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

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Three-component reaction between $RCF_2CH_2NH_2*HCl$, $NaNO_2$ and alkynes drastically depends on substituents "R" and "R¹". The reaction gives the fluorinated pyrazoles in high yields when "R" is fluorine atom or fluoroalkyl group, and "R¹" is an electron-withdrawing substituent. With other "R" unexpected products are formed.

Introduction

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Fluorinated heterocycles play a role in medicinal chemistry and agrochemistry.^{1,2} In particular, pyrazoles with diverse fluoroalkyl groups often comprise to bioactive molecules (Figure 1).^{3,4} Therefore, elaboration of practical and general methods to novel fluoroalkyl-substituted pyrazoles is truly important.



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

Among other methods to introduce fluoroalkyl groups into organic compounds,⁵ CF₃CHN₂ is worth mentioning. In 1943 *Gilman* and *Jones* synthesized this reagent from trifluoroethyl amine hydrochloride and sodium nitrite.⁶ Since than CF₃CHN₂ blossoms in organic chemistry⁷ and many research groups have been using it.⁸ In particular, recently a three-component reaction between CF₃CH₂NH₂*HCl (1), NaNO₂ and alkynes

(Scheme 1, a) towards CF_3 -substituted pyrazoles was elaborated.⁹ Mechanistically, the reaction proceeded via *in situ*-generated of CF_3CHN_2 , followed by [3+2]-cycloaddition with alkynes. Later, this transformation was expanded towards C_2F_5 -pyrazoles starting from amine **2** (Scheme 1, a).¹⁰ In both cases, however, only the electron-deficient alkynes reacted. Given that the target CF_3 -/ C_2F_5 -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)?



Results and Discussion

Scope of amines

To study the scope of the reaction, a model alkyne was selected first – methyl propyolate. Then, diverse amine hydrochlorides $RCF_2CH_2NH_2*HCl$ (**3-10***HCl) were tested under the previously discovered conditions.⁹ In particular, a mixture of an amine, NaNO₂ and methyl propyolate was stirred

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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.



aIsolated yields. b0.5 eq. of amine (H2NCH2C2F4)2*2HCl were used. ^c1.0 eq. of amine RCF₂CH₂NH₂*HCl was used. ^dProduct **6b** was of 80% purity. "Yield according to NMR of the reaction mixture.

Amine hydrochlorides 3*HCl and 4*HCl with fluorinated electron-withdrawing substituents gave the expected pyrazoles 3a and 4a in good yields of 87% and 97%, respectively.

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



Scheme 2. Proposed mechanistic profile of the reaction

The reaction of amine hydrochloride 5*HCl with nonfluorinated electron-withdrawing substituent (CO_2Me) . 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 acidcatalyzed 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 nitriloxide "W". [3+2]-cycloaddition of "W" with methyl propyolate might have given isoxazole 6c (Scheme 2, Paths "b" and "c").¹¹ Indeed, additional mechanistic studied are needed to support/reject this suggestion (that is outside the scope of this work).

Reaction of amine hydrochloride 7*HCl gave no pyrazolecontaining 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-rotamers 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 Journal Name

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formed alkyl diazo ketone $EtCOCHN_2$ was quite active to rapidly react with methyl propyolate (9d), rather than to be transformed into nitriloxide (and subsequently into 9c).

Amine hydrochloride 10*HCl gave pure cyclic product 10e (*X-Ray*, Figure 2) in 59% yield (Scheme 2, Path "e"). In this reaction no pyrazole/isoxazole-containg 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 Fatom (1) or fluoroalkyl group (2-4). Although only three groups - CF₃, C₂F₄H and C₃F₆X - were tested, it seems that the reaction would also work for all fluoroalkyl substituents "R". With other substitutents "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 CF₃CF₂CHN₂ reacted at room temperature only with electron-deficient alkynes.^{9,10a} The reactivity of HCF₂CF₂CHN₂, however, could differ much, because HCF₂substituent is a significantly weaker acceptor than the F- and CF₃-ones.¹⁵ Therefore, amine hydrochloride **4***HCl was selected next, and its reactivity was tested towards diverse alkynes (Table 2).¹⁶

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 alkyne **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.

