EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301852

One-Pot Synthesis of CF_3-Substituted Pyrazolines/Pyrazoles from Electron-Deficient Alkenes/Alkynes and CF_3CHN_2 Generated in situ: Optimized Synthesis of Tris(trifluoromethyl)pyrazole

Evgeniy Y. Slobodyanyuk,[a] Olexiy S. Artamonov,[b] Oleg V. Shishkin,[c] and Pavel K. Mykhailiuk*[a,d]

Keywords: Synthetic methods / Nitrogen heterocycles / Fluorine / Multicomponent reactions / Cycloaddition

The [3+2] cycloaddition of CF_3CHN_2, generated in situ, with electron-deficient alkenes/alkynes affords CF_3-substituted pyrazolines/pyrazoles in quantitative yields. The one-pot three-component reaction between $CF_3CH_2NH_2$·HCl, $NaNO_2$, and the substrate proceeds at room temperature in dichloromethane/water.

Introduction

Pyrazolines play an important role in drug discovery and organic synthesis: they exhibit a broad spectrum of biological activities (Figure 1),[1,2] and serve as precursors to cyclopropanes,[3] pyrazoles,[4] and diamines.[5] Considering that more than 45 drugs contain the CF_3 group,[6,7] CF_3-substituted pyrazolines look to be promising molecules for medicinal chemists.

In 1968, Atherton and Fields prepared CF_3-substituted pyrazolines by [3+2] cycloaddition between CF_3CHN_2 and alkenes.[8] The transformation, however, was technically challenging, because it required (i) generation of the toxic, potentially explosive gas CF_3CHN_2[9,10] from $CF_3CH_2NH_2$·HCl and $NaNO_2$ and (ii) purification of the reagent by two vacuum distillations at –80 and –196 °C.[11] Therefore, this method has had very little practical application so far.[12,13] In this context, we have developed a safe, one-pot procedure to prepare CF_3-substituted pyrazolines without isolation of the dangerous CF_3CHN_2.

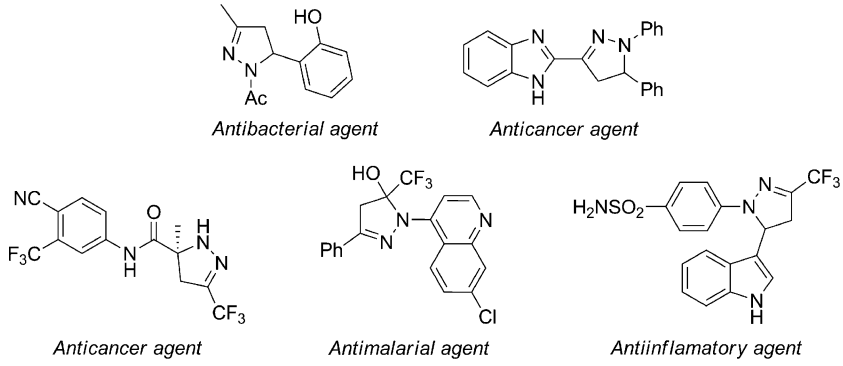


Figure 1. Bioactive pyrazolines.[1,2]

Results and Discussion

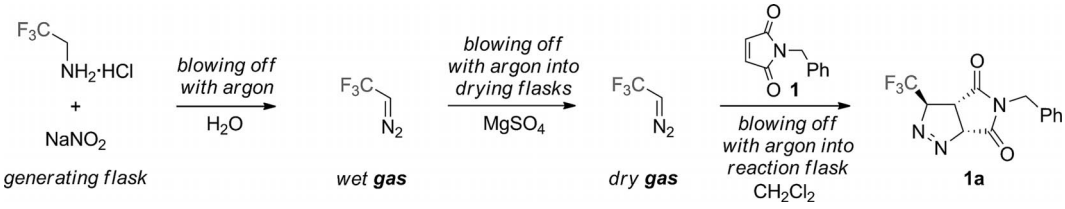
Reaction with Alkenes

Optimization of the Reaction

In 2012, we synthesized pyrazoline **1a** (Scheme 1).[12c] In that approach, we first generated CF_3CHN_2 from

[a] Organic Chemistry Department, Taras Shevchenko National University of Kyiv,
Volodymyrska 64, Kyiv 01601, Ukraine
[b] Institute of Organic Chemistry, National Academy of Sciences of Ukraine,
Murmanska 5, Kyiv 02660, Ukraine
[c] STC, Institute for Single Crystals, National Academy of Science of Ukraine,
Lenina ave. 60, Kharkiv 61001, Ukraine
[d] Enamine Ltd.,
Matrosova Street 23, Kyiv 01103, Ukraine
E-mail: Pavel.Mykhailiuk@gmail.com
Pavel.Mykhailiuk@enamine.net
www.enamine.net

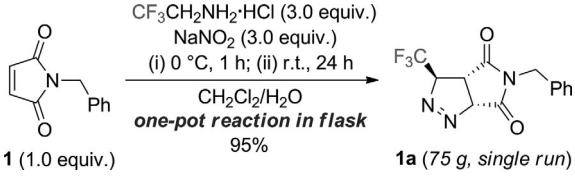
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301852.



Scheme 1. Previous synthesis of pyrazoline **1a**.[12c]

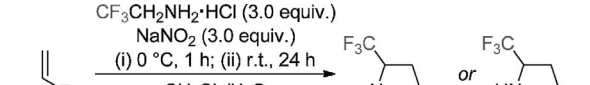
$CF_3CH_2NH_2$·HCl and $NaNO_2$ in water (*generating flask*), and blew it off by argon through magnesium sulfate (*drying flasks*) into a solution of maleimide **1** in dichloromethane (*reaction flask*). Unfortunately, the risks associated with gaseous CF_3CHN_2 prevented the large-scale synthesis (see the Supporting Information[14]).

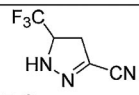
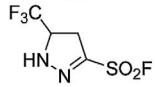
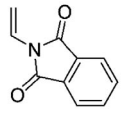
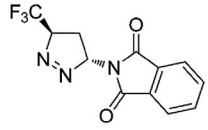
Recently, Carreira and Morandi used CF_3CHN_2 generated in situ in catalytic reactions.[15] Inspired by this work, we explored the [3+2] cycloaddition of CF_3CHN_2, generated in situ, with alkene **1**. In the experimental setup, $CF_3CH_2NH_2$·HCl[18] (3.0 equiv.) was added to a solution of $NaNO_2$ (3.0 equiv.) in dichloromethane/water at 0 °C under air. The reaction mixture was stirred for 1 h, during which the organic layer became yellow, and maleimide **1** (1.0 equiv.) was added. After 24 h at room temperature, evaporation of dichloromethane under vacuum afforded the pure product **1a** in 95% yield. The presence of water had no influence on the reaction. Because maleimide **1** reacts with neither $NaNO_2$ nor $CF_3CH_2NH_2$·HCl, we then simply mixed all reagents at once in dichloromethane/water (see the Supporting Information) and, after stirring the suspension at 0 °C for 1 h and at room temp. for 24 h, again obtained the pure product. The reaction also worked well on a large scale, and we easily synthesized 75 g of product **1a** in a single run (Scheme 2).



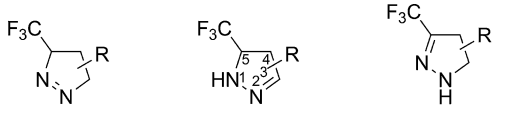
Scheme 2. Optimized one-pot synthesis of pyrazoline **1a**.

