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4,6-Dinitrobenzo[*c*]isothiazole: synthesis and 1,3-dipolar cycloaddition to azomethine ylide

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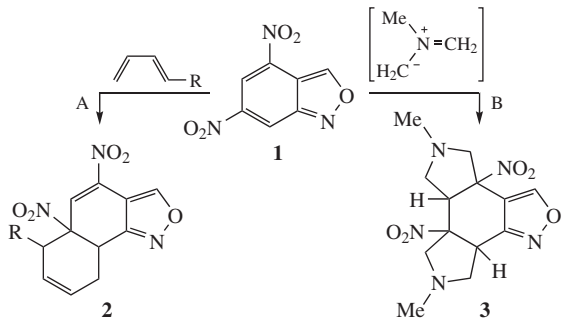
1,3-Dipolar cycloaddition of 4,6-dinitrobenzo[*c*]isothiazole to (*N*-methyl-*N*-methylideneammonio)methanide (2 equiv.) gives 5,8-dimethyl-3b,6b-dinitrodecahydroisothiazolo[3,4-*e*]pyrrolo[3,4-*g*]isoindole, whose structure was confirmed by X-ray diffraction analysis.

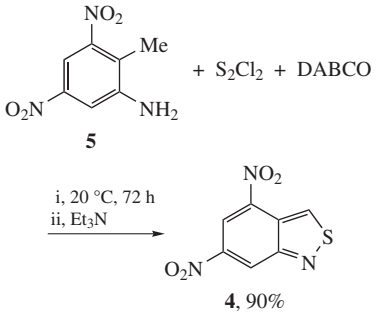
Recently, we have reported that 4,6-dinitrobenzo[*c*]isoxazole (4,6-dinitroanthranil **1**)[1] easily undergoes pericyclic [4 + 2]- and [3 + 2]-cycloaddition at NO_2-activated C=C bond, which is rather unusual for nitroarenes annelated with aromatic heterocycles. Thus, dinitroanthranil **1** forms cycloadducts **2** with dienes (Scheme 1, pathway A)[2] and undergoes double 1,3-dipolar cycloaddition as dipolarophile with azomethine ylide to afford decahydropyrrolo[3,4-*g*]isoindole **3** (Scheme 1, pathway B).[3]



Scheme 1

In continuation of our research, it was interesting to study the behaviour of S-analogue of compound **1**, namely, 4,6-dinitrobenzo[*c*]isothiazole **4** in pericyclic cycloaddition reaction.

Although isothiazole **4** was described,[4] its synthesis is a multi-step procedure and its structure was not unambigously confirmed. In the present study, we developed an easy procedure for the preparation of compound **4** from available[5] 2-methyl-3,5-dinitroaniline **5** (Scheme 2). In fact, compound **5** was found to be inert towards S_2Cl_2 in refluxing xylene for 24 h (*cf.* ref. 6); the starting material was recovered almost quantitatively from the reaction mixture. To prepare isothiazole **4**, we investigated in detail the reaction of aniline **5** with sulfur monochloride in the presence of a base taking into account our recent findings.[7] The nature of the base appeared to be crucial for successful transformation of compound **5**. In the absence of base or on using *N*-ethyldiisopropylamine or triethylamine isothiazole **4** was formed in low yields (from traces to 18%). However, raising excess of sulfur monochloride to 10 equiv. and using 1,4-diazabicyclooctane (DABCO) (8 equiv.) in $CHCl_3$ at room temperature for 72 h followed by addition of triethylamine gave isothiazole **4** in 90% yield (Scheme 2).†



Scheme 2

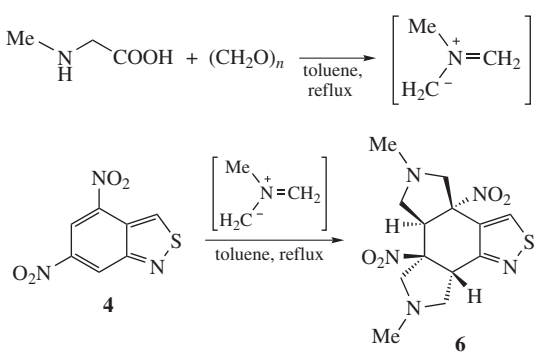
To the best of our knowledge, sulfur monochloride was previously used only in one case for the synthesis of fused isothiazoles from heterocycles bearing vicinal amino and methyl groups.[8]

Isothiazole **4**, similarly to isoxazole **1**, readily undergoes the double 1,3-dipolar cycloaddition reaction with *in situ* generated (*N*-methyl-*N*-methylideneammonio)methanide. Refluxing of compound **4** in toluene in the presence of *N*-methylglycine and paraformaldehyde for 2 h affords 5,8-dimethyl-3b,6b-dinitro-3b,4,5,6,6a,6b,7,8,9,9a-decahydroisothiazolo[3,4-*e*]pyrrolo[3,4-*g*]-isoindole **6** (Scheme 3).‡

Structure and stereochemistry of the adduct **6** was confirmed by X-ray diffraction analysis (Figure 1).§

Compound **6** crystallizes from $CHCl_3$ in the centrosymmetrical space group $P\bar{1}$ and has two independent molecules in

