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New strategy for the regioselective synthesis of 1-phenyl-3-trifluoromethyl-1H-pyrazoles

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ABSTRACT

A regioselective synthesis of 3-trifluoromethyl-1-phenyl-1*H*-pyrazoles (1,3-isomers) as well as their 1,5-isomers (5-trifluoromethyl-1-phenyl-1*H*-pyrazoles), is described. The 1,3-isomers were obtained from the reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with arylhydrazones followed by deprotective hydrolysis while the 1,5-isomer was obtained by direct cyclocondensation of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with phenylhydrazine. An unequivocal assignment of the 1,3- and 1,5-isomers of the pyrazole products is given.

Pyrazoles are an interesting class of the heteroaromatic ring system because they exhibit important biological activities[1] that find extensive application in agriculture,[2] microbiology,[3] and medicine[4] fields. Additionally, it is well known that the insertion of fluorine and fluorinated groups into organic molecules is often associated with positive changes in their physical, chemical, and biological proprieties.[1c,5] Therefore, the development of efficient and regioselective methods for the synthesis of pyrazoles bearing fluorinated groups in their structures is of great interest.

The most general method employed in the preparation of trifuoromethylpyrazoles is the [3+2] cyclocondensation reaction between a trifluoromethylated *CCC* building block and a *NN* building block.[6] Among the starting materials available for the 3-atom fragment, trifluoromethylated 1,3-diketones have been widely employed and their use is considered a general approach to the synthesis of these heterocycles. However, despite excellent yields and widespread application, this method suffers from poor regioselectivity and frequently affords a mixture of isomeric pyrazoles (Fig. 1).[6,7]

In previous Letters, we have demonstrated that the direct cyclocondensation between trifluoromethylated enones and phenylhydrazine is highly regioselective furnishing 1-substituted-5-trifluoromethyl-1*H*-pyrazoles (1,5-isomer, Fig. 1) as the only product.[8] In our estimation, the synthesis of 1-substituted-3-trifluoromethyl-1*H*-pyrazoles (1,3-isomer, Fig. 1) from these precursors under classical reaction conditions is quite unusual, having occurred in only two different occasions in the course of our investigations.[9] The high selectivity observed in those reactions can be ascribed to the well defined reactivity of the enones (compounds **1**–**7**, Scheme 1) which is mainly induced by the electron 'push–pull' effect of the carbonyl (π-acceptor) and the 4-alkoxy or 4-amino groups (π-donor), as reported previously.[10]

Thus, as part of our research program we aimed to develop novel synthetic strategies leading to the regioselective heterocyclization of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones, we now wish to report the synthesis of a series of 1-phenyl-3-trifluoromethyl-1*H*-pyrazoles **16**–**22** (Scheme 1) under regiochemical control. Additionally, in order to achieve a concise characterization of the products, we have also synthesized the 1-phenyl-5-trifluoromethyl-1*H*-pyrazole isomers **23**–**29** (Scheme 1) for comparing GC–MS and ^{1}H and ^{13}C NMR data.

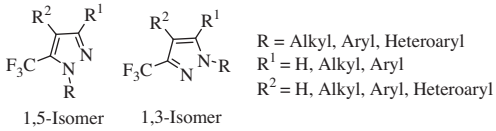

Figure 1. Structure of 1,3- and 1,5-pyrazole regioisomers.

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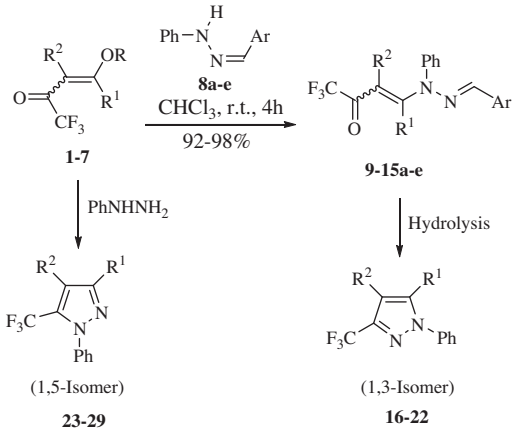


Compds.	R	R^1	R^2
1, **9**, **16**, **23**	Et	H	H
2, 10, 17, 24	Et	H	Me
3, **11**, **18**, **25**	Me	C_6H_5	H
4, **12**, **19**, **26**	Me	4-Me-C_6H_4	H
5, **13**, **20**, **27**	Me	4-MeO-C_6H_4	H
6, 14, 21, 28	Me	4-F-C_6H_4	H
7, 15, 22, 29	Me	2-Furyl	H

