Noncatalytic Electrophilic Oxyalkylation of 3-Aminopyrazoles with 2-(Trifluoroacetyl)-1,3-azoles

Pavel V. Khodakovskiy,[a,b] Pavel K. Mykhailiuk,*[a,b] Dmitriy M. Volochnyuk,[a,c] Andrey A. Tolmachev[a,b]

[a] Enamine Ltd., Oleksandra Matrosova Street 23, 01103 Kyiv, Ukraine

[b] Department of Chemistry, Kyiv National Taras Shevchenko University, Volodymyrska Street 64, 01033 Kyiv, Ukraine

[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, 02660 Kyiv-94, Ukraine
Fax +380(44)2351273; E-mail: Pashamk@gmx.de

Received 1 December 2009; revised 8 December 2009

Abstract: 2-(Trifluoroacetyl)-1,3-azoles reacted with 3-aminopyrazoles to give the corresponding trifluoromethyl-substituted alcohols. The conditions required for the reaction and the yields of the products were highly dependent on the electronic nature of the both the 1,3-azole and the 3-aminopyrazole units.

Key words: heterocycles, alkylations, fluoro compounds, alcohols, aminopyrazoles

The replacement of hydrogen by fluorine is a method that is widely used to improve the pharmacological characteristics of organic compounds.[1] Moreover, many commercially available pharmaceuticals containing contain fluorine, although fluorine rarely occurs in natural products.[2] The trifluoromethyl group, in particular, is one of the most attractive functional groups in organic chemistry, and the incorporation of this group into organic compounds remains a topic of growing interest.[3] Commercially available trifluoromethyl ketones, such as hexafluoroacetone and trifluoropyruvate, are highly valuable building blocks that are frequently used to prepare trifluoromethyl-containing compounds.[4] However, despite the considerable potential of both hexafluoroacetone and trifluoropyruvate,[4] the chemistry of other trifluoroacetyl ketones has received little attention.[5]

We recently began a project aimed at the synthesis and application of various trifluoroacetyl 1,3-azoles (**1**; Figure 1).[6] We have already shown that derivatives of indole, pyrrole, furan, thiophene, 1,3-thiazole, and 1,2-oxazole react smoothly with ketones **1** to form the corresponding trifluoromethyl-substituted alcohols.[6d,e] We now report an extension of this strategy to another electron-rich aromatic system, 3-aminopyrazole.[7]

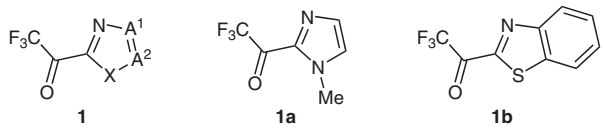


Figure 1 2-(Trifluoroacetyl)-1,3-azoles (**1**): 2-(trifluoroacetyl)-1-methyl-1*H*-imidazole (**1a**), and 2-(trifluoroacetyl)-1,3-benzothiazole (**1b**)

From a range of available representative ketones **1**,[6a] we selected 2-(trifluoroacetyl)-1-methyl-1*H*-imidazole (**1a**; Figure 1), which shows a relatively low activity of the carbonyl group, and the much more reactive 2-(trifluoroacetyl)-1,3-benzothiazole (**1b**) as model compounds, and we examined their *C*-oxyalkylation reactions with 3-aminopyrazoles **2**–**16** (Figure 2) to give the corresponding trifluoromethylated alcohols **2a**–**16a** and **2b**–**16b**, respectively (Scheme 1 and Table 1).

