DOI: 10.1002/ejoc.201201111

Comparative Study of the Regioselectivity and Reaction Media for the Synthesis of 1-*tert*-Butyl-3(5)-trifluoromethyl-1*H*-pyrazoles

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Keywords: Synthetic methods / Nitrogen heterocycles / Fluorinated substituents / Ionic liquids / Enones / Regioselectivity

A study is presented for the synthesis of a series of 1-*tert*-butyl-3(5)-(trifluoromethyl)-1*H*-pyrazoles from the reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [$CF_3C(O)CH=C-(R^1)(OR)$, where R = Et and R^1 = H or R = Me and R^1 = Me, Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, fur-2-yl, thien-2-yl, or naphth-2-yl] with *tert*-butylhydrazine hydrochloride. When [BMIM][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate) and pyridine were used as the reaction media, we obtained a mixture of 1-*tert*-butyl-3(5)-trifluoromethylpyrazoles. The formation of 5-trifluoromethyl-1-*tert*-butyl-1*H*-pyrazoles with high regioselectivity occurred when the reaction was carried out with NaOH in EtOH. The formation of 1-*tert*-butyl-3-trifluoromethyl-1*H*-pyrazoles occurred, after hydrolysis of the 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones in H_2O and H_2SO_4, followed by cyclization in [BMIM][BF_4] and pyridine.

Introduction

The pyrazole nucleus has pronounced pharmacological applications for analgesic and anti-inflammatory drugs.[1] The incorporation of fluorine into a drug allows the simultaneous modulation of electronic, lipophilic, and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs.[2–4] Celecoxib is the most recognized example of a drug that contains a trifluoromethylated pyrazole moiety.[5]

The reaction between trifluoromethylated 1,3-dielectrophilic compounds and hydrazines constitutes the main synthetic approach to the trifluoromethylated pyrazole ring. The synthesis of 3(5)-trifluoromethyl-1*H*-pyrazole from a fluorinated 1,3-dicarbonyl compound has been extensively studied, including regioselectivity studies in neutral media with the addition of acid[6–10] and fluorinated solvents.[11] Kinetic investigations of these condensation reactions with the addition of acid showed that the regioselectivity in the synthesis of pyrazole is influenced by a combination of steric effects, reactant ratio, and acidity.[10] In general, authors observed that the *1,5* regioisomer (CF_3 group at the 5-position) is formed by maintaining a pH $>$ 1.7, whereas more acidic conditions led to larger quantities of the *1,3* regioisomer.[6–11]

Our research group has extensively studied the reactions of 1,3-dielectrophilic compounds such as 4-alkoxy-1,1,1-trihalo-3-alken-2-ones, β-enaminones, and β-enamino ketones with hydrazines.[12–18] In general, we have observed that the regioselectivity of the reaction depends somewhat on the hydrazine, but mainly on the reactivity of the 1,3-dielectrophilic compound. The reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with methyl and phenyl hydrazines generally results in a mixture of isomers.[19–21] On the other hand, the reaction between *tert*-butylhydrazine hydrochloride and β-enamino ketones in ethanol is highly regioselective and furnishes 1-*tert*-butyl-4,5-disubstituted-1*H*-pyrazoles.[22] Similarly, the reaction between *tert*-butylhydrazine hydrochloride and β-enaminones using an ionic liquid results in the exclusive formation of 1-*tert*-butyl-5-substituted-1*H*-pyrazoles.[23] Thus, the problem of regioselectivity in the formation of pyrazoles is evident when 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones are used as the 1,3-dielectrophile. These 1,3-dielectrophiles are important precursors to the trifluoromethylated pyrazoles, however, the availability of diversely substituted 1,3-diketones is limited. In this context, we decided to study the regioselectivity in the formation of pyrazoles by studying the reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones with *tert*-butylhydrazine hydrochloride under neutral conditions and with basic and acidic additions to highlight the dependence of acidic or basic reaction media on the regioselectivity of this reaction.

Results and Discussion

To evaluate the reactivity of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1a**–**1c** with *tert*-butylhydrazine hydrochloride **2**, a series of experiments were performed. The 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones used in the optimization of

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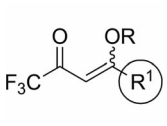
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201111.

the reaction were chosen according to the substituent at the 4-position. Hydrogen represents a substituent that does not have any electronic effects on the structure (i.e., **1a**), methyl represents a group with an electron-donating effect (i.e., **1b**), and phenyl represents a group with an electron-donating or -withdrawing effect (i.e., **1c**), as shown in Figure 1.



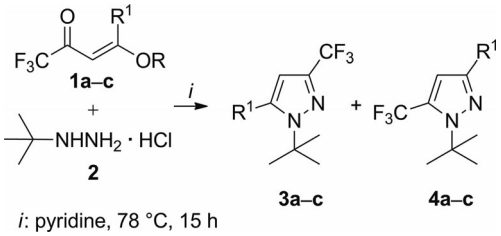
Enone	R	R^1
1a	Et	H
1b	Me	Me
1c	Me	Ph

Figure 1. Enones used in the optimization of the reaction.

Previously, we performed the reaction between *tert*-butylhydrazine hydrochloride and β-enamino ketones or β-enaminones in different solvents[22,23] and determined that it was worth evaluating the solvent used in the reaction. Therefore, we started our investigation with the reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1a**–**1c** and *tert*-butylhydrazine hydrochloride **2** (at a molar ratio of 1:1.5, respectively) using ethanol or the ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate ([BMIM][BF_4]) as the solvent. Initially, we performed the reaction between **1a**–**1c** and **2** in the presence of pyridine at room temperature (25 °C) for 15 h. However, in both solvents, the starting material was not totally converted into the desired products. The next reaction was carried out at 78 °C (boiling point of the ethanol) for 15 h using ethanol or the ionic liquid (see Table 1). At this temperature, we observed the complete conversion of the reactants into the pyrazoles (see Table 1). We also performed the reaction in the absence of pyridine and observed the loss of the *tert*-butyl group, which led to an undesired product (1*H*-pyrazole). Pyridine is probably needed to neutralize the hydrochloride present in the *tert*-butylhydrazine hydrochloride.[13] Under these conditions, the reactions of **1a**–**1c** furnished a mixture of *1,3* and *1,5* isomers, where the trifluoromethyl group is attached to C-3 or C-5, respectively, on the pyrazole ring. In particular, **1a** led to the formation of byproducts when ethanol was used as the solvent (see Table 1, Entry 1). From the experiments described in Table 1, we observed that the reactions performed in the ionic liquid resulted in higher yields. We also noted that **1c** (see Table 1, Entries 3 and 6) showed better performance in comparison to **1a** and **1b**.

