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Synthesis and reactions of 1-methyl-5-tributylstannyl-4-trifluoromethylpyrazole

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Abstract—N-Methylation at the pyrazole ring by sequential treatment of 5-tributylstannyl-4-trifluoromethylpyrazole with LDA and iodomethane regioselectively provided the title compound in high yield. The addition reaction of 5-lithiated-4-trifluoromethylpyrazole with a wide range of electrophiles allowed easy and high-yielding introduction of substituents on position 5.

1. Introduction

Much effort has been exerted to introduce fluorine into organic compounds due to its dramatic effects on structure, stability, reactivity, and biological activity.[1] These features have been exploited to design and prepare new, more selective, and more potent pharmaceuticals and agrochemicals, for instance, and consequently the number of new fluorinated compounds burgeons out in recent days. Among these, trifluoromethylated molecules display remarkable applications in the pharmaceutical field as exemplified by Celecoxib[2] and Efavirenz,[3] and additional developments of useful trifluoromethylated building blocks are much being sought.

In our study on the development of new fluorinated building blocks, we have recently reported the synthesis and some cross-coupling reactions of 5-tributylstannyl-4-trifluoromethylpyrazole.[4] The wide range of physical and biological activities of trifluoromethylated pyrazoles has thus made them significant synthetic targets.[5] Moreover, the *N*-methylpyrazole unit is part of several agrochemicals and pharmaceuticals.[6] For instance, pyrazosulfon-ethyl is a successful rice herbicide,[6l] and the *N*-methylpyrazole group is found in a structural element present in antibacterial 4-pyrrolidinythiocarbapenems.[6g]

As an extension of our work, the title trifluoromethylated pyrazole bearing a tributylstannyl group on position 5 can be considered as a promising candidate to build up more complex 1-methyl-4-trifluoromethylpyrazole compounds. Indeed transmetallation of the stannylpyrazole with ^{n}BuLi to generate the corresponding organolithium species and reaction with suitable electrophiles should give rise to the corresponding 1-methyl-4-trifluoromethyl-5-substituted-pyrazoles. However, to the best of our knowledge, there are no reports concerning the generation of the corresponding organolithium species from stannylpyrazoles.[5c,6h,7] We herein report the synthesis and reactions of the title compound including an application to the synthetic trifluoromethylated analogue of the analgesic Cizolirtine.

2. Results and discussion

We previously reported the preparation of 5-tributylstannyl-4-trifluoromethyl-1*H*-pyrazole **3** from 3,3,3-trifluoro-2-bromopropene **1** in two steps.[4] However, the moderate overall yield (40% in two steps) prompted us to improve the reaction procedure. Careful examination of the reaction conditions led to two improvements: (i) bis(tributylstannyl)-oxide [$(Bu_3Sn)_2O$] is a better electrophile than chlorotributylstannane (Bu_3SnCl) in the reaction of 3,3,3-trifluoro-1-propynyllithium generated in situ. (ii) No isolation of tributyl(3,3,3-trifluoro-1-propynyl)stannane **2** is necessary for the preparation of **3**. Thus, to a freshly prepared solution of **2** [from sequential treatment of **1** with LDA and $(Bu_3Sn)_2O$] was successively added an excess of ethereal diazomethane solution at −30 °C, and the mixture was gradually warmed to 0 °C to give the desired product **3** in 64% overall yield (Scheme 1).

Keywords: 1-Methyl-5-tributylstannyl-4-trifluoromethylpyrazole; 1-Methyl-5-substituted-4-trifluoromethylpyrazole; Cizolirtine CF_3-analogue; Tributyl(3,3,3-trifluoro-1-propynyl)stannane.
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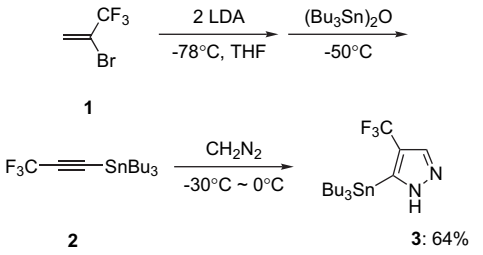
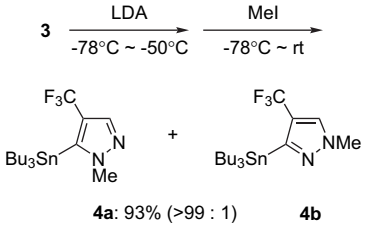


Scheme 1. One-pot synthesis of **3**.

