Haloacetylated Enol Ethers, 19:[1] Synthesis of 3-(2-Thienyl)- and 3-(2-Furyl)-5-trihalomethyl Substituted Azoles

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Abstract: Heterocyclization of 1,1,1-trifluoro[chloro]-4-methoxy-4-[2-tienyl]-3-buten-2-one and 1,1,1-trifluoro[chloro]-4-methoxy-4-[2-furyl]-3-buten-2-ones into isoxazoles and pyrazoles derivatives as a new type of trihalomethylated bicyclic heterocycles is reported.

Keywords: [3+2] cyclocondensation, furyl isoxazoles, thienyl isoxazoles, furyl pyrazoles, thienyl pyrazoles

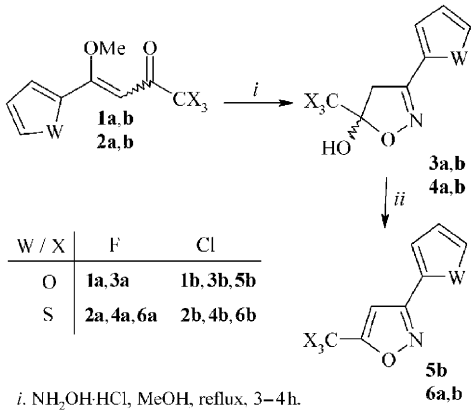
The wide range of biological activities of pyrazoles, isoxazoles has made them popular synthetic targets.[2] Numerous methods for the synthesis of these heterocycles involve approaches based on either intermolecular [2+3] cycloadditions of 1,3-dipoles to alkenes and alkynes, or cyclocondensations of hydroxylamine and hydrazines with 1,3-dielectrophiles.[3] Moreover the thiophenes and furans in oligosystems have attracted considerable attention as the active component of organic electronic devices.[4]

In recent years we have focused our interest on β-diketones and α,β-unsaturated ketones with trifluoromethyl or trichloromethyl substituent.[5] These represent interesting building blocks for the synthesis of heterocyclic systems, which often show high biological activities.[6] The regiospecific synthesis of fluorinated N-heterocyclic compounds have drawn much more attention, the literature has reported series of CF_3-substituted pyrazoles and isoxazoles obtained from the reactions of trifluoromethyl-β-diketones and α,β-unsaturated trifluoromethyl ketones (β-alkoxyvinyl trifluoromethyl ketones or diethylaminomethylene hexafluoromethylacetone) with the corresponding nitrogen nucleophiles.[7]

In connection with our studies on the synthesis of isoxazole and pyrazole derivatives,[8] we were interested in developing general and convenient methods for the synthesis of biheterocyclic systems from acetyl heterocycles. Here we report the syntheses of 2-thienyl- and 2-furylazoles with trihalomethyl and carboxyl substituents.

The trihaloacetylated precursors were obtained by acetal acylation method, from which 1,1,1-trihalo-4-heteroaryl-4-methoxybut-3-en-2-ones **1a**,**b** and **2a**,**b** were isolated as pure mixtures of *E*/*Z* isomers. The reaction of 1,1-dimethoxy-1-(2-heteroaryl)ethanes with trichloroacetyl chloride or trifluoroacetic anhydride in $CHCl_3$–pyridine is a very convenient approach to trichloro- and trifluoromethyl 1,3-dielectrophiles.[9]

In order to prepare isoxazole derivatives, compounds **1a**,**b** and **2a**,**b** were reacted with $NH_2OH{\cdot}HCl$ in MeOH under reflux for four hours. The crystalline products were obtained in 90–95% yields (Scheme 1). These compounds were characterized as 5-trihalomethyl-3-(2-heteroaryl)-5-hydroxy-4,5-dihydroisoxazole derivatives **3a**,**b** and **4a**,**b** based on the analysis and spectral data. The presence of the strong electron-withdrawing substituent at the 5-position guarantees the high stability of the 5-hydroxy-4,5-dihydroisoxazole structures. The dehydration of **3** and **4** with 98% H_2SO_4 at 50 °C for 2–6 hours afforded aromatic isoxazole derivatives **5b** and **6a**, **b**. The dehydration of **3a** did not occur in this medium; the high reflux temperature leads to complex mixtures probably from furyl ring opening. In an attempt to prepare the 3-thienyl-5-isoxazole carboxylic acid the 4,5-dihydroisoxazole **4b** was refluxed in 95% H_2SO_4; however after 12 hours only the reactant isoxazoline was isolated without any changes. The structure of **5**, **6** was supported by elemental analysis, mass spectrometry and ^1H, ^{13}C NMR spectral data (Table 1) and ^{19}F NMR.[10]



Scheme 1

Next we examined the synthesis of pyrazole derivatives by cyclocondensations of **1** and **2** with hydrazine as summarized in Scheme 2. The reaction of **1a** and **2a** with hydrazine hydrochloride in MeOH or EtOH at 50–60 °C

