Chemistry of 2,4,6-trinitrobenzonitrile

1. Nitro group substitution in 2,4,6-trinitrobenzonitrile under the action of anionic nucleophiles. Factors favoring substitution of the *ortho*-nitro group

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The direction of the nitro group substitution (the ratio of the *ortho*/*para* substitution) in 2,4,6-trinitrobenzonitrile under the action of anionic nucleophiles (MeO^-, RS^-, and N_3^-) as well as of HCl was studied. The factors favoring *ortho* substitution were revealed.

Key words: 2,4,6-trinitrobenzonitrile, nucleophilic substitution of nitro groups, anionic nucleophiles, intramolecular cyclization, benzo[*b*]thiophenes.

The present work is a part of our systematic studies aimed at the use of 2,4,6-trinitrotoluene (TNT) as a readily accessible versatile starting material for the design of different types of valuable products.[1]

From the practical standpoint, knowledge of the characteristic features of the nitro group substitution depending on the structure of the nitro compound and reaction conditions is of fundamental importance in the chemistry of TNT and products of transformations of its methyl group (2,4,6-trinitro-substituted derivatives of benzoic acid, benzaldehyde, their derivatives, 2,4,6-trinitrostilbenes, *etc.*). These important characteristic features are poorly studied not only for TNT and its derivatives, but also for all aromatic *meta*-di- and -polynitro compounds of various types.[2]

2,4,6-Trinitrobenzonitrile (TNB) is a readily accessible TNT transformation product, which is potentially valuable from the synthetic standpoint. This is prepared from TNT under the action of NOCl in one technological step.[3] The replacement of the *ortho*-nitro group by other functional groups which can undergo intramolecular cyclization involving the cyano group to form the corresponding benzoannelated heterocycles is one of the most attractive possibilities of the use of TNB in the synthesis. However, it was necessary to ascertain beforehand the regularities of the nucleophilic substitution of the nitro groups in TNB, including the possibility of the selective replacement of the *ortho*-nitro group.

Results and Discussion

We examined the reactions of some characteristic representatives of anionic O-, S-, and N-nucleophiles, *viz.*, MeO^-, RS^- (R = $PhCH_2$, Ph, or $AlkOCOCH_2$), and N_3^-, as well as of HCl with TNB under various conditions (Schemes 1—4). The reaction conditions were chosen (Table 1) so that they enabled the complete conversion of TNB and its transformation into products in preparative yields. The structures of the resulting individual products or mixtures of isomers were established by ^1H NMR spectroscopy (in some cases, by ^{13}C NMR spectroscopy), mass spectrometry (EI), and IR spectroscopy and confirmed by the satisfactory data from elemental analysis.

In the reaction of TNB with MeONa in MeOH, one, two, or even three nitro groups were replaced depending on the reagent ratio and the reaction conditions (see Scheme 1, Table 1), the first group being replaced even at below-zero temperatures. This reaction afforded methoxy derivatives **1—3** in high yields. It should be noted that mono- or disubstitution gave rise to mixtures of isomers (**1** and **2**), respectively. The effect of the temperature on the course of the reaction was examined using the monosubstitution reaction as an example. It was found that the fraction of *ortho*-substitution products increased as the temperature was decreased (see Table 1).

The effects of the nature of the solvent and the structure of the nucleophile on the direction of the replacement of the nitro groups in TNB were studied in reactions with thiols ($PhCH_2SH$, PhSH, and $HSCH_2CO_2R$, where R = Me or Et), which generated the corresponding thiolate anions *in situ* under the action of bases (see Schemes 2 and 3). It is known[2,4] that aromatic and aliphatic thiolate anions combine high nucleophilicity in S_NAr reactions and rather low basicity (at least, their basicity is much lower than that of the corresponding oxygen analogs).

We used solid K_2CO_3 (the molar ratio TNB : thiol : K_2CO_3 = 1 : 1 : 1.8) as the deprotonating

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2292—2296, December, 2001.

