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Ultrasonic irradiation assisted efficient regioselective synthesis of CF₃-containing pyrazoles catalyzed by Cu(OTf)₂/Et₃N

Abdullah S Al-Bogami^{1*}, Tamer S Saleh^{1,2} and Hassan M Albishri¹

Abstract

Background: Most of the known approaches to the synthesis of CF₃-containing organic compounds suffer from serious drawbacks. For example the starting materials required for these methods are rather difficult to obtain, or they are fairly toxic and inconvenient to work with and methods for direct fluorination and trifluoromethylation do not always allow the introduction of the CF₃-group at the required position of a molecule.

Results: An efficient and attractive regioselective synthesis of a series of novel pyrazoles containing the trifluoromethyl moiety was achieved using Cu(OTf)₂/Et₃N as an efficient catalytic system under ultrasonic irradiation.

Conclusions: Cu(OTf)₂/Et₃N catalyst showed a great advantage over all the investigated catalysts, and the ultrasonic irradiation method offered high yields of pyrazoles in short reaction time compared with classical conditions. gHMBC spectra of the product were used to rationalize the observed regioselectivity.

Keywords: Ultrasonic irradiation, Pyrazole, Trifluoromethyl moiety, HMBC, Copper(II)triflate

Background

Over the last two decades there has been rapid progress in synthetic organic chemistry associated with the search for new organic compound derivatives with desirable properties. Such compounds are widely used in the pharmaceutical industry. Among the several FDA approved pharmaceutical drugs, the pyrazole core is found in rimonabant (**1**), and celecoxib (**2**) (Figure 1) [1].

Pyrazoles exhibit significant biological properties such as antihyperglycemic [2], analgesic [3], anti-inflammatory [4], antipyretic [5], antibacterial [6], hypoglycemic [7] and sedative-hypnotic activities [8].

The trifluoromethyl group is a very important substituent in medicinal chemistry, due to its unique stereoelectronic properties. A trifluoromethyl group usually increases the lipophilicity of a molecule, improving its transport characteristics in vivo. Furthermore, the strength and durability of the C-F bond compared with the C-H bond (116 and 100 kcal/mol respectively) allows undesirable metabolic transformations to be avoided. So the introduction of

trifluoromethyl groups into bioactive molecules has become very important in pharmaceutical studies, stimulating work directed towards the elaboration of synthetic methodology for compounds containing trifluoromethyl groups. Because of all these factors, organofluorine chemistry has been vigorously developing during the past two decades [9].

Most of the known approaches to the synthesis of CF₃-containing organic compounds suffer from serious drawbacks. First of all, the starting materials required for these methods are rather difficult to obtain, or they are fairly toxic and inconvenient to work with. Additionally, methods for direct fluorination and trifluoromethylation do not always allow the introduction of the CF₃-group at the required position of a molecule.

It is worth mentioning that most of the reported methods for synthesis of CF₃-containing pyrazoles suffer from formation of mixtures of regioisomers. Pavlik *et al.* studied the reactivity of CF₃-enones towards *N*-substituted hydrazines where a mixture of regioisomers was obtained. Also, in the reaction of β -alkoxy substituted enones with *N*-methyl hydrazine two isomeric dihydropyrazoles were obtained [10,11]. Singh *et al.* investigated the reactivity of 3-(ethoxymethylene)1,1,1-trifluoropentan-2,4-dione

* Correspondence: chem_org@hotmail.com

¹Chemistry Department, Faculty of Science, King Abdulaziz University, North Jeddah, P.O box 80203, Jeddah 21589, Saudi Arabia

Full list of author information is available at the end of the article

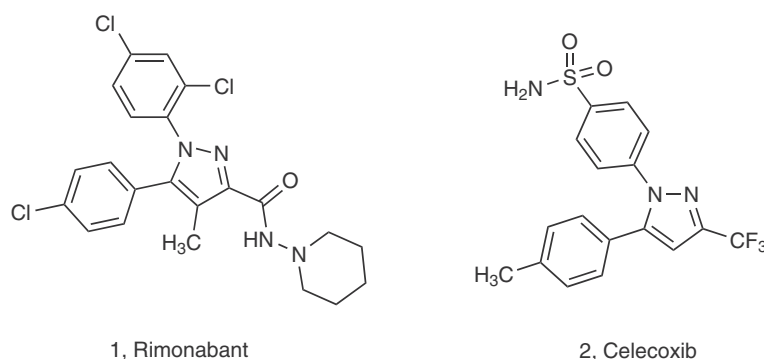


Figure 1 Examples of pharmaceutically relevant pyrazoles.

with various aryl and heteroaryl substituted hydrazines, and a mixture of pyrazoles formed [12].

Nenajdenko *et al.* obtained CF_3 -containing pyrazoles with 100% regioselectivity from the reaction of α -bromoethoxy-trifluoromethyl enone with aryl hydrazine, but with lower yield [13].

As a result the more flexible “synthon” approach, based on the application of simple and readily available fluorine-containing compounds has gained substantial interest [14]. Nitrilimines containing a fluoro or trifluoromethyl moiety (liberated in situ from the corresponding hydrazonyl halide) are easily available compounds which can be prepared by various methods [15] and fairly convenient building blocks to prepare heterocyclic compounds containing a trifluoromethyl group.