After optimizing the reaction conditions, we extended the scope to the syntheses of new 1-*tert*-butyl-1*H*-pyrazoles. Aryl and heteroaryl 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1c**–**1l** were treated with **2** in the presence of [BMIM][BF_4] and pyridine to furnish products **3c**–**3l** and **4c**–**4l** in good to excellent yields (70–93%), as shown in Table 2. To confirm the importance of the ionic liquid, we carried out the reactions in ethanol under the same conditions. The yields of the products **3c/4c** (65%), **3d/4d** (55%), **3g/4g** (75%), and **3l/4l** (75%) were lower than those obtained in [BMIM][BF_4], and formation of the byproduct (1*H*-pyrazole) was observed. Thus, in neutral media, the reactivity of aryl and heteroaryl enones towards *tert*-butylhydrazine hydrochloride was similar to the trifluoromethylated 1,3-diketones, as both led to the formation of a mixture of *1,3* and *1,5* isomers.[2–4,11]

Table 1. Optimization of the reaction conditions for the synthesis of 1-*tert*-butyl-1*H*-pyrazoles.

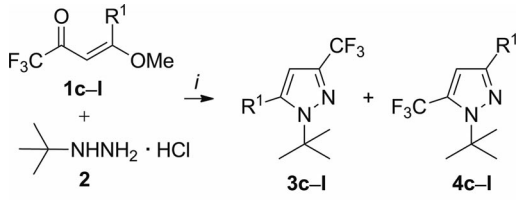


i: pyridine, 78 °C, 15 h

	Ethanol			[BMIM][BF_4]		
	Product	Molar ratio **3/4**	Yield[a] [%]	Product	Molar ratio[b] **3/4**	Yield[a] [%]
1a	(**3a** + **4a**) + byproducts			**3a** + **4a**	75:25	44
1b	**3b** + **4c**	24:76	56	**3b** + **4b**	66:34	58
1c	**3c** + **4c**	36:64	65	**3c** + **4c**	15:85	85

[a] Yield of the mixture of isomers **3** and **4**. [b] Molar ratio **3/4** was obtained from the integration of the signals of the *tert*-butyl group in the ^{1}H NMR spectra.

Table 2. Synthesis of 1-*tert*-butyl-1*H*-pyrazoles in [BMIM][BF_4].



i: pyridine, [BMIM][BF4], 78 °C, 15 h

Enone	R^1	Molar ratio **3/4**[a]	% Yield[b]
1c	Ph	15:85	85
1d	4-Me-C_6H_4	43:57	72
1e	4-MeO-C_6H_4	44:56	72
1f	4-F-C_6H_4	30:70	81
1g	4-Cl-C_6H_4	36:64	93
1h	4-Br-C_6H_4	39:61	93
1i	4-I-C_6H_4	40:60	81
1j	fur-2-yl	25:75	70
1k	thien-2-yl	57:43	75
1l	naphth-2-yl	47:53	84

[a] Molar ratio **3/4** was obtained from the integration of the signals in the ^{1}H NMR spectra. [b] Yield of the mixture of isomers **3** and **4**.

Isomers **3c**, **3f**–**3i** and **4c**, **4f**–**4i** were separated by washing with cold hexane. The solid isomer **3c** was submitted to X-ray crystal structure analysis, and the crystallographic data revealed that it was the *1,3* isomer, as shown in Figure 2. From this, the isomers were characterized by analyzing the ^{1}H and ^{13}C NMR spectra and mass spectrometric fragmentation. The ^{1}H NMR spectroscopic data of the *1,3* isomer showed a chemical shift of the *tert*-butyl group from δ = 1.47 to 1.54 ppm, whereas the spectroscopic data of the

1,*5* isomer showed a chemical shift for the same group from 1.69 to 1.71 ppm. In addition, the chemical shift for H-4 in each of the isomers was different, with a range of 6.37–6.59 ppm for the *1*,*3* isomer and a range of 6.87–6.98 ppm for the *1*,*5* isomer. The ^{13}C NMR chemical shift of the *tert*-butyl group was in the range of 29.7–30.9 ppm for the *1*,*3* isomer, whereas the spectra for the *1*,*5* isomer showed a chemical shift of 29.8–29.9 ppm for the same group. Interesting magnetic resonance behavior was observed for **4c**–**4l** (*1*,*5* isomer). The multiplicity of the signal for the methyl carbon in the *tert*-butyl group appeared as a quartet, because of a through-space ^{13}C–^{19}F coupling with J = 2 Hz.[24–27] The mass spectra of all of the compounds were characterized by the presence of the $[M]^+$ ion. The loss of the *tert*-butyl group resulted in the most stable fragment, which underwent a loss of one fluorine atom and then one N_2 molecule, thus generating less stable fragments. Another low stability fragment formed by the loss of the *tert*-butyl group and trifluoromethyl group was also observed. The spectral differences between the *1*,*3* and the *1*,*5* isomer were due to the abundance of fragments. In the majority of compounds, the most abundant fragments were observed for the *1*,*5* isomers.

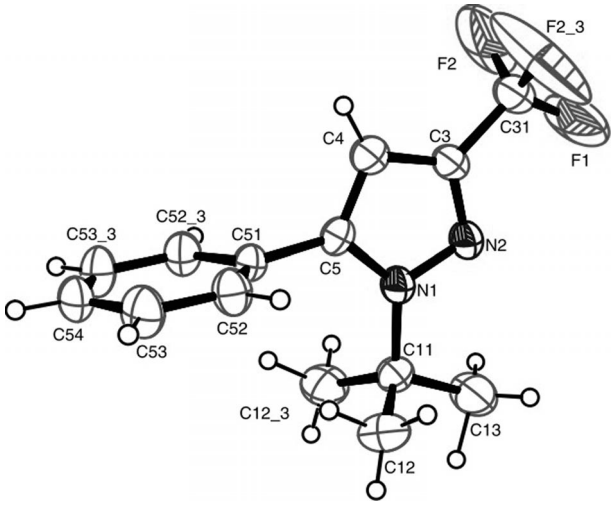
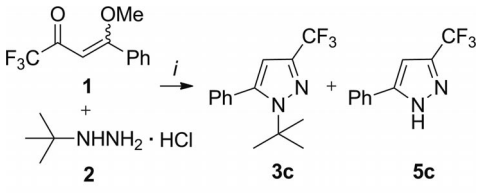


Figure 2. ORTEP of 1-(1,1-dimethylethyl)-5-phenyl-3-trifluoromethyl-1*H*-pyrazole (**3c**).[28] Displacement ellipsoids are drawn at the 40% probability level. H atoms are represented by circles of arbitrary radii.

