Microwave Assisted Regiospecific Synthesis of 5-Trifluoromethyl-4,5-Dihydropyrazoles and – Pyrazoles

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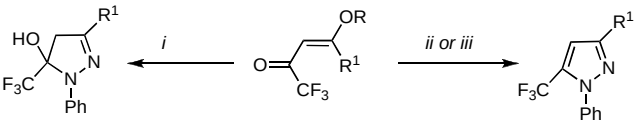

2a-f,h **1a-h** **3a-f,h 4a**

R^1 = Me, Et, Pr, *iso*-Pr, Bu, *iso*-Bu, Ph, H; R = Me, Et

(i) **2a-f,h**: Toluene, MW (200W), 3 min; **2g**: Toluene, MW (300W), 15 min; *(ii)* **3a-f,h,4a**: Toluene, MW (300W), 10 min; *(iii)* **3a-f,h,4a**: K-10, solvent free, MW (300W), 8 min

The regiospecific synthesis of a series of twelve 5-trifluoromethyl-4,5-dihydropyrazoles and -pyrazoles from the cyclocondesation reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [$F_3CC(O)CH=C(R^1)OR$, where R^1 = Me, Et, Pr, *iso*-Pr, Bu, *iso*-Bu, Ph, H; and R = Me, Et] with phenylhydrazine in toluene by environmentally benign microwave induced techniques is reported. It is shown that under appropriated conditions, the variation of microwave irradiation power leads to 4,5-dihydropyrazole or pyrazole derivatives. This paper also includes the use of montmorillonite K-10 as a solid support for the synthesis of pyrazoles under solvent free conditions.

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INTRODUCTION

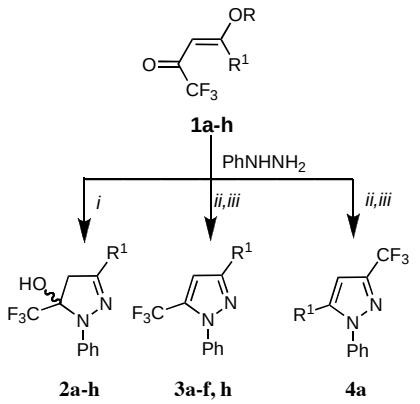
Trifluoromethyl pyrazoles and derivatives are an important class of compounds possessing a wide variety of pharmaceutical and agrochemical properties [1,2]. The introduction of fluorine and fluorinated groups into organic molecules often confers significant and useful changes in their chemical and physical properties and, importantly, in their biological activities. Therefore, methods for the synthesis of fluorinated compounds have received considerable interest in recent years [3]. The most convenient method for the construction of fluorinated compounds is to use fluorine-containing building blocks as starting reagents. Thus, in recent years, we have developed a general synthesis of 1,1,1-trihalo-4-methoxy-3-alken-2-ones [4], an important halogen-containing building block, and their usefulness in heterocyclic preparations (*e.g.*, isoxazoles [4a,5], pyrazoles [6], pyrazolium chlorides [7], pyrrolidines [8], pyrimidines [9], thiazines [10], diazepines [11], thiazoles [12], selenazoles [13], and quinolines [14]) has been extensively described [15]. Recently, we reported the application of microwave irradiation for the synthesis of trifluoromethyl- and trichloromethyl-substituted azoles [5f,7c]. The beneficial effects of microwave irradiation are playing an increasing role in process chemistry, especially in cases when classical methods require forcing conditions or prolonged reaction times. When processes involve sensitive reagents or there is the possibility of compound decomposition under prolonged reaction conditions, microwaves have also shown an advantage. The use of focused microwave irradiation to decrease times and improve yields has been demonstrated [16]. Microwave irradiation (MW), using commercial domestic ovens, has been recently used to accelerate organic reactions, due to its high heating efficiency, which gives remarkable rate enhancement and dramatic reduction in reaction times.

In connection with the study of fluoride heterocycles, the aim of this work is to demonstrate the advantages obtained by the use of microwave irradiation in the regiospecific synthesis of trifluoromethyl substituted 4,5-dihydropyrazoles and pyrazoles, using the same precursors of the *conventional method*, by the reaction of the 1,1,1-trifluoromethyl-4-alkoxy-3-alken-2-ones series with phenyl hydrazine in toluene and in solvent free conditions (Scheme 1).

RESULTS AND DISCUSSION

The 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1a–h** were synthesized from the reaction of the respective enol ether or acetal and trifluoroacetic anhydride [4].