Compd. **8**	Ar
a	C_6H_5
b	2-HOC_6H_4
c	4-$MeOC_6H_4$
d	4-$O_2NC_6H_4$
e	4-HOC_6H_4

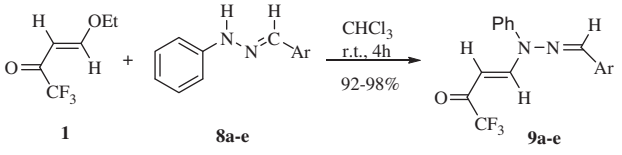
Scheme 1. Synthetic strategies leading to 1-phenyl-3(5)-trifluoromethyl-1*H*-pyrazoles from 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones.

The synthesis of the desired 1-phenyl-3-trifluoromethylpyrazoles (**16**–**22**) was envisioned using a two-step procedure that involves: (a) the reaction of trifluoromethylated enones with hydrazones derived from phenylhydrazine, and (b) hydrazone acidic deprotection. This synthetic approach is believed to proceed by a Michael addition–elimination of the hydrazones to the enones followed by the deprotective hydrolysis of the hydrazone azomethine linkage, and subsequent intramolecular nucleophilic heterocyclization (Scheme 1). In fact, we were actually able to isolate and characterize some enaminone intermediates (**9**–**15a**–**e**) suggesting that this reaction mechanism is probably plausible.

The reactions between enaminones and dinucleophiles addressing to heterocycles have been extensively reported.[8d,11] In these reactions, however, the amino group is frequently eliminated as the ring closure takes place and, as a result, this group does not take part in the final heterocycle structure. Thus, the use of hydrazone reagents for the regioselective synthesis of pyrazoles remains underexplored.[12]

Scheme 2 outlines the synthesis of novel enaminones **9a**–**e** from the Michael addition–elimination reaction of hydrazones (**8a**–**e**) to 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones. These reactions were monitored by thin-layer chromatography by following the disappearance of the enone.

The structures of the enaminones **9a**–**e** were examined by ^1H and ^{13}C NMR and mass spectra. High resolution mass spectra



Compds	a	b	c	d	e
8, 9	C_6H_5	2-OHC_6H_4	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	4-OHC_6H_4

Scheme 2.

and/or elemental analysis were registered to confirm the purity of compounds. Additionally, in order to unequivocally assign the stereochemistry of the enaminones **9**, the crystal structure of compound **9d** was determined by single-crystal X-ray diffraction. Crystals suitable for X-ray diffraction were obtained by slow evaporation of chloroform solutions of compound **9d**.[13] Crystallographic analysis revealed that both C–C double bond and benzyliminic moiety exhibit an (*E*)-configuration. In the course of our investigations, we observed that enaminone intermediates **10**–**15a**–**e** spontaneously decomposed to the corresponding pyrazole after isolation. Therefore, a complete characterization was unpractical.

Acid hydrolysis of the azomethine linkage of enaminones **9a**–**e** afforded the 3-trifluoromethyl-1-phenyl-1*H*-pyrazole **16**[14] as the only product in good yields (entries 1–5, Table 1). Reactions were carried out by stirring a solution of selected enaminones **9a**–**e** with hydrochloric acid in acetonitrile at room temperature for 1 h (method A, Table 1). The best hydrolysis condition was achieved when 2 equiv of concentrated hydrochloric acid was employed. Aqueous solutions of hydrochloric acid and basic reaction conditions were also tested, but did not furnish a complete conversion to the pyrazole.

Pyrazole **17**[14] was isolated after stirring enone **2** with hydrazones **8a**–**e** in chloroform for 24 h at room temperature followed by the addition of 2 equiv of hydrochloric acid, and stirring for an additional hour (method B, Table 1). Unfortunately, these reactions always afforded a small amount of the 1,5-pyrazole regioisomer, compound **24** (entries 6–10, Table 1).

It was also not possible to isolate enaminone **11a**–**e** because the pyrazole **18**[14] was directly obtained after stirring the reaction in chloroform under reflux for 24 h (method C, Table 1). Apparently, the hydrolysis of the intermediate was accomplished simply by heating the solution, thus, the addition of hydrochloric acid was not required for the cyclization step.

Finally, pyrazoles **19**–**22** were obtained with high regioselectivity from hydrazone **8a** using the same method as compound **17** (entries 16–19, method B, Table 1).

