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trans-3-Aryl-4-Nitro-Pyrrolidines via 1,3-Dipolar Cycloaddition of Nonstabilized Azomethine Ylide to ß-Nitro Styrenes

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Abstract: Various β-nitro styrenes undergo 1,3 dipolar cycloaddition with the azomethine ylide derived from sarcosine and paraformaldehyde to give 3-aryl-4-nitro-pyrrolidines in good yield.

INTRODUCTION

The 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with olefins represents one of the most convergent approaches for the construction of the pyrrolidine ring.[1] Their ease of generation coupled with the highly regio-, and stereoselective nature of their cycloaddition reactions has resulted in a number of syntheses which utilize such a reaction as the key step.[2]

Considerable efforts have been devoted to developing simple and efficient routes for generating these dipoles, for instance fluoride ion mediated desilylation method of *Vedejs,*[3] and *Padwa,*[4] or *Pandey*'s photoinduced electron transfer (PET)[5], by electrochemical oxidation,[6] and double desilylation strategy[7] or more recently with the thermally induced desilylation of benzotriazolylmethylaminosilanes by Katritzky.[8] As predicted by the principles of Frontier Molecular Orbital (FMO) theory[9] these nonstabilized ylides readily react with electron-deficient alkenes providing access to a wide array of 3-, and 3,4-disubstituted pyrrolidines. However, its synthetic potential is restricted to the use of a class of electron deficient alkenes, with the exception of *Roussi*'s method[10] started from tertiary amine N-oxides.

To the best of our knowledge to date there has been no report on cycloadditions of non-stabilized azomethine ylides generated by any method with aryl-nitro-olefins.[11] As a part of our ongoing program[12] concerning the synthesis of novel analogues of Cephalotaxus alkaloids we required a short and efficient procedure for the preparation of pyrrolidines bearing an aromatic substituent at C-3 and a nitro-group at C-4 position. Pursuant to our synthetic objective, we chose to investigate the effect of different substituents on the aromatic ring of the olefins upon the cycloaddition.

RESULTS AND DISCUSSION

Of the known generation procedures of these azomethine ylides we have used *Tsuge*'s protocol[13] for the decarboxylative condensation of sarcosine with paraformaldehyde, as previously described. Accordingly a solution of dipolarophile in toluene and an excess of sarcosine and paraformaldehyde were heated under reflux (the water formed was removed by the aid of Dean-Stark trap) resulted in formation of the corresponding cycloadducts (Fig.1) after 6-24 h in good yields.

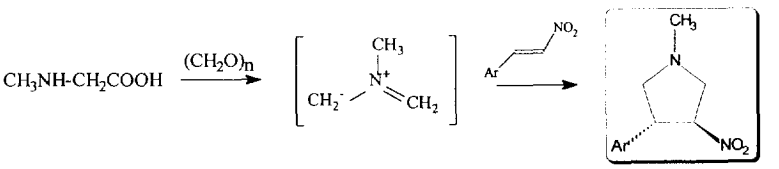


Fig.1

The olefins utilized in this study are summarized in the Table. The results are in good agreement with our theoretical AM1 calculations performed on the cycloaddition, which show that the reaction is $HOMO_{dipole}$ - $LUMO_{dipolarophile}$ controlled, since this process leads to smaller E_{HOMO}-E_{LUMO} difference similarly to other previous calculations.[9b,c] The energy differences (ΔE) between the corresponding frontier orbitals of dipole (E_{HOMO}= -7.91 eV) and the various substituted olefins are 5.5-6.5 eV. Comparing these ΔE values it is concluded that the nitro styrenes with more electron donating substituents should be less reactive than without, or with electron withdrawing substituents in accordance with experiments. The other factor which should modify the reactivity of dipolarophiles is the different solubility of appropriate nitro styrenes in toluene. The structure of cycloadduct (entry **1**) was confirmed by ^{1}H-NMR double resonance and ^{13}C-NMR HSC measurements, while the other (entry **2-9**) spectra were assigned by analogy.

In summary, the present strategy is a convergent synthesis of 3-aryl-4-nitro-pyrrolidines in a very convenient one pot procedure and broadens the scope of the 1,3-dipolar cycloaddition of nonstabilized azomethine ylide.