Table 1. Reaction scope.[a]



Alkene		Product		Yield [%][a]
2		2b		97 (*X-ray*)
3		3b		92
4		4a		80[b] (*X-ray*)
5		*no reaction*[c]		–
6		*no reaction*[c]		–

[a] Isolated yield. [b] Reaction time: 2 weeks; 12 equiv. of CF_3CHN_2. [c] Reaction time: 4 weeks.



Scope of the Reaction

Given the simplicity of the developed reaction, we then studied its scope. First, we investigated various monosubstituted alkenes **2**–**6** (Table 1). Substrates **2** and **3**, with strong electron-withdrawing groups (EWGs), reacted completely with CF_3CHN_2 generated in situ; however, substrates with either a weak EWG (**4**), or electron-donating groups (EDGs) (**5** and **6**) did not. Because the reaction conversion for alkene **4** was only 15%, we increased the reaction time to two weeks and used 12 equiv. of CF_3CHN_2 to obtain the pure product **4a**. These results suggest that CF_3CHN_2 generated in situ reacts only with electron-deficient alkenes.

We then investigated the steric requirements of the reaction. Diverse di- and trisubstituted alkenes (**1** and **7**–**20**), with at least one strong EWG (–COR, $–NO_2$), were examined (Table 2, Figure 2). The 1,1-disubstituted alkenes smoothly gave the corresponding pyrazolines, irrespective of the nature of the second substituent, EWG (**7**) or EDG (**8**). The 1,2-disubstituted alkenes behaved differently: alkenes with a second EWG (**1** and **9**–**12**) reacted completely, alkenes with an EDG (**13** and **14**) required longer reaction times, whereas those with strong EDGs (**15** and **16**) did not react. For reasons that are not yet clear, the five-membered substrates **17** and **18** did not react either. Trisubstituted alk-

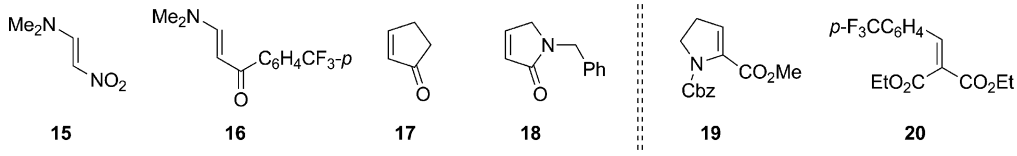
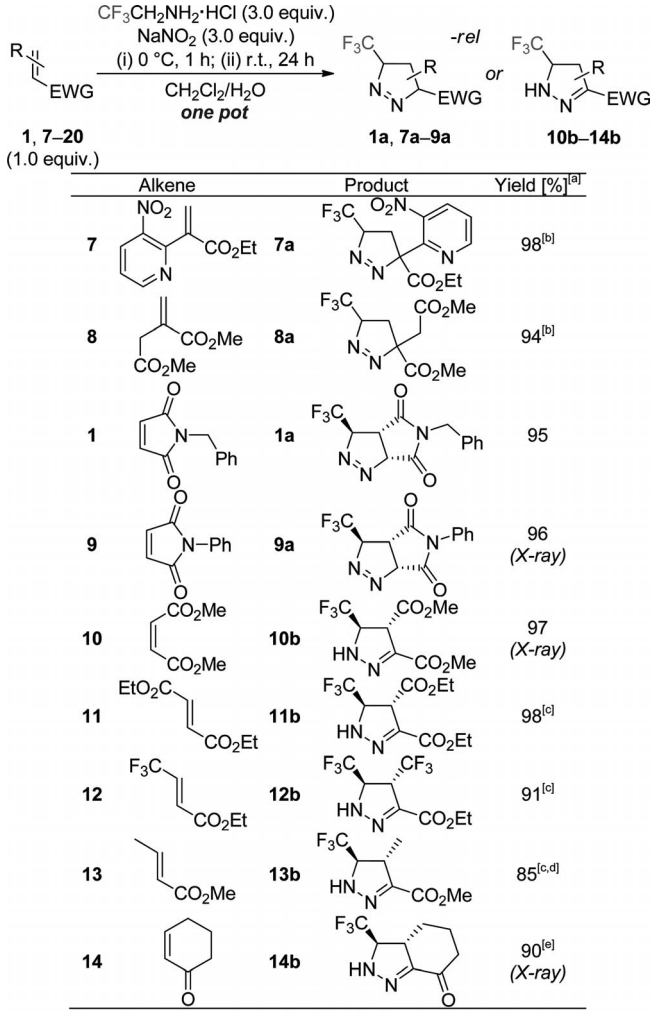


Figure 2. Alkenes that are inert to CF_3CHN_2 generated in situ (Table 2).

enes **19** and even **20** – with three EWGs – also remained unchanged. These data show that CF_3CHN_2 generated in situ reacts only with mono- and disubstituted alkenes.

Table 2. Reaction scope.[a]



forr 3 grau

[a] Isolated yield. [b] Mixture of *trans*/*cis* isomers, 9:1 (**7a**) and 1:1 (**8a**). Reaction time 2 weeks. [c] Formed as ca. 10% *cis* isomer. [d] Formed as ca. 10% Δ^1-pyrazoline. [e] Reaction time 48 h.

The structures of compounds **2b**, **4a**, **9a**, **10b**, and **14b** were confirmed by X-ray crystallographic analysis (Figure 3).

Regioselectivity

The [3+2] cycloaddition of CF_3CHN_2, generated in situ, with alkenes leads to pyrazolines with the CF_3 and EWG substituents at the 3- and 5-positions (Tables 1 and 2). We observed no corresponding 3,4-disubstituted isomers.

Δ^1-/Δ^2-Pyrazoline Isomerism

Monosubstituted alkenes formed the thermodynamically more stable Δ^2-pyrazolines with the conjugated N=C and the C≡N (**2b**)/S=O (**3b**) bonds. Alkene **4**, with no such groups, afforded Δ^1-pyrazoline **4a**. The 1,1-disubstituted alkenes gave the Δ^1-pyrazolines **7a**, **8a** [Δ^2-isomers (**b**) are not possible]. The 1,2-disubstituted substrates afforded Δ^2-pyrazolines **9b**–**14b**, except for **1a** and **9a**. Presumably, the putative bicyclic alkenes **1b** and **9b** are strained according to Bredt's rule.

Diastereoselectivity

Monosubstituted (**4**) and symmetric 1,2-*cis*-disubstituted (**1** and **9**) alkenes afforded the pure *trans*-Δ^1-pyrazolines (**1a**, **4a** and **9a**), whereas 1,1-disubstituted substrates (**7** and **8**) gave *trans*/*cis* mixtures.

Reaction with Alkynes

Having developed the reaction of CF_3CHN_2 with alkenes, we next investigated its application with alkynes. First, we examined the monosubstituted alkynes (Table 3) and found that those with EWGs (**21**–**23**) gave the corresponding pyrazoles **21a**–**23a** in quantitative yield; while alkynes with EDGs (**24** and **25**) remained intact. Similar to alkenes, the regioselective reaction gave only 3,5-disubstituted isomers.

In the next step, we studied the disubstituted alkynes with one EWG (–CO_2R or –CF_3) and various substituents. We found that alkynes with a second strong EWG (**26** and **27**) reacted completely, whereas alkynes with a second EDG (**28**) reacted slowly. The reaction of **28** reached only 72% conversion and afforded only one regioisomer. The crystalline product was obtained by purification of the starting liquid material by washing with hexane. Unexpectedly, inverted regioselectivity was observed for **28b** with an EWG group at the 4-position of the pyrazole core.[16] Presumably, the steric clash between the bulky CF_3 and $SiMe_3$ groups forced the reaction to take the inverted pathway.[17]

The structure of pyrazoles **21a** and **26a** was proven by X-ray crystallographic analysis (Figure 4).