Scheme 1



(i) **2a-f,h**: Toluene, MW (200W), 3 min; Toluene, MW (300W), 15 min; *(ii)* **3a-f,h,4a**: Toluene, MW (300W), 10 min; *(iii)* **3a-f,h,4a**: K-10, solvent free, MW (300W), 8 min

Compd.		**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
1	R	Me	Et	Et	Et	Et	Et	Me	Et
1, 2, 3, 4	R^1	Me	Et	Pr	*i*-Pr	Bu	*i*-Bu	Ph	H

We have shown that valuable compounds such as 5-hydroxy- 5 -trifluoromethyl- 4,5- dihydro-1*H*-1-phenyl pyrazoles **2a-h** and 5-trifluoromethyl-1-phenylpyrazoles **3a-f, h** and **4a** can be prepared by a cyclocondensation approach using an environmental benign methodology. Treatment of 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones **1** with phenylhydrazine in toluene for 3 minutes, using microwaves (200 W) at 86°C, produced 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-phenylpyrazoles **2a-f, h**. Compound **2h** was obtained as a mixture with **3h** in a molar ratio of 2:1, respectively. To obtain compound **2g**, it was necessary to increase the microwave power (300 W) and the reaction time (15 min). The treatment of **1** with phenylhydrazine in toluene for 10 minutes, using microwaves (300 W) at 104°C, furnished 5-trifluoromethyl-1-phenylpyrazoles **3a-f,h**. Compound **3g** was not obtained under the various reactional conditions tested. In the case of cyclocondensation of **1a** (R^1 = Me) with phenylhydrazine the reaction was not regiospecific and a mixture of pyrazoles 1,5-isomer (**3a**) and 1,3-isomer (**4a**) was obtained in a molar ratio of 1:1, respectively. The 1,5- and 1,3-isomer refers to the position of N-phenyl group (N1) in relation of trifluoromethyl group (C3 or C5) (Scheme 1).

Thus, in our procedure, it was established that, with the domestic oven's variation of power, 4,5-dihydropyrazoles or pyrazoles can be exclusively isolated in good yields (Table 1 and 2). This behavior was expected since the regiospecific synthesis of 4,5-dihydropyrazoles and pyrazoles from the cyclocondensation of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and hydrazines, has been extensively reported [6g,15]. In the pyrazoles syntheses, most of these reactions gave two isomers 3- and 5-trihalomethyl-pyrazoles, although our research group have demonstrated that when phenylhydrazine is a dinucleophile it is possible to isolate only the 1,5-isomer [15]. Our group, in previous works, demostred also that, in conventional method, the sole formation of pyrazolines **2**, from the reaction of phenylhydrazine and **1**, is probably due to the electronic conjugation between the π-system of phenyl group and n-electrons of nitrogen atom (N1) of pyrazoline-ring, which makes the aromatization of the pyrazole-ring more difficult. The attempt to obtain 5-trifluoromethyl-1*H*-1-phenyl-pyrazoles by dehydration of compound **2a-f** with sulfuric acid was unsuccessful. Therefore, the use of domestic oven's variation of power, permitted obtaining of the dehydrated product (except **3g**) [6a].

On the other hand, several papers reported microwave irradiation in solvent free conditions for the synthesis of heterocycles in very good yields [17]. Clay-catalyzed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attributes under heterogeneous reaction conditions [16d,18]. Yadav *et al.* [19] reported the synthesis of benzoxazinones utilizing montmorillonite K10 clay in solvent-free conditions.

Table 1

Yields [a] and reaction conditions used for the microwave assisted synthesis of **2**.

Reagents $PhNHNH_2$ +	Product	Microwave method [b] Reaction time (min)	Yield (%)	Conventional method [c] Reaction time (hours)	Yield (%)
1a	**2a**	3	91	4	70
1b	**2b**	3	89	2	70
1c	**2c**	3	87	2	69
1d	**2d**	3	83	2	73
1e	**2e**	3	85	2	73
1f	**2f**	3	81	2	71
1g	**2g** [d]	15	80	[f]	[f]
1h	**2h** + **3h** [e]	3	77	4	73 [g]

[a] Yields of isolated products; [b] Reaction conditions: toluene, 86°C, MW, 200W; [c] Reaction conditions: Ethanol, reflux (see Ref. [6a] and [4a]); [d] The product was obtained with reaction conditions: toluene, 104°C, MW, 300 W, 15 min. It was obtained the same product when the reaction was performed in presence of K-10 and solvent-free (yield of 78%). [e] Mixture of products **2h** and **3h**, in a molar ratio of 2:1, respectively. [f] Compound not described in the literature. [g] Obtained the product **2h**.

