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Short Communication

Resourceful synthesis of pyrazolo[1,5-*a*]pyrimidines under ultrasound irradiation

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ABSTRACT

Pyrazolo[1,5-*a*]pyrimidines were synthesized via the ultrasonic sonochemical method using the cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [$CF_3C(O)CH=C(R)(OMe)$ – where R = Me, Bu, *i*-Bu, Ph, 4-Me–C_6H_4, 4-F–C_6H_4, 4-Cl–C_6H_4, 4-Br–C_6H_4, naphth-2-yl and biphen-4-yl] – with 3-amino-5-methyl-1*H*-pyrazole in the presence of EtOH for 5 min. This methodology has several advantages, for example, it is a simple procedure, it has an easy work-up, mild conditions, short reaction times (5 min) and produces satisfactory yields (61–98%).

1. Introduction

Ultrasound irradiation has emerged as a powerful technique for the promotion of organic reactions. The advantages of using cavitation (the creation, growth, and collapse of micrometer-sized bubbles that are formed when an acoustic pressure wave propagates through a liquid) as an energy source to promote organic reactions include shorter reaction times and higher yields when compared with conventional thermal heating methods (oil bath) [1–3]. Consequently, ultrasound irradiation has been used to accelerate a number of synthetically useful reactions, especially in heterocyclic compounds such as pyrazoles [4], pyrazolo[3,4-*b*]pyridinones [5], thiazolidinones [6], 1,2,4-oxadiazoles [7], and triazoles [8].

Pyrazolo[1,5-*a*]pyrimidines are of considerable chemical and pharmacological importance, since they have shown COX-2 selective inhibition [9] and KDR kinase inhibition [10]. More recently, pyrazolo[1,5-*a*]pyrimidine was described as the first class of allosteric agonists for the nicotinic acid receptor GPR109A [11,12]. Also, the number of patents for pyrazolo[1,5-*a*]pyrimidines with pharmacological activity has increased drastically [13,14].

In the last 20 years, we have developed a general synthesis of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and shown their usefulness in heterocyclic preparations [15–17]. In these papers, we have supported the importance of these halogen-containing building blocks in the heterocyclic synthesis. Additionally, we have devoted our attention to improving yields, reducing reaction time, and minimizing waste generation by using ionic liquid [18,19], solvent-free [20,21], microwave [18,20,21], and ultrasound irradiation [4,7,22] to promote the reactions. Thus, in the continuation of our work, and considering the importance of pyrazolo[1,5-*a*]pyrimidine as well as the limited cases of pyrazolo[1,5-*a*]pyrimidine trifluoromethyl [23–25] described in the literature, the aim of this study was to present the synthesis of 7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines under ultrasonic irradiation and compare the results with those from conventional thermal heating and the microwave method.

2. Experimental

2.1. Materials

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The reactions in US were carried out with a tapered microtip probe (6.5 mm) connected to a 500 W Sonics Vibra-cell ultrasonic processor equipped with an integrated probe temperature control. The device operates at 20 kHz of frequency and the amplitude was set to 20% of the maximum power output. Reactions in MW were performed using a CEM Discover (300 W) microwave mono mode for synthesis with fiber optic temperature sensor controlled by Synergis Version 3.5.9 software. The irradiation power was established at a maximum level of 200 W, the internal vessel pressure at a maximum level of 250 psi. ^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) and Bruker DPX-200 (^1H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$/TMS solutions at 298 K, with chemical shifts (δ) given in ppm. Mass spectra were registered in a HP

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5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, cross-linked 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 using a Microquímica MQAPF 301.

2.2. Synthesis of enones

Enones **1a–j** were obtained from the acylation reaction of enol ether or acetal with trifluoroacetic anhydride, in accordance with the methodology developed in our laboratory [26–28].

