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Microwave-assisted synthesis of 5-trichloromethyl substituted 1-phenyl-1*H*-pyrazoles and 1,2-dimethylpyrazolium chlorides

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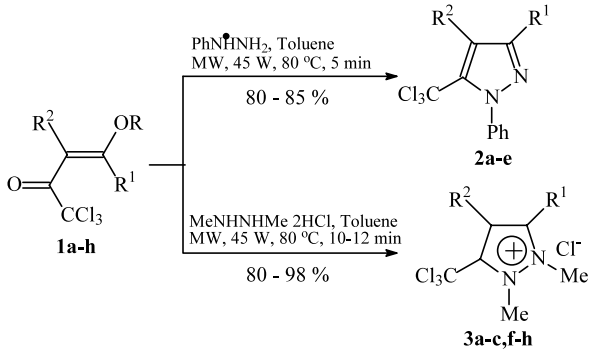
Abstract—A series of five 5-trichloromethyl-1-phenyl-1*H*-pyrazoles and six 5-trichloromethyl-1,2-dimethylpyrazolium chlorides have been synthesized in 80–98% yield by environmentally benign microwave induced techniques involving the cyclocondensation of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones [$Cl_3C(O)C(R^2)=C(R^1)OR$, where $R^2=H$, Me; $R^1=H$, alkyl, phenyl and R = Me, Et] with phenyl hydrazine and 1,2-dimethylhydrazine dihydrochloride, respectively, using toluene as solvent. The use of microwave and classical methods are comparable for making pyrazoles, but the formation of pyrazolium chlorides can be achieved in a significant shorter time, and in some cases better yield.

Pyrazoles have a long history of applications in the pharmaceutical and agrochemical industry due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties.[1] On the other hand, the pyrazolium salts derivatives possess very interesting applications, in special as herbicides, such as the patented herbicide difenzoquat.[2] Pyrazolium salts have also been used as coloring pigments[3] and as reagents in organic synthesis.[4]

The main synthetic method to prepare pyrazole and isoxazole involves [3+2] cyclization such as the classical β-diketone with hydrazines.[5–8] The most important route for the synthesis of 1,2-dialkylpyrazolium salts is through the *N*-alkylation of pyrazoles.[2,3,9] There are a few reports for the synthesis of these compounds using cyclocondensation methods such as the reaction of a β-diketone derivative with 1,2-dialkylhydrazines.[10–12]

In recent years, we have developed general synthesis of 1,1,1-trihalo-4-methoxy-3-alken-2-ones,[13,14] an important halogen-containing building block, and their usefulness in heterocyclic preparations, e.g. isoxazoles,[13,15,16] pyrazoles,[7,8,17] pyrazolium chlorides,[11,12] pyrrolidinones,[18] pyrimidines,[19] pyridines,[20] thiazines[21] and diazepines,[22] has been described. These compounds have been also used as precursors for the synthesis of (5)3-ethoxycarbonyl-pyrazoles[23] and -isoxazoles[24] in a one-pot procedure.

Considering that microwave irradiation (MW) using commercial domestic ovens has been recently used to accelerate organic reactions, the high heating efficiency



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

Scheme 1.

Keywords: microwave irradiations; pyrazoles; enones; halogen compounds.

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giving remarkable rate enhancement and dramatic reduction in reaction times,[25] the aim of this work is to demonstrate the advantages obtained by the use of microwave irradiation in the synthesis of 5-trichloromethyl-1-phenyl-1*H*-pyrazoles **2** and 5-trichloromethyl-1,2-dimethylpyrazolium chlorides **3** (Scheme 1) using the same precursors of the *classical method*.

The 4-methoxy-1,1,1-trihalo-3-alken-2-ones **1a–h** were synthesized from the reaction of the respective enol ether or acetal with trichloroacetyl chloride.[13,14]

The synthesis of **2a–e** were carried out from the cyclocondensation reaction of **1a–e** with dry phenyl hydrazine in a molar ratio of 1:1.3, respectively, in toluene and subjected to microwave irradiation for 5 min at the temperature $\leq$80°C. The synthesis of **3a–c**, **f–h** were carried out from the cyclocondensation reaction of **1a–e** with 1,2-dimethylhydrazine dihydrochloride in a molar ratio of 1:1, respectively, in toluene and subjected to microwave irradiation for 10–12 min at the temperature $\leq$80°C. Table 1 shows the reaction conditions, reaction times, and yields used to obtain compounds **2a–e** and **3a–c**, **f–h** by *Microwave* and *Classical Methods*.

