Straightforward Microwave-Assisted Synthesis of 1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles under Solvent-Free Conditions

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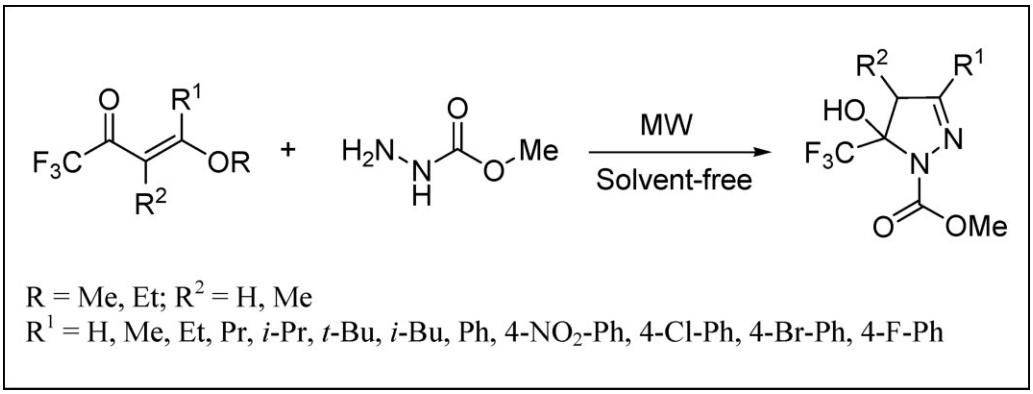

An efficient microwave-assisted synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles from the cyclocondensation reaction between enones [$CF_3C(O)C(R^2) = C(R^1)(OR)$, where R^2 = H, Me; R^1 = H, Me, Et, Pr, *i*-Pr, *t*-Bu, *i*-Bu, Ph, 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-Ph and R = Me, Et] and methyl hydrazinocarboxylate under solvent-free conditions is reported. This process is an efficient alternative to the traditional thermal heating and furnishes the heterocyclic compounds in good to excellent yields in a short reaction time. To show the versatility of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles, dehydration reactions of these compounds are also demonstrated.

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INTRODUCTION

In recent years, the progress in the field of solvent-free reactions has gained significance because of the high efficiency, operational simplicity and environmentally benign processes. The use of microwave energy to heat chemical reactions on a laboratory scale is growing at a rapid rate. In many instances, controlled microwave heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions when compared to conventional synthetic methods [1,2]. The advantages of this useful technology have more recently also been exploited in the context of multistep total synthesis [3] and medicinal chemistry/drug discovery [4] and have additionally penetrated other important fields [5–8]. The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale [9]. In this context, the use of microwave-assisted organic synthesis (MAOS) has emerged as an alternative and efficient tool, especially in heterocyclic synthesis [10]. 4,5-Dihydropyrazoles are important nitrogen-containing five-membered heterocyclic compounds, with an extensive application in the agrochemical [11] and pharmaceutical fields [12–15]. 4,5-Dihydropyrazoles are quite stable, and have inspired chemists to utilize this fragment in bioactive moieties to synthesize new compounds possessing biological activities. In addition, the presence of fluorine at strategic positions in the molecules can alter the course of the reaction as well as the biological properties of the product [16]. Several 4,5-dihydropyrazoles have played a crucial role in the development of theoretical studies in heterocyclic chemistry and are also extensively used building blocks in organic chemistry [11]. The introduction of halogens and halogenated groups into organic molecules often confers significant and useful changes in their chemical and physical properties.

Therefore, methods for the synthesis of halogenated compounds have received considerable interest in recent years, in particular, fluorinated compounds [17a,b]. The presence of a trifluoromethyl group into cyclic compounds especially at a strategic position of drug molecules has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine [17c]. The steric requirement of the fluorine atom resembles that of hydrogen (Van der Waals radii: CF_3 = 1.35 Å versus CH_3 = 1.29 Å). Thus substitution of a methyl by a trifluoromethyl group in a drug candidate usually allows the trifluoromethylated analog to be comparable in size and follow similar drug-protein interactions of parent methyl compound. However, the strong covalent bonding of C—F bond (116 kcal mol^{-1}) versus that of the C—H bond (100 kcal mol^{-1}) [17d] can often avoid unwanted metabolic transformations. The high electronegativity of fluorine enables a trifluoromethyl group to decrease the electron density and the basicity or enhance the electrophilicity of the neighboring functional groups within a molecule. In many systems, the substitution of the methyl group by a trifluoromethyl group results in added lipophilicity (π_{CF3} = 1.07 versus π_{CH3} = 0.50) [17e], which may lead to easier absorption and transportation of the molecules within biological systems and thereby improve the overall pharmacokinetic properties of drug candidates.