2.3. Synthesis of pyrazolo[1,5-a]pyrimidines under ultrasonic sonochemistry

Enone **1a–j** (1 mmol), 3-amino-5-methyl-1*H*-pyrazole **2** (1.2 mmol), and EtOH (10 mL) were placed in a 25 mL beaker. The reaction mixtures were then sonicated by a 6 mm ultrasonic probe with amplitude of 20%, using a programmed temperature of 75 °C. The reaction temperature was raised 68–72 °C during 5 min of sonication. After cooling to room temperature, 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 organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish the products **3a–j**.

2.4. Synthesis of pyrazolo[1,5-a]pyrimidines under microwave irradiation

Enone **1a**,**c**,**d**,**f**,**i** (1 mmol), 3-amino-5-methyl-1*H*-pyrazole **2** (1.2 mmol), and EtOH (5 mL) were placed in a vessel (10 mL) equipped with a standard cap (the vessel was supplied by CEM corporation). The reaction mixtures were irradiated at 75 °C for 5 min. The data were then plotted using Synergy software (version 3.5.9), applying an irradiation level of 200 W and internal vessel pressure of 250 psi. Subsequently, 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 organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish the products **3a**,**c**,**d**,**f**,**i**.

2.5. Synthesis of pyrazolo[1,5-a]pyrimidines using conventional thermal heating method (oil bath)

Enone **1a**,**c**,**d**,**f**,**i** (1 mmol), 3-amino-5-methyl-1*H*-pyrazole **2** (1.2 mmol), and EtOH (5 mL) were placed in a round-bottomed flask. The reaction mixtures were kept under magnetic stirring at 75 °C for 2 h. Subsequently, 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 organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish the products **3a**,**c**,**d**,**f**,**i**.

7-Trifluoromethyl-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (**3a**): Oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3H, H8), 2.64 (s, 3H, H9), 6.50 (s, 1H, H3), 6.96 (s, 1H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 24.7 (C9), 96.5 (C3), 105.9 (q, ^{3}J4, C6), 119.4 (q, ^{1}J274, CF_3), 133.1 (q, ^{2}J37, C7), 150.0 (C3a), 156.3 (C2), 157.7 (C5). MS (EI, 70 eV): *m*/*z* % = 215 (M^+, 100), 187 (15), 162 (39), 146 (17).

5-Butyl-7-trifluoromethyl-2-methylpyrazolo[1,5-*a*]pyrimidine (**3b**): Oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, 3H, H12), 1.44 (sext, 2H, H11), 1.78 (qui, 2H, H10), 2.56 (s, 3H, H8), 2.87 (t, 2H, H9), 6.53 (s, 1H, H3), 6.96 (s, 1H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (C12), 14.5 (CH_3), 22.2 (C11), 30.6 (C10), 38.0 (C9), 96.5 (C3), 105.2 (q, ^{3}J4, C6), 119.4 (q, ^{1}J274, CF_3), 132.7 (q, ^{2}J37, C7), 150.0 (C3a), 156.2 (C2), 161.5 (C5). MS (EI, 70 eV): *m*/*z* % = 257 (M^+, 18), 238 (4), 215 (100).

7-Trifluoromethyl-2-methyl-5-(1-methylpropil)pyrazolo[1,5-*a*]pyrimidine (**3c**): m.p. 43–46 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (d, 6H, H11, H11′), 2.19 (sext, 1H, H10), 2.55 (s, 3H, H8), 2.72 (d, 2H, H9), 6.52 (s, 1H, H3), 6.92 (s, 1H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 22.4 (C11, C11′), 28.8 (C10), 47.5 (C9), 96.7 (C3), 105.8 (q, ^{3}J4, C6), 119.6 (q, ^{1}J273, CF_3), 133.1 (q, ^{2}J36, C7), 150.1 (C3a), 156.4 (C2), 160.9 (C5). MS (EI, 70 eV): *m*/*z* % = 257 (M^+, 19), 242 (42), 215 (100).

7-Trifluoromethyl-2-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (**3d**): m.p. 123–124 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3H, H8), 6.65 (s, 1H, H3), 7.52 (s, 1H, H6), 7.52 (s, 3H, H Ar), 8.06–8.08 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 97.7 (C3), 102.6 (q, ^{3}J4, C6), 127.1, 129.0, 130.8, 136.3 (C–Ar), 119.5 (q, ^{1}J274, CF_3), 133.5 (q, ^{2}J37, C7), 150.3 (C3a), 154.9 (C2), 156.9 (C5). MS (EI, 70 eV): *m*/*z* % = 277 (M^+, 100), 256 (35), 224 (15), 128 (13).

