Direct Noncatalytic Electrophilic Trifluoroacetylation of Electron-Rich Pyrazoles

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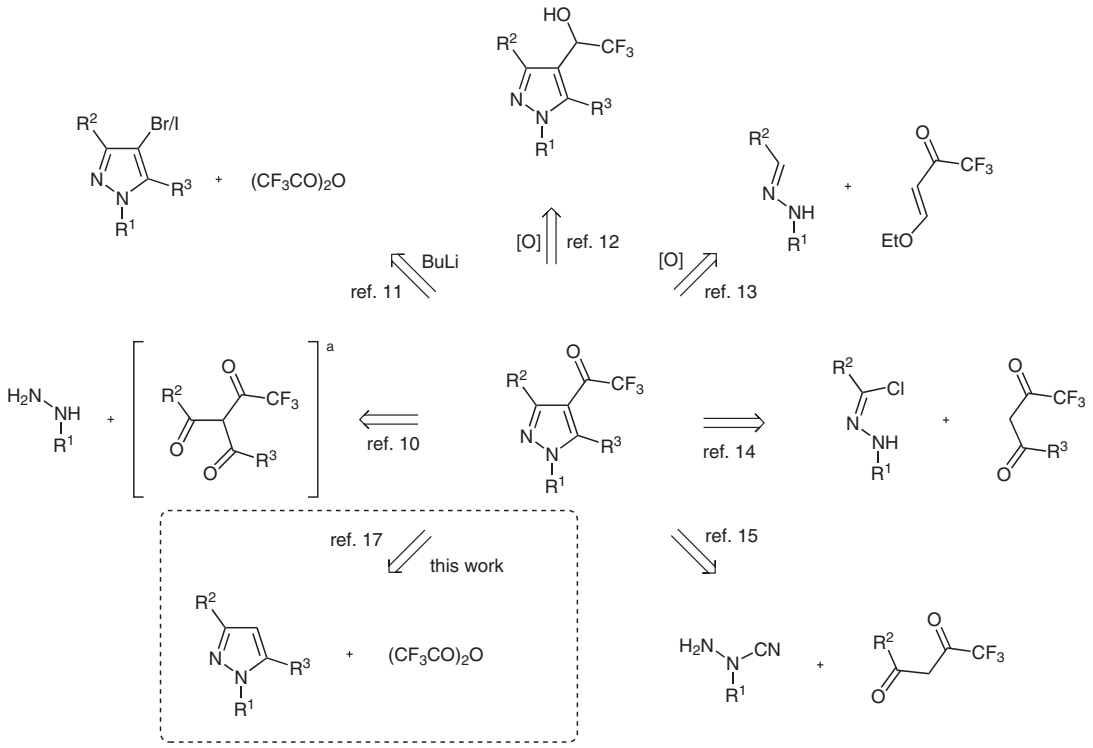
Abstract: Electron-rich N-substituted pyrazoles smoothly reacted with trifluoroacetic anhydride in pyridine to form the corresponding trifluoromethyl ketones in good yields.

Key words: trifluoromethyl group, trifluoroacetyl group, fluorine, pyrazole, building blocks

Fluorinated compounds have played an important role in chemistry: ~20% of all pharmaceuticals and agrochemicals contain at least one fluorine atom.[2,3] This is because the incorporation of fluorine, trifluoromethyl groups, or other fluorinated fragments into organic molecules significantly changes their physicochemical and biological properties. For example, the trifluoromethyl substituent effectively influences the pK_a of the neighboring functional groups, the compound lipophilicity, solubility, conformational preferences, and hydrolytic and metabolic stabilities.[4] Therefore, elaboration of practical, robust methods to prepare novel trifluoromethylated building blocks on a large scale from common starting materials is of interest to both academia and industry.[5]

Recently, our colleagues trifluoroacetylated 1,3-azoles with trifluoroacetic anhydride in pyridine.[6] The formed 2-(trifluoroacetyl)-1,3-azoles were subsequently used to prepare novel drug-like compounds.[7] We wanted to expand this methodology to the pharmacologically relevant pyrazole core.[8] Indeed, 4-trifluoroacetylated pyrazoles have already attracted attention in medicinal projects, ag-



Scheme 1 Chemical approaches to 4-(trifluoroacetyl)pyrazoles.[10–15] [a] Synthon for a tricarbonyl compound.