To achieve the conditions for the regioselective syntheses of 1-*tert*-butyl-1*H*-pyrazoles, we tested the addition of 4-toluenesulfonic acid (PTSA) to the reaction mixture. Reactions were performed in either [BMIM][BF_4] or ethanol

Table 3. Addition of PTSA in the synthesis of 1-*tert*-butyl-3(5)-trifluoromethyl-1*H*-pyrazoles.



i: 78 °C, 15 h

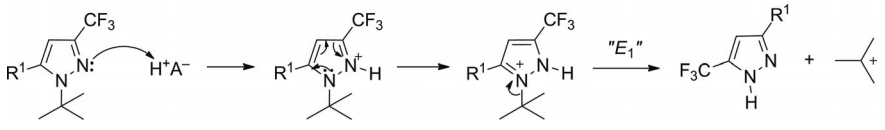
Entry	Solvent	PTSA	Molar ratio	% Yield **3c**[a]	% Yield **5c**[a]
1	EtOH	1	50:50	46	46
2	EtOH	0.25	83:17	75	15
3	[BMIM][BF_4]	1	90:10	59	6
4	[BMIM][BF_4]	0.25	75:25	49	16
5	[HMIM][HSO_4]	–	50:50	31	31

[a] Yield of isomers **3c** and **5c** in the mixture.

with the addition of the acid (see Table 3). The addition of acid induced the formation of the 1*H*-pyrazole byproduct, however, exclusive formation of *1*,*3* isomer was observed. From the experiments performed with the acid, we found that even very small amounts of acid led to the formation of 1*H*-pyrazole. In an attempt to avoid the use of an acid catalyst, we decided to employ the ionic liquid 3-methylimidazolium hydrogen sulfate ([HMIM][HSO_4]) as the solvent/catalyst. It is known that this protic ionic liquid (PIL) has an inherent Brönsted acidic nature, and thus it could perform the dual role in this reaction.[29,30] The reaction was performed using 1 mmol of [HMIM][HSO_4]. A mixture of products **3c**/**5c** was obtained, which showed a lower efficiency in obtaining **3c** in comparison to the reaction with [BMIM][BF_4] in the presence of PTSA. The formation of the 1*H*-pyrazole was expected, as it was also observed when the reaction was performed in the absence of pyridine (to neutralize the hydrazine hydrochloride).

Thus, we proposed a mechanism for the formation of the 1*H*-pyrazole in acidic media (see Scheme 1). Its formation can be explained by an initial protonation at N-2. After this protonation step, electron delocalization in the pyrazole occurs. As the molecule is charged, it is susceptible to an elimination reaction. The E1 elimination takes place, and the 1*H*-pyrazole and *tert*-butyl carbocation are formed. The carbocation probably undergoes an attack by a nucleophilic species present in the reaction media and then is eliminated as a byproduct of the reaction.

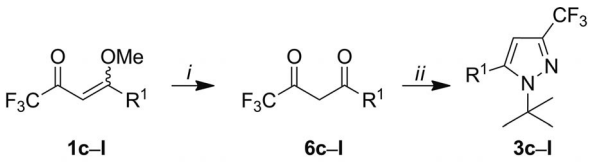
In acidic media, it is known that **1j** and **1k** undergo hydrolysis.[31] Thus, we decided to obtain the product in two



Scheme 1. Mechanism for the formation of 1*H*-pyrazole in acidic media.

steps: (i) the acid hydrolysis of **1c**–**1l** and (ii) a cyclocondensation reaction. Under these conditions, the desirable products 1-*tert*-butyl-3-trifluoromethyl-1*H*-pyrazoles were formed in high regioselectivity and good yields (65–82%), as depicted in Table 4. These results are in accordance with those reported by other authors, who describe the formation of the *1,3* isomers from the reaction between trifluoromethylated 1,3-diketones and methyl or phenyl hydrazine with the addition of acid.[6–10]

Table 4. Synthesis of 1-*tert*-butyl-3-trifluoromethyl-1*H*-pyrazoles.



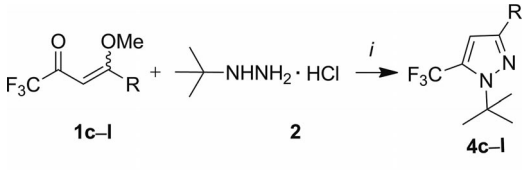
i: H_2O, H_2SO_4, 50 °C, 16 h
ii: *tert*-butylhydrazine hydrochloride, [BMIM][BF_4], Py, 78 °C, 15 h

Enone	R	% Yield **6**[a]	% Yield **3**[a]
1c	Ph	54	75
1d	4-Me-C_6H_4	77	82
1e	4-OMe-C_6H_4	70	65
1f	4-F-C_6H_4	55	81
1g	4-Cl-C_6H_4	70	82
1h	4-Br-C_6H_4	91	74
1i	4-I-C_6H_4	80	74
1j	fur-2-yl	85	77
1k	thien-2-yl	66	80
1l	naphth-2-yl	74	75

[a] Yield of isolated product.

As the addition of acid allowed the exclusive formation of the *1,3* isomer, we assumed that in reactions with the trifluoromethylated 1,3-diketones, basic media could permit the formation of the *1,5* isomer in high regioselectivity.[6,10] However, reactions performed with a molar excess amount of pyridine (3 equiv.) were not efficient enough to convert the reactants into the expected pyrazoles with high regioselectivity in either [BMIM][BF_4] or EtOH as the solvent. On the other hand, the addition of NaOH with an equimolar amount of hydrazine in both [BMIM][BF_4] and EtOH led to the formation of products. The reaction carried out in [BMIM][BF_4] resulted in a mixture of the *1,3* and *1,5* isomers, and the reaction performed in EtOH furnished the 1-*tert*-butyl-5-trifluoromethyl-1*H*-pyrazoles with high regioselectivity. Therefore, reactions performed in the presence of NaOH and ethanol led to the corresponding 1-*tert*-butyl-5-trifluoromethyl-1*H*-pyrazoles **4c**–**4l** in good yields (50–81%), as shown in Table 5. These results are in accordance with those reported by other authors[10] who describe the formation of the *1,5* isomer from the reaction of trifluoromethylated 1,3-diketones and methyl- or phenylhydrazine using a pH > 1.7. On the other hand, they are opposite to the results described by Singh et al.[6] who isolated the *1,3* isomer in acidic, basic, and neutral conditions, when treating 1-(4-methoxyphenyl)hydrazine with trifluoromethylated 1,3-diketones.