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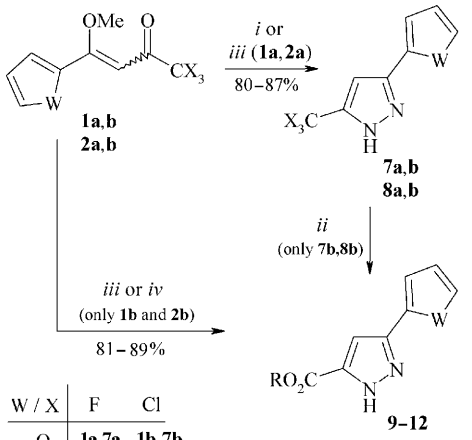
gave pyrazoles **7a** and **8a** as crystals, quantitatively. The same substrates reacting with hydrazine monohydrate gave the same pyrazoles in somewhat lower yields (70–75%). The ^{13}C NMR spectra of these tautomeric 3(5)-trifluoromethyl-5(3)-(2-heteroaryl)-1*H*-pyrazoles **7a**, **8a** in $CDCl_3$ revealed only one quartet signal assignable to CF_3 at δ = 121.6 ($J_{C,F}$ = 268.7) for **7a** and δ = 120.8 ($J_{C,F}$ = 269) for **8a**. The ^{19}F NMR spectra showed only one signal for 5-trifluoromethyl group at –64.10 for **7a** and at –64.30 for **8a**.[11]

The reactions of **1b** and **2b** with hydrazine hydrochloride in MeOH or EtOH at 50–60 °C afforded the respective 3(5)-ester pyrazoles **9**–**12** as crystals in good yields of 81–89% (Table 1). The same reaction with hydrazine monohydrate at 25 °C gave the same 3(5)-esters pyrazoles **9**–**12** quantitatively. The structural assignments were based on the signals due to the pyrazole ring carbons at ca δ = 140.1, 104.3 and 138.8 for **9**, and δ = 146.2, 105.9 and 138.4 for **11**. The signals from ester carboxyl groups were observed at δ = 160.2–160.9 (Table 1). The reaction of **1b** with hydrazine monohydrate in a concentrated solution of EtOH afforded a 40:60 mixture of **9** and **10** in 95% yield. The medium with hydrazine monohydrate was preferred to that with hydrazine hydrochloride when the targets were ester pyrazoles **9**–**12** (Table 1).



W / X	F	Cl
O	**1a**,**7a**	**1b**,**7b**
S	**2a**,**8a**	**2b**,**8b**

W / R	Me	Et
O	**9**	**10**
S	**11**	**12**

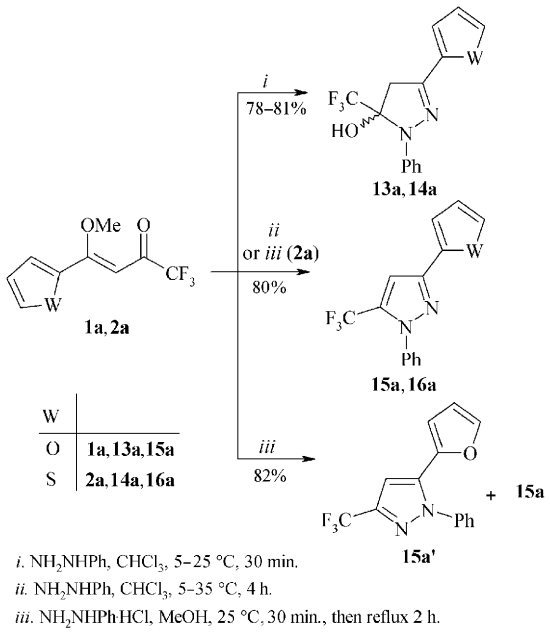
i. $NH_2NH_2{\cdot}H_2O$, $CHCl_3$, 25–30 °C, 2 h.
ii. HCl, ROH (R = Me, Et), 35 °C, 2 h.
iii. $NH_2NH_2{\cdot}HCl$, ROH (R = Me, Et), 35 °C, 6 h.
iv. $NH_2NH_2{\cdot}H_2O$, ROH (R = Me, Et), 35 °C, 1–2 h.

Scheme 2

However, intending to preserve the trichloromethyl group on pyrazole products the reaction of **1b** or **2b** with hydrazine monohydrate was carried out in a polar aprotic solvent ($CHCl_3$) at 25–30 °C for 30 minutes, which gave the 5-trichloromethyl-1*H*-pyrazoles **7b** and **8b** in quantitative yields (Table 1). The presence of the signals at δ = 101 from CCl_3, as well as the chemical shifts of the pyrazole carbons supported the assignment (Table 1).

