

Alcoholysis of trifluoromethyl groups attached to the pyridine ring

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Abstract

In dimethylformamide solution, trifluoroethoxylation and methoxylation of 5-chloro-3-trifluoromethylpyridine (**2**) yield 5-chloro-3-tris(trifluoroethoxy)methyl pyridine (**2a**) and a dimethyl ketal of 3-chloronicotinic acid anhydride (**2b**) with fluorines as leaving groups, respectively. The corresponding reactions of 2,3-dichloro-5-trifluoromethylpyridine (**3**) only yield the 2-alkoxy-substituted products **3a** and **3b** with chloro as the leaving group and the 2-dimethylamino product **3c** which was formed by the action of solvent dimethylformamide as a nucleophile. Differences in their reaction behaviour and possible mechanisms are also discussed.

Keywords: Alcoholysis; Trifluoromethyl groups; Pyridine rings; NMR spectroscopy; Mass spectrometry; IR spectroscopy

1. Introduction

Organic fluorides have good and extensive biological activities allowing their possible commercial application in pharmaceuticals and pesticides [1]. We are very interested in both introducing fluorine atoms into aromatic heterocyclic compounds via direct nucleophilic trifluoroalkoxylation [1–5] and in the substitution of fluorine atoms or a group containing fluorine atoms in these compounds [6]. We have reported that trifluoroethoxide can replace the chloro group of mono- or di-chloro-substituted trifluoromethylpyridines to form ethers, and can also directly replace a trifluoromethyl group on the ring in certain cases [3]. In addition, even at room temperature it can displace all the fluorine atoms of the trifluoromethyl group of 2,5-dichloro-3-trifluoromethylpyridine even at room temperature [6] (see Scheme 1).

Nucleophilic displacement reactions of the trihalomethyl groups and the halogen atoms of trichloromethyl- or tribromomethyl-substituted aromatic and heterocyclic compounds by, for example, methoxide and aliphatic amines, have been described [7–11]. However, with trifluoromethyl groups or their fluorine atoms this is much more difficult. The replacement of the whole trifluoromethyl group as the leaving group in the alcoholysis of 2-trifluoromethylquinoline and of 2- and 3-trifluoroindoles has been observed [12], but there are few reports of the hydrolysis or alcoholysis of all the fluorine atoms of a trifluoromethyl group attached to a heteroaromatic ring [13,14], although the alkaline and acid hydrolysis of

trifluoromethylbenzene derivatives to form the corresponding carboxylic acids is well known [15]. We report here on the influence of the positions of the chlorine on the alcoholysis of the trifluoromethyl group of chloro-substituted trifluoromethylpyridines.

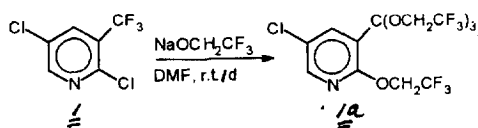
2. Results and discussion

We have compared the reaction behavior of pyridine derivatives with trifluoromethyl groups in the *meta* position and chlorine in the *ortho* or *meta* positions using two kinds of alcohol, i.e. trifluoroethanol or methanol, as the alkoxylation agent.

All reactions were carried out at room temperature for 24 h in the presence of trifluoroethanol or methanol and sodium hydride in dimethylformamide. The reaction was followed using TLC analysis, while the extent of conversion was established by ¹H NMR spectroscopy.

Under the above conditions, trifluoroethoxylation of 3-chloro-5-trifluoromethylpyridine (**2**) gives 3-chloro-5-tris(2',2',2'-trifluoroethoxy)methylpyridine (**2a**) in 15% yield on 40% conversion, similar to that of 2,5-dichloro-3-trifluoromethylpyridine (**1**) [6], although the latter reaction when carried out at room temperature for 4 h proceeded very slowly and almost gave virtually no product as there might be a induced period for the reaction [3]. However, trifluoroethoxylation of compound **2** at reflux temperature for 4 h gave mainly 3-(2',2',2'-trifluoroethoxy)-5-trifluoromethylpyridine (**Q₅**) and trace of 3,5-bis(2',2',2'-trifluoro-