In light of the above description and our continuing interest in the development of new methodologies for the synthesis of azoles [5,6], we tried to develope the simple and convenient synthetic procedure to prepare 5-trifluoro-methyl-1-phenyl pyrazoles from the reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones with phenyl hydrazine supported on montmorillonite K-10 clay, under solvent free conditions.

Thus, the treatment of **1** with phenyl hydrazine, for 8 minutes, using microwaves (200 W) at 86°C in the presence of solid support (montmorillonite K-10 clay) and in solvent free conditions, also produced compounds **3a-f, h** in good yields and high purity (Table 2). The formation of the products **2a-h** and **3a-f, h** in conventional and microwave method showed dependent of presence of solvents, while when we used montmorillonite K10 clay, the reaction can take place in the absence of any solvents. This result led us to hypothesize that montmorillonite K10 clay was able to substitute the effect of solvent in this reaction.

Thus, we conclude that while the conventional heating gives only moderate yield of the expected cyclocondensation products, microwave irradiation in toluene, or in the presence of K-10 and in solvent free conditions, leads to the same products with a drastic reduction of reaction time, improved yields and higher purity (Tables 1 and 2).

Table 2

Yields [a] and reaction conditions used for the microwave assisted synthesis of **3, 4**.

Reagents $PhNHNH_2$ +	Product	Microwave method [b] Reaction time (min)	Yield (%)	Microwave method [c] Reaction time (min)	Yield (%)	Conventional method [d] Reaction time (hours)	Yield (%)
1a	**3a + 4a** [e]	10	85	8	80	[e]	[e]
1b	**3b**	10	90	8	82	12	75
1c	**3c**	10	89	8	76	12	78
1d	**3d**	10	83	8	75	12	76
1e	**3e**	10	86	8	77	12	70
1f	**3f**	10	89	8	75	5	75

[a] Yields of isolated products; [b] Reaction conditions: Toluene, 104°C, MW, 300 W; [c] Reaction conditions: solvent-free, K-10, 104°C, MW, 300 W; [d] (1) Ethanol, reflux; (2) Sulfuric acid, CH_2Cl_2 (see Ref. [4c] and [6a]). [e] Mixture of products in a molar ratio of (**3a**) 1 : 1 (**4a**).

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purifications. The melting points were taken on a melting point microscope Reichert–Thermovar and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in $CDCl_3$/TMS solutions. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. Microwave irradiations were conducted in a Panasonic M720 domestic microwave oven at a frequency of 2450 MHz, with energy in the sample [16] of 200-300 W and a temperature at 86 – 104°C.

General Procedure for the Preparation of 5-Hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-phenylpyrazoles (2a-h) (Microwave method). A mixture of **1** (2 mmol), phenyl hydrazine (0.24 g, 2.2 mmol) and toluene (5 mL) was stirred for a few minutes, then the mixture was placed in a commercial domestic microwave oven and irradiated under 200 W (**2g**, 300 W) for 3 min (**2g**, 15 min) at 86°C (2 g, 104°C). The product was extracted with ethyl ether (1x15 mL), washed with distilled water (1x30 mL) and dried with $MgSO_4$. The solvent was removed in a rotatory evaporator, and the product was obtained in high purity. The product **2h** was obtained as a mixture with **3h**, in a molar ratio of 2:1, respectively.

General Procedure for the Preparation of 1-Phenyl-5-trifluoromethylpyrazoles (3a-f) and the 1-Phenyl-3-trifluoromethylpyrazole (4a) (Microwave method). A mixture of **1** (2 mmol) and phenyl hydrazine (0.24 g, 2.2 mmol) in toluene (5 mL) was stirred for a few minutes, and then the mixture was placed in a commercial domestic microwave oven and irradiated under 300 W for 10 min at 104°C. The product was extracted with chloroform (2x15 mL), washed with distilled water (2x30 mL) and dried with $MgSO_4$. The solvent was removed in a rotatory evaporator and the product was obtained in high purity. When necessary the product was recrystallized from cyclohexane. The product **3a** was obtained as a mixture with **4a**, in a molar ratio of 1:1, respectively.

