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Three-component synthesis of fluorinated pyrazoles from fluoroalkylamines, NaNO₂ and electron-deficient alkynes

Pavel K. Mykhailiukᵃᵇ⁺

Three-component reaction between RCF₂CH₂NH₂•HCl, NaNO₂ and alkynes drastically depends on substituents “R” and “R’”. The reaction gives the fluorinated pyrazoles in high yields when “R” is fluorine atom or fluoroalkyl group, and “R’” is an electron-withdrawing substituent. With other “R’” unexpected products are formed.

Introduction

Fluorinated heterocycles play a role in medicinal chemistry and agrochemistry. In particular, pyrazoles with diverse fluoroalkyl groups often comprise to bioactive molecules (Figure 1). Therefore, elaboration of practical and general methods to novel fluoroalkyl-substituted pyrazoles is truly important.

Among other methods to introduce fluoroalkyl groups into organic compounds, CF₃CH₂ is worth mentioning. In 1943 Gilman and Jones synthesized this reagent from trifluoroethyl amine hydrochloride and sodium nitrite. Since than CF₃CH₂ blossoms in organic chemistry and many research groups have been using it. In particular, recently a three-component reaction between CF₃CH₂NH₂•HCl (I), NaNO₂ and alkynes (Scheme 1, a) towards CF₃-substituted pyrazoles was elaborated. Mechanistically, the reaction proceeded via in situ-generated of CF₃CH₂N₂, followed by [3+2]-cycloaddition with alkynes. Later, this transformation was expanded towards CF₃-pyrazoles starting from amine 2 (Scheme 1, a). In both cases, however, only the electron-deficient alkynes reacted. Given that the target CF₃-CF₃-pyrazoles were synthesized in high yield and gram scale, herein I wanted to answer the following questions: is this reaction universal? Can other fluoroalkyl amines (scope of “R”) be used? Can other alkynes (scope of “R’”) be used (Scheme 1, b)?

Fig. 1. Drugs and agrochemicals – derivatives of pyrazoles with diverse fluoroalkyl groups.

Scope of amines

To study the scope of the reaction, a model alkyne was selected first – methyl propyolate. Then, diverse amine hydrochlorides RCF₂CH₂NH₂•HCl (3-10•HCl) were tested under the previously discovered conditions. In particular, a mixture of an amine, NaNO₂ and methyl propyolate was stirred...
in dichloromethane/water at room temperature for three days. The obtained unexpected results are summarized in Table 1.

Table 1. Scope of the reaction: amines.

<table>
<thead>
<tr>
<th>Amine</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1a</td>
<td>99% (X-Ray)</td>
<td>&quot;a&quot;</td>
</tr>
<tr>
<td>2</td>
<td>CF₃</td>
<td>2a</td>
<td>99%</td>
<td>&quot;a&quot;</td>
</tr>
<tr>
<td>3</td>
<td>H₂NCH₂CF₃</td>
<td>3a</td>
<td>87%</td>
<td>&quot;a&quot;</td>
</tr>
<tr>
<td>4</td>
<td>CHF₂</td>
<td>4a</td>
<td>97%</td>
<td>&quot;a&quot;</td>
</tr>
<tr>
<td>5</td>
<td>O₂Me</td>
<td>5b</td>
<td>51%</td>
<td>&quot;b&quot;</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>6b</td>
<td>17%</td>
<td>&quot;b&quot;</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>7b</td>
<td>ca. 50%</td>
<td>&quot;b&quot;</td>
</tr>
<tr>
<td>8</td>
<td>HOCH₂</td>
<td>8c</td>
<td>31%</td>
<td>&quot;c&quot;</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>9c</td>
<td>7%</td>
<td>&quot;c&quot;</td>
</tr>
<tr>
<td>10</td>
<td>BocNHCH₂</td>
<td>10e</td>
<td>47%</td>
<td>&quot;c&quot;</td>
</tr>
</tbody>
</table>

“Isolated yields. 0.5 eq. of amine (H₂NCH₂CF₃)₂*2HCl were used. 1.0 eq. of amine RCF₂CH₂NH₂*HCl was used. ²Product 6b was of 80% purity. ³Yield according to NMR of the reaction mixture.

Obviously, the reaction proceeded via in situ formation of RCF₂CHN₂ (Scheme 2, Path “a”).