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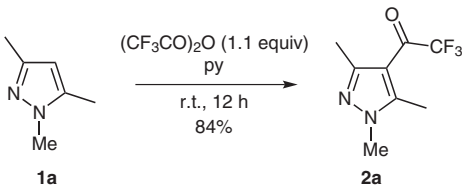
rochemistry, and coordination chemistry.[9] Scheme 1 summarizes the key synthetic approaches to 4-(trifluoroacetyl)pyrazoles.[10–15] Though functionalization of pyrazole at C4 by electrophilic substitution is known in the literature,[16] unexpectedly, direct incorporation of the trifluoroacetyl group into pyrazole core has scant coverage. There are several specific examples in recent patents on the trifluoroacetylation of pyrazoles activated by a (substituted) amino function.[17] Mostly, these reactions were performed in the presence of aluminum trichloride as a catalyst. In this work, therefore, we report on direct mild non-catalytic trifluoroacetylation of electron-rich N-substituted pyrazoles with trifluoroacetic anhydride in pyridine.

We selected the model pyrazole **1a** to validate the suggested transformation, because it contained three electron-rich methyl groups that maximally facilitate the electrophilic reaction. In fact, treating a solution of **1a** in pyridine at 0 °C with trifluoroacetic anhydride (2.0 equiv) followed by stirring the reaction mixture at room temperature for 12 hours completed the transformation. Moreover, we found that the amount of trifluoroacetic anhydride can be reduced to 1.1 equivalents without affecting the reaction conversion. The product **2a** was isolated from the reaction mixture in 84% yield by distillation (Scheme 2). We were also very pleased to find that the procedure was reproducible upon scaling up: 80 grams of the product were easily prepared in one synthesis run.



Scheme 2 Synthesis of ketone **2a**

Given the simplicity and efficiency of this protocol, we next studied its scope (Table 1). Pyrazoles **1b–f** bearing three electron-donating groups smoothly reacted to afford products **2b–f** in 62–91% yield. Aminopyrazole **1g** gave bis-trifluoroacetylated ketone **2g** when using excess trifluoroacetic anhydride. While disubstituted pyrazole **1h** also gave product **2h** at room temperature, mono-substituted pyrazoles **1i–k** showed low conversion (30–40%). We obtained the corresponding products **2i–k** in good yields, however, by performing the reaction under heating with two equivalents of trifluoroacetic anhydride.

Table 1 Synthesis of Ketones **2a–k**

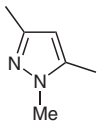
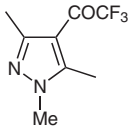
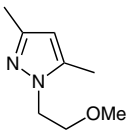
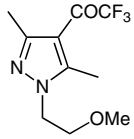
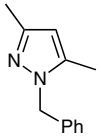
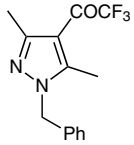
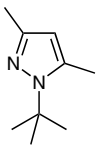
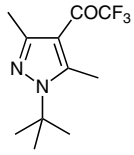
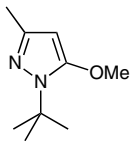
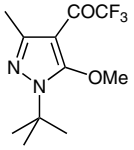
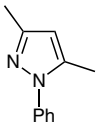
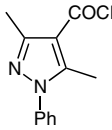
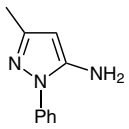
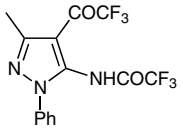
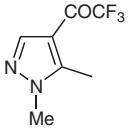
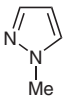
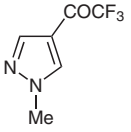
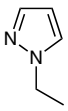
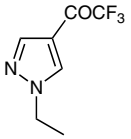
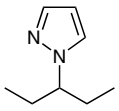
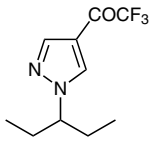
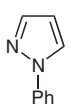
Entry	Substrate	Product	$(CF_3CO)_2O$ (equiv)	Temp	Time (h)	Yield (%)
1	 **1a**	 **2a**	1.1	r.t.	12	84
2	 **1b**	 **2b**	1.1	r.t.	12	74
3	 **1c**	 **2c**	1.1	r.t.	12	81
4	 **1d**	 **2d**	1.1	r.t.	12	91

Table 1 Synthesis of Ketones **2a–k** (continued)

Entry	Substrate	Product	$(CF_3CO)_2O$ (equiv)	Temp	Time (h)	Yield (%)
5	 **1e**	 **2e**	1.1	r.t.	12	62
6	 **1f**	 **2f**	1.1	r.t.	12	94
7	 **1g**	 **2g**	4.0	r.t.	12	74
8	 **1h**	 **2h**	1.1	r.t.	12	90
9	 **1i**	 **2i**	2.0	reflux	6	54
10	 **1j**	 **2j**	2.0	reflux	6	67
11	 **1k**	 **2k**	2.0	reflux	6	92

The reaction, however, did not work for pyrazoles bearing the electron-withdrawing substituents: substrates **3** and **4** (Figure 1) remained unchanged.