General Procedure for the Preparation of 1-Phenyl-5-trifluoromethylpyrazoles (3a-f) and the 1-Phenyl-3-trifluoromethylpyrazole (4a) (Microwave-solvent-free method). Montmorillonite K-10 clay (1.0 g) was added to a dichloromethane solution of trifluoromethyl vinyl ketone **1** (10 mmol) and phenyl hydrazine (1.31 g, 12 mmol), and then the mixture was stirred vigorously for a few minutes. The solvent was evaporated under reduced pressure and the residual powder was dried under vacuum. The powder was spread in an Erlenmeyer, placed in a commercial domestic microwave oven and irradiated (300 W) for 8 min at 104°C. After cooling, the product was extracted with chloroform (2x20 mL), washed with distilled water (2x30 mL) and dried with $MgSO_4$. The solvent was removed in a rotatory evaporator and the product was obtained in high purity. When necessary the product was recrystallized from cyclohexane. The product **3h** was obtained as a mixture with **2h**, in a molar ratio of 1:2, respectively.

5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-phenyl pyrazole (2a). This compound was obtained as a white solid, mp 110-111°C. ^1H NMR ($CDCl_3$) δ (*J*, Hz) 1.97 (s, 3H, CH_3), 2.87 (d, 1H, *J* = 18, H4a), 3.23 (d, 1H, *J* = 18, H4b), 7.30 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ ($J_{C\text{-}F}$, Hz) 149.7 (C3), 47.6 (C4), 93.2 (q, ^2J = 31, C5), 124.3 (q, ^1J = 283, CF_3), 15.3 (CH_3), 125.3, 128.6, 128.7, 141.3 (N-Ph). MS (*m/z*, %) 244 (M^+, 41), 175 (100), 77 (Ph, 40). *Anal.* Calcd. for $C_{11}H_{11}F_3N_2O$ (244.21): C, 54.10; H, 4.54; N, 11.47 %. Found: C, 53.85; H, 4.52; N, 11.42 %

3-Ethyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-phenyl pyrazole (2b). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 1.12 (t, 3H, CH_3), 2.28 (q, 2H, CH_2), 2.84 (d, 1H, *J* = 16, H4a), 3.20 (d, 1H, *J* = 16, H4b), 7.27 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 154.0 (C3), 45.9 (C4), 93.0 (q, ^2J = 31, C5), 123.9 (q, ^1J = 283, CF_3), 10.7 (CH_3), 23.0 (CH_2), 125.2, 128.5, 129.0 141.5 (N-Ph). MS (m/z, %) 240 (M^+ - H_2O, 100), 225 (45), 77 (Ph, 57). *Anal.* Calcd. for $C_{12}H_{13}F_3N_2O$ (258.24): C, 55.81; H, 5.07; N, 10.85%. Found: C, 55.50; H, 5.05; N, 10.78%.

5-Hydroxy-3-propyl-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2c). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 0.97 (t, 3H, CH_3), 1.65 (m, 2H, CH_2), 2.30 (t, 2H, CH_2), 2.91 (d, 1H, *J* = 18, H4a), 3.22 (d, 1H, *J* = 18, H4b), 7.31 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 153.2 (C3), 46.0 (C4), 93.0 (q, ^2J = 31, C5), 122.0 (q, ^1J = 284, CF_3), 13.6 (CH_3), 19.8 (CH_2), 31.6 (CH_2), 124.5, 128.7, 128.8, 141.2 (N-Ph). MS (m/z, %) 254 (M^+ - H_2O, 62), 239 (100), 77 (Ph, 43). *Anal.* Calcd. for $C_{13}H_{15}F_3N_2O$ (272.27): C, 57.35; H, 5.55; N, 10.29%. Found: C, 56.99; H, 5.52; N, 10.22%.

5-Hydroxy-3-(1-methylethyl)-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2d). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 1.15 (d, 6H, $2CH_3$), 2.65 (m, 1H, CH), 2.91 (d, 1H, *J* = 18, H4a), 3.23 (d, 1H, *J* = 18, H4b), 7.25 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 157.0 (C3), 44.0 (C4), 93.2 (q, ^2J = 31, C5), 123.9 (q, ^1J = 283, CF_3), 19.9 (CH_3), 20.1 (CH_3), 29.4 (CH), 125.1, 128.6, 128.8, 141.5 (N-Ph). MS (m/z, %) 254 (M^+ - H_2O, 62), 239 (100), 77 (Ph, 43). *Anal.* Calcd. for $C_{13}H_{15}F_3N_2O$ (272.27): C, 57.35; H, 5.55; N, 10.29%. Found: C, 56.96; H, 5.50; N, 10.21%.