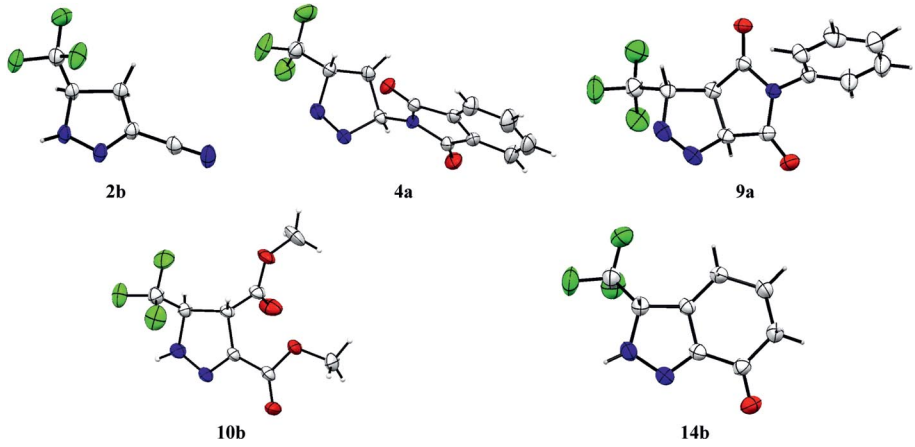
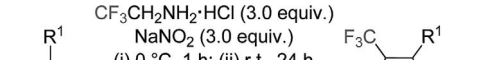
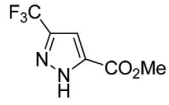
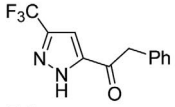
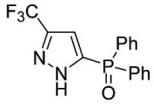
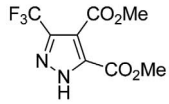
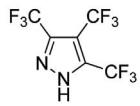
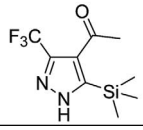


Figure 3. X-ray crystal structures of **2b**, **4a**, **9a**, **10b**, **14b**. Color code: C grey, N blue, O red, F green. Atom ellipsoids are shown at a 30% probability level.

These results suggest that the reaction between CF_3CHN_2 generated in situ and alkenes/alkynes belongs to type I [3+2] cycloadditions:[17b] the EWG of the substrate accelerates the reaction, whereas EDGs decelerate. The properties and reactivity of CF_3CHN_2 generated in situ closely resemble those of the individual reagent.[8b]

Table 3. Reaction scope.



Alkyne	Product	Yield [%][a]
21 	**21a** 	99 *(X-ray)*
22 	**22a** 	99
23 	**23a** 	99
24 	*no reaction*	–
25 	*no reaction*	–
26 	**26a** 	96 *(X-ray)*
27 	**27a** 	80
28 	**28b** 	65 (72)[b]

[a] Isolated yield. [b] Reaction conversion.

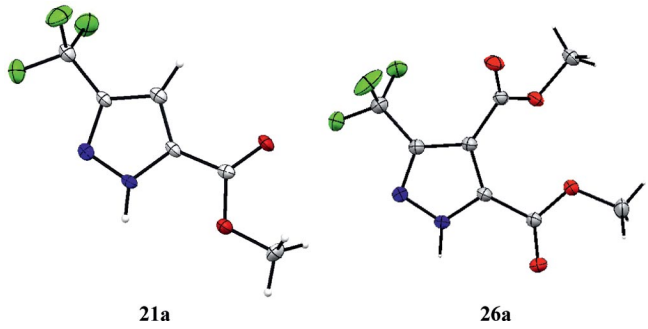


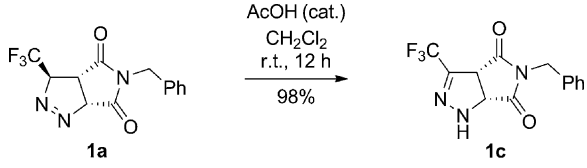
Figure 4. X-ray crystal structures of compounds **21a** and **26a**. Color code: C grey, N blue, O red, F green. Atom ellipsoids are shown at a 30% probability level.

Practical Application

Having developed a useful method to construct the CF_3-substituted pyrazolines/pyrazoles, we also wanted to briefly demonstrate its high synthetic potential.

Isomerization of Δ¹-Pyrazolines

Medicinal chemists extensively exploit Δ^2-pyrazolines as building blocks to synthesize bioactive compounds (Figure 1). Δ^1-Pyrazolines, in turn, isomerize to the Δ^2 isomers under acidic conditions.[2a,18] In this respect, treatment of an arbitrary Δ^1-pyrazoline **1a** with a catalytic amount of acetic acid in dichloromethane quantitatively afforded the pure Δ^2 isomer **1c** (Scheme 3).



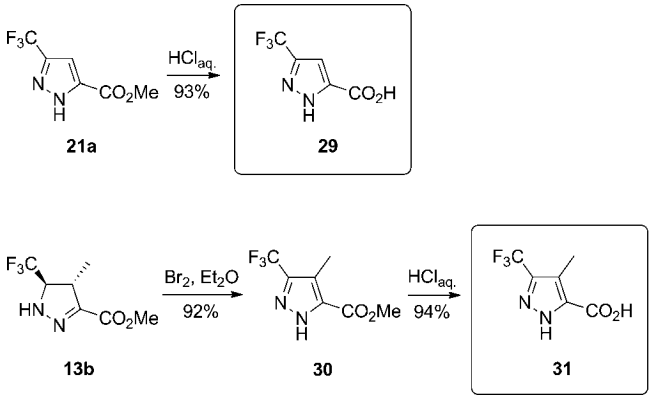
Scheme 3. Acidic isomerization of Δ^1-pyrazoline **1a** to Δ^2-pyrazoline **1c**.

Preparation of CF_3-Substituted Pyrazolecarboxylic Acids

CF_3-substituted pyrazolecarboxylic acid **29** is a useful building block in medicinal projects (Figure 5).[19] In this context, we synthesized acid **29** through a one-step acidic hydrolysis of the ester group in pyrazole **21a** (Scheme 4). We also prepared its homologue **31** by oxidation of pyrazoline **13b** with bromine (to give pyrazole **30**), followed by acidic hydrolysis of the ester group.

One-Pot Synthesis of Tris(trifluoromethyl)pyrazole

Recently, Diaz and colleagues synthesized complexes of tris(trifluoromethyl)pyrazole **27a** with Ag and CO (C_2H_4) to study their catalytic activity in the reaction between ethyldiazoacetate and alkanes.[20] Pyrazole **27a** was synthesized for the first time in 1968 by reaction between two gases, CF_3CHN_2 and bis(trifluoromethyl)acetylene (**27**), at –80 °C in a sealed tube (Scheme 5).[6] Given the inconvenience of this approach, recently Gerus and colleagues developed an alternative strategy to generate pyrazole **27a** from diketone **32** by employing SF_4/HF in the last synthesis step.[21]



Scheme 4. Synthesis of acids **29** and **31**.

Herein, we have elaborated a convenient, one-step procedure to obtain pyrazole **27a** from CF_3CHN_2 generated in situ. First, a solution of **27** in dichloromethane was prepared at –30 °C and added to a solution of CF_3CHN_2 generated in situ in water/dichloromethane. After 24 h at room temperature, the standard workup afforded the pure product in 80% yield. This attractive one-step synthesis of **27a** can be performed in a laboratory on a routine basis without any special equipment.

