The differing reactivity of the bromo and nitro groups in 4-bromo-5-nitrophthalonitrile towards nucleophilic attack

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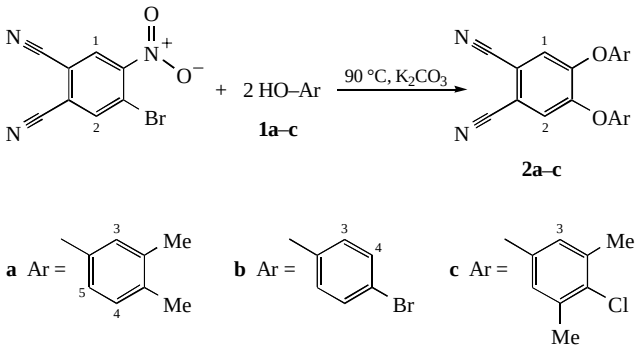
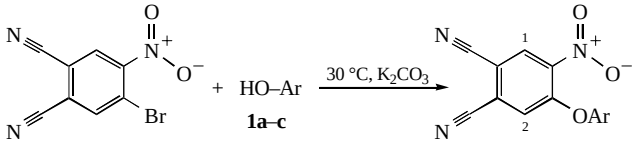
The high reactivity of 4-bromo-5-nitrophthalonitrile and different mobilities of the leaving groups (bromo and nitro) in aromatic nucleophilic substitution reactions offer new opportunities for the synthesis of substituted phthalonitriles and then various heterocyclic compounds.

A wide variety of benzene derivatives can be synthesised by aromatic nucleophilic substitution reactions (S_NAr reactions).[1,2] Aromatic compounds with different functional groups and bridging units between nuclei can be prepared by varying substrates and reagents. We used 4-bromo-5-nitrophthalonitrile (BNPN)† as a substrate in this reaction because of the reasons given below. First, a BNPN molecule bears a considerable number of electron-acceptor substituents. It is well known that this circumstance decreases the electron density in the aromatic system and facilitates a nucleophilic attack to form rather stable intermediates.[3,4] Second, bromo and nitro groups are extremely mobile nucleofuges (leaving groups) in S_NAr reactions.[5] In this connection, BNPN can be characterised as a highly activated system with the possibility of nucleophilic substitution at the 4- and (or) 5-positions.

Initially, we used phenoxide ions formed by the *in situ* interaction of phenols **1a**–**c** with potassium carbonate as a deprotonating agent under homogeneous and heterogeneous conditions (Scheme 1). We found that symmetric 4,5-diphenoxyphthalonitriles **2a**–**c** were formed under the above reaction conditions at 90 °C and a twofold molar excess of **1a**–**c**.‡,§ A decrease in the reaction temperature to 30 °C resulted only in the replacement of bromine in the 4-position to form corresponding 4-phenoxy-5-nitrophthalonitriles **3a**–**c** even with an excess of **1a**–**c** (Scheme 2).‡,§ This result indicates that nucleofuges of the BNPN molecule exhibit different mobilities under conditions of S_NAr reactions. The easier elimination of bromine as compared with that of the nitro group can be explained by the fact that in this case the nitro group acts as an activator of nucleophilic attack on the *ortho* position.[5] On the other hand, the bromine atom does not exert such an effect on the carbon atom at the nitro group. The found difference in the mobility of leaving groups at the 4- and 5-positions in BNPN allowed us to prepare asymmetric phthalonitrile **4** by successive reactions of BNPN with **1a** at 30 °C and of **3a** with **1b** at 90 °C (Scheme 3).§ Product **4** was also synthesised by successive reactions BNPN with **1b** at 30 °C and of **3b** with **1a** at 90 °C. Note that a depression of melting temperature was not observed upon mixing two samples of phthalonitrile **4** prepared by the different procedures.



