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ARTICLE

# Three-component synthesis of fluorinated pyrazoles from fluoroalkylamines, $NaNO_2$ 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 "$R^1$". The reaction gives the fluorinated pyrazoles in high yields when "R" is fluorine atom or fluoroalkyl group, and "$R^1$" is an electron-withdrawing substituent. With other "R" unexpected products are formed.

## Introduction

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.

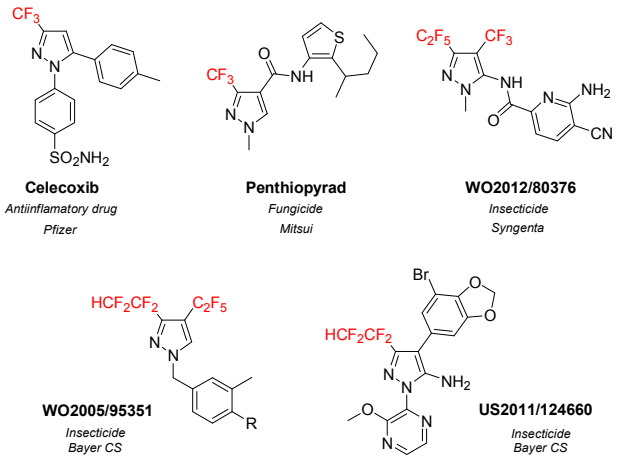
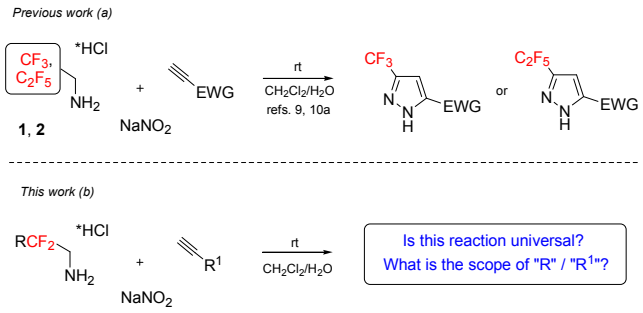



**Fig. 1.** Drugs and agrochemicals – derivatives of pyrazoles with diverse fluoroalkyl groups.

Among other methods to introduce fluoroalkyl groups into organic compounds,[5] $CF_3CHN_2$ is worth mentioning. In 1943 *Gilman* and *Jones* synthesized this reagent from trifluoroethyl amine hydrochloride and sodium nitrite.[6] Since than $CF_3CHN_2$ blossoms in organic chemistry[7] and many research groups have been using it.[8] In particular, recently a three-component reaction between $CF_3CH_2NH_2$*HCl (**1**), $NaNO_2$ 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)?




**Scheme 1.** (a) Literature data.[9,10a] (b) Aim of this work.

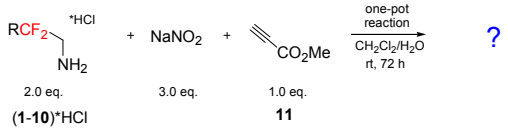
## Results and Discussion

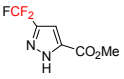
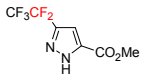
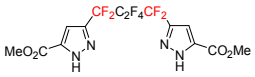
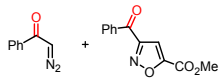
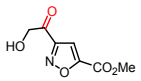
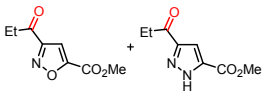
### Scope of amines

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, $NaNO_2$ and methyl propyolate was stirred

in dichloromethane/water at room temperature for three days. The obtained unexpected results are summarized in Table 1.