Conclusions

We have elaborated the reaction between CF_3CHN_2 generated in situ and alkenes/alkynes to construct CF_3-substituted pyrazolines/pyrazoles. The reaction belongs to type I [3+2] cycloadditions. At room temperature, CF_3CHN_2 generated in situ smoothly reacts with mono- and disubstituted alkenes/alkynes with at least one strong EWG. The synthetic protocol is practical, the reaction proceeds in air, at room temperature, without any catalysts, and in common solvents such as H_2O/CH_2Cl_2. Moreover, the reaction gives products in excellent yields without purification. Given the

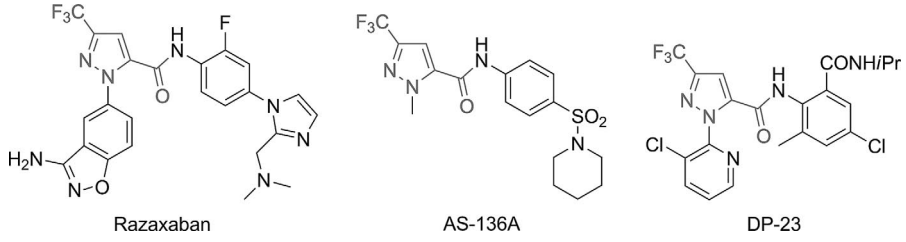
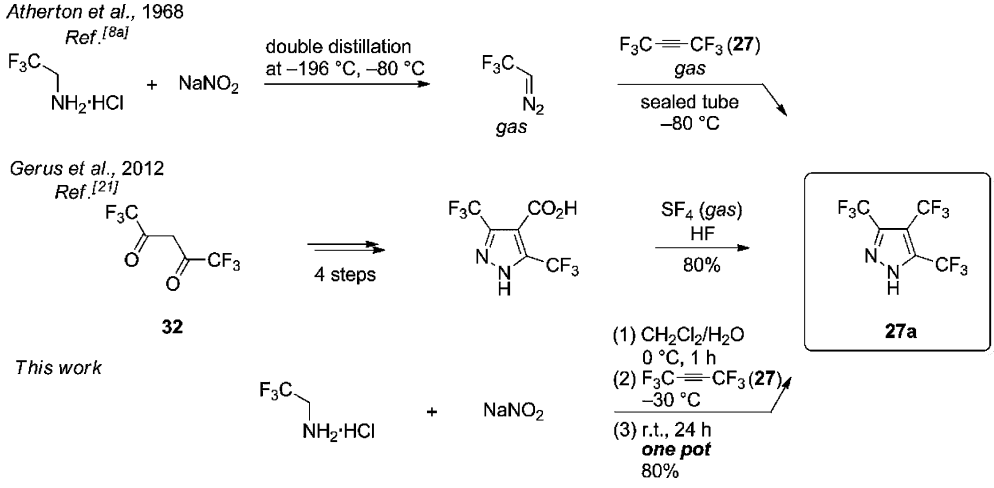


Figure 5. Bioactive derivatives of CF_3-substituted pyrazolecarboxylic acid **29** (grey).[18]



Scheme 5. Syntheses of pyrazole **27a**.

simplicity of the developed procedure, we believe that it will find wide application in both agrochemistry and medicinal chemistry.[22,23]

Experimental Section

General: Solvents were purified according to standard procedures. All reactions were performed in air. CH_2Cl_2 was distilled from CaH_2 (to remove the residual HCl). All the other starting materials were provided by Enamine Ltd. ^1H, ^{19}F, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker Avance 500 spectrometer at 499.9, 470.3, 124.9, and 202.4 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS (^1H, ^{13}C), OPA (85% phosphoric acid) (^{31}P) or C_6F_6 (^{19}F) as internal standards. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument by chemical ionization (CI, LC-MS).

Typical Procedure. 5-Benzyl-3-(trifluoromethyl)-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(3*H*,5*H*)-dione (1a): Alkene **1** (50.0 g, 0.27 mol) was dissolved in CH_2Cl_2 (400 mL), and a solution of $NaNO_2$ (27.9 g, 0.40 mol) in water (200 mL) was added at room temp. The suspension was cooled to 0 °C, and $CF_3CH_2NH_2$·HCl (54.2 g, 0.40 mol) was added in small portions while stirring. The reaction mixture was vigorously stirred for 1 h, then the cooling bath was removed, and stirring was continued for another 12 h. The organic layer was separated, washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give the title product **1a** (76.2 g, 0.26 mol, 95%) in the form of Δ^1-pyrazoline as single stereoisomer. An analytical sample of the product was obtained by crystallization of the material (hexane/EtOAc, 4:1) to give the pure product as a white solid. M.p. 108–109 °C. Analytical characteristics of that material are identical to those reported previously.[12c]

5-(Trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3-carbonitrile (2b): Obtained as Δ^2-pyrazoline as a white solid. Yield: 2.0 g (97%); m.p. 91–92 °C. ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.12 [dd, $^2J_{H,H}$ = 17.9, $^3J_{H,H}$ = 7.9 Hz, 1 H, C*H*H,], 3.24 [dd, $^2J_{H,H}$ = 17.9, $^3J_{H,H}$ = 12.6 Hz, 1 H, C*H*H], 4.44–4.52 (m, 1 H, C*H*CF_3), 6.69 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 34.2 (s, *C*H_2), 60.8 (q, $^2J_{C,F}$ = 32.0 Hz, *C*HCF_3), 113.1 (s, *C*H), 120.5–127.2 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F_3), 123.4 (s, *C*N) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –78.0 (d, $^3J_{F,H}$ = 7.0 Hz) ppm. MS: *m*/*z* = 163 [M]. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration of a solution of **2a** in diethyl ether.

5-(Trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3-sulfonyl Fluoride (3b): Obtained in the stable form of Δ^2-pyrazoline as a yellow oil with 94% purity (according to LC-MS analysis). Yield: 2.0 g (92%). ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.33 (dd, $^2J_{H,H}$ = 17.6, $^3J_{H,H}$ = 8.1 Hz, 1 H, C*H*H), 3.47 (dd, $^2J_{H,H}$ = 17.6, $^3J_{H,H}$ = 8.1 Hz, 1 H, CH*H*), 4.71 (m, 1 H, C*H*CF_3), 7.25 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 31.8 (s, *C*H_2), 62.7 (q, $^2J_{C,F}$ = 32.0 Hz, *C*HCF_3), 123.5 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F_3), 140.2 (d, $^2J_{C,F}$ = 38.0 Hz, *C*=N) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –78.2 (d, $^3J_{F,H}$ = 6.0 Hz, CF_3) ppm. MS: *m*/*z* = 220 [M].

2-[(5-Trifluoromethyl)-4,5-dihydro-3*H*-pyrazol-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (4a): The reaction was performed as described in the typical procedure. $CF_3CH_2NH_2$·HCl (2.0 g, 12 equiv. in total; 4 equiv. then 4 equiv. after 3 d, then 4 equiv. after 6 d); the reaction time was 14 d. The crude material was crystallized (Et_2O/hexane, 9:1) to afford the Δ^1-pyrazoline **4a**. Yield: 280 mg (80%); white solid; m.p. 137–139 °C. ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 2.08–2.21 (m, 2 H, C*H*$_2$), 5.74–5.79 (m, 1 H, C*H*CF_3), 6.86–6.90 (m, 1 H, NC*H*N), 7.79–7.82 (m, 2 H, Pht), 7.89–7.82 (m, 2 H, Pht) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 20.9 (s, CH_2), 89.5 (s, N*C*HN), 90.6 (q, $^2J_{C,F}$ = 28.0 Hz, *C*HCF_3), 123.7 (q, $^1J_{C,F}$ = 279.0 Hz, *C*F_3), 124.8 (s, 2*C*H of phthalimide), 131.4 (s, 2*C* of phthalimide), 134.8 (s, 2*C*H of phthalimide), 166.4 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –71.7 (d, $^3J_{F,H}$ = 7.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 283 [M]. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration of a solution of **4a** in $CDCl_3$.