Experimental part

Methods. Column chromatography was performed using *Merck Kieselgel 60* 70-230 mesh, TLC on aluminium sheets coated with *Kieselgel 60* F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml cc. sulphuric acid and 1 ml anisaldehyde) and heated at ca. 150°C. IR spectra were measured on a SPECORD75 IR instrument. NMR spectra were recorded in $CDCl_3$ as a solvent on a Bruker WM-250 spectrometer operating at 250 MHz (^{1}H-NMR) and 63 MHz (^{13}C-NMR). Chemical shifts are given on the δ scale, in all cases TMS served as the internal standard.

General procedures for the 1,3-dipolar cycloaddition reaction. A mixture of sarcosine (2.5 equiv) paraformaldehyde (6 equiv.), and the corresponding nitro styrene (1 equiv) was heated under reflux in toluene (10 ml for 1 mmol of dipolarophile). The water formed was removed by the aid of Dean- Stark trap. After

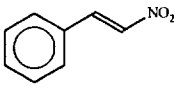
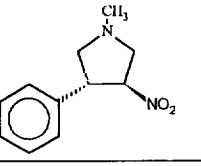
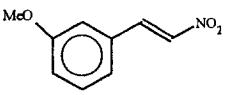
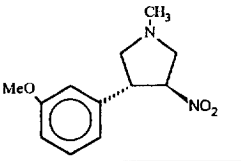
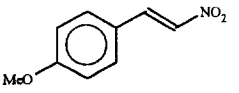
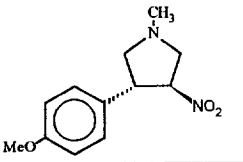
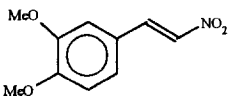
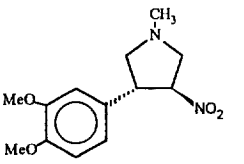
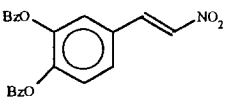
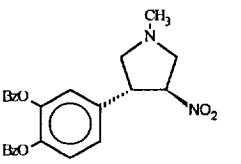
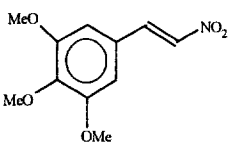
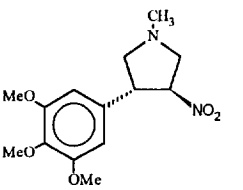
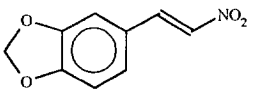
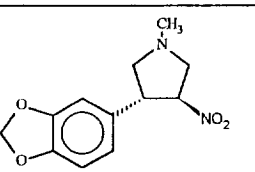
Entry	dipolarophile	dipolarophile E_{HOMO} E_{LUMO}	reaction time, yield	product
1		-9.737 eV -1.509 eV	1 h 78 %;	
2		- 9.278 eV - 1.507 eV	3 h 68 %	
3		-9.308 eV - 1.418 eV	4 h 66 %	
4		- 9.081 eV - 1.442 eV	6 h 58 %	
5		- 8.995 eV -1.458 eV.	5 h 54 %	
6		- 8.916 eV - 1.403 eV	12 h 46 %	
7		- 9.301 eV - 1.630 eV	3 h 62 %	

Table 1. (continued overleaf)

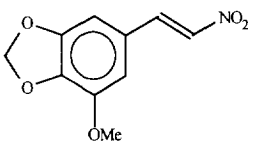
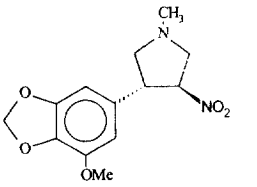
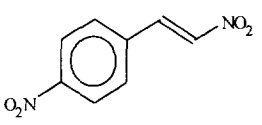
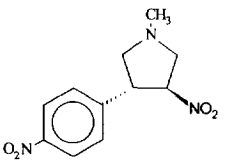
Entry	dipolarophile	dipolarophile E_{HOMO} E_{LUMO}	reaction time, yield	product
8		- 9.278 eV - 1.638 eV	3 h 58 %	
9		-10.520 eV - 2.397 eV	1h 83 %	

Table 1.

completion of the reaction the solvent was evaporated in vacuo. The residue was chromatographed over silica gel by using hexane-ethyl acetate (1:1 to 1:2 vol/vol) to give **1-9**. The reaction times and yields (based on the dipolarophiles) are summarized in the Table 1.