Scheme 1



Scheme 2

The mobility of bromine as the leaving group was found to be so high that it allowed us to perform the reactions of BNPN with primary aliphatic amine **5a**, secondary aliphatic amines **6a**–**e**, substituted anilines **5b**–**e** and diamines **7a**,**b** in a protogenic solvent to form corresponding phthalonitriles **8a**–**d**, **9a**–**e** and **10a**,**b** (Scheme 4).¶,†† In this case, the replacement of the nitro group in BNPN under the reaction conditions (boiling isopropanol; triethylamine) was not detected. Our attempts to perform analogous reactions of other activated systems such as

† 4-Bromo-5-nitrophthalonitrile was prepared by successive bromination of phthalic anhydride, imidization of 4-bromophthalic acid, nitration of 4-bromophthalimide, amidization of 4-bromo-5-nitrophthalimide and dehydration of 4-bromo-5-nitrophthalamide. 4-Bromophthalimide as a white crystalline powder was prepared according to the known procedure[8] in 90% yield; mp 233–235 °C. For the nitration, 200 g (0.88 mol) of 4-bromophthalimide and 480 ml of concentrated sulfuric acid were placed in a flask, and 72 ml of 100% nitric acid was added to the reaction mixture at 20–25 °C with intense stirring. After 5 h, the reaction mixture was poured into 1.5 l of water with ice. The precipitate formed was filtered off and washed with water until a neutral reaction of the filtrate. 4-Bromo-5-nitrophthalimide as a yellow crystalline powder was obtained; the yield was 185 g (0.68 mol, 77%); mp 216–218 °C. 4-Bromo-5-nitrophthalamide and 4-bromo-5-nitrophthalonitrile were prepared according to the procedure described in ref. 9. 4-Bromo-5-nitrophthalamide was obtained as a yellow crystalline powder in 85% yield; mp 216–218 °C (decomp.). 4-Bromo-5-nitrophthalonitrile was obtained as a yellow crystalline powder in 80% yield; mp 160–161 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.82 (s, 1H, H-1), 8.80 (s, 1H, H-2). Found (%): C, 38.15; H, 0.74; N, 16.39. Calc. for $C_{24}H_{20}N_2O_2$ (%): C, 38.13; H, 0.80; N, 16.67.

‡ *Preparation of* **2a**–**c** *and* **3a**–**c** *under homogeneous conditions.*

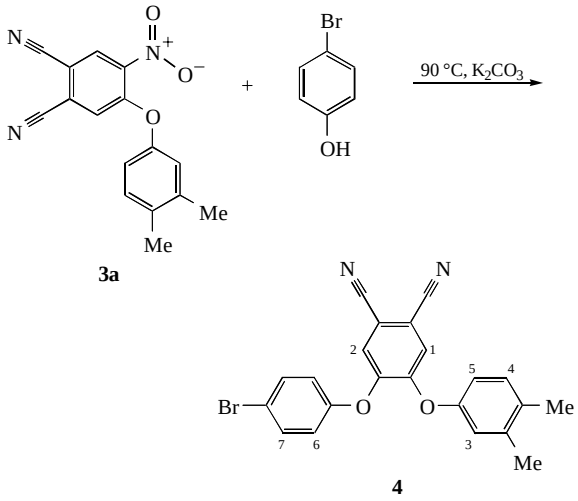
(i) 0.01 mol (2.52 g) of BNPN, 0.02 mol of **1a**–**c** and 15 ml of DMF were placed in a flask. A solution of 0.02 mol (2.76 g) of K_2CO_3 in 5 ml of water was added with stirring. The reaction was performed for 3.0–4.5 h at 90 °C. After completion of the reaction, the mixture was cooled, and precipitated products **2a**–**c** were filtered off and recrystallised from ethanol. Yields: **2a**, 60–70%; **2b**, 80–85%; **2c**, 70–80%.

(ii) 0.01 mol (2.52 g) of BNPN, 0.01 mol of **1a**–**c** and 15 ml of DMF were placed in a flask. A solution of 0.01 mol (1.38 g) of K_2CO_3 in 5 ml of water was added with stirring. The reaction was performed for 1.0–2.0 h at 30 °C. After completion of the reaction, the mixture was cooled, and precipitated products **3a**–**c** were filtered off and recrystallised from ethanol. Yields: **3a**, 70–75%; **3b**, 80–85%; **3c**, 85–90%.

