4-(1-Benzotriazolyl)-5-nitrophthalonitrile as a highly active substrate in aromatic nucleophilic substitution reactions

Alexey V. Smirnov, Igor G. Abramov,* Vladimir V. Plakhtinskii and Galina G. Krasovskaya

Department of Organic Chemistry, Yaroslavl State Technical University, 150023 Yaroslavl, Russian Federation. Fax: +7 0852 44 0729; e-mail: abramov.orgchem@staff.ystu.yar.ru

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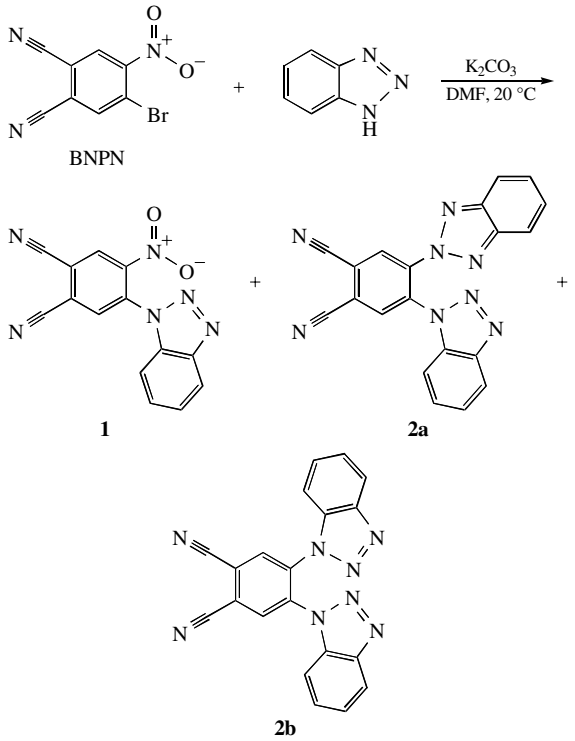
The title compound was synthesised, and its derivatives were prepared in high yields using the selective substitution of O-, S- and N-nucleophiles for the nitro group; an activating effect of the benzotriazolyl moiety on the above reactions was found.

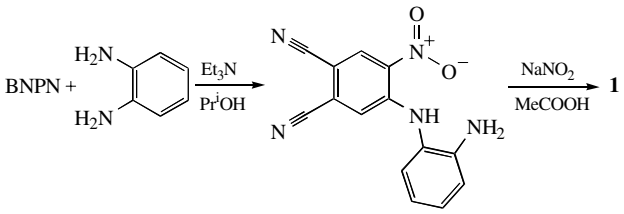
Previously,[1–6] we studied the activated aromatic nucleophilic substitution for the nitro group in 4-nitrophthalonitrile and for the bromine atom and the nitro group in 4-bromo-5-nitrophthalonitrile using various O-, S- and N-nucleophiles. Benzotriazole is widely used in S_NAr reactions as a nitrogen-containing nucleophile.[7–9] The procedure for preparing 4-(1-benzotriazolyl)-5-nitrophthalonitrile **1** in 48% yield was reported earlier.[3] The yield of the mono-substituted product was increased up to 59% by decreasing reaction temperature and using another alkaline agent. However, we failed to prevent the formation of disubstituted products **2a**,**b** (Scheme 1).



Scheme 1

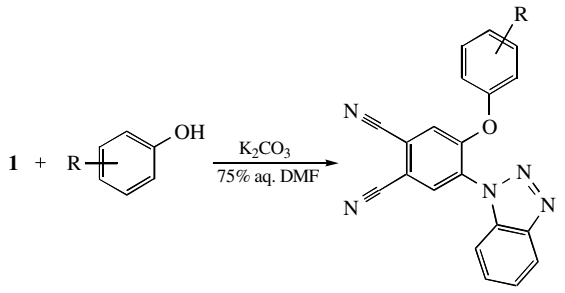
Therefore, we developed a two-step procedure (Scheme 2) to prepare chromatographically pure compound **1**. This procedure allowed us to synthesise the target product in 83% yield on a basis of starting 4-bromo-5-nitrophthalonitrile.† At the first step, 4-bromo-5-nitrophthalonitrile readily reacted with *o*-phenylenediamine in boiling isopropanol in the presence of triethylamine to form 4-(2-aminoanilino)-5-nitrophthalonitrile.[2] The second step consisted in the diazotisation of the isolated product on heating in acetic acid to result in the target compound.

