Synthesis and characterization of 5-chloro-2-(2′,2′,2′-trifluoroethoxy)-3-tris(2′,2′,2′-trifluoroethoxy)methylpyridine

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(Received January 19, 1993; accepted May 20, 1993)

Abstract

During direct trifluoroethoxylation, both the 2-chloro group and the three fluoro groups of 2,5-dichloro-3-trifluoromethylpyridine were substituted by trifluoroethoxy groups. The product was characterized by mass spectrometry and by IR, ^1H and ^{13}C NMR spectroscopy. A possible reaction mechanism is suggested.

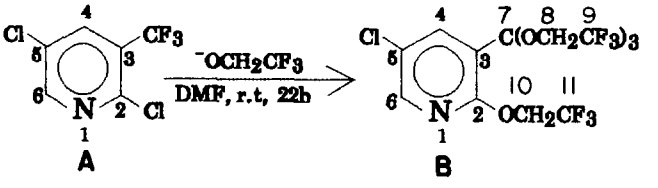
Introduction

In order to isolate organic fluorides with a biological activity in the agricultural area, we are interested in studying synthetic methods for introducing fluorine atoms into aromatic heterocyclic compounds via direct nucleophilic trifluoroalkoxylation. We have previously reported that trifluoroalkoxy anions can replace the chloro group of trifluoromethylpyridine derivatives to form the corresponding fluoroalkyl ethers, and have discussed the role of the trifluoromethyl group, the nitrogen heteroatom, the position of the leaving chloro group and the temperature of the reaction [1]. In this paper, we report the synthesis of 5-chloro-2-(2′,2′,2′-trifluoroethoxy)-3-tris(2′,2′,2′-trifluoroethoxy)methylpyridine from 2,5-dichloro-3-trifluoromethylpyridine.

Results and discussion

To date few reports of the hydrolysis or alcoholysis of a trifluoromethyl group attached to an aromatic heterocyclic ring have been published, with the exception of an example concerning the alkaline and acid hydrolysis of trifluoromethylbenzene derivatives. The following alcoholysis of the trifluoromethyl group attached to a pyridine heterocyclic ring is of considerable interest to us (Scheme 1).

After 22 h at room temperature in the presence of trifluoroethanol and sodium hydride in dimethylformamide, 2,5-dichloro-3-trifluoromethylpyridine (**A**) gave 5-chloro-2-(2′,2′,2′-trifluoroethoxy)-3-tris(trifluoroethoxy)methylpyridine (**B**). The reaction was followed



Scheme 1.

using TLC analysis, while the extent of conversion was established by ^1H NMR spectroscopy and the yield obtained after separation. When the mole ratio of the starting material to the nucleophile was *c.* 1:1, the yield was *c.* 47% at only 5% conversion; when the ratio was *c.* 1:4, the yield was *c.* 57% at 90% conversion. In addition to product **B**, trace amounts of 2-(2′,2′,2′-trifluoroethoxy)-5-chloro-3-trifluoromethylpyridine were also found both by ^1H NMR spectroscopy and TLC methods.

The EI mass spectrum of product **B** showed a molecular ion peak which matched the 2-chloro isotope pattern at 519 (M), 521 (M+2) and 523 (M+4). The ^1H NMR spectrum (Fig. 1) exhibited two $-CH_2-$ quartet peaks at 4.84 ppm (J_{HF} = 8.0 Hz) and 3.96 ppm (J_{HF} = 8.0 Hz) corresponding to the neighbouring trifluoromethyl groups, the integration area ratio of the latter to the former being *c.* 3:1. Since the product should possess two varieties of trifluoroethoxy groups, and since it is known that the chloro group in the 5-position is almost impossible to remove during trifluoroalkoxylation relative to that at the 2-position (especially at room temperature [1]), the only possible product should conform to structure **B** rather than structures **C** and **D**. This viewpoint has been further confirmed by ^{13}C NMR spectroscopy (Fig. 2).