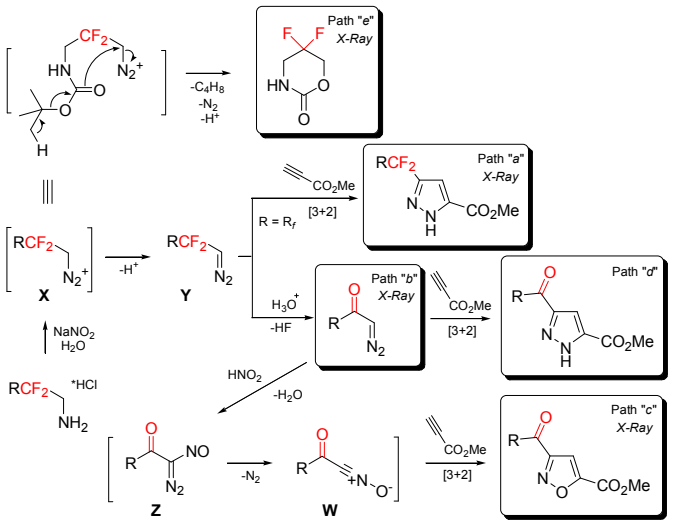
**Table 1.** Scope of the reaction: amines.




| Amine | R | | Product | Yield[a] | Path |
|---|---|---|---|---|---|
| 1 | F | 1a |  | 99% (*X-Ray*)[9] | "*a*" |
| 2 | $CF_3$ | 2a |  | 99%[10a] | "*a*" |
| 3 | $H_2NCH_2C_3F_6$ | 3a |  | 87%[b] | "*a*" |
| 4 | $CHF_2$ | 4a |  | 97% | "*a*" |
| 5 | $CO_2Me$ | 5b |  | 51%[c] (*X-Ray*) | "*b*" |
| 6 | Ph | 6b<br>6c |  | 17%[d]<br>10%[d] (*X-Ray*) | "*b*"<br>"*c*" |
| 7 | H | 7b |  | [ca. 50%][e] | "*b*" |
| 8 | $HOCH_2$ | 8c |  | 31%[c] (*X-Ray*) | "*c*" |
| 9 | Et | 9c<br>9d |  | 7%<br>21% | "*c*"<br>"*d*" |
| 10 | $BocNHCH_2$ | 10e |  | 47%[c] (*X-Ray*) | "*e*" |

[a]Isolated yields. [b]0.5 eq. of amine $(H_2NCH_2C_2F_4)_2$*2HCl were used. [c]1.0 eq. of amine $RCF_2CH_2NH_2$*HCl was used. [d]Product **6b** was of 80% purity. [e]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 $RCF_2CHN_2$ (Scheme 2, Path "*a*").




**Scheme 2.** Proposed mechanistic profile of the reaction.

The reaction of amine hydrochloride **5***HCl with non-fluorinated 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 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 $HNO_2$ 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 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 $CDCl_3$ 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 $CF_2HCHN_2$, 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 $EtCOCHN_2$ 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 F-atom (**1**) or fluoroalkyl group (**2-4**). Although only three groups - $CF_3$, $C_2F_4H$ and $C_3F_6X$ - were tested, it seems that the reaction would also work for all fluoroalkyl substituents "R". With other substitutents "R" - H, Alk, Ar, $CO_2Alk$ (**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).