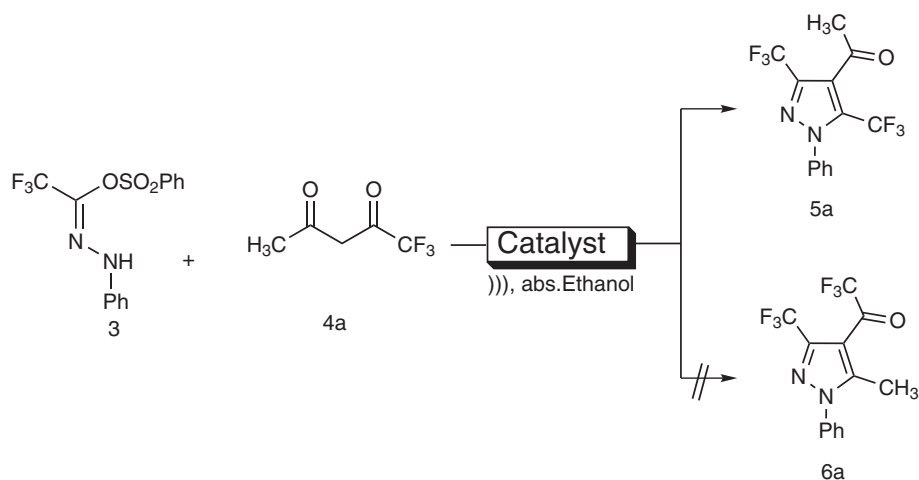
It is evident from the recent literature that copper triflate [$\text{Cu}(\text{OTf})_2$] has invoked enormous interest as a green and potential Lewis acid catalyst to construct carbon–carbon and carbon–heteroatom bonds in various organic transformations [16–23]. Despite its great importance, only a few papers have reported on its catalytic application in organic synthesis [24].

Ultrasound irradiation has been utilized to accelerate a number of synthetically useful reactions during the last few years. Cavitation is the formation, growth and collapse of bubbles in an irradiated liquid. This effect induces very high local pressure and temperatures inside the bubbles and enhances mass transfer and turbulent flow in the liquid [25]. Ultrasound has been utilized to accelerate a number of synthetically useful reactions, especially in heterocyclic chemistry [26–36].

As part of our ongoing interest in sonochemistry [37–42], and in a continuation of our interest in the synthesis of a wide range of heterocyclic systems for biological screening programme in our laboratory [43–51], we will introduce here a novel and efficient regioselective synthesis of trifluoromethyl containing pyrazoles under ultrasonic irradiation promoted by catalytic amount of copper triflate and triethylamine.

Results and discussion

A wide variety of catalysts were scanned for the reaction of *N*-phenyltrifluoromethylcarbohydrazonyl benzenesulfonate (**3**) and 1,1,1-trifluoropentane-2,4-dione (**4a**) (Scheme 1)



Scheme 1 Regioselective synthesis of pyrazole derivative 5a using various catalysts under ultrasonic irradiation.

in ethanol under ultrasound irradiation as a model reaction (Table 1). These catalysts are sodium ethoxide, triethylamine, copper triflate, copper triflate/triethyl amine, which were selected to promote the mentioned reaction.

Absolute ethanol was selected as solvent due to the solubility of the two starting materials. Thin layer chromatography (TLC) used to follow the reaction progress.

It is clear from the results cited in Table 1, that only one isolable unique product was obtained (as examined by TLC). The best yield of 90% of the isolated product was reached using $\text{Cu}(\text{OTf})_2$ and Et_3N , each of 0.05 equiv. (entry 7). The reaction gave relatively low yield when 0.05 or 0.1 equiv. of Et_3N alone was used (entry 3,4). Furthermore, sodium ethoxide base gave a trace amount of product (entry 2) and no reaction was observed in the absence of catalyst or using $\text{Cu}(\text{OTf})_2$ as catalyst in 5 or 10 mol% (entry 1,5,6 respectively). Also from Table 1, the effect of loading (Mol%) on the yield of isolated product was studied, and it is clear that 0.05:0.05 equiv. of $\text{Cu}(\text{OTf})_2$ and Et_3N furnishes the respective product in a quantitative yield (Table 1, entry 7,8).

It is worth mentioning that we followed the above reaction to completion using GC-MS and the resulting products were identified from their retention times. It was found that 100% regioselectivity was attained in presence of $\text{Cu}(\text{OTf})_2$ with Et_3N (Table 1, entry 7 and 8) but in the presence Et_3N only (Table 1, entry 3 and 4) there was a very small amount (traces) of other product detected by GC-MS, which completely disappeared in recrystallization of the crude product to give only pure **5a**.

The isolated product was identified as the pyrazole structure **5a**, although two regioisomeric cycloadducts **5a** and **6a** seemed possible (Scheme 1). Unambiguous structure determination of the obtained products is therefore crucial to rationalize the observed regioselectivity. Structure elucidation was conveniently achieved on the basis of the ^1H - ^{13}C connectivities (gHMBC) showed by methyl protons towards the carbonyl group and C-4 of pyrazole. On this basis, the analysis of gHMBC spectra of

the product led us to attribute the signal at δ 191.65 ppm to the quaternary carbon (carbonyl group) owing to its correlation peaks with the methyl protons at δ 2.65 ppm; also, the signal at δ 112.11 ppm to the C-4 of the pyrazole owing to its correlation peaks with the methyl protons at δ 2.65 ppm. This observation indicated that the methyl protons correlate to carbonyl functional group and the C-4 of the pyrazole, which is in accordance to the structure **5a** (Figure 2). Therefore, ^1H - ^{13}C HMBC of the product formed provides sharp evidence for the existence of regioisomer **5a** and rules out the other alternative structure **6a**. Consequently the reaction product was identified as the pyrazole structure **5a** (Scheme 1).

