. ^{1}H

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* We have observed a rapid degradation of the crude reaction product during purification. *The lability of five-membered rings with two heteroatoms is documented.*[9]

nmr spectra (in $CDCl_3$) were recorded on Perkin-Elmer R12, Brüker WP-200-54 (200 MHz) and Brüker WM-400 (400 MHz) spectrometers. Chemical shift from tetramethylsilane are given in δ. Purifications were achieved by preparative thin layer chromatography (tlc, elution).

Materials

Trimethylamine oxide 1 and diphenylacetylene 2 are commercially available. 1-Phenyl-2-trimethylsilylacetylene[10] 3, benzalaniline[11] 5, thiobenzophenone 6 and thioadamantane 7, were prepared by standard literature procedures.[12]

General procedure

The amine oxide 1 (1 eq.) was dried just before use by heating under vacuum at 30°C in a three-neck flask for 1 h. The dipolarophile (1 eq.) and anhydrous THF (50 mL) were then added with a syringe through a rubber septum and the suspension cooled at 0°C under stirring before introducing LDA (3.5 eq.). The reaction was monitored by vapor phase chromatography and thin layer chromatography (tlc, elution).

3,4-Diphenyl-1-methylpyrrole 9

A suspension of N-oxide 1 (0.165 g, 2.2 mmol) in anhydrous THF (50 ml) and diphenylacetylene 2 (0.360 g, 2 mmol) were treated with LDA for 3 h. Crude mixture (0.477 g) was obtained after extraction. Preparative tlc purification (hexane-CH_2Cl_2, 50/50) yielded unreacted 2 (0.135 g, 0.76 mmol, 38%) and 9 (0.290 g, 1.2. mmol, 62%) as a white solid, mp (EtOH) 125°C (lit.[9] mp 125-128°C).

1-Methyl-4-phenyl-3-trimethylsilyl-3,5-dihydropyrrole 10

N-oxide 1 (0.150 g, 2 mmol) and alkyne 3 (0.348 g, 2 mmol) were treated with LDA for 3 h. Crude product (0.42 g) contained quite pure 10 as shown by ^1H nmr. Preparative tlc purification (CH_2Cl_2-MeOH, 93/7) yielded 10 (0.26 g, 1.12 mmol, 55%): ms, m/e 231, 216, 214, 160, 159, 115, 73; hrms Calcd for $C_{14}H_{21}NSi$: 231.1443. Found: 231.1430; ^1H nmr (60 MHz) δ 0 (s, 9H), 2.6 (s, 3H, N-CH_3), 3.3 (m, 4H), 7.3 (m, 10H).

1-Methyl-3-(1',1'-diethoxymethine)-4-phenyl-2,5-dihydropyrrole 11 and 1-Methyl-3-(1',1'-diethoxymethylene)-4-phenylpyrrolidine 12

N-oxide 1 (0.112 g, 1.5 mmol) and alkyne 4 (0.30 g, 1.5 mmol) were treated with LDA for 1 h. Crude mixture (0.35 g) was obtained after extraction. Preparative tlc purification

(CH_2Cl_2-MeOH , 97/3) yielded a mixture of 11 and 12 (0.22 g, 0.85 mmol, 57%; 11/12 = 0.7). Ms, m/z 261, 260, 233, 232, 218, 176, 158, 121, 57; ^{1}H nmr (60 MHz) δ 0.6 and 1.1 (2t, 6H), 2.45 and 2.55 (2s), 2.6-4 (m), 5.1 (s), 7.1-7.6 (m).

1-Methyl-3-formyl-4-phenylpyrrole 13

The mixture 11 + 12 (0.10 g, 0.38 mmol) is treated with Pd/C in refluxing MeOH. Preparative tlc yielded unreacted starting product and 13 (0.024 g, 0.13 mmol, 33%): Ms, m/z 185, 184, 158, 115; cims, m/z 232 (M^+ + 57), 186; ^{1}H nmr (60 MHz) δ 3.9 (s, 3H), 7.0 (1H), 7.5 (m, 6H), 10.2 (1H).

3,4-Diphenyl-1-methylimidazolidine 14

Compound 1 (0.225 g, 3 mmol) and benzalaniline 5 (0.597 g, 3.3 mmol) gave a crude product (0.870 g) which after preparative tlc (CH_2Cl_2-MeOH, 98/2) afforded pure 14 (0.531 g, 71%). ^{1}H Nmr (400 MHz) δ 2.44 (s, 3H, CH_3), 2.94 (dd, J_{gem} 10 Hz, 1H), 3.93 (s, J_{gem} 5 Hz, 1H), 4.51 (d, 1H), 4.69 (dd, 1H), 6.3-7.5 (m, 10 H); ms, m/z 239, 238, 195, 194, 181, 180, 57. Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.76. Found: C, 80.50; H, 7.57; N, 11.50.