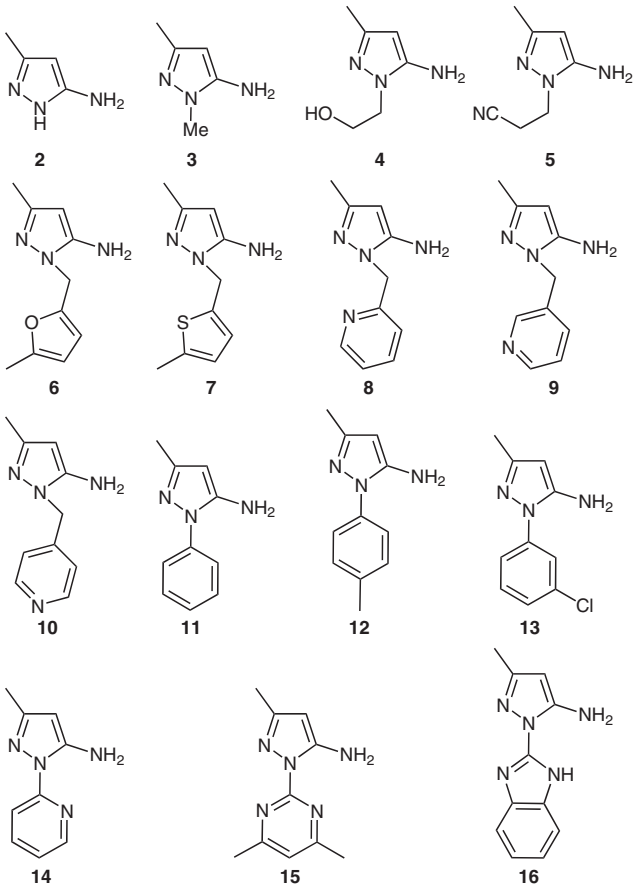
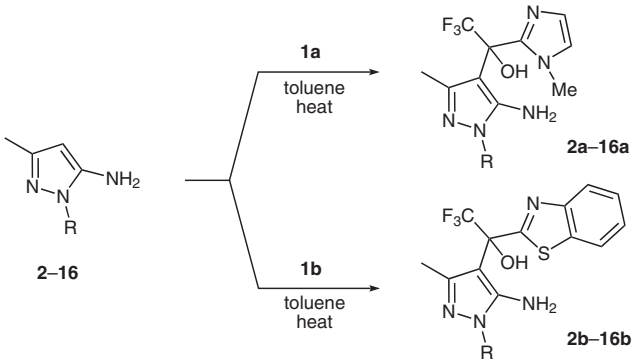


Figure 2 Substituted 3-aminopyrazoles **2**–**16**

The reaction proceeded smoothly when mixtures of the reactants were heated in toluene (Table 1). In most cases, the transformations of azole **1a** required longer reaction times than **1b**. For example, the products **3a**, **6a**, and **7a** were obtained by heating the reaction mixture at 100 °C

SYNTHESIS 2010, No. 7, pp 1195–1199
Advanced online publication: 29.01.2010
DOI: 10.1055/s-0029-1218657; Art ID: Z26009SS

for one hour, whereas the corresponding alcohols **3b**, **6b**, and **7b** were obtained within 30 minutes at the same temperature. The electronic nature of the 3-aminopyrazoles also affects the outcome of the reaction; for instance, replacing electron-donating alkyl groups at the *N*-atom in 3-aminopyrazoles **3**–**10** by electron-withdrawing phenyl or pyridyl substituents (compounds **11**–**14**) resulted in marked increases in the reaction time to two hours in the case of **1a** and one hour in the case of **1b**. Moreover, 3-aminopyrazoles **15** and **16**, which contain much more electron-withdrawing pyrimidine and benzoimidazole moieties, respectively, failed to react with **1a**. With **1b**, the products **15b** and **16b** were, however, obtained in 62% and 60% yields, respectively, by heating the appropriate reaction mixtures for two hours at 100 °C.



Scheme 1 Synthesis of trifluoroacetyl-substituted alcohols **2a**–**16a** and **2b**–**16b** from 3-aminopyrazoles and 2-(trifluoroacetyl)-1,3-azoles **1a** and **1b**

In summary, we have developed a very simple and efficient one-step procedure for preparing the trifluoroacetyl-substituted alcohols **2a**–**16a** and **2b**–**16b** from *N*-substituted derivatives of 3-aminopyrazole and 2-trifluoroacetyl-1,3-azoles. The necessary reaction conditions and yields of products depend markedly on the electronic natures of both the 1,3-azole and 3-aminopyrazole components.

Ketones **1a** and **1b** were synthesized as previously reported.[6a] The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer at 499.9, 124.9, and 470.3 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by atmospheric pressure chemical ionization (APCI).