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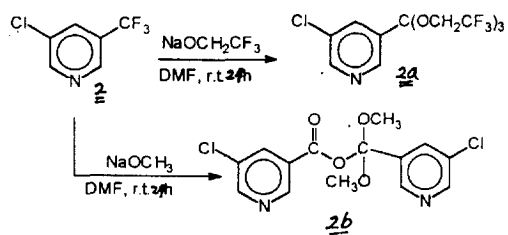
Scheme 1.

ethoxyl)pyridine (Q_{5b}) [3]. This difference in product formation between the two reactions under similar conditions (except reaction temperature and time) may arise because the reaction rate to produce **2a** was faster at room temperature than that for the production of Q_5 and Q_{5b} , whilst at reflux temperature the reverse situation applies. A possible reason for this difference may be that the Arrhenius frequency factor and activation energy for the former reaction are smaller than for the latter reaction (see Scheme 2).

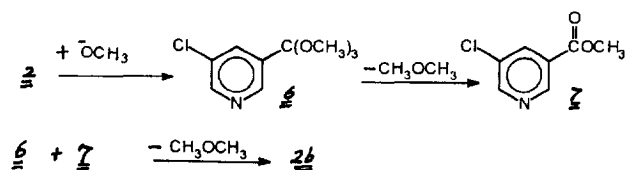
The ^1H NMR spectrum of **2a** exhibited a $-\text{CH}_2-$ quartet at 3.89 ppm ($J_{\text{H,F}} = 8.0$ Hz) corresponding to the tris(trifluoroethoxy) methyl group and peaks at 7.91 and 8.73 ppm for the three heteroaromatic protons. The EI mass spectrum of **2a** showed molecular ion peaks at 421 [M] and 423 [M + 2] which matched the chloro isotope pattern.

The trifluoromethyl group is often considered to be chemically inert with the high carbon–fluorine bond energy making the fluorine substituent a bad leaving group in nucleophilic substitution reactions and resistant to many metabolic transformations. However, the reactions depicted in Schemes 1 and 2 clearly indicate that under attack by the trifluoroethoxide anion, the trifluoromethylpyridine derivatives may undergo nucleophilic substitution with the fluorine anion as a leaving group with the subsequent reaction adding further support to this viewpoint. These results are different from other reports in which the trifluoromethyl groups attached to carbon atoms possessing acidic hydrogen, or in certain positions in heterocyclic systems [13,14,16,17], e.g. the trifluoromethyl group in 5-amino-4-trifluoromethyl-oxazoles and 2-trifluoromethylimidazole, undergo facile base-induced hydrolysis in addition–elimination steps with fluorine as a superior leaving group.

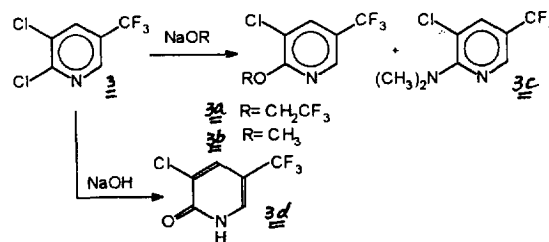
Methoxylation of **2** gives a fluorine-free product. On the basis of the spectral data, we have assigned the structure as a dimethyl ketal of 3-chloronicotinic acid anhydride (30% yield on 60% conversion). The ^1H NMR spectrum of **2b** showed three peaks with equal integration area at 8.27, 8.74 and 9.09 ppm corresponding to two *meta* disubstituted pyridine rings, and a peak at 3.96 (s) ppm corresponding to two magnetically equivalent methoxy groups. The IR spectrum of **2b** showed peaks at 1730, 1580 and 2920 cm^{-1} for $\text{C}=\text{O}$,



Scheme 2.



Scheme 3.



Scheme 4.

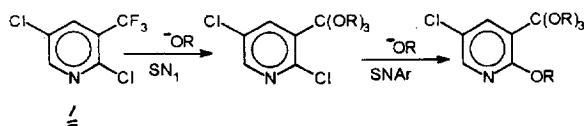
$\text{C}=\text{N}$ and CH_3 , respectively. The EI mass spectrum of **2b** exhibited molecular peaks at 342 [M] and 344 [m + 2], and fragment peaks at 311 [M – OCH_3], 313 [M + 2 – OCH_3] and 315 [M + 4 – OCH_3] corresponding to a two chloro isotope pattern.