† *4-(1-Benzotriazolyl)-5-nitrophthalonitrile* **1**. 4-(2-Aminoanilino)-5-nitrophthalonitrile (31.00 g, 0.11 mol) was dissolved in 300 ml of acetic acid. A solution of 7.60 g (0.11 mol) of $NaNO_2$ in 50 ml of water was added to the resulting solution. The reaction mixture was stirred at 70 °C for 3 h. The precipitate formed after cooling was filtered off, washed with 20 ml of acetic acid, and dried at 70 °C.



Scheme 2

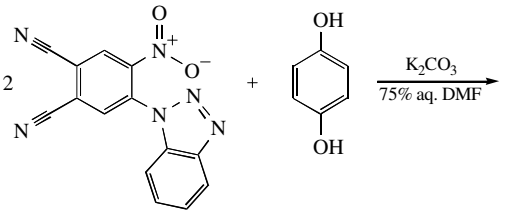
The synthesised substrate is of interest because a benzene ring bears four electron-acceptor substituents: two cyano groups and a benzotriazole moiety in the *ortho* position with respect to the nitro group. Although the reactions of substitution for the nitro group were studied in detail,[10] reactions with the participation of the above compound were not described in the literature. Substitution for the benzotriazole moiety was described for only aliphatic systems.



a R = H
b R = 3,4-Me
c R = 4-Cl
d R = 4-Br
e R = 4-(4-MeC_6H_4)
f R = 4-Ph
g R = 4-cyclohexyl
h R = 4-COMe
i R = 4-F
j R = 4-Cl-3,5-Me
k R = 4-Cl-3-Me
l R = 3-COMe

Scheme 3

We found that the presence of a comparatively strong electron-acceptor benzotriazole substituent increases the probability of a nucleophilic attack on the carbon atom bound to the nitro group. Moreover, this carbon atom is activated by two cyano groups; thus, the nitro group becomes more labile. Because of this, only the nitro group in compound **1** can be readily replaced by various O-, S- and N-nucleophiles under mild reaction conditions. Thus, compound **1** reacted with substituted phenols (Scheme 3) in a 75% aqueous DMF solution in the presence of potassium carbonate within 30 min even at room temperature (20 °C). Reaction products **3a–l**‡,†† precipitated from the reaction mixture and did not require further purification. The reaction of **1** with bisphenols occurred under analogous conditions with the formation of, for example, compound **4**§,†† (Scheme 4). The above nucleophiles can replace the nitro group[1] in 4-nitrophthalonitrile only at 60 °C, whereas substitution for the heterocyclic moiety in 4-benzotriazolylphthalonitrile did not occur at a higher temperature.[3] We



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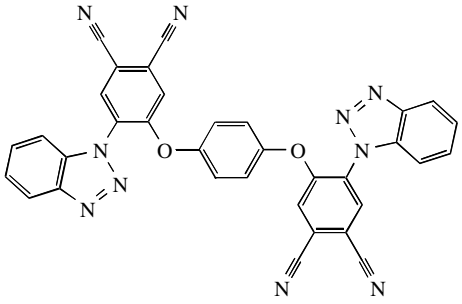

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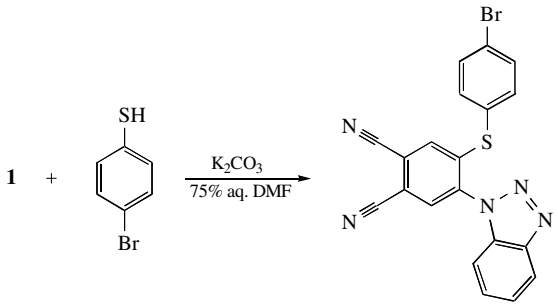
Scheme 4

partially replaced the benzotriazole unit by phenoxide (according to LC data) only in compound **2** upon refluxing the corresponding parent compounds in anhydrous DMF for a long time.