The formation of pyrazole product **5a** is in line with the well established earlier studies for β -diketones containing highly fluorinated groups, in which the enolic content predominates, as in Figure 3 [52-54].

It is reasonable to propose a mechanism for formation of the pyrazole **5a** under the adopted reaction conditions (Scheme 2). Pyrazole **5a** was assumed to form *via* nitrile imine **7** (liberated *in situ* from **3** by the action of triethylamine and release triethyl ammonium salt) which involved a more or less concerted cycloaddition reaction. In the $\text{Cu}(\text{OTf})_2$ -catalyzed addition reactions it reacts with the enolized form of β -diketone **4a_{II}** to generate copper(II) intermediate **8** and release of triflic acid (TfOH). The nitrile imine **7** reacts with intermediate **8** to give non isolable intermediate 5-hydroxy-2-pyrazoline

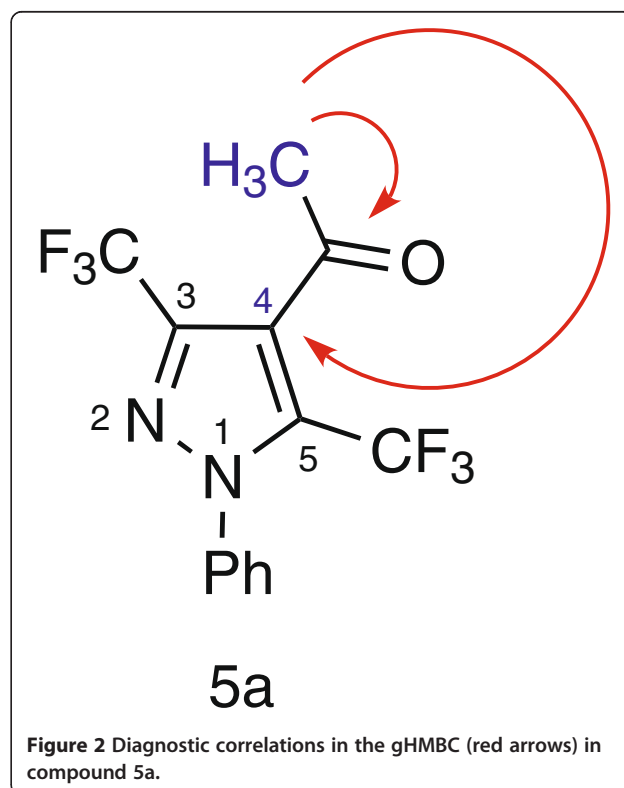
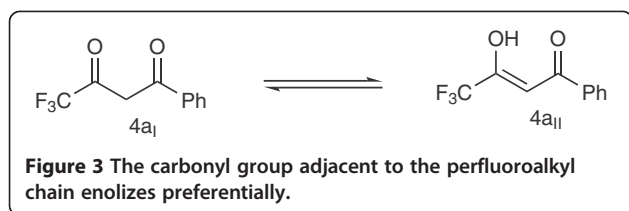


Table 1 The yield of pyrazole derivative **5a** obtained using various catalysts under ultrasonic irradiation

Entry	Catalyst	Loading (mol%)	Time (min.)	Yields (%)
1	None	-	180	No reaction
2	EtONa	100	60	Traces
3	Et_3N	5	45	73
4	Et_3N	10	45	67
5	$\text{Cu}(\text{OTf})_2$	5	60	No reaction
6	$\text{Cu}(\text{OTf})_2$	10	60	No reaction
7	$\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$	5:5	45	90
8	$\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$	10:5	60	90



derivative **9**, and cyclizes *via* elimination of molecule of water to yield the desired regioselective pyrazole derivatives **5a**.

Therefore, copper(II)triflate has an important role in which it activates the enolic O-H bond of β -diketone to initiate the reaction.

The scope and generality of this protocol was tested using another derivative of β -diketone **4b** with *N*-phenyltrifluoromethylcarbo-hydrazoneoyl benzenesulfonate (**3**) as shown in the Scheme 3 under the optimized reaction conditions, and the corresponding pyrazole derivatives **5b** were obtained in excellent yield.

Also, to find the specific effect of ultrasound on these reactions, all previously mentioned reactions were carried out under the same conditions in the absence of ultrasound irradiation (Table 2). It was observed that the reaction time increased considerably and the yield of the products decreased. Thus, ultrasound was found to have a beneficial effect on the synthesis of pyrazole derivatives, in which the time of the above reactions decreased from 8 to 10 h in the conventional procedure to less than 1 h. Also, there was an improvement in the yields of the reactions under ultrasonic irradiations.

We extended our study to find out the reactivity of β -diketone **4a,b** towards the α -keto-hydrazoneoyl halides **10a-f** under ultrasonic irradiation and/or conventional

method to give the corresponding pyrazole derivatives **11a-l** in 85–91% yields (Scheme 4, Table 3).