We assume that during methoxylation, 3-chloro-5-trifluoromethylpyridine (**2**) was first underwent alcoholysis to give the trimethoxymethyl compound **6**, followed by nicotinic acid methyl ester (**7**) and compound **2b** as shown in Scheme 3.

However, trifluoroethoxylation or methoxylation of 2,3-dichloro-5-trifluoromethylpyridine (**3**) gives only 2-alkoxy-substituted compounds **3a** or **3b** and the 2-dimethylamino compound **3c** which was formed by reaction with solvent dimethylformamide acting as a nucleophile. In the trifluoroethoxylation process the ratio of product **3a** to **3c** was ca. 32:68, whereas in the methoxylation process the ratio of **3b** to **3c** was ca. 70:30. The difference indicates that the nucleophilic activity of trifluoroethoxide is much less than that of methoxide. No trialkoxymethylpyridines were found during the reactions (see Scheme 4).

When the methoxide ion attacks an unsubstituted 2- or 6-position in a 3-trichloromethylpyridine, a hydrogen shift leads to a methoxy-substituted 3-dichloromethylpyridine; further reaction of the dichloromethyl group with methoxide gives the corresponding acetals or aldehyde [10]. However, during trifluoroethoxylation or methoxylation of **2**, **3** and **1**, at room temperature no compounds of this type were found. Also, no product was found in which the trifluoromethyl group was directly substituted by the nucleophile.

In the alcoholysis of **2** and **1**, all the fluorine atoms of the trifluoromethyl group at the *meta* position of the pyridine ring were substituted by nucleophiles. In addition, it was found the 2-chloro group of compound **3** is more readily substituted than the fluorine atoms of the trifluoromethyl group. For example, compound **3d** is formed with aqueous sodium hydroxide. However, a similar product was not found for compound **1**. Alcoholysis of **3** did not afford the trialkoxymethylpyridine as expected, a possible reason being that alcoholysis of the *o*-chloro group took place first, with the



Scheme 5.

resulting alkoxy group which possesses strong electronic donating activity inhibiting the loss of the fluorine atoms of the trifluoromethyl group at the *meta* position. Hence, the mechanism for the alkoxylation of **1**, which we proposed previously [6], should be modified as shown in Scheme 5.

We have reported that in the trifluoroethoxylation of chloro-substituted pyridines with a trifluoromethyl group at the *ortho* or *para* position, viz. 2,6-dichloro-4-trifluoromethylpyridine (**4**), 2-chloro-4-trifluoromethylpyridine (**5**) and 2-chloro-6-trifluoromethylpyridine (**6**), the major products arose from the loss of chlorine. Compound **5** also yielded a minor product of 2,4-bis(trifluoroethoxy)pyridine (Q_{36}) with the loss of both chlorine and the trifluoromethyl group (5%); a similar minor product also arose from **4**. However, no product was found in which the fluorine atoms of the trifluoromethyl group were substituted [3]. Similar results have been obtained in the methoxylation of **4**, **5**, **6** and other pyridines with a trifluoromethyl group in positions *ortho* or *para* position are too stable to undergo alcoholysis because of the influence of the N heteroatom whose effects are similar to that of a nitro group. A trifluoromethyl group at the *para* position with a low electronic density can be directly substituted. However, a trifluoromethyl group in a *meta* position on the pyridine ring with a high electronic density is not directly substituted by alkoxide and formation of a trialkoxymethyl group becomes possible.

3. Experimental details

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were measured using a Nicolet 20 SX FT-IR 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 undertaken with an Italian MOD.1106 analyser at the Analysis Center of the East China University of Science and Technology. TLC analyses 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.