N-Methyl-3-phenyl-4-nitro-pyrrolidine (1). yellow oil; ^{1}H-NMR δ: 7.3 - 7.1 (m, 5H, Ar), 4.90 (o, 1H, H-4), 3.99 (sx , 1H, H-3), 3.39 (dd, 1H, H-5), 3.25 (t, 1H, H-2), 2.94 (dd, 1H, H-5), 2.53 (dd, 1H, H-2), 2.38 (s, 3H, N-Me); ^{13}C-NMR δ: 139.9 (Ar-1'C), 128.5 (Ar-3'C, Ar-4'C, Ar-5'C), 127.0 (Ar-2'C, Ar-6'C), 91.1 (C-4), 62.7 (C-2), 60.1 (C-5), 49.6 (C-3), 41.0 (N-Me); IR (film, cm^{-1}): 2943, 2844, 2791, 1602, 1549, 1496, 1475, 1454, 1377, 1344, 1250, 1155, 1127, 1086, 1030. Anal. calcd. for $C_{11}H_{14}N_2O_2$: C 64.06, H 6.84, N 13.58; found C 64.12, H 6.81, N 13.52.

N-Methyl- 3-(3-methoxyphenyl)-4-nitro-pyrrolidine (2). yellow oil; ^{1}H-NMR δ: 7.23 (t, 1H, Ar-5'H), 6.7 - 6.9 (m, 3H, Ar), 4.92 (o, 1H, H-4), 3.94 (sx, 1H, H-3), 3.78 (s, 3H, OMe) 3.40 (dd, 1H, H-5), 3.26 (t, 1H, H-2), 2.95 (dd, 1H, H-5), 2.55 (dd, 1H, H-2), 2.39 (s, 3H, N-Me), ^{13}C-NMR δ: 159.6 (Ar-3'C), 141.5 (Ar-1'C), 129.5 (Ar-5'C), 119.1 (Ar-6'C), 113.1 (Ar-4'C), 112.1 (Ar-2'C), 91.0 (C-4), 62.5 (C-2), 60.1 (C-5), 54.7 (O-Me), 49.6 (C-3), 40.9 (N-Me); IR (film, cm^{-1}): 2942, 2838, 2790, 1602, 1585, 1549, 1490, 1455, 1376, 1356, 1339, 1291, 1263, 1152, 1127, 1049. Anal. calcd for $C_{12}H_{16}N_2O_2$: C 61.00, H 6.83, N 11.86; found C 59.94, H 6.81, N 11.91.

N-Methyl- 3-(4-methoxyphenyl)-4-nitro-pyrrolidine (3). yellow oil; ^{1}H-NMR δ: 7.19 (d, 2H, Ar-2'H and Ar-6'H), 6.86 (d, 2H, Ar-3'H and Ar-5'H), 4.87 (o, 1H, H-4), 3.94 (sx, 1H, H-3), 3.77 (s, 3H, O-Me), 3.41 (dd, 1H, H-5), 3.25 (t, 1H, H-2), 2.94 (dd, 1H, H-5), 2.51 (dd, 1H, H-2), 2.40 (s, 3H, N-Me); ^{13}C-NMR δ: 158.5 (Ar-4'C), 131.8 (Ar-1'C), 128.1 (Ar-2'C and Ar-6'C), 113.9 (Ar-3'C and Ar-5'C), 91.4 (C-4), 62.8 (C-2), 60.0 (C-5), 54.8 (O-Me), 49.2 (C-3), 41.1 (N-Me); IR (film, cm^{-1}): 2940, 2839, 2794, 1617, 1584, 1543, 1515, 1471, 1375, 1350, 1304, 1257, 1181, 1150, 1111, 1031. Anal. calcd. for $C_{12}H_{16}N_2O_3$: C 61.00, H 6.83, N 11.86; found C 61.11, H 6.80, N 11.83.