Table 1. Reactions of 2,4,6-trinitrobenzonitrile (TNB) with nucleophiles

Nucleophile (equivalents with respect to TNB)	Solvent	*T*/°C (*t*/h)	Product	Yield[a] (%)	Ratio of the *ortho*/*para* isomers[b]
MeONa (1)	MeOH	−25 (7)	**1a** + **1b**	93	2 : 1
MeONa (1)	MeOH	0 (7)	**1a** + **1b**	∼90	3 : 2
MeONa (1)	MeOH	20 (4)	**1a** + **1b**	93	1 : 1
MeONa (2)	MeOH	20 (7)	**2a** + **2b**	85	2 : 1
MeONa (5)	MeOH	Refluxing (7)	**3**	88	—
$PhCH_2SH$ (1) + K_2CO_3 (1.8)	DMF—H_2O (4 : 1)	0—2 (3)	**4a** + **4b**	90	2 : 1
$PhCH_2SH$ (1) + K_2CO_3 (1.8)	MeCN	Refluxing (3)	**4a** + **4b**	90	3 : 1
$PhCH_2SH$ (1) + K_2CO_3 (1.8)	PhMe	Refluxing (8)	**4a** + **4b**	40	5 : 1
MeONa [c]	MeOH	Refluxing (3)	**6**	68	—
PhSH (1) + K_2CO_3 (1.8)	DMF—H_2O (4 : 1)	0—2 (3)	**7a** + **7b**	76	2 : 1
PhSH (1) + K_2CO_3 (1.8)	PhMe	Refluxing (4)	**7a**	80	—
$HSCH_2CO_2Me$ (1) + KOH (1.8)	DMF—H_2O (4 : 1)	20 (23)	**9**	48	—
$HSCH_2CO_2Et$ (1) + KOH (1.8)	DMF—H_2O (4 : 1)	20 (23)	**10**	54	—
NaN_3 (1.2)	DMF	0—5 (3)	**11a** + **11b**	51	3 : 1
HCl	DMF	50—70 (1.5); 100 (1)	**12**	84	—
HCl	DMF	50—70 (2); refluxing (0.5)	**13**	93	—

[a] With respect to the individual product or the purified mixture of isomers.

[b] The ratio of the isomers for the crude reaction products isolated.

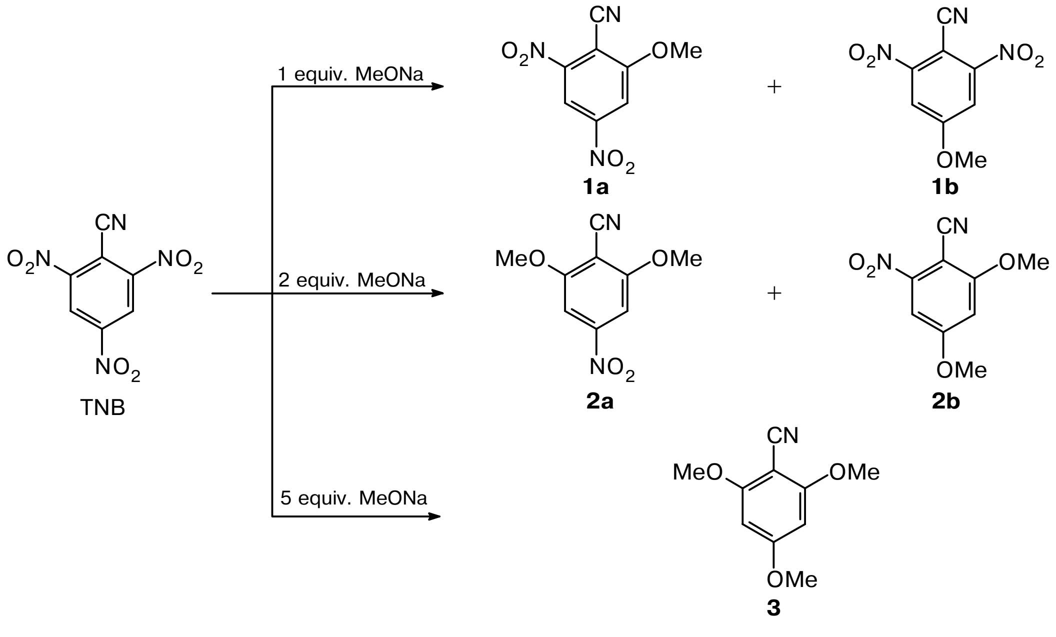
[c] A mixture of 2-benzylsulfonyl-4,6-dinitrobenzonitrile (**5a**) and 4-benzylsulfonyl-2,6-dinitrobenzonitrile (**5b**) was used as the starting substrate; the yield is given with respect to **5b**.