The cyclocondensations of **1** and **2** with phenylhydrazine are summarized in Scheme 3. The reaction of **1a** with phenylhydrazine hydrochloride in refluxing MeOH for four hours gave a mixture of 3- and 5-trifluoromethyl substituted pyrazole isomers (**15a** and **15a′**) in 82% yield (Scheme 3, Table 1). However, when **2a** was allowed to react with phenylhydrazine hydrochloride under the same conditions only one isomer was obtained in 75% yield. It was attributed as 5-trifluoromethyl-1-phenyl-3-thienyl-1*H*-pyrazole (**16a**). The regiochemical assignment of **15a**, **15a′** and **16a** was made on the basis of the ^{13}C (Table 1) and ^{19}F NMR spectra.[3b,11]

The reaction of **1a** or **2a** with free phenylhydrazine furnished different results on changing the reaction time and solvent of the reaction. A short reaction period (30 min) in $CHCl_3$ at 5–10 °C afforded the 4,5-dihydropyrazoles **13a** and **14a** in good yields. The ^1H NMR signals from diastereotopic hydrogens at 4 position of the pyrazole ring confirmed the assignment. Nevertheless, a longer period of four hours in the same solvent led to the aromatic products **15a** and **16a**. On using EtOH as solvent, a complex mixture of 4,5-dihydropyrazole, aromatic pyrazole isomers and tar material was obtained.



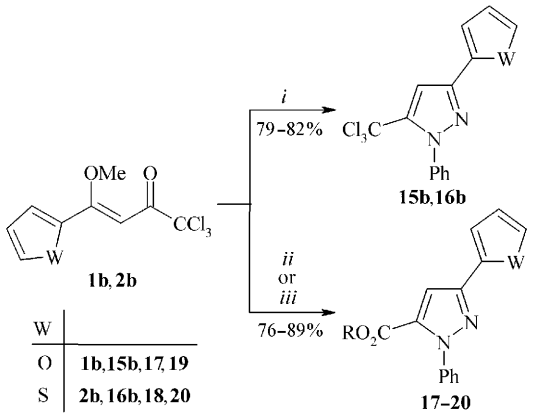
W	
O	**1a**,**13a**,**15a**
S	**2a**,**14a**,**16a**

i. NH_2NHPh, $CHCl_3$, 5–25 °C, 30 min.
ii. NH_2NHPh, $CHCl_3$, 5–35 °C, 4 h.
iii. $NH_2NHPh{\cdot}HCl$, MeOH, 25 °C, 30 min., then reflux 2 h.

Scheme 3

In reactions of **1b** and **2b** with phenylhydrazine hydrochloride in MeOH or EtOH at 25–50 °C the respective 5-ester pyrazoles **17**–**20** were furnished as crystals in good yields 76–89% (Table 1 and Scheme 4). Moreover when **1b** or **2b** were allowed to react with free phenylhydrazine in MeOH or EtOH at 25–35 °C the same 5-ester pyrazoles were obtained with equivalent yields. In order to preserve the trichloromethyl group at pyrazole ring the cyclocondensation reaction was carried out in $CHCl_3$ at 5–25 °C for one hour. It was then possible to isolate the 5-trichloromethyl-3-(2-heteroaryl)-1-phenyl-1*H*-pyrazoles **15b** and

16b. The ^1H and ^{13}C NMR spectra of these pyrazoles in $CDCl_3$ revealed only one set of signals assigned to the 3-heteroaryl substituted isomers.



i. NH_2NHPh, $CHCl_3$, 25 °C, 2 h.
ii. NH_2NHPh, ROH (R = Me, Et), 35 °C, 4 h.
iii. $NH_2NHPh{\cdot}HCl$, ROH (R = Mc, Et), r.t. 30–60 min. then 60 – 65 °C 2 h.

Scheme 4

The presented regiospecific reactions have been being useful and convenient alternative to obtain important biheterocyclic systems containing thiophene or furan ring. That one-pot cyclocondensation and conversion of trichloromethyl group into carboxyl groups allowed the production of a new series of pyrazole-5-carboxylic esters in good yields. Moreover, it was possible to verify that the effect of the 3-(2-heteroaryl) substituent on the isoxazole ring does not permit the conversion of the trichloromethyl group to carboxyl groups; the same trend observed with 3-aryl substituents.[12] On the other hand, the facile transformation of trichloromethyl group attached to 3-heteroaryl-1*H*-pyrazoles into alkoxycarbonyl groups have permitted us to conclude the azole effect over the trichloromethyl hydrolysis. The higher resonance energies[13] of 3-(2-heteroaryl)-1*H*-pyrazoles (**7b**, **8b**, **15b** and **16b**) have favored the trichloromethyl hydrolysis whereas the 3-(2-heteroaryl)isoxazoles **5b** and **6b** have blocked that transformation under mild cyclocondensation conditions.

EtOH, MeOH and $CHCl_3$ were purchased from Merck. Hydroxylamine, hydrazine and phenylhydrazine hydrochloride were purchased from Aldrich. All chemicals were used as obtained from suppliers. The 1,1,1-trihalo-4-(2-heteroaryl)-4-methoxy-3-buten-2-ones **1** and **2** were prepared according to ref.[9] All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K and digital resolution of ± 0.01 ppm, in $CDCl_3$ and using TMS as the internal reference. Mass spectra were registered on a HP 6890 GC equipment connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas. The elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University-USP/Brazil).

