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SYNTHESIS OF 3-TRIFLUOROMETHYL-4-HALOBENZONITRILES

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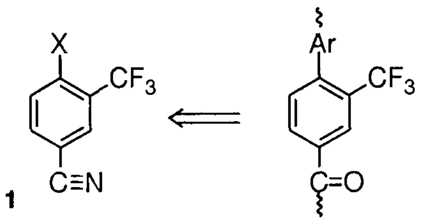
ABSTRACT: The practical synthetic method for a series of substantially novel fluorine-containing polyfunctional aromatic compounds, 3-trifluoromethyl-4-halobenzonitriles [halo = Cl, Br, and F], was established by using copper-cyano complexes as effective Sandmeyer cyanating reagents.

Aromatic compounds having a trifluoromethyl group and two or more functional groups of different chemoselectivities are considered to be potential building blocks for highly designed functional organic molecules. In the course of the synthetic study on highly-performed aromatic ketone molecules such as wholly aromatic polyketones,[1] we planned to use 3-trifluoromethyl-4-chlorobenzonitrile [**1**(X=Cl)] as a starting molecule. In this molecule chlorine is considered to be useful for direct aryl-aryl bond formation via aryl coupling reaction and cyano group for acyl carbon-aryl carbon bonding via electrophilic aromatic substitution reaction as a carbonyl-equivalent group, respectively.



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Contrary to our anticipation, there is only one report on the preparation of this type of compounds (**1**), which has an insufficient experimental description with low yield (30%) for nitrile **1**(X=Cl).[2] Thus we aimed at the general satisfactory synthetic method for substantially novel three homologues of 3-trifluoromethyl-4-halobenzonitriles (**1**) by Sandmeyer nitrile synthesis.

The physical properties of the compounds involved in this synthesis are somewhat troublesome to be handled probably arising from the trifluoromethyl group. In order to attain satisfactory yields of nitriles **1**, both appropriate cyanating reagent and pertinent work-up method were essential.

The choice of the cyanating reagents[3,4] had a critical effect on the yields of the products. For the Sandmeyer cyanation reaction of diazonium ions **3**, cuprous cyanide was scarcely effective. Contrarily, three copper-cyano complexes checked in the present study showed large advantages affording sufficiently high yields of nitriles **1**. Though the difference in effectiveness among these three complexes is not yet well understood, the cupric complex ($K_2[Cu(CN)_4 \cdot NH_3]$) showed rather lower efficiency for production of nitriles **1**. Between two cuprous complexes ($Na_3[Cu(CN)_4]$ and $K_3[Cu(CN)_4]$), distinct difference was not observed. The fluorine compound [**1**(X=F)] was formed with relatively less efficiency than others.

All of nitriles **1** showed easy sublimability, which had completely diminished on standing at room temperature within 1 month. The trifluoromethyl groups should afford such specific properties and this makes it difficult to isolate by extraction. The resulting target molecules (**1**) vaporized with the solvent in evaporation step. So water was more favorable than other reaction media containing organic solvents and direct sublimation of the solid collected by filtration from the reaction mixture was found to be the most effective purification method.

The results were summarized in Table 1.

The yields according to the method we established are enough high for the practical preparation of this series of 4-halo-3-trifluoromethylbenzonitriles (**1**).

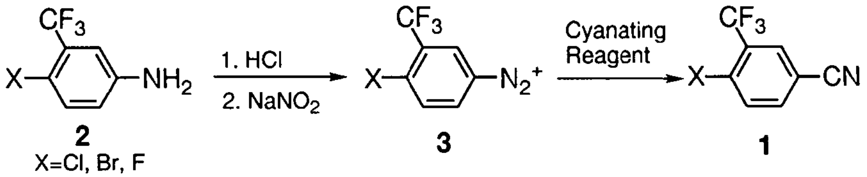

Table 1. Synthesis of 3-Trifluoromethyl-4-halobenzonitriles (**1**)[a)]

Compound	Cynating Reagent[b)]	Yield/%
1(X=Cl)	$Na_3[Cu(CN)_4]$	71
	$K_3[Cu(CN)_4]$	60
	$K_2[Cu(CN)_4 \cdot NH_3]$	55
1(X=Br)	$K_3[Cu(CN)_4]$	74
1(X=F)	$K_3[Cu(CN)_4]$	54

a) Reaction conditions: Temp. 0°C, Time 1 h.
b) The complexes were prepared *in situ*.