agent except for the reactions with $HSCH_2CO_2Alk$, where KOH was used. Under these conditions, only one nitro group was replaced by the RS fragment.[5]

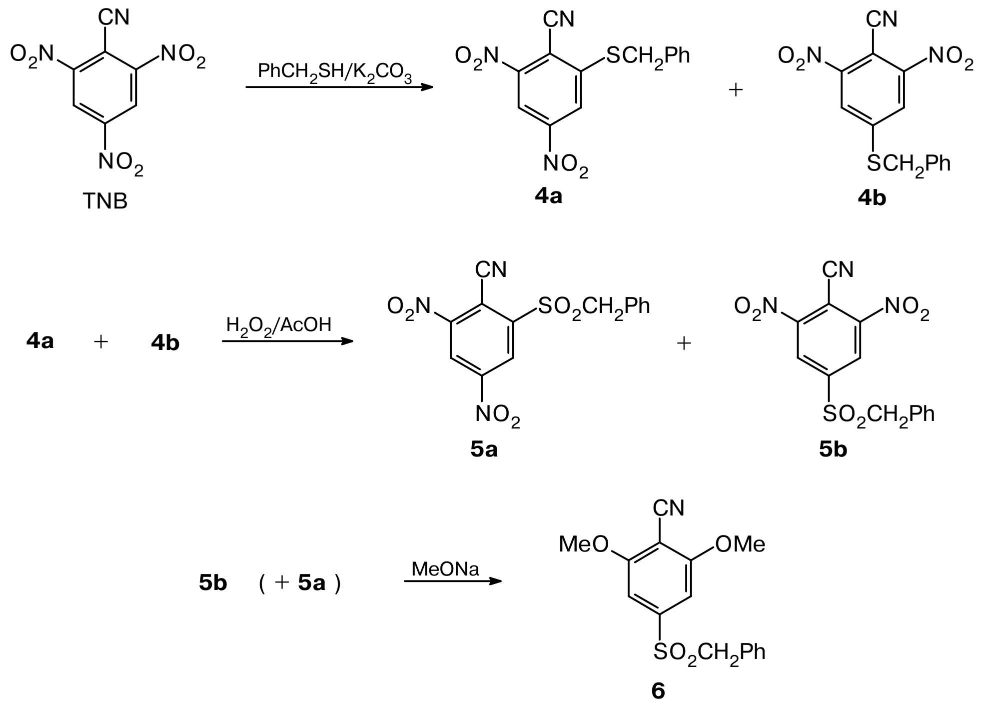
The effect of the polarity of the solvent on the direction of the reaction was followed in the reaction with $PhCH_2SH$ giving rise to a mixture of *ortho*/*para* isomers **4a** and **4b** (see Table 1). The results obtained demonstrate that the fraction of the *ortho*-substitution product increases substantially as the polarity of the solvent decreases in the series DMF—H_2O, MeCN, and PhMe.