Preparation of **2a**–**c** *and* **3a**–**c** *under heterogeneous conditions.*

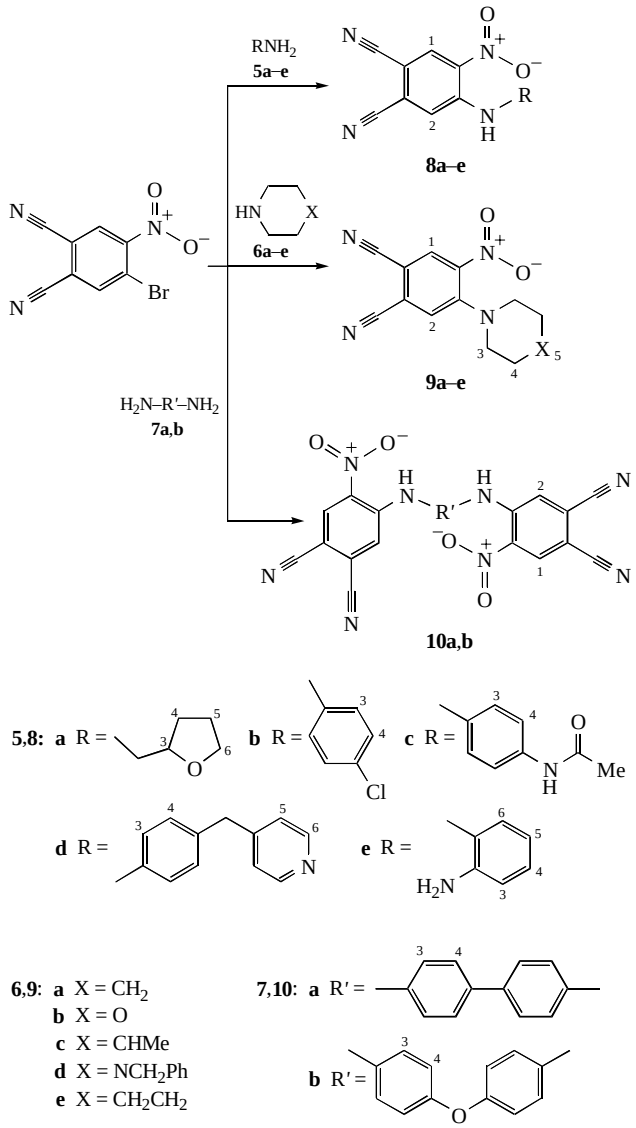
(i) 0.01 mol (2.52 g) of BNPN, 0.02 mol of **1a**–**c**, 0.02 mol (2.76 g) of K_2CO_3 and 30 ml of DMF were placed in a flask. The reaction was performed for 2.0–3.0 h at 130 °C. Next, the reaction mixture was cooled and poured into water; the precipitate was filtered off and recrystallised from ethanol. Yields: **2a**, 65–70%; **2b**, 70–75%; **2c**, 65–70%.

(ii) 0.01 mol (2.52 g) of BNPN, equimolar amounts of **1a**–**c** and K_2CO_3 and 30 ml of DMF were placed in a flask. The reaction was performed for 1.0–2.0 h at 30 °C. Next, the reaction mixture was cooled and poured into water; the precipitate was filtered off and recrystallised from ethanol. Yields: **3a**, 80–85%; **3b**, 75–80%; **3c**, 85–90%.



Scheme 3

4-nitrophthalonitrile and 4-bromophthalonitrile with amines **5** and **6** in a protogenic solvent were unsuccessful, although these reactions are known to proceed in aprotic solvents.[6] The reaction of BNPN with **5e** proceeded only at one amino group to form **8e**, whereas diamines **7a**,**b** afforded disubstitution products. With the use of diaminofurazan, the reaction was not observed at all; the possible reason is low nucleophilicity of the amine.