With the precursor of the title compound produced, we examined methylation at the pyrazole ring nitrogen. It is well-accepted that the reaction of unsymmetrical pyrazoles affords products in which the less hindered nitrogen is preferentially substituted. In a literature report, for example, 1-methyl-3,4-bis(trimethylsilyl)pyrazole was regioselectively prepared from 3,4-bis(trimethylsilyl)-1*H*-pyrazole under mild conditions.[6n] According to a slightly modified procedure, the preliminary reaction of **3** with iodomethane was conducted in acetone at 40 °C using potassium carbonate as a base to give a 62/38 mixture of regioisomers in 84% yield. Attempt to overcome this problem involved the preparation of the corresponding anionic nitrogen species with a strong base. Thus, deprotonation of pyrazole **3** was carried out using LDA in THF at −78 °C, the resultant mixture being gradually warmed up to −50 °C over 20 min, and then cooled again to −78 °C. Treatment with a slight excess iodomethane at −78 °C followed by a slow warming up to room temperature overnight afforded, after work-up, a crude product whose GC–MS analysis indicated the presence of a single regioisomer. Although the exact regioselectivity was not determined at this point, we tentatively assigned this *N*-methylpyrazole to 1-methyl-5-tributylstannyl-4-trifluoromethylpyrazole **4a** and continued our study (Scheme 2).



Scheme 2. N-Methylation of **3**.

The alkylation reaction of **4a** with benzaldehyde as a model compound was initially examined. It is well-known that transmetallation of tributylstannyl compound with ^{n}BuLi at low temperature gives the corresponding lithiated species in high yield.[8] The transmetallation of **4a** was performed by addition of ^{n}BuLi at −78 °C, and then warming up to −50 °C in THF. The resultant solution containing the corresponding 5-lithiated 4-trifluoromethylpyrazole was then reacted with benzaldehyde at −78 °C. The mixture was gradually warmed up to room temperature while being stirred to yield the desired product in 93% yield (Table 1, entry 1). Under similar conditions, the reaction of **4a** with other aromatic aldehydes bearing either an electron donating substituent or an electron withdrawing one on the ring gave the corresponding adducts in high yields (entries 2–6).

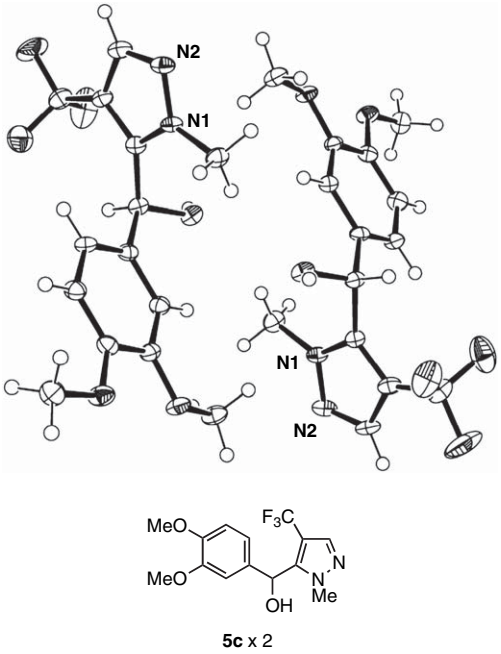


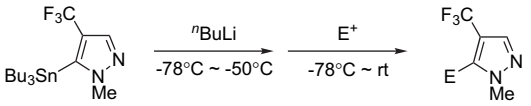
Figure 1. X-ray crystal structure of **5c** with thermal ellipsoids shown at the 50% probability level (hydrogen atoms are omitted for clarity).

To our delight, product **5c** gave single crystals suitable for X-ray crystallographic analysis. A crystal drawing of **5c** (two molecules) is shown in Figure 1. The result of this X-ray analysis revealed unambiguous proof of the regiochemistry of 1-methyl-5-alkylated-4-trifluoromethylpyrazoles and definitely assigned the structure of **4a** as 1-methyl-5-tributylstannyl-4-trifluoromethylpyrazole. For the findings stated above, our procedure turned out to be useful for the complete C-5-lithiation of 1-methylpyrazole.[6c,e,h,k–m,9]

