Synthesis of Ortho-Substituted Benzonitriles by Nitro Displacement

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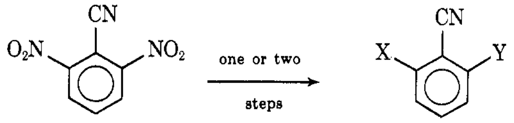
Novel ortho-substituted benzonitriles are synthesized by nitro displacement from *o*-nitrobenzonitriles and 2,6-dinitrobenzonitriles. The displacing nucleophiles include alkoxides, thiol anions, amines, and azide, chloride, and hydroxide ions.

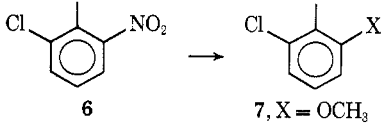
In a recent paper[1] we reported a facile synthesis of 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles. We now wish to describe the preparation of ortho-substituted benzonitriles, again by a process involving nucleophilic displacement of nitro groups activated by adjacent cyano functions. The nucleophilic lability of activated nitro groups has been well established by Bunnett and coworkers[2] and also by Bolto and Miller.[3] These authors studied the nucleophilic displacement of various functions activated by ortho and para nitro groups. The relative rate of nitro displacement by piperidine was reported to be more than 200 times that of chlorine and nearly equal to that of fluorine.

Numerous examples of activated nitro displacements in substituted benzenes are found in the chemical literature, although most cases involve intramolecular displacement.[4] The synthetic utility of intermolecular displacements of nitro functions, which are activated by ortho or para cyano groups, has received little attention. Ringer[5,6] reported the synthesis of *o*-anisonitrile and *p*-anisonitrile from *o*-nitrobenzonitrile and *p*-nitrobenzonitrile, respectively, by treatment with methoxide ion. Holmes and Loudon[7] reported examples of similar displacements using piperidine and benzyl mercaptan anion as nucleophiles. Another example is found in the synthesis of 2,6-dimethoxybenzonitrile (**2**)[8] from *m*-dinitrobenzene, but the overall yield was reported to be only 17%. We have obtained the same product (Table I) in 81% yield by the reaction of 2,6-dinitrobenzonitrile (**1**)[1] with 2 mol of sodium methoxide in refluxing methanol. Similarly, 6-nitro-*o*-anisonitrile (**3**) was prepared from **1** (80% yield) utilizing 1 mol of methoxide in DMF–methanol (room temperature). When **3** was allowed to react with excess methanethiol anion in aqueous DMF (0°), 6-(methylthio)-*o*-anisonitrile (**4**) was formed in 85% yield. Finally, the reaction of **1** with excess methanethiol anion under similar conditions gave 2,6-bis(methylthio)benzonitrile (**5**) in 75% yield. The nucleophilic lability of a nitro function *vs.* a chlorine atom is illustrated by the synthesis of compounds **7–9** from 2-chloro-6-nitrobenzonitrile (**6**). In each instance the nitro group is displaced preferentially and the yields are high.



1

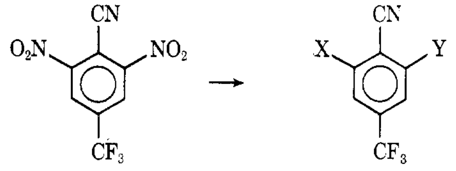
2, X = Y = OCH_3
3, X = NO_2; Y = OCH_3
4, X = OCH_3; Y = SCH_3
5, X = Y = SCH_3



6

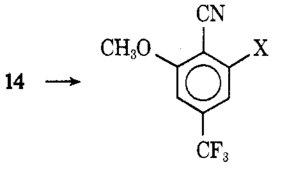
7, X = OCH_3
8, X = SCH_3
9, X = N_3

The versatility of the reaction is demonstrated by the synthesis of ortho-substituted benzonitriles obtained from α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile (**10**).[1] Both nitro groups can be displaced by the same nucleophile, and examples of this are compounds **11–13**. The conditions are quite mild and the yields are again high. The bisazide **13** was extremely light sensitive, and this might explain its lower yield. Compounds **14–17** illustrate the control of the reaction in displacing only one of the nitro functions present. Compounds **18–21** demonstrate the utility of the reaction in, first, displacement of one nitro group by a nucleophile, namely methoxide ion, and, second, displacement of the remaining nitro group by a different nucleophile. It is thus possible to synthesize mixed ethers, as in the case of **19**, which would be difficult to prepare by other routes. The same principle applies to the synthesis of compounds **22–25**, except that the initial displacement is by dimethylamine.

