Double 1,3-Dipolar Cycloaddition of *N*-Methyl Azomethine Ylide to Meta-Dinitrobenzene Annelated with Nitrogen Aromatic Heterocycles

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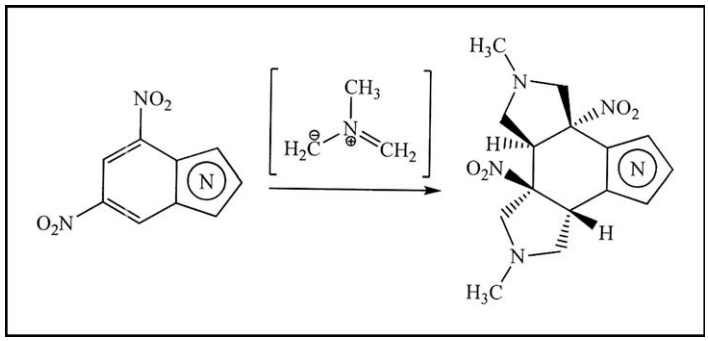

The 1,3-dipolar cycloaddition of unstabilized azomethine ylide **1** with meta-dinitrobenzene fused with nitrogen heterocycles affords the corresponding decahydropyrrolo[3,4-*e*]isoindole cycloadducts in good yields. This is a first example of [3+2]-cycloaddition of azomethine ylides to nitroarenes.

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INTRODUCTION

The 1,3-dipolar cycloaddition (1,3-DC) reactions play one of the most important roles in modern organic synthesis, being simple and available method for the preparation of different five-membered heterocycles. It is important that 1,3-DC usually proceeds regio- and stereoselectively [1]. A number of dipoles, including azomethine ylides, readily undergo cycloaddition reactions with conjugated nitroalkenes [2]. As a result, pyrrolidine derivatives are formed (Scheme 1); this heterocycle is a part of many natural compounds and pharmaceuticals [3].

RESULTS AND DISCUSSION

We have found that nitro arenes, e.g. 1,3-dinitrobenzene and 1,3,5-trinitrobenzene, do not form the cycloaddition products with azomethine ylides. We believe that 1,3-DC with nitro arenes requires the reduction of their aromaticity in order to carbon–carbon double bond of C— C—NO_2 fragment would approach to that of conjugated nitro alkenes. It is known that isoelectronic process – [4+2]-cycloaddition to unsaturated compounds (Diels-Alder reaction) takes place in case of meta-dinitroarenes, fused with some aromatic nitrogen heterocycles [4]. In this connection, we studied an interaction of *N*-methyl azomethine ylide **1** with meta-dinitrobenzene annelated with number of aromatic nitrogen heterocycles. Azomethine ylide **1** was generated *in situ* from sarcosine and paraformaldehyde refluxing in toluene [2(a)] in the presence of dinitro compounds **2a-e** [5] as dipolarophiles (Scheme 2).

In all cases, the double cycloaddition afforded the previously unknown tetracyclic heterosystems – fused decahydropyrrolo[3,4-*e*]isoindoles **3a-e**.

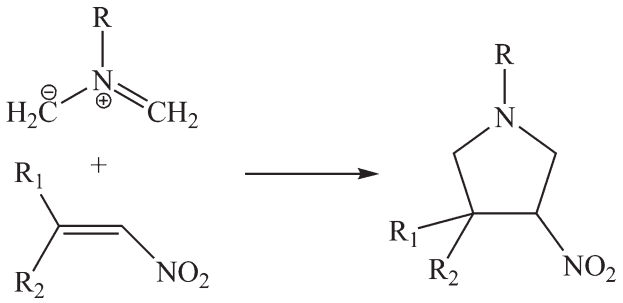
It should be noted that azomethine ylide **1** formed cycloaddition products more readily than dienes: dinitro compounds **2a** and **2d** did not undergo Diels-Alder reactions with dienes though they form cycloaddition adducts with azomethine ylide **1**.