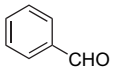
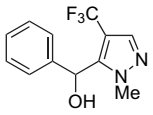
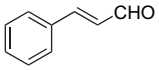
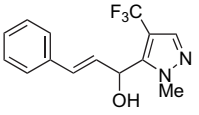
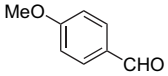
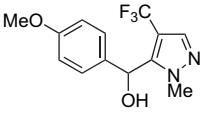
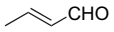
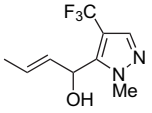
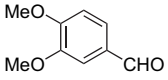
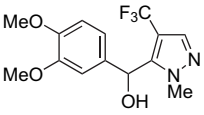
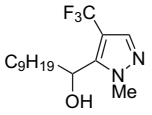
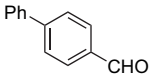
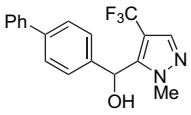
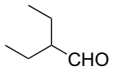
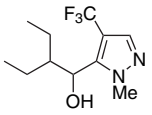
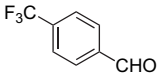
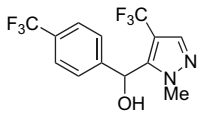
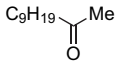
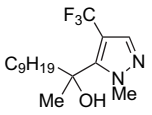
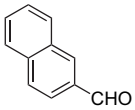
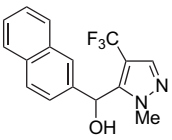
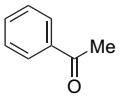
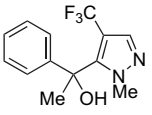
α,β-Unsaturated aldehydes such as cinnamaldehyde and crotonaldehyde also proved to be good electrophiles and delivered the adducts resulting from 1,2-addition fashion. No conjugated addition products were observed (entries 7 and 8). Linear and branched aliphatic aldehydes successfully underwent addition reaction to give the corresponding adducts in high yields (entries 9 and 10). Although 2-undecanone as an aliphatic ketone also functioned satisfactorily (entry 11), acetophenone as an aromatic counterpart led to a lower yield (46%) maybe due to either enolization or steric hindrance (entry 12). The compound **4a** was very capable of nucleophilic addition with a variety of aldehydes and aliphatic ketones.

Application of the above methodology to the preparation of potentially bioactive compounds was next considered. According to Hueso-Rodriguez's report, adduct **5a** was transformed into the corresponding *N*,*N*-dimethylaminoethyl ether derivative to yield the trifluoromethylated analogue of Cizolirtine.[6] Thus, reaction of **5a** with (2-chloroethyl)dimethylamine hydrochloride using 40% aqueous sodium hydroxide solution in the presence of a catalytic amount of tetrabutylammonium bromide in refluxing toluene for 8 h smoothly proceeded to give the desired product **6** in 78% yield (Scheme 3).

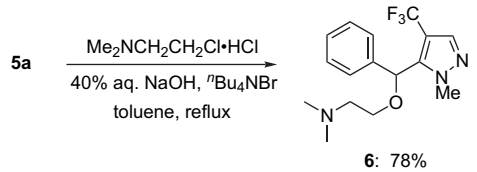
Table 1. Reaction of **4a** with various electrophiles[a]



4a **5**

Entry	E^+	Product yield[b] (%)	Entry	E^+	Product yield[b] (%)
1		 **5a**: 93	7		 **5g**: 96
2		 **5b**: 89	8		 **5h**: 93
3		 **5c**: 94	9	C_9H_{19}–CHO	 **5i**: 79
4		 **5d**: 93	10		 **5j**: 79
5		 **5e**: 85	11		 **5k**: 80
6		 **5f**: 86	12[c]		 **5l**: 46

[a] Aldehyde or ketone, 1.5 equiv.
[b] Isolated yield.
[c] Ketone, 3.0 equiv.

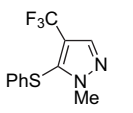


6: 78%

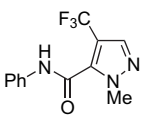
Scheme 3. Synthesis of Cizolirtine analogue **6**.

Further expansion of the synthetic value of the new methodology for the preparation of 1-methyl-5-substituted-4-trifluoromethylpyrazole involved the use of other electrophiles such as *S*-phenyl benzenethiosulfate, phenyl isocyanate, *N*,*N*-dimethylformamide, and methyl cyanoacetate. The former two electrophiles afforded the desired 1-methyl-5-functionalized-4-trifluoromethylpyrazoles in good yields; however, no adducts were obtained from the latter two electrophiles with despite a number of reaction conditions (temperature control, use of additives, and change of solvents; Fig. 2).