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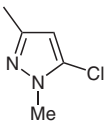

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Figure 1 Compounds that failed to give the trifluoroacetyl derivatives

The structure of product **2f** was confirmed by an X-ray diffraction study (Figure 2).[18]

Two interesting features are seen in the crystal phase of ketone **2f**: first, the phenyl and pyrazole rings are not coplanar, as the N(2)–N(1)–C(Ph)–C(Ph) torsion angle is –48.2(3)°. The twist is probably due to a steric repulsion between the phenyl ring and the methyl group at the C5 atom, which is confirmed by presence of shortened intramolecular contact C(13)···C(5) 3.19 Å, H(13c)···C(5) 2.75 Å, H(13c)···C(4) 2.67 Å (the van der Waals radii sum[19] is 3.42 Å for the C–C contact and 2.87 Å for the H–C). Second, the carbonyl group is not coplanar to the pyrazole

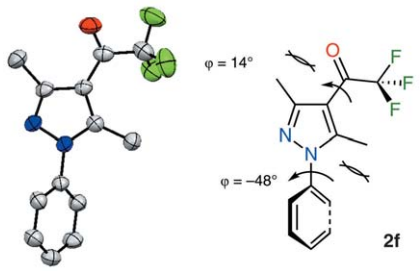
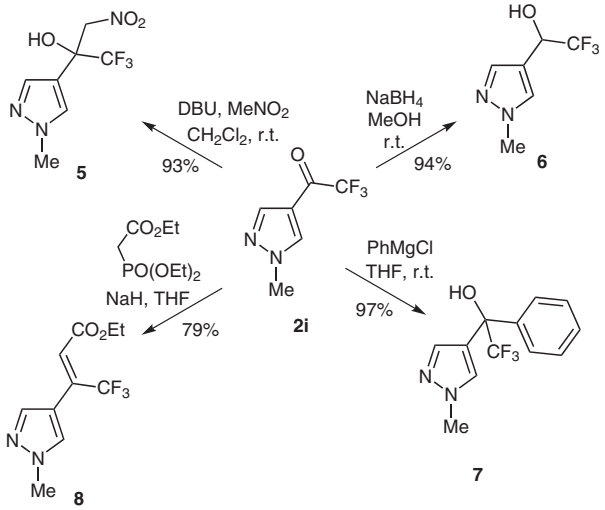


Figure 2 Molecular structure of compound **2f** according to XRD. Thermal ellipsoids are shown at 30% probability level. Atoms: C, grey; N, blue; O, red; F, yellow. Hydrogen atoms are omitted for clarity.

ring with the O(1)–C(11)–C(2)–C(1) torsion angle being 13.7(4)°. In this case, steric repulsion between trifluoroacetyl group and methyl substituents at C(1) and C(3) seems to be involved [the shortened intramolecular contacts O(1)–C(10) 2.95 Å (the van der Waals radii sum is 3.00 Å), C(13)···C(12) 3.31 Å (3.42 Å), H(13b)···C(12) 2.86 Å (2.87 Å), H(13b)···F(2) 2.45 Å (2.57 Å)].

To study the reactivity of the carbonyl group in the synthesized ketones, several representative reactions on the simplest pyrazole **2i** were performed (Scheme 3).



Scheme 3 Reactions of compound **2i**

Condensation of compound **2i** with nitromethane using DBU as the base smoothly afforded the corresponding product **5** in 93% yield. Reduction of the carbonyl group with sodium borohydride provided alcohol **6** in 94% yield. Addition of the Grignard reagent to **2i** gave alcohol **7**. The Horner–Wadsworth–Emmons reaction of **2i** led to alkene **8**.[20]

We have developed an easy practical method for trifluoroacetylation of electron-rich pyrazoles at C4. The reaction is performed in pyridine with trifluoroacetic anhydride as an acylating agent. Di- and trisubstituted pyrazole reacted at room temperature, while monosubstituted required heating.[21]

Solvents were purified according to standard procedures. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh). ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 499.9 MHz, 470.3 MHz, and 124.9 MHz referenced to TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded either on GC/MS instrument by electronic ionization (EI) or on LC/MS instrument by chemical ionization (CI).

