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Three-component synthesis of C_2F_5-substituted pyrazoles from $C_2F_5CH_2NH_2$·HCl, $NaNO_2$ and electron-deficient alkynes

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Full Research Paper

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In memory of Prof. Oleg V. Shishkin.

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Abstract

A one-pot reaction between $C_2F_5CH_2NH_2$·HCl, $NaNO_2$ and electron-deficient alkynes gives C_2F_5-substituted pyrazoles in excellent yields. The transformation smoothly proceeds in dichloromethane/water, tolerates the presence of air, and requires no purification of products by column chromatography. Mechanistically, $C_2F_5CH_2NH_2$·HCl and $NaNO_2$ react first in water to generate $C_2F_5CHN_2$, that participates in a [3 + 2] cycloaddition with electron-deficient alkynes in dichloromethane.

Introduction

Incorporation of fluorinated fragments into organic compounds might affect their physicochemical and biological properties [1-8]. It is not surprising, therefore, that up to 20% of all modern drugs contain at least one fluorine atom [9-11]. Fluorinated pyrazoles, for example, do play a role in medicinal chemistry: among them are inhibitors of the measles virus RNA polymerase complex [12], CRAC channel, cyclogenases [13-15], 5-lipoxygenase [16], heat shock protein 90 [17]; inducers of G0–G1 phase arrest [18], modulators of the AMPA receptor [19], activators of the Kv7/KCNQ potassium channel [20], regulators of the NFAT transcription factor [21], etc. Approved drugs and agrochemicals – Bixafen, Fipronyl, Celecoxib, Pyroxasulfone and Penflufen – are also pyrazoles with diverse fluorine-containing substituents (Figure 1) [22,23]. Moreover, fluorinated NH-pyrazoles have also found an application as ligands in coordinational chemistry [24-27].

While the trifluoromethylated derivatives play a major role in chemistry [28], their more lipophilic analogues – C_2F_5 [1,29,30] and SF_5 [1,31] – only gain popularity. The C_2F_5-substituted derivatives, for example, often have higher activity compared with the CF_3-counterparts [32,33]. Therefore, some bioactive compounds including several drugs contain a C_2F_5 group (Figure 2) [34-36].

The conceptually attractive C_2F_5-pyrazoles [37], however, still remain somewhat in the shadow [38], probably because of the lack of the corresponding chemical approaches. Predominantly,

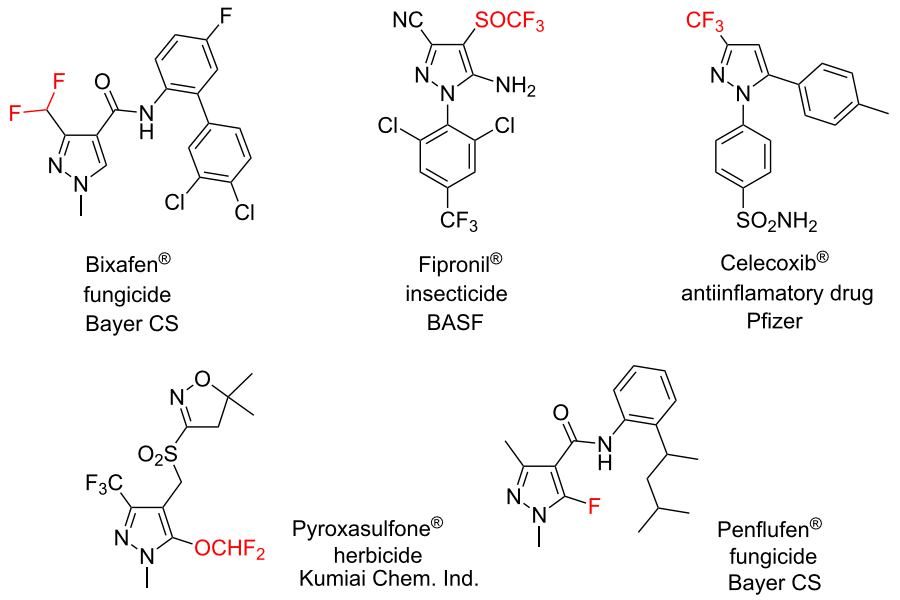


Figure 1: Bioactive compounds and agrochemicals with fluorinated pyrazoles.