Trifluoroacetyl Alcohols; General Procedure

A mixture of an appropriate trifluoromethyl ketone (1 mmol), 3-aminopyrazole (1 mmol), and toluene (2 mL) was stirred at 100 °C for the time shown in Table 1. The mixture was then cooled to r.t., and the resulting crystalline solid was filtered off. The product on the filter was washed with CCl_4 and recrystallized (*i*-PrOH).

1-(5-Amino-3-methyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (2a)

Colorless solid; yield: 42%; mp > 250 °C.

Table 1 Syntheses of Trifluoroacetyl-Substituted Alcohols **2a**–**16a** and **2b**–**16b**[a]

Azole	Ketone	Time (h)	Product	Yield (%)
2	**1a**	1	**2a**	42
2	**1b**	1	**2b**	52
3	**1a**	1	**3a**	76
3	**1b**	0.5	**3b**	74
4	**1b**	0.5	**4b**	88
5	**1b**	0.5	**5b**	92
6	**1a**	1	**6a**	93
6	**1b**	0.5	**6b**	59
7	**1a**	1	**7a**	61
7	**1b**	0.5	**7b**	69
8	**1b**	0.5	**8b**	68
9	**1b**	0.5	**9b**	64
10	**1b**	0.5	**10b**	79
11	**1a**	2	**11a**	65
11	**1b**	1	**11b**	75
12	**1a**	2	**12a**	70
13	**1b**	1	**13b**	78
14	**1a**	2	**14a**	64
14	**1b**	1	**14b**	73
15	**1a**	4	**15a**	0
15	**1b**	2	**15b**	62
16	**1a**	4	**16a**	0
16	**1b**	2	**16b**	60

[a] The reactions were all performed in toluene at 100 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.39 (s, 3 H), 3.37 (s, 3 H), 4.47 (br s, 3 H), 6.84 (s, 1 H), 7.18 (s, 1 H), 7.42 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 10.51, 33.98, 73.50 (q, $^2J_{CF}$ = 30.6 Hz), 96.71, 123.99, 125.68, 126.10 (q, $^1J_{CF}$ = 287.1 Hz), 140.02, 144.26, 152.35.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.65.

MS (APCI): *m/z* = 276 [M + 1].

1-(5-Amino-3-methyl-1*H*-pyrazol-4-yl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (2b)

Yield: 52%; mp 172–173 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.70 (s, 3 H), 3.90–5.90 (br s, 3 H), 7.50 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 7.0 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.32 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.22, 76.63 (q, $^2J_{CF}$ = 30.2 Hz), 97.93, 122.79, 123.97, 125.70 (q, $^1J_{CF}$ = 288.0 Hz), 126.49, 126.90, 135.53, 140.47, 152.04, 172.25.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.89.

MS (APCI): *m/z* = 329 [M + 1].

1-(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (3a)
Colorless solid; yield: 76%; mp >235 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.25 (s, 3 H), 3.37 (s, 3 H), 3.42 (s, 3 H), 4.95 (br s, 2 H), 6.86 (s, 1 H), 7.19 (s, 1 H), 7.49 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.27, 34.01, 34.28, 73.46 (q, $^2J_{CF}$ = 30.6 Hz), 94.41, 123.98, 125.77, 126.13 (q, $^1J_{CF}$ = 286.7 Hz), 144.01, 144.02, 146.40.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –77.06.

MS (APCI): *m/z* = 290 [M + 1].

1-(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (3b)
Colorless solid; yield: 74%; mp >245 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.54 (s, 3 H), 3.45 (s, 3 H), 5.23 (s, 2 H), 7.50 (dd, *J* = 7.2 Hz, 1 H), 7.56 (dd, *J* = 7.6, 7.2 Hz, 1 H), 8.11 (d, *J* = 7.6 Hz, 1 H), 8.13 (d, *J* = 7.2 Hz, 1 H), 8.30 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.94, 34.33, 76.60 (q, $^2J_{CF}$ = 30.2 Hz), 95.42, 122.80, 123.99, 125.79 (q, $^1J_{CF}$ = 288.0 Hz), 126.56, 126.94, 135.52, 144.20, 146.48, 151.93, 172.21.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.32.

MS (APCI): *m/z* = 343 [M + 1].