Diels-Alder reactions can be carried out in case of aromatic nitro carbocycles only if they are fused with some strong electron-withdrawing five-membered nitrogen heterocycles – furoxan, furazan, and some of their analogs [4]. This increases the electrophilicity dramatically (by many orders of magnitude), e.g. the ability to add nucleophiles to the benzene ring that indicates the considerable reduction of aromaticity in comparison with 1,3,5-trinitrobenzene [6].

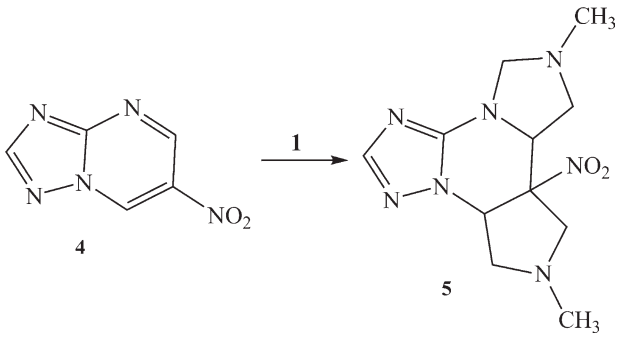
In case of azomethine ylide **1**, the cycloaddition takes place also if less electron-deficient *N*-heterocycle is fused with dinitro arene.

The formation of cycloaddition products **3a-e** seems to be diastereoselective. In case of compound **3a**, the crystal and molecular structure (Fig. 1) confirmed the expected cis-addition of the azomethine ylide [7].

Scheme 1



Scheme 3



X-ray analysis data shows that the cycloaddition occurred from the opposite sides of the dinitro arene plane.

Interestingly that double cycloaddition of azomethine ylide **1** was possible even in the presence of one nitro group as was illustrated by the reaction with nitrotriazolo[1,5-a]pyrimidine [8] (**4**) (Scheme 3):

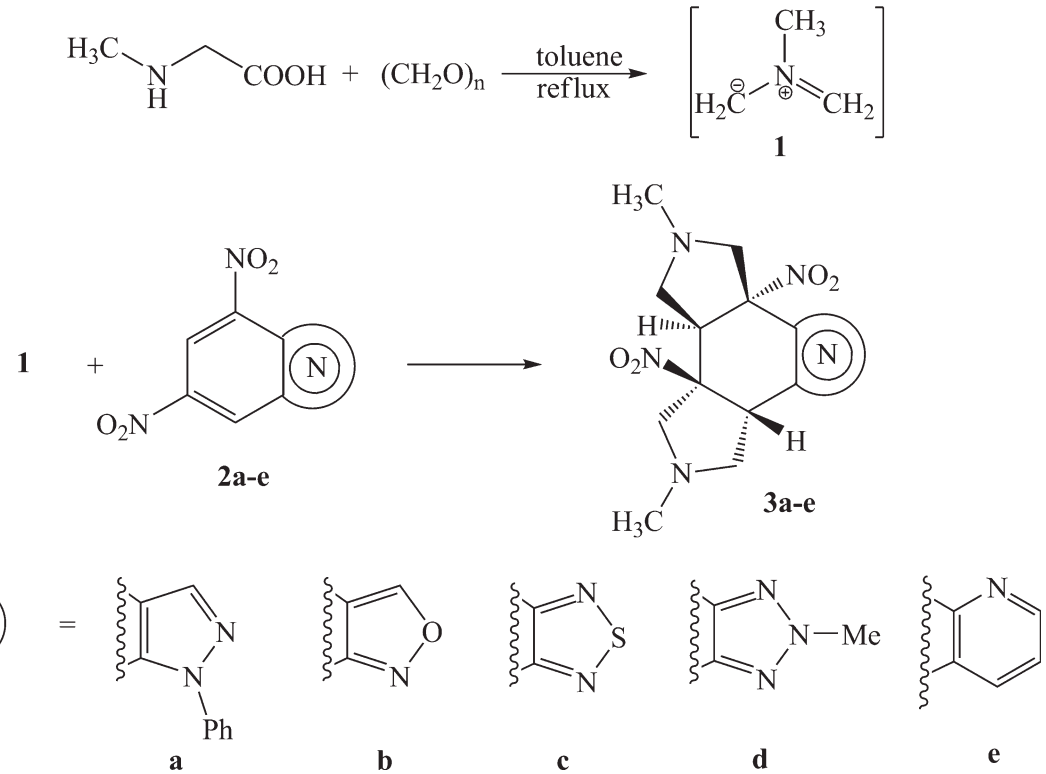
In summary, the 1,3-dipolar cycloaddition of meta-dinitrobenzene fused with nitrogen heterocycles with unstabilized *N*-methylazomethine ylide generated *in situ* from sarcosine and paraformaldehyde in refluxing toluene affords decahydropyrrolo[3,4-*e*]isoindole cycloadducts in good yields.