Synthesis of 5-Trihalomethyl-5-hydroxy-3-(2-heteroaryl)-4,5-dihydroisoxazoles (3a,b, 4a,b)

A solution of 1,1,1-trihalo-4-(2-heteroaryl)-4-methoxy-3-buten-2-ones **1** or **2** (5 mmol) and hydroxylamine hydrochloride (5.5 mmol) in MeOH (7 mL) was stirred for 2–4 h at reflux. The solvent was removed and the residue was dissolved in $CHCl_3$ (20 mL) and washed with water (2 × 10 mL). The solution was dried with Na_2SO_4 and the solvent was evaporated, which gave the pure isoxazoles **3a**,**b** and **4a**,**b**. Yields, melting points, and ^1H, ^{13}C NMR data are presented in Table 1 and elemental analysis in Table 2.

Table 1 Yields, Melting Points and ^1H and ^{13}C NMR Data of Heteroarylazoles **3**–**20**

Product	X/R	W	Yield (%)[a]	Mp (°C)	NMR data[c]
3a[d]	F	O	90	117–119	^1H NMR: δ = 3.52 (d, *J* = 18.0 Hz, 1 H), 3.83 (d, *J* = 18.0 Hz, 1 H), 6.62 (dd, *J* = 3.4, 1.8 Hz, 1 H), 6.95 (d, *J* = 3.4 Hz, 1 H), 7.74 (d, *J* = 1.8 Hz, 1 H) ^{13}C NMR: δ = 148.7 (C-3), 42.5 (C-4), 103.6 (J_{CF} = 33.5 Hz, C-5), 122.6 (J_{CF} = 283.6 Hz, CF_3), 143.6 (C-2′), 113.8 (C-3′), 111.9 (C-4′), 145.5 (C-5′)
4a[d]	F	S	90	123–125	^1H NMR: δ = 3.56 (d, *J* = 18.5 Hz, 1 H), 3.93 (d, *J* = 18.5 Hz, 1 H), 7.18 (dd, *J* = 5.6, 3.7 Hz, 1 H), 7.50 (dd, *J* = 3.7, 1.0 Hz, 1 H), 7.73 (dd, *J* = 5.6, 1.0 Hz, 1 H) ^{13}C NMR: δ = 153.0 (C-3), 42.8 (C-4), 103.8 (J_{CF} = 33.1 Hz, C-5), 122.4 (J_{CF} = 284.2 Hz, CF_3), 129.7 (C-2′), 130.0 (C-3′), 127.9 (C-4′), 131.3 (C-5′)
3b[d]	Cl	O	95	155–157	^1H NMR: δ = 3.66 (d, *J* = 18.5 Hz, 1 H), 4.02 (d, *J* = 18.5 Hz, 1 H), 6.61 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.96 (d, *J* = 3.5 Hz, 1 H), 7.74 (d, *J* = 1.8 Hz, 1 H) ^{13}C NMR: δ = 149.0 (C-3), 44.0 (C-4), 111.4 (C-5), 101.2 (CCl_3), 143.5 (C-2′), 113.5 (C-3′), 111.8 (C-4′), 145.2 (C-5′)
4b[d]	Cl	S	93	168–171	^1H NMR: δ = 3.73 (d, *J* = 18.5 Hz, 1 H), 4.16 (d, *J* = 18.5 Hz, 1 H), 7.15 (dd, *J* = 5.0, 3.7 Hz, 1 H), 7.50 (dd, *J* = 3.7, 1.0 Hz, 1 H), 7.65 (dd, *J* = 5.0, 1.0 Hz, 1 H) ^{13}C NMR: δ = 154.1 (C-3), 45.9 (C-4), 112.8 (C-5), 102.2 (CCl_3), 131.5 (C-2′), 130.1 (C-3′), 128.6 (C-4′), 131.3 (C-5′)

Table 1 Yields, Melting Points and ^{1}H and ^{13}C NMR Data of Heteroarylazoles **3**–**20** (continued)