Under the specified conditions (20 °C, 75% aqueous DMF), the reaction with S-nucleophiles such as 4-bromothiophenol occurred more readily (Scheme 5). The product of selective substitution for the nitro group precipitated from the reaction mixture 1 to 2 min after mixing the reactant solutions.



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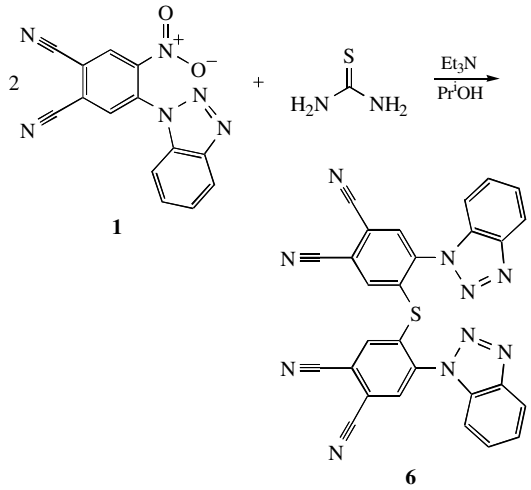
Scheme 5

If benzotriazole was used as an N-nucleophile in the considered reaction with compound **1** under the specified conditions, the substitution of the benzotriazole ring for the nitro group primarily took place at the second nitrogen atom. In this case, the yield of compound **2a** was as high as 76%. According to ^{1}H NMR data, compound **2a** precipitated from the reaction mixture exhibited a non-symmetrical structure identical to that described previously.[4] Compound **2b** was not precipitated from the reaction mixture, and it was detected in a mixture with **2a** in the analysis of the product obtained after diluting the filtrate with water. For comparison, note that the nitro group in 4-nitrophthalonitrile can be replaced[3] with benzotriazole only at 70 °C in anhydrous DMF to result in a mixture of 1- and 2-substituted derivatives in the ratio 1.4:1.

The substrate under consideration can also react with ambident nucleophiles such as thiourea and the nitrite ion.



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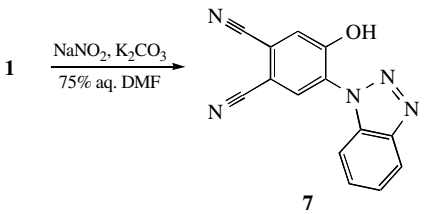
Scheme 6

The reaction of **1** with thiourea began with the formation of an isothiuronium salt, which was rearranged into a mercapto derivative in the presence of a base (triethylamine). The resulting thiophenoxide is reactive, and it attacked substrate **1** in the presence of triethylamine to afford 4-(1-benzotriazolyl)-5-[2-(1-benzotriazolyl)-4,5-dicyanophenylsulfanyl]phthalonitrile **6**[‡,††] (Scheme 6).



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Scheme 7

Compound **1** can react with alkali metal nitrites in the presence of potassium carbonate at elevated temperatures (Scheme 7). Compound **7**[¶,††] was formed by the replacement of the nitro group on an O-attack of the nitrite ion.[11] In contrast to thiophenoxide, the resulting compound is inactive in nucleophilic substitution reactions, and it can be easily separated from the reaction mixture.

Thus, the above results are indicative of a higher reactivity of 4-(1-benzotriazolyl)-5-nitrophthalonitrile in nucleophilic substitution reactions than that of 4-nitrophthalonitrile. It is believed that the benzotriazole unit has a considerable activating effect on the test reaction of selective substitution for the nitro group. Both donor and acceptor substituents are simultaneously present in the prepared compounds, and this fact is responsible for their unique properties. On this basis, new promising materials with special photophysical properties, for example, phthalocyanines[12] and hexazocyclanes,[13] can be synthesised.

