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Convenient preparation of 1-(indol-3-yl)-2,2,2-trifluoroethylamines via Friedel–Crafts reaction of α-trifluoroacetaldehyde hemiaminal

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Abstract

Electrophilic substitution of indole with trifluoroacetaldehyde hemiaminals **1a–f**, prepared from primary amines and trifluoroacetaldehyde ethyl hemiacetal (TFAE), proceeds readily in the presence of Lewis acids. Formation of *N*-alkyl 1-(indol-3-yl)-2,2,2-trifluoroethylamines (**2**) is preferred in the presence of BF_3, but yield of 2,2,2-trifluoroethyl alcohol (**3**) markedly increases when ZnI_2 is used. A stereochemistry study clearly showed that ethylamines **2e** and **2f** are produced with high diastereoselective excess when the optically active hemiaminals **1e** and **1f** are used.

Keywords: α-Trifluoromethyl hemiaminal; Friedel–Crafts reaction; Indole; α-Trifluoromethyl amine

1. Introduction

Much attention has been devoted to the preparation of new trifluoromethylated compounds because of their potential important applications in the pharmaceutical, agrochemical and material sciences. Many methods and reagents, e.g. CF_3SiMe_3, the hemiacetal and other derivatives of trifluoroacetaldehyde [1–3], have been developed over past decades for the preparation of α-trifluoromethyl carbinols. In contrast, little has been reported on the synthesis of α-trifluoromethyl amines [4–6].

We found that the reaction of electron-rich heteroarenes with trifluoroacetaldehyde ethyl hemiacetal (TFAE) is an efficient way to prepare 1-heteroaryl-2,2,2-trifluoroethyl alcohols [7]. Recently, we have turned to the synthesis of α-trifluoromethyl amines and investigated the possibility of obtaining 1-heteroaryl-2,2,2-trifluoroethyl amines via the Mannich-like reaction done with indole, isopropylamine and TFAE. Here, we report a convenient way of preparing 1-(indol-3-yl)-2,2,2-trifluoroethyl amines by the Friedel–Crafts reaction of indole with trifluoroacetaldehyde hemiaminals.

2. Results and discussion

The general procedure of Mannich reaction was alternatively used to avoid the direct reaction between indole and TFAE. The reaction of isopropylamine with TFAE was first done at room temperature for 4 h, *N*-isopropyl hemiaminal (**1b**) being formed in good yield as shown by ^1H and ^{19}F NMR. This means the following equilibrium (1) lies markedly to the right.

An equivalent amount of indole dissolved in glacial acetic acid was added to this solution, and the mixture heated at 60–70°C for 6 h. Final product analysis clearly showed that the reaction only afforded about 20% of the α-trifluoromethyl amine (**2b**) and considerable amounts of other compounds characterized as the α-trifluoromethyl alcohol (**3**) and its condensation products [8]. We, therefore, looked for conditions more appropriate to the preparation of compound **2b** by purifying hemiaminal **1b** and by choosing an efficient agent which would catalyze the substitution reaction at a lower temperature.

The attempt to separate the hemiaminal **1b** from the ethanol by fractional distillation failed because of its facile decomposition above 70°C. Fortunately, ethanol could be easily removed by evaporation under reduced pressure at room temperature. By this means, a variety of *N*-alkyl hemiaminals **1a–f** have been prepared in excellent yields. This method appears to be more convenient than that using gaseous trifluoroacetaldehyde [9].