Oxidation of a mixture of **4a** and **4b** (2 : 1) with 37% H_2O_2 in AcOH afforded a mixture of isomeric sulfones **5a** and **5b** (1 : 1). Under the action of MeONa

Scheme 1



Scheme 2

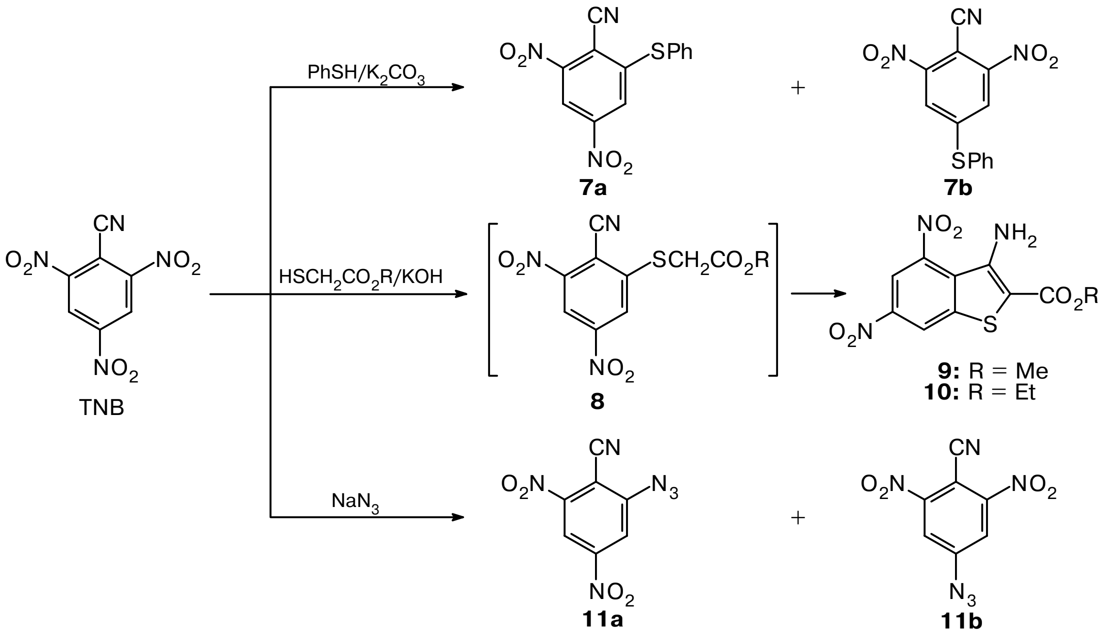


in boiling MeOH, these products were transformed into a mixture of compounds from which the major product, *viz.*, sulfone **6**, was isolated (see Scheme 2, Table 1). The possible intramolecular cyclization of **5a** was not observed.

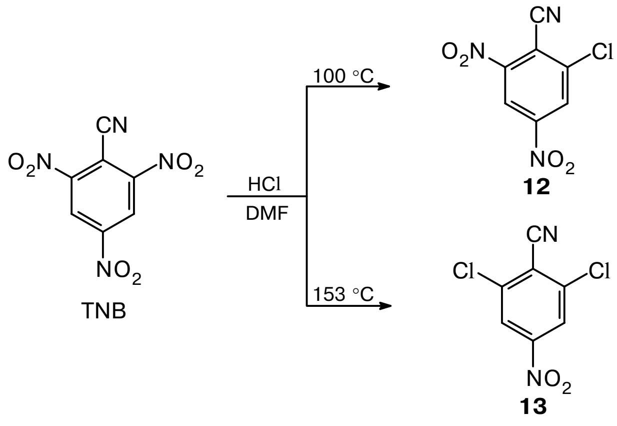
The reaction of PhSH with TNB in aqueous DMF, like the reaction of $PhCH_2SH$, produced a mixture of *ortho*/*para* isomers **7a** and **7b**. However, the reaction in toluene proceeded regiospecifically. Thus exclusively the *ortho*-nitro group was replaced to give the only product, *viz.*, sulfide **7a**, in high yield (see Scheme 3, Table 1).