2,2,2-Trifluoro-1-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)ethanone (2a), Typical Procedure

To a solution of pyrazole **1a** (50.0 g, 0.45 mol) in pyridine (200 mL, 2.6 mol) cooled to 0 °C $(CF_3CO)_2O$ (69.5 mL, 0.50 mol) was added dropwise. The mixture was stirred at r.t. for 12 h. H_2O (1000 mL) was added. The formed suspension was washed with CH_2Cl_2 (3 × 500 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under vacuum. The residue was purified by vacuum distillation (bp 107–110 °C/26.7 mbar) to afford pure **2a** (78.6 g, 0.38 mmol, 84%) as a yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 3.65 (s, 3 H), 2.35 (s, 3 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 174.2 (q, $^2J_{C,F}$ = 37.5 Hz), 150.4 (s), 146.6 (s), 116.2 (q, $^1J_{C,F}$ = 287.5 Hz), 112.5 (s), 35.7 (s), 13.8 (s), 11.6 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –74.3 (s).

MS: *m*/*z* = 207 $[M + 1]^+$.

2,2,2-Trifluoro-1-[1-(2-methoxyethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]ethanone (2b)

Following the typical procedure for **2a** from **1b** gave **2b** as a yellowish liquid; yield: 1.2 g (74%).

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 4.22 (t, *J* = 5.0 Hz, 2 H), 3.70 (t, *J* = 5.0 Hz, 2 H), 3.27 (s, 3 H), 2.51 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 175.3 (q, $^2J_{C,F}$ = 36.5 Hz), 150.7 (s), 147.8 (s), 115.8 (q, $^1J_{C,F}$ = 288.7 Hz), 112.2 (s), 70.3 (s), 56.6 (s), 48.5 (s), 13.7 (s), 11.4 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.3 (s).

MS: *m*/*z* = 251 $[M + 1]^+$.

1-(1-Benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2c)

Following the typical procedure for **2a** from **1c** gave **2c** as a yellowish liquid; yield: 14.2 g (81%).

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.34–7.28 (m, 3 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 5.29 (s, 2 H), 2.47 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 175.4 (q, $^2J_{C,F}$ = 35.1 Hz), 150.6 (s), 146.6 (s), 134.7 (s), 128.6 (s), 127.8 (s), 126.4 (s), 115.5 (q, $^1J_{C,F}$ = 280.4 Hz), 112.8 (s), 52.7 (s), 14.6 (q, $^5J_{C,F}$ = 3.8 Hz), 11.6 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.2 (s).

MS: *m*/*z* = 283 $[M + 1]^+$.

1-(1-*tert*-Butyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2d)

Following the typical procedure for **2a** from **1d** gave **2d** as a yellowish liquid; yield: 14.2 g (91%); bp 95–97 °C/0.53 mbar.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 2.70 (s, 3 H), 2.40 (s, 3 H), 1.68 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 176.3 (q, $^2J_{C,F}$ = 36.3 Hz), 147.4 (s), 147.0 (s), 116.3 (q, $^1J_{C,F}$ = 288.7 Hz), 114.2 (s), 61.5 (s), 29.9 (s), 14.3 (s), 14.2 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.0 (s).

MS: *m*/*z* = 249 $[M + 1]^+$.

1-(1-*tert*-Butyl-5-methoxy-3-methyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2e)
Following the typical procedure for **2a** from **1e** gave **2e** as a yellowish liquid; yield: 3.1 g (62%).

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 3.99 (s, 3 H), 2.35 (s, 3 H), 1.56 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 173.3 (q, $^2J_{C,F}$ = 36.3 Hz), 159.2 (s), 146.6 (s), 116.4 (q, $^1J_{C,F}$ = 283.5 Hz), 102.5 (s), 62.4 (s), 60.1 (s), 28.8 (s), 15.1 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.2 (s).

MS: *m*/*z* = 265 $[M + 1]^+$.

1-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2f)
Following the typical procedure for **2a** from **1f** gave **2f** as a yellowish solid; yield: 140.0 g (94%); bp 85–87 °C/0.53 mbar; mp 48 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.52 (m, 3 H), 7.41 (d, *J* = 7.5 Hz, 2 H), 2.53 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 175.9 (q, $^2J_{C,F}$ = 36.3 Hz), 151.6 (s), 141.2 (s), 137.9 (s), 129.4 (s), 129.2 (s), 125.8 (s), 116.2 (q, $^1J_{C,F}$ = 287.5 Hz), 113.6 (s), 14.5 (s), 13.1 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.9 (s).