The results shown in Table 1 imply that the presence of different groups attached to the benzylidene portion of hydrazones **8a**–**e** do not indicate a great influence on the reaction yields and times, but it may have a small effect on the regioisomer proportion. The ratio of isomers was determined by integration of the GC–MS total ion chromatograms (Table 1).

To further confirm the correct isomer assignment, direct cyclization of enones **1**–**7** with phenylhydrazine was carried out to obtain preferentially 5-trifluoromethyl-1-phenyl-1*H*-pyrazoles (1,5-isomer). Table 2 shows the reaction conditions, yields and proportion of 1,3- and 1,5-isomers. The results state that the direct cyclization of enones **1**–**7** with phenylhydrazine furnished the 1,5-isomer of pyrazoles with high regioselectivity, as expected.[15] In addition, by having both isomers in hands, it was easy to establish unequivocally the ^1H and ^{13}C NMR and GC–MS spectral data of each regioisomer. In particular, GC–MS was very useful for assigning the 1,3- and 1,5-isomers of pyrazoles since each one eluted from the capillary column in different retention times allowing a simple and direct comparison. This trend was the simplest, fastest, and reliable information for assigning the correct structure of the title compounds.

The structure assignment of the pyrazole isomers was also supported by the study done by Laurent et al., which described the synthesis of both 1,5-diphenyl-3(5)-trifluoromethyl-1*H*-pyrazoles **18** and **25** from the reaction of β-chloro-β-trifluoromethylenone and phenylhydrazine.[16] ^1H and ^{13}C NMR chemical shifts of their compounds are in agreement with the data collected from our pyrazoles. Data from our previous study was also helpful for the confirmation of the 5-trifluormethyl-1-phenyl-1*H*-pyrazoles.[15]

Table 1
Reaction conditions and yields for the synthesis of 1-phenyl-3-trifluoromethyl-1*H*-pyrazoles (**16**–**22**)

Entry	Enone	R	R^1	R^2	Hydrazone	Ar	Method	Yield[a] (%)	Pyrazole	Isomer 1,3:1,5[b]
1	**1**	Et	H	H	**8a**	C_6H_5	A	87	**16**	100:0
2	**1**	Et	H	H	**8b**	2-OH–C_6H_4	A	76	**16**	100:0
3	**1**	Et	H	H	**8c**	4-OMe–C_6H_4	A	82	**16**	100:0
4	**1**	Et	H	H	**8d**	4-NO_2–C_6H_4	A	91	**16**	100:0
5	**1**	Et	H	H	**8e**	4-OH–C_6H_4	A	63	**16**	100:0
6	**2**	Et	H	Me	**8a**	C_6H_5	B	84	**17+24**	87:13
7	**2**	Et	H	Me	**8b**	2-OH–C_6H_4	B	76	**17+24**	85:15
8	**2**	Et	H	Me	**8c**	4-OMe–C_6H_4	B	82	**17+24**	83:17
9	**2**	Et	H	Me	**8d**	4-NO_2–C_6H_4	B	72	**17+24**	90:10
10	**2**	Et	H	Me	**8e**	4-OH–C_6H_4	B	74	**17+24**	94: 6
11	**3**	Me	C_6H_5	H	**8a**	C_6H_5	C	87	**18**	100:0
12	**3**	Me	C_6H_5	H	**8b**	2-OH–C_6H_4	C	56	**18**	100:0
13	**3**	Me	C_6H_5	H	**8c**	4-OMe–C_6H_4	C	60	**18**	100:0
14	**3**	Me	C_6H_5	H	**8d**	4-NO_2–C_6H_4	C	40	**18**	100:0
15	**3**	Me	C_6H_5	H	**8e**	4-OH–C_6H_4	C	63	**18**	100:0
16	**4**	Me	4-MeC_6H_4	H	**8a**	C_6H_5	B	78	**19**	100:0
17	**5**	Me	4-$MeOC_6H_4$	H	**8a**	C_6H_5	B	76	**20+27**	88:12
18	**6**	Me	4-FC_6H_4	H	**8a**	C_6H_5	B	81	**21+28**	97:3
19	**7**	Me	2-Furyl	H	**8a**	C_6H_5	B	75	**22**	100:0

Reaction conditions: method A: (1) $CHCl_3$, rt, 4 h. (2) MeCN, HCl, 2.0 equiv, rt, 1 h; method B: (1) $CHCl_3$, rt, 24 h. (2) HCl, 2.0 equiv, rt, 1 h; method C: $CHCl_3$, reflux, 24 h.
[a] Yields of isolated compounds.
[b] Isomeric proportion calculated from the GC/MS total ion chromatogram.