The reaction of amine hydrochloride 5*HCl with non-fluorinated electron-withdrawing substituents (O₂Me), unexpectedly gave the pure diazo ketone 5b (X-Ray, Figure 2) in 51% yield and the starting alkyne. Presumably, the initially formed fluorinated diazo intermediate “Y” underwent acid-catalyzed aqueous hydrolysis (Scheme 2, Path “b”). Individual diazo ketone 5b, in turn, did not react with methyl propyolate even under heating.

Amine hydrochloride 6*HCl gave even more astonishing results: along with many unidentified products, diazo ketone 6b, and pure isoxazole 6c (X-Ray, Figure 2) were isolated in poor yields. Although the mechanism of formation of isoxazole 6c is not totally clear, it seems that the initially formed ketone 6b reacted with HNO₂ to give intermediate “Z” that further transformed into nitroloxide “W”. [3+2]-cycloaddition of “W” with methyl propyolate might have given isoxazole 6c (Scheme 2, Paths “b” and “c”). Indeed, additional mechanistic studies are needed to support/reject this suggestion (that is outside the scope of this work).

Reaction of amine hydrochloride 7*HCl gave no pyrazole-containing products, but unidentified side materials, the starting alkyne and diazo acetaldehyde 7b. The pure compound 7b was described in the literature before – in CDCl₃ it exists as a mixture of cis- and trans-totamers that have very characteristic signals in ¹H NMR. ¹² Worth mentioning, that previously Atherton, Fields, and Haszeldine also tried to generate CF₂HCHN₂, but with no success. ¹³

Amine hydrochloride 8*HCl also afforded isoxazole 8d (X-Ray, Figure 2) as a main reaction product (Scheme 2, Path “c”).

Amine hydrochloride 9*HCl with an alkyl substituent (Et) provided the complex mixture from which the two pure products were obtained: minor isoxazole 9c and major pyrazole 9d (Scheme 2, Paths “c” and “d”). Presumably, the initially
formed alkyl diazo ketone EtCOCHN₂ was quite active to rapidly react with methyl propionate (9d), rather than to be transformed into nitrile oxide (and subsequently into 9c).

Amine hydrochloride 10-HCl gave pure cyclic product 10e (X-Ray, Figure 2) in 59% yield (Scheme 2, Path “c”). In this reaction no pyrazole/isoxazole-containing products was observed in any significant amounts.

In a short summary, the studied reaction (Scheme 1) gives the needed fluorinated pyrazoles only if substituent “R” is F-atom (1) or fluoroalkyl group (2-4). Although only three groups - CF₃, C₂F₅H and C₂F₅X - were tested, it seems that the reaction would also work for all fluoroalkyl substituents “R”. With other substituents “R” - H, Alk, Ar, CO₂Alk (5-10) - the reaction gives unexpected products in low to moderate yields. Although, detailed mechanistic studies are needed to explain formation of these compounds (which is outside of the scope of the current project), the putative overall mechanistic profile is summarized in Scheme 2. These suggestions are supported by X-Ray data of all products and stable intermediates (Figure 2).

**Scope of alkynes**

Previously, we showed that *in situ*-generated FCF₂CHN₂ and CF₂CF₂CHN₂ reacted at room temperature only with electron-deficient alkynes. The reactivity of HCF₂CF₂CHN₂, however, could differ much, because HCF₂-substituent is a significantly weaker acceptor than the F- and CF₃-substituents. Therefore, amine hydrochloride 4-HCl was selected next, and its reactivity was tested toward diverse alkynes (Table 2). It was experimentally found that amine 4 behaved similar to the previously reported amines 1 and 2 (Table 2). In fact, electron-deficient alkynes 12-19 smoothly reacted to give pyrazoles 12a-19a in excellent yields of 91-97%. The reaction was extremely clean - no side products, - and practical - evaporation of organic phase afforded the pure pyrazoles without any further purification. For mono-substituted alkynes, regioselective formation of only 3,5-disubstituted pyrazoles was observed, that was supported by X-Ray studies (Figure 3).

While heterocyclic alkynes 20 gave pyrazole 20a in good yield of 73%, aromatic less- (21) or none activated (22) alkynes did not react, however.