Table 5. Synthesis of 1-*tert*-butyl-5-trifluoromethyl-1*H*-pyrazoles.



i: EtOH, NaOH, 78 °C, 15 h

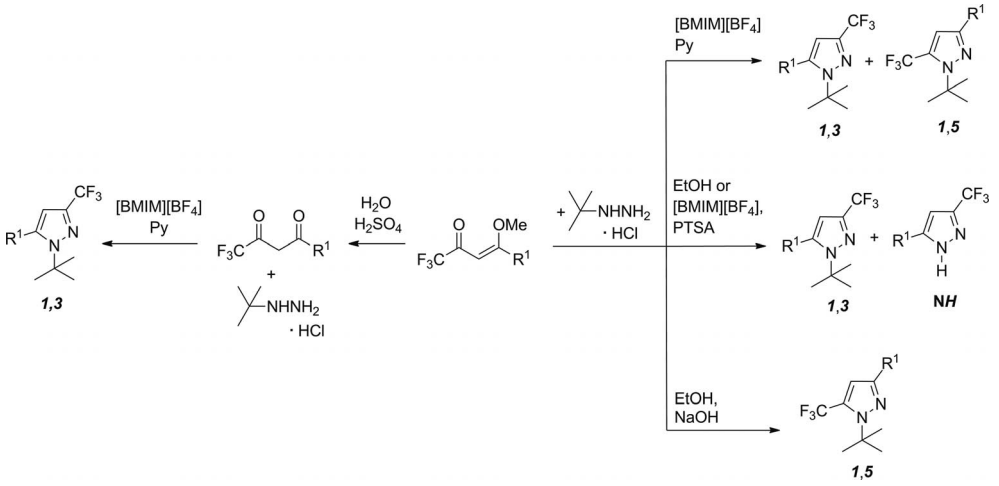
Entry	Enone	R	% Yield **4**[a]
1	**1c**	Ph	76
2	**1d**	4-Me-C_6H_4	65
3	**1e**	4-OMe-C_6H_4	50
4	**1f**	4-F-C_6H_4	68
5	**1g**	4-Cl-C_6H_4	65
6	**1h**	4-Br-C_6H_4	78
7	**1i**	4-I-C_6H_4	66
8	**1j**	fur-2-yl	56
9	**1k**	thien-2-yl	66
10	**1l**	naphth-2-yl	81

[a] Yield of isolated product.

Our study using 4-alkoxy-1,1,1-trifluoro-3-alken-2-one furnished similar results to those found for trifluoromethylated 1,3-diketones under neutral conditions or with the addition of acid or base. The PTSA addition led to formation of a *1,3* regioisomer, indicating the possible hydrolysis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one to form the 1,3-diketone. The hydrolysis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one went to completion when using aqueous sulfuric acid, confirming that under the addition of acid, the 1,3-diketone was likely to be the dielectrophilic reactant. The hydrolysis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one also explains the exclusive formation of the *1,3* regioisomer, which is formed under acidic conditions by the addition of acid.[6–10] The advantage of the hydrolysis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one is in the creation of trifluoromethylated 1,3-diketones that are not available by other sources. Trifluoromethylated 1,3-diketones form an equilibrium with their enol forms. Thus, the most electrophilic carbon is the one attached to the trifluoromethyl group, which has its LUMO energy reduced by protonation from the addition of acid.

On the other hand, the hydrolysis reaction is avoided with the addition of NaOH, and the β-carbon of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one, which is more reactive, suffers attack by the *tert*-butyl hydrazine hydrochloride (NH_2). Thus, the *1,5* regioisomer is formed in high regioselectivity, different from the 1,3-diketone.

Finally, these observations support the result found when 4-alkoxy-1,1,1-trifluoro-3-alken-2-one was treated with *tert*-butyl hydrazine hydrochloride in the presence of pyridine and [BMIM][BF_4]. A part of 4-alkoxy-1,1,1-trifluoro-3-alken-2-one underwent hydrolysis and led to formation of the *1,3* regioisomer, but the other part was not hydrolyzed (stabilized by pyridine/[BMIM][BF_4]) and led to the formation of the *1,5* regioisomer. These results are depicted in Scheme 2.



Scheme 2. Summary of results described in this paper.

Conclusions

This work presents the synthesis of a series of new 1-*tert*-butyl-3(5)-trifluoromethyl-1*H*-pyrazoles with high regioselectivity. The most important aspect is that the *1*,*3* isomer is formed with high regioselectivity from β-diketones (or enols), after the hydrolysis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones. In addition, the presence of a base in the reaction media leads 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones to form *1*,*5* isomers with high regioselectivity. When mixtures of isomers are isolated, they can be obtained individually by washing with hexane. These results are highly innovative, when one considers the use of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones in the regioselective syntheses of 1-alkyl-1*H*-pyrazoles. Structures with hydrazine features (especially those displaying steric factors) may be affecting this regioselectivity. Studies are in progress in our laboratories and will be published hereafter.

Experimental Section

General Methods: Unless otherwise indicated, all of the common reagents and solvents were used as obtained from commercial suppliers without further purification. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker DPX 400 (^{1}H NMR at 400.13 MHz and ^{13}C NMR at 100.62 MHz) in $CDCl_3$/TMS solutions at 298 K, and the chemical shifts (δ values) are given in ppm. Mass spectra were registered with a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, crosslinked to a HP-5 capillary column (30 m, 0.32 mm i.d.), and helium was used as the carrier gas. The melting points were measured with a Microquímica MQAPF 301. Elemental analyses were performed with a Perkin–Elmer CHN 2400 elemental analyzer, and the results agreed favorably with the calculated values.