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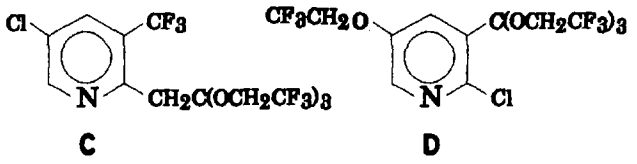
SSDI 0022-1139(93)02940-G



C D

For the starting material **A**, using the broad-band heterodecoupling technique for C–H because of coupling from the fluorine atoms at the trifluoromethyl group, the ^{13}C NMR spectrum (Fig. 3) showed that the carbon at the 4-position gave a quartet at δ 137.1 ppm with a long-range coupling constant $J_{CF}=7.2$ Hz. The carbons at the 3- and 7-positions also exhibited quartet peaks at δ 124.7, 126.1, 127.6, 129.0 ppm with $J_{CF}=36.0$ Hz and at δ 105.9, 116.6, 127.3, 138.0 ppm with $J_{CF}=269.1$ Hz, respectively.

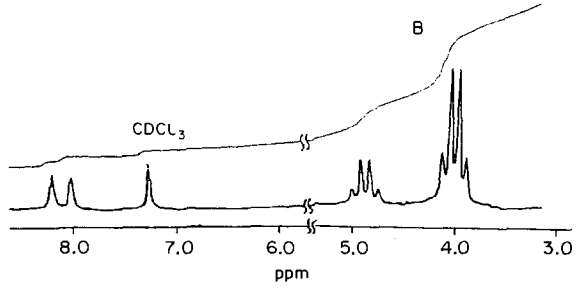


Fig. 1. ^{1}H NMR spectrum of product **B**.

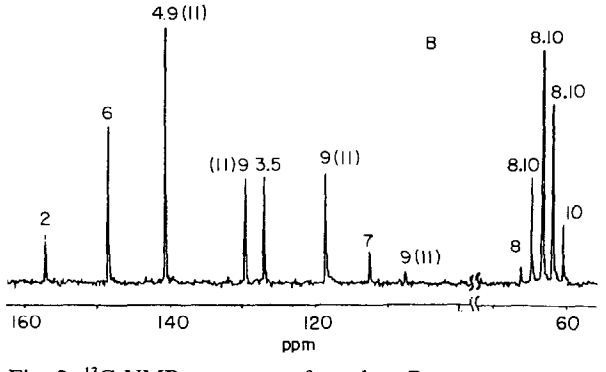


Fig. 2. ^{13}C NMR spectrum of product **B**.

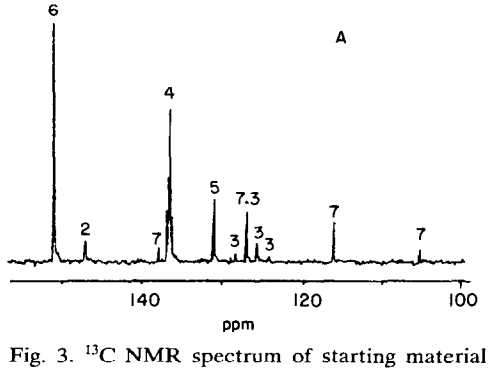


Fig. 3. ^{13}C NMR spectrum of starting material **A**.

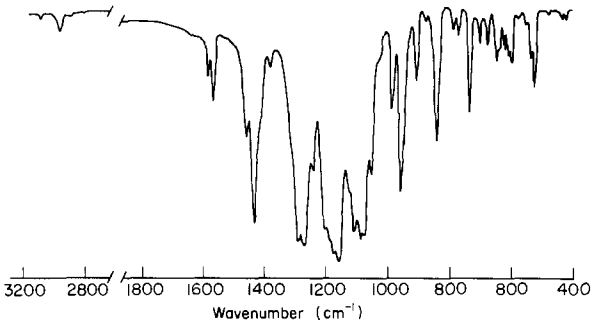
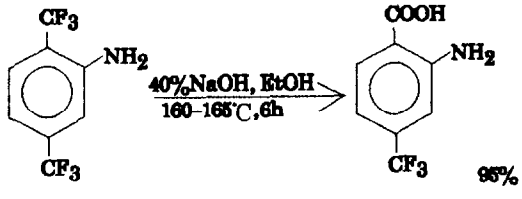