1-[5-Amino-1-(2-hydroxyethyl)-3-methyl-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (4b)
Colorless solid; yield: 88%; mp 233–234 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.54 (s, 3 H), 3.65 (m, 2 H), 3.85 (m, 2 H), 4.97 (m, 1 H), 5.17 (s, 2 H), 7.51 (dd, *J* = 8.0, 6.0 Hz, 1 H), 7.57 (dd, *J* = 8.0, 6.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.27 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.08, 49.45, 60.43, 76.64 (q, $^2J_{CF}$ = 30.2 Hz), 95.46, 122.81, 123.98, 125.78 (q, $^1J_{CF}$ = 288.0 Hz), 126.55, 126.93, 135.51, 144.51, 146.71, 151.96, 172.20.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.95.

MS (APCI): *m/z* = 373 [M + 1].

3-{5-Amino-4-[1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoro-1-hydroxyethyl]-3-methyl-1*H*-pyrazol-1-yl}propanenitrile (5b)
Colorless solid; yield: 92%; mp 195 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.56 (s, 3 H), 2.90 (t, *J* = 6.5 Hz, 2 H), 4.08 (t, *J* = 6.5 Hz, 2 H), 5.40 (br s, 2 H), 7.51 (dd, *J* = 8.0, 6.5 Hz, 1 H), 7.57 (dd, *J* = 8.0, 6.5 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.14, 17.58, 42.28, 76.58 (q, $^2J_{CF}$ = 30.2 Hz), 95.42, 119.06, 122.83, 123.99, 125.73 (q, $^1J_{CF}$ = 288.0 Hz), 126.59, 126.96, 135.52, 145.52, 146.57, 151.93, 172.06.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.00.

MS (APCI): *m/z* = 382 [M + 1].

1-{5-Amino-1-[(5-methyl-2-furyl)methyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (6a)
Colorless solid; yield: 93%; mp 217–219 °C (sublimation).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.20 (s, 3 H), 3.44 (s, 3 H), 4.90 (br s, 2 H), 5.00 (s, 2 H), 5.98 (s, 1 H), 6.09 (s, 1 H), 6.85 (s, 1 H), 6.88 (s, 1 H), 7.18 (s, 1 H), 7.42 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.70, 34.43, 44.20, 73.34 (q, $^2J_{CF}$ = 30.2 Hz), 97.57, 106.98, 109.31, 124.46, 125.62 (q, $^1J_{CF}$ = 288.0 Hz), 125.96, 137.45, 143.71, 144.91, 148.85, 151.65.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.91.

MS (APCI): *m/z* = 356 [M + 1].

1-{5-Amino-1-[(5-methyl-2-furyl)methyl]-1*H*-pyrazol-4-yl}-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (6b)
Colorless solid; yield: 59%; mp 174–175 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.19 (s, 3 H), 5.03 (s, 2 H), 5.34 (s, 2 H), 5.98 (s, 1 H), 6.19 (s, 1 H), 7.29 (s, 1 H), 7.50 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 7.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.29 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 13.74, 44.14, 75.91 (q, $^2J_{CF}$ = 30.2 Hz), 97.46, 107.02, 109.95, 122.78, 123.70, 125.13 (q, $^1J_{CF}$ = 288.0 Hz), 126.22, 126.92, 134.97, 137.40, 145.28, 148.59, 151.82, 153.23, 172.32.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.77.

MS (APCI): *m/z* = 409 [M + 1].

1-{5-Amino-1-[(5-methyl-2-thienyl)methyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (7a)
Colorless solid; yield: 61%; mp 185–186 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.36 (s, 3 H), 3.43 (s, 3 H), 4.94 (br s, 2 H), 5.16 (s, 2 H), 6.61 (m, 1 H), 6.74 (m, 1 H), 6.85 (s, 1 H), 6.87 (s, 1 H), 7.18 (s, 1 H), 7.40 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.36, 34.43, 45.95, 73.30 (q, $^2J_{CF}$ = 30.2 Hz), 97.53, 124.45, 125.14, 125.60 (q, $^1J_{CF}$ = 288.0 Hz), 125.92, 126.36, 137.58, 137.68, 139.70, 143.71, 144.63.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.93.

MS (APCI): *m/z* = 372 [M + 1].