Synthesis of Enones: Enones **1a**–**1l** were obtained from the acylation reaction of the enol ether or acetal with trifluoroacetic anhydride in accordance with the methodology developed in our laboratory.[32]

Synthesis of the β-Diketones: β-Diketones **5c**–**5j** were obtained from the hydrolysis reaction of enones **1c**–**1j** in accordance with the procedure described in the literature.[31]

Synthesis of the Mixture of 1-(1,1-Dimethylethyl)-3(5)-trifluoromethyl-1*H*-pyrazoles: An enone (**1a**–**1l**, 1 mmol), hydrazine **2** (1.5 mmol), pyridine (1.5 mmol), and [BMIM][BF_4] (0.5 mmol) or EtOH (5 mL) were placed in a round-bottomed flask. The mixture was magnetically stirred at 78 °C for 15 h. When the reaction was performed in EtOH, the mixture was evaporated under reduced pressure. Chloroform (5 mL) was then added, and the reaction mixture was washed with water (3 × 5 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The pyrazole mixtures were obtained in pure form without further purification. The mixtures of pyrazoles **3c**/**4c** and **3f**/**4f**–**3i**/**4i** were washed with hexane and then separated.

Synthesis of the 1-(1,1-Dimethylethyl)-5-trifluoromethyl-1*H*-pyrazoles: An enone (**1a**–**1l**, 1 mmol), hydrazine **2** (1.5 mmol), NaOH (1.5 mmol), and EtOH (5 mL) were placed in a round-bottomed flask. The mixture was magnetically stirred at 78 °C for 15 h. After completion of the reaction time, the EtOH was evaporated under reduced pressure. Chloroform (5 mL) was then added, and the reaction mixture was washed with water (3 × 5 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The *1*,*5* isomer of the pyrazole was obtained in pure form without further purification.

Synthesis of the 1-(1,1-Dimethylethyl)-3-trifluoromethyl-1*H*-pyrazoles: A 1,3-dicarbonyl compound (**6c**–**6j**, 1 mmol), hydrazine **2** (1.5 mmol), pyridine (1.5 mmol), and [BMIM][BF_4] (0.5 mmol) were placed in a round-bottomed flask. The mixture was magnetically stirred at 78 °C for 15 h. Chloroform (5 mL) was then added, and the reaction mixture was washed with water (3 × 5 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The *1*,*3* isomer of the pyrazole was obtained in pure form without further purification.

1-(1,1-Dimethylethyl)-5-phenyl-3-trifluoromethyl-1*H*-pyrazole (3c): M.p. 87–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 6.38 (s, 4-H), 7.31–7.44 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (*t*Bu), 62.7 (C), 107.3 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.7 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 125.4, 127.9, 128.6, 132.5

(Ar), 139.2 (q, $^2J_{C,F}$ = 38 Hz, C-3), 144.0 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 268 (36) $[M]^+$, 212 (100), 193 (40), 164 (49), 143 (35). $C_{14}H_{15}F_3N_2$ (268.28): calcd. C 62.68, H 5.64, N 10.44; found C 62.21, H 5.67, N 10.45.

1-(1,1-Dimethylethyl)-5-(4-methylphenyl)-3-trifluoromethyl-1*H*-pyrazole (3d): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*Bu), 2.41 (s, 3 H, CH_3), 6.35 (s, 4-H), 7.25–7.70 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (Me), 30.9 (*t*Bu), 62.6 (C), 107.4 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.7 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 125.4, 128.6, 129.7, 138.9 (Ar), 139.1 (q, $^2J_{C,F}$ = 39 Hz, C-3), 144.1 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 282 (23) $[M]^+$, 226 (100), 207 (17), 177 (8), 157 (12). $C_{15}H_{17}F_3N_2$ (282.31): calcd. C 63.82, H 6.07, N 9.92; found C 64.66, H 6.05, N 9.29.

1-(1,1-Dimethylethyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole (3e): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 3.83 (s, 3 H, CH_3), 6.50 (s, 4-H), 7.25–7.70 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 55.2 (OMe), 62.5 (C), 107.4 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.7 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 114.0, 126.7, 130.5, 159.5 (Ar), 139.0 (q, $^2J_{C,F}$ = 37 Hz, C-3), 143.8 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 298 (25) $[M]^+$, 242 (100), 227 (63), 223 (10). $C_{15}H_{17}F_3N_2O$ (298.31): calcd. C 60.40, H 5.74, N 9.39; found C 60.6, H 5.76, N 8.81.

1-(1,1-Dimethylethyl)-5-(4-fluorophenyl)-3-trifluoromethyl-1*H*-pyrazole (3f): M.p. 96–97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*Bu), 6.38 (s, 4-H), 7.06–7.36 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 62.7 (C), 107.6 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.5 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 115.2 (d, $^2J_{C,F}$ = 21 Hz, Ar), 128.6 (d, $^4J_{C,F}$ = 3 Hz, Ar), 132.3 (d, $^3J_{C,F}$ = 8 Hz, Ar), 163.0 (d, $^1J_{C,F}$ = 248 Hz, Ar), 139.3 (q, $^2J_{C,F}$ = 38 Hz, C-3), 142.7 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 286 (12) $[M]^+$, 230 (100), 211 (17), 182 (22), 161 (13). $C_{14}H_{14}F_4N_2$ (286.27): calcd. C 58.74, H 4.93, N 9.79; found C 58.59, H 4.94, N 9.77.

5-(4-Chlorophenyl)-1-(1,1-dimethylethyl)-3-trifluoromethyl-1*H*-pyrazole (3g): M.p. 139–141 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 6.37 (s, 4-H), 7.20–7.64 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 62.8 (C), 107.5 (q, $^3J_{C,F}$ = 1.4 Hz, C-4), 121.5 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 121.9, 127.0, 131.5, 131.7 (Ar), 139.4 (q, $^2J_{C,F}$ = 38 Hz, C-3), 142.6 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 302 (23) $[M]^+$, 248 (100), 227 (23), 198 (24), 177 (15). $C_{14}H_{14}ClF_3N_2$ (302.73): calcd. C 55.55, H 4.66, N 9.25; found C 55.26, H 4.70, N 9.13.

