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Synthesis of substituted azines with the participation of 4-bromo-5-nitrophthalonitrile

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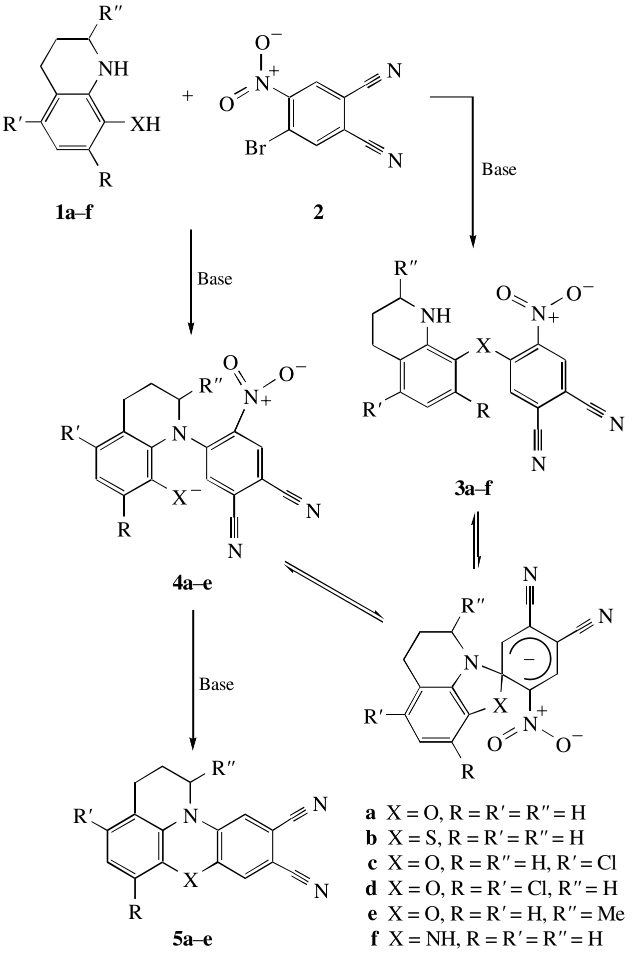
New cyan-containing azines were synthesised by activated aromatic nucleophilic substitution for the bromine atom and the nitro group in 4-bromo-5-nitrophthalonitrile with bifunctional O-, N-, and S-nucleophiles.

The reactions of activated nitrobenzenes and halobenzenes with primary and secondary aliphatic amines, as well as O- and S-nucleophiles (phenoxide and thiophenoxide ions), which are formed *in situ* in the reactions of phenols and thiophenols with bases, are well known.[1–3] Here, we discuss new possibilities of these reactions using the interaction of 4-bromo-5-nitrophthalonitrile[†] with a number of bifunctional reagents as an example.

To prepare cyan-containing azine compounds, we synthesised bifunctional amine-containing nucleophiles **1**, **6** and **10**, which were used in the subsequent reaction without separation, in accordance with published procedures.[4–6] These compounds contain two active nucleophilic centres [O (S), phenol (thiophenol) and N, secondary amine], which can enter nucleophilic substitution reactions in the presence of bases to form a six-membered heterocyclic azine system.



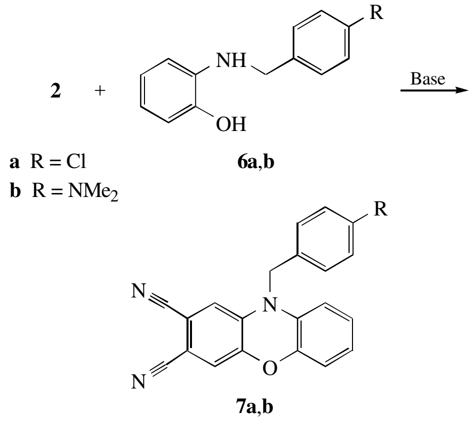
a X = O, R = R′ = R″ = H
b X = S, R = R′ = R″ = H
c X = O, R = R″ = H, R′ = Cl
d X = O, R = R′ = Cl, R″ = H
e X = O, R = R′ = H, R″ = Me
f X = NH, R = R′ = R″ = H

Scheme 1

The reactivity of activated substrate **2** was considered previously.[3,7–9] We believed that, for example, in the reaction with 1,2,3,4-tetrahydro-8-quinolinol **1a** (Scheme 1), the phenol initially underwent deprotonation in the presence of potassium carbonate with the *in situ* formation of the corresponding phenoxide. This compound enters a heterogeneous reaction of intermolecular nucleophilic substitution for bromine in **2** to form monosubstituted product **3a**. It is likely that product **3a** is converted into compound **4a**, which simultaneously bears a nitro group and an O-nucleophilic centre, *via* the intramolecular Smiles rearrangement.[10–12] Next, this nucleophile in the presence of K_2CO_3 enters an intramolecular nucleophilic substitution reaction for the nitro group to result in ring closure and the formation of 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazine-9,10-dicarbonitrile **5a**.[‡]

We prepared 10-[4-(dimethylamino)benzyl]-10*H*-phenoxazine-2,3-dicarbonitrile **7b** with the use of 2-{[4-(dimethylamino)-benzyl]amino}phenol **6b** as a bifunctional nucleophile in the reaction with **2** under mild conditions (Scheme 2). We believe that this product is also formed by the above mechanism. Note that, if reactant **6** contains a primary amino group or an N-alkylamino group is the second reaction centre, an azine ring was not formed from these compounds even under more severe conditions.