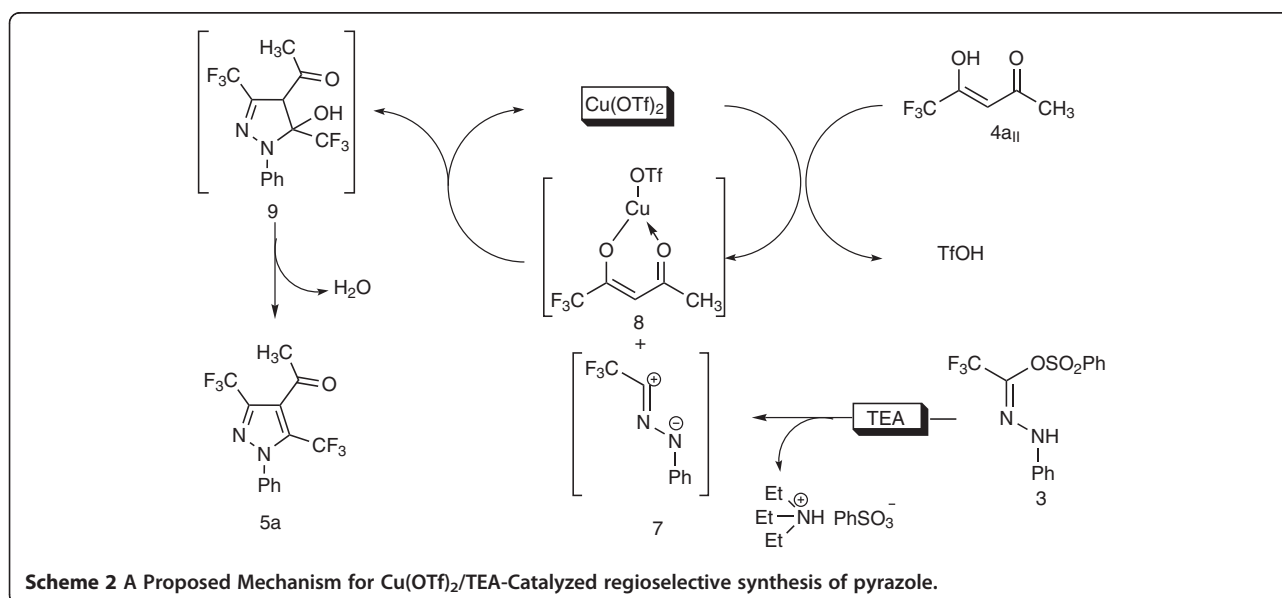
The structure of pyrazole derivatives **11a-l** was assigned on the basis of their elemental analyses and spectral data. For example, the ^1H NMR spectrum of compound **11a** revealed two singlet signals at δ 2.29 and 2.74 due to the two methyl groups in addition to aromatic multiplet at δ 7.31–7.71. The mass spectrum of the same compound revealed a peak corresponding to its molecular ion at m/z 296. The mechanism of the formation of compounds **11a-l** is in line with those depicted in Scheme 2.

From the data cited in Table 3, it was observed that the reaction time increased considerably and the yield of the products decreased under conventional method. Thus, ultrasound was found to have beneficial effect on the synthesis of pyrazole derivatives in which decrease time of above reactions from 7 to 11 h in conventional procedure to 45 min. to 1 h. Also, there was a noticeable improvement in the yields of the reactions under ultrasonic irradiations.

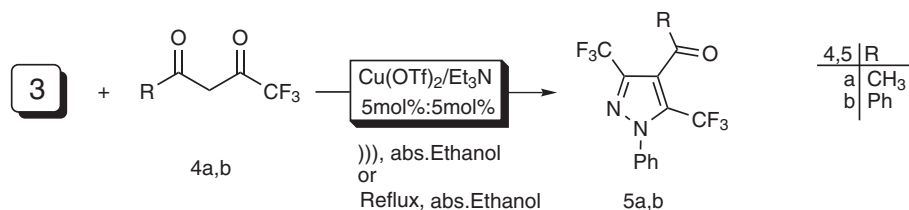
The improvement induced by ultrasound in the above mentioned reactions can be attributed to the well established theory for the cavitation, The collapse of bubbles caused by cavitation produces intense local heating and high pressures [55,56], so reaction time decreases clearly and high% yield was obtained.

Conclusion

An ultrasonic assisted efficient protocol for the regioselective synthesis a series of novel pyrazoles containing the trifluoromethyl moiety utilizing an efficient catalytic system $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ was reported. $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ catalyst showed a great advantage over all the investigated catalysts



Scheme 2 A Proposed Mechanism for $\text{Cu}(\text{OTf})_2/\text{TEA}$ -Catalyzed regioselective synthesis of pyrazole.



Scheme 3 Regioselective synthesis of pyrazole derivatives **5a,b** using $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ catalyst under both ultrasonic irradiation and conventional method.

and ultrasonic irradiation method offered high yields of pyrazoles in short reaction times compared with classical conditions. gHMBC spectra of the product were used to rationalize the observed regioselectivity.