General methods for the preparation of these compounds involve reactions of hydrazine derivatives with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones [18], β-alkoxyvinyl trifluoromethyl ketones [19], β-trifluoromethyl enaminones [20], and others [21–25]. 1,3-Dipolar cycloaddition reactions of diazoalkanes or nitrilimines with olefins or alkynes have also been carried out, but this procedure has been little used in pyrazole synthesis because 1,3-dipoles are often difficult to prepare and are potentially explosive [26]. In recent years, we have developed a general synthesis of 1,1,1-trihalo-4-methoxy-3-alken-2-ones [27], important halogen-containing building blocks, and shown their usefulness in heterocyclic preparations, such as isoxazoles, pyrazoles, pyrrolidinones, pyrimidines, pyridines, thiazines, and diazepines [27]. Our research group is continuously interested in a more environmentally benign synthesis, which can be demonstrated by our recent articles that focus on solvent-free synthesis [28] and the use of ionic liquids as reaction media [29], associated to efficient techniques such as microwave [30] and ultrasound irradiation [31]. In our sustained interest on the study of heterocyclic synthesis, herein, we wish to report a mild and efficient microwave-assisted method for the preparation of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles and their derivatives, 5-trifluoromethylpyrazoles, under solvent-free conditions.

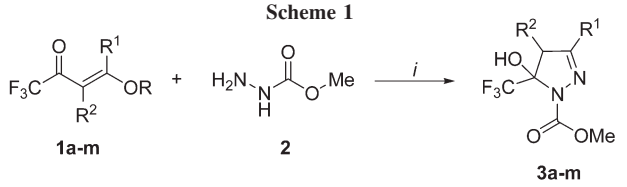
RESULTS AND DISCUSSION

The enones **1a–m** were obtained from the acylation reaction of enol ether or acetal with trifluoroacetic anhydride in accordance with the methodology developed in our laboratory [27]. Methyl hydrazinocarboxylate **2** was obtained commercially.

The synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles **3a–m** was performed in a microwave equipment specially designed for organic synthesis. The reaction was carried out under solvent-free conditions by the mixture of enones **1a–m** with methyl hydrazinocarboxylate **2**, in a molar ratio of 1:1.25, respectively, under solvent-free conditions in a range of time between 6 and 8 min and at temperatures indicated in Scheme 1. Under these reaction conditions, the products 4,5-dihydro-1*H*-pyrazoles **3a–m** were obtained in good to high yields and in short reaction times (Scheme 1).

The scope of this microwave-assisted method developed for 4,5-dihydropyrazoles was demonstrated by using enones with various substituents (R^1). The results obtained show that the presence of a substituent R^1 in the 4-position of the enone **1** influenced the reaction conditions. Enones containing 4-alkyl and 4-aryl substituents were more reactive and presented shorter reaction times, while the non-substituted enone **1a** (R^1 = H) required a longer reaction time. This behavior can be explained by the inductive and hyperconjugative/mesomeric effects of the alkyl and aryl substituents, which make the C-β of the enone more

Scheme 1



i: Solvent-free, MW

Reactant[a]	R	R^2	R^1	Product	*T* (°C)	Time (min)	Yield (%)[b]
1a	Et	H	H	**3a**	100	8	78
1b	Me	H	Me	**3b**	100	6	90
1c	Me	H	Et	**3c**	100	6	92
1d	Me	H	Pr	**3d**	100	6	89
1e	Me	H	*i*-Pr	**3e**	100	6	90
1f	Me	H	*t*-Bu	**3f**	100	6	80
1g	Me	H	*i*-Bu	**3g**	100	6	87
1h	Me	H	Ph	**3h**	50	6	82
1i	Me	H	4-NO_2-Ph	**3i**	50	6	73
1j	Me	H	4-Cl-Ph	**3j**	50	6	90
1k	Me	H	4-Br-Ph	**3k**	50	6	85
1l	Me	H	4-F-Ph	**3l**	50	6	80
1m	Et	Me	H	**3m**	100	6	50

[a] Molar ratio of reactants **1**:**2** was of 1:1.25.
[b] Yields of isolated products.