In conclusion, we have developed a facile method for the preparation of a variety of 1-methyl-4-trifluoromethyl-5-substituted-pyrazoles. The important key trifluoromethylated building block, 1-methyl-5-tributylstannyl-4-trifluoromethylpyrazole **4a**, was prepared from the *N*-unsubstituted



7: 63%



8: 69%

Figure 2. Structure of pyrazoles **7** and **8**.

precursor, 5-tributylstannyl-4-trifluoromethylpyrazole **3**, through completely regioselective N-methylation using LDA and MeI at low temperature.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared (IR) spectra are reported in inverse centimeter. ^{1}H, ^{19}F, and ^{13}C NMR spectra were measured in $CDCl_3$ solutions. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^{1}H NMR and ^{13}C NMR spectra and benzylidyne trifluoride ($CF_3C_6H_5$) for ^{19}F NMR spectra.

3.1.1. Preparation of 5-tributylstannyl-4-trifluoromethylpyrazole (3). A 100 mL two-necked flask equipped with a magnetic stir bar, a stopcock, and a three-way stopcock, were charged with diisopropylamine (1.6 mL, 11.4 mmol) and 10 mL of THF under argon atmosphere. To the stirring mixture was added dropwise ^{n}BuLi (2.67 M in hexane solution, 4.4 mL, 11.8 mmol) via syringe at 0 °C. After the addition was completed, the mixture was cooled to −78 °C, and then 2-bromo-3,3,3-trifluoropropene (0.54 mL, 5.21 mmol) was slowly added to the mixture. After the mixture was gradually warmed to −50 °C, $(Bu_3Sn)_2O$ (2.6 mL, 4.87 mmol) was added dropwise at this temperature. The mixture was gradually warmed to −30 °C while being stirred and an excess of ethereal CH_2N_2 solution was added to the mixture at this temperature. The whole mixture was gradually warmed to 0 °C, and stirring was continued for several hours until the reaction was complete. The reaction was quenched with hexane (ca. 10 mL) and sodium sulfate decahydrate ($Na_2SO_4\cdot 10H_2O$, ca. 10 g). After the mixture was dried over sodium sulfate and filtered through a short sodium sulfate column (ether as an eluent), the solution was concentrated in vacuo. The resulting oily residue was purified by column chromatography (silica gel, hexane/ethyl acetate/triethylamine=200/40/1) to give the desired compound (**3**) as a colorless oil (1.42 g, 64%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (9H, t, J=7.3 Hz), 1.16–1.21 (6H, m), 1.27–1.39 (6H, m), 1.48–1.58 (6H, m), 7.87 (1H, s), 10.22 (1H, br s).[4]

3.1.2. Preparation of *N*-methyl-5-tributylstannyl-4-trifluoromethylpyrazole (4a). To a solution containing 889.5 mg (2.09 mmol) of pyrazole (**3**) in THF (8 mL) was added LDA (0.38 M in THF solution, 7.0 mL, 2.66 mmol) by means of double-ended needle at −78 °C. The reaction mixture was gradually warmed to −50 °C, and then again cooled to −78 °C. At this temperature 0.17 mL (2.72 mmol) of MeI was added to the mixture, and the temperature of the stirring mixture was allowed to warm to room temperature overnight. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with hexane/ether=3/1. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate/triethylamine=200/40/1) to give the desired compound (**4a**) as a colorless oil (853.1 mg, 93%, >99/1): IR (neat) 2958, 1529, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (9H, t, J=7.3 Hz), 1.17–1.22 (6H, m), 1.29–1.36 (6H, m), 1.46–1.57 (6H, m), 3.96 (3H, s), 7.72 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 13.3, 27.0, 28.6, 41.1, 121.4 (q, J=35.5 Hz), 124.0 (q, J=265.9 Hz), 137.2 (q, J=3.1 Hz), 143.1 (d, J=3.1 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.14 (s); GC–MS *m*/*z* 382 (3.4, M$^+$−Bu), 250 (21), 248 (14), 104 (15), 84 (100), 83 (40); Anal. Calcd for $C_{17}H_{31}F_3N_2Sn$: C, 46.50; H, 7.12; N, 6.38. Found: C, 46.53; H, 7.11; N, 6.37.