3.1. Preparation of 3-chloro-5-[tris(2',2',2'-trifluoroethoxy)methyl]pyridine (**2a**)

Sodium hydride (0.31 g of the 80% reagent) was placed in 8 ml of dimethylformamide (dried over 4 Å molecular

sieves) and 0.7 ml of 2,2,2-trifluoroethanol was added dropwise over 10 min at room temperature. After 20 min, 0.28 g of 3-chloro-5-trifluoromethylpyridine (**2**) was added and the reaction mixture stirred for 24 h at room temperature. After cautious addition of 20 ml of 10% hydrochloric acid, the reaction mixture was extracted with ether (4×25 ml), washed with 3×10 ml of water, dried over magnesium sulfate and the solvent removed to give the crude product. After thin layer chromatography with methylene chloride/cyclohexane (2:5 v/v) as eluent, 0.039 g (15% yield at 40% conversion) of a colorless solid was obtained, m.p. 82.7–83 °C. IR (KBr) (cm^{-1}): 3010; 2900; 1585; 1430; 1290; 1190; 1100; 1015; 960. ^1H NMR δ : 3.89 (q, $J_{\text{H,F}} = 8.0$ Hz, 6H, 1'- CH_2); 7.91 (s, 1H, 4-H); 8.73 (s, 2H, 2- and 6-H) ppm. MS (EI 70 eV) m/e (%): 423 (0.6) [$\text{M}+2$]; 421 (1.8) [M]; 322 (100) [$\text{M}-\text{OCH}_2\text{CF}_3$]; 309 (41) [$\text{M}-\text{C}_5\text{H}_3\text{NCl}$]; 240 (17) [$\text{M}-\text{OCH}_2\text{CF}_3, -\text{CHCF}_3$]; 220 (9) [$\text{M}-\text{OCH}_2\text{CF}_3, -\text{CH}_2\text{CF}_3$]; 140 (30) [$\text{M}-\text{OCH}_2\text{CF}_3, -\text{CF}_3\text{CH}_2\text{OCH}_2\text{CF}_3$]; 112 (16) [$\text{M}-\text{C}(\text{OCH}_2\text{CF}_3)_3$]. TLC (methylene chloride/cyclohexane = 2:5 v/v): $R_f = 0.40$ (0.56 for starting material **2**). Analysis: Calc. for $\text{C}_{12}\text{H}_9\text{F}_9\text{ClNO}_3$ (421.65): C, 34.18; H, 2.15; N, 3.32%. Found: C, 34.63; H, 2.14; N, 3.23%.

3.2. Preparation of the dimethyl ketal of 3-chloronicotinic acid anhydride (**2b**)

Sodium hydride (0.17 g of the 80% reagent) was placed in 5 ml of dimethylformamide and 0.26 ml of methanol was added over 10 min at room temperature. The following step was similar to that described in the above procedure. After cautious addition of dilute hydrochloric acid, 0.092 g of a colorless solid was obtained after filtration and washing with water (28% yield on 60% conversion), m.p. 84.5–86.0 °C. IR (KBr) (cm^{-1}): 3050; 2930; 2850; 1725; 1580; 1450; 1420; 1320; 1280; 1200. ^1H NMR δ : 3.96 (s, 6H, OCH_3); 8.27 (s, 2H, 4- and 4'-H); 8.74 (s, 2H, 2- and 2'-H); 9.09 (s, 2H, 6- and 6'-H) ppm. MS (EI 70 eV) m/e (%): 344 (4) [$\text{M}+2$]; 342 (6) [M]; 315 (24), 313 (78), 311 (27) [$\text{M}+4, \text{M}+2, \text{M}-\text{OCH}_3$]; 291 (18) [$\text{M}-\text{CH}_3, -\text{HCl}$]; 189 (36), 187 (100) [$\text{M}+2, \text{M}+\text{C}_5\text{H}_3\text{NClCOO}$]; 140 (68) [$\text{M}-\text{C}_5\text{H}_3\text{NClC}(\text{OCH}_3)_2$]; 112 (38) [$\text{M}-\text{C}_5\text{H}_3\text{NCl}(\text{OCH}_3)_2, -\text{CO}$]. TLC (methylene chloride): $R_f = 0.53$ (0.73 for starting material **2**). Analysis: Calc. for $\text{C}_{14}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_4$ (343.17): C, 49.00; H, 3.52; N, 8.16%. Found: C, 48.78; H, 3.67; N, 8.02%.