5-(4-Bromophenyl)-1-(1,1-dimethylethyl)-3-trifluoromethyl-1*H*-pyrazole (3h): M.p. 141–143 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 6.37 (s, 4-H), 7.20–7.64 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 62.8 (C), 107.5 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.5 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 126.7, 126.9, 128.7, 131.7 (Ar), 139.3 (q, $^2J_{C,F}$ = 37 Hz, C-3), 142.7 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 346 (7) $[M]^+$, 290 (100), 273 (4), 242 (2), 221 (2). $C_{14}H_{14}BrF_3N_2$ (347.18): calcd. C 48.43, H 4.06, N 8.07; found C 48.37, H 4.08, N 7.94.

1-(1,1-Dimethylethyl)-5-(4-iodophenyl)-3-trifluoromethyl-1*H*-pyrazole (3i): M.p. 139–141 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*Bu), 6.37 (s, 4-H), 7.12 (d, 2 H, Ar), 7.70–7.78 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 62.8 (C), 93.4 (Ar), 107.4 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.5 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 127.2, 132.2, 137.2 (Ar), 139.3 (q, $^2J_{C,F}$ = 39 Hz, C-3), 142.7 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 394 (12) $[M]^+$, 338 (100), 319 (6), 211 (6), 191 (28). $C_{14}H_{14}IF_3N_2$ (394.17): calcd. C 42.66, H 3.58, N 7.11; found C 42.39, H 3.47, N 6.81.

1-(1,1-Dimethylethyl)-5-(fur-2-yl)-3-trifluoromethyl-1*H*-pyrazole (3j): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.57 (s, 9 H, *t*Bu), 6.49 (s, 4-H), 6.45 (dd, 1 H, Ar), 6.65 (d, 1 H, Ar), 7.45 (d, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7 (*t*Bu), 62.5 (C), 108.9 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.4 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 106.1, 111.2, 142.0, 143.1 (C-2′, C-3′, C-4′, C-5′), 139.2 (q, $^2J_{C,F}$ = 38 Hz, C-3), 133.3 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 258 (6) $[M]^+$, 202 (100), 183 (5), 154 (7). $C_{12}H_{13}F_3N_2O$ (258.24): calcd. C 55.81, H 5.07, N 10.85; found C 54.43, H 5.06, N 8.66.

1-(1,1-Dimethylethyl)-5-thien-2-yl-3-trifluoromethyl-1*H*-pyrazole (3k): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.54 (s, 9 H, *t*Bu), 6.86 (s, 4-H), 7.02–7.11 (m, 1 H, Ar), 7.27 (d, 1 H, Ar), 7.30 (d, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.5 (*t*Bu), 63.0 (C), 109.6 (q, $^3J_{C,F}$ = 2 Hz, C-4), 121.4 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 123.8, 124.7, 127.7, 131.5 (C-2′, C-3′, C-4′, C-5′), 139.6 (q, $^2J_{C,F}$ = 38 Hz, C-3), 135.6 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 274 (5) $[M]^+$, 218 (100), 199 (3), 170 (9), 149 (2). $C_{12}H_{13}F_3N_2S$ (274.30): calcd. C 52.54, H 4.78, N 10.21; found C 52.25, H 4.64, N 9.82.

1-(1,1-Dimethylethyl)-5-(naphth-2-yl)-3-trifluoromethyl-1*H*-pyrazole (3l): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, *t*Bu), 6.45 (s, 4-H), 7.40–8.21 (m, 7 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (*t*Bu), 62.7 (C), 107.6–107.7 (m, C-4), 121.8 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 125.9, 126.2, 127.7, 127.7, 128.1, 128.3, 129.7, 133.0, 133.1, 133.5 (Ar), 139.3 (q, $^2J_{C,F}$ = 38 Hz, C-3), 143.9 (C-5) ppm. $C_{18}H_{17}F_3N_2$ (318.34): calcd. C 67.91, H 5.38, N 8.80; found C 67.93, H 5.28, N 8.51.

1-(1,1-Dimethylethyl)-3-phenyl-5-trifluoromethyl-1*H*-pyrazole (4c): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.71 (s, 9 H, *t*Bu), 6.98 (s, 4-H), 7.31–7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.1 (C), 107.4 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.5 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 127.9, 128.9, 130.4, 132.7 (Ar), 132.2 (q, $^2J_{C,F}$ = 38 Hz, C-5), 147.8 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 268 (97) $[M]^+$, 212 (100), 193 (36), 164 (74), 143 (57). $C_{14}H_{15}F_3N_2$ (268.28): calcd. C 62.68, H 5.64, N 10.44; found C 62.21, H 5.67, N 10.45.

1-(1,1-Dimethylethyl)-3-(4-methylphenyl)-5-trifluoromethyl-1*H*-pyrazole (4d): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (s, 9 H, *t*Bu), 2.36 (s, 3 H, CH_3), 6.94 (s, 4-H), 7.25–7.70 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (Me), 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.0 (C), 107.3 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.5 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 129.3, 129.7, 130.2, 137.7 (Ar), 132.1 (q, $^2J_{C,F}$ = 39 Hz, C-5), 147.9 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 282 (52) $[M]^+$, 226 (100), 206 (20), 177 (11), 157 (16). $C_{15}H_{17}F_3N_2$ (282.31): calcd. C 63.82, H 6.07, N 9.92; found C 64.66, H 6.05, N 9.29.

1-(1,1-Dimethylethyl)-3-(4-methoxyphenyl)-5-trifluoromethyl-1*H*-pyrazole (4e): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68 (s, 9 H, *t*Bu), 3.85 (s, 3 H, CH_3), 6.35 (s, 4-H), 7.25–7.70 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 55.2 (OMe), 62.9 (C), 106.9 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.4 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 113.3, 129.9, 131.7, 160.0 (Ar), 132.1 (q, $^2J_{C,F}$ = 39 Hz, C-5), 147.6 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 298 (42) $[M]^+$, 242 (100), 223 (6), 227 (77). $C_{15}H_{17}F_3N_2O$ (298.31): calcd. C 60.40, H 5.74, N 9.39; found C 60.6, H 5.76, N 8.81.

1-(1,1-Dimethylethyl)-3-(4-fluorophenyl)-5-trifluoromethyl-1*H*-pyrazole (4f): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.69 (s, 9 H, *t*Bu), 6.93 (s, 4-H), 7.04–7.80 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.2 (C), 107.6 (q, $^3J_{C,F}$ = 2 Hz, C-4), 120.4 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 115.5 (d, $^2J_{C,F}$ = 22 Hz, Ar), 127.2 (d, $^3J_{C,F}$ = 8 Hz, Ar), 128.8 (d, $^4J_{C,F}$ = 3 Hz, Ar), 162.7 (d, $^1J_{C,F}$ = 248 Hz, Ar), 132.4 (q, $^2J_{C,F}$ = 38 Hz, C-5), 147.0 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 286 (71) $[M]^+$, 230 (100), 211 (32), 182 (76), 161 (44). $C_{14}H_{14}F_4N_2$ (286.27): calcd. C 58.74, H 4.93, N 9.79; found C 58.59, H 4.94, N 9.77.

