A facile synthesis of 3-trifluoromethylpyrazole and its derivatives

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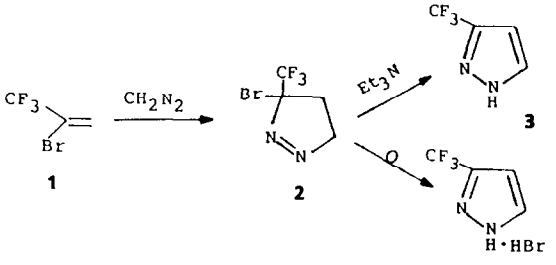
Abstract

3-Trifluoromethylpyrazole has been synthesized from readily available 2-bromotrifluoropropene in quantitative yield. Functionalized trifluoromethylpyrazoles have been conveniently obtained by the reaction of a variety of electrophiles with the N-protected carbanion of 3-trifluoromethylpyrazole in good yield.

Introduction

Heteroaromatic compounds form a class of drug which have widespread use as antiviral, antibiotic, herbicidal or fungicidal agents. On the other hand, it has been shown that the introduction of the fluorine atom into organic compounds often brings about unique chemical and biological properties [1]. Thus, recently, syntheses of fluorinated heteroaromatic compounds have received considerable interest and much effort has been made to explore synthetic methods or intermediates for this purpose, particularly those biologically active heteroaromatic compounds bearing a trifluoromethyl group [2]. However, the methods of introduction of a trifluoromethyl group at a specific position in a heteroaromatic compound in good yield are still quite limited [3]. Hence, it seems highly desirable to seek out an effective method for the regiospecific synthesis of trifluoromethylated heteroaromatic compounds. Herein, we describe a facile synthesis of 3-trifluoromethylpyrazole and its derivatives in good to excellent yields.

We have found that 2-bromotrifluoropropene (BTFP, **1**), which is easily obtainable from trifluoropropene (TFP) by dehydrobromination of the dibromo adduct of TFP in high yield [4], can be employed as a useful and economic precursor for the preparation of 3-trifluoromethylpyrazole. Thus, BTFP (**1**) was simply treated with ethereal diazomethane at room temperature for several minutes, followed by dehydrobromination with an appropriate base to afford the 3-trifluoromethylpyrazole in quantitative yield (Scheme 1).



Scheme 1.

The 1,3-dipolar cycloaddition between diazomethane and BTFP (**1**) took place regioselectively. Only one single intermediate (**2**) was detected via the single signal at δ −8.0 ppm in its ^{19}F NMR spectrum. This compound was found to be labile and to tautomerize to a stable aromatic system in the form of its hydrogen bromide salt **4** after being stored for 2 d at room temperature. In the presence of triethylamine, **2** was completely transformed into pyrazole **3** within several minutes. 3-Trifluoromethylpyrazole (**3**) has been prepared previously by treatment of acetylene with 2,2,2-trifluorodiazoethane [5] (which is nearly as explosive as TNT [6]), but the cycloaddition reaction took place only very sluggishly (4 weeks) [5]. Thus, the present method provides a new, simple and efficient synthesis of 3-trifluoromethylpyrazole (**3**).

Taking advantage of the ready accessibility of 3-trifluoromethylpyrazole (**3**), which could serve as a facile and versatile parent compound for entry into a variety of functionalized trifluoromethylpyrazoles, we have embarked on the preparation of derivatives which might possess some intriguing biological activities. The HN group in **3** was first protected via a Mannich reaction [7] to give a 1-(1-pyrrolidinomethyl)pyrazole **5** in 94%

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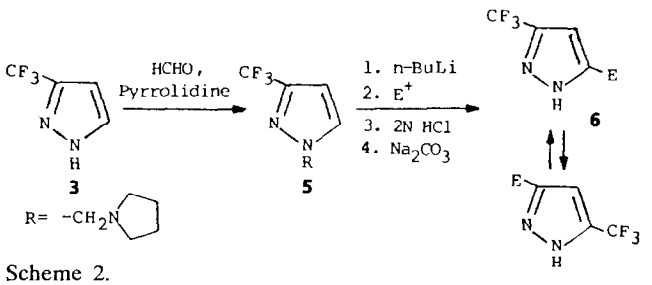

Scheme 2.