3-Butyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2e). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 0.92 (t, 3H, CH_3), 1.36 (m, 4H, $2CH_2$), 2.30 (t, 2H, CH_2), 2.86 (d, 1H, *J* = 18, H4a), 3.18 (d, 1H, *J* = 18, H4b), 7.33 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 153.1 (C3), 46.2 (C4), 93.2 (q, ^2J = 31, C5), 122.0 (q, ^1J = 285, CF_3), 13.8 (CH_3), 21.4 (CH_2), 27.6 (CH_2), 29.5 (CH_2), 124.5, 128.5, 129.0, 141.8 (N-Ph). MS (m/z, %) 268 (M^+ - H_2O, 10), 226 (100), 77 (Ph, 33). *Anal.* Calcd. for $C_{14}H_{17}F_3N_2O$ (286.30): C, 58.74; H, 5.99; N, 9.78%. Found: C, 58.46; H, 5.96; N, 9.73%.

5-Hydroxy-3-(2-methylpropyl)-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2f). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 0.92 (d, 6H, $2CH_3$), 1.85 (m, 1H, CH), 2.01 (d, 2H, CH_2), 2.82 (d, 1H, *J* = 20, H4a), 3.16 (d, 1H, *J* = 20, H4b), 7.27 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 152.8 (C3), 46.2 (C4), 93.1 (q, ^2J = 31, C5), 123.9 (q, ^1J = 284, CF_3), 22.2 (CH_3), 22.4 (CH_3), 26.5 (CH), 38.7 (CH_2),124.0, 128.7, 129.1, 141.8 (N-Ph). MS (m/z, %) 268 (M^+ - H_2O, 5), 226 (100), 77 (Ph, 29). *Anal.* Calcd. for $C_{14}H_{17}F_3N_2O$ (286.30): C, 58.74; H, 5.99; N, 9.78%. Found: C, 58.39; H, 5.95; N, 9.73%.

3-Phenyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2g). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) 3.40 (d, 1H, *J* =19, H4a), 3.60 (d, 1H, *J* = 19, H4b), 6.64-7.88 (m, 10H, N-Ph, C3-Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 151.2 (C3), 43.7 (C4), 93.0 (q, ^2J = 31, C5), 124.3 (q, ^1J = 282, CF_3), 124 – 128 (N-Ph, C3-Ph). *Anal.* Calcd. For $C_{16}H_{13}F_3N_2O$ (306.29): C, 62.74%; H, 4.28% ; N, 9.15%. Found: C, 62.45; H, 4.26; N, 9.10%.

5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-phenylpyrazole (2h) and 5-trifluoromethylphenylpyrazole (3h). The data listed refers to a mixture of **2h** and **3h**, with a molar ratio of 2:1, respectively. The mixture of compounds was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ (*J*, Hz) **2h:** 3.10 (d, 1H, *J* = 19, H4a), 3.40 (d, 1H, *J* = 19, H4b), 6.90 (t, 1H, H3), 7.34 (m, 5H, Ph); **3h**: 6.82 (d, 1H, H4) 7.90 (d, 1H, H3), 7.73 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) **2h:** 148.2 (C3), 47.8 (C4), 92.5 (q, ^2J = 32, C5), 124.0 (q, ^1J = 282, CF_3), 125.6, 129.0, 129.2, 140.1 (N-Ph); **3h:** 139.9 (C3), 109.2 (C4), 132.9 (q, ^2J = 39, C5),120.2 (q, ^1J = 269, CF_3), 125.6, 129.0, 129.2, 138.0 (N-Ph).

3(5)-Methyl-1-phenyl-5(3)-trifluoromethylpyrazole (3a + 4a). The data listed refers to a mixture of **3a** and **4a**, with molar ratio of 1:1. The mixture of compounds was obtained as an oil. **3a**: ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 6.52 (s, 1H, H4), 7.50 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 149.0 (C3), 108.5 (C4), 125.0–139.0 (N-Ph), 132.9 (q, ^2J = 39, C5), 120.1 (q, ^1J = 267, CF_3), 13.2 (CH_3). MS (m/z, %) 226 (M^+, 100), 77 (Ph, 70). **4a**: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3), 6.44 (s, 1H, H4), 7.33 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 149.6 (C3), 109.4 (C4), 125.0–139.0 (N-Ph), 132.7 (q, ^2J = 39, C5), 118.4 (q, ^1J = 259, CF_3), 12.2 (CH_3). MS (m/z, %) 226 (M^+, 100), 77 (Ph, 45). *Anal.* Calcd. for (mixture of **3a** + **4a**) $C_{11}H_9F_3N_2$ (226.20): C, 58.41; H, 4.01; N, 12.31%. Found: C, 58.02; H, 3.98; N, 12.30%.