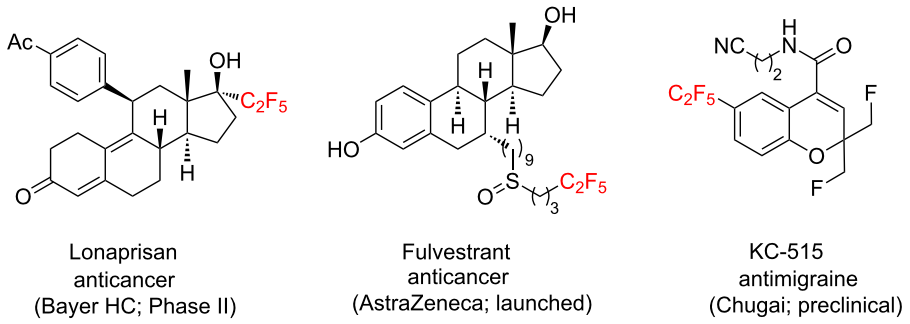


Figure 2: Bioactive compounds with C_2F_5 group [34-36].

C_2F_5-pyrazoles are synthesized by a reaction of 1,3-dicarbonyl compounds (or their synthons) with hydrazines [39-44]. In this context, novel practical methods to C_2F_5-pyrazoles are needed.

Last year, Ma and colleagues synthesized CF_3-pyrazoles by [3 + 2] cycloaddition between in situ generated CF_3CHN_2 and alkynes [45]. This method, however, required a) the preliminary preparation of a dry solution of toxic CF_3CHN_2; b) the use of inert atmosphere; c) an addition of a catalyst (Ag_2O); and d) purification of products by column chromatography. Also, the reaction worked only for mono-substituted alkynes. In parallel, an alternative practical approach to CF_3-pyrazoles by a three-component reaction between electron-deficient alkynes, sodium nitrite and trifluoroethylamine hydrochloride was developed [46]. This method worked for both the mono- and disubstituted alkynes. Because of similar electronic properties of CF_3 and C_2F_5 groups [1], it was supposed that a reaction between in situ generated $C_2F_5CHN_2$ [47], and electron-deficient alkynes would lead to C_2F_5-pyrazoles. In this work, this hypothesis was proven; the scope and selectivity of this transformation was studied and the high practical potential of the developed method is shown.

Results and Discussion

Validation and optimization

To challenge the putative transformation, the simple mono-substituted alkyne **1** with one electron-withdrawing CO_2Me-group (EWG) was selected. A mixture of alkyne **1**, $C_2F_5CH_2NH_2{\cdot}HCl$ (1.0 equiv) [48] and $NaNO_2$ (2.0 equiv) in water/dichloromethane was stirred at room temperature. After

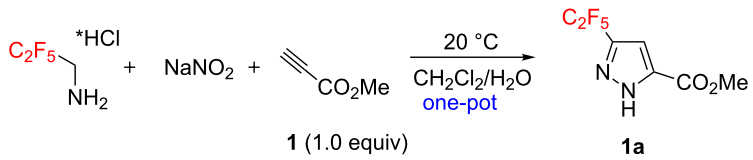
10 min the organic layer became yellow indicating the formation of $C_2F_5CHN_2$. After 24 h the reaction conversion was 55%, but no side products were observed. Optimization of the reaction conditions – $C_2F_5CH_2NH_2$·HCl (3.0 equiv), $NaNO_2$ (5.0 equiv), 72 h – allowed achieving the full reaction conversion (Table 1, entry 6). The standard work-up afforded pyrazole **1a** as a white crystalline solid in 99% yield without any purification (neither recrystallization, nor column chromatography). The reaction required no inert gas atmosphere, and was performed in air.

Reaction scope

Having these encouraging results on pyrazole **1a** at hand, the reaction scope was studied. First, various mono-substituted alkynes **2**–**14** were tested under the already optimized reaction conditions (Table 2).