3.1.3. Preparation of *N*-methyl-5-[(hydroxy)(phenyl)]-methyl-4-trifluoromethylpyrazole (5a). To a solution containing 112.3 mg (0.256 mmol) of pyrazole (**4a**) in THF (1 mL) was added ^{n}BuLi (2.67 M in hexane solution, 0.125 mL, 0.332 mmol) by means of syringe at −78 °C. The reaction mixture was gradually warmed to −50 °C, and then again cooled to −78 °C. At this temperature 40 mL (0.384 mmol) of benzaldehyde was added to the mixture, and the temperature was allowed to warm to room temperature with stirring for 30 min. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1 then 3/1) to give the desired compound (**5a**) as a white solid (61.2 mg, 93%): mp 112.5–114.2 °C; IR (KBr) 3252, 1574, 759, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (1H, d, J=4.4 Hz), 3.66 (3H, s), 6.31 (1H, d, J=4.4 Hz), 7.28–7.41 (5H, m), 7.66 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.3, 65.2 (d, J=1.3 Hz), 111.8 (q, J=37.4 Hz), 122.8 (q, J=266.6 Hz), 125.3, 127.8, 128.5, 136.0 (q, J=3.7 Hz), 138.7, 142.0 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.8 (s); GC–MS *m*/*z* 255 (9.3, M$^+$), 105 (50), 103 (32), 79 (90), 78 (73), 77 (100), 51 (36); Anal. Calcd for $C_{12}H_{11}F_3N_2O$: C, 56.25; H, 4.33; N, 10.93. Found: C, 56.35; H, 4.32; N, 10.90.

3.1.4. *N*-Methyl-5-[(hydroxy)(4′-methoxyphenyl)]-methyl-4-trifluoromethylpyrazole (5b). White solid; yield 89%; mp 109.0–110.9 °C; IR (KBr) 3194, 2957, 1574, 877 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (1H, d, J=3.1 Hz), 3.67 (3H, s), 3.81 (3H, s), 6.26 (1H, d, J=3.1 Hz), 6.90 (2H, d, J=7.9 Hz), 7.22 (2H, d, J=7.9 Hz), 7.65 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 55.3, 65.4, 111.8 (q, J=36.8 Hz), 114.0, 122.4 (q, J=266.6 Hz), 130.9, 136.1 (q, J=3.7 Hz), 142.3 (q, J=2.5 Hz), 159.2; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.7 (s); GC–MS *m*/*z* 285 (4.2, M$^+$), 109 (100), 108 (64), 77 (11); Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.62; H, 4.58; N, 9.72.

3.1.5. *N*-Methyl-5-[(hydroxy)(3′,4′-dimethoxyphenyl)]-methyl-4-trifluoromethylpyrazole (5c). White solid; yield 94%; mp 133.8–135.9 °C; IR (KBr) 3203, 2938, 1574, 869 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55 (1H, d, J=4.4 Hz), 3.70 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 6.25 (1H, d, J=4.4 Hz), 6.77 (1H, ddd, J=8.3, 1.8, 0.9 Hz), 6.84 (1H, d, J=8.3 Hz), 6.90 (1H, d, J=1.8 Hz), 7.66 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.9, 56.2, 56.3, 65.8, 109.3, 111.4, 112.0 (q, J=37.4 Hz), 118.2, 123.3 (q, J=266.6 Hz), 131.8, 136.5 (q, J=3.7 Hz), 142.6 (q, J=2.5 Hz), 149.0, 149.5; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.7 (s); GC–MS *m*/*z* 315 (24, M$^+$), 264 (21), 139

(100), 138 (75), 108 (12), 77 (13); Anal. Calcd for $C_{14}H_{15}F_3N_2O_3$: C, 53.17; H, 4.78; N, 8.86. Found: C, 53.26; H, 4.82; N, 8.77.

3.1.6. *N*-Methyl-5-[(hydroxy)(4′-biphenyl)]methyl-4-trifluoromethylpyrazole (5d). White solid; yield 93%; mp 146.8–149.1 °C; IR (KBr) 3252, 2956, 1574, 1402, 876 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.63 (1H, d, J=3.9 Hz), 3.71 (3H, s), 6.35 (1H, d, J=3.9 Hz), 7.30–7.48 (5H, m), 7.56–7.63 (4H, m), 7.68 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.6, 65.4, 111.8 (q, J=37.4 Hz), 123.0 (q, J=266.6 Hz), 126.0, 127.0, 127.4, 127.5, 128.8, 136.2 (q, J=3.4 Hz), 137.7, 140.3, 140.9, 141.9 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.8 (s); GC–MS m/z 331 (17, M^+), 155 (100), 154 (73), 152 (43), 151 (31), 77 (33); Anal. Calcd for $C_{18}H_{15}F_3N_2O_2$: C, 65.06; H, 4.55; N, 8.43. Found: C, 65.08; H, 4.62; N, 8.48.