### Table 2. Scope of the reaction: alkynes.

<table>
<thead>
<tr>
<th>Alkyne</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>4a</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>12a</td>
<td>97</td>
</tr>
<tr>
<td>13</td>
<td>13a</td>
<td>96 (X-Ray)</td>
</tr>
<tr>
<td>14</td>
<td>14a</td>
<td>96</td>
</tr>
<tr>
<td>15</td>
<td>15a</td>
<td>95</td>
</tr>
<tr>
<td>16</td>
<td>16a</td>
<td>94</td>
</tr>
<tr>
<td>17</td>
<td>17a</td>
<td>91</td>
</tr>
<tr>
<td>18</td>
<td>18a</td>
<td>92</td>
</tr>
<tr>
<td>19</td>
<td>19a</td>
<td>93 (X-Ray)</td>
</tr>
<tr>
<td>20</td>
<td>20a</td>
<td>73</td>
</tr>
<tr>
<td>21</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>no reaction</td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yields. 5.0 eq. of amine 4 were used*

In short summary, the studied reaction (Scheme 1) gives the needed fluorinated pyrazoles only with electron-deficient alkynes. The nature of fluoroalkyl-substituent “R” (F, CF₃,
CHF₂, etc) in amines does not have any significant impact on the reactivity of the corresponding diazo intermediate RCF₂CHN₂, and hence on the selection of alkynes.

Conclusions

The studied reaction towards fluorinated pyrazoles (Schemes 1, 3) is universal. It ideally works if substituent “R” is F-atom or fluoroalkyl group, and substituent R¹ is an electron-withdrawing group (EWG). With other “R” the reaction gives unexpected products in low yields. This method is highly practical: it works under air, in common solvents (water, dichloromethane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, whereas the reaction gives unexpected products in low yields. This method is highly practical: it works under air, in common solvents (water, dichloromethane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, whereas the reaction gives unexpected products in low yields. This method is highly practical: it works under air, in common solvents (water, dichloromethane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, whereas the reaction gives unexpected products in low yields. This method is highly practical: it works under air, in common solvents (water, dichloromethane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, whereas the reaction gives unexpected products in low yields. This method is highly practical: it works under air, in common solvents (water, dichloromethane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, whereas the reaction gives unexpected products in low yields.

Experimental part

Dichloromethane was purified by distillation. All reagents were available from Enamine Ltd. Melting points are uncorrected. ¹H- and ¹³C-NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9 MHz and 124.9 MHz, respectively). ¹³F-NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 376.7 Hz). Chemical shifts are reported in ppm downfield from Me₂Si (¹H, ¹³C) or upfield from CFCl₃ (¹³F) using conventional deuterium lock referencing as internal standards. MS analysis was performed on an LCMS instrument with chemical ionization, or on GCMS with ionization by electrospray.

General procedure

Representative synthesis:

**Methyl 3-(pentafluoroethyl)-1H-pyrazole-5-carboxylate (2a)**

To a stirred suspension of C₂F₅CH₂NH₂·HCl (120 mg, 0.64 mmol, 2.0 eq.) in CH₂Cl₂ (8.0 mL) / water (0.4 mL), sodium nitrite (64 mg, 0.96 mmol, 3.0 eq.) and methyl propionate (26 mg, 0.32 mmol, 1.0 eq.) were added. The reaction mixture was vigorously stirred 72 h at 20 °C. Water (2.0 mL) and CH₂Cl₂ (6 mL) were added. The organic layer was separated. The aqueous layer was washed with CH₂Cl₂ (2 × 6 mL). The combined organic layers were dried over Na₂SO₄ and evaporated under vacuum to provide the pure product 2a as a white solid (78 mg, 99%). M.p. = 79-80 °C.

**1H NMR** (500 MHz; CDCls; Me₂Si), δ: 11.81 (broad s, 1H, NH), 7.11 (s, 1H, CH), 3.96 (s, 3H, CH₃).

**13C NMR** (125 MHz; CDCls; Me₂Si), δ: 159.0 (s, CO), 142.8 (broad s, C), 135.5 (broad s, C), 118.6 (qt, ¹JCF = 285 Hz, ²JCF = 36 Hz, CF₂CF₂), 110.2 (qt, ¹JCF = 250 Hz, ²JCF = 39 Hz, CF₂CF₃), 108.6 (s, CH₂), 52.7 (s, CH₃).

**19F NMR** (375 MHz; CDCls; CFCl₃), δ: -85.1 (s, 3F, CF₂CF₃), -113.8 (s, 2F, CF₂CF₃).

**MS (CI):** m/z (%): 245 [M+1]⁺.

Anal. calcd for C₇H₅F₂N₂O₂: C, 34.44; H, 2.06; N, 11.48. Found: C, 34.14; H, 2.34; N, 11.68.