N-Methyl- 3-(3,4-dimethoxyphenyl)-4-nitro-pyrrolidine (4). yellow oil; ^{1}H-NMR δ: 6.6 - 6.9 (m, 3H, Ar-2'H, Ar-5'H and Ar-6'H), 4.88 (o, 1H, H-4), 3.93 (sx, 1H, H-3), 3.85, 3.82 (2 s, 6H, O-Me), 3.38 (dd, 1H, H-5), 3.25 (t, 1H, H-2), 2.96 (dd, 1H, H-5), 2.58 (m, 1H, H-2), 2.41 (s, 3H, N-Me); ^{13}C-NMR δ: 149.1, 148.8 (Ar-3'C, Ar-4'C), 129.1 (Ar-1'C), 119.3 (Ar-6'C), 112.7 (Ar-2'C), 110.8 (Ar-5'C), 88.1 (C-4), 64.3 (C-2), 61.0 (C-5), 56.0, 55.8 (2 O-Me), 47.8 (C-3), 42.2 (N-Me); IR (film, cm^{-1}): 2941, 2834, 2781, 1606, 1590, 1538,

1518, 1454, 1422, 1343, 1294, 1257, 1145, 1027. Anal. calcd. for $C_{13}H_{18}N_2O_4$: C 58.63, H 6.81, N 10.52; found C 58.57, H 6.83, N 10.56.

N-Methyl- 3-(3,4-dibenzyloxyphenyl)-4-nitro-pyrrolidine (5). yellow oil; ^{1}H-NMR δ: 7.2 - 7.5 (m, 10H, Ar(Bz)), 6.7 - 6.9 (m, 3H, Ar), 5.15, 5.14 (2s, 4H, CH_2(Bz)), 4.80 (o, 1H, H-4), 3.89 (sx, 1H, H-3), 3.35 (dd, 1H, H-5), 3.20 (t, 1H, H-2), 2.92 (dd, 1H, H-5), 2.49 (dd, 1H, H-2), 2.39 (s, 3H, N-Me), ^{13}C-NMR δ: 149.1, 148.5 (Ar-3'C, Ar-4'C), 137.1, 137.0 (2 Bz(1)), 133.5 (Ar-1'C), 128 - 127 (5 s, 2 Bz(2,3,4,5,6)), 120.2 (Ar-6'C), 115.3 (Ar-2'C), 114.9 (Ar-5'C), 91.5 (C-4), 71.5, 71.3 (2 CH_2(Bz)), 62.6 (C-2), 60.2 (C-5), 49.3 (C-3), 41.3 (N-Me); IR (film, cm^{-1}): 2991, 2912, 2830, 1551, 1525, 1487, 1430, 1392, 1278, 1150, 1029. Anal. calcd. for $C_{25}H_{26}N_2O_4$: C 71.75, H 6.26, N 6.69; found C 71.82, H 6.23, N 6.67.

N-Methyl- 3-(3,4,5-trimethoxyphenyl)-4-nitro-pyrrolidine (6). yellow oil; ^{1}H-NMR δ: 6.51 (s, 2H, Ar(2'H and Ar-6'H), 4.94 (o, 1H, H-4), 3.96 (sx, 1H, H-3), 3.86, 3.83 (2s, 6H, O-Me), 3.38 (dd, 1H, H-5), 3.26 (t, 1H, H-2), 3.04 (dd, 1H, H-5), 2.62 (sx, 1H, H-2), 2.44 (s, 3H, N-Me), ^{13}C-NMR δ: 153.3 (Ar-3'C and Ar-5'C) ,137.2 (Ar-4'C), 135.9 (Ar-1'C), 104.3 (Ar-2'C and Ar-6'C), 91.4 (C-4), 62.7 (C-2), 60.6 (C-5), 60.4, 56.0 (3 O-Me), 50.1 (C-3), 41.3 (N-Me); IR (film, cm^{-1}): 2960, 2855, 2800, 1592, 1558, 1508 1464, 1429, 1378, 1249, 1326, 1247, 1132, 1001. Anal. calcd. for $C_{14}H_{20}N_2O_5$: C 56.75, H 6.80, N 9.45; found C 56.70, H 6.81, N 9.42.