Substrates **2**, **3**, **6**–**9** with strong EWGs smoothly reacted with $C_2F_5CHN_2$ at room temperature to afford products **2a**, **3a**, **6a**–**9a** in excellent yields of 95–99% without any purification. Substrates **4**, **5** and **10**–**12** with weak EWG reacted slowly, and

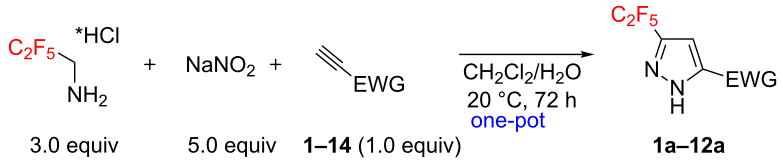
Table 1: Optimization of the reaction conditions.



1 (1.0 equiv) **1a**

Entry	$C_2F_5CH_2NH_2$·HCl (equiv)	$NaNO_2$ (equiv)	Time (h)	Conversion (%)
1	1.0	2.0	24	55
2	1.0	2.0	72	76
3	2.0	3.0	24	75
4	2.0	3.0	72	95
5	3.0	5.0	24	96
6	3.0	5.0	72	100

Table 2: Synthesis of C_2F_5-substituted pyrazoles from mono-substituted alkynes.



3.0 equiv 5.0 equiv **1**–**14** (1.0 equiv) **1a**–**12a**

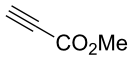
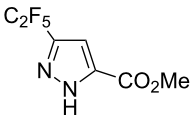
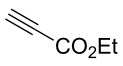
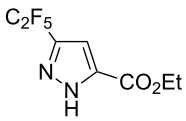
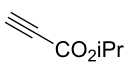
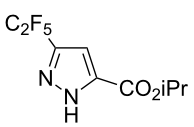
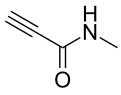
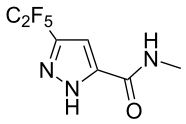
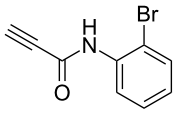
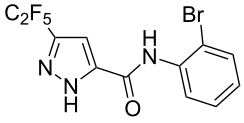
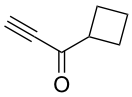
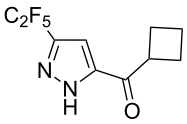
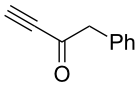
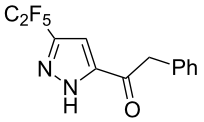
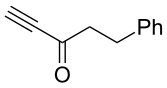
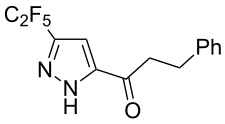
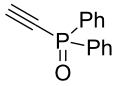
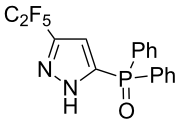
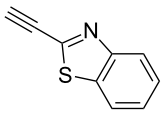
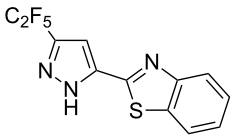
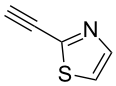
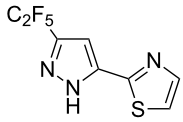
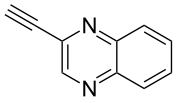
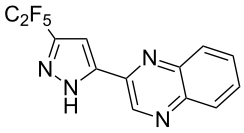
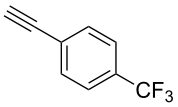
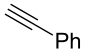
Entry		Alkyne		Product	Yield (%)[a]
1	**1**		**1a**		99
2	**2**		**2a**		98
3	**3**		**3a**		97

Table 2: Synthesis of C_2F_5-substituted pyrazoles from mono-substituted alkynes. (continued)

4	**4**		**4a**		59 (76)[b] 78[c]
5	**5**		**5a**		22 (55)[b] 88[c]
6	**6**		**6a**		99
7	**7**		**7a**		98
8	**8**		**8a**		97
9	**9**		**9a**		95
10	**10**		**10a**		23 (33)[b] 45[c] X-ray
11	**11**		**11a**		57[d]
12	**12**		**12a**		38[d]
13	**13**			no reaction	–[b,c]
14	**14**			no reaction	–[b,c]