**Dimethyl 3,3′-(1,1,2,2,3,3,4,4-octafluorobutane-1,4-diyl)bis(1H-pyrazole-5-carboxylate) (3a)**

The reaction was performed following the general procedure, except for: 0.5 eq. (H₂NCH₂CF₂CF₂)₂2HCl + 1.0 eq. methyl propionate + 2 eq. NaNO₂. After 72 h at 20 °C, the reaction mixture was placed into the fridge at 0 °C for 12h. The formed light-yellow precipitate was filtered off, washed with water, and dried on air. Yellow solid (125 mg, 87%). M.p. > 200 ºC.

**1H NMR** (500 MHz; DMSO-d₆; Me₂Si), δ: 7.20 (s, 2H, CH₂), 3.86 (s, 6H, CH₃).

**13C NMR** (125 MHz; DMSO-d₆; Me₂Si), δ: 158.9 (s, CO), 140.8 (broad s, C), 135.6 (broad s, C), one CF₂ is not seen, 109.4 (tt, ¹JCF = 250 Hz, ²JCF = 38 Hz, CF₂), 108.6 (s, CH₂), 52.5 (s, CH₃).

**19F NMR** (375 MHz; DMSO-d₆; CFCl₃), δ: -108.1 (t, J = 11.3 Hz, 4F, CF₂), -121.5 (t, J = 11.3 Hz, 4F, CF₂).

**MS (CI):** m/z (%): 451 [M⁺+1]⁺.

Anal. calcd for C₇H₉F₄N₂O₂: C, 37.35; H, 2.24; N, 12.44. Found: C, 37.11; H, 2.03; N, 12.78.

**Methyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-5-carboxylate (4a)**

The reaction was performed following the general procedure. White solid (70 mg, 97%). M.p. 67-68 °C.

**1H NMR** (500 MHz; CDCls; Me₂Si), δ: 7.12 (s, 1H, CH), 6.13 (t, J = 52.0 Hz, 1H, CHF₂), 3.97 (s, 3H, CH₃).

**13C NMR** (125 MHz; CDCls; Me₂Si), δ: 159.1 (s, CO), 143.2 (t, J = 30 Hz, C), 135.1 (s, C), 109.3 (tt, ¹JCF = 250 Hz, ²JCF = 38 Hz, CF₂), tetra-CF₂ is not seen, 108.1 (s, CH₂), 52.4 (s, CH₃).

**19F NMR** (375 MHz; CDCls; CFCl₃), δ: -113.6 (broad s, 2F, CF₂), -136.4 (dt, ²JF₂ = 52.0 Hz, ²JF₂ = 7.5 Hz).

**MS (CI):** m/z (%): 227 [M⁺+1]⁺.


**Methyl 3-diazo-2-oxopropanoate (5b)**
The reaction was performed following the general procedure, except for: 1 eq. MeO₂CCF₂CH₂NH₂+HCl + 1.0 eq. methyl propionate + 3.0 eq. NaNO₂. ¹H NMR of the crude reaction mixture revealed the starting alkyne, diazo compound 5b and an unidentified side product (5-10% mol). The isolated reaction mixture was left at 20 °C for 24 h, whereas the partial crystallization occurred. The mixture was washed with cyclohexane (0.5 mL) to remove the liquid products (the alkyne and the side product). The remaining white solid was dried on air to afford the diazo ketone 5b (42 mg, 51%). M.p. 44-45 °C (dec.).

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 6.18 (s, 1H, CH), 3.88 (s, 3H, CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₂Si), δ: 176.1 (s, CO), 160.4 (s, CO), 56.7 (s, CH), 53.0 (s, CH₂).

MS (ES): m/z (%) = 128 [M]+.

Anal. calcd for C₇H₁₌N₂O₂: C, 58.71; H, 4.12; N, 7.33. Found: C, 58.40; H, 5.32; N, 7.63.

The experiment was also performed on 4-times larger scale, all results being reproducible.

2-Diazo-1-phenylethanone (6b), Methyl 3-benzoylisoxazole-5-carboxylate (6c)

The reaction was performed following the general procedure, except for: 1 eq. PhCF₂CH₂NH₂+HCl + 1.0 eq. methyl propionate + 3.0 eq. NaNO₂. The crude reaction mixture was purified by column chromatography using hexane/EtOAc = 5/1 as an eluent. The fraction with Rₑ = 0.4 (11 mg) contained ca. 90% of isoxazole 6c. This fraction was recrystallized from cyclohexane to afford the pure isoxazole 6c (8 mg, 10%) as a white solid. M.p. 95-96 °C.