A six-membered phenothiazine ring was also formed in the reaction of 4-bromo-5-nitrophthalonitrile **2** with 8-methyl-5*H*-pyrimido[5,4-*b*]indole-4-thiol **8** (Scheme 3). This reaction occurred only on strong heating in DMF in the presence of



a R = Cl
b R = NMe_2

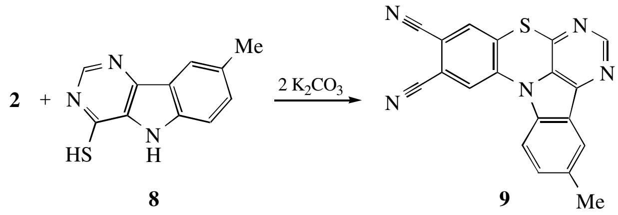
7a,**b**

Scheme 2

[†] 4-Bromo-5-nitrophthalonitrile was prepared according to a published procedure.[16]

[‡] *2,3-Dihydro-1*H*-pyrido[3,2,1-*kl*]phenoxazine-9,10-dicarbonitrile* **5a**. 2.8 g (0.02 mol) of anhydrous K_2CO_3 and 2.52 g (0.01 mol) of **2** were added to 30 cm^3 of a DMF solution containing 1.7 g (0.01 mol) of 1,2,3,4-tetrahydro-8-quinolinol **1a** with stirring. The resulting mixture was intensely stirred at 40–60 °C for 1 h. After cooling to room temperature, it was poured into 100 cm^3 of water; the resulting precipitate was filtered off, washed with 50 cm^3 of water, and crystallised from isopropanol. Compound **5a** (2.08 g, 72%) was obtained as yellow crystalline powder with mp 194–196 °C. Compounds **5b–e** and **7a**,**b** were prepared in a similar manner.

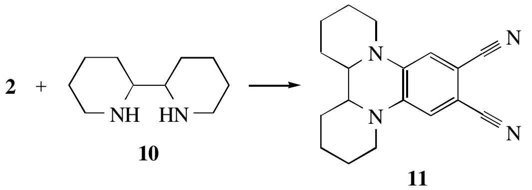
potassium carbonate. The thiazine ring is formed by a two-step mechanism, which is analogous to that described above. Product **9**§ precipitated from the reaction mixture did not require additional purification.



Scheme 3

Upon the reaction of **2** with compound **1f**, which contains a primary amino group, only monosubstituted product **3f** was separated from the reaction mixture. This fact provides indirect evidence for the occurrence of the reaction by the proposed mechanism. It is well known that the Smiles rearrangement does not occur in such aromatic systems with insignificant differences in the nucleophilicity of N-reaction centres; the reaction was terminated at the first step, as was found experimentally.

The use of reduced α,α-dipyridyl **10** and similar compounds[13] in the reaction with **2** (Scheme 4) demonstrated that the reactivity of aromatic amines in the bifunctional N-nucleophiles is lower than that of aliphatic amines. In this case, the corresponding N,N-substituted tetrahydroquinoxaline **11**¶ was readily formed in boiling isopropanol in the presence of triethylamine. Triethylamine is required as a scavenger of HBr; otherwise, this role is played by the starting diamine.



Scheme 4

Thus, new *ortho*-dicyan heterocyclic compounds from the azine series can be synthesised using 4-bromo-5-nitrophthalonitrile and various bifunctional nucleophiles.†† These compounds can be converted into phthalocyanines[14] and hexazocyclanes,[15] which possess unique photophysical properties.

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§ *3-Methyl-8-thia-5,7,12b-triazabenzo[a]aceanthrylene-10,11-dicarbonitrile* **9**. 8-Methyl-5*H*-pyrimido[5,4-*b*]indole-4-thiol **8** (2.01 g, 0.01 mol), 2.8 g (0.02 mol) of anhydrous K_2CO_3 and 2.52 g (0.01 mol) of 4-bromo-5-nitrophthalonitrile **1** were sequentially added to 30 cm^3 of DMF with stirring. The resulting mixture was intensely stirred at 100–120 °C for 1 h. After cooling to room temperature, the resulting precipitate was filtered off and washed with 50 cm^3 of water. Compound **9** (2.92 g, 86%) was obtained as yellow crystalline powder with mp > 300 °C.