3-Ethyl-1-phenyl-5-trifluoromethylpyrazole (3b). This compound was obtained as a white solid, mp 73-75 °C. ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, CH_3), 2.71 (q, 2H, CH_2), 6.62 (s, 1H, H4), 7.46 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 154.8 (C3), 107.1 (C4), 125.5, 128.8, 128.9, 139.1, (N-Ph), 132.8 (q, ^2J = 39, C5), 119.8 (q, ^1J = 259, CF_3), 13.5 (CH_3), 21.2 (CH_2). MS (m/z, %) 240 (M^+, 100), 77 (Ph, 57). *Anal.* Calcd. for $C_{12}H_{11}F_3N_2$ (240.23): C, 60.00; H, 4.62; N, 11.66%. Found: C, 59.83; H, 4.60; N, 11.63%.

1-Phenyl-3-propyl-5-trifluoromethylpyrazole (3c). This compound was obtained as a white solid, mp 69-71 °C. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, CH_3), 1.65 (m, 2H,CH_2), 2.65 (t, 2H, CH_2), 6.60 (s, 1H, H4), 7.42 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 153.5 (C3), 107.7 (C4), 125.6, 128.6, 128.9, 139.2, (N-Ph), 132.8 (q, ^2J = 38, C5), 122.8 (q, ^1J = 268, CF_3), 13.7 (CH_3), 21.5, 31.6 ($2CH_2$). MS (m/z, %) 254 (M^+, 29), 226 (100), 77 (Ph, 47). *Anal.* Calcd. for $C_{13}H_{13}F_3N_2$ (254.26): C, 61.41; H, 5.15; N, 11.02%. Found: C, 61.30; H, 5.14; N, 11.00%.

3-(1-Methylethyl)-1-phenyl-5-trifluoromethylpyrazole (3d). This compound was obtained as a white solid, mp 45-47 °C. ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3H, $2CH_3$), 1.28 (m, 1H, CH), 6.60 (s, 1H, H4), 6.63 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 159.3 (C3), 105.9 (C4), 126.0, 128.9, 129.0, 139.2, (N-Ph), 132.3 (q, ^2J = 40, C5), 119.9 (q, ^1J = 269, CF_3), 22.5 ($2CH_3$), 30.3 (CH). MS (m/z, %) 254 (M^+, 57), 239 (100), 77 (Ph, 47). *Anal.* Calcd. for $C_{13}H_{13}F_3N_2$ (254.26): C, 61.41; H, 5.15; N, 11.02%. Found: C, 61.24; H, 5.13; N, 10.99%.

3-Butyl-1-phenyl-5-trifluoromethylpyrazole (3e). This compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H, CH_3), 1.4 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 6.67 (s, 1H, H4), 7.50 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 153.7 (C3), 107.6 (C4), 125.5, 128.7, 128.9, 139.1, (N-Ph), 132.8 (q, ^2J = 39, C5), 122.5 (q, ^1J = 269, CF_3), 13.8 (CH_3), 22.3 (CH_2), 27.3 (CH_2), 31.5 (CH_2). MS (m/z, %) 268 (M^+, 9), 226 (100), 77 (Ph, 29). *Anal.* Calcd. for $C_{14}H_{15}F_3N_2$ (268.28): C, 62.68; H, 5.64; N, 10.44%. Found: C, 62.36; H, 5.61; N, 10.39%.

3-(2-Methylpropyl)-1-phenyl-5-trifluoromethylpyrazole (3f). This compound was obtained as a white solid, mp 59-60 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6H, $2CH_3$), 1.92(m, 1H, CH), 1.41 (m, 2H, CH_2), 2.5 (d, 2H, CH_2), 6.52 (s, 1H, H4), 7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) δ (J_{C-F}, Hz) 154.8 (C3), 107.8 (C4), 125.1,

128.4, 128.5, 138.7, (N-Ph), 132.3 (q, ^2J = 39, C5), 119.5 (q, ^1J = 269, CF_3), 22.0 ($2CH_3$), 28.4 (CH), 36.7 (CH_2). MS (m/z, %) 268 (M^+, 14), 226 (100) 77 (Ph, 33). *Anal*. Calcd. for $C_{14}H_{15}F_3N_2$ (268.28): C, 62.68; H, 5.64; N, 10.44%. Found: C, 62.55; H, 5.62; N, 10.42%.

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