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 8.32 (d, J = 8.0 Hz, 2H, Ph), 7.69 (t, J = 8.0 Hz, 1H, Ph), 7.55 (t, J = 8.0 Hz, 2H, Ph), 7.41 (s, 1H, CH), 4.02 (s, 3H, CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₂Si), δ: 184.0 (s, CO), 161.8 (s), 156.4 (s), 134.8 (s), 134.1 (s), 130.3 (s), 128.4 (s), 109.9 (s), 52.8 (s, CH₂).

MS (ES): m/z (%) = 231 [M]+.

Anal. calcd for C₁₂H₁₃N₂O₂: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.71; H, 3.59; N, 6.44.

Fraction with Rₑ = 0.3 (8 mg, 17%) contained ca. 90% of diazoketone 6b.

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 7.75 (d, J = 8.0 Hz, 2H, Ph), 7.55 (t, J = 8.0 Hz, 1H, Ph), 7.45 (t, J = 8.0 Hz, 2H, Ph), 7.91 (s, 1H, CH). M.p. 158-159 °C.

¹H NMR (500 MHz; DMSO-d₆; Me₂Si), δ: 7.58 (s, 1H, CH), 5.50 (broad s, 1H, CH), 4.77 (broad s, 2H, CH₂), 3.92 (s, 3H, CH₃).

¹³C NMR (125 MHz; DMSO-d₆; Me₂Si), δ: 192.6 (s, CO), 161.0 (s), 160.3 (s), 156.3 (s), 108.1 (s), 66.1 (s, CH₂), 53.3 (s, CH₃).

MS (ES): m/z (%) = 185 [M]+.

Anal. calcd for C₇H₁₅NO₂: C, 45.41; H, 3.81; N, 7.57. Found: C, 45.05; H, 4.12; N, 7.33.

The experiment was also successfully performed on 4-times larger scale.

Methyl 3-propionyloxazol-5-carboxylate (9e), Methyl 3-propionyl-1H-pyrazole-5-carboxylate (9d)

The reaction was performed following the general procedure. The crude reaction mixture was purified by column chromatography using hexane/EtOAc = 1/1 as an eluent. The fraction with Rₑ = 0.7 contained the pure isoxazole 9e (4 mg, 7%) as a white crystalline. M.p. 53-54 °C.

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 7.26 (s, 1H, CH), 4.00 (s, 3H, OCH₃), 3.12 (q, J = 8.0 Hz, 2H, CH₂CH₃), 1.24 (q, J = 8.0 Hz, 3H, CH₂CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₂Si), δ: 193.7 (s, CO), 161.5 (s), 161.0 (s), 144.3 (s), 107.4 (s), 52.8 (s, OCH₃), 33.1 (s, CH₂), 6.7 (s, CH₃).

MS (ES): m/z (%) = 183 [M]+.

Anal. calcd for C₉H₁₅NO₂: C, 54.26; H, 4.95; N, 7.65. Found: C, 52.22; H, 5.27; N, 7.31.

The fraction with Rₑ = 0.3 contained the pure isoxazole 9d (12 mg, 21%) as a white solid. M.p. 116-117 °C.

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 7.33 (s, 1H, CH), 3.96 (s, 3H, CH₂), 2.99 (q, J = 7.0 Hz, 2H, CH₂), 1.23 (t, J = 7.0 Hz, 3H, CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₂Si), δ: 193.7 (s, CO), 160.6 (s, CO), 109.5 (s, CH), tert-C are not seen, 53.3 (s), 32.2 (s), 7.4 (s). MS (ES): m/z (%) = 183 [M]+.

Anal. calcd for C₉H₁₅NO₂: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.41; H, 5.25; N, 15.69.

The experiment was also performed on 5-times larger scale.

5,5-Difluoro-1,3-oxazinan-2-one (10e)

The reaction was performed following the general procedure, except for: 1 eq. BocNHCH₂CF₂CH₂NH₂+HCl + 1.0 eq. methyl propionate + 3.0 eq. NaNO₂. The oil+crystalline crude reaction mixture was washed with cyclohexane (0.5 mL) to give the pure product 10e (21 mg, 47%) as a white crystalline. M.p. 66-67 °C.