	HCF ₂ CF ₂	+ NaNO ₂	+ R ¹ CH ₂ Cl ₂ /H	<u>→</u> ?
	2.0 eq.	3.0 eq.	1.0 eq. one-pot reaction	
	4*HCl		11-22	
Alkyne		Product		Yield (%) ^a
11	CO ₂ Me	4a	HCF ₂ CF ₂ N _N CO ₂ Me H	97
12	CO ₂ Et	12a	HCF ₂ CF ₂ N.N.CO ₂ Et	97
13	CO ₂ iPr	13 a	HCF ₂ CF ₂	96 (X-Ray)
14		14a	HCF ₂ CF ₂	96
15	Ph	15a	HCF_2CF_2 N N Ph	95
16	Ph O	16a	HCF_2CF_2 N H O	94
17	MeO ₂ C CO ₂ Me	17a	HCF ₂ CF ₂ CO ₂ Me	91
18	EtO ₂ C CO ₂ Et	18 a	HCF ₂ CF ₂ CO ₂ Et	92
19	Ph P'-Ph O	19a	HCF ₂ CF ₂ NNP-Ph HO	93 (X-Ray)
20	N N N N N N N N N N N N N N N N N N N	20a	HCF ₂ CF ₂ NNN H	73 ^b
21	CF3		no reaction ^b	
22			no reaction ^b	

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,

 CHF_2 , *etc*) in amines does not have any significant impact on the reactivity of the corresponding diazo intermediate RCF_2CHN_2 , and hence on the selection of alkynes.



Conclusions

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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 \mathbb{R}^1 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, dichloromehane), without any catalysts and at room temperature. Moreover, it gives pyrazoles in excellent yields, and mostly without purification (just evaporation of an organic phase). Gram quantities of the products can be rapidly synthesized. I believe that the developed useful protocol will find very soon wide practical application in medicinal chemistry and agrochemistry – areas, where fluoroalkyl pyrazoles play an important role.



Scheme 3. Scope of three-component synthesis of fluorinated pyrazoles.

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). ¹⁹F-NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 376.7 Hz). Chemical shifts are reported in ppm downfield from Me₄Si (¹H, ¹³C) or upfield from CFCl₃ (¹⁹F) 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 $C_2F_5CH_2NH_2 \cdot HCl$ (120 mg, 0.64 mmol, 2.0 eq.) in CH_2Cl_2 (8.0 mL) / water (0.4 mL), sodium nitrite (64 mg, 0.96 mmol, 3.0 eq.) and methyl propyolate (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 CH_2Cl_2 (6 mL) were added. The organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 × 6 mL). The combined organic layers were dried over Na_2SO_4 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; CDCl₃; Me₄Si), δ: 11.81 (broad s, 1H, N*H*), 7.11 (s, 1H, C*H*), 3.96 (s, 3H, C*H*₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 159.0 (s, CO), 142.8 (broad s, *C*), 135.5 (broad s, *C*), 118.6 (qt, ${}^{1}J_{C-F} = 285$ Hz, ${}^{2}J_{C-F} = 36$ Hz, CF₂CF₃), 110.2 (tq, ${}^{1}J_{C-F} = 250$ Hz, ${}^{2}J_{C-F} = 39$ Hz, CF₂CF₃), 108.6 (s, CH), 52.7 (s, CH₃).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -85.1 (s, 3F, CF₂CF₃), -113.8 (s, 2F, CF₂CF₃).

MS (CI): m/z (%) = 245 [M+1]⁺.

Anal. calcd for $C_7H_5F_5N_2O_2$: 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-1,4diyl)bis(1H-pyrazole-5-carboxylate) (3a)

The reaction was performed following the general procedure, except for: 0.5 eq. $(H_2NCH_2CF_2CF_2)_2*2HC1 + 1.0$ eq. methyl propyolate + 2 eq. NaNO₂. After 72 h at 20 °C, the reaction mixture was placed into the fringe 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 °C.

¹H NMR (500 MHz; DMSO-d₆; Me₄Si), δ: 7.20 (s, 2H, CH), 3.86 (s, 6H, CH₃).