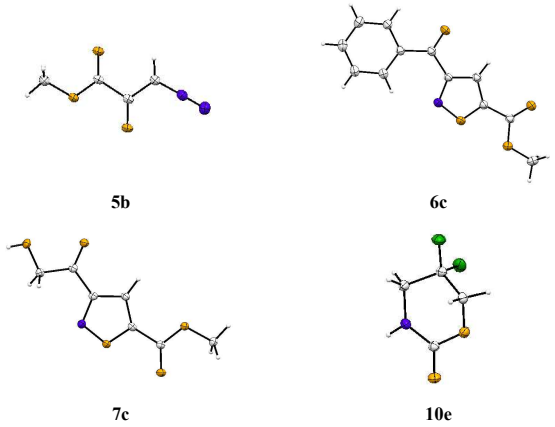



**Fig. 2.** X-Ray crystallographic structures of compounds **5b**, **6c**, **7c**, and **10e**.[14]

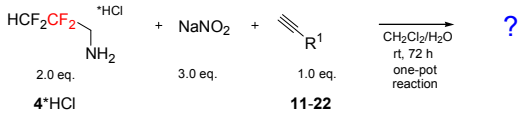
### Scope of alkynes

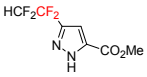
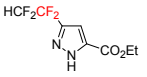
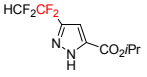
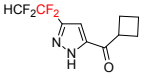
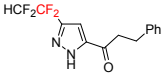
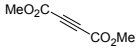
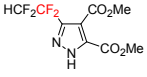
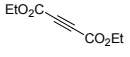
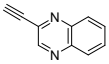
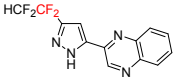
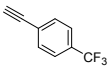
Previously, we showed that *in situ*-generated $FCF_2CHN_2$ and $CF_3CF_2CHN_2$ reacted at room temperature only with electron-deficient alkynes.[9,10a] The reactivity of $HCF_2CF_2CHN_2$, however, could differ much, because $HCF_2$-substituent is a significantly weaker acceptor than the F- and $CF_3$-ones.[15] 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.

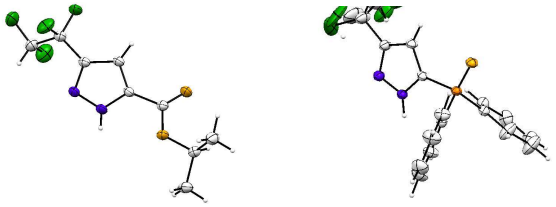



| | Alkyne | | Product | Yield (%)[a] |
|---|---|---|---|---|
| **11** |  | **4a** |  | 97 |
| **12** |  | **12a** |  | 97 |
| **13** |  | **13a** |  | 96 (*X-Ray*) |
| **14** |  | **14a** |  | 96 |
| **15** |  | **15a** |  | 95 |
| **16** |  | **16a** |  | 94 |
| **17** |  | **17a** |  | 91 |
| **18** |  | **18a** |  | 92 |
| **19** |  | **19a** |  | 93 (*X-Ray*) |
| **20** |  | **20a** |  | 73[b] |
| **21** |  | | *no reaction*[b] | |
| **22** |  | | *no reaction*[b] | |

[a] Isolated yields. [b]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, $CF_3$,

$CHF_2$, *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.

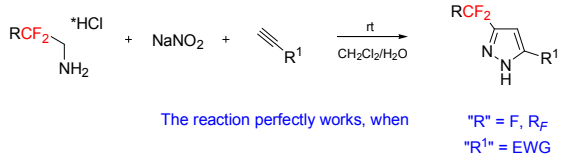


13a 19a

**Fig. 3.** X-Ray crystallographic structures of compounds **13a**, **19a**.[17]

## 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 $R^1$ 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. $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9 MHz and 124.9 MHz, respectively). $^{19}$F-NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 376.7 Hz). Chemical shifts are reported in ppm downfield from $Me_4Si$ ($^1$H, $^{13}$C) or upfield from $CFCl_3$ ($^{19}$F) 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 $C_2F_5CH_2NH_2$·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 ºC. 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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 11.81 (broad s, 1H, N*H*), 7.11 (s, 1H, C*H*), 3.96 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 159.0 (s, CO), 142.8 (broad s, *C*), 135.5 (broad s, *C*), 118.6 (qt, $^1J_{C\text{-}F}$ = 285 Hz, $^2J_{C\text{-}F}$ = 36 Hz, $CF_2CF_3$), 110.2 (tq, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 39 Hz, *C*$F_2$CF$_3$), 108.6 (s, *C*H), 52.7 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -85.1 (s, 3F, $CF_2CF_3$), -113.8 (s, 2F, $CF_2CF_3$).

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-1,4-diyl)bis(1H-pyrazole-5-carboxylate) (3a)**

The reaction was performed following the general procedure, except for: 0.5 eq. $(H_2NCH_2CF_2CF_2)_2$*2HCl + 1.0 eq. methyl propyolate + 2 eq. $NaNO_2$. After 72 h at 20 ºC, the reaction mixture was placed into the fringe at 0 ºC 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.

$^1$H NMR (500 MHz; DMSO-$d_6$; $Me_4Si$), δ: 7.20 (s, 2H, C*H*), 3.86 (s, 6H, C$H_3$).