¹H NMR (500 MHz; CDCl₃; Me₂Si), δ: 6.41 (broad s, 1H, NH), 4.37 (t, J = 10.5 Hz, 4H, CH₂), 3.69 (t, J = 10.5 Hz, 4H, CH₂).

¹³C NMR (125 MHz; CDCl₃; Me₂Si), δ: 152.0 (s, CO), 113.6 (t, J = 244 Hz, CF₂), 67.2 (t, J = 33 Hz, CH₂CF₂), 46.4 (t, J = 33 Hz, CH₂CF₂).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -1123 (qv, 2J(F,H) = 11.3 Hz, 2F, CF₂).

MS (ES): m/z (%) = 137 [M]+.

Anal. calcd for C₇F₁₂NO₂: C, 35.05; H, 3.68; N, 10.22. Found: C, 35.43; H, 3.46; N, 10.57.
Ethyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-5-carboxylate (12a)

Compound 12a was obtained as a white solid (74 mg, 97%) following the general procedure. M.p. = 67-68°C.

1H NMR (500 MHz; CDCl3; Me2Si), δ: 7.09 (s, 1H, CH), 6.11 (t, J = 52.0 Hz, 1H, CHF2), 4.40 (q, J = 7.0 Hz, 2H, CH2CH3), 1.38 (t, J = 7.0 Hz, 3H, CH2CH3).

13C NMR (125 MHz; CDCl3; Me2Si), δ: 158.6 (s, CO), 143.5 (t, J = 30 Hz, C), 135.3 (s, C), 111.7 (tt, JCHF = 245 Hz, JCF = 28 Hz, CF2), 109.3 (tt, JCHF = 250 Hz, JCF = 38 Hz, CF2), 107.9 (s, CH), 61.8 (s, OCH3), 13.8 (s, CH3).

19F NMR (375 MHz; CDCl3; CFCl3), δ: -113.6 (pseudo q, J = 4.0 Hz, 2F, CF2), -136.5 (dt, JH = 52.0 Hz, JF = 4.0 Hz).

MS (CI): m/z (%) = 241 [M+1]+.

Anal. calcd for C11H10F3N2O: C, 48.35; H, 3.82; N, 11.49.

The compound was obtained as a colorless oil (87 mg, 95%) following the general procedure.

Isopropyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-5-carboxylate (13a)

Compound 13a was obtained as a white solid (78 mg, 96%) following the general procedure. M.p. = 72-73°C.

1H NMR (500 MHz; CDCl3; Me2Si), δ: 7.08 (s, 1H, CH), 6.11 (tt, JH = 52.0 Hz, J = 16.0 Hz, 1H, CHF2CF2), 5.27 (m, J = 6.5 Hz, 1H, CHCH2), 1.36 (t, J = 6.5 Hz, 6H, CH2CH3).

13C NMR (125 MHz; CDCl3; Me2Si), δ: 158.1 (s, CO), 143.6 (t, J = 30 Hz, C), 135.6 (s, C), 111.6 (tt, JCHF = 245 Hz, JCF = 28 Hz, CF2), 109.3 (tt, JCHF = 250 Hz, JCF = 38 Hz, CF2), 107.7 (s, CH), 69.9 (s, OCH3), 21.3 (s, CH3).

19F NMR (375 MHz; CDCl3; CFCl3), δ: -113.7 (pseudo q, J = 4.0 Hz, 2F, CF2), -136.5 (dt, JH = 52.0 Hz, JF = 4.0 Hz).

MS (CI): m/z (%) = 255 [M+1]+.

Anal. calcd for C14H16F3N2O: C, 45.78; H, 3.97; N, 11.02. Found: C, 45.84; H, 4.31; N, 11.25.

Cyclobutyl-3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-5-ylmethanone (14a)

Compound 14a was obtained as a colorless oil (77 mg, 96%) following the general procedure.

1H NMR (500 MHz; CDCl3; Me2Si), δ: 6.97 (s, 1H, CH), 6.15 (tt, JH = 52.0 Hz, J = 16.0 Hz, 1H, CHF2CF2), 3.82 (qv, J = 7.0 Hz, 1H, CH2), 2.46 (m, 2H), 2.33 (m, 2H), 2.14 (m, 2H).