MS: *m*/*z* = 270 $[M + 1]^+$.

2,2,2-Trifluoro-*N*-[3-methyl-1-phenyl-4-(trifluoroacetyl)-1*H*-pyrazol-5-yl]acetamide (2g)
Following the typical procedure for **2a** from **1g** using $(CF_3CO)_2O$ (4 equiv) gave **2g** as a yellowish oil that crystallized upon standing; yield: 23.1 g (74%). An analytically pure sample was obtained by crystallization (CH_2Cl_2) as a white solid; mp >200 °C.

^{1}H NMR (500 MHz DMSO-d_6, TMS): δ = 7.82 (d, *J* = 7.7 Hz, 2 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 7.29 (t, *J* = 7.7 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ = 175.5 (q, $^2J_{C,F}$ = 35.0 Hz), 158.5 (q, $^2J_{C,F}$ = 31.2 Hz), 154.0 (s), 150.2 (s), 139.9 (s), 128.8 (s), 126.5 (s), 123.4 (s), 117.2 (q, $^1J_{C,F}$ = 288.8 Hz), 116.5 (q, $^1J_{C,F}$ = 287.5 Hz), 105.4 (s), 14.8 (s).

^{19}F NMR (375 MHz, DMSO-d_6, $CFCl_3$): δ = –72.8 (s), –74.5 (s).

MS: *m*/*z* = 366 $[M + 1]^+$.

1-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2h)
Following the typical procedure for **2a** from **1h** gave **2h** as a yellowish liquid; yield: 2.5 g (90%); bp 98–100 °C/26.7 mbar.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.90 (s, 1 H), 3.84 (s, 3 H), 2.59 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 174.6 (q, $^2J_{C,F}$ = 36.5 Hz), 146.4 (q, $^4J_{C,F}$ = 5.0 Hz), 140.6 (q, $^4J_{C,F}$ = 5.0 Hz), 112.9 (s), 35.8 (s), 10.8 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –76.1 (s).

MS: *m*/*z* = 193 $[M + 1]^+$.

2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrazol-4-yl)ethanone (2i)
Following the typical procedure for **2a** from **1i** using $(CF_3CO)_2O$ (2 equiv) at reflux for 6 h gave **2i** as a yellowish solid; yield: 11.2 g (54%) ; bp 90–93 °C/26.7 mbar; mp 36 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 8.04 (s, 1 H), 7.96 (s, 1 H), 3.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 174.2 (q, $^2J_{C,F}$ = 37.5 Hz), 141.8 (s), 135.0 (s), 116.4 (s), 116.3 (q, $^1J_{C,F}$ = 287.5 Hz), 39.5 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.6 (s).

MS: *m*/*z* = 179 $[M + 1]^+$.

1-(1-Ethyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanone (2j)
Following the typical procedure for **2a** from **1j** using $(CF_3CO)_2O$ (2 equiv) at reflux for 6 h gave **2j** as a yellowish liquid; yield: 8.2 g (67%); bp 104–106 °C/13.3 mbar.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.99 (s, 1 H), 7.79 (s, 1 H), 4.05 (q, *J* = 7.5 Hz, 2 H), 1.29 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 174.1 (q, $^2J_{C,F}$ = 36.4 Hz), 141.3 (s), 133.5 (s), 116.1 (q, $^1J_{C,F}$ = 288.8 Hz), 115.1 (s), 47.5 (s), 14.3 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –76.2 (s).

MS: *m*/*z* = 193 $[M + 1]^+$.

1-[1-(1-Ethylpropyl)-1*H*-pyrazol-4-yl]-2,2,2-trifluoroethanone (2k)
Following the typical procedure for **2a** from **1k** using $(CF_3CO)_2O$ (2 equiv) at reflux for 6 h gave **2k** as a yellowish liquid; yield: 2.3 g (92%); bp 90–94 °C/0.53 mbar.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 8.10 (s, 1 H), 8.05 (s, 1 H), 3.98 (m, 1 H), 1.90 (m, 4 H), 0.79 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 174.2 (q, $^2J_{C,F}$ = 37.1 Hz), 141.4 (q, $^4J_{C,F}$ = 5.0 Hz), 133.3 (q, $^4J_{C,F}$ = 5.0 Hz), 117.2 (q, $^1J_{C,F}$ = 286.4 Hz), 67.5 (s), 27.5 (s), 10.0.