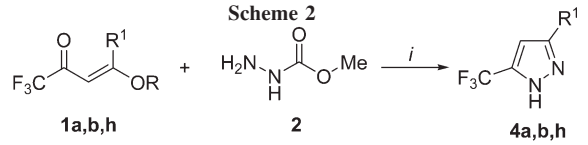
reactive. It is also possible to note that aryl substituted enones (**1h–l**) furnished the products at lower temperatures.

Although the 4,5-dihydropyrazoles **3b,m** have been reported in the literature, their synthesis and spectral characterization have not yet been reported. 4,5-Dihydropyrazoles **3** showed sets of ^{1}H and ^{13}C NMR data that correspond to the proposed structures. Compounds **3** showed ^{1}H NMR chemical shifts of the diastereotopic methylene protons (H-4a and H-4b) as a characteristic AB-system and as a doublet at the range of 3.10–3.74 ppm, respectively, with a geminal coupling constant at the range of ^{2}J 18–20 Hz. Previous studies have demonstrated that the doublet in the low field is correspondent to the hydrogen ''cis'' in relation to the hydroxyl group [32]. The same compounds showed ^{13}C NMR spectra with typical chemical shifts of 4,5-dihydropyrazole rings at the ranges of 144.3–153.9 (C-3), 38.5–45.6 (C-4), 89.3–92.0 (C-5), 122.5–124.3 (CF_3).

The efficiency of this synthetic route was more apparent when the same reaction was performed using conventional thermal heating. Under these conditions of heating, the addition of a solvent was necessary. Ethanol was the solvent chosen due to its polarity and environmental properties that make it a good solvent for cyclocondensation reactions. The reaction of enone **1m** with methyl hydrazinocarboxylate **2** was performed in a molar ratio of 1:1.25, respectively. After 20 h, at room temperature the product **3m** was isolated in moderate yield (70%).

Many studies have shown that the presence of the trifluoromethyl group in 4,5-dihydro-1*H*-pyrazoles is one of the important factors involved in their stability [27]. Thus, it is extremely important to investigate the possibility of dehydrating 4,5-dihydropyrazoles to obtain the aromatic 1-carboxymethyl-pyrazoles. In a strategy to obtain the dehydrated products using microwave irradiation, the reaction of enones **1** with methyl hydrazinocarboxylate **2** was carried out in a molar ratio of 1:1.2 under solvent-free conditions at 200°C. However, the 1-carboxy-5-trifluoromethylpyrazole was not obtained, and the formation of 5-dehydropyrazoles **4a,b,h** was observed, as a result of dehydration with simultaneous loss of the carboxylate group (Scheme 2). Product **4h** was obtained after only 12 min of irradiation at 200°C, demonstrating that the dehydration reaction under MW conditions was sensitive to the substituent effect, and that the phenyl substituent stabilized the products 1-carboxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles.

Scheme 2



1a,b,h **2** **4a,b,h**

i: Solvent-free, MW

Enone	R	R^1	*T* (°C)	Time (min)	Product[a]	Yield[b] (%)
1[a]	Et	H	200	8	**4a**	74
1b	Me	Me	200	6	**4b**	94
1h	Me	Ph	200	12	**4h**	80

[a] Molar ratio of reactants **1**:**2** was 1:1.2.
[b] Yield of isolated products.

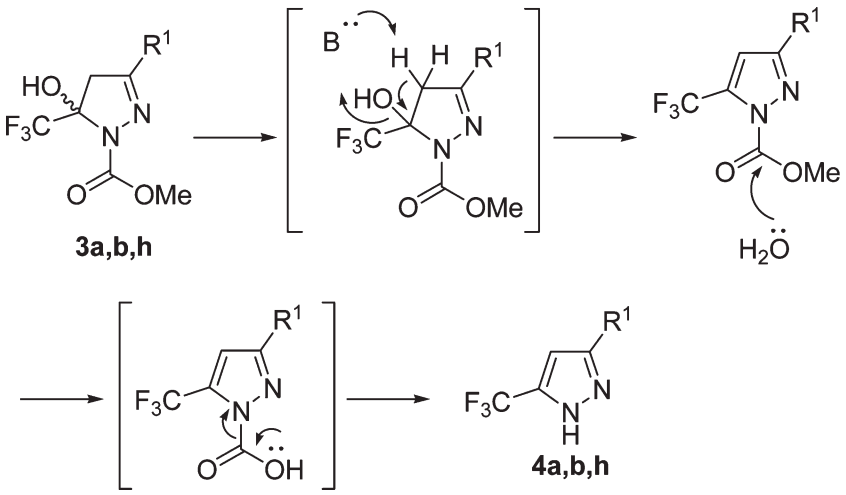
This failure to obtain dehydrated 5-trifluoromethyl-1*H*-pyrazole was a surprise, considering that in previous studies [33], we obtained similar trihalomethylated 4,5-dihydropyrazoles containing a strong electron-withdrawing group attached to the N1-atom, where it was possible to eliminate a water molecule and to obtain the aromatic pyrazole without the loss of the N1-group, by stirring the reaction mixture in ethanol, for 24 hours, at 45°C, followed by reflux in the presence of sulfuric acid for 4 hours. However, we also observed that some 4,5-dihydropyrazoles with an electron-withdrawing group attached to the N1-atom underwent dehydration when heated, with the simultaneous loss of the methyl carboxylate group leading to the formation of 5-trifluoromethylpyrazole [34]. Scheme 3 shows the mechanistic pathway for the formation of products **4a,b,h** [35]. Firstly, the base removes the acid hydrogen leading to water elimination. Then, ester hydrolysis occurs by nucleophilic attack of water on the carboxyl carbon of the ester and subsequent decarboxylation, leading to NH-pyrazole formation.

