

Regioselectivity of the substitution for the nitro group in 2,4,6-trinitrobenzonitrile under the action of thiols. The synthesis of 4,6-dinitro derivatives of benzo-annulated sulfur-containing heterocycles

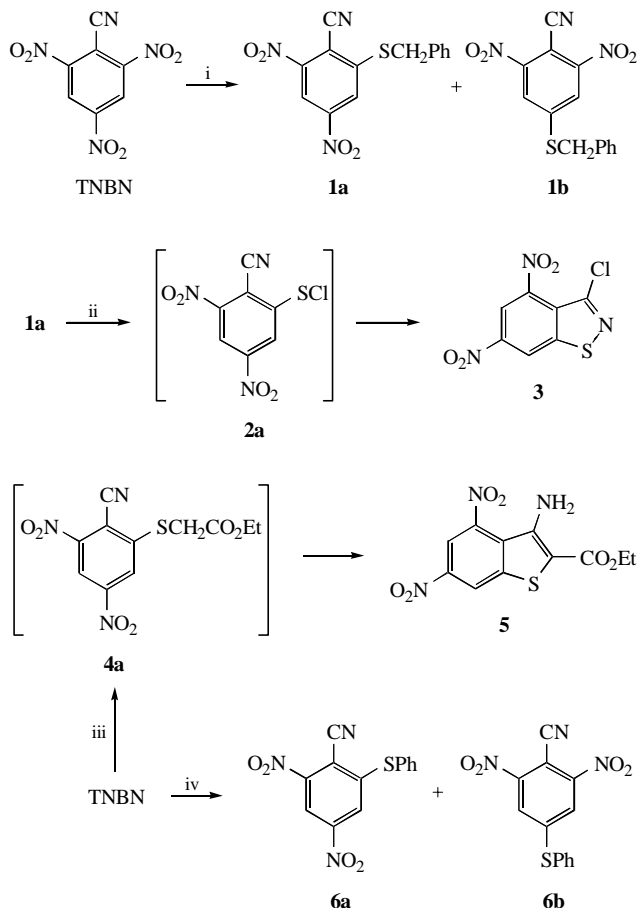
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Conditions for the regioselective substitution for a nitro group in the *ortho*-position in 2,4,6-trinitrobenzonitrile under the action of thiols (PhCH_2SH , $\text{HSCH}_2\text{CO}_2\text{Et}$ or PhSH) in the presence of K_2CO_3 or KOH were found, and the intramolecular cyclization of the *ortho*-fragments $-\text{SX}$ and $-\text{CN}$ ($\text{X} = \text{Cl}$ or $\text{CH}_2\text{CO}_2\text{Et}$) was performed to afford 3-chloro-4,6-dinitrobenzo[*d*]isothiazole and 3-amino-2-ethoxycarbonyl-4,6-dinitrobenzo[*b*]thiophene, respectively.

We are concerned with the chemistry of primary conversion products of 2,4,6-trinitrotoluene (TNT) in the context of the utilisation of this explosive.¹ These products include 2,4,6-trinitrobenzonitrile (TNBN), which can be easily prepared from TNT by the treatment with nitrosyl chloride.² One of the promising synthetic applications of TNBN is the production of benzo-annulated heterocycles, which can be performed, in particular, by the selective replacement of a nitro group in the *ortho*-position with a unit capable of intramolecular cyclization with the nitrile group.



Scheme 1 Reagents, conditions and results: i, 1 equiv. PhCH_2SH + 1.8 equiv. K_2CO_3 ; i_1 , DMF/ H_2O (4:1, v/v; 0.42 M PhCH_2SH), 0–2 °C, 3 h, 91% yield of **1a** + **1b**, **1a**:**1b** = 2:1; i_2 , MeCN (0.42 M PhCH_2SH), 80 °C (boiling), 3 h, 90% yield of **1a** + **1b**, **1a**:**1b** = 3:1; i_3 , toluene (0.25 M PhCH_2SH), 110 °C (boiling), 8 h, 40% yield of **1a** + **1b**, **1a**:**1b** = 5:1; ii, **1a**:**1b** = 5:1, 7 equiv. $\text{SO}_2\text{Cl}_2/\text{DCE}$, boiling, 8 h, 50% yield of **3** (in terms of **1a**); iii, 1 equiv. $\text{HSC}_2\text{CO}_2\text{Et}$ + 1.8 equiv. KOH , MeCN/ H_2O (4:1, v/v, 0.42 M $\text{HSC}_2\text{CO}_2\text{Et}$), 0 °C, 0.5 h, 20 °C, 3 h, 54% yield of **5**; iv, 1 equiv. PhSH + 1.8 equiv. K_2CO_3 ; iv_1 , DMF/ H_2O (4:1, v/v; 0.42 M PhSH), 0–2 °C, 3 h, 76% yield of **6a** + **6b**, **6a**:**6b** = 2:1; iv_2 , toluene, (0.25 M PhSH), 110 °C (boiling), 4 h, 80% yield of **6a**.