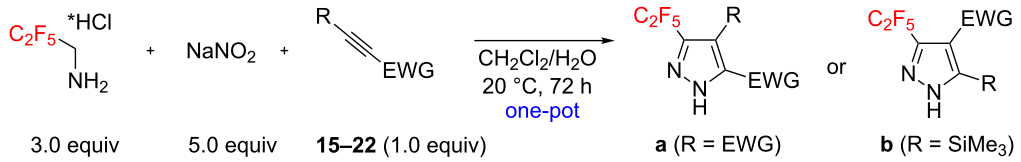
[a]Isolated yields. [b]rt, 168 h, dichloromethane/water. The reaction conversion is in brackets: ( ). [c]45 °C, 72 h, toluene/water. [d]40 °C, 72 h, dichloromethane/water.

even after one week the reaction was not complete (33–76% conversion). The pure products **4a**, **5a**, and **10a–12a** (Table 2) were obtained in bad yields after crystallization of the reaction mixtures. For these compounds, however, the yields were improved to 38–88% by performing the reaction at increased temperature: 40–45 °C.

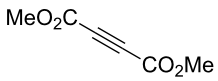
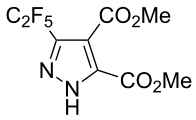
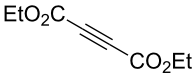
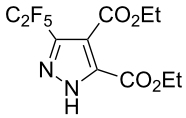
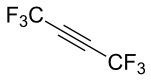
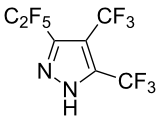
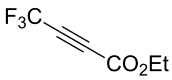
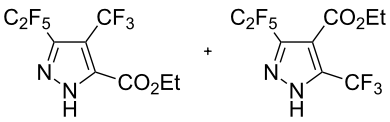
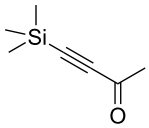
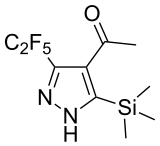
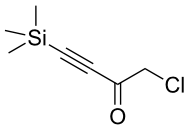
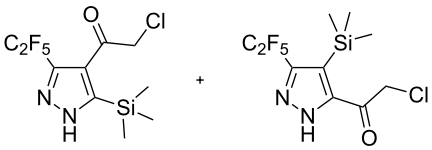
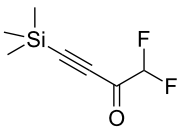
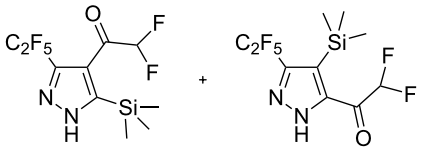
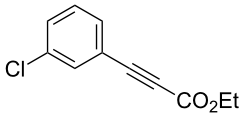
This method, however, did not work for aromatic alkynes with either weak EWG (**13**) or electron-donating group (EDG, **14**) – all attempts to react substrates **13** and **14** failed. These results suggest that the reaction between $C_2F_5CHN_2$ and alkynes belongs to type I of [3 + 2] cycloadditions [49]: It is accelerated by the alkyne`s EWGs and decelerated by EDGs.

Next diverse disubstituted alkynes **15**–**22** (Table 3) with at least one strong EWG (–CO_2Alk or –COAlk) were studied. Substrates **15**–**18** with the second EWG smoothly reacted with $C_2F_5CHN_2$ to afford pyrazoles in almost quantitative yield. Substrate **19** with the second EDG ($SiMe_3$), however, reacted slowly. The reaction conversion was 52% after 7 days leading

Table 3: Synthesis of C_2F_5-substituted pyrazoles from disubstituted alkynes.



3.0 equiv 5.0 equiv **15–22** (1.0 equiv) **a** (R = EWG) **b** (R = $SiMe_3$)

Entry		Alkyne		Product	Yield (%)[a]
1	**15**		**15a**		99
2	**16**		**16a**		98
3	**17**		**17a**		65
4	**18**		**18a/b** (2.6/1.0)		99[b]
5	**19**		**19b**		43 (52)[c] 73[d] X-ray
6	**20**		**20b/a** (4.0/1.0)		62[e] X-ray
7	**21**		**21b/a** (2.6/1.0)		89[b]
8	**22**			no reaction[c,d]	