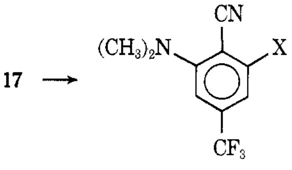


10

11, X = Y = OCH_3
12, X = Y = SCH_3
13, X = Y = N_3
14, X = OCH_3; Y = NO_2
15, X = N_3; Y = NO_2
16, X = $NHCH_3$; Y = NO_2
17, X = $N(CH_3)_2$; Y = NO_2
26, X = Cl; Y = NO_2
27, X = OH; Y = NO_2

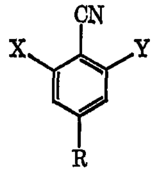


18, X = SCH_3
19, X = OCH_2CH_3
20, X = N_3
21, X = $NHCH_3$



22, X = OCH_3
23, X = SCH_3
24, X = N_3
25, X = $N(CH_3)_2$

Table I
Synthesis of Ortho-Substituted Benzonitriles[a]



Compd	Reactant	Method of prepn	Mp, °C	Yield, %	Crystn solvent[b]	Reaction conditions
2	**1**	I	120–121[c]	81	B	65°, 43 hr
3	**1**		175–177[d]	80	B	
4	**3**	II	120–121	85	B	0°, 0.5 hr; 25°, 2 hr
5	**1**	II	167–169	75	B	0°, 0.5 hr; 25°, 2 hr
7	**6**		115–116[e]	67	B	
8	**6**	II	118–119	83	B	0°, 0.5 hr
9	**6**	III	101–102	74	B	25°, 22 hr
11	**10**	I	113–115	78	A	0°, 0.5 hr; 25°, 1.5 hr
12	**10**	II	133–134	85	B	0°, 5 min
13	**10**	III	94–95	58	B	0°, 1.5 hr
14	**10**	I	82–83.5	83	A	0°, 5 min
15	**10**	III	51–52	50	A	0°, 10 min
16	**10**	IV	164–165.5	63	B	0°, 2 hr
17	**10**		68–69	78	C	
18	**14**	II	113–114	77	B	0°, 0.5 hr; 25°, 2.5 hr
19	**14**		61.5–63	92	C	
20	**14**	III	84–85.5	73	B	25°, 3 hr
21	**14**	IV	143–145	72	B	100°, 1 hr
22	**17**	I	80–81	74	B	0°, 1.5 hr; 65°, 1 hr
23	**17**	II	74–74.5	76	B	0°, 0.5 hr; 25°, 2 hr
24	**17**	III	77–78	90	C	0°, 0.5 hr; 100°, 3 hr
25	**17**		111.5–113	66	B	
26	**10**		52–53	74	C	
27	**10**		194–196	65	D	

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [b] A = Methanol–water; B = alcohol; C = alcohol–water; D = water. [c] Lit.[8] mp 117–118°. [d] Lit.[9] mp 173°. [e] Lit.[10] mp 114.5°.

Related examples are the synthesis of the chloronitrile **26** and the salicylonitrile **27**. The reaction of hydrogen chloride with **10** in DMF yields **26**. Compound **27** is formed by the reaction of hydroxide ion with **10** in moist refluxing DMF. This reaction appears to be catalyzed by fluoride ion.

In conclusion, we have shown the synthetic utility of nucleophilic displacements of nitro groups activated by adjacent cyano functions. The procedure can be utilized for a variety of nucleophiles, including alkoxides, thiol anions, amines, and azide, chloride, and hydroxide ions. The procedure has failed with hindered alkoxides, hindered amines, thiocyanate ion, and ammonia. Electron-withdrawing groups in the 4 or 6 position of the starting *o*-nitrobenzonitrile appear to accelerate the displacement rates, as is evident from the reaction conditions in Table I. Readily available starting materials, coupled with the many known transformations of the nitrile function, make this method attractive for the synthesis of uniquely substituted benzene derivatives.