¹³C NMR (125 MHz; DMSO-d₆; Me₄Si), δ: 158.9 (s, CO), 140.8 (broad s, *C*), 135.6 (broad s, *C*), one *C*F₂ is not seen, 109.4 (tt, ${}^{1}J_{C-F}$ = 250 Hz, ${}^{2}J_{C-F}$ = 38 Hz, *C*F₂), 108.6 (s, *C*H), 52.5 (s, *C*H₃).

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 $C_{14}H_{10}F_8N_4O_4$: 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; CDCl₃; Me₄Si), δ: 7.12 (s, 1H, CH), 6.13 (t, J = 52.0 Hz, 1H, CHF₂), 3.97 (s, 3H, CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ : 159.1 (s, CO), 143.2 (t, J = 30 Hz, C), 135.1 (s, C), 109.3 (tt, ${}^{1}J_{C-F} = 250$ Hz, ${}^{2}J_{C-F} = 38$ Hz, CF₂), tetr-CF₂ is not seen, 108.1 (s, CH), 52.4 (s, CH₃).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -113.6 (broad s, 2F, C*F*₂), -136.4 (dt, ${}^{2}J_{F-H}$ = 52.0 Hz, ${}^{2}J_{F-F}$ = 7.5 Hz).

MS (CI): m/z (%) = 227 [M+1]⁺.

Anal. calcd for $C_7H_6F_4N_2O_2$: C, 37.18; H, 2.67; N, 12.39. Found: C, 37.45; H, 2.32; N, 12.71.

Methyl 3-diazo-2-oxopropanoate (5b)

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The reaction was performed following the general procedure, except for: 1 eq. $MeO_2CCF_2CH_2NH_2*HCl + 1.0$ eq. methyl propyolate + 3.0 eq. $NaNO_2$. 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; Me₄Si), δ: 6.18 (s, 1H, C*H*), 3.88 (s, 3H, C*H*₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 176.1 (s, CO), 160.4 (s, CO), 56.7 (s, CH), 53.0 (s, CH₃).

MS (ES): m/z (%) = 128 [M]⁺.

Anal. calcd for $C_4H_4N_2O_3:$ C, 37.51; H, 3.15; N, 21.87. Found: C, 37.15; H, 3.38; N, 21.69.

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 propyolate + 3.0 eq. NaNO₂. The crude reaction mixture was purified by column chromatography using hexane/EtOAc = 5/1 as an eluent. The fraction with $R_F = 0.4$ (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; Me₄Si), 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; Me₄Si), δ: 184.0 (s, CO), 161.8 (s), 160.4 (s), 156.3 (s), 134.8 (s), 134.1 (s), 130.3 (s), 128.4 (s), 109.9 (s), 52.8 (s, CH₃).

MS (ES): m/z (%) = 231 [M]⁺.

Anal. calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.71; H, 3.59; N, 6.44.

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

¹H NMR (500 MHz; CDCl₃; Me₄Si), 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).

¹H NMR of **6b** was identical to that described for the individual compound.

The experiment was also performed on 10-times larger scale, all results being reproducible.

Methyl 3-glycoloylisoxazole-5-carboxylate (8c)

The reaction was performed following the general procedure, except for: 1 eq. HOCH₂CF₂CH₂NH₂*HCl + 1.0 eq. methyl propyolate + 3.0 eq. NaNO₂. ¹H NMR of the crude reaction mixture revealed ca. 50% of isoxazole **8c**. The oil+crystalline reaction mixture was washed with cyclohexane (0.5 mL) to give the pure isoxazole **8c** (18 mg, 31%) as a white solid. M.p. 158-159 °C. ¹H NMR (500 MHz; DMSO-d₆; Me₄Si), δ: 7.58 (s, 1H, CH), 5.50 (broad s, 1H, OH), 4.77 (broad s, 2H, CH₂), 3.92 (s, 3H, CH₃).

 13 C NMR (125 MHz; DMSO-d_6; Me₄Si), 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 C₇H₇NO₅: 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-propionylisoxazole-5-carboxylate (9c), 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 $R_F = 0.7$ contained the pure isoxazole **9c** (4 mg, 7%) as a white crystalline. M.p. 53-54 °C.

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 7.26 (s, 1H, C*H*), 4.00 (s, 3H, OC*H*₃), 3.12 (q, *J* = 8.0 Hz, 2H, C*H*₂CH₃), 1.24 (q, *J* = 8.0 Hz, 3H, CH₂CH₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), 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 $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.22; H, 5.27; N, 7.31.