Experimental

General

All organic solvents were purchased from commercial sources and used as received unless otherwise stated. All chemicals were purchased from Merck, Aldrich or Acros and used without further purification, thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. All melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded in IR spectra were recorded in the Smart iTR which is an ultra-high-performance, versatile Attenuated

Total Reflectance (ATR) sampling accessory on The Nicolet iS10 FT-IR spectrometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^1H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethyl sulphoxide ($\text{DMSO}-d_6$). Chemical shifts were related to that of the solvent. Assignments are made using ^1H , ^{13}C , gHMBC, 2D experiments was done using standard Varian methods.

Mass spectra were recorded on the Thermo ISQ Single Quadrupole GC-MS. The resulting products were identified from their retention times by GC-MS analysis. Elemental analyses were carried out on EuroVector instrument C, H, N, S analyzer EA3000 Series. Sonication was performed by Techno-gaz sonicator (with a frequency of 37 kHz and ultrasonic peak max. 320 W).

N-phenyltrifluoromethylcarbohydrazonoyl benzenesulfonate (**3**) [15], α -keto hydrazonoyl halides **10a-f** [57] were prepared according to the reported literature.

Table 2 The yields of pyrazole derivatives **5a,b** using $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ catalyst under conventional and ultrasonic irradiations conditions

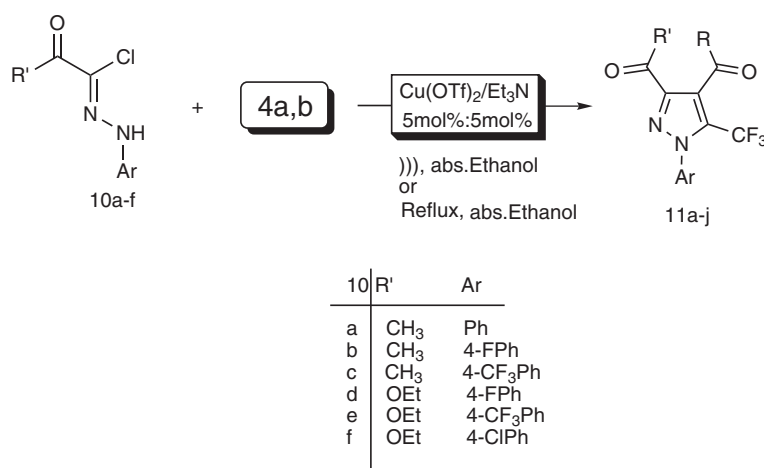
Entry	Product	Ultrasonic irradiation		Silent condition	
		Time (min.)	Yield %	Time (h)	Yield %
1	<p style="text-align: center;">5a</p>	45	90	6	80
2	<p style="text-align: center;">5b</p>	45	88	8	78

General procedure and characterization data

Typical procedure for synthesis of pyrazole derivatives **5a,b** and **11a-j**.

Sonicated reactions

In an Erlenmeyer flask, a mixture of β -diketone (**4a,b**) (1 mmol) and appropriate hydrazonoyl benzenesulfonate (**3**) and/or hydrazonoyl halides (**10a-e**) (1 mmol) (**3**) was taken in absolute ethanol (30 ml) in the presence of $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ (5:5 mol%) as catalyst then subjected to ultrasonic irradiations for appropriate time (*cf.* Tables 1, 2,3). All The reactions were kept at 70–80°C (the temperature inside reaction vessel was 70–76°C and the reaction flask was put in the mid of sonicator bath to to achieve effective cavitations). The sonochemical reactions were continued until the starting materials were no longer detectable by TLC. After the completion of the reaction, EtOAc (30 mL) was added to dilute the reaction solution. Then, the mixture was washed with water. The combined organic phases were dried and concentrated in *vacuo*, and the remaining residue was purified by recrystallization from ethanol to afford pyrazole derivatives



Scheme 4 Regioselective synthesis of pyrazole derivatives 11a-l using $\text{Cu}(\text{OTf})_2/\text{Et}_3\text{N}$ catalyst under both ultrasonic irradiation and conventional method.

5a,b and **11a-j**. The above reaction was studied also by using various condition and catalysts.

(i) in absence of catalyst: this process was performed as described above and no product formed (ii) in presence of equivalent amount from sodium methoxide, this process was performed as described above and only a trace of product obtained identified as **5a** (*cf.* Table 1) (iii) in presence of different ratio of triethylamine (0.05 mmol) or (0.1 mmol) also, these processes were performed as described above and the progress of the reaction was monitored by TLC, the product formed was identified as **5a** in each case (*cf.* Table 1) in different percent yield, (iv) in presence of different ratio of copper (II) triflate (0.05 mmol) or (0.1 mmol) also, these processes were performed as described above and no product formed.

Silent reactions

These processes were performed on the same scale described above for sonicated reaction. Here the reactant and catalyst were put in ethanol under reflux for suitable time (*cf.* Tables 2 and 3) until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in sonicated reaction.

Physical and spectral data of the compounds **5a,b** and **11a-j** are listed below

4.2.2.1. 4-Acetyl-3,5-di(trifluoromethyl)-1-phenylpyrazole (**5a**) [58]

M.p. = 211–213°C; IR (KBr): 1712 (C = O), 1611 (C = N) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ : 2.65 (s, 3H, CH₃), 6.52–7.23 (m, 5H, ArH's); ^{13}C NMR (75.46 MHz, CDCl_3) δ : 31.42, 112.11, 118.00, 119.58, 123.89, 126.24, 129.30, 136.87, 139.00, 154.62, 191.65. MS (m/z): 322 (M^+).