3-(4-Chlorophenyl)-1-(1,1-dimethylethyl)-5-trifluoromethyl-1*H*-pyrazole (4g): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (s, 9 H, *t*Bu), 6.95 (s, 4-H), 7.26–7.38 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.4 (C), 107.4 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.3 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 123.4, 131.3, 131.6, 132.0 (Ar), 132.5 (q, $^2J_{C,F}$ = 38 Hz, C-5), 146.7 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 302 (35) $[M]^+$, 248 (100), 227 (12), 198 (20), 177 (14). $C_{14}H_{14}ClF_3N_2$ (302.73): calcd. C 55.55, H 4.66, N 9.25; found C 55.26, H 4.70, N 9.13.

3-(4-Bromophenyl)-1-(1,1-dimethylethyl)-5-trifluoromethyl-1*H*-pyrazole (4h): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.69 (s, 9 H, *t*Bu), 6.95 (s, 4-H), 7.48–7.56 (m, 4 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.4 (C), 107.4 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.3 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 128.3, 129.4, 131.4, 133.6 (Ar), 131.1 (q, $^2J_{C,F}$ = 38 Hz, C-5), 146.7 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 346 (10) $[M]^+$, 290 (100), 271 (2), 242 (2), 221 (2). $C_{14}H_{14}BrF_3N_2$ (347.18): calcd. C 48.43, H 4.06, N 8.07; found C 48.37, H 4.08, N 7.94.

3-(4-Iodophenyl)-1-(1,1-dimethylethyl)-5-trifluoromethyl-1*H*-pyrazole (4i): Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (s, 9 H, *t*Bu), 6.96 (s, 4-H), 7.55 (d, 2 H, Ar), 7.70–7.78 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (*t*Bu), 63.4 (C), 91.5 (Ar), 107.3 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.3 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 132.0, 132.1 (Ar), 132.5 (q, $^2J_{C,F}$ = 39 Hz, C-3), 137.6, 146.7 (C-5) ppm. MS (EI, 70 eV): *m*/*z* (%) = 394 (11) $[M]^+$, 338 (100), 319 (3), 211 (4), 191 (18). $C_{14}H_{14}IF_3N_2$ (394.17): calcd. C 42.66, H 3.58, N 7.11; found C 42.39, H 3.47, N 6.81.

1-(1,1-Dimethylethyl)-3-(fur-2-yl)-5-trifluoromethyl-1*H*-pyrazole (4j): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.73 (s, 9 H, *t*Bu), 6.94 (s, 4-H), 6.48–6.59 (m, 2 H, Ar), 7.55 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.3 (C), 107.5 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.3 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 111.3, 112.2, 142.3, 147.9 (C-2′, C-3′, C-4′, C-5′), 139.2 (q, $^2J_{C,F}$ = 38 Hz, C-5), 140.8 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 258 (11) $[M]^+$, 202 (100), 183 (5), 154 (6). $C_{12}H_{13}F_3N_2O$ (258.24): calcd. C 55.81, H 5.07, N 10.85; found C 54.43, H 5.06, N 8.66.

1-(1,1-Dimethylethyl)-3-(thien-2-yl)-5-trifluoromethyl-1*H*-pyrazole (4k): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.69 (s, 9 H, *t*Bu), 6.91 (s, 4-H), 6.48–6.59 (m, 2 H, Ar), 7.55 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8 (q, $^5J_{C,F}$ = 2 Hz, *t*Bu), 63.2 (C), 107.4 (q, $^3J_{C,F}$ = 4 Hz, C-4), 120.2 (q, $^1J_{C,F}$ = 269 Hz, CF_3), 126.7, 127.3, 130.4, 135.9 (C-2′, C-3′, C-4′, C-5′), 139.6 (q, $^2J_{C,F}$ = 38 Hz, C-5), 143.4 (C-3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 274 (22) $[M]^+$, 218 (100), 199 (6), 170 (20), 149 (5). $C_{12}H_{13}F_3N_2S$ (274.30): calcd. C 52.54, H 4.78, N 10.21; found C 52.25, H 4.64, N 9.82.

1-(1,1-Dimethylethyl)-3-(naphth-2-yl)-5-trifluoromethyl-1*H*-pyrazole (4l): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.74 (s, 9 H, *t*Bu), 7.12 (s, 4-H), 7.40–8.21 (m, 7 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (*t*Bu), 63.2 (C), 107.6–107.7 (m, C-4), 120.5 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 123.7, 124.1, 126.8, 126.9, 127.5, 127.7, 128.0, 129.9, 129.9, 132.4 (Ar), 132.2 (q, $^2J_{C,F}$ = 39 Hz, C-5), 147.8 (C-3) ppm. $C_{18}H_{17}F_3N_2$ (318.34): calcd. C 67.91, H 5.38, N 8.80; found C 67.93, H 5.28, N 8.51.

Supporting Information (see footnote on the first page of this article): Mass spectra and ^{1}H and ^{13}C NMR spectra of **3c**–**3l** and **4c**–**4l**.

Acknowledgments

The authors are grateful to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/Universal Proc. Nos. 578426/2008-0 and 471519/2009-0), the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS/CNPq-PRONEX Edital No. 008/2009 and Proc. No. 10/0037-8), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/PROEX) for financial support. The fellowships from CNPq (to M. A. P. M., M. R. B. M., M. Z., N. Z., V. P. A., and H. G. B.) and CAPES (to C. P. F. and L. B.) are also acknowledged.