The reactions of three *N*-alkyl hemiaminals, **1a–c,** with indole were done with one of the two typical Lewis acids, BF_3Et_2O or ZnI_2, as the catalyst. In the presence of $BF_3{\cdot}Et_2O$, the reaction went smoothly at 10°C and was completed in 1 h. The *N*-alkyl α-trifluoromethyl amines **2a–c** were formed in moderate and excellent yields. In

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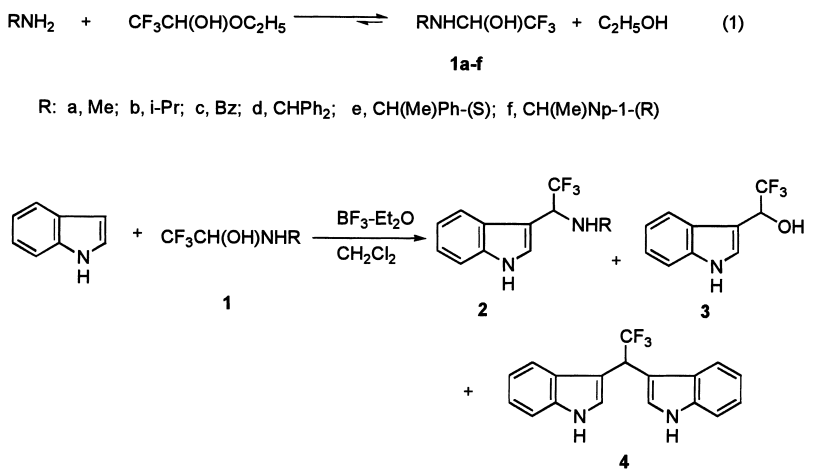


Scheme 1.

addition, α-trifluoromethyl alcohol **3** and bisindole alkane **4** [8] were also generated (Scheme 1). The product distribution was easily determined according to the distinguishable chemical shifts (δ **2a**: 87.86, **3**: 83.99, **4**: 93.79) of their fluorine atoms. Details are given in Table 1 (runs 1–6).

In contrast, the yield of α-trifluoromethyl alcohol (**3**) increased markedly when ZnI_2 was used instead of $BF_3{\cdot}Et_2O$. This means that cleavage of the C–O bond of the *N*-alkyl hemiaminal (path a) was promoted preferably by BF_3, whereas that of the C–N bond (path b) was obviously favored in the presence of ZnI_2 (Scheme 2). A reasonable explanation for the great different behavior can be deduced from the HSAB theory.

We then attempted to prepare 1-(indol-3-yl)-2,2,2-trifluoroethylamines (**5**). As reported in the literature, removal of the *N*-diphenylmethyl group from the amines can be achieved by reflux in aqueous hydrochloric acid [10,11]. Thus, a high yield of *N*-diphenylmethyl α-trifluoromethyl amine (**2d**) was prepared using *N*-diphenylmethyl hemiaminal (**1d**) (run 7). Unfortunately, no detectable amount of the target amine **5** was formed, however, when subsequent hydrolysis of **2d** was done in 6N aqueous hydrochloric acid. For this reason, we tried to prepare the compound **5** using an amine such as trimethylsilyl amine, because trimethylsilyl group is easily removed in acidic aqueous media. In practice, 1,1,1,3,3,3-hexamethyldisilazane, a commercially available reagent, has been used for this purpose.

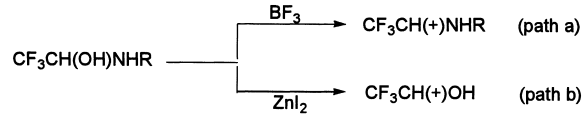
The reaction of 1,1,1,3,3,3-hexamethyldisilazane with TFAE was done at 50°C. ^{1}H, ^{19}F NMR and GC/MS analyses clearly showed that only little amount of *N*,*N*-bis(trimethylsilyl) hemiaminal was generated, and three main components were assigned to be compounds **6–8** as illustrated in Scheme 3. The mixture was used without further isolation to react with equivalent amounts of indole in the presence of BF_3 at 10°C. Product analysis showed that **5** was afforded in 62%, and **4** in 12% yields.