(Calc.: C, 48.46; H, 2.50; N, 8.69. $\text{C}_{13}\text{H}_8\text{F}_6\text{N}_2\text{O}$ Found: C, 48.72; H, 2.38; N,8.55).

4-Benzoyl-3,5-di(trifluoromethyl)-1-phenylpyrazole (**5b**)

M.p. = 227–228°C; IR (KBr): 1708 (C = O), 1601 (C = N) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ : 7.22–7.69 (m, 10H, ArH's); ^{13}C NMR (75.46 MHz, CDCl_3) δ : 116.05, 119.18, 121.94, 125.54, 126.33, 128.52, 128.53, 129.14, 130.25, 136.89, 139.34, 139.74, 152.87, 193.16. MS (m/z): 384 (M^+). (Calc.: C, 56.26; H, 2.62; N, 7.29. $\text{C}_{18}\text{H}_{10}\text{F}_6\text{N}_2\text{O}$ Found: C, 56.50; H, 2.52; N,7.15).

3,4-Diacetyl-1-phenyl-5-trifluoromethylpyrazole (**11a**)

M.p. = 192–194°C; IR (KBr): 1712, 1699 (2 C = O), 1594 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ : 2.29 (s, 3H, CH₃), 2.74 (s, 3H, CH₃), 7.31–7.71 (m, 5H, ArH's); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ : 29.15, 31.54, 115.15, 122.01, 125.53, 125.54, 127.41, 129.14, 131.06, 139.98, 150.98, 196.24, 199.09. MS (m/z): 296 (M^+). (Calc.: C, 56.76; H, 3.74; N, 9.46. $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_2$ Found: C, 56.50; H, 2.52; N,7.15).

3-Acetyl-4-benzoyl-1-phenyl-5-trifluoromethylpyrazole (**11b**)

M.p. = 213–214°C; IR (KBr): 1710, 1701 (2 C = O), 1599 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ : 2.24 (s, 3H, CH₃), 7.16–7.67 (m, 10H, ArH's); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ : 28.98, 115.24, 120.07, 124.13, 126.22, 128.11, 128.12, 129.85, 133.54, 139.47, 152.00, 194.01, 198.19. MS (m/z): 358 (M^+). (Calc.: C, 63.69; H, 3.66; N, 7.82. $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2$ Found: C, 63.96; H, 3.14; N,7.67).

3,4-Diacetyl-1-(4-fluorophenyl)-5-trifluoromethylpyrazole (**11c**)

M.p. = 175–177°C; IR (KBr): 1711, 1697 (2 C = O), 1601 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ : 2.31 (s, 3H, CH₃), 2.59 (s, 3H, CH₃), 7.24 (d, 2H, $J = 8.4$ Hz,

Table 3 Synthesis of pyrazole 11a–l under both ultrasonic irradiation and conventional method

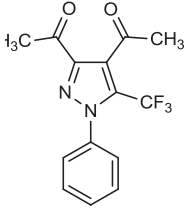
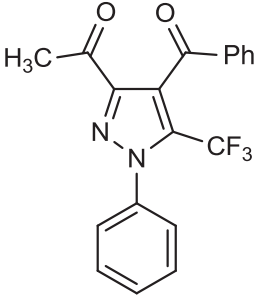
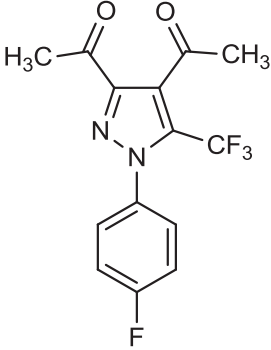
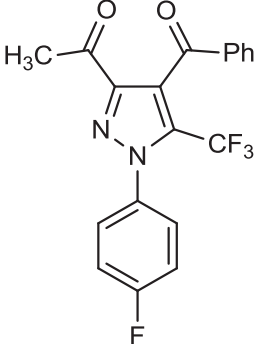
Compound no.	Product	Ultrasonic irradiation		Silent condition	
		Time (min.)	Yield%	Time (h)	Yield%
11a		45	90	7	80
11b		45	88	7	76
11c		45	90	6	77
11d		45	88	8	75

Table 3 Synthesis of pyrazole 11a–l under both ultrasonic irradiation and conventional method (Continued)