EXPERIMENTAL

Melting points were uncorrected and were determined on a Reichert Kofler thermopan apparatus. NMR spectra were measured in $CDCl_3$ using the Bruker DRX 500 spectrometer operating at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C). Tetramethylsilane was used as internal standard for ^{1}H (δ 0.05). The ^{13}C NMR spectra were standardized by means of the middle signal of the solvent multiplet (δ 76.9).

General procedure for the reaction of compounds 2a–e and 4 with sarcosine and paraformaldehyde. A mixture of compound **2** or **4** (1 mmol), paraformaldehyde (0.18 g, 6 mmol), and *N*-methylglycine (0.44 g, 5 mmol) in dry toluene (15 mL) was refluxed for 2 h until all the starting material disappeared by TLC. Then the reaction mixture was cooled,

Scheme 2



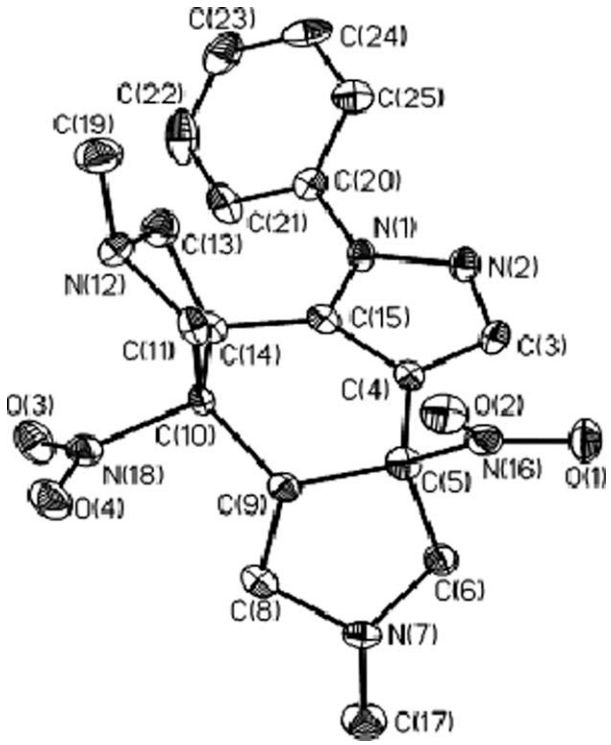


Figure 1. General view of **3a**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn with probability 50%.

filtered and the solvent was removed by rotary evaporation. The products were purified by dissolving in minimal volume of THF, following by adding of excess of hexane to this solution with further filtering of the precipitate formed.