TABLE 1. Preparation of trifluoromethylpyrazole derivatives

Entry No.	Electrophile	Substituent in	6	Yield (%)
1	CH_3I	CH_3	**6a**	80
2	$PhCH_2Br$	$PhCH_2$	**6b**	55
3	PhCHO	PhCH(OH)	**6c**	70
4	Ph_2CO	$Ph_2C(OH)$	**6d**	81
5	CH_3SSCH_3	CH_3S	**6e**	83
6	PhSSPh	PhS	**6f**	72

yield. Compound **5** smoothly underwent lithiation with n-butyllithium at low temperature. The resulting carbanion reacted with a variety of electrophiles and subsequent work-up under the usual conditions effected the facile acid hydrolysis of the protecting group to provide the corresponding 3(5)-trifluoromethyl-5(3)-substituted pyrazole (**6**) in fair to good yield (Scheme 2). The results obtained are summarized in Table 1.

In conclusion, we have succeeded in preparing the 3-trifluoromethylpyrazole (**3**) from the readily available, cheap precursor, 2-bromotrifluoropropene, in quantitative yield. This process is easy to scale up. A variety of functionalized pyrazoles bearing a trifluoromethyl group at the 3(5)-position were prepared from **3** in good yield.

Experimental

^1H NMR spectra were recorded on a Varian XL-200 spectrometer with TMS as internal standard and $CDCl_3$ as the solvent. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (δ 0.00) as external standard, downfield shifts being designated negative. Infrared spectra were obtained with a Shimadzu 440-IR spectrometer, and mass spectra were measured on a Finnigan 4021 GC/MS/DC instrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or ^{19}F NMR spectroscopy.

2-Bromotrifluoromethylpropene was prepared according to Henne and Nager [4]. Ethereal diazomethane (*c.* 0.9 M mol l^{-1}) was freshly prepared from nitromethylurea and used without further purification [8].

Preparation of 3-trifluoromethylpyrazole (3)

To a solution of 2-bromotrifluoropropene (10.5 g, 60 mmol) in diethyl ether (10 ml) was added dropwise an ethereal solution of diazomethane (*c.* 0.9 mol l^{-1}, 70 ml) at room temperature until the yellow colour of the solution did not fade. The mixture was then treated with triethylamine (10 ml) for 0.5 h. The salt which precipitated was filtered off and the filtrate washed with saturated $NaHCO_3$ (3×15 ml), brine (3×15 ml) and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, white crystalline **4** was obtained in quantitative yield, m.p. 46–48 °C (lit. value [5], 47–48 °C). H NMR δ: 6.55 (d, J=2.2 Hz, 1H); 7.57 (d, J=2.2 Hz, 1H) ppm. ^{19}F NMR δ: −14.7 ppm. IR (KCl) (cm^{-1}): 3300; 1500; 1390; 1320. MS, *m/z* (relative intensity): 136 (M, 100); 117 (58). Analysis: Calc. for $C_3H_3F_3N_2$: C, 35.30; H, 2.22; N, 20.59; F, 41.88%. Found: C, 35.50; H, 1.96; N, 20.23; F, 41.86%.

Preparation of 1-(1-pyrrolidinomethyl)-3-trifluoromethylpyrazole (5)

A mixture of pyrazole **3** (5 g, 36.8 mmol), 37% formaldehyde solution (3.1 ml) and pyrrolidine (3.1 ml) in ethanol (15 ml) was heated under reflux for 4 h. After removal of the solvent *in vacuo*, the residue was extracted with ethyl ether (3×10 ml). The extract was washed with saturated $NaHCO_3$ (2×10 ml), brine (2×10 ml) and dried over anhydrous Na_2SO_4. After concentration, the crude product was distilled under reduced pressure to give **5** (7.5 g, 94%), b.p. 96–98 °C/4 mmHg. ^1H NMR δ: 1.75 (m, 4H); 2.71 (m, 4H); 5.10 (s, 2H); 6.55 (d, J=2.2 Hz, 1H); 7.56 (d, J=2.2 Hz, 1H) ppm. ^{19}F NMR δ: −15.1 ppm. IR (neat) (cm^{-1}): 1520; 1495; 1380. MS, *m/z* (relative intensity): 219 (M+1, 3); 84 (100). Analysis: Calc. for $C_9H_{12}F_3N_3$: C, 49.31; H, 5.52; N, 19.16; F, 26.10%. Found: C, 49.40; H, 5.58; N, 19.25; F, 26.18%.