Table 2
Proportion of 1,3- versus 1,5-isomers of *N*-phenyl pyrazoles from the direct condensation between enones **1**–**4** and phenylhydrazine ('*classical approach*')

Enone	R	R^1	R^2	Yield[a] (%)	Pyrazole	Isomer[b] (**1,3**:**1,5**)
1	Et	H	H	90	**16+23**	12:88
2	Et	H	Me	79	**17+24**	2:98
3	Me	C_6H_5	H	87	**18+25**	1:99
4	Me	4-MeC_6H_5	H	90	**19+26**	0:100
5	Me	4-$MeOC_6H_5$	H	94	**20+27**	0:100
6	Me	4-FC_6H_5	H	95	**21+28**	1:99
7	Me	2-Furyl	H	78	**22+29**	0:100

[a] Yields of isolated compounds.
[b] Reaction conditions: $PhNHNH_2$, MeCN, reflux, 24 h.

In conclusion, this work described a regioselective synthesis of 1-phenyl-3-trifluoromethyl-1*H*-pyrazoles from 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones using a simple and efficient one pot method. The desired trifluoromethylpyrazoles were easily prepared in a two-step procedure that involved the reaction of enones with hydrazones derived from phenylhydrazine and commercially available aldehydes, followed by deprotective hydrolysis of the hydrazone azomethine linkage, and subsequent intramolecular nucleophilic heterocyclization. Additionally, a series of novel (*E*)-4-(*N*′-benzylidene-*N*-phenyl-hydrazino)-1,1,1-trifluoro-but-3-en-2-ones was obtained in good to excellent yields. A series of 1,5-pyrazole isomers was synthesized from the direct cyclization of enones and phenylhydrazine ('*classical approach*') to provide an unequivocal assignment of the obtained products. Thus, by combining the method developed in this study with the direct cyclocondensation of enones one can obtain both 1,3- and 1,5-isomers of pyrazole under regioselective control.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.103. These data include MOL files and InChiKeys of the most important compounds described in this article.