13C NMR (125 MHz; CDCl3; Me2Si), δ: 191.4 (s, CO), 143.8 (t, J = 30 Hz, C), 140.2 (s, C), 111.5 (tt, JCHF = 245 Hz, JCF = 28 Hz, CF2), 109.3 (tt, JCHF = 250 Hz, JCF = 38 Hz, CF2), 107.0 (s, CH), 42.4 (s), 26.5 (s), 24.3 (s), 17.8 (s, CH3).

19F NMR (375 MHz; CDCl3; CFCl3), δ: -113.5 (pseudo q, J = 4.0 Hz, 2F, CF2), -136.6 (dt, JH = 52.0 Hz, JF = 4.0 Hz).

MS (CI): m/z (%) = 251 [M+1]+.

Anal. calcd for C10H10F3N2O: C, 48.01; H, 4.03; N, 11.20. Found: C, 48.35; H, 3.82; N, 11.49.

1-[3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazol-5-yl]-2-phenylethanol (15a)

Compound 15a was obtained as a colorless oil (87 mg, 95%) following the general procedure.

Diethyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-4,5-dicarboxylate (17a)

Compound 17a was obtained as a yellowish oil (83 mg, 91%) following the general procedure.

1H NMR (500 MHz; CDCl3; Me2Si), δ: 6.28 (tt, JH = 52.0 Hz, J = 16.0 Hz, 1H, CHF2CF2), 3.92 (s, 3H, CH3), 3.90 (s, 3H, CH3).

13C NMR (125 MHz; CDCl3; Me2Si), δ: 161.9 (s, CO), 158.0 (s, CO), 141.3 (t, J = 28.7 Hz, CCF2), 134.7 (s, C), 115.6 (s, C), 111.4 (tt, JCF = 245 Hz, JCF = 28 Hz, CF2), 109.1 (tt, JCF = 250 Hz, JCF = 38 Hz, CF2), 53.8 (s, CH3), 53.7 (s, CH3).

19F NMR (375 MHz; CDCl3; CFCl3), δ: -114.9 (pseudo q, J = 4.0 Hz, 2F, CF2), -137.4 (dt, JH = 52.0 Hz, JF = 4.0 Hz).

MS (CI): m/z (%) = 285 [M+1]+.

Anal. calcd for C14H10F4N2O2: C, 38.04; H, 2.84; N, 9.86. Found: C, 38.37; H, 3.05; N, 9.51.

Diethyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-4,5-dicarboxylate (18a)

Compound 18a was obtained as colorless oil (92 mg, 92%) following the general procedure.
1H NMR (500 MHz; CDCl3; Me2Si), δ: 6.27 (tt, 2J.H,F = 52.0 Hz, 3J.H,F = 16.0 Hz, 1H, CHF2CF2), 4.41 (m, 4H, CH2+CH2), 1.37 (m, 6H, CH2+CH2).

13C NMR (125 MHz; CDCl3; Me2Si), δ: 161.4 (s, CO), 157.5 (s, CO), 141.5 (t, J = 28.7 Hz, CFC1), 134.5 (s, C), 116.1 (s, C), tert-CF2 is not seen, 109.4 (tt, 1J.C=C = 250 Hz, 2J.C=C = 38 Hz, CF2), 62.3 (s, OCH3), 61.9 (s, OCH3), 13.6 (s, CH3), 13.5 (s, CH3).

19F NMR (375 MHz; CDCl3; CFC1), δ: -114.7 (pseudo q, J = 4.0 Hz, 2F, CF2), -137.4 (dt, 2J.F,F = 52.0 Hz, 2J.F,P = 4.0 Hz).

MS (CI): m/z (%) = 313 [M+1]+

Anal. calc for C11H7F9N4O: C, 52.71; H, 3.87; N, 18.91. Found: C, 52.43; H, 2.58; N, 19.22.

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Notes and references


6 Gaseous CF3CHN was first described in: Gilman, H.; Jones, R. G. J. Am. Chem. Soc. 1943, 65, 1458.

7 More than 70 papers on CF3CHN have been published so far (Reaxys DB).


11 For a review on [3+2]-cycloadditions, see: G. Maas in Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, 2002, pp. 359-621.


14 CCDC numbers: 1036133 (5b), 1036136 (6c), 1036137 (7c), 1036137 (10e) 1036136 (13a), 1036134 (19a) and 1036135 (23a).


17 CCDC numbers: 1036133 (5b), 1036136 (6c), 1036137 (7c), 1036137 (10e) 1036136 (13a), 1036134 (19a) and 1036135 (23a).