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –75.4 (s).

MS: *m*/*z* = 235 $[M + 1]^+$.

1,1,1-Trifluoro-2-(1-methyl-1*H*-pyrazol-4-yl)-3-nitropropan-2-ol (5)
To a solution of compound **2i** (1.00 g, 5.6 mmol) in CH_2Cl_2 (20 mL) was added $MeNO_2$ (0.68 g, 11.2 mmol) and DBU (1.20 g, 7.9 mmol). The mixture stirred for 16 h at r.t. 1 M aq HCl (20 mL) was added. The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under vacuum. The product was purified by column chromatography (EtOAc–hexane, 1:1) to provide pure **5** (1.25 g, 93%) as a white solid; mp 125 °C.

^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ = 7.86 (s, 1 H), 7.57 (s, 1 H), 7.47 (s, 1 H), 5.17 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H), 5.07 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ = 137.8 (s), 130.6 (s), 125.8 (q, $^1J_{C,F}$ = 285.0 Hz), 116.3 (s), 79.4 (s), 73.0 (q, $^2J_{C,F}$ = 30.0 Hz), 39.1 (s).

^{19}F NMR (375 MHz, DMSO-d_6, $CFCl_3$): δ = –78.76 (s).

MS: *m*/*z* = 240 $[M + 1]^+$.

2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrazol-4-yl)ethanol (6)
To a solution of compound **2i** (10.0 g, 56 mmol) in MeOH (100 mL) at –10 °C was added $NaBH_4$ (2.1 g, 56 mmol) in small portions, so that the temperature did not rise above 0 °C. After the addition, the mixture was allowed to warm to r.t. with stirring for 3 h. The mixture was diluted with EtOAc (150 mL) and H_2O (150 mL). The organic layer was separated and washed with H_2O (2 × 150 mL). The organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum to give pure **6** (9.5 g, 94%) as a white solid; mp 53–55 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.44 (s, 1 H), 7.43 (s, 1 H), 5.06 (br s, 1 H), 4.96 (q, $^3J_{H,F}$ = 7.5 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 138.0 (s), 129.8 (s), 124.6 (q, $^1J_{C,F}$ = 280.0 Hz), 116.4 (q, $^3J_{C,F}$ = 1.3 Hz), 65.5 (q, $^2J_{C,F}$ = 32.5 Hz), 38.7 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –79.7 (d, $^3J_{F,H}$ = 3.8 Hz).

MS: *m*/*z* = 181 $[M + 1]^+$.

3,3,3-Trifluoro-2-(1-methyl-1*H*-pyrazol-4-yl)-2-phenylpropanol (7)
To a solution of compound **2i** (500 mg, 2.8 mmol) in anhyd THF (5 mL) at 0 °C was added a solution of PhMgCl in THF (3.1 mmol, 1.1

equiv). The mixture was stirred at r.t. for 12 h. The mixture was evaporated under vacuum, and H_2O (1 mL) was added to the residue. The formed suspension was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under vacuum to afford pure **7** (690 mg, 2.7 mmol, 97%) as a grey solid; mp 114–116 °C.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.53 (s, 2 H), 7.35–7.31 (2 s, 4 H), 7.23 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 137.8 (s), 129.5 (s), 128.3 (s), 127.6 (s), 126.9 (s), 124.4 (q, $^1J_{C,F}$ = 281.2 Hz), 121.7 (s), 74.4 (q, $^2J_{C,F}$ = 30.0 Hz), 38.4 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –78.01 (s).

MS: m/z = 257 $[M + 1]^+$.

Ethyl (2*E*)-4,4,4-Trifluoro-3-(1-methyl-1*H*-pyrazol-4-yl)but-2-enoate (8)

To a suspension of NaH (248 mg, 60%, 6.2 mmol) in THF (10 mL) at 0 °C under stirring was added a solution of $(EtO)_2P(O)CH_2CO_2Et$ (1.38 g, 6.2 mmol) in THF (3 mL) dropwise. The mixture was vigorously stirred at r.t. for 30 min. The mixture was cooled to 0 °C again, and a solution of **2i** (1.0 g, 5.6 mmol) in anhyd THF (5 mL) was added dropwise. The mixture was additionally stirred at r.t. for 12 h. The solvent was evaporated under vacuum and H_2O (5 mL) was added. The formed suspension was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum to give pure **8** (1.1 g, 4.4 mmol, 79%) as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.96 (s, 1 H), 7.75 (s, 1 H), 6.36 (s, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.91 (s, 3 H), 1.28 (t, J = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$ TMS): δ = 164.5 (s), 140.0 (s), 133.1 (q, $^2J_{C,F}$ = 36.5 Hz), 132.2 (s), 122.5 (q, $^1J_{C,F}$ = 281.1 Hz), 118.4 (s), 110.4 (s), 60.8 (s), 38.7 (s), 13.7 (s).