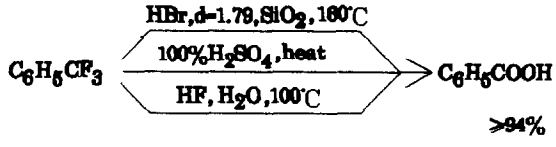
Fig. 4. FT-IR spectrum of product **B**.

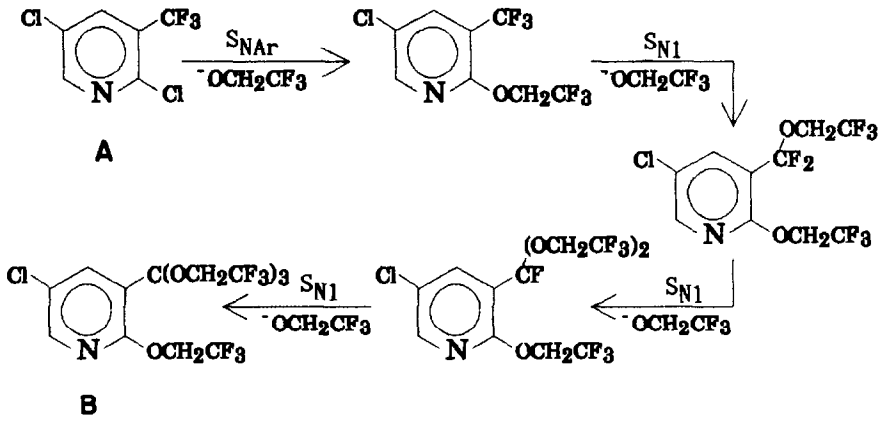
For product **B**, the carbon at the 7-position gave rise to a singlet at δ 112.6 ppm which is almost in the same region as that of $HC(OEt)_3$ at δ 112.9 ppm, the latter data being obtained using the same method with the same NMR spectrometer. The carbons at the 3- and 4-positions also gave rise to singlets at δ 126.6 and 140.6 ppm, respectively, the former being obscured by the peak corresponding to the carbon at the 5-position. The carbons of the four trifluoromethyl groups gave rise to quartet peaks at δ 107.4, 118.6, 129.8 and 140.9 ppm with $J_{CF}=281.5$ Hz.

The IR spectrum for product **B** (Fig. 4) showed several very strong peaks for C–F at 1090–1290 cm^{-1}, peaks for $-CH_2-$ at 2980 and 1440 cm^{-1}, and aromatic ether peaks for C–O at 1075 and 1270 cm^{-1}.

The reaction behaviour towards trifluoroethoxylation of compound **A** is quite different from that of other analogues. Normally the major product formed arises only from leaving chloro groups [1]. It seems that there is some similarity between the trifluoroethoxylation of compound **A** and the hydrolysis of trifluoromethylbenzene derivatives. Thus, it is known that the hydrolysis of a trifluoromethyl group attached to an aromatic nucleus requires quite energetic conditions, its alkaline hydrolysis being assisted by the presence of a very strong electron-donating substituent in the aromatic ring (especially in the *ortho* or *para* positions) whereas its acid hydrolysis occurs more easily [2].



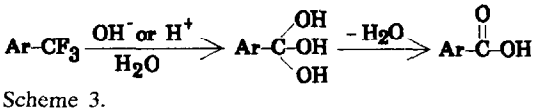




Scheme 2.