The reactions of $HSCH_2CO_2R$ (R = Me or Et) with TNB in the presence of KOH yielded the corresponding alkyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxy-

Scheme 3



Scheme 4



lates **9** and **10**, respectively, even in a polar medium ($MeCN-H_2O$) (see Scheme 3, Table 1). These compounds are representatives of previously unknown 4,6-dinitrobenzo[*b*]thiophenes. According to the published data,[6] benzothiophenes **9** and **10** were generated by base-catalyzed intramolecular cyclization of *ortho*-substitution product **8**.

These results suggest that the lowering of the basicity of the thiolate anion favors *ortho*-substitution in TNB (in water, pK_a values for $PhCH_2SH$, PhSH, and $HSCH_2CO_2Et$ are 9.43,[7] 6.5,[7] and 7.68,[8] respectively; in DMSO, pK_a for $PhCH_2SH$ and PhSH are 15.4 [9] and 10.3,[9] respectively).

In the case of the azide ion, which combines low basicity and high nucleophilicity, *ortho*-substitution prevails even in a strongly polar solvent (DMF) (see Scheme 3, Table 1). In this connection, recall that no pronounced tendency for *ortho*-substitution was observed in the case of the highly basic methoxide anion (see Scheme 1).

Heating of TNB at 100 °C with DMF saturated with gaseous HCl led to the replacement of only one of the *ortho*-nitro groups to form 2-chloro-4,6-dinitrobenzonitrile **12**, whereas heating at 153 °C resulted in the replacement of both *ortho*-nitro groups giving rise to 2,6-dichloro-4-nitrobenzonitrile **13** (see Scheme 4, Table 1). It should be noted that the chloride ion, which possesses very low basicity, acts as a moderate nucleophile in S_NAr reactions performed in aprotic media.[10]

The results of the present study suggest that the decrease in polarity of the solvent, reduction of the reaction temperature, and the use of nucleophiles which combine rather high nucleophilicity in S_NAr reactions and low basicity (*i.e.*, soft Lewis bases), all other conditions being the same, favor the selective nucleophilic substitution of the *ortho*-nitro group in TNB. These conclusions can serve as the basis for directed syntheses starting from TNB. The synthesis of alkyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylates **9** and **10** provides an example. The reasons for the substantial influence of the above-considered factors on the selectivity of the reaction call for further investigation.

Experimental

The melting points were determined on a Boetius stage (the heating rate was 4 deg min^{-1}). The IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets. The course of the reactions was monitored by TLC on Silufol UV-254 plates. The ^1H and ^{13}C NMR spectra were measured on a Bruker AC-200 spectrometer in DMSO-d_6 (200.13 MHz for ^1H; 50.32 MHz for ^{13}C; Me_4Si as the internal standard).

2,4,6-Trinitrobenzonitrile was prepared by the reaction of nitrosyl chloride with TNT in anhydrous pyridine.[3]

2-Methoxy-4,6-dinitrobenzonitrile (1a) and 4-methoxy-2,6-dinitrobenzonitrile (1b). A solution of MeONa (13 mmol) in MeOH (20 mL) was added to a solution of TNB (13 mmol) in MeOH (80 mL). The reaction mixture was stirred under conditions indicated in Table 1. Then the solvent was distilled off. The solid residue was washed with water and dried to yield a mixture of compounds **1a** and **1b**. ^1H NMR, δ, **1a**: 4.21 (s, OMe); 8.39 (s, H(3)); 8.51 (s, H(5)); **1b**: 4.09 (s, OMe); 8.20 (s, H(3), H(5)).

2,6-Dimethoxy-4-nitrobenzonitrile (2a) and 2,4-dimethoxy-6-nitrobenzonitrile (2b). A solution of MeONa (36 mmol) in MeOH (20 mL) was added to a solution of TNB (18 mmol) in MeOH (100 mL). The reaction mixture was stirred at 20 °C for 7 h. The precipitate that formed was filtered off, washed with water, and dried to yield a mixture of compounds **2a** and **2b** in a ratio of 2 : 1. ^1H NMR, δ, **2a**: 4.05 (s, OMe); 7.42 (s, H(3), H(5)); **2b**: 4.05—4.00 (m, OMe); 7.15 (s, H(3)); 7.56 (s, H(5)).