^{19}F NMR (375 MHz, $CDCl_3$, $CFCl_3$): δ = –66.8 (s).

MS: m/z = 249 $[M + 1]^+$.

X-ray Diffraction Study

The colorless crystals of **2f** ($C_{13}H_{11}N_2OF_3$) are orthorhombic. At 293 K a = 25.174(2), b = 25.175(2), c = 8.123(1) Å, V = 5148.3(9) Å^3, M_r = 268.24, Z = 16, space group $Fdd2$, d_{calc} = 1.384 g/cm^3, μ(MoKα) = 0.119 mm^{-1}, F(000) = 2208. Intensities of 5809 reflections (1980 independent, R_{int} = 0.026) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 50°). The structure was solved by direct method using SHELXTL package.[22] Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for hydrogen atoms of methyl groups and n – 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 1971 reflections was converged to wR_2 = 0.092 (R_1 = 0.036 for 1477 reflections with $F > 4\sigma(F)$, S = 0.997). The final atomic coordinates, and crystallographic data for molecule **2f** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 951419).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) These authors contributed equally to this work.
(2) Selected reviews: (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Filler, R.; Saha, R. *Future Med. Chem.* **2009**, *1*, 777. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (e) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.
(3) For selected books, see: (a) *Modern Fluoroorganic Chemistry*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, **2004**. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, **2009**. (c) *Bioorganic and Medicinal Chemistry of Fluorine*; Begue, J.-P.; Bonnet-Delpon, D., Eds.; John Wiley & Sons: New Jersey, **2008**.
(4) (a) Yale, H. L. *J. Med. Pharm. Chem.* **1959**, *1*, 121. (b) Walborsky, H. M.; Lanc, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 4314. (c) Muller, N. *J. Pharm. Sci.* **1986**, *75*, 87. (d) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443. (e) Della, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 5221. (f) Chaume, G.; Barbeau, O.; Lesot, P.; Brigaud, T. *J. Org. Chem.* **2010**, *75*, 4135.
(5) (a) Ward, R. A.; Kettle, J. G. *J. Med. Chem.* **2011**, *54*, 4670. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
(6) Khodakovskiy, P. V.; Volochnyuk, D. M.; Panov, D. M.; Pervak, I. I.; Zarudnitskii, E. V.; Shishkin, O. V.; Yurchenko, A. A.; Shivanyuk, A.; Tolmachev, A. A. *Synthesis* **2008**, 948.
(7) (a) Khodakovskiy, P. V.; Volochnyuk, D. M.; Shivanyuk, A.; Shishkin, O. V.; Tolmachev, A. A. *Synthesis* **2008**, 3245. (b) Khodakovskiy, P. V.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2009**, 1099. (c) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, 967. (d) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, 979. (e) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, 1195. (f) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, 1633.
(8) For some reviews on the synthesis of pyrazoles and in particular trifluoromethyl-substituted pyrazoles, see: (a) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135.
(9) For the recent examples, see: (a) Marchetti, F.; Pettinari, C.; Pettinari, R.; Cerquetella, A.; Cingolani, A.; Chan, E. J.; Kozawa, K.; Skelton, B. W.; White, A. H.; Wanke, R.; Kuznetsov, M. L.; Martins, L. M. D. R. S.; Pombeiro, A. J. L. *Inorg. Chem.* **2007**, *46*, 8245. (b) Cingolani, A.; Marchetti, F.; Pettinari, C.; Pettinari, R.; Skelton, B. W.; Somers, N.; White, A. H. *Polyhedron* **2006**, *25*, 124. (c) Cingolani, A.; Marchetti, F.; Pettinari, C.; Pettinari, R.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **2004**, *43*, 4387. (d) Marchetti, F.; Pettinari, C.; Pettinari, R.; Cingolani, A.; Drozdov, A.; Troyanov, S. *J. Chem. Soc., Dalton Trans.* **2002**, 2616. (e) Cingolani, A.; Marchetti, F.; Pettinari, C.; Pettinari, R.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **2002**, *41*, 1151. (f) Pettinari, C.; Marchetti, F.; Cingolani, A.; Gindulyte, A.; Massa, L.; Rossi, M.; Caruso, F. *Eur. J. Inorg. Chem.* **2001**, *8*, 2171. (g) Marchetti, F.; Pettinari, C.; Pettinari, R.; Cingolani, A.; Camalli, M.; Spagna, R. *Inorg. Chim. Acta* **2000**, *299*, 65.