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

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 7.33 (s, 1H, C*H*), 3.96 (s, 3H, C*H*₃), 2.99 (q, J = 7.0 Hz, 2H, C*H*₂), 1.23 (t, J = 7.0 Hz, 3H, C*H*₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), 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 (CI): m/z (%) = 183 [M+1]⁺. Anal. calcd for C₈H₁₀N₂O₃: 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 propyolate + 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; Me₄Si), δ : 6.41 (broads, 1H, N*H*), 4.37 (t, *J* = 10.5 Hz, 4H, CH₂), 3.69 (t, *J* = 10.5 Hz, 4H, CH₂).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), 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: -112.3 (qv, ³J(F,H) = 11.3 Hz, 2F, CF₂).

MS (ES): m/z (%) = 137 [M]⁺.

Anal. calcd for $C_4H_5F_2NO_2$: C, 35.05; H, 3.68; N, 10.22. Found: C, 35.43; H, 3.46; N, 10.57.

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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; Me₄Si), 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; Me₄Si), δ: 158.6 (s, CO), 143.5 (t, J = 30 Hz, C), 135.3 (s, C), 111.7 (tt, ¹J_{C-F} = 245 Hz, ²J_{C-F} = 28 Hz, CF₂), 109.3 (tt, ¹J_{C-F} = 250 Hz, ²J_{C-F} = 38 Hz, CF₂),107.9 (s, CH), 61.8 (s. OCH₂), 13.8 (s, CH₃).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -113.6 (pseudo q, J = 4.0 Hz, 2F, CF₂), -136.5 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 241 [M+1]⁺.

Anal. calcd for $C_8H_8F_4N_2O_2$: C, 40.01; H, 3.36; N, 11.66. Found: C, 40.33; H, 3.72; N, 11.47.

Isopropyl 3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-5carboxylate (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; Me₄Si), δ: 7.08 (s, 1H, C*H*), 6.11 (tt, ${}^{2}J_{\text{H-F}} = 52.0 \text{ Hz}$, ${}^{3}J_{\text{H-F}} = 16.0 \text{ Hz}$, 1H, C*H*F₂CF₂), 5.27 (m, *J* = 6.5 Hz, 1H, C*H*CH₃), 1.36 (t, *J* = 6.5 Hz, 6H, CHCH₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 158.1 (s, CO), 143.6 (t, J = 30 Hz, C), 135.6 (s, C), 111.6 (tt, ${}^{1}J_{C-F}$ = 245 Hz, ${}^{2}J_{C-F}$ = 28 Hz, CF₂), 109.3 (tt, ${}^{1}J_{C-F}$ = 250 Hz, ${}^{2}J_{C-F}$ = 38 Hz, CF₂),107.7 (s, CH), 69.9 (s, OCH), 21.3 (s, CH₃).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -113.7 (pseudo q, J = 4.0 Hz, 2F, CF₂), -136.5 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 255 [M+1]⁺.

Anal. calcd for $C_9H_{10}F_4N_2O_2$: C, 42.53; H, 3.97; N, 11.02. Found: C, 42.84; H, 4.31; N, 11.25.

Cyclobutyl[3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazol-5yl]methanone (14a)

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

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ: 6.97 (s, 1H, C*H*), 6.15 (tt, ${}^{2}J_{\text{H-F}} = 52.0$ Hz, ${}^{3}J_{\text{H-F}} = 16.0$ Hz, 1H, C*H*F₂CF₂), 3.82 (qv, *J* = 7.0 Hz, 1H, C*H*), 2.46 (m, 2H), 2.33 (m, 2H), 2.14 (m, 2H).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 191.4 (s, CO), 143.8 (t, J = 30 Hz, C), 140.2 (s, C), 111.5 (tt, ${}^{1}J_{C-F} = 245$ Hz, ${}^{2}J_{C-F} = 28$ Hz, CF₂), 109.3 (tt, ${}^{1}J_{C-F} = 250$ Hz, ${}^{2}J_{C-F} = 38$ 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, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 251 [M+1]⁺.