N-Methyl-3-(1,3-benzodioxo-5-yl)-4-nitro-pyrrolidine (7). yellow oil; ^{1}H-NMR δ 6.80 (s,1H, Ar-6'H), 6.73 (s, 2H, Ar-2'H and 5'H), 5.93 (s, 2H, OCH_2O), 4.87 (o, 1H, H-4), 3.9 (dd, 1H, H-3), 3.37 (dd, 1H, H-4), 3.22 (t, 1H, H-2), 2.99 (dd, 1H, H-4), 2.54 (q, 1H, H-2), 2.40 (s, 3H, N-Me); ^{13}C-NMR δ: 147.9, 146.7 (Ar-3'C, Ar-4'C), 134.0 (Ar-1'C), 120.6 (Ar-6'C), 107.5 (Ar-2'C), 106.3 (Ar-5'C), 101.0 (O-CH_2-O), 91.6 (C-4), 63.0 (C-2), 60.3 (C-5) , 49.7 (C-3), 41.3 (N-Me); IR (film, cm^{-1}): 2930, 2890, 2830, 2775, 2040, 1600, 1550, 1480, 1430, 1360, 1340, 1320, 1220, 1150, 1100, 1090, 1020, 920, 870, 840, 800, 610. Anal. calcd. for $C_{12}H_{14}N_2O$: C 57.59, H 5.64, N 11.19; found C 57.50, H 5.66, N 11.21.

N-Methyl-3-(7-methoxy-1,3-benzodioxo-5-yl)-4-nitro-pyrrolidine (8). yellow oil; ^{1}H-NMR δ: 6.50 (d, 1H, Ar-2'H), 6.45 (d, 1H, Ar-6'H), 5.95 (s, 2H, O-CH_2-O), 4.88 (o, 1H, H-4), 3.90 (sx, 1H, H-3), 3.90 (s, 3H, O-Me), 3.37 (dd, 1H, H-5), 3.23 (t, 1H, H-2), 3.01 (dd, 1H, H-5), 2.57 (sx, 1H, H-2), 2.42 (s, 3H, N-Me); ^{13}C-NMR δ: 149.2, 143.5 (Ar-3'C, Ar-5'C), 137.5 (Ar-4'C), 134.8 (Ar-1'C), 107.4 (Ar-2'C), 101.4 (Ar-6'C), 101.1 (O-CH_2-O), 91.6 (C-4), 62.9 (C-2), 60.4 (C-5), 56.7 (O-Me), 50.0 (C-3), 41.4 (N-Me) IR (film, cm^{-1}): 2942, 2845, 2787, 1634, 1546, 1513, 1451, 1433, 1372, 1351, 1289, 1244, 1198, 1137, 1094, 1045. Anal. calcd. for $C_{13}H_{16}N_2O_5$: C 55.71, H 5.75, N 9.99; found C 55.64, H 5.77, N 10.01.

N-Methyl-3-(4-nitrophenyl)-4-nitro-pyrrolidine (9). yellow oil ; ^{1}H-NMR δ: 8,20 (d', 2H, Ar-3'H and Ar-5'H), 7.51 (d, 2H, Ar-2'H and Ar-6'H), 4.90 (o, 1H, H-4), 4.08 (sx, 1H, H-3), 3.36 (dd, 1H, H-5), 3.25 (t, 1H, H-2), 3.12 (dd, 1H, H-5), 2.65 (dd, 1H, H-2), 2.45 (s, 3H, N-Me); ^{13}C-NMR δ: 147.7 (Ar-4'C),129.9 (Ar-1'C), 128.3 (Ar-2'C and Ar-6'C), 123.9 (Ar-3'C and Ar-5'C), 90.5 (C-4), 62.4 (C-2), 60.0 (C-5),49.2 (C-3), 41.1 (N-Me); IR (film, cm^{-1}): 2946, 2849, 2795, 1603, 1549, 1518, 1475, 1452, 1377, 1349, 1285, 1254, 1154, 1110, 1077, 1015. Anal. calcd. for $C_{11}H_{13}N_3O_4$: C 52.59, H 5.22, N 16.72; found C 52.51, H 5.24, N 16.72.

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