We found that in the reaction of TNBN with PhCH_2SH in the presence of K_2CO_3 both *ortho* and *para* nitro groups were replaced with the PhCH_2S unit: an isomer mixture of *ortho* and *para* sulfides **1a** and **1b** was formed, the ratio between which depends on the polarity of the solvent (Scheme 1, i).

It can be seen that the fraction of *ortho* substitution considerably increased with decreasing polarity of solvents in the order aqueous DMF, MeCN and PhMe (Scheme 1, i, i_1 – i_3). We used a mixture (5:1) of *ortho* and *para* isomers **1a** and **1b** prepared in a medium of PhMe for the intramolecular cyclization starting from **1a** (via **2a**). It is well known that the $\text{ArS}-\text{CH}_2\text{Ph}$ bond is easily cleaved under the action of chlorinating agents to form ArSCl .³ It is also known that spontaneous intramolecular cyclization with the formation of 3-chlorobenzo[*d*]isothiazoles proceeds in the presence of CN and SCl units in the *ortho* position.⁴ Indeed, 3-chloro-4,6-dinitrobenzo[*d*]isothiazole **3** (Scheme 1, ii) was prepared by the treatment of the above mixture of sulfides **1a** and **1b** with SO_2Cl_2 .

The substitution for the *para* nitro group was not observed in the reaction of $\text{HSCH}_2\text{CO}_2\text{Et}$ with TNBN (in the presence of KOH in aqueous acetonitrile); 3-amino-2-ethoxycarbonyl-4,6-dinitrobenzo[*b*]thiophene **5**, a representative of previously unknown 4,6-dinitrobenzo[*b*]thiophenes (Scheme 1, iii), was the only reaction product.

According to published data,⁵ benzothiophene **5** is formed by base-catalysed intramolecular cyclization of *ortho*-substitution product **4a** (Scheme 1, iii).

A representative of aromatic thiols, PhSH , reacting with TNBN (in the presence of K_2CO_3) in aqueous DMF gives a mixture of isomer *ortho* and *para* sulfides **6a** and **6b** (Scheme 1, iv, iv_1). However, the reaction proceeds regiospecifically in a toluene medium: only a nitro group in the *ortho* position of TNBN is replaced, and the only product, *ortho*-sulfide **6a**, is formed in high yield (Scheme 1, iv, iv_2).

The identity of the individual products or isomer mixtures obtained was supported by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy and elemental analysis. The yields in Scheme 1 are specified for isolated individual products or purified isomer mixtures. At the same time, the ratio between *ortho* and *para* isomers (^1H NMR data) is given for isolated crude reaction products. In all cases, the reaction was performed until the complete conversion of TNBN.[†]

[†] ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer, solvent [$^2\text{H}_6$]DMSO.

3: mp 200–202 °C (PrOH). ^1H NMR, δ : 8.9 (s, 1H, H⁷), 9.1 (s, 1H, H⁵). ^{13}C NMR, δ : 112.18, 112.73, 120.21, 129.30, 144.95, 149.42, 150.37.

5: mp 200 °C (PrOH). ^1H NMR, δ : 1.3 (t, 3H, OEt), 4.3 (qw, 2H, OEt), 6.6 (br. s, 2H, NH₂), 8.7 (s, 1H, H⁷), 9.4 (s, 1H, H⁵). ^{13}C NMR, δ : 14.22, 61.25, 105.79, 116.89, 124.06, 124.93, 125.45, 141.62, 144.90, 145.89, 163.65.

6a: mp 110–112 °C (PrOH). ^1H NMR, δ : 7.7 (m, 5H, Ph), 8.0 (s, 1H, H³), 8.7 (s, 1H, H⁵).

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