The stereochemistry of the substitution reaction was also investigated. Two commonly used optically active amines, (*S*)-(−)-1-phenylethylamine [12] and (*R*)-(+)-1-(1-naphthyl)ethylamine, reacted with TFAE, yielding the corresponding optically active *N*-(1-aryl)ethyl hemiaminals **1e** and **1f** almost quantitatively. The reaction with indole took place at 10°C. High yields of the α-trifluoromethyl amines **2e** and **2f** were isolated by silica-gel column chromatography. The diastereomer ratio (runs 8 and 9) was determined by HPLC and ^{19}F NMR. The high diastereomeric excess clearly showed that asymmetric substitution really did occur when a chiral auxiliary was introduced into the *N*-alkyl hemiaminals. The steric effect may be the main factor because the de value for the bulkier 1-naphthyl derivative is higher than that of the phenyl derivative.

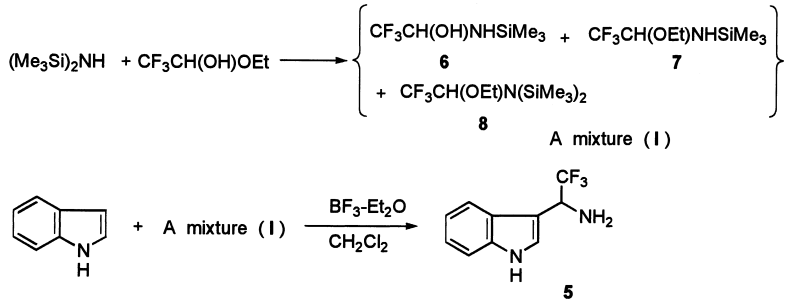
Table 1
Reaction of the hemiaminal **1a–c** with indole at 10°C

Run	Hemiaminal	Lewis acid	Yields of **2** (%)[a]	**2/3/4**[b]
1	**1a**	BF_3	**2a**: 56.1 (46)[c]	63.0/4.4/32.6
2	**1a**	ZnI_2	**2a**: 55.5	61.1/37.7/1.2
3	**1b**	BF_3	**2b**: 83.0 (78)[c]	90.3/5.1/4.6
4	**1b**	ZnI_2	**2b**: 0.6	0.6/75.3/24.0
5	**1c**	BF_3	**2c**: 88.5 (82)[c]	96.2/1.3/2.5
6	**1c**	ZnI_2	**2c**: 18.1	19.7/62.1/18.1
7	**1d**	BF_3	**2d**: (67)[c]	
8	**1e**	BF_3	**2e**: (76)[c]	88.8 (de)[d]
9	**1f**	BF_3	**2f**: (82)[c]	99.0 (de)[d]

[a] Determined by HPLC.
[b] Determined by ^{19}F NMR.
[c] Isolated yield in parentheses.
[d] Determined by ^{19}F NMR, and confirmed by HPLC.



Scheme 2.



Scheme 3.

In conclusion, the *N*-alkyl hemiaminals of trifluoroacetaldehyde can be conveniently prepared from primary amines and trifluoroacetaldehyde ethyl hemiacetal. Moreover, the reaction with electron-rich heteroarenes is an efficient way to prepare 1-heteroaryl-2,2,2-trifluoroethylamine in the presence of BF_3.

3. Experimental details

3.1. General

^{1}H NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard at 90 MHz on a Hitachi R-90H FT spectrometer. ^{19}F NMR spectra were recorded with hexafluorobenzene as an internal standard at 84.7 MHz on the same spectrometer. Mass spectra (70 eV) were measured on a Hitachi M-80 instrument. High-resolution mass spectra were measured on a JEOL JMS-SX102A MS spectrometer.

3.2. Preparation of N-alkyl hemiaminal of trifluoroacetaldehyde *1a–f*

In a typical procedure, 2.95 g (50 mmol) of isopropylamine was added dropwise to 7.20 g (50 mmol) of TFAE over 30 min with continuous stirring at 5–10°C. After being stirred for 4 more hours, the mixture was evaporated below 25°C under reduced pressure until most of the ethanol evolved had been removed. The residue was dried in a vacuum desiccator, giving 7.70 g (98%) of *N*-isopropyl hemiaminal (**1b**) as white crystals. **1b**: ^{1}H NMR ($CDCl_3$) δ 4.65 (1H, q, $J = 6.4$ Hz), 3.22, 3.16 (1H, q, $J = 5.5$ Hz), 2.17 (2H, s, w), 1.14, 1.08 (6H, d, $J = 5.5$ Hz). ^{19}F NMR ($CDCl_3$) 79.42 (3F, d, $J = 6.4$ Hz). MS *m/e* 157 (M^+, 12.4), 142 (100.0), 124 (89.5), 88 (56.9), 60 (58.6). HRMS calcd: 157.0715, found: 157.0715.