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‡ *4-(1-Benzotriazolyl)-5-phenoxyphthalonitrile* **3a**. Compound **1** (2.00 g, 0.07 mol), phenol (0.66 g, 0.07 mol) and K_2CO_3 (0.97 g, 0.07 mol) dissolved in 5 ml of water were added to 15 ml of DMF. The resulting mixture was intensely stirred at room temperature for 0.5 h. The formed precipitate was filtered off, washed with 20 ml of ethanol and then 100 ml of water, and dried at 70 °C.

Compounds **3b–l**, **5** and **6** were prepared in a similar manner with the use of equimolar amounts of other phenols, 4-bromothiophenol and thioacetamide as reactants.

§ *4-(1-Benzotriazolyl)-5-{4-[2-(1-benzotriazolyl)-4,5-dicyanophenoxy]-phenoxy}phthalonitrile* **4**. Compound **1** (2.00 g, 0.07 mol), a bisphenol (0.04 mol) and K_2CO_3 (0.97 g, 0.07 mol) dissolved in 5 ml of water were added to 15 ml of DMF. The resulting mixture was intensely stirred at room temperature for 1 h. The formed precipitate was filtered off, washed with 20 ml of ethanol and then 100 ml of water, and dried at 70 °C.

¶ *4-(1-Benzotriazolyl)-5-hydroxyphthalonitrile* **7**. Compound **1** (2.00 g, 0.07 mol), $NaNO_2$ (0.69 g, 0.07 mol) and K_2CO_3 (0.97 g, 0.07 mol) dissolved in 5 ml of water were added to 15 ml of DMF. The resulting mixture was heated to 70 °C and intensely stirred at this temperature for 0.5 h. After cooling to room temperature, HCl was added to the reaction mixture to pH 1. The formed precipitate was filtered off, washed with 20 ml of ethanol and dried at 70 °C.

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†† The ^{1}H NMR spectra of 5% sample solutions in [$^2H_6$]DMSO were measured on a Bruker DRX-500 instrument using TMS as an internal standard.

3a: yield 89%, mp 188–191 °C. ^{1}H NMR, δ: 8.62 (s, 1H), 7.13 (d, 1H, *J* 8.2 Hz), 7.80 (d, 1H, *J* 8.2 Hz), 7.75 (s, 1H), 7.64 (t, 1H), 7.50 (t, 1H), 7.42 (t, 2H), 7.27 (t, 1H), 7.18 (d, 2H, *J* 8.81 Hz). Found (%): C, 71.09; H, 3.30; N, 20.80. Calc. for $C_{20}H_{11}N_5O$ (%): C, 71.21; H, 3.29; N, 20.76.

3b: yield 94%, mp 236–238 °C. ^{1}H NMR, δ: 8.62 (s, 1H), 8.14 (d, 1H, *J* 8.1 Hz), 7.80 (d, 1H, *J* 8.1 Hz), 7.72 (s, 1H), 7.63 (t, 1H), 7.50 (t, 1H), 6.90 (s, 1H), 6.75 (s, 2H), 2.25 (s, 6H). Found (%): C, 72.15; H, 4.14; N, 19.25. Calc. for $C_{22}H_{15}N_5O$ (%): C, 72.32; H, 4.14; N, 18.17.

3c: yield 92%, mp 237–239 °C. ^{1}H NMR, δ: 8.62 (s, 1H), 8.15 (d, 1H, *J* 8.2 Hz), 7.90 (s, 1H), 7.80 (d, 1H, *J* 8.0 Hz), 7.63 (t, 1H), 7.50 (t, 1H), 7.40 (d, 2H, *J* 8.4 Hz), 7.15 (d, 2H, *J* 8.1 Hz). Found (%): C, 64.51; H, 2.72; N, 18.90. Calc. for $C_{20}H_{10}ClN_5O$ (%): C, 64.61; H, 2.71; N, 18.84.