Product	X/R	W	Yield (%)[a]	Mp (°C)	NMR data[c]
6a	F	S	89	112–115	^{1}H NMR: δ = 6.56–6.59 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.97 (s, 1 H), 7.02 (d, *J* = 3.5 Hz, 1 H), 7.60 (d, *J* = 1.8 Hz, 1 H) ^{13}C NMR: δ = 157.7 (C-3), 103.4 (C-4), 159.0 (J_{CF} = 34.0 Hz, C-5), 117.7 (J_{CF} = 280.2 Hz, CF_3), 128.5 (C-2′), 128.6 (C-3′), 127.9 (C-4′), 128.8 (C-5′).
5b	Cl	O	76	55–57	^{1}H NMR: δ = 6.47–6.49 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.81 (s, 1 H), 6.92 (d, *J* = 3.5 Hz, 1 H), 7.51 (d, *J* = 1.8 Hz, 1 H) ^{13}C NMR: δ = 168.7 (C-3), 101.3 (C-4), 154.7 (C-5), 84.2 (CCl_3), 142.7 (C-2′), 111.9 (C-3′), 111.3 (C-4′), 144.5 (C-5′)
6b	Cl	S	82	101–103	^{1}H NMR: δ = 6.85 (s, 1 H), 7.14 (dd, *J* = 5.0, 3.6 Hz, 1 H), 7.45–7.52 (m, 2 H) ^{13}C NMR: δ = 169.0 (C-3), 101.7 (C-4), 157.7 (C-5), 84.3 (CCl_3), 129.1 (C-2′), 128.6 (C-3′), 128.3 (C-4′), 128.6 (C-5′)
7a	F	O	80	48–50	^{1}H NMR: δ = 6.67 (s, 1 H, H-4), 6.46 (dd, *J* = 1.8, 3.4 Hz, 1 H, H-4′), 6.65 (d, *J* = 3.4 Hz, 1 H, H-3′), 7.43(d, *J* = 1.8 Hz, 1 H, H-5′) ^{13}C NMR: δ = 143.3 (C-3), 99.9 (J_{CF} = 1.8 Hz, C-4), 143.2 (J_{CF} = 26.0 Hz, C-5), 121.6 (J_{CF} = 268.7 Hz, CF_3), 136.4 (C-2′), 108.0 (C-3′), 111.6 (C-4′), 143.0 (C-5′).
8a	F	S	84	103–105	^{1}H NMR: δ = 6.66 (s, 1 H, H-4), 7.07 (dd, *J* = 3.7, 4.9 Hz, 1 H, H-4′), 7.30 (d, *J* = 3.7 Hz, 1 H, H-3′), 7.35(d, *J* = 4.9 Hz, 1 H, H-5′) ^{13}C NMR: δ = 139.9 (C-3), 101.5 (J_{CF} = 1.6 Hz, C-4), 143.0 (J_{CF} = 31.2 Hz, C-5), 120.8 (J_{CF} = 269.0 Hz, CF_3), 129.8 (C-2′), 128.0 (C-3′), 125.5 (C-4′), 126.5 (C-5′)
7b	Cl	O	82	53–54	^{1}H NMR: δ = 6.47 (dd, *J* = 1.7, 3.2 Hz, 1 H, H-4′), 6.77 (d, *J* = 3.2 Hz, 1 H, H-3′), 6.81 (s, 1 H, H-4), 7.45 (d, *J* = 1.7 Hz, 1 H, H-5′) ^{13}C NMR: δ = 154.8 (C-3), 100.3 (C-4), 143.3 (C-5), 89.52 (CCl_3), 136.9 (C-2′), 108.6 (C-3′), 111.77 (C-4′), 143.16 (C-5′)
8b	Cl	S	87	115–117	^{1}H NMR: δ = 6.80 (s, 1 H, H-4), 7.09 (dd, *J* = 3.4, 4.4 Hz, 1 H, H-4′), 7.36 (d, *J* = 3.9 Hz, 1 H, H-3′), 7.37 (d, *J* = 4.4 Hz, 1 H, H-5′) ^{13}C NMR: δ = 154.8 (C-3), 101.8 (C-4), 140.3 (C-5), 89.6 (CCl_3), 130.3 (C-2′), 125.6 (C-3′), 126.5 (C-4′), 128.0 (C-5′)