3.1.7. *N*-Methyl-5-[(4′-trifluoromethylphenyl)(hydroxy)]-methyl-4-trifluoromethylpyrazole (5e). White solid; yield 85%; mp 130.0–132.5 °C; IR (KBr) 3223, 2957, 1576, 866 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.34 (1H, d, J=3.5 Hz), 3.62 (3H, s), 6.33 (1H, d, J=3.5 Hz), 7.46 (2H, d, J=8.1 Hz), 7.64 (2H, d, J=8.1 Hz), 7.64 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 64.9, 112.3 (q, J=37.4 Hz), 122.9 (q, J=266.6 Hz), 123.9 (q, J=264.8 Hz), 125.7 (q, J=3.7 Hz), 126.0, 130.2 (q, J=32.4 Hz), 136.3 (q, J=3.1 Hz), 141.2, 142.7; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.9 (s), −64.1 (s); GC–MS m/z 323 (1.9, M^+), 234 (52), 159 (66), 158 (81), 145 (27), 130 (20), 127 (100), 103 (66); Anal. Calcd for $C_{13}H_{10}F_6N_2O_2$: C, 48.16; H, 3.11; N, 8.64. Found: C, 48.24; H, 3.07; N, 8.70.

3.1.8. *N*-Methyl-5-[(hydroxy)(2′-naphthyl)]methyl-4-trifluoromethylpyrazole (5f). White solid; yield 86%; mp 169.1–170.0 °C; IR (KBr) 3241, 3064, 2956, 1574, 1403 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67 (1H, d, J=4.2 Hz), 3.65 (3H, s), 6.47 (1H, d, J=4.2 Hz), 7.32 (1H, dd, J=8.6, 1.5 Hz), 7.48–7.54 (2H, m), 7.70 (1H, s), 7.81–7.87 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.0, 66.1, 112.5 (q, J=37.4 Hz), 123.5 (q, J=266.6 Hz), 123.8, 124.8, 126.9, 127.0, 128.1, 128.6, 129.1, 133.3, 133.5, 136.5, 136.6 (q, J=3.7 Hz), 142.2 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.7 (s); GC–MS m/z 306 (0.01, M^+), 304 (11), 130 (11), 129 (59), 128 (100), 127 (67), 103 (11), 102 (18), 101 (10); Anal. Calcd for $C_{16}H_{13}F_3N_2O_2$: C, 62.74; H, 4.28; N, 9.15. Found: C, 62.79; H, 4.31; N, 9.19.

3.1.9. *N*-Methyl-5-[(cinnamyl)(hydroxyl)]methyl-4-trifluoromethylpyrazole (5g). White solid; yield 96%; mp 95.5–96.8 °C; IR (KBr) 3234, 3030, 2953, 1572 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (1H, d, J=4.0 Hz), 3.99 (3H, s), 6.47 (1H, d, J=4.0 Hz), 6.32 (1H, dd, J=15.9, 5.1 Hz), 6.66 (1H, dd, J=15.9, 1.7 Hz), 7.26–7.40 (5H, m), 7.64 (1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.1, 65.8, 111.2 (q, J=37.4 Hz), 121.6 (q, J=266.6 Hz), 126.9, 127.0, 128.8, 129.2, 132.3, 136.1, 136.7 (q, J=3.7 Hz), 141.6 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −56.0 (s); GC–MS m/z 281 (0.76, M^+), 105 (100), 104 (85), 103 (66), 91 (69), 77 (38); Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 59.57; H, 4.64; N, 9.92. Found: C, 59.40; H, 4.61; N, 9.97.

3.1.10. *N*-Methyl-5-[(crotyl)(hydroxy)]methyl-4-trifluoromethylpyrazole (5h). Colorless oil; yield 93%; IR (neat) 3331, 3034, 2957, 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.74 (3H, d, J=4.8 Hz), 2.25 (1H, br s), 3.95 (3H, s), 5.53–5.79 (3H, m), 7.59 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5, 38.4, 65.3, 110.5 (q, J=38.0 Hz), 122.0 (q, J=265.9 Hz), 128.65, 128.73, 136.0 (q, J=3.7 Hz), 142.1 (q, J=3.1 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.9 (s); GC–MS m/z 219 (0.63, M^+), 199 (50), 184 (63), 176 (52), 158 (88), 156 (82), 130 (83), 103 (87), 102 (100); HRMS (EI) m/z calcd for $C_9H_{11}F_3N_2O$ 221.0902, found 221.0883.