Scheme 4

Thus, BNPN derivatives **2a**–**c**, **3a**–**c**, **4**, **8a**–**e**, **9a**–**e** and **10a**,**b** are new compounds, which can be used as starting materials for the synthesis of hexazocyclanes,[7] phthalocyanines[6] and heterocyclic systems of the thianthrene, phenoxazine and benzodioxocin series.

§ ^{1}H NMR spectra of 5% solutions of samples in [$^2H_6$]DMSO were recorded on a Bruker-AC-200P instrument; TMS was used as an internal standard.

2a: mp 183–185 °C. ^{1}H NMR, δ: 7.40 (s, 2H, H-1 and H-2), 7.28 (d, 2H, H-4, *J* 8 Hz), 6.89 (d, 2H, H-3, *J* 2 Hz), 6.80 (d, 2H, H-5, *J* 8 Hz), 2.30 (s, 12H, Me). Found (%): C, 78.21; H, 5.39; N, 7.44. Calc. for $C_{24}H_{20}N_2O_2$ (%): C, 78.24; H, 5.47; N, 7.60.

2b: mp 206–208 °C. ^{1}H NMR, δ: 7.72 (s, 2H, H-1 and H-2), 7.55 (d, 4H, H-4, *J* 8 Hz), 7.07 (d, 4H, H-3, *J* 8 Hz). Found (%): C, 51.05; H, 2.10; N, 5.64. Calc. for $C_{20}H_{10}Br_2N_2O_2$ (%): C, 51.10; H, 2.14; N, 5.96.

2c: mp 225–227 °C. ^{1}H NMR, δ: 7.60 (s, 2H, H-1 and H-2), 7.00 (s, 4H, H-3), 2.40 (s, 12H, Me). Found (%): C, 65.88; H, 4.02; N, 6.11. Calc. for $C_{24}H_{18}Cl_2N_2O_2$ (%): C, 65.92; H, 4.15; N, 6.40.

3a: mp 176–178 °C. ^{1}H NMR, δ: 8.82 (s, 1H, H-1), 7.60 (s, 1H, H-2), 7.26 (d, 1H, H-4, *J* 8 Hz), 7.01 (d, 1H, H-3, *J* 2 Hz), 6.93 (d, 1H, H-5, *J* 8 Hz), 2.30 (s, 6H, Me). Found (%): C, 65.55; H, 3.66; N, 14.22. Calc. for $C_{16}H_{11}N_3O_3$ (%): C, 65.53; H, 3.78; N, 14.33.

3b: mp 193–195 °C. ^{1}H NMR, δ: 8.85 (s, 1H, H-1), 7.90 (s, 1H, H-2), 7.65 (d, 2H, H-4, *J* 8 Hz), 7.17 (d, 2H, H-3, *J* 8 Hz). Found (%): C, 48.89; H, 1.68; N, 12.07. Calc. for $C_{14}H_6BrN_3O_3$ (%): C, 48.87; H, 1.76; N, 12.21.

3c: mp 185–187 °C. ^{1}H NMR, δ: 8.85 (s, 1H, H-1), 7.80 (s, 1H, H-2), 7.08 (s, 2H, H-3), 2.40 (s, 6H, Me). Found (%): C, 58.60; H, 2.91; N, 12.51. Calc. for $C_{16}H_{10}ClN_3O_3$ (%): C, 58.64; H, 3.08; N, 12.82.

4: mp 171–173 °C. ^{1}H NMR, δ: 7.62 (d, 2H, H-1 and H-2, *J* 4 Hz), 7.51 (d, 2H, H-7, *J* 8 Hz), 7.20 (d, 1H, H-4, *J* 8 Hz), 7.01 (d, 2H, H-6, *J* 8 Hz), 6.90 (d, 1H, H-3, *J* 2 Hz), 6.81 (d, 1H, H-5, *J* 8 Hz), 2.30 (s, 6H, Me). Found (%): C, 63.05; H, 3.54; N, 6.38. Calc. for $C_{22}H_{15}BrN_2O_2$ (%): C, 63.02; H, 3.61; N, 6.68.