[a]Isolated yields. [b]Yield of the inseparable mixture of pyrazoles. [c]rt, 168 h, dichloromethane/water. Conversion of the reaction is in brackets: ( ). [d]40 °C, 72 h, dichloromethane/water. [e]A mixture of **20b**/**20a** (4/1) is formed, from which pure isomer **20b** is isolated by crystallization in 62% yield.

to the sole regioisomer **19b** without side products. The crystalline product **19b** was purified from the liquid starting material by washing with cyclohexane. The yield of **19b** was improved to 73% by performing the reaction at 40 °C (Table 3, entry 5). $SiMe_3$-substituted substrates **20**, **21** also reacted slowly, but again performing the reaction at 40 °C allowed to obtain the target products **20b**, **21a**/**b** in good yields. Substrate **22** with the second EDG – aryl – did not react, however.

Structures of compounds **10a**, **19b**, **20b** were confirmed by X-ray crystal structure analysis (Figure 3) [50].

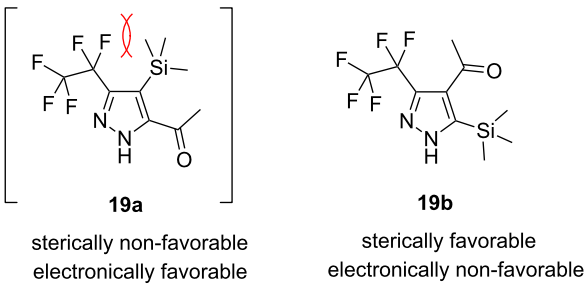


Figure 4: Structure of the expected product **19a**, and the observed isomeric one – **19b**.

Reaction regioselectivity

Monosubstituted alkynes **1**–**12** regioselectively reacted with $C_2F_5CHN_2$ to give only 3,5-disubstituted pyrazoles. Formation of 3,4-disubstituted isomers was observed.

Disubstituted alkynes behaved differently, because of controversial electronic and steric effects. According to the orbital symmetry rules, the [3 + 2] cycloaddition must lead to pyrazoles with the C_2F_5 group and EWG at 3,5-positions [49]. Product **18a/b** was obtained as a mixture of isomers because the C_2F_5 and CO_2Et had similar electron-withdrawing nature. On the contrary, reaction of alkyne **19** having both the electron-withdrawing (–COMe) and electron-donating ($–SiMe_3$) substituents afforded the isomer **19b** with EWG at the 4th position, violating the orbital symmetry rules (Figure 3 and Figure 4). Presumably, the steric repulsion between bulky C_2F_5 and $SiMe_3$ groups forced the reaction to follow the reversed regioselectivity – the steric effect has overcompensated the electronic one (Figure 4) [51,52].

Replacing one hydrogen atom in alkyne **19** by a bulkier chlorine atom – alkyne **20** – led to mixture of products **20b**/**a** = 4.0/1.0 (the pure product **20b** was obtained by crystallization). Replacing two hydrogen atoms in **20** by bulkier fluorine atoms – alkyne **21** – led to mixture **21b**/**a** = 2.6/1.0. In compounds **13**–**15** the steric effect overcompensated the electronic one, but the impact of steric effect decreased with increasing the size of the second substituent: CH_3CO (**19**), $ClCH_2CO$ (**20**), HF_2CCO (**21**) increasing the percentage of α-isomers (0% in **19b**, 20% in **20a**/**b**, 28% in **21a**/**b**).

Reactivity of $C_2F_5CHN_2$ vs CF_3CHN_2

To compare the reactivities of $C_2F_5CHN_2$ and CF_3CHN_2 in [3 + 2] cycloadditions with alkynes, one must take into account two factors: steric and electronic [49]. On one hand, the C_2F_5 substituent is bulkier than the CF_3 one, decreasing thereby the reactivity of $C_2F_5CHN_2$ compared with CF_3CHN_2. On the other hand, C_2F_5 and CF_3 groups have similar electron-withdrawing abilities [1], and hence the both diazoalkanes might have similar reactivities. In reality, under the same conditions, after seven days at room temperature alkyne **19** reacted with CF_3CHN_2 completely, while the corresponding reaction with $C_2F_5CHN_2$ reached only 52% conversion. Obviously, the steric effect overcompensated the electronic one; and $C_2F_5CHN_2$ was less active than CF_3CHN_2 (Scheme 1).