Anal. calcd for $C_{10}H_{10}F_4N_2O$: 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]-2phenylethanone (15a)

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

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 7.36-7.26 (m, 5H, *Ph*), 7.05 (s, 1H, *CH*), 6.12 (tt, ²*J*_{H-F} = 52.0 Hz, ³*J*_{H-F} = 16.0 Hz, 1H, *CH*F₂CF₂), 4.16 (s, 2H, *CH*₂).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 188.0 (s, CO), 143.4 (t, J = 28.7 Hz, CCF₂), 141.5 (s, C), 132.0 (s, Ph), 129.1 (s, Ph), 128.6 (s, Ph), 127.2 (s, Ph), 111.6 (tt, ¹ $J_{C-F} = 245$ Hz, ² $J_{C-F} = 28$ Hz, CF₂), 109.3 (tt, ¹ $J_{C-F} = 250$ Hz, ² $J_{C-F} = 38$ Hz, CF₂), 107.8 (s, CH), 46.1 (s, CH₂).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -113.4 (pseudo q, J = 4.0 Hz, 2F, CF₂), -136.4 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 287 [M+1]⁺.

Anal. calcd for $C_{13}H_{10}F_4N_2O$: C, 54.55; H, 3.52; N, 9.79. Found: C, 54.21; H, 3.78; N, 9.61.

1-[3-(1,1,2,2-tetrafluoroethyl)-1H-pyrazol-5-yl]-3-phenyl-1propanone (16a)

Compound **16a** was obtained as a colorless oil (91 mg, 94%) following the general procedure.

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 7.33-7.21 (m, 5H, *Ph*), 7.02 (s, 1H, *CH*), 6.12 (tt, ²*J*_{H-F} = 52.0 Hz, ³*J*_{H-F} = 16.0 Hz, 1H, *CH*F₂CF₂), 3.22 (t, J = 7.5 Hz, 2H, CH₂), 3.06 (t, J = 7.5 Hz, 2H, CH₂).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 190.0 (s, CO), 143.4 (t, *J* = 28.5 Hz, *C*CF₂), 141.6 (s, *C*), 139.7 (s, Ph), 128.3 (s, Ph), 128.0 (s, Ph), 126.1 (s, Ph), 111.6 (tt, ${}^{1}J_{C-F} = 245$ Hz, ${}^{2}J_{C-F} = 28$ Hz, *C*F₂), 109.3 (tt, ${}^{1}J_{C-F} = 250$ Hz, ${}^{2}J_{C-F} = 38$ Hz, *C*F₂), 107.3 (s, *C*H), 40.9 (s, *C*H₂), 29.2 (s, *C*H₂).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -113.5 (pseudo q, J = 4.0 Hz, 2F, CF₂), -136.4 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 301 [M+1]⁺.

Anal. calcd for $C_{14}H_{12}F_4N_2O$: C, 56.00; H, 4.03; N, 9.33. Found: C, 56.34; H, 3.76; N, 9.52.

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

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

¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 6.28 (tt, ²*J*_{H-F} = 52.0 Hz, ³*J*_{H-F} = 16.0 Hz, 1H, C*H*F₂CF₂), 3.92 (s, 3H, C*H*₃), 3.90 (s, 3H, C*H*₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), 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, ¹*J*_{C-F} = 245 Hz, ²*J*_{C-F} = 28 Hz, CF₂), 109.1 (tt, ¹*J*_{C-F} = 250 Hz, ²*J*_{C-F} = 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, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 285 [M+1]⁺.

Anal. calcd for $C_9H_8F_4N_2O_4{:}$ 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-4,5dicarboxylate (18a)

Compound **18a** was obtained as colorless oil (92 mg, 92%) following the general procedure.

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¹H NMR (500 MHz; CDCl₃; Me₄Si), δ : 6.27 (tt, ²*J*_{H-F} = 52.0 Hz, ³*J*_{H-F} = 16.0 Hz, 1H, C*H*F₂CF₂), 4.41 (m, 4H, C*H*₂+C*H*₂), 1.37 (m, 6H, C*H*₃+C*H*₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 161.4 (s, CO), 157.5 (s, CO), 141.5 (t, J = 28.7 Hz, CCF₂), 134.5 (s, C), 116.1 (s, C), *tert*-CF₂ is not seen, 109.4 (tt, ¹ $J_{C-F} = 250$ Hz, ² $J_{C-F} = 38$ Hz, CF₂), 62.3 (s, OCH₂), 61.9 (s, OCH₂), 13.6 (s, CH₃), 13.5 (s, CH₃).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -114.7 (pseudo q, J = 4.0 Hz, 2F, CF₂), -137.4 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

MS (CI): m/z (%) = 313 [M+1]⁺.