It is generally considered that replacement in Sandmeyer reaction proceeds by $S_{RN}1$ mechanism.[5] But, in this reaction, aryl radical should be hardly generated or should be very unstable if formed because of the strongly electron-withdrawing property of the substituents. On the other hand, all cyanating reagents (copper-cyano complexes) take polyhedron structures. Thus we suspect that replacement reactions affording 3-trifluoromethyl-4-halobenzonitriles (**1**) could proceed by mainly S_NAr mechanism.

Experimental

A typical procedure is as follows: To a mixture of haloaniline **2** (1 mmol), water (1.5 mL), 28% hydrochloric acid (1 mL), and crushed ice (0.5 g), $NaNO_2$ (1.25 mmol) in water (1 mL) was gradually added. The solution was neutralized by ice-cooled $NaHCO_3$ aq. and dropped into the solution of the relevant cyanating reagents (1.25 mmol) at 0°C for 0.5 h with vigorous mechanical stirring, and the mixture was kept at 0°C for further 1 h with vigorous mechanical stirring. The solid materials were collected by filtration from the reaction mixture, and the obtained crude product was purified by sublimation. Reaction of 4-fluoro-3-(trifluoromethyl)aniline [**2**(X=F)] was carried out in a closed vessel for its high volatileness. Purification of reagents was performed according to the literature[6] as occasion calls.

Data for 3-Trifluoromethyl-4-chlorobenzonitrile [1(X=Cl)]: Sublimable. Colorless cubic. M.p. 65°C. ^{1}H NMR (500 MHz) δ ($CDCl_3$): 8.01(1 H, d, J = 2 Hz), 7.83(1 H, dd, J = 2 and 8 Hz), and 7.70(1 H, d, J = 8 Hz) ppm. ^{13}C NMR (125 MHz) δ ($CDCl_3$): 162.97, 160.87, 138.12, 138.04, 131.72, 131.70, 131.67, 124.54, 122.37, 120.36, 120.25, 120.20, 120.09, 119.98, 118.67, 118.49, 118.04, 116.53, 109.16, and 109.12 ppm. IR υ (KBr): 2240, 1609, and 1478 cm^{-1}.

Data for 3-Trifluoromethyl-4-bromobenzonitrile [1(X=Br)]: Sublimable. Colorless cubic. M.p. 80-82°C. ^{1}H NMR (500 MHz) δ ($CDCl_3$): 7.97(1 H, d, J = 2 Hz), 7.89(1 H, d, J = 8 Hz), and 7.69(1 H, dd, J = 2 and 8 Hz) ppm. ^{13}C NMR (125 MHz) δ ($CDCl_3$): 136.15, 135.79, 131.99, 131.87, 131.61, 131.50, 131.23, 131.19, 131.14, 131.10, 125.72, 125.04, 122.86, 120.68, 118.50, 116.69, and 111.95 ppm. IR υ (KBr): 2236, 1601, and 1476 cm^{-1}.

Data for 3-Trifluoromethyl-4-fluorobenzonitrile [1(X=F)]: Sublimable. Colorless cubic. M.p. 65-66°C. ^{1}H NMR (500 MHz) δ ($CDCl_3$): 7.97(1 H, dd, J = 1.3 and 6.3 Hz), 7.92(1 H, m), and 7.40(1 H, t, J = 2.5 Hz) ppm. ^{13}C NMR (125 MHz) δ ($CDCl_3$): 162.97, 160.87, 138.12, 138.04, 131.72, 131.70, 131.67, 124.54, 122.37, 120.36, 120.25, 120.20, 120.09, 119.98, 118.67, 118.49, 118.04, 116.53, 109.16, and 109.12 ppm. IR υ (KBr): 2238, 1624, and 1505 cm^{-1}.

Reference and Notes

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