In summary, the use of microwave and classical methods are comparable for making pyrazoles, but the formation of pyrazolium chlorides can be achieved in significant shorter time, and in some cases better yield (Table 1). It was observed that the average of the reaction time between the two methods is 1:6 for the synthesis of 5-trichloromethyl-1-phenyl-1*H*-pyrazoles **2** and 1:20 for the synthesis of 5-trichloromethyl-1,2-dimethyl pyrazolium chlorides **3** in favor to the microwave method.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The melting points were taken on a melting point microscope Reichert-Thermovar and are uncorrected. ^{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 mm sample tubes at 298 K (digital resolution ±0.01 ppm) in $CDCl_3$/TMS solutions. The physical and the ^{1}H and ^{13}C NMR data of compounds **2**, **3** are in accordance with the data presented in Refs. 8 and 11.

Microwave irradiations were conducted in a Panasonic M720 at a frequency of 2450 MHz, with energy in the sample[26] of 45 W and temperature $\leq$80°C.

Synthesis of 5-trichloromethyl-1-phenyl-1*H*-pyrazoles 2a–e; (Microwave Method)

A solution of **1** (2 mmol) and dry phenyl hydrazine (0.28 g, 2.6 mmol) in toluene (5 mL) was stirred a few minutes, then the mixture was irradiated in a microwave oven at 45 W for 5 min, time sufficient to complete the reaction. The solvent was evaporated in rotatory evaporator and to the residue was added distilled water (20 mL) and the product was extracted with dichloromethane (2×20 mL) and dried with $MgSO_4$. The solvent was removed under vacuum and the product was obtained in high purity. The pyrazoles **2a–e** were obtained as crystalline solids (**2a–c**) or oils (**2d**,**e**) and were purified by recrystallization from hexane.

2a: $C_{10}H_7N_2Cl_3$, M.wt 261.54, mp 109–110°C.
2b: $C_{11}H_9N_2Cl_3$, M.wt 275.57, mp 196–197°C.
2c: $C_{12}H_{11}N_2Cl_3$, M.wt 289.59, mp 151–153°C.
2d: $C_{13}H_{13}N_2Cl_3$, M.wt 303.62, oil.
2e: $C_{14}H_{15}N_2Cl_3$, M.wt 317.64, oil.

Yields are listed in Table 1 and the ^{1}H and ^{13}C NMR data of compounds **2a–e** are presented in Ref. 8.

Synthesis of 5-trichloromethyl-1,2-dimethylpyrazolium chlorides 3a–c,f–h; (Microwave Method)

A solution of **1** (2 mmol) and 1,2-dimethylhydrazine dihydrochloride (0.25 g, 2.0 mmol) in toluene (5 mL) was stirred a few minutes, then the mixture was irradiated in a microwave oven at 45 W for 10–12 min, time sufficient to complete the reaction. The solvent was evaporated in rotatory evaporator and the residue was washed with dry ethyl ether (3×20 mL). The solvent

Table 1. Yields[a] and reaction conditions used for the microwave assisted synthesis of **2a–e** and **3a–c**, **f–h**

	Microwave Method[b]		Classical Method[c]			Microwave Method[b]		Classical Method[d]	
Product	Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)	Product	Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)
2a	5	82	30	80	**3a**	10	80	4	95
2b	5	85	30	85	**3b**	12	98	4	90
2c	5	80	30	90	**3c**	12	90	4	81
2d	5	80	30	90	**3f**	12	95	4	76
2e	5	81	30	91	**3g**	12	84	12	70
					3h	12	94	4	90

[a] Yields of isolated products. The physical and the ^{1}H/^{13}C NMR spectra of compounds **2**,**3** are in accordance with the data presented in Refs. 8 and 11.
[b] *Reaction conditions*: toluene, 80°C MW, 45 W.
[c] Ref. 8, *reaction conditions*: chloroform, −10 to 0°C.
[d] Ref. 11, *reaction conditions*: ethanol/HCl, reflux.

was removed under vacuum and the product was obtained in high purity. The pyrazolium chloride were obtained in good purity as a crystalline solids (**3a**–**c**, **f**) or oils (**3g**,**h**).

3a: $C_6H_8N_2Cl_4$, M.wt 249.96, mp 106–107°C.
3b: $C_7H_{10}N_2Cl_4$, M.wt 263.98, mp 110–112°C.
3c: $C_8H_{12}N_2Cl_4$, M.wt 278.01, mp 125–127°C.
3f: $C_9H_{14}N_2Cl_4$, M.wt 292.04, mp 128–130°C.
3g: $C_{12}H_{12}N_2Cl_4$, M.wt 326.05, oil.
3h: $C_7H_{10}N_2Cl_4$, M.wt 263.98, oil.

Yields are listed in Table 1 and the ^1H and ^{13}C NMR data of compounds **3a**–**c**, **f**–**h** are presented in Ref. 11.

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