7-Trifluoromethyl-2-methyl-5-(4-methylphenyl)-pyrazolo[1,5-*a*]pyrimidine (**3e**): m.p. 142–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3H, 4-CH_3–Ar), 2.57 (s, 3H, H8), 6.60 (s, 1H, H3), 7.29 (d, 2H, Ar), 7.46 (s, 1H, H6), 7.94 (d, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 21.3 (CH_3), 97.4 (C3), 102.4 (q, ^{3}J4, C6), 127.0, 129.7, 133.5, 141.3 (C–Ar), 119.6 (q, ^{1}J274, CF_3), 133.4 (q, ^{2}J37, C7), 150.3 (C3a), 154.9 (C2), 156.7 (C5). MS (EI, 70 eV): *m*/*z* % = 291 (M^+, 100), 276 (11), 256 (13).

7-Trifluoromethyl-5-(4-fluorophenyl)-2-methylpyrazolo[1,5-*a*]pyrimidine (**3f**): m.p. 141–144 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3H, H8), 6.63 (s, 1H, H3), 7.21 (dd, 2H, Ar), 7.47 (s, 1H, H6), 8.09 (dd, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 97.8 (C3), 102.3 (q, ^{3}J4, C6), 116.2 (d, ^{2}J21, Ar), 119.6 (q, ^{1}J274, CF_3), 129.3 (d, ^{3}J8, Ar), 132.6 (d, ^{4}J3, Ar), 133.4 (q, ^{2}J36, C7), 150.3 (C3a), 153.9 (C2), 157.1 (C5), 164.6 (d, ^{1}J251, Ar). MS (EI, 70 eV): *m*/*z* % = 295 (M^+, 100), 274 (13), 242 (6).

5-(4-Chlorophenyl)-7-trifluoromethyl-2-methylpyrazolo[1,5-*a*]pyrimidine (**3g**): m.p. 164–166 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3H, H8), 6.64 (s, 1H, H3), 7.47 (s, 1H, H6), 7.50 (d, 2H, Ar), 8.03 (d, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 97.9 (C3), 102.2 (q, ^{3}J4, C6), 119.5 (q, ^{1}J273, CF_3), 128.4, 129.3, 134.7, 137.2 (CAr), 134.4 (q, ^{2}J36, C7), 150.2 (C3a), 153.6 (C2), 157.2 (C5). MS (EI, 70 eV): *m*/*z* % = 311 (M^+, 100), 290 (5), 162 (7).

5-(4-Bromophenyl)-7-trifluoromethyl-2-methylpyrazolo[1,5-*a*]pyrimidine (**3h**): m.p. 171–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3H, H8), 6.66 (s, 1H, H3), 7.49 (s, 1H, H6), 7.67 (d, 2H, Ar), 7.98 (d, 2H Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 97.9 (C3), 102.2 (q, ^{3}J4, C6), 119.5 (q, ^{1}J274, CF_3), 125.7, 128.6, 132.3, 135.2 (C–Ar), 133.8 (q, ^{2}J37, C7), 150.3 (C3a), 153.7 (C2), 157.2 (C5). MS (EI, 70 eV): *m*/*z* % = 355 (M^+, 100), 336 (5), 255 (12).