¶ *Preparation of compounds* **8**–**10**.

0.01 mol (2.52 g) of BNPN, equimolar amounts of triethylamine and amine **5a**–**e** (**6a**–**e**) or 0.005 mol of diamine **7a**,**b** and 50 ml of isopropanol were placed in a flask. The reaction mixture was boiled for 2.0 h. After cooling, the precipitate (target product) was filtered off. Yields: **8a**–**e**, 85–90%; **9a**–**e**, 85–90%; **10a**,**b**, 70–75%.

†† **8a**: mp 178–180 °C. ^{1}H NMR, δ: 8.75 (s, 1H, NH), 8.63 (s, 1H, H-1), 7.90 (s, 1H, H-2), 4.10–3.40 (m, 5H, H-3 and H-6 and CH_2, *J* 175 Hz), 2.10–1.60 (m, 4H, H-4 and H-5, *J* 150 Hz). Found (%): C, 57.34; H, 4.32; N, 20.42. Calc. for $C_{13}H_{12}N_4O_3$ (%): C, 57.35; H, 4.44; N, 20.58.

8b: mp 206–208 °C. ^{1}H NMR, δ: 10.05 (s, 1H, NH), 8.72 (s, 1H, H-1), 7.57 (s, 1H, H-2), 7.49 (d, 2H, H-4, *J* 8 Hz), 7.40 (d, 2H, H-3, *J* 8 Hz). Found (%): C, 56.27; H, 2.33; N, 18.38. Calc. for $C_{14}H_7ClN_4O_2$ (%): C, 56.30; H, 2.36; N, 18.76.

8c: mp 204–206 °C. ^{1}H NMR, δ: 10.05 (s, 1H, NH), 9.95 (s, 1H, CONH), 8.70 (s, 1H, H-1), 7.72 (d, 2H, H-4, *J* 8 Hz), 7.45 (s, 1H, H-2), 7.25 (d, 2H, H-3, *J* 8 Hz), 2.10 (s, 3H, COMe). Found (%): C, 59.88; H, 3.40; N, 21.56. Calc. for $C_{16}H_{11}N_5O_3$ (%): C, 59.81; H, 3.45; N, 21.80.

8d: mp 198–200 °C. ^{1}H NMR, δ: 10.05 (s, 1H, NH), 8.71 (s, 1H, H-1), 8.45 (d, 2H, H-6, *J* 8 Hz), 7.50 (s, 1H, H-2), 7.37 (d, 2H, H-5, *J* 8 Hz), 7.30 (d, 2H, H-3, *J* 8 Hz), 7.23 (d, 2H, H-4, *J* 8 Hz), 4.00 (s, 2H, CH_2). Found (%): C, 48.26; H, 2.49; N, 13.79. Calc. for $C_{20}H_{13}N_5O_2$ (%): C, 48.20; H, 2.63; N, 14.05.

References

1 G. Barlin, in *Aromatic and Heteroaromatic Chemistry*, Oxford University Press, London, 1976, vol. 4, p. 277.

2 S. M. Shein, *Zh. Vses. Khim. O-va im. D. I. Mendeleeva*, 1976, **21**, 256 (in Russian).

3 J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.

4 E. Buncel, M. Crampton and M. Strauss, *Electron-Deficient Aromatic- and Heteroaromatic-Base Interaction*, Elsevier, Amsterdam, 1984.

5 F. Terrier, *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*, VSH Publishers, New York, 1991.

6 S. A. Mikhalenko, V. M. Derkacheva and E. A. Luk'yanets, *Zh. Obshch. Khim.*, 1981, **51**, 1650 [*J. Gen. Chem. USSR* (*Engl. Transl.*), 1981, **51**, 1405].