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13. CCDC No. 773176 for **6d** contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).
14. *3-Trifluoromethyl-1-phenyl-1H-pyrazole* (**16**)*:* yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, J = 2.4 Hz, 1H, H-5), 7.64–7.59 (m, 2H, Ph), 7.43–7.26 (m, 3H, Ph), 6.63 (d, J = 2.4 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (q, $^2J_{CF}$ = 38.4 Hz, C-3), 139.4, 129.6 (Ph), 128.3 (C-5), 127.7 (Ph), 121.2 (q, $^1J_{CF}$ = 275.3 Hz, CF_3), 119.9 (Ph), 105.9 (C-4); MS-EI (m/z): 212 (100, M^+), 193 (18), 143 (26), 116 (30), 96 (5), 77 (90), 69 (39), 51 (78). HRMS-ESI: MH^+, calcd for $C_{10}H_8F_3N_2$, 213.0639; found: 213.0630.
3-Trifluoromethyl-1-phenyl-4-methyl-1H-pyrazole (**17**)*:* yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (s, 1H, H-5), 7.63 (d, J = 7.8 Hz, 2H, Ph), 7.43 (t, J = 7.9 Hz, 2H, Ph), 7.30 (t, J = 7.4 Hz, 1H, Ph), 2.22 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (q, $^2J_{CF}$ = 36.7 Hz, C-3), 139.3, 129.4 (Ph), 127.6 (C-5), 127. 2 (Ph), 121.9 (q, $^1J_{CF}$ = 269.2 Hz, CF_3), 117.1 (C-4), 8.1 (Me); MS-EI (m/z): 226 (100, M^+), 207 (74), 157 (82), 130 (89), 104 (77), 96 (23), 77 (98), 69 (62), 51 (97); HRMS-ESI: MH^+, calcd for $C_{11}H_{10}F_3N_2$, 227.0796; found 227.0786.
3-Trifluoromethyl-1,5-diphenyl-1H-pyrazole (**18**)*:* yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24–7.12 (m, 10H, Ph), 6.66 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (Ph), 143.2 (q, $^2J_{CF}$ = 38.8 Hz, C-3), 139.2 (Ph), 129.2–128.4 (Ph, C-5), 125.4 (Ph), 121.3 (q, $^1J_{CF}$ = 268.6 Hz, CF_3), 105.5 (C-4); MS-EI (m/z): 288 (100, M^+), 267 (28), 219 (4), 134 (19), 116 (6), 89 (12), 77 (35), 51 (5). HRMS-ESI: MH^+ calcd for $C_{16}H_{12}F_3N_2$, 289.0952; found: 289.0947.
3-Trifluoromethyl-1-phenyl-5-(4-methylphenyl)-1H-pyrazole (**19**)*:* yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.33 (m, 3H, Ph), 7.31–7.29 (m, 2H, Ph), 7.10 (m, 4H, Ph), 6.71 (s, 1H, H-4), 2.33 (s. 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C-5), 143.1 (q, $^2J_{CF}$ = 38.78 Hz, C-3), 139.4 (Ph), 139.0 (Ph), 129.3 (Ph), 129.0 (Ph), 128.6 (Ph), 128.3 (Ph), 126.2 (Ph), 125.5 (Ph), 121.1 (q, $^2J_{CF}$ = 269.3 Hz, CF_3), 105.2 (C-4), 21.2 (Me); MS-EI (m/z): 302 (100, M^+), 281 (33), 269 (13), 233 (5), 140 (5), 77 (5). HRMS-ESI: MNa^+ calcd for $C_{17}H_{13}F_3N_2Na$, 325.0929; found: 325.1000.
3-Trifluoromethyl-1-phenyl-5-(4-methoxyphenyl)-1H-pyrazole (**20**)*:* brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, J = 8.55 Hz, Ph), 7.36–7.33 (m, 3H, Ph), 7.32–7.29 (m, 2H, Ph), 6.82 (d, 2H, J = 8.80 Hz, Ph), 6.68 (s, 1H, H-4), 3.79 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (Ph), 144.5 (C-5), 143.1 (q, $^1J_{CF}$ = 38.5 Hz, C-3), 139.5 (Ph), 130.1 (Ph), 129.0 (Ph), 128.3 (Ph), 125.5 (Ph), 121.5 (Ph), 120.8 (q, $^2J_{CF}$ = 268.5 Hz, CF3) 114.1 (Ph), 104.9 (C-4), 55.23 (OMe); MS-EI (m/z): 318 (100, M^+), 303 (20), 275 (7), 205 (7), 77 (17). HRMS-ESI: MH^+ calcd for $C_{17}H_{14}F_3N_2O$, 319.1058; found: 319.1056.
3-Trifluoromethyl-1-phenyl-5-(4-fluorophenyl)-1H-pyrazole (**21**)*:* brown oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.34 (m, 2H, Ph), 7.29–7.27 (m, 2H, Ph), 7.20 – 7.17 (m, 3H, Ph), 6.99 (m, 2H, Ph), 6.70 (s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (Ph), 143.6 (C-5), 143.2 (q, $^2J_{CF}$ = 38.1 Hz, C-3), 139.0 (Ph), 130.7 (d, J = 8.1 Hz, Ph), 130.1 (Ph), 129.2 (Ph), 128.6 (Ph), 125.5 (Ph), 121.2 (q, $^1J_{CF}$ = 269.3 Hz, CF_3), 115.8 (d, J = 22.0 Hz, Ph), 105.5 (C-4); MS-EI (m/z): 306 (100, M^+), 285 (46), 237 (6), 77 (9). HRMS-ESI: MH^+ calcd for $C_{16}H_{11}F_4N_2$, 307.0858; found: 307.0856.
3-Trifluoromethyl-1-phenyl-5-(2-furyl)-1H-pyrazole (**22**)*:* brown oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.47 (m, 3H, Ph), 7.43–7.40 (m, 2H, Ph), 7.41–7.39 (m, 1H, furyl), 6.89 (s, 1H, H-4), 6.32 (dd, J = 3.42 Hz, 1,66 Hz, 1H, furyl), 6.97 (d, 1H, J = 3.42 Hz, furyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (*C*-furyl), 143.1 (q, $^2J_{CF}$ = 38.4 Hz, C-3), 139.4 (furyl), 136.2 (Ph), 130.2 (C-5), 129.4 (Ph), 129.2 (Ph), 126.1 (Ph), 121.7 (q, $^1J_{CF}$ = 269,3 Hz, CF3), 111.4 (*C*-furyl), 109.8 (*C*-furyl), 103.8 (C-4); MS-EI (m/z): 278 (100, M^+), 249 (12), 224 (8), 77 (4). HRMS-ESI: MH^+ calcd for $C_{14}H_9F_3N_2ONa$, 301.0565; found: 301.0560.
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