In summary, we have developed a simple and fast microwave-assisted and solvent-free method to obtain both 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles and their 5-dehydropyrazoles derivatives. This method furnished the products in high to excellent yields through the employment of an environmentally benign approach.

EXPERIMENTAL

Unless otherwise indicated, all common reactants and solvents were used as obtained from commercial suppliers without further purifications. Reactions were performed using a CEM Discover (300 W) microwave mono Mode for Synthesis 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. The exact power and pressure was different for each reaction and depended on the reaction temperature, as shown in Figures 1 and 2. The reaction temperatures were constant and recorded by an infrared probe provided by the instrument manufacturer for direct monitoring of the internal temperature, as shown in Figures 1 and 2. Reactions to obtain **3a–m** were performed in simultaneous cooling mode (Power On) and with maximum stirring, while the reactions to obtain **4a,b,h** were performed in Power Off mode.

Scheme 3



^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5 ppm sample tubes at 298 K (digital resolution ± 0.01 ppm) in $CDCl_3$/TMS solutions. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked to a HP-5 capillary column (30 m 0.32 mm of internal diameter), and helium was used as the carrier gas. All melting points were determined on a Reichert Thermovar apparatus.

Conventional method typical procedure for the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles (3m). Enones **1m** (1 mmol), methyl hydrazinocarboxylate **2** (1.2 mmol) and ethanol (3 mL) were placed into a round-bottom flask equipped with a stir bar. The mixture was stirred at room temperature during 20 h. After the completion of the reaction, ethanol was removed, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The product **3m** was obtained in their pure form without further purification.

Microwave irradiation typical procedure for the synthesis of 1-carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles (3a–m). Enones **1a–m** (1 mmol) and methyl hydrazinocarboxylate **2** (1.25 mmol) were placed into a 10 mL reaction vessel equipped with a stir bar. The mixture was irradiated at 50 or 100°C (Scheme 1), the power irradiated during the reaction was in the range of 45–80 W, where the internal pressure was of 31–34 psi. The reaction was performed in simultaneous cooling mode (Power On) with high magnetic stirring, during the times and temperatures described in Scheme 1. After completion of the reaction, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The products **3a-m** were obtained in their pure form without further purification.