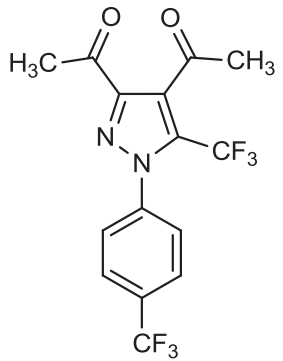
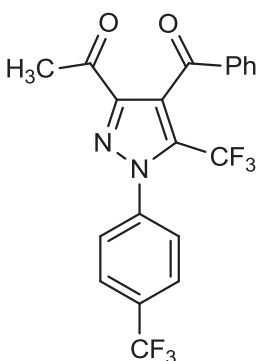
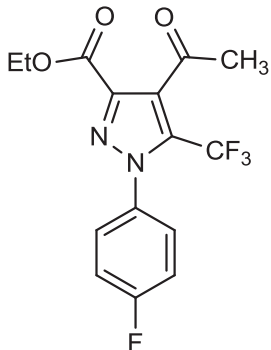
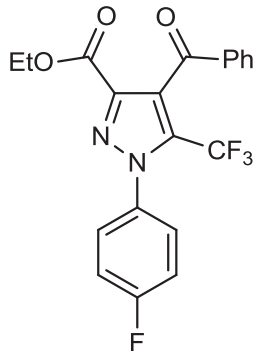
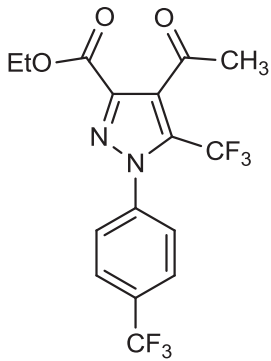
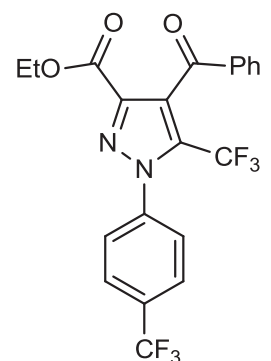
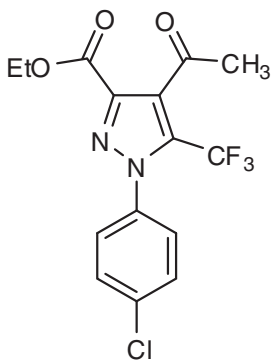
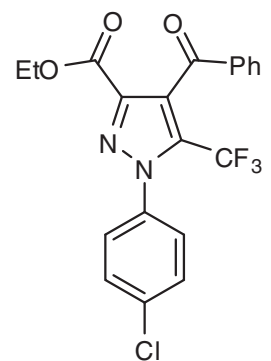
11e		45	88	10	76
11f		45	85	10	76
11g		60	89	10	76
11h		60	90	10	77

Table 3 Synthesis of pyrazole 11a–l under both ultrasonic irradiation and conventional method (Continued)

11i		60	85	11	73
11j		60	85	11	77
11k		60	86	9	75
11l		60	90	10	77

ArH's), 7.55 (d, 2H, $J = 8.4$ Hz, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 26.94, 31.20, 113.54, 115.23, 119.08, 123.94, 132.15, 137.65, 152.89, 162.41, 195.00, 198.23. MS (m/z): 314 (M^+). (Calc.: C, 53.51; H, 3.21; N, 8.91. $\text{C}_{14}\text{H}_{10}\text{F}_4\text{N}_2\text{O}_2$ Found: C, 53.78; H, 3.10; N, 8.75).

3-Acetyl-4-benzoyl-1-(4-fluorophenyl)-5-trifluoromethylpyrazole (11d)

M.p. = 201–203°C; IR (KBr): 1719, 1701 (2 C = O), 1603 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 2.28 (s, 3H, CH_3), 7.21–7.84 (m, 9H, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 27.98, 112.03, 115.87, 119.26, 125.44, 128.31, 132.05, 135.16, 136.49, 149.97, 162.00, 191.24, 196.20. MS (m/z): 376 (M^+). (Calc.: C, 60.64; H, 3.21; N, 7.44. $\text{C}_{19}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_2$ Found: C, 60.95; H, 3.07; N, 7.27).

3,4-Diacetyl-1-(4-trifluoromethylphenyl)-5-trifluoromethylpyrazole (11e)

M.p. = 194–196°C; IR (KBr): 1707, 1697 (2 C = O), 1600 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 2.26 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.44 (d, 2H, $J = 8.1$ Hz, ArH's), 7.67 (d, 2H, $J = 8.1$ Hz, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 29.91, 32.42, 117.21, 123.94, 124.36, 124.85, 126.03, 129.54, 138.03, 143.11, 151.98, 192.10, 196.85. MS (m/z): 364 (M^+). (Calc.: C, 49.46; H, 2.77; N, 7.69. $\text{C}_{15}\text{H}_{10}\text{F}_6\text{N}_2\text{O}_2$ Found: C, 49.75; H, 2.63; N, 7.54).

3-Acetyl-4-benzoyl-1-(4-trifluoromethylphenyl)-5-trifluoromethylpyrazole (11f)

M.p. = 210°C; IR (KBr): 1706, 1699 (2 C = O), 1598 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 2.26 (s, 3H, CH_3), 7.42–7.85 (m, 9H, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 27.58, 113.13, 119.26, 121.35, 124.08, 125.65, 127.11, 128.45, 129.69, 132.45, 134.00, 135.04, 143.01, 149.19, 190.98, 196.01. MS (m/z): 426 (M^+). (Calc.: C, 56.35; H, 2.84; N, 6.57. $\text{C}_{20}\text{H}_{12}\text{F}_6\text{N}_2\text{O}_2$ Found: C, 56.68; H, 2.71; N, 6.37).

Ethyl 4-acetyl-1-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11g)

M.p. = 180–182°C; IR (KBr): 1723, 1699 (2 C = O), 1598 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 1.29 (t, 3H, $J = 7.2$ Hz, CH_3), 2.23 (s, 3H, CH_3), 4.01 (q, 2H, $J = 7.2$ Hz, CH_2), 7.28 (d, 2H, $J = 8.4$ Hz, ArH's), 7.65 (d, 2H, $J = 8.4$ Hz, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.11, 29.18, 58.11, 113.26, 119.01, 125.36, 132.58, 136.00, 148.39, 160.07, 162.37, 192.10. MS (m/z): 344 (M^+). (Calc.: C, 52.33; H, 3.51; N, 8.14. $\text{C}_{15}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_3$ Found: C, 52.61; H, 3.38; N, 7.99).