$^{13}$C NMR (125 MHz; DMSO-$d_6$; $Me_4Si$), δ: 158.9 (s, CO), 140.8 (broad s, *C*), 135.6 (broad s, *C*), one *C*$F_2$ is not seen, 109.4 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$), 108.6 (s, *C*H), 52.5 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; DMSO-$d_6$; $CFCl_3$), δ: -108.1 (t, *J* = 11.3 Hz, 4F, C$F_2$), -121.5 (t, *J* = 11.3 Hz, 4F, C$F_2$).

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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.12 (s, 1H, C*H*), 6.13 (t, *J* = 52.0 Hz, 1H, C*H*$F_2$), 3.97 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 159.1 (s, CO), 143.2 (t, *J* = 30 Hz, *C*), 135.1 (s, *C*), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$), *tetr*-$CF_2$ is not seen, 108.1 (s, *C*H), 52.4 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.6 (broad s, 2F, C$F_2$), -136.4 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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)**

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. $NaNO_2$. $^1$H 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 ºC 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 ºC (*dec*.)

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 6.18 (s, 1H, C*H*), 3.88 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 176.1 (s, CO), 160.4 (s, CO), 56.7 (s, *C*H), 53.0 (s, *C*$H_3$).

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. $PhCF_2CH_2NH_2$*HCl + 1.0 eq. methyl propyolate + 3.0 eq. $NaNO_2$. 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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), 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, C*H*), 4.02 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), 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, *C*$H_3$).

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**.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), 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, C*H*).

$^1$H 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. $HOCH_2CF_2CH_2NH_2$*HCl + 1.0 eq. methyl propyolate + 3.0 eq. $NaNO_2$. $^1$H 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 ºC.

$^1$H NMR (500 MHz; DMSO-$d_6$; $Me_4Si$), δ: 7.58 (s, 1H, C*H*), 5.50 (broad s, 1H, O*H*), 4.77 (broad s, 2H, C$H_2$), 3.92 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; DMSO-$d_6$; $Me_4Si$), δ: 192.6 (s, CO), 161.0 (s), 160.3 (s), 156.3 (s), 108.1 (s), 66.1 (s, *C*$H_2$), 53.3 (s, *C*$H_3$).

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

Anal. calcd for $C_7H_7NO_5$: 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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.26 (s, 1H, C*H*), 4.00 (s, 3H, OC$H_3$), 3.12 (q, *J* = 8.0 Hz, 2H, C$H_2$CH$_3$), 1.24 (q, *J* = 8.0 Hz, 3H, CH$_2$C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 193.7 (s, CO), 161.5 (s), 161.0 (s), 144.3 (s), 107.4 (s), 52.8 (s, OC$H_3$), 33.1 (s, *C*$H_2$), 6.7 (s, *C*$H_3$).

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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), 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$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 193.7 (s, *C*O), 160.6 (s, *C*O), 109.5 (s, *C*H), tert-*C* are not seen, 53.3 (s), 32.2 (s), 7.4 (s).

MS (CI): *m/z* (%) = 183 $[M+1]^+$.

Anal. calcd for $C_8H_{10}N_2O_3$: 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. $BocNHCH_2CF_2CH_2NH_2$*HCl + 1.0 eq. methyl propyolate + 3.0 eq. $NaNO_2$. 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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 6.41 (broads, 1H, N*H*), 4.37 (t, *J* = 10.5 Hz, 4H, C$H_2$), 3.69 (t, *J* = 10.5 Hz, 4H, C$H_2$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 152.0 (s, *C*O), 113.6 (t, *J* = 244 Hz, *C*$F_2$), 67.2 (t, *J* = 33 Hz, *C*$H_2CF_2$), 46.4 (t, *J* = 33 Hz, *C*$H_2CF_2$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -112.3 (qv, $^3J$(F,H) = 11.3 Hz, 2F, $CF_2$).

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.