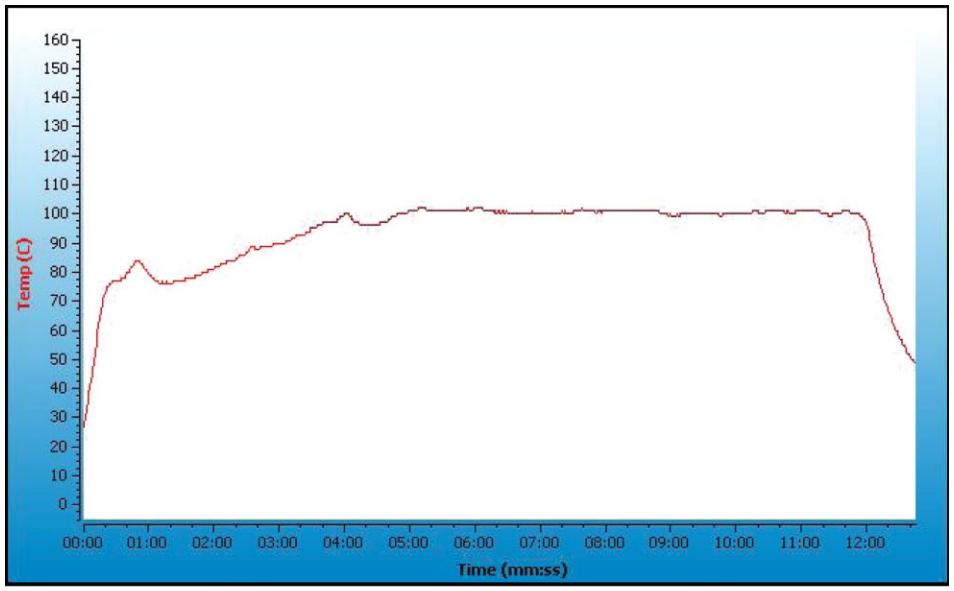
Typical procedure for the synthesis of 5-trifluoromethyl-1*H*-pyrazoles (4a,b,h). Enones **1a,b,h** (1 mmol) and methyl hydrazinocarboxylate **2** (1.2 mmol) were placed into a 10 mL reaction vessel equipped with a stir bar. The mixture was irradiated at 200°C, the power irradiated during the reaction was in the range of 25–200 W, where the internal pressure was of 54–86 psi. The reaction was performed without simultaneous cooling (Power Off) at high magnetic stirring, during the times and temperatures described in Scheme 2. After the completion of the reaction, dichloromethane (10 mL) was added and the solution was washed with water (3 × 10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The products **4a,b,h** were obtained in their pure form without further purification.

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3a). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.17 (d, 1H, ^2J = 19 Hz, H4b), 3.36 (d, 1H, ^2J = 19 Hz, H4a), 3.89 (s, 3H, OMe), 6.95 (s, 1H, H3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 44.8 (C4), 53.5 (OMe), 89.3 (q, ^2J = 33 Hz, C5), 122.85 (q, ^1J = 286 Hz, CF_3), 144.3 (C3), 153.5 (C=O). GC/MS (m/z, %) 212 (M^+, 8), 181 (5), 143 (100), 69 (25).

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazole (3b). M.p. 54-56°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.07 (t, 3H, CH_3, H9), 3.13 (d, 1H, ^2J = 19 Hz, H4b), 3.38 (d, 1H, ^2J = 19 Hz, H4a), 3.88 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 15.1 (CH_3), 44.8 (C4), 53.3 (OMe), 90.6 (q, ^2J = 34 Hz, C5), 122.9 (q, ^1J = 286 Hz, CF_3), 153.4 (C3), 153.9 (C=O). GC/MS (m/z, %) 226 (M^+, 23), 195 (5), 157 (100), 126 (5) 98 (10), 81 (18).

1-Carboxymethyl-3-ethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3c). M.p. 82–84°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.17 (t, 3H, CH_3, H10), 2.43 (q, 2H, CH_2, H9), 3.07 (d, 1H, ^2J = 19 Hz, H4b), 3.23 (d, 1H, ^2J = 19, H4a), 3.85 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.3 (CH_3), 22.9 (CH_2), 44.7 (C4), 53.4 (OMe), 90.4 (q, ^2J = 34 Hz, C5), 122.9 (q, ^1J = 286 Hz, CF_3), 153.7 (C3), 158.5 (C=O). GC/MS (m/z, %) 240 (M^+, 15), 209 (5), 171 (100), 112 (10), 95 (18).

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-propyl-4,5-dihydro-1*H*-pyrazole (3d). M.p. 49–53°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.94 (t, 3H, CH_3, H11), 1.60 (q, 2H, CH_2, H10), 2.35 (t, 2H, CH_2, H9), 3.08 (d, 1H, ^2J = 19 Hz, H4b), 3.24 (d, 1H, ^2J = 19 Hz, H4a), 3.87 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.2 (CH_3), 19.5 (CH_2),