[1] L. Yet, *Pyrazoles*, in: *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Pergamon, Oxford, UK, **2008**, vol. 4, pp. 1–141.
[2] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11.
[3] F. M. D. Ismail, *J. Fluorine Chem.* **2002**, *118*, 27–33.
[4] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.
[5] M. Williams, E. A. Kowaluk, S. P. Arneric, *J. Med. Chem.* **1999**, *42*, 1481–1500.
[6] S. K. Singh, M. S. Reddy, S. Shivaramakrishna, D. Kavitha, R. Vasudev, J. M. Babu, A. Sivalakshmidevi, Y. K. Rao, *Tetrahedron Lett.* **2004**, *45*, 7679–7682.
[7] P. S. Humphries, J. M. Finefield, *Tetrahedron Lett.* **2006**, *47*, 2443–2446.
[8] S. W. Djuric, N. Y. BaMaung, A. Basha, H. Liu, J. R. Luly, D. J. Madar, R. J. Sciotti, N. P. Tu, F. L. Wagenaar, P. E. Wiedeman, X. Zhou, S. Ballaron, J. Bauch, Y.-W. Chen, X. G. Chiou, T. Fey, D. Gauvin, E. Gubbins, G. C. Hsieh, K. C. Marsh, K. W. Mollison, M. Pong, T. K. Shaughnessy, M. P. Sheets, M. Smith, J. M. Trevillyan, U. Warrior, C. D. Wegner, G. W. Carter, *J. Med. Chem.* **2000**, *43*, 2975–2981.
[9] T. Norris, R. Colon-Cruz, D. H. B. Ripin, *Org. Biomol. Chem.* **2005**, *3*, 1844–1849.
[10] J. C. Sloop, B. Lechner, G. Washington, C. L. Bumgardner, W. D. Loehle, W. Creasy, *Int. J. Chem. Kinet.* **2008**, *40*, 370–383.
[11] S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simón-Fuentes, A. A. Cuñat, S. Villa Nova, M. Murguía, *J. Org. Chem.* **2008**, *73*, 3523–3529.
[12] H. G. Bonacorso, L. M. F. Porte, C. A. Cechinel, G. R. Paim, E. D. Deon, N. Zanatta, M. A. P. Martins, *Tetrahedron Lett.* **2009**, *50*, 1392–1394.
[13] H. G. Bonacorso, R. P. Vezzosi, I. R. Rodrigues, R. L. Drekener, L. M. F. Porte, A. F. C. Flores, N. Zanatta, M. A. P. Martins, *J. Braz. Chem. Soc.* **2009**, *20*, 1370–1378.
[14] L. Buriol, C. P. Frizzo, M. R. B. Marzari, D. N. Moreira, L. D. T. Prola, N. Zanatta, H. G. Bonacorso, M. A. P. Martins, *J. Braz. Chem. Soc.* **2010**, *21*, 1037–1044.
[15] S. Moura, A. F. C. Flores, F. R. Paula, E. Pinto, P. Machado, M. A. P. Martins, *Lett. Org. Chem.* **2008**, *5*, 91–97.
[16] M. A. P. Martins, C. M. P. Pereira, S. Moura, C. P. Frizzo, P. Beck, N. Zanatta, H. G. Bonacorso, A. F. C. Flores, *J. Heterocycl. Chem.* **2007**, *44*, 1195–1199.
[17] M. A. P. Martins, C. M. P. Pereira, P. Beck, P. Machado, S. Moura, M. V. M. Teixeira, H. G. Bonacorso, N. Zanatta, *Tetrahedron Lett.* **2003**, *44*, 6669–6672.
[18] A. F. C. Flores, M. A. P. Martins, A. Rosa, D. C. Flores, N. Zanatta, H. G. Bonacorso, *Synth. Commun.* **2002**, *32*, 1585–1594.
[19] M. A. P. Martins, R. A. Freitag, A. Rosa, A. F. C. Flores, N. Zanatta, H. G. Bonacorso, *J. Heterocycl. Chem.* **1999**, *36*, 217–219.
[20] J. W. Pavlik, T. I. Na Ayudhya, S. Tantayanon, *J. Heterocycl. Chem.* **2003**, *40*, 1087–1089.
[21] M. A. P. Martins, G. P. Bastos, A. P. Sinhorin, N. E. K. Zimmermann, A. Rosa, S. Brondani, D. Emmerich, H. G. Bonacorso, N. Zanatta, *J. Fluorine Chem.* **2003**, *123*, 249–253.
[22] F. A. Rosa, P. Machado, P. S. Vargas, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *Synlett* **2008**, 1673–1678.

[23] C. P. Frizzo, M. R. B. Marzari, L. Buriol, D. N. Moreira, F. A. Rosa, P. S. Vargas, N. Zanatta, H. G. Bonacorso, M. A. P. Martins, *Catal. Commun.* **2009**, *10*, 1967–1970.
[24] F. R. Jerome, K. L. Servis, *J. Am. Chem. Soc.* **1972**, *94*, 5896–5897.
[25] P. Szczecinski, M. Maminski, *J. Chem. Res. Synop.* **2001**, 88–89.
[26] J. W. Lyga, R. N. Henrie, G. A. Meier, W. Creekmore, R. M. Patera, *Magn. Reson. Chem.* **1993**, *31*, 323–328.
[27] I. D. Rae, J. A. Weigold, R. H. Contreras, R. R. Biekosfsky, *Magn. Reson. Chem.* **1993**, *31*, 836–840.
[28] CCDC-721171 (for **3c**) contains 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.
[29] T. L. Greaves, C. J. Drummond, *Chem. Rev.* **2008**, *108*, 206–237.
[30] M. A. P. Martins, C. P. Frizzo, D. N. Moreira, N. Zanatta, H. G. Bonacorso, *Chem. Rev.* **2008**, *108*, 2015–2050.
[31] A. F. C. Flores, S. Brondani, N. Zanatta, A. Rosa, M. A. P. Martins, *Tetrahedron Lett.* **2002**, *43*, 8701–8705.
[32] a) M. A. P. Martins, E. A. Guarda, C. P. Frizzo, D. N. Moreira, M. R. B. Marzari, N. Zanatta, H. G. Bonacorso, *Catal. Lett.* **2009**, *130*, 93–99; b) M. A. P. Martins, E. A. Guarda, C. P. Frizzo, E. Scapin, P. Beck, A. C. da Costa, N. Zanatta, H. G. Bonacorso, *J. Mol. Catal. A* **2007**, *266*, 100–103; c) M. A. P. Martins, W. Cunico, C. M. P. Pereira, A. F. C. Flores, H. G. Bonacorso, N. Zanatta, *Curr. Org. Synth.* **2004**, *1*, 391–403; d) S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko, *Tetrahedron* **2007**, *63*, 7753–7808.

Received: August 15, 2012
Published Online: November 6, 2012