1-{5-Amino-1-[(5-methyl-2-thienyl)methyl]-1*H*-pyrazol-4-yl}-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (7b)
Colorless solid; yield: 69%; mp 209–210 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.35 (s, 3 H), 5.19 (s, 2 H), 5.41 (s, 2 H), 6.60 (s, 1 H), 6.81 (m, 1 H), 7.30 (s, 1 H), 7.49 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 7.0 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.35 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.36, 45.82, 75.92 (q, $^2J_{CF}$ = 31.0 Hz), 97.37, 122.79, 123.69, 125.13, 125.14 (q, $^1J_{CF}$ = 288.0 Hz), 126.21, 126.92, 134.98, 137.22, 137.61, 139.97, 145.06, 153.22, 172.43.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.81.

MS (APCI): *m/z* = 425 [M + 1].

1-[5-Amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (8b)
Colorless solid; yield: 68%; mp 168–169 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.22 (s, 2 H), 5.45 (s, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.28 (dd, *J* = 8.0, 4.5 Hz, 1 H), 7.35 (s, 1 H), 7.50 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.56 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.74 (dd, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.34 (br s, 1 H), 8.52 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.79, 75.94 (q, $^2J_{CF}$ = 31.0 Hz), 97.76, 121.81, 122.81, 123.02, 123.73, 125.14 (q,

$^1J_{CF}$ = 288.0 Hz), 126.25, 126.95, 135.01, 137.52, 137.87, 146.12, 149.51, 153.24, 157.40, 172.34.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.81.

MS (APCI): *m/z* = 406 [M + 1].

1-[5-Amino-1-(pyridin-3-ylmethyl)-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (9b)
Colorless solid; yield: 64%; mp 175–176 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.19 (s, 2 H), 5.47 (s, 2 H), 7.30–7.39 (m, 2 H), 7.46–7.60 (m, 3 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.33 (br s, 1 H), 8.40 (s, 1 H), 8.46 (d, *J* = 3.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 48.16, 75.91 (q, $^2J_{CF}$ = 30.2 Hz), 97.66, 122.80, 123.72, 123.94, 125.13 (q, $^1J_{CF}$ = 288.0 Hz), 126.24, 126.93, 133.44, 135.02, 135.65, 137.94, 145.78, 148.96, 149.17, 153.23, 172.28.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.81.

MS (APCI): *m/z* = 406 [M + 1].

1-[5-Amino-1-(pyridin-4-ylmethyl)-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (10b)
Colorless solid; yield: 79%; mp 180–181 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.20 (s, 2 H), 5.44 (s, 2 H), 7.04 (m, 2 H), 7.38 (s, 1 H), 7.50 (dd, *J* = 8.0, 6.5 Hz, 1 H), 7.56 (dd, *J* = 8.0, 6.5 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.34–8.57 (m, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.50, 75.91 (q, $^2J_{CF}$ = 30.2 Hz), 97.65, 122.49, 122.81, 123.72, 125.17 (q, $^1J_{CF}$ = 288.0 Hz), 126.24, 126.94, 135.05, 138.15, 146.16, 146.95, 150.05, 153.25, 172.41.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.79.

MS (APCI): *m/z* = 406 [M + 1].

1-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (11a)
Colorless solid; yield: 65%; mp 247 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.35 (s, 3 H), 3.46 (s, 3 H), 5.16 (br s, 2 H), 6.91 (s, 1 H), 7.25 (s, 1 H), 7.32 (t, *J* = 7.0 Hz, 1 H), 7.47 (dd, *J* = 8.0, 7.0 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.75 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.48, 34.06, 73.54 (q, $^2J_{CF}$ = 30.6 Hz), 95.75, 123.52, 124.19, 125.89, 126.12 (q, $^1J_{CF}$ = 286.7 Hz), 126.85, 129.59, 139.22, 143.71, 146.49, 146.85.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.92.

MS (APCI): *m/z* = 352 [M + 1].

1-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (11b)
Colorless solid; yield: 75%; mp 237 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.63 (s, 3 H), 5.39 (br s, 2 H), 7.34 (t, *J* = 7.3, 7.2 Hz, 1 H), 7.48 (dd, *J* = 8.0, 7.5 Hz, 1 H), 7.51–7.63 (m, 5 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.52 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.15, 76.69 (q, $^2J_{CF}$ = 30.6 Hz), 96.54, 122.90, 123.85, 124.08, 125.79 (q, $^1J_{CF}$ = 288.0 Hz), 126.68, 127.04, 127.11, 129.66, 135.55, 138.98, 146.51, 146.92, 151.93, 172.75.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.07.