¶ *1,2,3,4,11,12,13,14,14a,14b-Decahydrodipyrido[1,2-a:2,1-c]quinoxaline-7,8-dicarbonitrile* **11**. Triethylamine (2.8 g, 0.02 mol) and 2.52 g (0.01 mol) of compound **2** were sequentially added to 50 cm^3 of an isopropanol solution containing 1.65 g (0.01 mol) of compound **10**. The resulting mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into 100 cm^3 of water; the resulting precipitate was filtered off, washed with 50 cm^3 of water and crystallised from isopropanol. Compound **11** (2.87 g, 80%) was obtained as beige crystalline powder with mp 205–206 °C.

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

5a: yield 72%, mp 194–196 °C. ^{1}H NMR, δ, 7.05 (s, 1H), 6.94 (s, 1H), 6.60 (d, 2H, *J* 8.1 Hz), 6.44 (t, 1H), 3.35 (t, 2H), 2.56 (t, 2H), 2.07 (m, 2H). Found (%): C, 74.61; H, 4.06; N, 15.42. Calc. for $C_{17}H_{11}N_3O$ (%): C, 74.71; H, 4.06; N, 15.38.

5b: yield 79%, mp > 290 °C. ^{1}H NMR, δ: 7.15 (s, 1H), 7.00 (s, 1H), 6.70 (d, 2H, *J* 8.2 Hz), 6.48 (t, 1H), 3.35 (t, 2H), 2.54 (t, 2H), 2.05 (m, 2H). Found (%): C, 70.41; H, 3.84; N, 14.58; S, 11.10. Calc. for $C_{17}H_{11}N_3S$ (%): C, 70.57; H, 3.83; N, 14.52; S, 11.08.

5c: yield 92%, mp 246–248 °C. ^{1}H NMR, δ: 7.16 (s, 1H), 6.95 (s, 1H), 6.63 (d, 1H, *J* 8.3 Hz), 6.59 (d, 1H, *J* 8.2 Hz), 3.36 (t, 2H), 2.62 (t, 2H), 2.07 (m, 2H). Found (%): C, 66.15; H, 3.29; N, 13.59. Calc. for $C_{17}H_{10}ClN_3O$ (%): C, 66.34; H, 3.28; N, 13.65.

5d: yield 96%, mp 251–253 °C. ^{1}H NMR, δ: 7.36 (s, 1H), 7.30 (s, 1H), 7.00 (s, 1H), 3.15 (t, 2H), 2.60 (t, 2H), 1.95 (m, 2H). Found (%): C, 59.53; H, 2.65; N, 12.24. Calc. for $C_{17}H_9Cl_2N_3O$ (%): C, 59.67; H, 2.65; N, 12.28.

5e: yield 89%, mp 215–217 °C. ^{1}H NMR, δ: 7.10 (s, 1H), 6.85 (s, 1H), 6.60 (m, 2H), 6.40 (d, 2H, *J* 8.0 Hz), 4.21 (m, 1H), 2.62 (m, 2H), 1.90 (d, 2H), 1.20 (d, 3H). Found (%): C, 75.09; H, 4.55; N, 14.69. Calc. for $C_{18}H_{13}N_3O$ (%): C, 75.23; H, 4.56; N, 14.62.

7a: yield 76%, mp 217–219 °C. ^{1}H NMR, δ: 7.29 (d, 2H, *J* 8.3 Hz), 7.21 (d, 2H, *J* 8.1 Hz), 7.02 (s, 1H), 6.90 (s, 1H), 6.76 (m, 2H), 6.67 (d, 1H, *J* 8.2 Hz), 6.54 (d, 1H, *J* 8.2 Hz), 4.79 (s, 2H).

7b: yield 72%, mp 231–233 °C. ^{1}H NMR, δ: 7.20 (d, 2H, *J* 8.1 Hz), 7.00 (s, 1H), 6.90 (s, 1H), 6.75 (m, 2H), 6.64 (m, 3H), 6.55 (d, 1H, *J* 8.2 Hz), 4.75 (s, 2H), 2.90 (s, 6H).

9: yield 86%, mp > 300 °C. ^{1}H NMR, δ: 8.60 (s, 1H), 8.40 (d, 2H, *J* 8.3 Hz), 8.10 (s, 1H), 8.00 (s, 1H), 7.60 (d, 1H, *J* 8.1 Hz). Found (%): C, 67.09; H, 2.68; N, 20.58; S, 9.47. Calc. for $C_{19}H_9N_5S$ (%): C, 67.24; H, 2.67; N, 20.64; S, 9.45.

11: yield 96%, mp 278–280 °C. ^{1}H NMR, δ: 7.00 (s, 2H), 4.03 (d, 2H, *J* 8.6 Hz), 2.80 (m, 4H), 1.85 (m, 4H), 1.60 (m, 4H), 1.30 (m, 4H).