3.1.11. *N*-Methyl-5-[(hydroxy)(nonyl)]methyl-4-trifluoromethylpyrazole (5i). Colorless oil; yield 79%; IR (neat) 3228, 2957, 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (3H, t, J=6.2 Hz), 1.26 (12H, br s), 1.74–1.79 (2H, m), 1.89–1.94 (2H, m), 2.09 (1H, d, J=4.1 Hz), 4.02 (3H, s), 5.06 (1H, d, J=4.1 Hz), 7.58 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.7, 29.1, 29.2, 29.371, 29.429, 31.8, 35.9, 38.6, 65.4, 110.5 (q, J=36.7 Hz), 122.0 (q, J=266.6 Hz), 136.2 (q, J=3.7 Hz), 143.3 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.9 (s); GC–MS m/z 306 (0.17, M^+), 179 (23), 178 (22), 159 (100); HRMS (EI) m/z calcd for $C_{15}H_{25}F_3N_2O$ 307.1997, found 307.2015.

3.1.12. *N*-Methyl-5-[(1′-ethylpropyl)(hydroxy)]methyl-4-trifluoromethylpyrazole (5j). White solid; yield 79%; mp 71.0–72.3 °C; IR (KBr) 3225, 2940, 1573 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (3H, t, J=7.4 Hz), 0.91 (3H, t, J=7.4 Hz), 0.94–1.05 (1H, m), 1.10–1.26 (1H, m), 1.55–1.75 (2H, m), 1.75–1.90 (1H, m), 3.01 (1H, d, J=4.2 Hz), 4.86 (1H, dd, J=9.5, 4.2 Hz), 7.54 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 14.5, 21.3, 21.5, 39.3, 45.2, 67.6, 111.0 (q, J=36.7 Hz), 123.0 (q, J=265.9 Hz), 136.9 (q, J=3.7 Hz), 141.6 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.7 (s); GC–MS m/z 249 (1.4, M^+), 180 (25), 179 (50), 178 (26), 159 (86), 158 (100), 55 (20); Anal. Calcd for $C_{11}H_{17}F_3N_2O$: C, 52.79; H, 6.85; N, 11.19. Found: C, 53.02; H, 6.77; N, 11.26.

3.1.13. *N*-Methyl-5-[(hydroxy)(methyl)(nonyl)]methyl-4-trifluoromethylpyrazole (5k). Colorless oil; yield 80%; IR (neat) 3349, 2927, 1548 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (3H, t, J=6.3 Hz), 1.15–1.35 (14H, m), 1.68 (3H, s), 1.70–1.98 (2H, m), 2.09 (1H, s), 4.06 (3H, s), 7.61 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 23.0, 24.1, 29.6, 29.84, 29.87, 30.0, 32.2, 32.2, 41.4, 42.5, 73.3, 111.5 (q, J=36.7 Hz), 123.6 (q, J=266.6 Hz), 138.0 (q, J=5.0 Hz), 146.8 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −53.9 (s); GC–MS m/z 193 (13), 192 (28), 173 (100), 172 (80), 131 (26); Anal. Calcd for $C_{16}H_{27}F_3N_2O$: C, 59.98; H, 8.49; N, 8.74. Found: C, 59.95; H, 8.45; N, 8.64.

3.1.14. *N*-Methyl-5-[(hydroxy)(methyl)(phenyl)]methyl-4-trifluoromethylpyrazole (5l). Colorless oil; yield 46%; IR (neat) 3312, 3063, 3027, 2988, 1552 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (3H, s), 2.67 (1H, s), 3.50 (3H, s), 7.27–7.38 (5H, m), 7.66 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8 (q, J=3.7 Hz), 39.7, 73.1, 111.6 (q, J=37.4 Hz), 122.3 (q, J=224.2 Hz), 124.9, 127.8, 128.7,

137.2 (q, J=5.0 Hz), 144.3, 145.9 (q, J=3.1 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −53.6 (s); GC–MS m/z 269 (1.7, M^+), 234 (91), 105 (58), 78 (43), 77 (100), 51 (45); HRMS (FAB) m/z calcd for $C_{13}H_{13}F_3N_2O$ 271.1058 (M^++1), found 271.1056.