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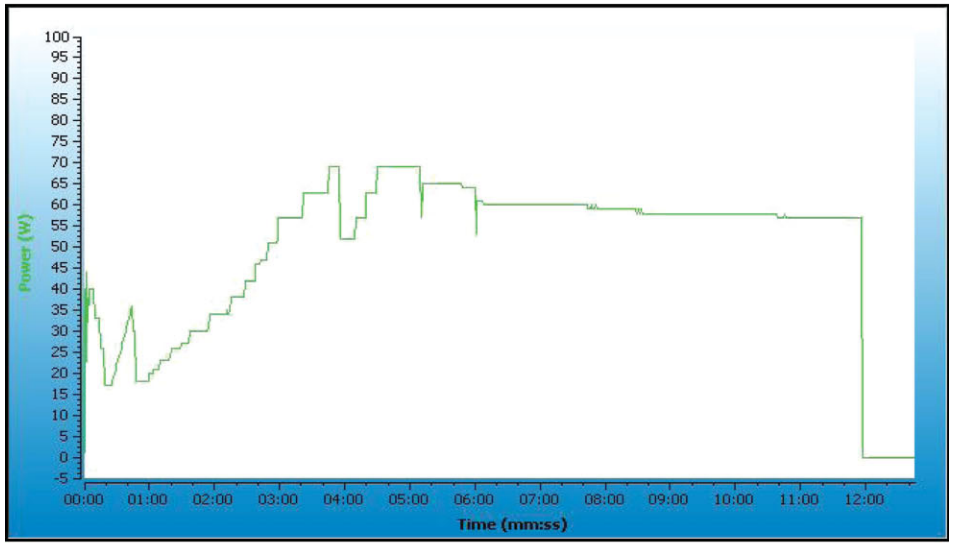

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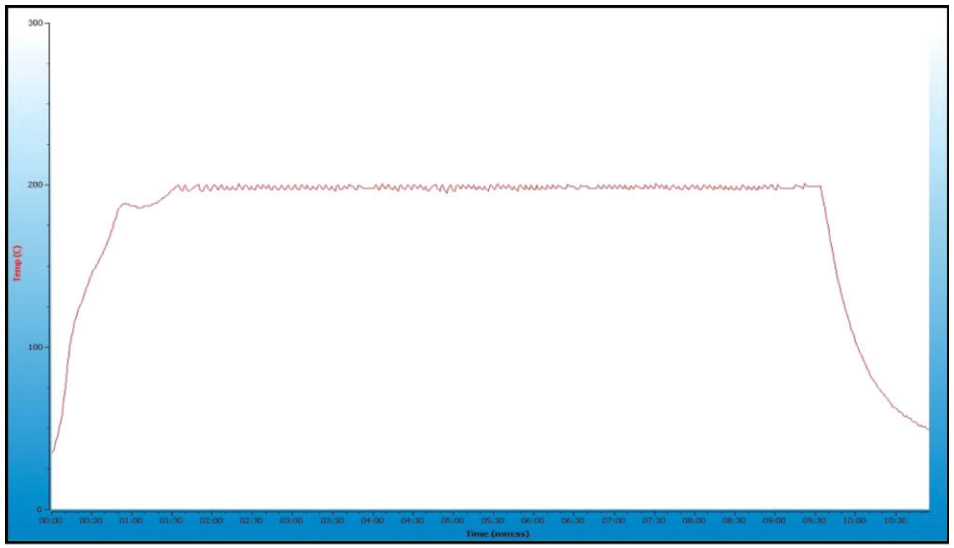
Figure 1. Range of temperature (1) and power (2) furnished by MW for obtaining compound **3a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

31.4 (CH_2), 44.9 (C4), 53.4 (OMe), 90.4 (q, ^2J = 34 Hz, C5), 122.9 (q,^1J = 286 Hz, CF_3), 153.8 (C3), 157.5 (C=O). GC/MS (m/z, %) 254 (M^+, 19), 185 (100), 153 (38), 142 (10), 125 (10).

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(1-methylethyl)-4,5-dihydro-1*H*-pyrazole (3e). M.p. 69–71°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 (s, 6H, $2CH_3$, H10), 2.76 (d, 1H, CH, H9), 3.10 (d, 1H, ^2J = 18 Hz, H4b), 3.27 (d, 1H, ^2J = 18 Hz, H4a), 3.88 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.4 (CH_3), 21.9 (CH_3), 22.3 (CH), 38.5 (C4), 53.5 (OMe), 90.4 (q, ^2J = 34 Hz, C5), 153.6 (C3), 157.0 (C=O), 123.2 (q,^1J = 286 Hz, CF_3); GC/MS (m/z, %) 254 (M^+, 30), 211 (5), 185 (100), 153 (38), 126 (8.5).