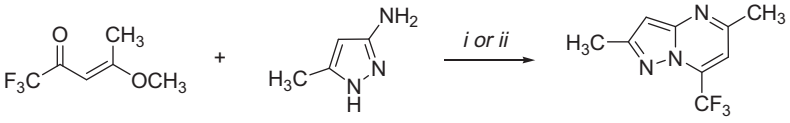
7-Trifluoromethyl-2-methyl-5-(naphth-2-yl)-pyrazolo[1,5-*a*]pyrimidine (**3i**): m.p. 152–154 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3H, H8), 6.67 (s, 1H, H3), 7.53–8.50 (m, 7H, Ph), 7.65 (s, 1H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 97.8 (C3), 102.7 (q, ^{3}J4, C6), 119.7 (q, ^{1}J274, CF_3), 123.8, 126.8, 127.4, 127.6, 127.7, 128.9, 129.0, 133.1, 133.6, 134.4 (C–Ar), 133.6 (q, ^{2}J37, C7), 150.4 (C3a), 154.8 (C2), 157.0 (C5). MS (EI, 70 eV): *m*/*z* % = 327 (M^+, 100), 305 (6), 258 (1), 163 (5).

7-Trifluoromethyl-2-methyl-5-(biphen-4-yl)pyrazolo[1,5-*a*]pyrimidine (**3j**): m.p. 192–195 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3H, CH_3), 6.65 (s, 1H, H3), 7.39–8.18 (m, 9H, HAr), 7.55 (s, 1H, H6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_3), 97.7 (C3), 102.5 (q, ^{3}J4, C6), 119.6 (q, ^{1}J274, CF_3), 127.1, 127.5, 127.6, 128.0, 128.9, 135.1, 139.9, 143.6 (C–Ar), 133.6 (q, ^{2}J37, C7), 150.4 (C3a), 154.5 (C2), 157.0 (C5). MS (EI, 70 eV): *m*/*z* % = 353 (M^+, 100), 332 (4), 276 (2), 176 (6).

3. Results and discussion

The study of reaction conditions to furnish the pyrazolo[1,5-*a*]pyrimidine **3a** using ultrasound irradiation is shown in Scheme 1. All the reactions were performed with enone **1a** and 3-amino-5-methyl-1*H*-pyrazole **2** at a molar ratio of 1:1.2. We had previously developed a conventional thermal heating method using AcOH for a similar reaction [25]. Thus, we initially performed the reaction in AcOH as the solvent at 75 °C for 10 min under ultrasound irradiation and we observed the formation of product **3a** at a 62% yield which was considered unsatisfactory. From this negative result, we decided to use ethanol as the solvent. Generally, cyclocondensation reactions performed in the presence of ethanol are good and ethanol is an environmentally friendly solvent [4]. The progression of the reactions was monitored by CG–MS to obtain a conversion of 100% and a yield of isolated product of 82% after analysis by ^{1}H NMR. The reaction in ethanol resulted in the product with an excellent yield. Thus, it can clearly be seen that the best condition was achieved when using ethanol as the solvent at 75 °C for 5 min.

In order to evaluate the scope and limitations of this reaction, we extended it to other enones **1b–j**. All the reactions were performed in EtOH using reactants **1** with **2** at a molar ratio of 1:1.2 and employing ultrasound irradiation for 5 min at 75 °C. The pyrazolo[1,5-*a*]pyrimidines **3a–j** were obtained at 61–98% yields (Scheme 2). Products **3a–e**,**g**,**j** were isolated in a pure form without needing further purification. Product **3i** was purified by recrystallization in EtOH and $CHCl_3$ at a ratio of 1.5:1.0, respectively; and products **3f**,**g** were recrystallized in EtOH and DMSO at a ratio of 1.5:1.0, respectively. All products were fully characterized with ^{1}H and ^{13}C NMR and GC–MS and showed spectral data typical for these compounds. For example, compound **3h** presented ^{1}H NMR spectra with chemical shifts at 6.67 ppm that were assigned to the pyrazole H3, a signal at 7.65 ppm that was assigned to the pyrimidine H6, a signal at 2.60 ppm that was assigned to the CH_3 and a signal at 7.53–8.50 ppm assigned to the aromatic ring. The same compound showed ^{13}C NMR spectra with chemical shifts at the C3, C3a and C5 at 97.8, 150.4 and 157.0, respectively. The ^{13}C NMR signal of C6, C7 and CF_3 group appeared at 102.7, 119.7 and

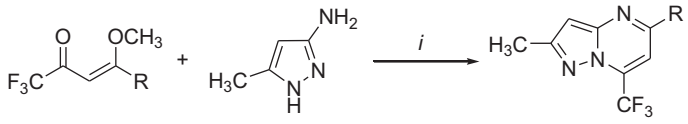


1a **2** **3a**

i = US, AcOH, 10 min (62 %)

ii = US, EtOH, 5 min (82 %)

Scheme 1.