MS (APCI): *m/z* = 405 [M + 1].

1-[5-Amino-3-methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl]-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (12a)
Colorless solid; yield: 70%; mp > 250 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.36 (s, 3 H), 2.34 (s, 3 H), 3.46 (s, 3 H), 5.06 (s, 2 H), 6.90 (s, 1 H), 7.23 (s, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.70 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.46, 21.01, 34.03, 73.53 (q, $^2J_{CF}$ = 30.6 Hz), 95.51, 123.58, 124.15, 125.89, 126.11 (q, $^1J_{CF}$ = 286.7 Hz), 129.99, 136.22, 136,74, 143.76, 146.33, 146.51.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.61.

MS (APCI): *m/z* = 366 [M + 1].

1-[5-Amino-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (13b)
Colorless solid; yield: 78%; mp 245–246 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.63 (s, 3 H), 5.54 (s, 2 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.46–7.61 (m, 4 H, 3 × CH, OH), 7.63 (s, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.55 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.14, 76.64 (q, $^2J_{CF}$ = 30.2 Hz), 97.08, 122.02, 122.91, 123.21, 124.08, 125.73 (q, $^1J_{CF}$ = 288.0 Hz), 126.72, 126.77, 127.06, 131.26, 133.90, 135.53, 140.33, 146.91, 147.64, 151.90, 171.55.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.93.

MS (APCI): *m/z* = 439 [M + 1].

1-(5-Amino-3-methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)-2,2,2-trifluoro-1-(1-methyl-1*H*-imidazol-2-yl)ethanol (14a)
Colorless solid; yield: 64%; mp 218 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.36 (s, 3 H), 3.47 (s, 3 H), 6.66 (s, 2 H), 6.91 (s, 1 H), 7.24 (m, 2 H), 7.73 (s, 1 H), 7.79 (d, *J* = 8.5 Hz, 1 H), 7.92 (dd, *J* = 8.5 Hz, 1 H), 8.39 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.59, 34.03, 73.56 (q, $^2J_{CF}$ = 30.2 Hz), 94.29, 113.49, 120.36, 124.16, 125.95, 126.20 (q, $^1J_{CF}$ = 287.6 Hz), 139.40, 143.60, 147.18, 148.47, 148.68, 154.40.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.77.

MS (APCI): *m/z* = 353 [M + 1].

1-(5-Amino-3-methyl-1-pyridin-2-yl-1*H*-pyrazol-4-yl)-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (14b)
Colorless solid; yield: 73%; mp 184–185 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.66 (s, 3 H), 6.93 (s, 2 H), 7.25 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.53 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.59 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.93 (dd, *J* = 8.0 Hz, 1 H), 8.15 (m, 2 H), 8.40 (d, *J* = 4.0 Hz, 1 H), 8.45 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.32, 76.67 (q, $^2J_{CF}$ = 30.2 Hz), 95.26, 113.65, 120.51, 122.87, 124.11, 125.84 (q, $^1J_{CF}$ = 288.0 Hz), 126.68, 127.02, 135.56, 139.78, 147.18, 148.54, 148.82, 151.92, 154.35, 171.62.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.95.

MS (APCI): *m/z* = 406 [M + 1].

1-[5-Amino-1-(4,6-dimethylpyrimidin-2-yl)-3-methyl-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (15b)
Colorless solid; yield: 62%; mp 187 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.68 (s, 3 H), 2.45 (s, 6 H), 6.84 (s, 2 H), 7.12 (s, 1 H), 7.53 (dd, *J* = 8.0, 6.5 Hz, 1 H), 7.59 (dd, *J* = 8.5, 6.5 Hz, 1 H), 8.14 (d, *J* = 8.5 Hz, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 8.45 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.36, 23.91, 76.62 (q, $^2J_{CF}$ = 29.8 Hz), 94.91, 116.98, 122.89, 124.11, 125.82 (q, $^1J_{CF}$ = 288.0 Hz), 126.69, 127.02, 135.54, 148.90, 149.30, 151.90, 157.17, 168.60, 171.62.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –75.94.