Ethyl 3-(3-Nitropyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-3*H*-pyrazole-3-carboxylate (7a): Obtained in the form of Δ^1-pyrazoline as a 90:10 mixture of isomers. Yield: 200 mg (98%); yellowish oil that solidified upon standing; m.p. 67–68 °C. ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ (major isomer) = 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $COCH_2CH_3$), 2.72 (d, $^3J_{H,H}$ = 9.1 Hz, 2 H, C*H*$_2$), 4.29 (m, 2 H, $COCH_2$), 5.13 (m, 1 H, C*H*CF_3), 7.58 (dd, $^3J_{H,H}$ = 4.5 Hz, 1 H, C*H* of pyridine), 8.46 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, C*H* of pyridine), 8.73 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, C*H* of pyridine) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ (major isomer) = 13.7 (s, *C*H_3), 28.4 (s, *C*H_2), 63.3 (s, *C*H_2CH$_3$), 90.5 (q, $^3J_{C,F}$ = 29.3 Hz, *C*HCF_3), 103.6 (s, *C*COOEt), 123.1 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F_3), 124.6 (s, *C*H of pyridine), 133.8 (c, *C*H of pyridine), 144.4 (s, *C* of pyridine), 149.3 (s, *C*NO_2), 152.5 (s, *C*H of pyridine), 166.0 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ (major isomer) = –71.2 (d, $^3J_{F,H}$ = 8.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 305 [M – 28].

Methyl 3-(2-Methoxy-2-oxoethyl)-5-(trifluoromethyl)-4,5-dihydro-3*H*-pyrazole-3-carboxylate (8a): Obtained in the form of Δ^1-pyrazoline as a 50:50 mixture of isomers. Yield: 5.0 g (94%); clear oil. ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 1.57 (m, 0.46 H, C*H*H of pyrazoline cycle), 2.12 (m, 0.51 H, CH*H* of pyrazoline cycle), 2.24 (m, 0.51 H, C*H*H of pyrazoline cycle), 2.73 (overlap, 0.91 H, C*H*H of pyrazoline cycle, CH*H*COOMe), 2.90 [d, $^2J_{H,H}$ = 17.6 Hz, 0.52 H, C*H*HCOOMe], 3.27 (d, $^2J_{H,H}$ = 17.2 Hz, 0.52 H, CH*H*COOMe), 3.63 (s, 1.49 H, COOC*H*$_3$), 3.68 (s, 1.42 H, COOC*H*$_3$), 3.73 (s, 1.40 H, COOC*H*$_3$), 3.77–3.81 (overlap, 1.98 H, COOC*H*$_3$, C*H*HCOOMe), 5.19–5.29 (m, 0.5 H, CF_3C*H*), 5.30–5.36 (m, 0.5 H, CF_3C*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ (diastereoisomers A and B) = 37.7 (s, *C*H$_2$ of pyrazoline cycle), 39.4 (s, *C*H$_2$COOMe), 51.9 (s, CH$_2$COO*C*H$_3$ of A), 51.0 (s, CH$_2$COO*C*H$_3$ of B), 53.3 (s, COO*C*H$_3$), 90.4–91.3 (m, overlap *C*HCF_3 of A,B), 98.4 [s, *C*(COOMe)CH$_2$COOMe of A], 98.0 [s, *C*(COOMe)CH$_2$COOMe of B] 123.5 (q, $^1J_{C,F}$ = 279.0 Hz, *C*F_3 of A), 123.6 (q, $^1J_{C,F}$ = 279.0 Hz, *C*F_3 of B), 167.4 (s, CH$_2$*C*OOMe of A), 168.3 (s, CH$_2$*C*OOMe of B), 169.4 (s, *C*OOMe of A), 169.6 (s, *C*OOMe of B) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –72.3 (d, $^3J_{F,H}$ = 8.0 Hz, C*F*$_3$ of A), –71.8 (d, $^3J_{F,H}$ = 8.0 Hz, C*F*$_3$ of B) ppm. MS: *m*/*z* = 268.

5-Phenyl-3-(trifluoromethyl)-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(3*H*,5*H*)-dione (9a): Obtained in the form of Δ^1-pyrazoline as one stereoisomer. Yield: 2.0 g (96%); white solid; m.p. 166–168 °C. ^1H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.53 (dd, $^3J_{H,H}$ = 3.0, $^3J_{H,H}$ = 7.3 Hz, 1 H, CHC*H*CO), 5.81 (m, 1 H, C*H*CF_3), 6.03 (dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 2.4 Hz, 1 H, NC*H*CO), 7.23 (m, 2 H, Ph), 7.47 (m, 3 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 38.8 (s, *C*HCO), 92.9 (q, $^2J_{C,F}$ = 29.0 Hz, *C*HCF_3), 94.8 (s, N*C*HCO), 122.3 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F_3), 126.1 (s, 2*C*H of phenyl), 129.4 (s, overlap of 3 *C*H of phenyl), 130.4 (s, *C* of phenyl), 166.4 (s, *C*O), 171.6 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –72.0 (d, $^3J_{F,H}$ = 8.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 283 [M]. Crystals of the compound suitable for X-ray crystallographic

analysis were obtained by slow concentration of a solution of **9a** in THF.

Dimethyl 5-(Trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (10b): Obtained in the form of Δ^2-pyrazoline as a single isomer. Yield: 2.5 g (97%); white solid; m.p. 90–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.78 (s, 3 H, CHCOOC*H*$_3$), 3.82 (s, 3 H, N=CCOOC*H*$_3$), 4.20 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C*H*COOMe), 4.63–4.71 (m, 1 H, C*H*CF_3), 7.02 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 50.1 (q, $^3J_{C,F}$ = 3 Hz, *C*HCOOCH$_3$), 52.2 (s, CHCOO*C*H$_3$), 53.0 (s, N=CCOO*C*H$_3$), 65.5 (q, $^2J_{C,F}$ = 32.0 Hz, *C*HCF_3), 123.2 (q, $^1J_{C,F}$ = 279.0 Hz, *C*F_3), 138.5 (s, N=*C*), 160.8 (s, CH*C*OOMe), 168.6 (s, N=C*C*OOMe) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –87.5 (d, $^3J_{F,H}$ = 7.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 255 [M + 1]. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration of a solution of **10b** in CH_2Cl_2.