3.1.15. *N*-Methyl-5-[(*N*′,*N*′-dimethylaminoethoxy)(phenyl)]methyl-4-trifluoromethylpyrazole (6). To a mixture containing 49.8 mg (0.196 mmol) of pyrazole **5a**, 69.9 mg (0.485 mmol) of (2-chloroethyl)dimethylamine hydrochloride, and 8.4 mg (0.026 mmol) of tetrabutylammonium bromide in toluene (1 mL) was added 40% aqueous sodium hydroxide solution (0.12 mL, 1.18 mmol) by means of syringe. After the whole reaction mixture was refluxed for 8 h, the reaction was quenched with water and extracted with hexane/ethyl acetate=3/1 solution. The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/dichloromethane/triethylamine=200/200/1) to give the desired compound (**6**) as colorless oil (49.7 mg, 69%): IR (neat) 2946, 1571, 1397, 1232, 1114, 982, 760, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (6H, s), 2.57 (1H, dt, J=12.8, 5.7 Hz), 2.63 (1H, dt, J=12.8, 5.7 Hz), 3.57 (1H, dt, J=9.9, 5.7 Hz), 3.63 (3H, s), 3.70 (1H, dt, J=9.9, 5.7 Hz), 5.89 (1H, s), 7.27–7.37 (5H, m), 7.68 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 45.9 (2C), 58.6, 68.2, 73.1, 113.7 (q, J=37.1 Hz), 123.1 (q, J=264.5 Hz), 125.7 (2C), 127.8, 128.5 (2C), 136.1 (q, J=3.1 Hz), 137.8, 140.1 (q, J=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.7 (s); GC–MS m/z 238 (0.5), 73 (7), 72 (6), 58 (100), 57 (33); HRMS (FAB) calcd for $C_{16}H_{20}F_3N_3O$: 328.1637 ($M+H^+$), found 328.1634.

3.1.16. *N*-Methyl-5-*S*-phenyl-4-trifluoromethylpyrazole (7). Colorless oil; yield 63%; IR (neat) 3067, 2953, 1583, 1228, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (3H, s), 7.08–7.31 (5H, m), 7.80 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.7, 118.6 (q, J=36.7 Hz), 124.3 (q, J=266.6 Hz), 127.6, 128.5, 129.9, 131.3 (q, J=3.1 Hz), 133.7, 137.6 (q, J=3.1 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ −58.3 (s); GC–MS m/z 258 (8.7, M^+), 257 (100), 91 (25), 77 (63), 69 (24), 51 (41); Anal. Calcd for $C_{11}H_9F_3N_2S$: C, 51.16; H, 3.51; N, 10.85. Found: C, 51.30; H, 3.58; N, 10.78.

3.1.17. *N*-Methyl-5-(*N*-phenylcarbamoyl)-4-trifluoromethylpyrazole (8). White solid; yield 79%; mp 92.8–94.0 °C; IR (KBr) 3256, 3142, 2951, 1652, 1558, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.13 (3H, s), 7.23 (1H, t, J=7.5 Hz), 7.39 (2H, t, J=7.5 Hz), 7.57 (2H, d, J=7.5 Hz), 7.72 (1H, s), 7.87 (1H, br s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.5, 111.7 (q, J=37.4 Hz), 120.4, 122.4 (q, J=267.2 Hz), 125.7, 129.3, 135.0 (q, J=2.5 Hz), 136.4 (q, J=3.7 Hz), 136.5, 156.2; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −55.8 (s); GC–MS m/z 268 (13, M^+), 177 (23), 176 (100), 102 (26), 77 (6), 64 (13); Anal. Calcd for $C_{12}H_{10}F_3N_3O$: C, 53.54; H, 3.74; N, 15.61. Found: C, 53.83; H, 3.80; N, 15.57.

3.1.18. Crystal data for 5c. $C_{14}H_{15}F_3N_2O_3$: M_r=316.28, T=93(2) K, orthorhombic, space group $Pbn21$, a=11.062(7) Å, b=11.683(17) Å, c=22.423(7) Å, V=2898(5) Å^3, Z=8, D_x=1.450 Mg m^{-3}, m=0.127 mm^{-1}, l=0.71073 Å, q_{max}=27.48°, 25,011 measured reflection, 3400 independent reflections, 405 refined parameters, GOF=1.069, $R[F^2>2s(F^2)]$=0.0419, $wR(F^2)$=0.1103. The intensity data were collected on a Rigaku RAXIS-RAPID diffractometer. The structure was solved by direct methods (SIR2002[10]) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL-97[11]). All hydrogen atoms were positioned geometrically and refined as riding. CCDC-297123 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing to data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.043.

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