9	Me	O	85	Oil	3.90 (s, 3 H, Me), 6.46 (dd, *J* = 1.8, 3.4 Hz, 1 H, H-4′), 6.73 (d, *J* = 3.4 Hz, 1 H, H-3′), 6.99 (s, 1 H, H4), 7.44 (d, *J* = 1.8 Hz, 1 H, H-5′) ^{13}C NMR: δ = 140.9 (C-3), 104.8 (C-4), 139.0 (C-5), 160.9 (CO_2R), 145.8 (C-2′), 107.2 (C-3′), 111.5 (C-4′), 142.5 (C-5′)
10	Et	O	81	Oil	1.32 (t, *J* = 7.0 Hz, 3 H, Me), 4.34 (q, *J* = 7.0 Hz, 2 H, CH_2), 6.56 (dd, *J* = 1.8, 3.4 Hz, 1 H, H-4′), 6.96 (d, *J* = 3.4 Hz, 1 H, H-3′), 7.05 (s, 1 H, H-4), 7.65 (d, *J* = 1.8 Hz, 1 H, H-5′) ^{13}C NMR: δ = 140.1 (C-3), 104.3 (C-4), 138.8 (C-5), 160.7 (CO_2R), 145.6 (C-2′), 107.5 (C-3′), 111.9 (C-4′), 143.3 (C-5′)
11	Me	S	87	Oil	^{1}H NMR: δ = 3.89 (s, 3 H, Me), 6.96 (s, 1 H, H-4), 7.03 (dd, *J* = 3.6, 5.1 Hz, 1 H, H-4′), 7.26 (d, *J* = 5.1 Hz, 1 H, H3′), 7.37 (d, *J* = 3.6 Hz, 1 H, H-5′) ^{13}C NMR: δ = 144.8 (C-3), 105.5 (C-4), 137.9 (C-5), 160.5 (CO_2R), 133.4 (C-2′), 127.6 (C-3′), 124.8 (C-4′), 125.5 (C-5′)
12	Et	S	89	132–134	^{1}H NMR: δ = 1.34 (t, *J* = 7.1 Hz, 3 H, Me), 4.35 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.11 (dd, *J* = 3.6, 5.1 Hz, 1 H, H-4′), 7.27 (s, 1 H, H-4), 7.47 (dd, *J* = 1.06, 5.1 Hz, 1 H, H-3′), 7.58 (dd, *J* = 1.06, 3.6 Hz, 1 H, H-5′). ^{13}C NMR: δ = 146.2 (C-3), 105.9 (C-4), 138.4 (C-5), 160.2 (CO_2R), 135.2 (C-2′), 128.6 (C-3′), 125.8 (C-4′), 126.5 (C-5′)
13a	F	O	81	Oil	^{1}H NMR: δ = 3.59 (dd, *J* = 18.6, 1.6 Hz, 1 H, H-4a), 3.83(d, *J* = 18.6 Hz, 1 H, H-4b), 6.57 (dd, *J* = 3.5, 1.84 Hz, 1 H, H-4′), 6.79 (d, *J* = 3.5 Hz, 1 H, H-3′), 7.27 (m, 3 H, Ph), 7.51 (m, 2 H, Ph), 7.66 (d, *J* = 1.84 Hz, 1 H, H-5′) ^{13}C NMR: δ = 139.7 (C-3), 45.0 (C-4), 94.1 (J_{CF} = 31.7 Hz, C-5), 120.3 (J_{CF} = 284.0 Hz, CF_3), 143.5 (C-2′), 111.0 (C-3′), 113.3 (C-4′), 144.7 (C-5′)
14a	F	S	78	Oil	^{1}H NMR: δ = 3.42 (d, *J* = 18.15 Hz, 1 H, H-4a), 3.71 (d, *J* = 18.15 Hz, 1 H, H-4b), 7.05 (d, 1 H, H-3′), 7.31 (dd, 1 H, H-4′), 7.30–7.60 (m, 6 H, H-5′, Ph) ^{13}C NMR: δ = 140.9 (C-3), 44.8 (C-4), 93.5 (J_{CF} = 31.8 Hz, C-5), 121.0 (J_{CF} = 284.8 Hz, CF_3), 144.3 (C-2′), 129.1 (C-3′), 128.7 (C-4′), 140.9 (C-5′)