Ethyl 4-benzoyl-1-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11h)

M.p. = 212°C; IR (KBr): 1725, 1701 (2 C = O), 1598 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 0.91 (t, 3H,

$J = 7.6$ Hz CH_3), 4.23 (q, 2H, $J = 7.6$ Hz, CH_2), 7.21–7.78 (m, 9H, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.26, 58.25, 112.31, 115.25, 118.01, 119.27, 125.87, 128.97, 131.98, 132.68, 134.85, 137.50, 148.05, 159.98, 163.00, 194.28. MS (m/z): 406 (M^+). (Calc.: C, 59.12; H, 3.47; N, 6.89. $\text{C}_{20}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_3$ Found: C, 59.39; H, 3.34; N, 6.75).

Ethyl 4-acetyl-1-(4-trifluoromethylphenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11i)

M.p. = 192–194°C; IR (KBr): 1721, 1699 (2 C = O), 1599 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 0.89 (t, 3H, $J = 7.2$ Hz, CH_3), 2.29 (s, 3H, CH_3), 4.00 (q, 2H, $J = 7.2$ Hz, CH_2), 7.67 (d, 2H, $J = 7.8$ Hz, ArH's), 7.89 (d, 2H, $J = 7.8$ Hz, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.56, 28.88, 59.58, 116.48, 121.33, 123.58, 125.47, 126.05, 127.89, 132.11, 141.05, 146.36, 159.87, 192.01. MS (m/z): 394 (M^+). (Calc.: C, 48.74; H, 3.07; N, 7.11. $\text{C}_{16}\text{H}_{12}\text{F}_6\text{N}_2\text{O}_3$ Found: C, 49.05; H, 2.94; N, 6.93).

Ethyl 4-benzoyl-1-(4-trifluoromethylphenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11j)

M.p. = 207–208°C; IR (KBr): 1722, 1701 (2 C = O), 1602 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 1.16 (t, 3H, $J = 7.2$ Hz CH_3), 3.91 (q, 2H, $J = 7.2$ Hz, CH_2), 7.51–7.88 (m, 9H, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.98, 59.04, 114.52, 118.12, 121.54, 121.55, 125.87, 126.02, 128.11, 128.95, 132.05, 132.97, 134.23, 142.31, 148.00, 162.45, 196.10. MS (m/z): 456 (M^+). (Calc.: C, 55.27; H, 3.09; N, 6.14. $\text{C}_{21}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_3$ Found: C, 55.58; H, 2.95; N, 5.97).

Ethyl 4-acetyl-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11k)

M.p. = 227–229°C; IR (KBr): 1725, 1705 (2 C = O), 1602 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 1.19 (t, 3H, $J = 7.00$ Hz, CH_3), 2.21 (s, 3H, CH_3), 3.95 (q, 2H, $J = 7.00$ Hz, CH_2), 7.60 (d, 2H, $J = 7.8$ Hz, ArH's), 7.52 (d, 2H, $J = 7.8$ Hz, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.52, 28.06, 58.56, 115.18, 121.33, 125.18, 127.51, 132.55, 133.00, 146.15, 159.11, 190.00. MS (m/z): 360 (M^+). (Calc.: C, 49.95; H, 3.35; N, 7.77. $\text{C}_{15}\text{H}_{12}\text{ClF}_3\text{N}_2\text{O}_3$ Found: C, 50.21; H, 3.27; N, 7.59).

Ethyl 4-benzoyl-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (11l)

M.p. = 250–251°C; IR (KBr): 1723, 1703 (2 C = O), 1602 (C = N) cm^{-1} ; ^1H NMR (300 MHz, DMSO- d_6) δ : 0.95 (t, 3H, $J = 7.2$ Hz CH_3), 3.99 (q, 2H, $J = 7.2$ Hz, CH_2), 7.62–7.95 (m, 9H, ArH's); ^{13}C NMR (75.46 MHz, DMSO- d_6) δ : 13.90, 59.22, 114.00, 117.45, 121.17, 126.89, 128.12, 128.57, 132.00, 133.09, 133.89, 139.11, 147.52, 159.47, 192.13. MS (m/z): 422 (M^+). (Calc.: C, 56.82; H, 3.34; N, 6.63. $\text{C}_{20}\text{H}_{14}\text{ClF}_3\text{N}_2\text{O}_3$ Found: C, 57.03; H, 3.28; N, 6.48).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The current study is the outcome of constructive discussions between ASA and TSS, ASA and TSS carry out the synthesis and characterization experiments. HMA carried out the GC-MS analysis and ASA and TSS carried out the ¹H NMR, ¹³C NMR and 2D NMR. ASA and TSS carried out the elemental analyses. ASA and TSS, were involved in revising the manuscript. All authors have read and approve of the final manuscript.

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Author details

¹Chemistry Department, Faculty of Science, King Abdulaziz University, North Jeddah, P.O box 80203, Jeddah 21589, Saudi Arabia. ²Green Chemistry Department, National Research Centre, Dokki, Cairo 12622, Egypt.

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