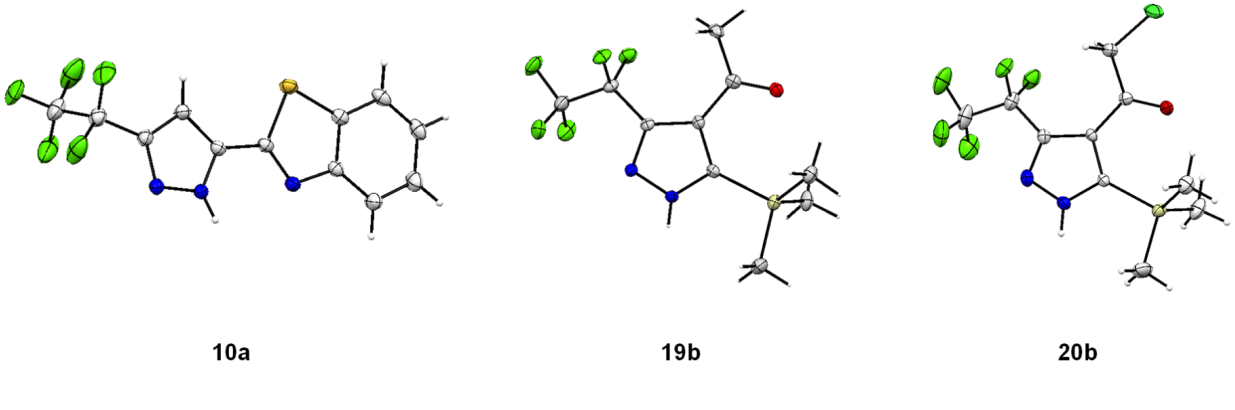
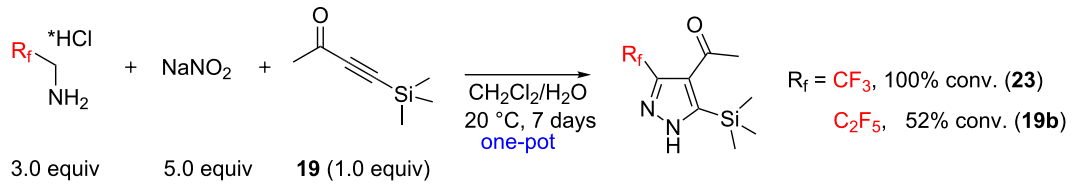


Figure 3: X-ray crystal structure of pyrazoles **10a**, **19b** and **20b** [50].



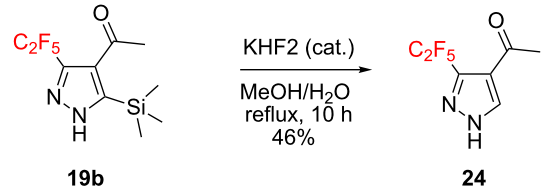
Scheme 1: Comparison of CF_3CHN_2 *vs* $C_2F_5CHN_2$ in the reaction with alkyne **19**.

Another factor, however, must be kept in mind while comparing the reactivities of $C_2F_5CHN_2$ and CF_3CHN_2: the reactions of $C_2F_5CHN_2$ can be safely heated up to 40–45 °C without evaporation of the reagent while those with CF_3CHN_2 cannot (bp = 13 °C) [53]. Therefore, the yield of product **19b** was improved to 73% by performing the reaction at 40 °C.

Selected chemical transformations

Having developed a robust practical method to C_2F_5-pyrazoles, the true practical potential of the obtained compounds was demonstrated. First, the standard cleavage of TMS group in **19b** led to ketone **24** (Scheme 2). This strategy gives an opportunity for preparing the 3,4-disubstituted pyrazoles from TMS-derivatives, while the direct reaction of monosubstituted alkynes **1**–**12** with $C_2F_5CHN_2$ gives 3,5-disubstituted ones.