5,8-Dimethyl-3b,6b-dinitro-1-phenyl-3b,4,5,6,6a,6b,7,8,9,9a-decahydro-1H-dipyrrolo[3,4-e:3′,4′-g]indazole (3a). This compound was obtained as yellow needles, yield 69%; mp 175–176°C; ^{1}H NMR δ 1.89 (dd, 1H, J = 5.1, 4.5 Hz), 2.10 (s, 3H), 2.32 (s, 3H), 2.55–2.60 (m, 2H), 2.88 (t, 1H, J = 8.8 Hz), 3.09 (t, 1H, J = 8.9 Hz), 3.19 (d, 1H, J = 10.0 Hz), 3.61 (d, 1H, J = 11.0 Hz), 3.77 (d, 1H, J = 10.0 Hz), 4.34 (t, 1H, J = 8.8 Hz), 4.77–4.90 (m, 1H), 7.45–7.48 (m, 1H), 7.55 (m, 4H), 7.91 (s, 1H); ^{13}C NMR δ 36.1, 40.6, 41.5, 45.0, 57.2, 59.5, 63.8, 69.7, 89.6, 98.8, 122.9, 124.2, 128.6, 129.7, 139.0, 139.2, 139.6; Anal. Calcd. for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09. Found: C, 56.98; H, 5.68; N, 20.92.

5,8-Dimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydroisoxazolo[3,4-e]pyrrolo[3,4-g]isoindole (3b). This compound was obtained as dark brown solid, yield 50%; mp 193–195°C; 1H NMR δ 2.27 (s, 6H), 2.53 (t, 1H, J = 9.1 Hz), 2.71 (d, 1H, J = 11.3 Hz), 2.87–2.91 (m, 2H), 3.08 (d, 1H, J = 9.9 Hz), 3.52 (d, 1H, J = 11.3 Hz), 3.59 (t, 1H, J = 8.1 Hz), 3.67 (d, 1H, J = 9.9 Hz), 4.36–4.45 (m, 2H), 8.77 (s, 1H); ^{13}C NMR δ 35.6, 41.0, 41.1, 44.3, 56.9, 60.0, 63.4, 70.3, 88.2, 97.6, 112.3, 158.7, 160.5. Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.38; H, 5.18; N, 21.51.

5,8-Dimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydropyrrolo[3,4-e][1,2,5]thiadiazolo[3,4-g]isoindole (3c). This compound was obtained as brown solid, yield 40%; mp 123–124°C; ^{1}H NMR δ 2.26 (s, 3H), 2.27 (s, 3H), 2.51 (t, 1H, J = 8.6 Hz), 2.87–2.90 (m, 2H), 2.94 (t, 1H, J = 9.3 Hz), 3.40 (d, 1H, J = 10.1 Hz), 3.48 (d, 1H, J = 11.2 Hz), 3.60 (dd, 1H, J = 9.5, 7.4 Hz), 3.87 (d, 1H, J = 10.1 Hz), 4.27 (t, 1H, J = 8.6 Hz), 4.62–4.64 (m, 1H); ^{1}3C NMR δ 40.9, 41.3, 41.5, 47.6, 57.3, 60.6, 64.2, 67.3, 90.1, 97.2, 151.3, 160.4; Anal. Calcd. for $C_{12}H_{16}N_6O_4S$: C, 42.35; H, 4.74; N, 24.69. Found: C, 42.35; H, 4.87; N, 24.75.

2,5,8-Trimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydro-2H-pyrrolo[3,4-e][1,2,3]triazolo[4,5-g]isoindole (3d). This compound was obtained as brown solid, yield 67%; mp 118–120°C; ^{1}H NMR δ 2.25 (s, 3H), 2.27 (s, 3H), 2.46 (t, 1H, J = 9.4 Hz), 2.65 (dd, 1H, J = 9.3 Hz, 3.7 Hz), 2.75 (d, 1H, J = 11.3 Hz), 2.86 (t, 1H, J = 9.0 Hz), 3.25 (d, 1H, J = 10.1), 3.50 (d, 1H, J = 11.2), 3.58 (t, 1H, J = 7.7), 3.79 (d, 1H, J = 10.1 Hz), 4.20–4.23 (m, 1H), 4.25 (s, 3H), 4.46 (dd, 1H, J = 7.6 Hz, 3.4 Hz); ^{13}C NMR δ 36.1, 41.0, 41.4, 42.6, 47.3, 57.2, 60.3, 63.6, 67.4, 88.3, 97.9, 137.1, 146.1; Anal. Calcd. for $C_{13}H_{19}N_7O_4$: C, 46.29; H, 5.68; N, 29.07. Found: C, 46.56; H, 6.00; N, 28.81.