Other hemiaminals **1c–f** was obtained according to the same procedure. **1a** was prepared by bubbling methylamine into TFAE at room temperature. **1a**, **1b** and **1e** are white crystals, but decompose over 40°C. **1c**, **1d** and **1f** are colorless liquid. **1a**: ^{1}H NMR ($CDCl_3$) δ 4.51 (1H, q, $J = 4.6$ Hz), 2.57 (3H, s), 2.50 (2H, br). ^{19}F NMR ($CDCl_3$) 79.86 (3F, d, $J = 4.6$ Hz).

3.3. Reactions of *1a–f* with indole in the presence of boron trifluoride

A solution of *N*-methyl hemiaminal (**1a**) (3.0 mmol, 0.39 g) and indole (3.0 mmol, 0.35 g) in dichloromethane (10 ml) was cooled to 0–5°C by an ice bath. To this solution, boron trifluoride diethyl ether complex (3.0 mmol, 0.43 g) was added with vigorous stirring. The mixture was then stirred for 1 h at about 10°C. To the reaction mixture, 10 ml of distilled water was added. The mixture was then neutralized (pH 8–9) with aqueous sodium bicarbonate, extracted with ethyl acetate three times. The organic layer, dried over sodium sulfate, was evaporated under reduced pressure. The residue was analyzed by ^{1}H and ^{19}F NMR, and purified (eluted with 5:1 to 2:1 hexane/ethyl acetate) by silica-gel column chromatography to give 0.32 g (46%) of *N*-methyl 1-(indol-3-yl)-2,2,2-trifluoroethyl amine (**2a**).

The corresponding reactions of **1b–f** with indole were performed in the same way. The spectroscopic data for the compounds **2a–f** are given below.

2a: A white needle, mp 102–103°C. ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, br), 7.70 (1H, m), 7.15–7.44 (4H, m), 4.39 (1H, q, $J = 7.7$ Hz), 2.50 (3H, s), 1.78 (1H, s, br). ^{19}F NMR ($CDCl_3$) 87.90 (3F, d, $J = 7.7$ Hz). MS *m/e* 228 (M^+, 39.8), 198 (18.9), 159 (100.0), 117 (33.6). HRMS calcd: 228.0874, found: 228.0870.

2b: A white solid, 73–74°C. ^{1}H NMR ($CDCl_3$) δ 8.26 (1H, m), 7.72 (1H, m), 7.18–7.44 (4H, m), 4.55 (1H, q, $J = 6.4$ Hz), 2.91 (1H, m, $J = 6.3$ Hz), 1.55 (1H, s), 1.06 (6H, d, $J = 6.3$ Hz). ^{19}F NMR ($CDCl_3$) 87.55 (3F, d, $J = 6.4$ Hz). MS *m/e* 256 (M^+, 39.6), 198 (38.3), 187 (100.0), 145 (72.3), 60 (76.6). HRMS calcd: 256.1187, found: 256.1175.

2c: A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, br), 7.10–7.70 (5H, m), 7.28 (5H, s), 4.42 (1H, q, $J = 7.7$ Hz), 3.83, 3.73 (2H, s), 1.76 (1H, s, br). ^{19}F NMR ($CDCl_3$) 87.79 (3F, d, $J = 7.7$ Hz). MS *m/e* 304 (M^+, 35.6), 235 (100.0), 198 (6.6), 117 (33.6), 91 (96.2). HRMS calcd: 304.1187, found: 304.1177.