Also, alkaline hydrolysis of the ester group in **1a** gave acid **25** – potential building blocks for medicinal chemistry and drug discovery: many bioactive compounds, including the insecticidal agent **DP-23**, contain the residue of the CF_3-analogue of **25** (Scheme 3) [54].

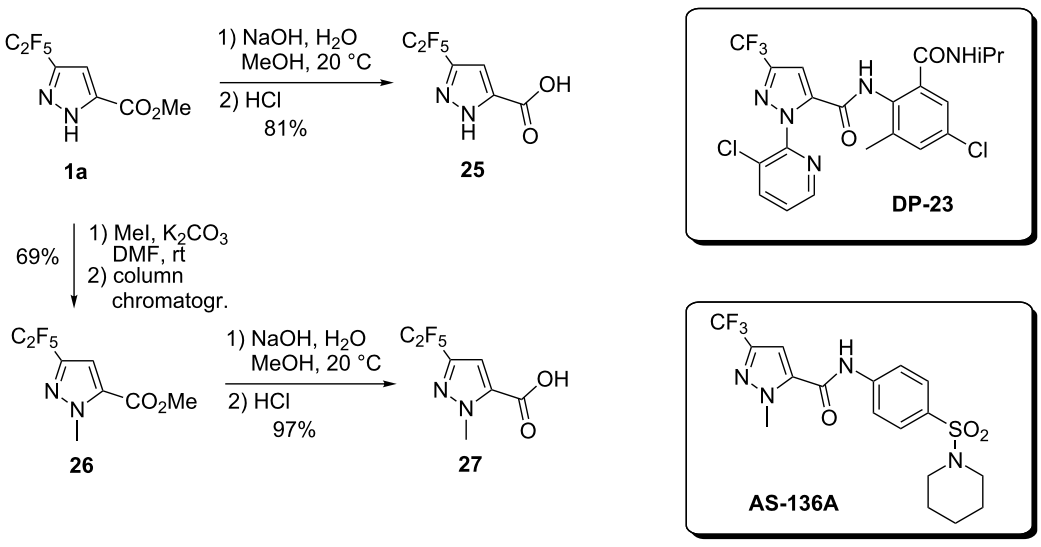


Scheme 2: Synthesis of 3,4-disubstituted pyrazole **24**.

Finally, alkylation of pyrazole **1a** with MeI afforded the product **26** in 69% yield after column chromatography. Basic hydrolysis of the ester group in **26** gave acid **27** – another potential building block for drug discovery (the corresponding CF_3-acid constitutes to the known antiviral agent **AS-136A** [55]) (Scheme 3).

Conclusion

In summary, a novel approach to C_2F_5-substituted pyrazoles has been elaborated by a three-component reaction between $C_2F_5CH_2NH_2{\cdot}HCl$, $NaNO_2$ and electron-deficient alkynes. This



Scheme 3: Synthesis of C_2F_5-substituted acids **25** and **27**. In brackets are the known bioactive compounds **DP-23**, **AS-136A** (CF_3-analogues of **25** and **27**).

method is highly practical: it does not require a) the pre-isolation of toxic diazo intermediates; b) inert gas atmosphere (the reaction is performed in air); c) any catalysts; d) purification of the products by column chromatography. Also, the reaction works for both the mono- and disubstituted alkynes; and allows preparing of 3,5- and 3,4-disubstituted pyrazoles (via $SiMe_3$-alkynes).

Therefore, given the importance of fluorinated pyrazoles, it is desirable that scientists will soon use this extremely useful practical reaction in synthetic organic chemistry, drug discovery and agrochemistry (where the need for robust reactions is high).

Experimental

General procedure: To a stirred suspension of $C_2F_5CH_2NH_2{\cdot}HCl$ (90 mg, 0.48 mmol, 3.0 equiv) in CH_2Cl_2 (4.0 mL)/water (0.2 mL), sodium nitrite (54 mg, 0.78 mmol, 5.0 equiv) and alkyne (0.16 mmol, 1.0 equiv) were added. The reaction mixture was vigorously stirred at 20 °C for 72 h. Water (1.0 mL) and CH_2Cl_2 (3 mL) were added. The organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to provide the pure product.

Supporting Information

Supporting Information File 1

Experimental procedures and copies of NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-3-S1.pdf]

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