Obviously, the synthesis of product **B** suggests an efficient and convenient route for the preparation of some tris-(2',2',2'-trifluoroethoxy)methyl aromatic heterocycles in good yield. The trifluoroethoxy group probably replaces the chloro group at the 2-position via an S_NAr process, followed by S_N1 substitution of the fluorines of the trifluoromethyl group (Scheme 2).

If so, the hydrolysis of the trifluoromethylbenzene derivatives may be understood in terms of the following process (Scheme 3):



Scheme 3.

Experimental

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were measured using a Nicolet FT-IR-20SX instrument. Mass spectra were measured on a Hitachi M80 instrument. ^1H and ^{13}C NMR spectra were obtained using a Bruker WP-100SY (100 MHz) spectrometer with $CDCl_3$ or TMS as the internal standard. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyser run by the Analysis Center of the East China University of Science and Technology. Thin layer chromatography (TLC) employed silicon HF UV254 made in the Fusan factory for biochemical agents, whereas column chromatography was conducted with silica gel (200–300 mesh) made in the Tsing Dao factory for chemical agents. Removal of the solvent was achieved using a rotary evaporator.

Preparation of 5-chloro-2-(2',2',2'-trifluoroethoxy)-3-tris(2',2',2'-trifluoroethoxy)methylpyridine

Sodium hydride (0.45 g of 80%) was placed in 18 ml of dimethylformamide (dried over 4 Å molecular sieves) and 1 ml of 2,2,2-trifluoroethanol (0.014 mol) was added dropwise over 10 min at room temperature. After 20 min, 0.54 g (0.0025 mol) of 2,5-dichloro-3-trifluoromethylpyridine (**A**) was added and reaction mixture stirred for 22 h at room temperature. After addition of 36 ml of 5% hydrochloride, the reaction mixture was extracted with ether (3×30 ml), washed with 3×10 ml of water, dried over magnesium sulfate, and the solvent removed to give a crude oily product. After column chromatography with cyclohexane as eluent, 0.66 g (57% yield at 90% conversion) of a colorless solid was obtained, m.p. 43–45 °C (ether). IR (KBr) (cm^{-1}): 2980; 1585; 1570; 1460; 1440; 1270; 1150; 1075; 985; 970. ^1H NMR δ: 3.96 (q, $J_{HF}=8.0$ Hz, 6H, $8CH_2$); 4.84 (q, $J_{HF}=8.0$ Hz, 2H, $10CH_2$); 8.04 (s, 1H, 4-H); 8.24 (s, 1H, 6-H) ppm. ^{13}C NMR δ: 60.0, 61.4, 62.9, 64.4 (q, $J_{CF}=37.0$ Hz, C-8); 61.4, 62.9, 64.4, 65.9 (q, $J_{CF}=37.0$ Hz, C-10); 107.4, 118.6, 129.8, 140.9 (q, $J_{CF}=281.5$ Hz, C-9 and C-11); 112.6 (s, C-7); 126.6 (s, C-3 and C-5); 140.9 (d, C-4); 148.6 (d, C-6); 157.4 (s, C-2) ppm. MS (EI 70 eV), *m/e* (%): 523 (0.4) [M+4]; 521 (4) [M+2]; 519 (9) [M]; 500 (4) [M−F]; 420 (96) [M−OCH_2CF_3]; 309 (33) [M−OCH_2CF_3, −CH_2CF_3, −CO]; 238 (50) [M−2OCH_2CF_3, −CH_2CF_3]. TLC (cyclohexane): $R_f=0.219$ (0.305 for starting material **A**). Analysis: Calc. for $C_{14}H_{10}O_4F_{12}Cl$ (519.5): C, 32.33; H, 1.92; N, 2.69%. Found: C, 32.22; H, 2.07; N, 2.68%.

Acknowledgements

The starting material was a gift from Ishihara Sanyo Kaisha, Ltd. (Japan). The study was partly supported by the Shanghai Foundation of Natural Science.

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