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(1,1-dimethylethyl)-4,5-dihydro-1*H*-pyrazole (3f). M.p. 97–99°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (s, 9H, $3CH_3$, H10), 3.13 (d, 1H, ^2J = 18 Hz, H4b), 3.29 (d, 1H, ^2J = 18 Hz, H4a), 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.6 (3 CH_3), 42.5 (C4), 58.0 (OMe), 90.9 (q, ^2J = 34 Hz, C5), 123.1 (q, ^1J = 286 Hz, CF_3), 153.9 (C3), 164.2 (C=O); GC/MS (m/z, %) 268 (M^+, 19), 199 (100), 167 (19), 140 (10).



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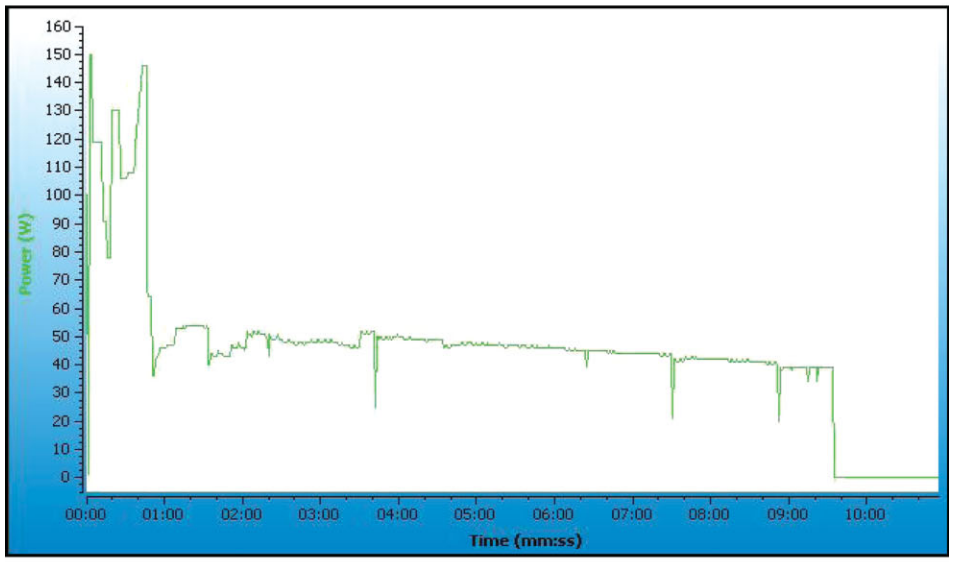

(2)

Figure 2. Range of temperature (1) and power (2) furnished by MW for obtaining compound **4a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-3-(2-methylpropyl)-4,5-dihydro-1*H*-pyrazole (3g). M.p. 41–43°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.99 (2s, 6H, $2CH_3$, H11), 1.94 (q, 1H, CH, H10), 2.30 (t, 2H, CH_2, H9), 3.12 (d, 1H, ^2J = 19 Hz, H4b), 3.28 (d, 1H, ^2J = 19 Hz, H4a), 3.91 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.1 (CH_3), 29.0 (CH_2), 28.0 (CH_2), 21.8 (CH_2), 45.06 (C4), 57.38 (OMe), 90.8 (q, ^2J = 34 Hz, C5), 122.7 (q,^1J = 286 Hz, CF_3), 153.17 (C3), 157.35 (C=O); GC/MS (m/z, %) 268 (M^+, 33), 251 (4.5), 199 (100), 167 (40).

1-Carboxymethyl-3-phenyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3h). M.p. 153–155°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.55 (d, 1H, ^2J = 18 Hz, H4a), 3.69 (d, 1H, ^2J = 18 Hz, H4b), 3.94 (s, 3H, OCH_3), 7.43–7.45 (m, 3H, H-Ar), 7.69–7.73 (m, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.3 (C4), 53.8 (OMe), 91.6 (q, ^2J = 34 Hz, C5), 123.5 (q, ^1J = 286 Hz, CF_3), 130.9, 129.7, 128.7, 126.6 (C-Ar), 152.9 (C3), 158.2 (C=O); GC/MS (m/z, %) 288 (M^+, 85), 257 (2), 229 (2), 219 (100).

1-Carboxymethyl-3-(4-nitrophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3i). M.p. 180–182°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.59 (d, 1H, ^2J = 18 Hz, H4b), 3.74 (d, 1H, ^2J = 18 Hz, H4a), 3.97 (s, 3H, OCH_3), 8.20–8.31 (m, 4H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.1 (C4), 54.1 (OMe), 92.0 (q, ^2J = 34 Hz, C5), 122.85 (q, ^1J = 286 Hz, CF_3), 150.5, 135.7, 127.5, 124.0 (C-

Ar), 148.9 (C3), 153.7 (C=O); GC/MS (m/z, %) 333 (M^+, 28), 316 (1), 274 (1), 264 (100).