3d: yield 96%, mp 251–253 °C. ^{1}H NMR, δ: 8.65 (s, 1H), 8.14 (d, 1H, *J* 8.2 Hz), 7.90 (s, 1H), 7.80 (d, 1H, *J* 8.1 Hz), 7.64 (t, 1H), 7.56 (d, 2H, *J* 8.0 Hz), 7.50 (t, 1H), 7.15 (d, 2H, *J* 8.1 Hz). Found (%): C, 57.60; H, 2.43; N, 16.78. Calc. for $C_{20}H_{10}BrN_5O$ (%): C, 57.71; H, 2.42; N, 16.83.

3e: yield 84%, mp 215–217 °C. ^{1}H NMR, δ: 8.67 (s, 1H), 8.17 (d, 1H, *J* 8.3 Hz), 7.87 (d, 1H, *J* 8.0 Hz), 7.83 (s, 1H), 7.67 (m, 3H), 7.50 (t, 3H), 7.25 (d, 4H, *J* 7.9 Hz), 2.33 (s, 3H). Found (%): C, 75.68; H, 4.01; N, 16.45. Calc. for $C_{27}H_{17}N_5O$ (%): C, 75.86; H, 4.01; N, 16.38.

3f: yield 87%, mp 208–210 °C. ^{1}H NMR, δ: 8.66 (s, 1H), 8.16 (d, 1H, *J* 8.3 Hz), 7.88 (s, 1H), 7.83 (d, 1H, *J* 8.0 Hz), 7.67 (m, 3H), 7.60 (d, 2H, *J* 7.9 Hz), 7.50 (t, 1H), 7.45 (t, 2H), 7.35 (t, 1H), 2.27 (d, 2H, *J* 8.1 Hz). Found (%): C, 75.38; H, 3.67; N, 17.01. Calc. for $C_{26}H_{15}N_5O$ (%): C, 75.53; H, 3.66; N, 16.94.

3g: yield 82%, mp 204–206 °C. ^{1}H NMR, δ: 8.62 (s, 1H), 8.14 (d, 1H, *J* 8.2 Hz), 7.80 (d, 2H, *J* 8.2 Hz), 7.70 (s, 1H), 7.65 (t, 1H), 7.50 (t, 1H), 7.25 (d, 2H, *J* 8.1 Hz), 7.10 (d, 2H, *J* 8.0 Hz), 2.55 (s, 1H), 1.80 (d, 4H, *J* 7.8 Hz), 1.60 (d, 1H, *J* 8.5 Hz), 1.35 (m, 4H), 1.25 (m, 1H). Found (%): C, 74.31; H, 5.05; N, 14.64. Calc. for $C_{26}H_{21}N_5O$ (%): C, 74.44; H, 5.05; N, 16.70.

3h: yield 91%, mp 215–217 °C. ^{1}H NMR, δ: 8.70 (s, 1H), 8.12 (d, 1H, *J* 8.3 Hz), 8.00 (s, 1H), 7.93 (d, 2H, *J* 8.3 Hz), 7.80 (d, 1H, *J* 8.0 Hz), 7.65 (t, 1H), 7.50 (t, 1H), 7.20 (d, 2H, *J* 8.2 Hz). Found (%): C, 69.52; H, 3.46; N, 18.50. Calc. for $C_{22}H_{13}N_5O_2$ (%): C, 69.65; H, 3.45; N, 18.46.

3i: yield 83%, mp 209–211 °C. ^{1}H NMR, δ: 8.65 (s, 1H), 8.15 (d, 1H, *J* 8.1 Hz), 7.84 (d, 1H, *J* 8.3 Hz), 7.78 (s, 1H), 7.65 (t, 1H), 7.50 (t, 1H), 7.25 (m, 4H). Found (%): C, 67.49; H, 2.85; N, 19.70. Calc. for $C_{20}H_{10}FN_5O$ (%): C, 67.60; H, 2.84; N, 19.71.