General procedure for the preparation of 3(5)-trifluoromethyl-5(3)-substituted pyrazoles (6)

A solution of **5** (1.09 g, 5 mmol) in THF (20 ml) was cooled to −70 °C under nitrogen and a solution of n-butyllithium in n-hexane (5 ml, 1 mol l^{-1}) was added slowly in a dropwise manner. The resulting suspension was maintained at −70 °C for 2 h. The electrophile (5 mmol) in THF (2 ml) was added at −70 °C. The mixture was allowed to warm up to room temperature and stirred at the temperature for several hours. Hydrochloric acid (2 N, 2 ml) was added, followed by removal of the organic solvent and neutralization with saturated $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate. The extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was

purified by column chromatography on silica gel to afford **6**.

3(5)-Trifluoromethyl-5(3)-methylpyrazole (**6a**): m.p. 84–85 °C (lit. value [6], 85–86 °C). ^{1}H NMR δ: 2.36 (s, 3H); 6.33 (s, 1H) ppm. ^{19}F NMR δ: −15.0 ppm. IR (KCl) (cm^{-1}): 3200; 1500; 1380; 1310. MS, *m/z* (relative intensity): 150 (100); 131 (26); 101 (35). Analysis: Calc. for $C_5H_5F_3N_2$: C, 40.00; H, 3.36; N, 18.68; F, 37.97% Found: C, 39.80; H, 3.28; N, 18.28; F, 37.49%.

3(5)-Trifluoromethyl-5(3)-benzylpyrazole (**6b**): Colourless oil. ^{1}H NMR δ: 4.04 (s, 2H); 6.29 (s, 1H); 7.25 (m, 5H) ppm. ^{19}F NMR δ: −14.6 ppm. IR (neat) (cm^{-1}): 3300; 1600; 1500; 1380; 1310. MS, *m/z* (relative intensity): 226 (18); 206 (20); 162 (30); 147 (100). Analysis: Calc. for $C_{11}H_9F_3N_2$: C, 58.40; H, 4.01; N, 12.39; F, 25.22%. Found: C, 58.49; H, 3.68; N, 12.51; F, 25.12%.

[3(5)-Trifluoromethylpyrazole-5(3)-yl]phenyl methanol (**6c**): m.p. 102–104 °C. ^{1}H NMR δ: 5.89 (s, 1H); 6.24 (s, 1H); 71.0–7.30 (m, 5H) ppm. ^{19}F NMR δ: −14.8 ppm. IR (KCl) (cm^{-1}): 3300; 1590; 1550; 1390; 1320. MS, *m/z* (relative intensity): 242 (6); 225 (18); 147 (100). Analysis: Calc. for $C_{11}H_9F_3N_2O$: C, 54.54; H, 3.75; N, 11.57; F, 23.53%. Found: C, 54.31; H, 3.72; N, 11.80; F, 23.14%.

[3(5)-Trifluoromethylpyrazole-5(3)-yl]diphenyl methanol (**6d**): m.p. 115–116 °C. ^{1}H NMR δ: 6.26 (s, 1H); 7.28–7.38 (m, 10H) ppm. ^{19}F NMR δ: −15.6 ppm. IR (KCl) (cm^{-1}): 3300; 1600; 1500; 1380; 1320. MS, *m/z* (relative intensity): 318 (56); 241 (98); 163 (100). Analysis: Calc. for $C_{17}H_{13}F_3N_2O$: C, 64.14; H, 4.25; N, 8.80; F, 17.90%. Found: C, 64.44; H, 4.12; N, 8.76; F, 18.10%.

3(5)-Trifluoromethyl-5(3)-methylthiopyrazole (**6e**): Colourless oil. ^{1}H NMR δ: 2.78 (s, 3H); 6.56 (s, 1H) ppm. ^{19}F NMR δ: −14.5 ppm. IR (neat) (cm^{-1}): 3200; 1500; 1390; 1310. MS *m/z* (relative intensity): 182 (100); 167 (71). Analysis: Calc. for $C_5H_5F_3N_2S$: C, 32.96; H, 2.76; N, 15.38; F, 31.2% Found: C, 32.95; H, 2.67; N, 15.08; F, 31.16%.

3(5)-Trifluoromethyl-5(3)-phenylthiopyrazole (**6f**): Colourless oil. ^{1}H NMR δ: 6.72 (s, 1H); 7.31 (m, 5H) ppm. ^{19}F NMR δ: −14.7 ppm. IR (neat) (cm^{-1}): 3200; 1590; 1500; 1440; 1380. MS, *m/z* (relative intensity): 244 (100); 223 (21); 164 (47). Analysis: Calc. for $C_{10}H_7F_3N_2S$: C, 49.17; H, 2.89; N, 11.48; F, 23.33%. Found: C, 49.52; H, 2.71; N, 11.58; F, 23.36%.

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