1a-j **2** **3a-j**

i = US, EtOH, 5 min

Entry	R	Product	Yield (%)[a]
1	Me	**3a**	82
2	Bu	**3b**	61
3	*i*-Bu	**3c**	77
4	Ph	**3d**	82
5	4-Me-C_6H_4	**3e**	98
7	4-F-C_6H_4	**3f**	96
8	4-Cl-C_6H_4	**3g**	79
9	4-Br-C_6H_4	**3h**	76
10	Naphth-2-yl	**3i**	89
11	Biphen-4-yl	**3j**	92

[a]Yield of isolated product.

Scheme 2.

Table 1
Comparative study for synthesis of pyrazolo[1,5-*a*]pyrimidines **3a**,**c**,**d**,**f**,**i**.

Entry	R	Product	Ultrasound[a]	Oil Bath[b]	Microwave[c]
			Yield (%)[d]	Yield (%)[d]	Yield (%)[d]
1	Me	**3a**	82	87	87
2	*i*-Bu	**3c**	77	83	84
3	Ph	**3d**	82	52	80
4	4-F–C_6H_4	**3f**	96	51	81
5	Naphth-2-yl	**3i**	89	73	93

[a] Conditions: ultrasound, EtOH, 5 min.
[b] Conditions: EtOH, 75 °C, 2 h.
[c] Conditions: MW, EtOH, 5 min.
[d] Yield of isolated product.

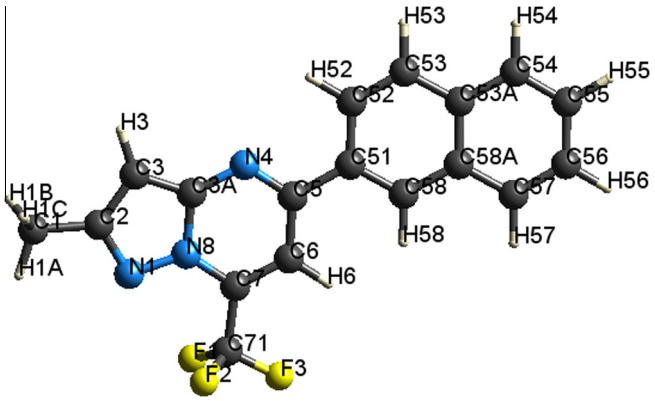


Fig. 1. Structure [34] of 7-trifluoromethyl-2-methyl-5-(naphth-2-yl)-pyrazolo[1,5-*a*]pyrimidine (**3i**).

Table 2
Crystal data and structural refinement for 7-trifluoromethyl-2-methyl-5-(naphth-2-yl)-pyrazolo[1,5-*a*]pyrimidine (**3i**).

CCDC No.	914143
Formula	$C_{18}H_{12}F_3N_3$
Mr	327.31
Temperature (K)	296 (2)
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, P21/n
Unit cell parameters	
a (Å)	7.8462 (5)
b (Å)	11.2089 (9)
c (Å)	16.8641 (12)
α (°)	90
β (°)	92.389 (5)
γ (°)	90
V (Å^3)	1481.86 (18)
Z	4
Density (calculated) (mg/m^3)	1.467
Absorption coefficient (mm^{-1})	0.115
F(000)	672
Crystal size (mm)	0.42 × 0.08 × 0.08
θ Range for data collection (°)	2.18–30.08
Limiting indices	$-10 \leqslant h \leqslant 10$, $-15 \leqslant k \leqslant 15$, $-23 \leqslant l \leqslant 23$
Reflections collected/unique	23,457/4299 [*R*(int) = 0.0735]
Completeness to θ = 30.08 (%)	98.8
Absorption correction	Gaussian
Max. and min. transmission	0.9908 and 0.9531
Refinement method	Full-matrix least-square on F^2
Data/restraints/parameters	4299/0/217
Goodness-of-fit on F^2	0.954
Final *R* indices [$I > 2\delta(I)$]	R_1 = 0.0535, wR_2 = 0.1099
R indices (all data)	R_1 = 0.1910, wR_2 = 0.1521
Extinction coefficient	None
Largest diff. peak and hole (e A^{-3})	0.200 and −0.161

