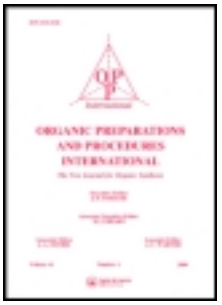

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A FACILE SYNTHESIS OF 3-CHLORO-4-(2′,2′,2′-TRIFLUOROETHOXY)BENZONITRILE

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A FACILE SYNTHESIS OF 3-CHLORO-4-(2',2',2'-TRIFLUOROETHOXY)BENZONITRILE

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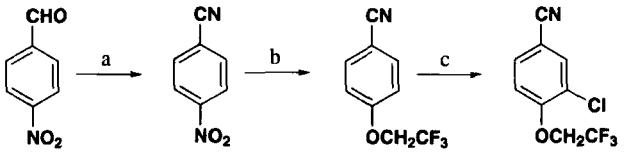
3-Chloro-4-(2',2',2'-trifluoroethoxy)benzonitrile (**4**) is an intermediate of potential use for the preparation of a variety of biologically active insecticides and antibiotics.[1] The reported preparation [2] of **4** involves the reaction of 3,4-dichlorobenzonitrile with sodium 2,2,2-trifluoroethoxide for 18hrs in HMPA at 150° under an atmosphere of nitrogen. We now report a mild, high yield synthesis of **4** from **1** as shown in the equation. *p*-Nitrobenzaldehyde (**1**) readily reacted with hydroxylamine hydrochloride in 85% formic acid to give nitrile **2**. Compound **3** was conveniently obtained by the reaction of **2** with 2,2,2-trifluoroethoxide anion in DMF at room temperature according to the procedure described by Idoux and Gupton.[3] Chlorination of **3** with chlorine (generated *in situ* from the reaction of potassium chlorate with hydrochloric acid) provided **4**.



1 **2** **3** **4**

a) $NH_2OH{\bullet}HCl$, HCOOH b) CF_3CH_2ONa, DMF c) $KClO_3$, HCl, C_2H_5OH

EXPERIMENTAL SECTION

Mps were taken on a digital melting point apparatus manufactured in Shanghai. ^1H NMR spectra were obtained using a Bruker WP-100sy (100 MHz) spectrometer in $(CD_3)_2CO$ containing TMS as the internal standard. Mass spectra were measured on the Hitachi M80 instrument. Microanalyses were determined on an Italian MOD1106 analyzer. Evaporations were carried out on a rotary evaporator *in vacuo*.

4-Nitrobenzonitrile (2).- A solution of 4-nitrobenzaldehyde (**1**, 4.53 g, 0.03 mol) and hydroxylamine hydrochloride (2.70 g, 0.039 mol) in 85% formic acid (30 mL) was refluxed for 15 min and allowed to cool. The mixture was then diluted with ice-water (150 mL), neutralized with 5% sodium hydroxide solution and extracted with ether (2 x 80 mL). The ethereal extract was dried over $MgSO_4$ and concentrated to give pale yellow plates (4.20 g, 94.6%), mp. 146.0-146.9°, lit.[4] mp. 146-148°. This material was used in the next step without further purification.

4-(2',2',2'-trifluoroethoxy)benzonitrile (3).- 2,2,2-Trifluoroethanol (3.75 g, 0.0375 mol) was added dropwise to the suspension of sodium hydride (80%, 1.13 g, 0.0375 mol) in dimethylformamide (40mL, dried over 4Å molecular sieves), and then stirred for 20 min at room temperature. After

adding 4-nitrobenzonitrile (**2**, 3.7 g, 0.025 mol), the mixture was stirred at room temperature for 1 day, and added hydrochloric acid (20%, 90 mL), extracted with ether (3 x 150 mL); the ethereal layer was washed with water (3 x 15 mL), dried over $MgSO_4$ and concentrated to yield pale yellow plates (4.77 g, 95%), mp. 58.0-59.9°. Recrystallization from ethanol-water (3:1, v:v) gave an analytical sample (**3**), mp. 60.6-61.5°, lit.[3] mp. 60-61°.

3-Chloro-4-(2',2',2'-trifluoroethoxy)benzonitrile (4).- A solution of 4-(2',2',2'-trifluoroethoxy)-benzonitrile (**3**, 4.02g, 0.02mol) in ethanol (40 mL) was added into conc. hydrochloric acid (60 mL) and stirred, then a solution of potassium chlorate (1.25 g, 0.01 mol) in water (48 mL) was added dropwise over a period of 2 hrs, the reaction temperature was maintained below 40°. After complete addition, it was stirred for another 2 hrs at room temperature. Upon cooling, the first crop was collected by filtration. Neutralization with dilute sodium hydroxide solution and concentration of the solvent resulted in the isolation of a second crop of product. The two crops were combined and washed with water to give the product (**4**, 4.52g, 96%). Recrystallization from ethanol-water (3:1, v:v) gave 3.92g. (83.3%) of yellow crystals, mp. 74.7-75.3°, lit.[2] mp. 74-75°. ^1H NMR (CD_3COCD_3): δ 4.87 (q, J = 8Hz, 2H), 7.45 (d, J = 8Hz, 1H), 7.75-8.05 (m, 2H). MS(EI): m/z 237, 235$[M]^+$.

Anal. Calcd for $C_9H_5ClF_3NO$: C, 45.88; H, 2.14; N, 5.95. Found: C, 45.86; H, 2.12; N, 5.98

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