2,4,6-Trimethoxybenzonitrile (3). A solution of MeONa (23 mmol) in MeOH (10 mL) was added to a solution of TNB (4.7 mmol) in MeOH (40 mL). The reaction mixture was refluxed for 7 h and then cooled. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from MeOH to yield compound **3**, m.p. 142—144 °C. Found (%): C, 61.87; H, 5.57; N, 7.30. $C_{10}H_{11}NO_3$. Calculated (%): C, 62.17; H, 5.74; N, 7.25. ^1H NMR, δ: 3.38 (s, 3 H, OMe); 3.39 (s, 6 H, OMe); 6.32 (s, 2 H, H(3), H(5)). ^{13}C NMR, δ: 55.7; 56.1; 82.5; 90.9; 114.1; 163.1; 165.2.

2-Benzylthio-4,6-dinitrobenzonitrile (4a) and 4-benzylthio-2,6-dinitrobenzonitrile (4b). ***A.*** A solution of K_2CO_3 (7.6 mmol) in water (2 mL) was added to a solution of TNB (4.2 mmol) and $PhCH_2SH$ (4.2 mmol) in DMF (8 mL) at 0—2 °C. The reaction mixture was stirred at this temperature for 3 h and then poured into water. The precipitate that formed was filtered off, washed with water, and dried to yield a mixture of sulfides **4a** and **4b**. Found (%): C, 53.14; H, 2.76; N, 13.34. $C_{14}H_9N_3O_4S$. Calculated (%): C, 53.30; H, 2.86; N, 13.33. ^1H NMR, δ, **4a**: 4.70 (s, CH_2); 7.30—7.50 (m, Ph); 8.67 (s, H(3)); 8.73 (s, H(5)); **4b**: 4.65 (s, CH_2); 7.30—7.50 (m, Ph); 8.50 (s, H(3), H(5)).

B. A mixture of TNB (2.1 mmol), $PhCH_2SH$ (2.1 mmol), and K_2CO_3 (3.8 mmol) in MeCN (5 mL) was refluxed for 3 h, the solvent was distilled off, and the residue was dried to yield a mixture of sulfides **4a** and **4b**.

C. A mixture of TNB (1.26 mmol), $PhCH_2SH$ (1.26 mmol), and K_2CO_3 (2.3 mmol) in toluene (5 mL) was refluxed for 8 h, the solvent was distilled off, and the solid residue was dried to yield a mixture of sulfides **4a** and **4b**.

2-Benzylsulfonyl-4,6-dinitrobenzonitrile (5a) and 4-benzylsulfonyl-2,6-benzonitrile (5b). A mixture of sulfides **4a** and **4b** (2 : 1) (2.5 mmol), 37% H_2O_2 (18 mmol), and glacial AcOH (5 mL) was refluxed for 3 h, cooled, poured into water, and extracted with ethyl acetate. The organic layer was washed with water and dried with $MgSO_4$, the solvent was distilled off, and the solid residue was dried to yield a mixture of sulfones **5a** and **5b** in a ratio of 1 : 1 (74%). Found (%): C, 48.48; H, 3.26; N, 12.01; S, 9.45. $C_{14}H_9N_3O_6S$. Calculated (%): C, 48.41; H, 2.59; N, 12.10; S, 9.22. ^1H NMR, δ, **5a**: 5.00 (s, CH_2); 7.30—7.50 (m, Ph); 8.70 (s, H(3)); 9.20 (s, H(5)); **5b**: 5.00 (s, CH_2); 7.30—7.50 (m, Ph); 8.80 (s, H(3), H(5)).