Table 1 Yields, Melting Points and ^{1}H and ^{13}C NMR Data of Heteroarylazoles **3**–**20** (continued)

Product	X/R	W	Yield (%)[a]	Mp (°C)	NMR data[c]
15a	F	O	80	Oil	^{1}H NMR: δ = 5.96 (d, *J* = 3.3 Hz, 1 H, H-3′), 6.32 (dd, *J* = 1.8, 3.3 Hz, 1 H, H-4′), 6.89 (s, 1 H, H-4), 7.42 (d, *J* = 1.8 Hz, 1 H, H-5′), 7.43 (m, 2 H, Ph), 7.47–7.51 (m, 3 H,Ph) ^{13}C NMR: δ = 136.1 (C-3), 103.7 (J_{CF} = 1.8 Hz, C-4), 143.1 (J_{CF} = 38.5 Hz, C-5), 121.0 (J_{CF} = 269.0 Hz, CF_3), 143.1 (C-2′), 109.8 (C-3′), 111.3 (C-4′), 143.1 (C-5′)
15a[1,3]					^{1}H NMR: δ = 6.47 (dd, *J* = 1.8, 3.3 Hz, 1 H, H-4′), 6.79 (d, *J* = 3.3 Hz, 1 H, H-4′), 7.03 (s, 1 H, H-4), 7.39 (d, *J* = 1.8 Hz, 1 H, H-5′), 7.47–7.51 (m, 5 H, Ph) ^{13}C NMR: δ = 133.6 (J_{CF} = 39.5 Hz, C-3), 105.7 (J_{CF} = 2.4 Hz, C-4), 147.0 (C-5), 119.5 (J_{CF} = 269.3 Hz, CF_3), 144.1 (C-2′), 107.1 (C-3′), 111.4 (C-4′), 142.5 (C-5′)
16a	F	S	81	53–55	^{1}H NMR: δ = 6.98(s, 1 H, H-4), 7.06 (dd, *J* = 5.06, 3.6 Hz, 1 H, H-4′), 7.28 (dd, *J* = 5.05, 1.1 Hz, 1 H, H-3′), 7.39 (dd, *J* = 3.6, 1.1 Hz, 1 H, H-5′), 7.46 (m, 3 H, Ph), 7.51 (m, 2 H, Ph) ^{13}C NMR: δ = 147.1 (C-3), 105.7 (J_{CF} = 1.8 Hz, C-4), 133.8 (J_{CF} = 39.6 Hz, C-5), 121.4 (J_{CF} = 269.0 Hz, CF_3), 144.1 (C-2′), 129.8 (C-3′), 127.3 (C-4′), 141.4 (C-5′)
15b	Cl	O	79	119–121	^{1}H NMR: δ = 5.97 (d, *J* = 3.5 Hz, 1 H, H-3′), 6.32 (dd, *J* = 3.5, 1.9 Hz, 1 H, H-4′), 6.99 (s, 1 H, H-4), 7.40 (d, *J* = 1.9 Hz, 1 H, H-5′), 7.43–7.49 (m, 5 H, Ph). ^{13}C NMR: δ = 136.2 (C-3), 103.8 (C-4), 143.09 (C-5), 90.5 (CCl_3), 143.2 (C-2′), 109.8 (C-3′), 111.3 (C-4′), 139.4 (C-5′)
16b	Cl	S	82	134–136	^{1}H NMR: δ = 7.07 (dd, *J* = 5.6, 1.2 Hz, 1 H, H-3′), 7.08 (s, 1 H, H-4), 7.28 (dd, *J* = 5.6, 3.6 Hz, 1 H, H-4′), 7.41 (dd, *J* = 3.6, 1.2 Hz, 1 H, H-5′), 7.44–7.49 (m, 3 H, Ph), 7.58 (m, 2 H, Ph) ^{13}C NMR: δ = 145.6 (C-3), 105.9 (C-4), 139.6 (C-5), 86.5 (CCl_3), 134.7 (C-2′), 129.6 (C-3′), 125.4 (C-4′), 127.5 (C-5′)
17	Me	O	80	65–67	^{1}H NMR: δ = 3.94 (s, 3 H, Me), 5.94 (d, *J* = 3.34 Hz, 1 H, H-3′), 6.32 (dd, *J* = 3.34, 1.7 Hz, 1 H, H-4′), 7.17 (s, 1 H, H-4), 7.39 (d, *J* = 1.7 Hz, 1 H, H-5′), 7.40–7.48 (m, 5 H, Ph) ^{13}C NMR: δ = 139.5 (C-3), 107.9 (C-4), 136.1 (C-5), 162.4 (CO_2Me), 143.2 (C-2′), 109.4 (C-3′), 111.2 (C-4′), 142.9 (C-5′)
18	Et	O	89	Oil	^{1}H NMR: δ = 1.40 (t, *J* = 7.1 Hz, 3 H, Me), 4.43 (q, *J* = 7.1 Hz, 2 H, CH_2), 5.94 (d, *J* = 3.4 Hz, 1 H, H-3′), 6.31 (dd, *J* = 3.4, 1.76 Hz, 1 H, H-4′), 7.17 (s, 1 H, H-4), 7.39 (d, *J* = 1.76 Hz, 1 H, H-5′), 7.40–7.48 (m, 5 H, Ph) ^{13}C NMR: δ = 139.4 (C-3), 107.9 (C-4), 136.0 (C-5), 161.9 (CO_2Et), 143.2 (C-2′), 109.4 (C-3′), 111.1 (C-4′), 142.9 (C-5′)
19	Me	S	76	68–70	^{1}H NMR: δ = 3.94 (s, 3 H, Me), 6.82(d, *J* = 3.74 Hz, 1 H, H-3′), 6.92 (dd, *J* = 5.0, 3.34 Hz, 1 H, H-4′), 7.08 (s, 1 H, H-4), 7.26 (d, *J* = 5.0 Hz, 1 H, H-5′), 7.38–7.43 (m, 5 H, Ph) ^{13}C NMR: δ = 138.9 (C-3), 109.3 (C-4), 138.6 (C-5), 162.4 (CO_2Me), 143.7 (C-2′), 129.1 (C-3′), 127.0 (C-4′), 127.6 (C-5′)
20	Et	S	83	Oil	^{1}H NMR: δ = 1.41 (t, *J* = 7.2 Hz, 3 H, Me), 4.44(q, *J* = 7.2 Hz, 2 H, CH_2), 6.82 (d, *J* = 2.8 Hz, 1 H, H-3′), 6.93 (dd, *J* = 4.8, 2.8 Hz, 1 H, H-4′), 7.08 (s, 1 H, H-4), 7.28 (d, *J* = 4.8 Hz, 1 H, H-5′), 7.40–7.45 (m, 5 H, Ph) ^{13}C NMR: δ = 139.0 (C-3), 109.4 (C-4), 138.7 (C-5), 162.1 (CO_2Et), 144.1 (C-2′), 129.1 (C-3′), 127.1 (C-4′), 127.7 (C-5′)