**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 ºC.

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.09 (s, 1H, C*H*), 6.11 (t, *J* = 52.0 Hz, 1H, C*H*$F_2$), 4.40 (q, *J* = 7.0 Hz, 2H, C$H_2$$CH_3$), 1.38 (t, *J* = 7.0 Hz, 3H, $CH_2$C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 158.6 (s, CO), 143.5 (t, *J* = 30 Hz, *C*), 135.3 (s, *C*), 111.7 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$),107.9 (s, *C*H), 61.8 (s. O*C*$H_2$), 13.8 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.6 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.5 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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-5-carboxylate (13a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.08 (s, 1H, C*H*), 6.11 (tt, $^2J_{H\text{-}F}$ = 52.0 Hz, $^3J_{H\text{-}F}$ = 16.0 Hz, 1H, C*H*$F_2$$CF_2$), 5.27 (m, *J* = 6.5 Hz, 1H, C*H*$CH_3$), 1.36 (t, *J* = 6.5 Hz, 6H, CHC$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 158.1 (s, CO), 143.6 (t, *J* = 30 Hz, *C*), 135.6 (s, *C*), 111.6 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$),107.7 (s, *C*H), 69.9 (s, O*C*H), 21.3 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.7 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.5 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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-5-yl]methanone (14a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 6.97 (s, 1H, C*H*), 6.15 (tt, $^2J_{H\text{-}F}$ = 52.0 Hz, $^3J_{H\text{-}F}$ = 16.0 Hz, 1H, C*H*$F_2$$CF_2$), 3.82 (qv, *J* = 7.0 Hz, 1H, C*H*), 2.46 (m, 2H), 2.33 (m, 2H), 2.14 (m, 2H).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 191.4 (s, *C*O), 143.8 (t, *J* = 30 Hz, *C*), 140.2 (s, *C*), 111.5 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$),107.0 (s, *C*H), 42.4 (s), 26.5 (s), 24.3 (s), 17.8 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.5 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.6 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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]-2-phenylethanone (15a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.36-7.26 (m, 5H, *Ph*), 7.05 (s, 1H, C*H*), 6.12 (tt, $^2J_{H\text{-}F}$ = 52.0 Hz, $^3J_{H\text{-}F}$ = 16.0 Hz, 1H, C*H*$F_2$$CF_2$), 4.16 (s, 2H, C$H_2$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 188.0 (s, CO), 143.4 (t, *J* = 28.7 Hz, *C*$CF_2$), 141.5 (s, *C*), 132.0 (s, Ph), 129.1 (s, Ph), 128.6 (s, Ph), 127.2 (s, Ph), 111.6 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$), 107.8 (s, *C*H), 46.1 (s, *C*$H_2$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.4 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.4 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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-1-propanone (16a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 7.33-7.21 (m, 5H, *Ph*), 7.02 (s, 1H, C*H*), 6.12 (tt, $^2J_{H\text{-}F}$ = 52.0 Hz, $^3J_{H\text{-}F}$ = 16.0 Hz, 1H, C*H*$F_2$$CF_2$), 3.22 (t, J = 7.5 Hz, 2H, $CH_2$), 3.06 (t, J = 7.5 Hz, 2H, $CH_2$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 190.0 (s, CO), 143.4 (t, *J* = 28.5 Hz, *C*$CF_2$), 141.6 (s, *C*), 139.7 (s, Ph), 128.3 (s, Ph), 128.0 (s, Ph), 126.1 (s, Ph), 111.6 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.3 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$), 107.3 (s, *C*H), 40.9 (s, *C*$H_2$), 29.2 (s, *C*$H_2$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -113.5 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.4 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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-4,5-dicarboxylate (17a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 6.28 (tt, $^2J_{H\text{-}F}$ = 52.0 Hz, $^3J_{H\text{-}F}$ = 16.0 Hz, 1H, C*H*$F_2$$CF_2$), 3.92 (s, 3H, C$H_3$), 3.90 (s, 3H, C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 161.9 (s, CO), 158.0 (s, CO), 141.3 (t, *J* = 28.7 Hz, *C*$CF_2$), 134.7 (s, *C*), 115.6 (s, *C*), 111.4 (tt, $^1J_{C\text{-}F}$ = 245 Hz, $^2J_{C\text{-}F}$ = 28 Hz, *C*$F_2$), 109.1 (tt, $^1J_{C\text{-}F}$ = 250 Hz, $^2J_{C\text{-}F}$ = 38 Hz, *C*$F_2$), 53.8 (s, *C*$H_3$), 53.7 (s, *C*$H_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -114.9 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -137.4 (dt, $^2J_{F\text{-}H}$ = 52.0 Hz, $^2J_{F\text{-}F}$ = 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-4,5-dicarboxylate (18a)**