MS (APCI): *m/z* = 435 [M + 1].

1-[5-Amino-1-(1*H*-benzimidazol-2-yl)-3-methyl-1*H*-pyrazol-4-yl]-1-(1,3-benzothiazol-2-yl)-2,2,2-trifluoroethanol (16b)
Colorless solid; yield: 60%; mp 210–211 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.73 (s, 3 H), 7.00 (s, 2 H), 7.17 (m, 2 H), 7.41 (m, 1 H), 7.49–7.63 (m, 3 H), 8.16 (m, 2 H), 8.53 (s, 1 H), 12.78 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.22, 76.50 (q, $^2J_{CF}$ = 30.2 Hz), 95.02, 111.69, 118.16, 122.27, 122.49, 122.92, 124.16, 125.75 (q, $^1J_{CF}$ = 288.0 Hz), 126.73, 127.07, 132.61, 135.50, 141.70, 147.33, 148.38, 150.12, 151.96, 171.43.

^{19}F NMR (470 MHz, DMSO-d_6): δ = –76.28.

MS (APCI): *m/z* = 445 [M + 1].

References

(1) (a) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645. (b) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**. (c) Smits, R.; Damiano Cadicamo, C.; Burger, K.; Koksch, B. *Chem. Soc. Rev.* **2008**, *37*, 1727. (d) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (e) Dave, R.; Badet, B.; Meffre, P. *Amino Acids* **2004**, *24*, 245. (f) *Fluorine-Containing Amino Acids*; Kukhar, V. P.; Soloshonok, V. A., Eds.; Wiley: New York, **1995**.

(2) (a) Harper, D. B.; O'Hagan, D. *Nat. Prod. Rep.* **1994**, 123. (b) Murphy, C. D.; Schaffrath, C.; O'Hagan, D. *Chemosphere* **2003**, 455.

(3) (a) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (c) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (d) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189. (e) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.

(4) (a) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635. (b) Nenaidenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Russ. Chem. Rev.* **1999**, *68*, 437. (c) Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207. (d) Dolenský, B.; Kvíčala, J.; Paleček, J.; Paleta, O. *J. Fluorine Chem.* **2002**, *115*, 67. (e) Friezer, R. W.; Ducharme, Y.; Ball, R. G.; Blouin, M.; Boulet, L.; Côté, B.; Frenette, R.; Girard, M.; Guay, D.; Huang, Z.; Jones, T. R.; Laliberté, F.; Lynch, J. J.; Mancini, J.; Martins, E.; Masson, P.; Muise, E.; Pon, D. J.; Siegl, P. K. S.; Styhler, A.; Tsou, N. N.; Turner, M. J.; Young, R. N.; Girard, Y. *J. Med. Chem.* **2003**, *46*, 2413. (f) Middleton, L. *J. Am. Chem. Soc.* **1964**, *86*, 4948. (g) Palecek, J.; Paleta, O. *Synthesis* **2004**, 521. (h) Braun, R. A. *J. Org. Chem.* **1966**, *31*, 3828. (i) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron* **2003**, *59*, 1647.

(5) (a) Regel, E.; Buechel, K. H. *Liebigs Ann. Chem.* **1977**, 145. (b) Kawase, M.; Sakagami, H.; Kusama, K.; Motohashi, N.; Saito, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3113. (c) Fujii, S.; Maki, Y.; Kimoto, H. *J. Fluorine Chem.* **1987**, *35*, 437. (d) Salvador, R. L.; Saucier, M. *Tetrahedron* **1971**, *27*, 1221.

(6) (a) 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. (b) Khodakovskiy, P. V.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2009**, 1099. (c) Khodakovskiy, P. V.; Volochnyuk, V.; Shivanyuk, A.; Shishkin, O. V.; Tolmachev, A. A. *Synthesis* **2008**, 3245. (d) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, DOI: 10.1055/s-0029-1219219. (e) Khodakovskiy, P. V.; Mykhailiuk, P. K.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2010**, DOI: 10.1055/s-0029-1218633.

(7) Pushechnikov, A. O.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2002**, 1140.