[a] Yield refers of the pure products.
[b] Melting points were determined with a Reichert Thermovar apparatus and are uncorrected.
[c] NMR spectra were recorded on a Bruker DPX400 spectrometer in $CDCl_3$–TMS.
[d] In DMSO-d_6/TMS. See ref.[9]

Synthesis of 5-Trihalomethyl-3-(2-heteroaryl)isoxazoles (5b, 6a,b)

To the respective 4,5-dihydroisoxazole **3b** or **4a**,**b** (1 mmol) was added at room temperature 98% H_2SO_4. The black mixture was stirred for 2 h (**3b** and **4b**) or 6 h for **4a**. After that the acidic solution was diluted with cooled water and precipitated solid was filtered and dried over $CaCl_2$ under vacuum. Yields, melting points and ^{1}H, ^{13}C NMR data for the obtained pure isoxazoles **5b** and **6a**,**b** are presented in Table 1 and elemental analysis in Table 2.

Synthesis of 3(5)-Trihalomethyl-5(3)-(2-heteroaryl)-1*H*-pyrazoles (7a,b, 8a,b)

To a stirred solution of 1,1,1-trihalo-4-(2-heteroaryl)-4-methoxy-3-buten-2-ones **1** or **2** (5 mmol) in $CHCl_3$ (20 mL) was added hydrazine monohydrate (5.2 mmol). The mixture was stirred for 2 h at r.t. After that the solution was dried with Na_2SO_4, filtered and the solvent was removed. Then pure 1*H*-pyrazoles **7a**,**b**, **8a**,**b** were obtained. Yields, melting points and ^{1}H, ^{13}C NMR data are presented in Table 1 and elemental analysis in Table 2. The synthesis of 5-trifluoromethyl-3-(2-thienyl)-1*H*-pyrazole (**8a**) has been previously

Table 2 Elemental Analyses of Isolated Compounds[a]

Product	Molecular Formula	C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found
3a	$C_8H_6F_3NO_3$	43.45	43.40	2.73	2.75
4a	$C_8H_6F_3NO_2S$	40.51	40.50	2.55	2.50
3b	$C_8H_6Cl_3NO_3$	35.52	35.70	2.24	2.35
4b	$C_8H_6Cl_3NO_2S$	33.53	33.40	2.11	2.13
6a	$C_8H_5F_3NOS$	43.84	43.80	1.84	2.00
5b	$C_8H_5Cl_3NO_2$	38.06	38.00	1.60	1.65
6b	$C_8H_5Cl_3NOS$	35.78	35.75	1.50	1.50
7a	$C_8H_5F_3N_2O$	47.54	47.40	2.49	2.45
8a	$C_8H_5F_3N_2S$	44.04	44.00	2.31	2.30
7b	$C_8H_5Cl_3N_2O$	38.21	38.20	2.00	2.00
8b	$C_8H_5Cl_3N_2S$	35.91	36.10	1.88	1.90
9	$C_9H_8N_2O_3$	56.25	56.30	4.20	4.35
10	$C_{10}H_{10}N_2O_3$	51.91	51.95	3.87	4.00
11	$C_9H_8N_2O_2S$	58.25	58.25	4.89	4.90
12	$C_{10}H_{10}N_2O_2S$	54.04	54.10	4.53	4.55
15a	$C_{14}H_9F_3N_2O$	60.44	60.50	3.26	3.35
16a	$C_{14}H_9F_3N_2S$	57.14	57.20	3.08	3.15
15b	$C_{14}H_9Cl_3N_2O$	51.33	51.50	2.77	2.90
16b	$C_{14}H_9Cl_3N_2S$	48.93	48.90	2.64	2.65
17	$C_{15}H_{12}N_2O_3$	67.16	67.10	4.51	4.50
18	$C_{15}H_{12}N_2O_2S$	68.08	68.10	5.00	4.90
19	$C_{16}H_{14}N_2O_3$	63.36	63.35	4.25	4.30
20	$C_{16}H_{14}N_2O_2S$	64.41	64.30	4.73	4.65

[a] Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University-USP/Brazil)

reported and the analytical and spectral data are reported in reference 11a.

Synthesis of 3(5)-(2-Heteroaryl)-1*H*-pyrazole-5(3)-carboxylic Acids (9–12)

A solution of 1,1,1-trihalo-4-(2-heteroaryl)-4-methoxy-3-buten-2-ones **1** or **2** (5 mmol) and hydrazine hydrochloride (5.2 mmol) in MeOH or EtOH (7 mL) was stirred for 2 h at reflux. The solvent was removed and the residue was dissolved in $CHCl_3$ (20 mL) and washed with water (2 × 10 mL). The solution was dried with Na_2SO_4 and the solvent was evaporated. Then pure 1*H*-pyrazole-5-carboxylic acids **9**–**12** were obtained. Yields, melting points, mass and ^1H, ^{13}C NMR data are presented in Table 1 and elemental analysis in Table 2.

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