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

$^1$H NMR (500 MHz; $CDCl_3$; $Me_4Si$), δ: 6.27 (tt, $^2J_{H-F}$ = 52.0 Hz, $^3J_{H-F}$ = 16.0 Hz, 1H, C*H*F$_2$CF$_2$), 4.41 (m, 4H, C$H_2$+C$H_2$), 1.37 (m, 6H, C$H_3$+C$H_3$).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 161.4 (s, CO), 157.5 (s, CO), 141.5 (t, *J* = 28.7 Hz, *C*CF$_2$), 134.5 (s, *C*), 116.1 (s, *C*), *tert*-*C*F$_2$ is not seen, 109.4 (tt, $^1J_{C-F}$ = 250 Hz, $^2J_{C-F}$ = 38 Hz, *C*F$_2$), 62.3 (s, O*C*H$_2$), 61.9 (s, O*C*H$_2$), 13.6 (s, *C*H$_3$), 13.5 (s, *C*H$_3$).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -114.7 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -137.4 (dt, $^2J_{F-H}$ = 52.0 Hz, $^2J_{F-F}$ = 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)-1H-pyrazole (19a)**

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

$^1$H NMR (500 MHz; DMSO-d6; $Me_4Si$), δ: 14.66 (broad s, NH), 7.67 (broad s, 6H, *Ph*+*Ph*), 7.59 (broad s, 4H, *Ph*+*Ph*), 6.84 (pseudo t, $^2J_{H-F}$ = 52.0 Hz, 2H, C*H*F$_2$CF$_2$+ C*H*).

$^{13}$C NMR (125 MHz; $CDCl_3$; $Me_4Si$), δ: 142.7 (broad s, *C*), 137.9 (d, $^1J$(C,P) = 111.9 Hz, *C*), 132.9 (s, p-*C*H, Ph), 132.5 (d, $^1J$(C,P) = 116.5 Hz, *C*), 131.2 (d, $^3$J(C,P) = 11.3 Hz, *C*H, Ph), 120.1 (d, $^2$J(C,P) = 12.5 Hz, *C*H, Ph), 111.8 (d, $^2$J(C,P) = 16.3 Hz, *C*H).

$^{19}$F NMR (375 MHz; $CDCl_3$; $CFCl_3$), δ: -111.1 (pseudo q, *J* = 4.0 Hz, 2F, C*F*$_2$), -136.7 (dt, $^2J_{F-H}$ = 52.0 Hz, $^2J_{F-F}$ = 4.0 Hz).

$^{31}$P NMR (202 MHz DMSO-d6; $H_3PO_4$), 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. $NaNO_2$. 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 ºC.

$^1$H NMR (500 MHz; DMSO-$d_6$; $Me_4Si$), δ: 14.19 (broad s, 1H, N*H*), 9.55 (s, 1H, C*H*), 8.14 (d, *J* = 8.0 Hz, 2H, C*H*), 7.91 (m, 2H, C*H*), 7.75 (s, 1H, C*H*), 6.91 (t, $^2J_{H-F}$ = 52.0 Hz, 1H, C*H*F$_2$CF$_2$).

$^{13}$C NMR (125 MHz; DMSO-$d_6$; $Me_4Si$), 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*F$_2$ is not seen, 110.0 (tt, $^1J_{C-F}$ = 250 Hz, $^2J_{C-F}$ = 38 Hz, *C*F$_2$), 105.1 (s).

$^{19}$F NMR (375 MHz; DMSO-$d_6$; $CFCl_3$), δ: -111.3 (broad s, 2F, C*F*$_2$), -136.5 (dt, $^2J_{F-H}$ = 52.6 Hz, $^2J_{F-F}$ = 7.6 Hz).

MS (CI): *m/z* (%) = 297 $[M+1]^+$.

Anal. calcd for $C_{13}H_8F_4N_4$: 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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