† *Synthesis of compound* **4**. Sulfur monochloride (2 ml, 25 mmol) was added dropwise to a stirred solution of anhydrous DABCO (2.24 g, 20 mmol) and 2-methyl-3,5-dinitroaniline **5** (0.49 g, 2.5 mmol) in $CHCl_3$ (50 ml) at –35 to –25 °C under argon. The mixture was stirred at room temperature for 72 h. Triethylamine (3.2 ml) was added, the mixture was heated under reflux for 1 h, filtered and the solvent was evaporated. The residue was separated by column chromatography (silica gel Merck 60, light petroleum, then light petroleum–CH_2Cl_2 mixtures) to afford 0.50 g of **4** (90%) as yellow crystals, mp 206–207 °C (lit.,[4] mp 198–198.5 °C.) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (s, 2H, Ar), 10.24 (s, 1H, Ar). ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 116.74, 124.43, 127.74, 140.45, 146.59, 151.21, 159.55. MS (EI, 70 eV), *m*/*z* (%): 225 (M^+, 100), 193 (13), 173 (42), 138 (38). IR (KBr, ν/cm^{-1}): 1620 (C=N), 1528 and 1344 (NO_2). Found (%): C, 37.48; H, 1.79; N, 18.32. Calc. for $C_7H_4N_3O_4S$ (%): C, 37.17; H, 1.78; N, 18.58.



Scheme 3

the unit cell representing different stereoisomers. Both independent molecules have similar geometry, the isothiazole ring is planar, with the bond lengths being close to those found for 3-butyl-1-(5-nitrobenzo[*c*][1,2]thiazol-3-yl)-3-phenyltriazene.[9] The conformations of both 5-membered hydropyrrole rings and the central 6-membered ring fragment can be described as the flattened twisted envelopes with the nitrogen atoms and C(5) atom shifted from the planes formed by the other atoms of the rings. The superimposition of the independent molecules has revealed that the relative conformations of their N(5)–C(8)–C(7)–C(6)–C(9) rings differ, with N(5) atom (and its equivalent) being shifted in different directions from the plane formed by the other four atoms. The molecules are held together in crystal by the numerous weak C–H···O interactions as well as one S(1)···N(10) [3.152(1) Å] interaction formed between every pair of the independent molecules.

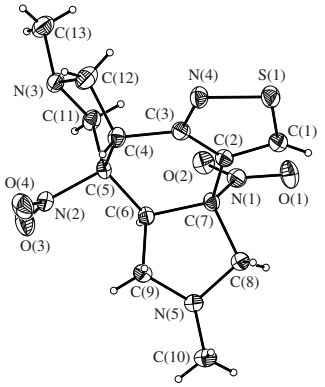


Figure 1 General view of one of two independent molecules in the crystal of **6**. Thermal ellipsoids are drawn at 50% probability level. Selected bond lengths (Å): S(1)–N(4) 1.6572(15), S(1)–C(1) 1.6946(18), C(7)–C(8) 1.558(2), C(6)–C(9) 1.537(2); selected bond angle (°): C(1)–S(1)–N(4) 95.59(8).

Thus, a new method for the synthesis of 4,6-dinitrobenzo[*c*]isothiazole from readily available 2-methyl-3,5-dinitrophenylamine has been proposed and the representative of the previously unknown heterocyclic system, decahydroisothiazolo[3,4-*e*]pyrrolo[3,4-*g*]isoindole, has been synthesised.

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‡ *Synthesis of compound* **6**. A mixture of compound **4** (0.23 g, 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 was consumed (TLC). Then the mixture was cooled, filtered and the solvent was removed *in vacuo*. The product **6** was purified by dissolving in minimal volume of THF, following by precipitation with hexane and filtration of the precipitate formed. Yield 0.15 g (45%), yellow crystals, mp 194–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27 (s, 6H), 2.49 (t, 1H, *J* 9.3 Hz), 2.81 (d, 1H, *J* 11.2 Hz), 2.93 (t, 1H, *J* 9.0 Hz), 2.99–3.04 (m, 2H), 3.55–3.65 (m, 2H), 3.86 (d, 1H, *J* 10.1 Hz), 4.35–4.43 (m, 2H), 8.99 (s, 1H). Found (%): C, 46.01; H, 5.05; N, 20.64; S, 9.45. Calc. for $C_{13}H_{17}N_5O_4S$ (%): C, 45.83; H, 5.04; N, 20.48; S, 9.85.

§ *Crystallographic data.* Crystals of **6** ($C_{13}H_{17}N_5O_4S$, M = 339.38) are triclinic, space group $P\bar{1}$, at 120 K: a = 7.9821(3), b = 8.4618(3) and c = 22.0023(8) Å, α = 90.466(2)°, β = 90.721(2)°, γ = 90.150(2)°, V = = 1485.93(9) Å^3, Z = 4 (Z' = 2), d_{calc} = 1.517 g cm^{-3}, μ(MoKα) = 2.48 cm^{-1}, F(000) = 712. Intensities of 15314 reflections were measured with a Bruker SMART 1K CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 58°$] and 7164 independent reflections (R_{int} = 0.0170) were used in further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The H(C) atom positions were calculated and refined in isotropic approximation in riding model with U_{iso}(H) parameters equal to 1.2U_{eq}(C_i) for CH and CH_2 groups and 1.5U_{eq}(C_{ii}), where U(C_i) and U(C_{ii}) are the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. The refinement converged to wR_2 = 0.0874 and GOF = 1.021 for all independent reflections [R_1 = = 0.0434 was calculated against F for 5727 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[10]

CCDC 779007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.