3.3. Preparation of 2-(2',2',2'-trifluoroethoxy)-3-chloro-5-trifluoromethylpyridine (**3a**) and 2-dimethylamino-3-chloro-5-trifluoromethylpyridine (**3c**)

The procedure was similar to the synthesis of **2a**. The amounts of reagents used were as follows: sodium hydride (0.23 g of the 80% reagent), dimethylformamide (5 ml), trifluoroethanol (0.5 ml) and 2,3-dichloro-5-trifluoromethylpyridine (**3**) (0.22 g). The proportion of **3a** and **3c** in

the reaction mixture was 32:68. After separation using TLC with cyclohexane/methylene chloride (4:1, v/v) as eluent, 0.045 g of **3a** as a yellow liquid and 0.075 g of **3c** colorless liquid were obtained in 47% and 44% yield, respectively.

Compound **3a**: IR (KBr) (cm^{-1}): 2980; 1620; 1580; 1450; 1335; 1290; 1260; 1175; 1145; 1090. MS (EI 70 eV) m/e (%): 281 (32) [M+2]; 279 (100) [M]; 262 (15) [M+2-F]; 260 (46) [M-F]; 212 (28) [M+2-CF₃]; 210 (84) [M-CF₃]; 180 (47) [M-OCH₂CF₃]. TLC (cyclohexane/methylene chloride=4:1 v/v): R_f =0.58 (0.52 for starting material **3**). Analysis: Calc. for C₈H₄F₆ClNO (279.57): C, 34.37; H, 1.44; N, 5.01%. Found: C, 34.53; H, 1.66; N, 4.97%.

Compound **3c**: IR (KBr) (cm^{-1}): 2970; 1610; 1520; 1415; 1330; 1265; 1200; 1130; 1100; 1050. ¹H NMR δ : 3.13 (s, 6H, 2-NCH₃); 7.69 (d, $J=1.0$ Hz, 1H, 4-H); 8.33 (d, $J=1.0$ Hz, 1H, 6-H) ppm. TLC (cyclohexane/methylene chloride=4:1 v/v): R_f =0.33. Analysis: Calc. for C₈H₈F₃ClN₂ (224.61): C, 42.78; H, 3.59; N, 12.47%. Found: C, 43.01; H, 3.75; N, 12.52%.

3.4. Preparation of 2-methoxy-3-chloro-5-trifluoromethylpyridine (**3b**)

The procedure was similar to the synthesis of **2a** and the amounts of reagents used were as follows: sodium hydride (0.18 g of the 80% reagent), dimethylformamide (5 ml), **3** (0.22 g) and methanol (0.28 ml) rather than trifluoroethanol. After separation with TLC, 0.150 g (60% yield) of a colorless oily liquid **3b** was obtained. MS (EI 70 eV) m/e (%): 213 (32) [M+2]; 211 (94) [M]; 183 (39), 181 (100) [M+2, M-OCH₃]; 145 (66) [M-OCH₃, -HCl]; 69 (46) [CF₃]. TLC (cyclohexane/methylene chloride=4:1 v/v): R_f =0.57. Analysis: Calc. for C₇H₅F₃ClNO (211.57): C, 39.74; H, 2.38; N, 6.62%. Found: C, 40.11; H, 2.47; N, 6.91%.

3.5. Preparation of 3-chloro-5-trifluoromethylpyridine-2-one (**3d**)

Sodium hydroxide (0.24 g) in water (5 ml) mixed with **3** (0.22 g) was stirred for 24 h at room temperature. After extraction with ether (4×25 ml), washing with water

(2×15 ml), drying over MgSO₄ and removal of solvent, a colorless solid (0.140 g, 60% yield) was obtained, m.p. 160.8–161.5°C. IR (KBr) (cm^{-1}): 3160; 2980; 1700; 1640; 1615; 1445; 1415; 1350; 1300; 1230; 1160. MS (EI 70 eV) m/e (%): 198 (33) [M+2]; 196 (100) [M]; 169 (58) [M-CO]; 150 (23) [M-CO, -F]; 134 (12) [M-CO, -Cl]; 114 (8) [M-CO, -F, -HCl]. TLC (ether): R_f =0.58. Analysis: Calc. for C₆H₂ClF₃NO (196.54): C, 36.67; H, 1.52; N, 7.13; F, 29.00%. Found: C, 36.94; H, 1.71; N, 6.98; F, 28.68%.

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