Experimental Section[11]

Materials. 2-Chloro-6-nitrobenzonitrile was obtained from the Aldrich Chemical Co. 2,6-Dinitrobenzonitrile[1] and α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile[1] were prepared by procedures described in the literature.

General Procedure I. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of methanol was added dropwise a solution containing a 20–50% molar excess (equimolar quantity in the preparation of **14**) of sodium methoxide in 25 ml of methanol. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water, and the product was collected and crystallized from the appropriate solvent (Table I).

General Procedure II. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) and 5–10 ml of methanethiol (excess) in 50 ml of DMF was added dropwise a solution containing 2 g of potassium hydroxide in 10 ml of water. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

General Procedure III. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of DMF was slowly added portionwise a 20% molar excess of sodium azide. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

General Procedure IV. To a cold solution (ice bath) containing 20 mmol of reactant (Table I) in 50 ml of DMF was added dropwise 10 ml of 40% aqueous methylamine solution. The mixture was stirred at the temperature and for the time shown in Table I. It was then poured into ice water and the product was isolated as in procedure I.

6-Nitro-*o*-anisonitrile (3). To a cold solution (ice bath) containing 30 g (0.156 mol) of 2,6-dinitrobenzonitrile in 250 ml of DMF was added dropwise a solution containing 9 g (0.166 mol) of sodium methoxide in 75 ml of methanol. The mixture was stirred in the cold for 0.5 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 23.5 g of product, mp 175–177° (lit.[9] mp 173°).

6-Chloro-*o*-anisonitrile (7). Sodium methoxide (1.8 g, 33 mmol) was added portionwise to a cold solution (ice bath) containing 5.5 g (30 mmol) of 2-chloro-6-nitrobenzonitrile in 60 ml of DMF. The mixture was stirred in the cold for 0.5 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 3.4 g of product, mp 115–116° (lit.[10] mp 114.5°).

2-Dimethylamino-*α*,*α*,*α*-trifluoro-6-nitro-*p*-tolunitrile (17). To a cold solution (ice bath) containing 10.4 g (40 mmol) of *α*,*α*,*α*-trifluoro-2,6-dinitro-*p*-tolunitrile and 5 g (62 mmol) of dimethylamine hydrochloride in 80 ml of DMF was added dropwise a solution containing 6 g of potassium hydroxide in 20 ml of water. The mixture was stirred in the cold for 1.5 hr and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 8.1 g of product, mp 67–69°. An analytical sample, mp 68–69°, was recrystallized from alcohol–water.

2-Ethoxy-*α*,*α*,*α*-trifluoro-6-methoxy-*p*-tolunitrile (19). To a cold solution (ice bath) containing 4.9 g (20 mmol) of 6-nitro-4-trifluoromethyl-*o*-anisonitrile (14) in 60 ml of absolute alcohol was added dropwise a solution containing 2 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 0.5 hr and at room temperature for 2 hr and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 4.5 g of product, mp 61.5–63°.

2,6-Bis(dimethylamino)-*α*,*α*,*α*-trifluoro-*p*-tolunitrile (25). A solution containing 5.2 g (20 mmol) of 2-dimethylamino-*α*,*α*,*α*-trifluoro-6-nitro-*p*-tolunitrile (17), 4.5 g (55 mmol) of dimethylamine hydrochloride, and 7 g of anhydrous potassium carbonate in 50 ml of DMF was heated at steam-bath temperature for 68 hr and then poured into ice water. The crude product was collected and crystallized from alcohol to yield 3.4 g of product, mp 111.5–113°.

2-Chloro-*α*,*α*,*α*-trifluoro-6-nitro-*p*-tolunitrile (26). Hydrogen chloride gas was bubbled into a warm solution containing 15 g (58 mmol) of *α*,*α*,*α*-trifluoro-2,6-dinitro-*p*-tolunitrile in 60 ml of DMF. An exothermic reaction occurred at about 100°, and the solution was heated to reflux for 10 min and then poured into ice water. The solid was collected and crystallized from alcohol–water to yield 9.7 g of product, mp 52–53°.