3j: yield 96%, mp 225–227 °C. ^{1}H NMR, δ: 8.60 (s, 1H), 8.13 (d, 1H, *J* 8.2 Hz), 7.87 (s, 1H), 7.80 (d, 1H, *J* 7.9 Hz), 7.65 (t, 1H), 7.50 (t, 1H), 7.00 (s, 2H), 2.30 (s, 6H). Found (%): C, 65.93; H, 3.53; N, 17.49. Calc. for $C_{22}H_{14}ClN_5O$ (%): C, 66.09; H, 3.53; N, 17.43.

3k: yield 94%, mp 213–215 °C. ^{1}H NMR, δ: 8.60 (s, 1H), 7.12 (d, 1H, *J* 8.0 Hz), 7.90 (s, 1H), 7.80 (d, 1H, *J* 8.3 Hz), 7.62 (t, 1H), 7.50 (t, 1H), 7.40 (d, 1H, *J* 8.0 Hz), 7.15 (s, 1H), 7.0 (d, 1H, *J* 7.9 Hz), 2.30 (s, 3H). Found (%): C, 65.20; H, 3.14; N, 18.20. Calc. for $C_{21}H_{12}ClN_5O$ (%): C, 65.38; H, 3.14; N, 18.15.

3l: yield 89%, mp 186–188 °C. ^{1}H NMR, δ: 8.67 (s, 1H), 8.12 (d, 1H, *J* 8.0 Hz), 7.90 (s, 1H), 7.83 (d, 2H, *J* 8.4 Hz), 7.70 (s, 1H), 7.65 (t, 1H), 7.56 (t, 1H), 7.50 (t, 1H), 7.45 (d, 1H, *J* 8.1 Hz). Found (%): C, 69.57; H, 3.46; N, 18.41. Calc. for $C_{22}H_{13}N_5O_2$ (%): C, 69.65; H, 3.45; N, 18.46.

4: yield 77%, mp > 300 °C. ^{1}H NMR, δ: 8.60 (s, 2H), 8.15 (d, 2H, *J* 8.2 Hz), 7.90 (s, 2H, *J* 8.1 Hz), 7.80 (d, 2H, *J* 7.9 Hz), 7.65 (t, 2H), 7.50 (t, 2H), 7.20 (s, 4H). Found (%): C, 68.33; H, 2.71; N, 23.54. Calc. for $C_{34}H_{16}N_{10}O_2$ (%): C, 68.45; H, 2.70; N, 23.48.

5: yield 97%, mp 181–183 °C. ^{1}H NMR, δ: 8.40 (s, 1H), 7.15 (d, 1H, *J* 8.2 Hz), 7.70 (d, 2H, *J* 8.5 Hz), 7.65 (t, 1H), 7.57 (d, 1H, *J* 7.9 Hz), 7.50 (t, 1H), 7.40 (d, 1H, *J* 8.0 Hz). Found (%): C, 55.45; H, 2.33; N, 16.25; S, 7.43. Calc. for $C_{20}H_{10}BrN_5S$ (%): C, 55.57; H, 2.33; N, 16.20; S, 7.42.

6: yield 86%, mp 285–287 °C. ^{1}H NMR, δ: 8.45 (s, 2H), 8.35 (s, 2H), 8.13 (d, 2H, *J* 8.5 Hz), 7.60 (m, 4H), 7.50 (d, 2H, *J* 8.3 Hz). Found (%): C, 64.47; H, 2.33; N, 27.01; S, 6.17. Calc. for $C_{28}H_{12}N_{10}S$ (%): C, 64.61; H, 2.32; N, 26.91; S, 6.16.

7: yield 90%, mp > 300 °C. ^{1}H NMR, δ: 12.60 (s, 1H), 8.40 (s, 1H), 8.15 (d, 1H, *J* 8.0 Hz), 7.70 (s, 1H), 7.63 (t, 1H), 7.57 (t, 1H), 7.48 (d, 1H, *J* 8.1 Hz). Found (%): C, 64.20; H, 2.70; N, 26.70. Calc. for $C_{14}H_7N_5O$ (%): C, 64.37; H, 2.70; N, 26.81.

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