Diethyl 5-(Trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (11b): Obtained in the form of Δ^2-pyrazoline as a 92:8 mixture of isomers. Yield: 2.3 g (98%); clear oil. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ (major isomer) = 1.18–1.25 (m, 6 H, overlap two signals of CH_2CH_3), 4.09–4.24 (m, 5 H, overlap three signals of two CH_2CH_3 and C*H*COOEt), 4.57–4.65 (m, 1 H, C*H*CF_3), 7.25 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ (major isomer) = 13.4 (s, CCOOCH$_2$*C*H$_3$), 13.6 (s, N=CCOOCH$_2$*C*H$_3$), 50.4 (s, *C*HCOOEt), 61.2 (s, CCOO*C*H$_2$CH$_3$), 62.0 (s, N=CCOO*C*H$_2$CH$_3$), 65.5 (q, $^2J_{C,F}$ = 32.0 Hz, *C*HCF_3), 123.4 (q, $^1J_{C,F}$ = 279.0 Hz, CF_3), 138.7 (s, *C*=N), 160.4 (s, CH*C*OOEt), 168.3 (s, N=C*C*OOEt) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ (major isomer) = –87.5 (d, $^3J_{F,H}$ = 7.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 283 [M + 1].

Ethyl 4,5-Bis(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (12b): Obtained in the form of Δ^2-pyrazoline as a 91:9 mixture of isomers. Yield: 5.0 g (91%); white solid; m.p. 66–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 1.32 (t, $^3J_{H,H}$ = 7.1 Hz, 0.36 H), 1.37 (t, $^3J_{H,H}$ = 7.1 Hz, 2.64 H), 4.15–4.22 (m, 1 H, C*H*CF_3), 4.30–4.40 (m, 2 H, C*H*$_2$CH$_3$), 4.53–4.60 [m, 0.91 H, C*H*(CF$_3$)NH], 4.89 [m, 0.8 H, C*H*(CF$_3$)NH], 6.47 (s, 0.08 H, N*H*), 6.87 (s, 0.81 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ (diastereomer A and B) = 13.4 (s, *C*H$_3$ of A), 13.7 (s, *C*H$_3$ of B), 49.1–50.1 (m, overlap *C*HCF_3 of A,B), 61.7 (s, *C*H$_2$), 61.7–62.7 [m, overlap *C*H(CF$_3$)NH of A,B], 122.7 (q, $^1J_{C,F}$ = 281.0 Hz, *C*F$_3$ of A), 123.2 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F$_3$ of B), 134.9 (s, *C*=N), 159.8 (s, *C*=O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –82.3 (d, $^3J_{F,H}$ = 7.0 Hz, CHC*F*$_3$), –91.5 (d, $^3J_{F,H}$ = 7.0 Hz, NHCHC*F*$_3$) ppm. MS: *m*/*z* = 279 [M + 1].

Methyl 4-Methyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (13b): Obtained in the form of Δ^2-pyrazoline as a 90:10 mixture of isomers and ca. 10% of Δ^1-pyrazoline. The product purity was ca. 90%. This material was used directly in the synthesis of pyrazole **30**. Yield: 75 g (85%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ (major isomer) = 1.39 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CHC*H*$_3$), 3.51 (m, 1 H, C*H*CH$_3$), 3.85 (s, 3 H, COOC*H*$_3$), 3.97 (m, 1 H, C*H*CF_3), 6.53 (s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 17.5 (s, CH*C*H$_3$), 40.4 (s, *C*HCH$_3$), 52.2 (s, COOC*H*$_3$), 68.3 (q, $^1J_{C,F}$ = 31.0 Hz, *C*HCF_3), 124.4 (q, $^1J_{C,F}$ = 280.0 Hz, *C*F$_3$), 145.6 (s, *C*=N), 161.9 (s, *C*OOMe) ppm. MS: *m*/*z* = 211 [M + 1].

3-(Trifluoromethyl)-2,3,3a,4,5,6-hexahydro-7*H*-indazol-7-one (14b): $CF_3CH_2NH_2$·HCl (4.5 g, 3 equiv.) was used; the reaction time was 48 h. Yield: 1.1 g (90%); white solid; m.p. 168–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 1.66–1.74 (m, 1 H, C*H* of cyclohexanone), 1.91–1.99 (m, 1 H, C*H* of cyclohexanone), 2.17–2.30 (m, 2 H, C*H*$_2$ of cyclohexanone), 2.42–2.49 (m, 1 H, C*H* of cyclohexanone), 2.72–2.76 (m, 1 H, C*H* of cyclohexanone), 3.41–3.47 (m, 1 H, C*H*CHCF_3), 4.25–4.30 (m, 1 H, C*H*CF_3), 6.55 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 23.2 (s, *C*H$_2$), 28.5 (s, *C*H$_2$CH), 40.7 (s, *C*H$_2$CO), 46.5 (s, *C*HC=N), 70.1 (q, $^2J_{C,F}$ = 31.0 Hz, *C*HCF_3), 124.6 (q, $^1J_{C,F}$ = 277.0 Hz, *C*F_3), 150.4 (s, *C*=N), 193.2 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –82.4 (d, $^3J_{F,H}$ = 5.0 Hz, C*F*$_3$) ppm. MS: *m*/*z* = 207 [M + 1]. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration of a solution of **14b** in THF.

Methyl 5-(Trifluoromethyl)-1*H*-pyrazol-3-carboxylate (21a): Yield: 2.0 g (99%); white solid; m.p. 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.99 (s, 3 H, COOC*H*$_3$), 7.10 (s, 1 H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 52.8 (s, COO*C*H$_3$), 107.4 (s, *C*H), 120.5 (q, $^1J_{C,F}$ = 269.0 Hz, *C*F_3), 135.2 (s, *C*=N), 144.2 (q, $^2J_{C,F}$ = 37.0 Hz, *C*CF_3), 159.1 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –62.9 (s, C*F*$_3$) ppm. MS: *m*/*z* = 195 [M + 1].

2-Phenyl-1-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]ethanone (22a): Yield: 180 mg (99%); yellowish solid; m.p. 74–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 4.17 (s, 2 H, C*H*$_2$Ph), 7.05 (s, 1 H, C*H* of pyrazole), 7.27–7.38 (m, 5 H, C*H* of phenyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 46.2 (s, *C*H$_2$Ph), 106.7 (s, *C*H of pyrazole), 120.1 (q, $^1J_{C,F}$ = 268.0 Hz, *C*F_3), 127.3 (s, *p*-*C*H of phenyl), 128.6 (s, *m*-*C*H of phenyl), 129.0 (s, *o*-*C*H of phenyl), 132.1 (s, *C* of phenyl), 141.0 (s, *C*COCH$_2$Ph), 143.3 (q, $^2J_{C,F}$ = 39.0 Hz, *C*CF_3), 188.0 (s, *C*O) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –61.5 (s, C*F*$_3$) ppm. MS: *m*/*z* = 255 [M + 1].

3-(Diphenylphosphoryl)-5-(trifluoromethyl)-1*H*-pyrazole (23a): Yield: 200 mg (99%). White solid; sublimation at ca. 220 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 6.48 (s, 1 H, C*H* of pyrazole), 7.44–7.61 (m, 10 H, C*H* of phenyls) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 110.6 (d, $^2J_{C,P}$ = 17.0 Hz, *C*H of pyrazole), 120.7 (q, $^1J_{C,F}$ = 269.0 Hz, *C*F_3), 128.4 (d, $^3J_{C,P}$ = 13.0 Hz, *m*-*C*H of phenyls), 129.8 (d, $^1J_{C,P}$ = 113.0 Hz, *C* of phenyls), 131.2 (d, ^2J(C,F) = 11.0 Hz, *o*-*C*H of phenyls], 132.5 (d, $^4J_{C,F}$ = 2.0 Hz, *p*-*C*H of phenyls], 135.7 (d, $^1J_{C,F}$ = 117.0 Hz, *C*POPh$_2$), 142.3–143.3 (m, *C*CF_3) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –60.8 (s, C*F*$_3$) ppm. ^{31}P NMR (202.4 MHz, $CDCl_3$; OPA): δ = 19.8 (pseudo t, $^3J_{P,H}$ = 12.1 Hz, *P*Ph$_2$) ppm. MS: *m*/*z* = 337 [M + 1].