7 S. A. Siling and S. V. Vinogradova, *Usp. Khim.*, 1994, **63**, 810 (*Russ. Chem. Rev.*, 1994, **63**, 767).

8 *Laboratornye raboty po organicheskoi khimii* (*Laboratory Works of Organic Chemistry*), eds. O. F. Ginzburg and A. A. Petrov, Vysshaya Shkola, Moscow, 1974 (in Russian).

9 J. R. Griffith and J. G. O'Rear, *Proceedings of Symposium 'Copolymers, Polyblends and Composites'*, Los Angeles, 1976, p. 458.

8e: mp 168–170 °C. ^{1}H NMR, δ: 9.66 (s, 1H, NH), 8.70 (s, 1H, H-1), 7.12 (t, 1H, H-3, *J* 16 Hz), 7.05 (d, 1H, H-6, *J* 8 Hz), 6.93 (s, 1H, H-2), 6.85 (d, 1H, H-5, *J* 8 Hz), 6.75 (t, 1H, H-3, *J* 16 Hz), 5.15 (s, 2H, NH_2). Found (%): C, 60.19, H, 3.12, N, 24.76. Calc. for $C_{14}H_9N_5O_2$ (%): C, 60.22; H, 3.25; N, 25.08.

9a: mp 198–200 °C. ^{1}H NMR, δ: 8.40 (s, 1H, H-1), 8.00 (s, 1H, H-2), 3.25 (s, 4H, H-3), 1.70 (s, 6H, H-4 and H-5). Found (%): C, 60.95; H, 4.63; N, 21.57. Calc. for $C_{13}H_{12}N_4O_2$ (%): C, 60.93; H, 4.72; N, 21.86.

9b: mp 188–190 °C. ^{1}H NMR, δ: 8.45 (s, 1H, H-1), 8.08 (s, 1H, H-2), 3.70 (t, 4H, H-3, *J* 16 Hz), 3.30 (t, 4H, H-4, *J* 16 Hz). Found (%): C, 55.79; H, 3.79; N, 21.61. Calc. for $C_{12}H_{10}N_4O_3$ (%): C, 55.81; H, 3.90; N, 21.70.

9d: mp 181–182 °C. ^{1}H NMR, δ: 8.43 (s, 1H, H-1), 8.05 (s, 1H, H-2), 7.30 (d, 5H, Ph, *J* 8 Hz), 3.55 (s, 2H, CH_2), 3.3 (d, 4H, H-3, *J* 8 Hz), 3.1 (s, 4H, H-4). Found (%): C, 65.73; H, 4.79; N, 20.01. Calc. for $C_{19}H_{17}N_5O_2$ (%): C, 65.70; H, 4.93; N, 20.16.

9e: mp 203–204 °C. ^{1}H NMR, δ: 8.48 (s, 1H, H-1), 7,90 (s, 1H, H-2), 3.35 (t, 4H, H-3, *J* 16 Hz), 1.70 (s, 4H, H-4), 1.55 (s, 4H, H-5). Found (%): C, 61.18; H, 5.19; N, 20.51. Calc. for $C_{14}H_{14}N_4O_2$ (%): C, 62.21; H, 5.22; N, 20.73.

10a: mp 285–287 °C. ^{1}H NMR, δ: 10.10 (s, 2H, NH), 8.72 (s, 2H, H-1), 7.65 (d, 4H, H-3, *J* 8 Hz), 7.56 (s, 2H, H-2), 7.36 (d, 4H, H-4, *J* 8 Hz). Found (%): C, 63.84; H, 2.35; N, 21.14. Calc. for $C_{28}H_{14}N_8O_4$ (%): C, 63.88; H, 2.68; N, 21.28.

10b: mp 298–300 °C. ^{1}H NMR, δ: 10.08 (s, 2H, NH), 8.71 (s, 2H, H-1), 7.55 (s, 2H, H-2), 7.42 (d, 4H, H-3, *J* 8 Hz), 7.20 (d, 4H, H-4, *J* 8 Hz). Found (%): C, 61.93; H, 2.48; N, 20.33. Calc. for $C_{28}H_{14}N_8O_5$ (%): C, 61.99; H, 2.60; N, 20.66.

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