4-Benzylsulfonyl-2,6-dimethoxybenzonitrile (6). A mixture of sulfones **5a** and **5b** (1 : 1) (2.4 mmol) and a 1.5% solution of MeONa in MeOH (2 mL) was refluxed for 3 h, cooled, poured into water, and extracted with ethyl acetate. The organic layer was washed with water and dried with $MgSO_4$. The solvent was distilled off and an oil was obtained in a yield of 0.7 g. The oil was passed through a column with silica gel (32—63 μm; a 5 : 2 CCl_4—ethyl acetate mixture was used as the eluent) to yield compound **6**, m.p. 177—178 °C (EtOH). Found (%): C, 60.48; H, 5.24; N, 4.39; S, 9.06. $C_{16}H_{15}NO_4S$. Calculated (%): C, 60.57; H, 4.73; N, 4.42; S, 10.09. ^1H NMR, δ: 3.92 (s, 6 H, OMe); 4.80 (s, 2 H, CH_2); 7.08 (s, 2 H, H(3), H(5)); 7.21 (m, 2 H, Ph); 7.39 (m, 3 H, Ph).

4,6-Dinitro-2-phenylthiobenzonitrile (7a) and 2,6-dinitro-4-phenylthiobenzonitrile (7b). ***A.*** A solution of K_2CO_3 (7.6 mmol) in water (2 mL) was added to a solution of TNB (4.2 mmol) and PhSH (4.2 mmol) in DMF (8 mL) at 0—2 °C. The reaction mixture was stirred at this temperature for 3 h and then poured into water. The precipitate that formed was filtered off, washed with water, and dried to yield a mixture of sulfides **7a** and **7b**. ^1H NMR, δ, **7a**: 7.60 (m, Ph); 8.20 (s, H(3)); 8.70 (s, H(5)); **7b**: 7.60 (m, Ph); 7.70 (s, H(3), H(5)).

B. A mixture of TNB (1.26 mmol), PhSH (1.26 mmol), and K_2CO_3 (2.4 mmol) in toluene (5 mL) was refluxed for 4 h. The solvent was distilled off and the solid residue was dried to yield sulfide **7a**, m.p. 152—154 °C (propan-2-ol). Found (%): C, 51.62; H, 2.03; N, 13.85; S, 10.73; $C_{13}H_7N_3O_4S$. Calculated (%): C, 51.87; H, 2.32; N, 13.96; S, 10.65. ^1H NMR, δ: 7.60 (m, 5 H, Ph); 8.20 (s, 1 H, H(3)); 8.70 (s, 1 H, H(5)).

Methyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylate (9). A solution of KOH (7.5 mmol) in water (2 mL) was carefully added dropwise with stirring to a solution of TNB (4.2 mmol) and methyl thioglycolate (4.2 mmol) in MeCN (10 mL) at 0—2 °C. The reaction mixture was stirred at 20 °C for 3 h and then kept without stirring for 20 h. The precipitate that formed was filtered off, washed several times with MeCN, and dried to yield compound **9**, m.p. 196—198 °C (propan-2-ol). Found (%): C, 40.88; H, 2.62; N, 13.98; S, 11.01; $C_{10}H_7N_3O_6S$. Calculated (%): C, 40.40; H, 2.35; N, 14.14; S, 10.77. ^1H NMR, δ: 3.85 (s, 3 H, Me); 6.60 (br.s, 2 H, NH_2); 8.70 (s, 1 H, H(7)); 9.40 (s, 1 H, H(5)).

Ethyl 3-amino-4,6-dinitrobenzo[*b*]thiophene-2-carboxylate (10) was prepared analogously, m.p. 200 °C (propan-2-ol). Found (%): C, 42.87; H, 3.35; N, 13.23; S, 9.89. $C_{11}H_9N_3O_6S$. Calculated (%): C, 42.44; H, 2.89; N, 13.50; S, 10.29. ^1H NMR, δ: 1.36 (t, 3 H, Me, J = 4.4 Hz); 4.37 (q, 2 H, CH_2, J = 4.4 Hz); 6.56 (br.s, 2 H, NH_2); 8.67 (s, 1 H, H(7)); 9.26 (s, 1 H, H(5)). ^{13}C NMR, δ: 14.2; 61.3; 105.8; 116.9; 124.1; 124.9; 125.5; 141.6; 144.9; 145.9; 163.7. IR (KBr), ν/cm^{-1}: 1350 (NO_2); 1550 (NO_2); 1730 (C=O).