Dimethyl 5-(Trifluoromethyl)-1*H*-pyrazole-3,4-dicarboxylate (26a): Yield: 500 mg (96%); yellowish solid; m.p. 65–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 3.94 (s, 3 H, C=CCOOC*H*$_3$), 3.97 (s, 3 H, N=CCOOCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 53.0 (s, C=CCOO*C*H$_3$), 53.3 (s, N=CCOO*C*H$_3$), 115.0 (s, C=*C*COOCH$_3$), 119.9 (q, $^1J_{C,F}$ = 270.0 Hz, CF_3), 134.9 (s, N=*C*COOMe), 141.8 (q, $^2J_{C,F}$ = 39.0 Hz, CF_3C), 158.2 (s, C=C*C*OOMe), 161.6 (s, N=C*C*OOMe) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –62.3 (s, C*F*$_3$) ppm. MS: *m*/*z* = 253 [M + 1]. Crystals of the compound suitable for X-ray crystallographic analysis were obtained by slow concentration of a solution of **26a** in CH_2Cl_2.

3,4,5-Tris(trifluoromethyl)-1*H*-pyrazole (27a): A solution of bis(trifluoromethyl)acetylene (**27**) in CH_2Cl_2 was prepared at –30 °C (Flask 1). An aliquot of a solution of **27** (1.0 g, 6.2 mmol) in CH_2Cl_2 (ca. 50 mL) was added to a previously generated solution (Flask 2) of CF_3CHN_2 (obtained from 1.3 g of $CF_3CH_2NH_2$·HCl, 1.5 equiv.) in dichloromethane at –10 °C. The reaction mixture was allowed to warm slowly to room temp. for 12 h. The organic layer was separated, washed with brine, dried with sodium sulfate, and concentrated under vacuum to give pyrazole **27a** (1.3 g, 4.9 mmol, 80% yield) as a white solid (***CAUTION:*** The product is very vola-

tile!). An analytical sample was obtained by low-temperature recrystallization from pentane. Analytical characteristics of that material are identical to those reported previously.[17]

1-[3-(Trifluoromethyl)-5-(trimethylsilyl)-1*H*-pyrazol-4-yl]ethanone (28b): The crude material was crystallized from hexane to afford the pure product **28b**. Yield: 140 mg. (65%); white solid; m.p. 120–121 °C (subl.). ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 0.39 [s, 9 H, Si(CH_3)$_3$], 2.57 (s, 3 H, COCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = –2.6 [s, Si(CH_3)$_3$], 29.2 (s, CH_3), 120.8 (q, $^1J_{C,F}$ = 270.0 Hz, CF_3), 127.1 (s, CTMS), 141.0 (q, $^2J_{C,F}$ = 36.0 Hz, CCF_3), 151.3 (s, CCO), 192.6 (s, CO) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –58.1 (s,CF_3) ppm. MS: *m*/*z* = 251 [M + 1].

5-(Trifluoromethyl)-1*H*-pyrazole-3-carboxylic Acid (29): Pyrazole **21a** (1.0 g, 5.15 mmol) was suspended in dioxane/water (2:1, 20 mL), and aq. 20% HCl (5 mL) was added. The reaction mixture was heated at reflux overnight; then the solvent was evaporated under vacuum, and the formed solid residue was crystallized from 2-propanol to obtain the pure product **29**. Yield: 0.862 g (4.79 mmol, 93%); white solid; m.p. 167–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 2.31 (s, 3 H, CH_3), 4.72 (br. s, 2 H, NH, COOH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 106.7 (s, CH), 121.0 (q, $^1J_{C,F}$ = 268.0 Hz, CF_3), 136.4 (s, C=N), 141.3 (q, $^2J_{C,F}$ = 38.3 Hz, CCF_3), 159.4 (s, COOH) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –70.7 (s, CF_3) ppm. MS: *m*/*z* = 180 [M].

Methyl 4-Methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylate (30): In a reactor equipped with a dropping funnel and a thermometer, pyrazoline **27a** (75.0 g, 0.36 mol) was dissolved in Et_2O (700 mL). The solution was cooled to 0 °C followed by slow dropwise addition of bromine (22.3 mL, 0.43 mol). The reaction mixture was stirred at room temp. for 24 h; then the solvent was evaporated under vacuum. The solid residue was dissolved in CH_2Cl_2 (500 mL), and this solution was washed twice with a saturated solution of $NaHCO_3$ (150 mL) and brine. The organic phase was dried with sodium sulfate, filtered, and the solvents were evaporated under vacuum to obtain the crude product. Crystallization from hexane gave pure pyrazole **30**. Yield: 68.9 g (0.33 mmol, 92%); white solid; m.p. 77–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 2.42 (s, 3 H, CH_3), 3.99 (s, 3 H, COOCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 8.1 (s, CCH_3), 52.4 (s, COOCH_3), 120.1 (s, CCH_3), 121.2 (q, $^1J_{C,F}$ = 269.0 Hz, CF_3), 132.3 (s, CCOOMe), 142.7 (q, $^2J_{C,F}$ = 37.0 Hz, CCF_3), 159.6 (s, COOMe) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –62.4 (s, CF_3) ppm. MS: *m*/*z* = 209 [M + 1].

4-Methyl-5-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic Acid (31): Pyrazole **30** (67.0 g, 0.32 mol) was suspended in dioxane/water (2:1, 300 mL), and aq. 20% HCl (100 mL) was added. The reaction mixture was heated at reflux overnight; then the solvent was evaporated under vacuum, and the formed solid residue was crystallized from 2-propanol to obtain the pure product **31**. Yield: 58.3 g (0.3 mol, 94%); white solid; m.p. >250 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$; Me_4Si): δ = 2.30 (s, 3 H, CH_3), 14.34 (s, 1 H, COOH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; Me_4Si): δ = 7.9 (s, CH_3), 118.3 (s, CCH_3), 121.8 (q, $^1J_{C,F}$ = 268.0 Hz, CF_3), 133.0 (s, CCOOH), 140.2 (q, $^2J_{C,F}$ = 36.0 Hz, CCF_3), 160.1 (s, COOH) ppm. ^{19}F NMR (375 MHz, $CDCl_3$; $CFCl_3$): δ = –58.4 (s, CF_3) ppm. MS: *m*/*z* = 195 [M + 1].

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra for all new compounds.

Acknowledgments

The authors are grateful to Prof. Andrei Tolmachev for financial support of the work; to Dr. Andrii Kysil, Rustam Iminov, Bohdan Chalyc, Sergii Yasik for starting alkenes; and to Dr. Sci. Dmytro Volochnyuk and Prof. Igor V. Komarov for support.

[1] For reviews on bioactive pyrazolines, see: a) S. Kumar, S. Bawa, S. Drabu, R. Kumar, H. Gupta, *Recent Pat. Antiinfect. Drug Discov.* **2009**, *4*, 154; b) M. A. Rahman, A. A. Siddiqui, *Int. J. Pharm. Sci. Drug Res.* **2010**, *2*, 165; c) X.-H. Liu, B.-F. Ruan, J. Li, F.-H. Chen, B.-A. Song, H.-L. Zhu, P. S. Bhadury, J. Zhao, *Mini-Rev. Med. Chem.* **2011**, *11*, 771; d) M. R. Shaaban, A. S. Mayhoub, A. M. Farag, *Expert Opin. Ther. Pat.* **2012**, *22*, 253; e) A. Ganesh, *Int. J. Pharma Bio Sci.* **2013**, *4*, 727; f) A. Marella, M. R. Ali, M. T. Alam, R. Saha, O. Tanwar, M. Akhter, M. Shaquiquzzaman, M. Mumtaz Alam, *Mini-Rev. Med. Chem.* **2013**, *13*, 921.