Anal. calcd for $C_{11}H_{12}F_4N_2O_4$: C, 42.32; H, 3.87; N, 8.97. Found: C, 42.05; H, 4.23; N, 9.36.

5-(Diphenylphosphoryl)-3-(1,1,2,2-tetrafluoroethyl)-1Hpyrazole (19a)

Compound **19a** was obtained as a white solid (109 mg, 93%) following the general procedure. M.p. > 200 °C.

¹H NMR (500 MHz; DMSO-d6; Me₄Si), δ: 14.66 (broad s, NH), 7.67 (broad s, 6H, *Ph*+*Ph*), 7.59 (broad s, 4H, *Ph*+*Ph*), 6.84 (pseudo t, ${}^{2}J_{H-F}$ = 52.0 Hz, 2H, *CH*F₂CF₂+ *CH*).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 142.7 (broad s, *C*), 137.9 (d, ¹*J*(C,P) = 111.9 Hz, *C*), 132.9 (s, p-CH, Ph), 132.5 (d, ¹*J*(C,P) = 116.5 Hz, *C*), 131.2 (d, ³*J*(C,P) = 11.3 Hz, CH, Ph), 120.1 (d, ²*J*(C,P) = 12.5 Hz, CH, Ph), 111.8 (d, ²*J*(C,P) = 16.3 Hz, CH).

¹⁹F NMR (375 MHz; CDCl₃; CFCl₃), δ: -111.1 (pseudo q, J = 4.0 Hz, 2F, CF₂), -136.7 (dt, ² $J_{F-H} = 52.0$ Hz, ² $J_{F-F} = 4.0$ Hz).

³¹P NMR (202 MHz DMSO-d6; H₃PO₄), δ: 14.7 (broad s, P). MS (CI): m/z (%) = 369 [M+1]⁺.

Anal. calcd for $C_{17}H_{13}F_4N_2OP$: C, 55.45; H, 3.56; N, 7.51. Found: C, 55.11; H, 3.87; N, 7.72.

2-[3-((1,1,2,2-tetrafluoroethyl)-1*H*-pyrazol-5-yl]-quinoxaline (20a)

The reaction was performed following the general procedure, except for: 5.0 eq. $HCF_2CF_2CH_2NH_2*HCl + 1.0$ eq. alkyne + 8.0 eq. NaNO₂. The formed product was washed out with $CHCl_3$ (0.5 mL) to afford the pure pyrazole **20a** a grey solid (69 mg, 73%). M.p. > 200 °C.

¹H NMR (500 MHz; DMSO-d₆; Me₄Si), δ: 14.19 (broad s, 1H, N*H*), 9.55 (s, 1H, *CH*), 8.14 (d, J = 8.0 Hz, 2H, *CH*), 7.91 (m, 2H, *CH*), 7.75 (s, 1H, *CH*), 6.91 (t, ² $J_{H-F} = 52.0$ Hz, 1H, *CH*F₂CF₂).

¹³C NMR (125 MHz; DMSO-d₆; Me₄Si), δ: 143.7 (s), 142.5 (s), 141.5 (s), 141.1 (s), 131.2 (s), 130.6 (s), 129.2 (s), 128.9 (s), *tert-C*F₂ is not seen, 110.0 (tt, ${}^{1}J_{C-F} = 250$ Hz, ${}^{2}J_{C-F} = 38$ Hz, *C*F₂), 105.1 (s).

¹⁹F NMR (375 MHz; DMSO-d₆; CFCl₃), δ: -111.3 (broad s, 2F, CF₂), -136.5 (dt, ${}^{2}J_{F-H} = 52.6$ Hz, ${}^{2}J_{F-F} = 7.6$ Hz).

MS (CI): m/z (%) = 297 [M+1]⁺.

Anal. calcd for C₁₃H₈F₄N₄: C, 52.71; H, 2.72; N, 18.91. Found: C, 52.34; H, 2.58; N, 19.22.

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Notes and references

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