2-Azido-4,6-dinitrobenzonitrile (11a) and 4-azido-2,6-dinitrobenzonitrile (11b). Sodium azide (1.1 mmol) was added to a solution of TNB (0.84 mmol) in anhydrous DMF (3 mL) at 0—5 °C. The reaction mixture was stirred at this temperature for 3 h and then poured into water. The precipitate that formed was filtered off, washed with water, and dried to yield a mixture of azides **11a** and **11b**. ^1H NMR, δ, **11a**: 8.60 (s, H(3)); 8.65 (s, H(5)); **11b**: 8.00 (s, H(3), H(5)). IR, ν/cm^{-1}: 1350 (NO_2); 1540 (NO_2); 2160 (N_3); 2246 (CN).

2-Chloro-4,6-dinitrobenzonitrile (12). A solution of TNB (4.2 mmol) in anhydrous DMF (6 mL) was saturated with gaseous HCl at 50—60 °C with stirring for 1.5 h. The reaction mixture was kept at 100—110 °C for 1 h, cooled, and poured onto ice. The precipitate that formed was filtered off, washed with water, and dried to yield chloride **12**, m.p. 118—120 °C (propan-2-ol). Found (%): C, 36.74; H, 0.94; N, 18.14; Cl, 15.38. $C_7H_2N_3O_4Cl$. Calculated (%): C, 36.93; H, 0.88; N, 18.46; Cl, 15.59. ^1H NMR, δ: 8.89 (s, 1 H, H(3)); 9.04 (s, 1 H, H(5)). ^{13}C NMR, δ: 119.2; 129.7; 139.9; 149.5; 150.5.

2,6-Dichloro-4-nitrobenzonitrile (13). A solution of TNB (4.2 mmol) in anhydrous DMF (6 mL) was saturated with gaseous HCl at 50—70 °C with stirring for 2 h. The reaction mixture was refluxed for 30 min, cooled, and poured onto ice. The precipitate that formed was filtered off, washed with water, and dried to yield dichloride **13**, m.p. 145—147 °C (EtOH). Found (%): C, 38.58; H, 1.01; Cl, 32.70. $C_7H_2N_2O_2Cl_2$. Calculated (%): C, 38.71; H, 0.92; Cl, 32.72. ^1H NMR, δ: 8.55 (s, 2 H, H(3), H(5)). ^{13}C NMR, δ: 117.7; 123.8; 128.8; 143.7; 155.3.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 01-03-32261) and by the International Science and Technology Center (ISTC, Grant 419).

References

1. V. A. Tartakovsky, S. A. Shevelev, M. D. Dutov, A. Kh. Shakhnes, A. L. Rusanov, L. G. Komarova, and A. M. Andrievsky, *Problems of Trotyl (TNT) Processing into Condensation Monomers, Polymers and Dyes*, in *Conversion Concepts for Commercial Applications and Disposal Technologies of Energetic Systems*, Ed. H. Krause, Kluwer Academic Publishers, Dordrecht, 1997, 137.
2. F. Terrier, *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*, VCH, Weinheim—New York, 1991.
3. M. E. Sitzman and J. C. Dacons, *J. Org. Chem.*, 1973, **38**, 4363.
4. G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, 1977, **10**, 125.
5. I. L. Dalinger, T. I. Cherkasova, V. M. Khutoretskii, and S. A. Shevelev, *Mendeleev Commun.*, 2000, 72.
6. J. R. Beck, *J. Org. Chem.*, 1972, **37**, 3224.
7. M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, and L. T. Ditsch, *J. Am. Chem. Soc.*, 1960, **82**, 4899.
8. J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.*, 1960, **82**, 2511.
9. F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.
10. A. J. Parker, *Quart. Rev.*, 1962, **16**, 1631; *Adv. Phys. Org. Chem.*, 1967, **5**, 173.

Received March 1, 2001;
in revised form June 14, 2001