[2] a) X. Zhang, X. Li, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen, Z. Sui, *J. Med. Chem.* **2007**, *50*, 3857; b) M. Shaharyar, M. M. Abdullah, M. A. Bakht, J. Majeed, *Eur. J. Med. Chem.* **2010**, *45*, 114; c) X. H. Liu, P. C. Lv, B. Li, H. L. Zhu, B. A. Song, *Aust. J. Chem.* **2008**, *61*, 223; d) L. S. Bai, Y. Wang, X. H. Liu, H. L. Zhu, B. A. Song, *Chin. Chem. Lett.* **2009**, *20*, 427; e) M. V. R. Reddy, V. K. Billa, V. R. Pallela, M. R. Mallireddigari, R. Boominathan, J. L. Gabriel, E. P. Reddy, *Bioorg. Med. Chem.* **2008**, *16*, 3907.

[3] In *The Chemistry of The Cyclopropyl Group* (Ed.: Z. Rappoport), Wiley-VCH, Weinheim, **1987**.

[4] a) A. P. Molchanov, A. V. Stepakov, R. R. Kostikov, *Russ. J. Org. Chem.* **2001**, *37*, 128; b) V. Padmavathi, C. P. Kumari, B. C. Venkatesh, A. Padmaja, *Eur. J. Med. Chem.* **2011**, *46*, 5317; c) A. Muralikrishna, B. C. Venkatesh, V. Padmavathi, A. Padmaja, P. Kondaiah, N. S. Krishna, *Eur. J. Med. Chem.* **2012**, *54*, 605.

[5] a) R. Chenevert, F. Jacques, *Tetrahedron: Asymmetry* **2006**, *11*, 1017; b) E. A. Yatsynich, D. V. Petrov, V. A. Dokichev, Y. V. Tomilov, *Russ. J. Org. Chem.* **2005**, *41*, 1187; c) K. V. Yakovlev, D. V. Petrov, V. A. Dokichev, Y. V. Tomilov, *Russ. J. Org. Chem.* **2011**, *47*, 168.

[6] D. S. Wishart, C. Knox, A. C. Guo, D. Cheng, S. Shrivastaya, D. Tzur, B. Gautam, M. Hassanali, *Nucleic Acids Res.* **2008**, 36 database issue, D.901 (http://www.drugbank.ca).

[7] For selected reviews, see: a) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305; b) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; d) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; e) H.-J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637.

[8] a) J. H. Atherton, R. Fields, *J. Chem. Soc. C* **1968**, 1507; b) R. Fields, J. P. Tomlinson, *J. Fluorine Chem.* **1979**, *13*, 147.

[9] *Prudent Practices for Handling Hazardous Chemicals in Laboratories* (Ed.: H. O. House), National Academy Press, Washington D.C., **1981**, pp. 57–68.

[10] H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1943**, *65*, 1458.

[11] J. H. Atherton, R. Fields, *J. Chem. Soc. C* **1967**, 1450.

[12] a) R. Fields, J. P. Tomlinson, *J. Fluorine Chem.* **1979**, *13*, 147; b) O. S. Artamonov, P. K. Mykhailiuk, N. M. Voievoda, D. M. Volochnyuk, I. V. Komarov, *Synthesis* **2010**, 443; c) O. S. Artamonov, E. Y. Slobodyanyuk, O. V. Shishkin, I. V. Komarov, P. K. Mykhailiuk, *Synthesis* **2013**, 225.

[13] Preparation of trifluoromethyldiazomethane in situ and its reaction with alkenes was previously briefly mentioned, see: F. Jin, Y. Xu, Y. Ma, *Tetrahedron Lett.* **1992**, *33*, 6161. The authors, however, used unique starting material that was not commercially available, and did not provide experimental details.

[14] The Supporting Information includes a photograph of the system used to initially synthesize pyrazoline **1a**.

[15] a) B. Morandi, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 950; *Angew. Chem. Int. Ed.* **2010**, *49*, 938; b) B. Morandi, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 4390; *Angew. Chem. Int. Ed.* **2010**, *49*, 4294; c) B. Morandi, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 9251; *Angew. Chem. Int. Ed.* **2011**, *50*, 9085; d) B. Morandi, E. M. Carreira, *Org. Lett.* **2011**, *13*, 5984; e) S. A. Künzi, B. Morandi, E. M. Carreira, *Org. Lett.* **2012**, *14*, 1900.

[16] In the ^{13}C NMR spectrum the methyl group is observed as a quartet ($^5J_{C,F}$ = 6.3 Hz).

[17] For a discussion of steric effects in [3+2] cycloadditions, see: a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 742; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633; b) G. Maas, *Diazoalkanes in Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, p. 539.

[18] See, for example: a) C. H. Yang, H.-J. Shen, R.-H. Wang, J.-C. Wang, *J. Chin. Chem. Soc.* **2002**, *49*, 95; b) P. Schiess, H. Stalder, *Tetrahedron Lett.* **1980**, *21*, 1413.

[19] a) J. G. Varnes, D. A. Wacker, D. J. P. Pinto, M. J. Orwat, J. P. Theroff, B. Wells, R. A. Galemo, J. M. Luettgen, R. M. Knabb, S. Bai, K. He, P. Y. S. Lam, R. R. Wexler, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 749 (Razaxaban); b) A. Sun, N. Chandrakumar, J.-J. Yoon, R. K. Plemper, J. P. Snyder, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5199 (AS-136A); c) G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark, D. Cordova, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4898 (DP-23).

[20] N. B. Jayaratna, I. I. Gerus, R. V. Mironets, P. K. Mykhailiuk, M. Yousufuddin, H. V. R. Dias, *Inorg. Chem.* **2013**, *52*, 1691.

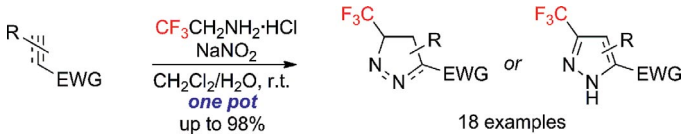
[21] I. I. Gerus, R. X. Mironetz, I. S. Kondratov, A. V. Bezdudny, Y. V. Dmytriv, O. V. Shishkin, V. S. Starova, O. A. Zaporozhets, A. A. Tolmachev, P. K. Mykhailiuk, *J. Org. Chem.* **2012**, *77*, 47.

[22] During the preparation of this manuscript a publication on the Ag-catalyzed addition of CF_3CHN_2 to terminal alkynes appeared, see: F. Li, J. Nie, L. Sun, Y. Zheng, J.-A. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 6255.

[23] CCDC-950992 (**2b**), -972780 (**4a**), -951420 (**9a**), -972779 (**10b**), -951421 (**14b**), -972781 (**21a**), and -951422 (**26a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: December 17, 2013
Published Online: ■

Fluorinated Heterocycles



Three-component reaction between $CF_3CH_2NH_2$·HCl, $NaNO_2$ and electron-deficient alkenes/alkynes gives CF_3-substituted pyrazolines/pyrazoles at room temperature in excellent yields.

Keywords: Synthetic methods / Nitrogen heterocycles / Fluorine / Multicomponent reactions / Cycloaddition