5,5-Diphenyl-3-methylthiazolidine 15

Compound 1 (0.045 g, 0.6 mmol) and benzothiophenone (0.110 g, 0.55 mmol) gave a crude reaction product (0.160 g) which, after preparative tlc (CH_2Cl_2), gave 15 (0.086 g, 0.34 mmol, 72%), crystallized from methylene chloride/hexane: mp 84-85°C. ^{1}H nmr (60 MHz) δ 2.4 (s, 3H), 3.55 (s, 2H), 4.08 (s, 2H), 7-7.7 (m, 10H); ms, m/z 255, 212, 211, 179, 178, 165, 57. Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.29; H, 6.66; N, 5.49; S, 12.54. Found: C, 75.10; H, 6.72; N, 5.46; S, 12.27.

3'-Methyladamantane-2-spiro-5'-(1',3'-thiazolidine) 16

Compound 1 (0.090 g, 1.2. mmol) and adamantanethione 7 (0.20 g, 1.2 mmol) gave crude reaction product (0.220 g) which after preparative tlc (CH_2Cl_2-MeOH, 95/5) gave 16 (0.044 g, 0.197 mmole, 16%), crystallized from methylene chloride/hexane: mp 75°C. ^{1}H nmr (60 MHz) δ 1.5-2.1 (m, 14H), 2.48 (s, 3H), 2.86 (s, 2H), 3.75 (s, 2H). Ms, m/z 223, 180, 57. Anal. Calcd. for $C_{13}H_{21}NS$: C, 69.95; H, 9.41. Found: C, 69.70; H, 9.21.

REFERENCES

1. J.W. Lown in "1,3-Dipolar Cycloaddition Chemistry" (General Heterocyclic Chemistry Series), A. Padwa Ed., Wiley Interscience Publication, New York, 1984, Vol. I, P. 653.
2. R. Huisgen, V. Martin-Ramos, and W. Scheer, *Tetrahedron Lett.*, 1971, 477; J.W. Lown and B.E. Landberg, *Can. J. Chem.*, 1970, **48**, 3399; J.W. Lown and K. Matsumoto, *ibid.*, 1974, **52**, 798; J.W. Lown and B.E. Landberg, *ibid.*, 1975, **53**, 3782; F. Texier and R. Carrié, *Bull. Soc. Chim. Fr.*, 1973, **12**, 3437.
3. J.W. Lown, G. Dallas, and T.W. Maloney, *Can. J. Chem.*, 1969, **47**, 3557.
4. E. Vedejs and F.G. West, *Chem. Rev.*, 1986, **86**, 945 and references therein.
5. R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 180; R. Grigg, M.F Aly, V. Shridharanand, and S. Thianpatanagul, *ibid.*, 1984, 182; P.N. Confalone and E.M. Huie, *J. Am. Chem. Soc.*, 1984, **106**, 7175; M. Joucla and J. Mortier, *J. Chem. Soc., Chem. Commun.*, 1985, 1566.
6. R. Beugelmans, G. Negron, and G. Roussi, *J. Chem. Soc., Chem. Commun.*, 1983, 31; R. Beugelmans, L. Benadjilla-Iguertsira, J. Chastanet, G. Negron, and G. Roussi, *Can. J. Chem.*, 1985, **63**, 725; J. Chastanet and G. Roussi, *J. Org. Chem.*, 1985, **50**, 2910; J. Chastanet and G. Roussi, *Heterocycles*, 1985, **23**, 653.
7. T. Katada, S. Eguchi, and T. Sasaki, *J. Chem. Soc., Perkin Trans I*, 1984, 2641.
8. R. Huisgen in "1,3-Dipolar Cycloaddition Chemsitry" (General Heterocyclic Chemistry Series), A. Padwa Ed., Wiley Interscience Publication, New York, 1984, Vol. I, p. 1.
9. S. Witek, A. Bielawska, and J. Bielawski, *Heterocycles*, 1980, **14**, 1313; J.B. Lambert and M.W. Majchrzak, *J. Am. Chem. Soc.*, 1980, **102**, 3588.
10. R.B. Miller and S. McGarvey, *J. Org. Chem.*, 1978, **43**, 4424.
11. L.A. Bigelow and H. Eatough, "Organic Synthesis", New York, 1956, Collect. Vol. 1, pp. 80-81.
12. B.S. Pedersen, S. Scheibye, N.H. Nilsson, and S.O. Lawesson, *Bull. Soc. Chim. Belge*, 1978, **8**, 223.

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