6,9-Dimethyl-7a,10a-dinitro-4b,5,6,7,7a,7b,8,9,10,10a-decahydrodipyrrolo[3,4-f:3′,4′-h]quinoline (3e). This compound was obtained as yellow-brown solid, yield 24%; mp 159–160°C; ^{1}H NMR δ 2.29 (s, 6H), 2.39 (t, 1H, J = 9.4 Hz), 2.59 (dd, 1H, J = 5.5 Hz, 3.5 Hz), 2.97 (m, 2H), 3.24 (d, 1H, J = 11.0 Hz), 3.62, (m, 2H), 4.00 (t, 1H, J = 8.8 Hz), 4.13 (d, 1H, J = 11.0 Hz), 4.55 (t, 1H, J = 6.0 Hz), 7.37 (dd, 1H, J = 7.9 Hz, 4.2 Hz), 7.58 (d, 1H, J = 7.9 Hz), 8.61 (d, 1H, J = 4.2 Hz). ^{13}C NMR δ 41.1, 41.7, 41.8, 47.6, 58.3, 63.0, 64.6, 67.2, 95.0, 95.5, 124.9, 132.6, 137.0, 147.9, 149.5; Anal. Calcd. for $C_{15}H_{19}N_5O_4$: C, 54.05; H, 5.75; N, 21.01. Found: C, 53.83; H, 5.81; N, 20.37.

7b-Nitro-7,7a,7b,8,10,10a-hexahydro-5H-imidazo[1,5-c]pyrrolo[3,4-e][1,2,4]triazolo[1,5-a]pyrimidine-6,9-diamine (5). This compound was obtained as white needles, yield 42%; mp 147–148°C; ^{1}H NMR δ 2.36 (s, 3H), 2.37 (s, 3H), 2.79 (dd, 1H, J = 10.2 Hz, 5.9 Hz),z), 3.07–3.10 (m, 1H), 3.15–3.22 (m, 2H), 3.43 (d, 1H, J = 10.6 Hz), 3.96 (d, 1H, 10.6 Hz), 4.13 (d, 1H, J = 5.1 Hz), 4.18–4.21 (m, 2H), 4.90 (dd, 1H, J = 7.7, 5.8 Hz), 7.61 (s, 1H). ^{13}C NMR δ 40.1, 41.0, 56.0, 60.2, 60.3, 60.8, 71.1, 88.4, 151.0, 152.1; Anal. Calcd. for $C_{11}H_{17}N_7O_2$: C, 47.30; H, 6.14; N, 35.10. Found: C, 47.36; H, 6.02; N, 35.23.

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[6] Cottyn, B.; Starosotnikov, A.; Vichard, D.; Goumont, R.; Shevelev, S.; Terrier, F. Org Biomol Chem 2009, 7, 1137 (and references cited therein).

[7] Crystallographic data for the structure of **3a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 737503. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **3a**: Intensity data were collected on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and a MoKa fine-focus sealed tube ($\lambda = 0.71073$ Å) at 100(2) K, using the ϕ- and ω-scan scan technique to a maximum θ angle of 26°. $C_{19}H_{22}N_6O_4$, M = 398.43, orthorhombic, a = 15.691(4) Å, b = 8.5090(19) Å, c = 27.905(6) Å, V = 3725.8(15) Å^3, space group Pbcn, Z = 8, d_{calcd} = 1.421 g/cm^3, 22222 reflections measured, 3669 reflections [$I > 2\sigma(I)$] were used in all calculations, R = 0.0566, Rw = 0.1005. Structure solution and refinement were performed by Bruker SHELXTL.

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