(10) (a) Soufyane, M.; Mirand, C.; Levy, J. *Tetrahedron Lett.* **1993**, *34*, 7737. (b) Okada, E.; Masuda, R.; Hojo, M. *Heterocycles* **1992**, *34*, 791. (c) Mellor, J. M.; Schofield, S. R.; Korn, S. R. *Tetrahedron* **1997**, *53*, 17163. (d) Singh, S. P.; Kumar, D. *J. Chem. Res., Synop.* **1997**, *4*, 142. (e) Touzot, A.; Soufyane, M.; Berber, H.; Toupet, L.; Mirand, C. *J. Fluorine Chem.* **2004**, *125*, 1299. (f) Rosa, F. A.; Machado, P.; Vargas, P. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synlett* **2008**, 1673.
(11) Sirisoma, N. S.; Ratra, G. S.; Tomizawa, M.; Casida, J. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2979.
(12) Sammelson, R. E.; Casida, J. E. *J. Org. Chem.* **2003**, *68*, 8075.
(13) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujishiro, M.; Nakamura, I.; Yamamoto, K. *J. Heterocycl. Chem.* **1993**, *30*, 389.
(14) Bravo, P.; Diliddo, D.; Resnati, G. *Tetrahedron* **1994**, *50*, 8827.
(15) Ryckmans, T.; Viehe, H.-G.; Feneau-Dupont, J.; Tinant, B.; Declerco, J.-P. *Tetrahedron* **1997**, *53*, 1729.
(16) (a) Balbiano, L. *Gazz. Chim. Ital.* **1889**, *19*, 131. (b) von Auwers, K.; Mauss, H. *J. Prakt. Chem.* **1927**, *117*, 331. (c) Shvartsberg, M. S.; Vasilevskii, S. F.; Kostrovskii, V. G.; Kotlyarevskii, I. L. *Chem. Heterocycl. Compd.* **1969**, *5*, 797. (d) Kano, K.; Scarpetti, D.; Warner, J. C.; Anselme, J.-P.; Springer, J. H.; Arison, B. H. *Can. J. Chem.* **1986**, *64*, 2211. (e) Usami, Y.; Watanabe, R.; Fujino, Y.; Yoneyama, H.; Harusawa, S.; Ichikawa, H.; Shibano, M.; Ishida, C. *Chem. Pharm. Bull.* **2012**, *60*, 1550.
(17) (a) Billen, D.; Chubb, N. A. L.; Gethin, D. M.; Hall, K. T.; Roberts, L. R.; Walshe, N. D. A. US 2005,148,649, **2005**. (b) Gebauer, O.; Heinemann, U.; Herrmann, S.; Gayer, H.; Hillebrand, S.; Elbe, H.-L.; Ebbert, R.; Wachendorff-Neumann, U.; Dahmen, P.; Kuck, K.-H. US 2007,259,893, **2007**. (c) Heinemann, U.; Herrmann, S.; Gayer, H.; Hillebrand, S.; Elbe, H.-L.; Ebbert, R.; Wachendorff-Neumann, U.; Dahmen, P.; Kuck, K.-H. WO 2005,056,558, **2005**. (d) Kataoka, K.; Suzuki, N.; Kosugi, T.; Imai, M.; Makino, H.; Takakuwa, M.; Unoki, G.; Fujino, A.; Oue, Y.; Yamakoshi, Y.; Sugiura, S.; Mitchell, D. R.; Simpson, D. J.; Harris, C. J.; Le, J. WO 2004,076,458, **2004**. (e) Albright, J.; Dusza, J. P. US 4178449, **1979**.
(18) Atomic coordinates and crystallographic parameters for compound **2f** were deposited at the Cambridge Crystallographic Data Centre under CCDC 951419.
(19) Zefirov, Y. V. *Kristallographiya* **1997**, *42*, 936.
(20) Wadsworth, W. S. Jr. *Org. React.* **1977**, *25*, 73.
(21) During preparation of this manuscript, a related publication appeared in the literature: Taydakov, I. V.; Krasnoselskiy, S. S. *Synthesis* **2013**, *45*, 2188.
(22) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