2d: A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, br), 7.10–7.69 (15H, m), 4.88, 4.80 (1H, s), 4.40 (1H, q, $J = 7.7$ Hz), 1.53 (1H, br). ^{19}F NMR ($CDCl_3$) 88.21 (3F, d, $J = 7.7$ Hz). MS *m/e* 380 (M^+, 4.9), 311 (19.6), 263

(28.3), 182 (100.0), 198 (6.6), 167 (93.8). HRMS calcd: 380.1500, found: 380.1497.

2e: A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 8.20 (1H, br), 7.13–7.65 (5H, m), 7.28 (5H, s), 4.20 (1H, q, $J = 7.7$ Hz), 3.71 (1H, q, $J = 6.8$ Hz), 1.92 (1H, br), 1.31 (3H, d, $J = 6.8$ Hz). ^{19}F NMR ($CDCl_3$) 87.64 (3F, d, $J =$ 7.7 Hz). MS *m/e* 318 (M^+, 31.3), 249 (68.2), 198 (43.6), 145 (46.5), 117 (100.0), 106 (76.3). HRMS calcd: 318.1344, found: 318.1343.

2f: A white needle, mp 116–117°C. ^{1}H NMR ($CDCl_3$) δ 6.88–8.10 (13H, m), 4.58 (1H, q, $J = 6.4$ Hz), 4.26 (1H, q, $J = 6.4$ Hz), 2.03 (1H, s, w), 1.40 (3H, d, $J = 6.4$ Hz). ^{19}F NMR ($CDCl_3$) 88.30 (3F, d, $J = 6.4$ Hz). MS *m/e* 368 (M^+, 50.3), 299 (36.2), 198 (39.6), 170 (68.9), 156 (100.0). HRMS calcd: 368.1500, found: 368.1500.

*3.4. Reactions of hemiaminal **1a–c** with indole in the presence of zinc iodide*

A mixture of indole (0.35 g, 3.0 mmol), *N*-methyl hemiaminal (**1a**) (0.39 g, 3.0 mmol), zinc iodide (0.48 g, 1.5 mmol) and dichloromethane (10 ml) was stirred for 24 h at room temperature. The mixture was transferred into a separating funnel, and the flask was washed with ethyl acetate (20 ml). The combined organic layer was washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate. After removing the solvents under reduced pressure, the residue was analyzed by ^{1}H and ^{19}F NMR.

*3.5. Preparation of 1-(indol-3-yl)-2,2,2-trifluoroethyl amine (**5**)*

Trifluoroacetaldehyde ethyl hemiacetal (10.0 mmol, 1.44 g) was mixed with 1,1,1,3,3,3-hexamethyldisilazane (10.0 mmol, 1.61 g) at 0–5°C. The mixture was heated and stirred at 50°C for 2 h. After cooled, a solution of indole (10.0 mmol, 1.17 g) in dichloromethane (20 ml) was added into the mixture. Into the solution, chilled by an ice bath to 0–5°C, boron trifluoride diethyl ether complex (10.0 mmol, 1.42 g) was dropped slowly to keep the reaction temperature. The mixture was continued to stir for 2 h at 10°C. The mixture was then poured into 20 ml of distilled water and stirred for 30 min, then neutralized with saturated aqueous sodium bicarbonate, extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography using 5:1 and 1:1 (v/v) of hexane-ethyl acetate as the elution, giving 1.33 g (62%) of the amine **5**, a colorless needle. mp 130–131°C. ^{1}H NMR (acetone-d_6) δ 10.35 (1H, br), 7.75 (1H, m), 7.10–7.60 (4H, m), 4.84 (1H, q, $J = 7.7$ Hz), 2.30 (2H, s, br). ^{19}F NMR (acetone-d_6) 87.42 (3F, d, $J = 7.7$ Hz). Anal. found: C, 56.34; H, 4.25; N, 12.82. Calcd for $C_{10}H_9F_3N_2$: C, 56.06; H, 4.24; N, 13.08.

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