133.6 ppm as a quartet with J = 4, 274 and 37 Hz respectively, because of a ^{13}C–^{19}F scalar coupling.

The synthesis of pyrazolo[1,5-*a*]pyrimidines shown here is very important, because the synthesis and spectral data of these compounds are not well represented in the literature. Only the synthesis of compounds **3d,e,h** has been described [29].

Additionally, to highlight even more the importance of ultrasound for promoting pyrazolo[1,5-*a*]pyrimidine synthesis, the reaction of enones **1a**,**c**,**d**,**f**,**i** (1.0 equivalent) with 3-amine-5-methyl-1*H*-pyrazole **2** (1.2 equivalent) was performed under conventional thermal heating (oil bath) in EtOH at 75 °C for 2 h. The products were obtained at 51–87% yields (Table 1). These yields are similar to or lower than those obtained under ultrasonic irradiation. For the enones **1d**,**f**,**i**, which have Ph, 4-F–C_6H_4 and naphth-2-yl attached, the yields were higher when using ultrasound irradiation. Moreover, the reaction time using ultrasound irradiation was shorter and yields were better than for conventional thermal heating (oil bath).

The reaction of enones **1a**,**c**,**d**,**f**,**i** (1.0 equivalent) with 3-amine-5-methyl-1*H*-pyrazole **2** (1.2 equivalent) was also performed under microwave irradiation, using EtOH as the solvent at 75 °C for 5 min, resulting in the products at 80–93% yield (Table 1). The yields are similar to those obtained under ultrasonic irradiation. From these results it can be seen that there was no appreciable increase in yield; the effect of microwaves on the synthesis of pyrazolo[1,5-*a*]pyrimidines is as efficient as ultrasound, and both are better than the conventional thermal heating (oil bath). Thus, the ultrasonic irradiation method offers advantages including faster reaction rates and satisfactory yields for obtaining pyrazolo[1,5-*a*]pyrimidines. Accordingly, these results demonstrate that alternative energies are favorable for the synthesis of these trifluoromethylated compounds.

The ultrasound effect in this reaction probably is physics [30,31], in other words, the ultrasonic cavitation process, which is formation, growth, and collapse of microscale bubbles in a liquid solution increase the local temperatures and pressures inside the cavities ('hot spots') [30,31]. In the process, ultrasonic irradiation accelerates the formation of the stable colloidal particles, thus it can shorten the reaction time. The formation of any chemical specie able to accelerate the reaction during ultrasound irradiation was not monitored in this reaction. Thus, is not possible affirm that chemical effects is occurring [30,31].

The mechanism proposed for the formation of the compounds of **3** was described in previous work [25,32]. It initially involves a C–N bond formation from the attack of the nitrogen atom of the NH_2 group on the β-carbon of enone **1**, with subsequent substitution of the alkoxy group to furnish the enamino ketone intermediates. Subsequently, there was an intramolecular nucleophilic addition of the pyrazole ring nitrogen atom to the carbonyl carbon of enone **1**, with subsequent elimination of one molecule of water. The X-ray structure of compound **3i** (Fig. 1) confirms the structure proposed. The crystal data and details concerning data collection and structural refinement are given in Table 2 [33].

4. Conclusion

In summary, we have developed an effective methodology for the synthesis of pyrazolo[1,5-*a*]pyrimidines under ultrasound irradiation. The methodology has several advantages which make it highly attractive, for example, it is a simple procedure, it has an easy work-up, mild conditions, short reaction times (5 min) and produces excellent yields (61–98%). Furthermore, this series may provide new classes of biologically active compounds.

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