6-Nitro-4-trifluoromethylsalicylonitrile (27). A solution containing 25 g (96 mmol) of *α*,*α*,*α*-trifluoro-2,6-dinitro-*p*-tolunitrile and 10 g of moist potassium fluoride in 100 ml of DMF was heated to reflux for 1 hr and then poured into ice water. The crude product was collected, but was not washed with water since it appeared to dissolve, and crystallized from water to yield 14.5 of product, mp 194–196°.

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Registry No.—**1**, 35213-00-4; **2**, 16932-49-3; **3**, 38469-85-1; **4**, 51271-32-0; **5**, 51271-33-1; **6**, 6575-07-1; **7**, 6575-10-6; **8**, 51271-34-2; **9**, 51271-35-3; **10**, 35213-02-6; **11**, 51271-36-4; **12**, 51271-37-5; **13**, 51364-43-3; **14**, 51271-38-6; **15**, 51271-39-7; **16**, 51271-40-0; **17**, 51271-41-1; **18**, 51271-42-2; **19**, 51271-43-3; **20**, 51271-44-4; **21**, 51271-45-5; **22**, 51271-46-6; **23**, 51271-47-7; **24**, 51271-48-8; **25**, 51271-49-9; **26**, 51271-50-2; **27**, 51271-51-3.

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(11) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

Synthesis of Several Phenanthridines and a Quinazoline from Ortho-Substituted Arenediazonium Salts and Organic Nitriles[1]

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The thermal decomposition of 2-biphenyldiazonium tetrafluoroborates **3a** (R′ = H) and **3b** (R′ = NO_2) in the presence of representative aliphatic or aromatic nitriles is shown to afford the substituted phenanthridines **4a–g**. Little competition from the Baltz–Schiemann reaction was noted and in only one case was the competitive Meerwein quinazoline-forming reaction observed. The infrared spectrum of all phenanthridines studied exhibited two very strong absorption bands at 720–730 and 750–765 cm^{-1}, probably characteristic of this ring system.

The thermal decomposition of arenediazonium tetrafluoroborate salts (**1**) in the presence of organic nitriles results in the formation of *N*-arenenitrilium tetrafluoroborate salts (**2**). In several cases, it has been possible to isolate these salts and characterize them.[3,4] Infrared studies[5,6] on **2** have shown that *N*-alkyl- and *N*-arylnitrilium ion derivatives exhibit carbon–nitrogen triple bond stretching frequencies between 2300 and 2400 cm,$^{-1}$ while nmr investigations[6] of *N*-alkyl- and *N*-H nitrilium salts also indicate that only the linear nitrilium ions **2a** are present in detectable amounts. The imino carbocation form of the nitrilium ions **2b** can contribute very little to the resonance hybrid. However if the *N*-arylnitrilium ion could react with an adjacent substituent either as **2** or as a true carbocation, with which it might be in equilibrium (the angular form shown in 7), then a new synthetic route to various N heterocycles would become available. We describe here the use of this approach as applied to the synthesis of phenanthridines.

$$\underset{\mathbf{1}}{\mathrm{ArN_2^{+}BF_4^{-}}} \qquad \Big[\underset{\mathbf{2a}}{\mathrm{Ar\overset{+}{N}{\equiv}CR}} \longleftrightarrow \underset{\mathbf{2b}}{\mathrm{ArN{=}\overset{+}{C}R}}\Big]\,\mathrm{BF_4^{-}}$$

Phenanthridines. The thermal decomposition of the 2-biphenyldiazonium tetrafluoroborates **3a** (R′ = H) and **3b** (R′ = NO_2) in anhydrous aliphatic or aromatic nitriles leads to the formation of 6-substituted phenanthridines (**4a–g**). The yield of these phenanthridines was sensitive to both the time and temperature of the reaction. Thus, for example, the addition of **3a** to boiling acetonitrile over a 1-hr period, followed by hydrolysis, gave the 6-methyl derivative **4a** in 20% yield. The formation of **4a** was accompanied by a considerable amount of 2-acetamidobiphenyl (**5**) from hydrolysis of unreacted nitrilium ions. When the reaction time was increased to 12 hr, **4a** was obtained in 86% yield. In this case none of the amide **5** was