1-Carboxymethyl-3-(4-chlorophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3j). M.p. 107–109°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.61 (d, 1H, ^2J = 19 Hz, H4a), 3.66 (d, 1H, ^2J = 19 Hz, H4b), 3.94 (s, 3H, OCH_3), 7.40 (d, 2H, H-Ar), 7.69 (d, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.2 (C4), 55.9 (OMe), 91.4 (q, ^2J = 34 Hz, C5), 124.3 (q, ^1J = 286 Hz, CF_3), 137.1, 129.1, 128.4, 127.6 (C-Ar), 151.8 (C3), 153.9 (C=O); GC/MS (m/z, %) 323 ($M^+ + H^+$, 30), 322 (90), 253 (100), 209 (70), 137 (60).

1-Carboxymethyl-3-(4-bromophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3k). M.p. 148–151°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.51 (d, 1H, ^2J = 18 Hz, H4a), 3.65 (d, 1H, ^2J = 18 Hz, H4b), 3.94 (s, 3H, OCH_3), 7.56 (s, 4H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.1 (C4), 53.8 (OMe), 90.4 (q, ^2J = 32 Hz, C5), 122.9 (q, ^1J = 287 Hz, CF_3), 132.1, 128.8, 128.1, 125.5 (C-Ar), 151.8 (C3), 153.8 (C=O); GC/MS (m/z, %) 367 (M^+, 82), 297 (100), 280 (1).

1-Carboxymethyl-3-(4-fluorophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (3l). M.p. 145–147°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.52 (d, 1H, ^2J = 18 Hz, H4a), 3.66 (d, 1H, ^2J = 18 Hz, H4b), 3.94 (s, 3H, OCH_3), 7.11 (d, 2H, H-Ar), 7.72 (d, 2H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 43.3 (C4), 53.8 (OCH_3), 91.3 (q, ^2J = 34 Hz, C5), 122.5 (q,^1J = 286 Hz, CF_3), 165.6, 163.1, 128.8, 115.9 (C-Ar), 151.8 (C3), 153.9 (C=O); GC/MS (m/z, %) 306 (M^+, 75), 237 (100), 218 (6).

1-Carboxymethyl-5-trifluoromethyl-5-hydroxy-4-methyl-4,5-dihydro-1*H*-pyrazole (3m). M.p. 68–71°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (d, 1H, CH_3), 1.43 (q, 1H, CH), 3.92 (s, 3H, OCH_3), 6.87 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 9.9 (CH_3), 47.7 (C4), 53.7 (OMe), 89.4 (q, ^2J = 34 Hz, C5), 123.2 (q, ^1J = 286 Hz, CF_3), 149.7 (C3), 154.1 (C=O); GC/MS (m/z, %) 227 ($M^+ + H^+$, 13), 209 (27), 157 (100), 113 (24).

5-Trifluoromethyl-1*H*-pyrazole (4a). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.60 (d, 1H, ^3J = 2.0 Hz, H4), 7.86 (d, 1H, ^3J = 2.0 Hz, H3), 13.57 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.3 (q, ^2J = 36.7 Hz, C5), 130.5 (C3), 122.1 (q, ^1J = 267.7 Hz, CF_3), 103.2 (C4). GC/MS (m/z, %) 136 (M^+, 100), 117 (49), 69 (65).

5-Trifluoromethyl-3-methyl-1*H*-pyrazole (4b). M.p. 89–90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 3H, Me), 6.30 (s, 1H, H4), 12.89 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.3 (Me), 102.8 (C4), 121.5 (q, ^1J = 287 Hz, CF_3), 141.4 (C3), 142.8 (q, ^2J = 34 Hz, C5); GC/MS (m/z, %) 150 (M^+, 100), 131 (45), 101 (40), 81 (40), 51 (22).

5-Trifluoromethyl-3-phenyl-1*H*-pyrazole (4h). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.80 (s, 1H, H4), 7.26–7.59 (m, 5H, H-Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.1 (C3), 143.5 (q, ^2J = 38.1 Hz, C5), 121.1 (q, ^1J = 268.6 Hz, CF_3), 100.9 (C4), 125.6, 127.9, 129.1, 129.3 (C-Ar). GC/MS (m/z, %) 212 (M^+, 100), 193 (9), 143 (25), 77 (27).

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