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Silica-supported 1,3-dichloro-5,5-dimethylhydantoin (DCH) as a useful reagent for microwave-assisted aromatization of 1,3,5-trisubstituted pyrazolines under solvent-free conditions

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Abstract

1,3,5-Trisubstituted pyrazolines are rapidly and conveniently oxidized to their corresponding pyrazoles by 1,3-dichloro-5,5-dimethylhydantoin (DCH) in solution and solvent-free conditions under microwave irradiation. The presence of silica gel as a supporting agent is shown to be effective in reducing the reaction times and increasing the yields.
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Keywords: Pyrazolines; 1,3-Dichloro-5,5-dimethylhydantoin (DCH); Aromatization; Solid-surface; Microwave irradiation

Microwave irradiation is an unconventional energy source, which has recently become of considerable interest in organic chemistry. During the last decade, a number of publications and reviews have advocated the advantages and versatility of microwave irradiation in easy and high yielding oxidation of organic compounds. This novel method is therefore a fast growing and clean practice in organic synthesis which has several advantages over classical thermal conditions, including increased reaction rates, simplicity and high reaction yields [1]. The use of supported reagents has gained popularity because of the improved selectivity, reactivity and associated ease of manipulation [2]. Since only the polar reagents adsorbed on the surfaces of various supporting mineral adsorb microwave energy, a variety of reagent supported on such surfaces can be utilized for the enhancement of organic reactions using a simple microwave (MW) oven. Solvent free organic synthesis seems to be highly useful technique, especially when inorganic solid supports are used [3]. The oxidation of 1,3,5-trisubstituted pyrazolines **1** to pyrazoles **2** is biologically very important, since many pyrazole derivatives **2** possess analgesic, anti-inflammatory, anti-pyretic, anti-arrhythmic, muscle relaxant, psychoanaleptic, anti-diabetic and anti-bacterial activities [4]. 1,3,5-Trisubstituted pyrazolines **1** can be easily prepared from phenylhydrazine and chalcon derivatives [5]. Therefore, oxidative aromatization of pyrazolines **1** by oxidizing reagents should provide an efficient method for the preparation of pyrazole derivatives **2**. Although a variety of reagents such as $Zr(NO_3)_4$ [6], Pd/C [7], Co(II) and oxygen [8], iodobenzene diacetate [9], lead tetraacetate [10], MnO_2 [11], potassiumpermanganate [12], and *N*-bromosuccinimide (NBS) [13], have been previously reported,

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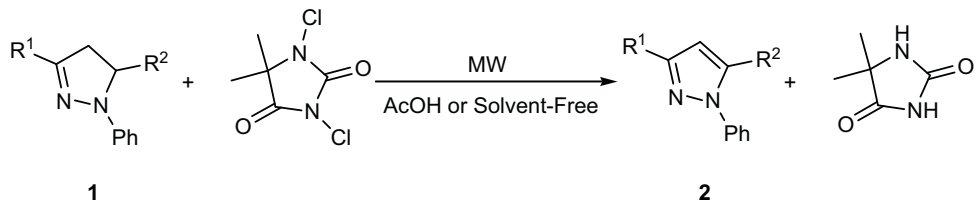


Scheme 1.

we report here in a facile microwave-accelerated oxidation of pyrazolines **1** to pyrazoles **2** by 1,3-dichloro-5,5-dimethylhydantoin (DCH) in solution (AcOH) and under solvent-free conditions using silica gel. As part of our current studies on the development of new routes in heterocyclic synthesis [14–16], we now report an efficient one-pot synthesis of pyrazoles **2** (Scheme 1).

Our objective in this work focused on some interesting features such as the rapid reaction rates, higher yields, cleaner reaction conditions and solvent-free conditions which seems to be a highly useful technique, especially it has many industrial advantages including reduced pollution, low costs, inprocessing and handling [17]. The reaction of 1,3,5-trisubstituted pyrazolines **1** with DCH in solution and using silica gel under microwave irradiation afforded pyrazoles **2** with no side products (Scheme 1). The results obtained from the conversion of various 1,3,5-trisubstituted pyrazolines **1** to their corresponding pyrazoles **2** are recorded in Table 1.

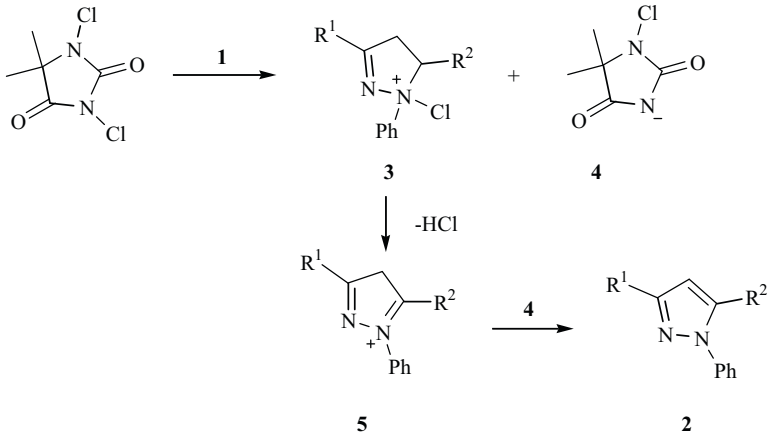
Although we have not yet established the mechanism of formation of **2** in an experimental manner, a possible explanation is proposed in Scheme 2. Presumably, the ionic intermediate **3**, formed from the Cl^+ and the pyrazolines, undergo eliminate HCl to produce the intermediates **5**, which apparently **4** is attacked by the **5**. Finally, a proton shift and the rearrangement to produce the final products **2** in excellent yields.

In conclusion, solvent-free microwave-assisted thermolysis proved to be a rapid oxidation of pyrazolines **1** to pyrazoles **2** when compared with conventional solution phase or heterogeneous reactions. The results indicated that the presence of silica gel support in the reaction can increase the efficiency of the oxidant in reducing the reaction times and improving the yields. Finally, the proposed procedure for the synthesis of pyrazole derivatives **2** is advantageous due to its experimental simplicity, short reaction time, and excellent yields.

Table 1
Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles (1 mmol) **2a**–**r** with DCH in AcOH at r.t (I) and under microwave-irradiated condition in AcOH (II) and under microwave-irradiated condition in solvent free (III).

Substrate	Product[a]	R^1	R^2	Time (h)			Yield[b](%)			Mp (°C)	
				I	II	III	I	II	III	Found	Reported[a]
1a	**2a**	Ph	Ph	4	0.16	0.083	79	86	86	134–136	139–140
1b	**2b**	Ph	3-ClC_6H_4	5	0.25	0.1	85	78	82	116–118	112–114
1c	**2c**	Ph	4-$CH_3OC_6H_4$	4.5	0.16	0.05	78	70	69	80–82	78–80
1d	**2d**	Ph	4-$NO_2C_6H_4$	5	0.13	0.06	86	78	78	140–142	142–143
1e	**2e**	Ph	4-$(CH_3)_2NC_6H_4$	4.5	0.16	0.05	78	69	70	68–70	68–71
1f	**2f**	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$	5	0.183	0.05	89	82	80	92–94	94–96
1g	**2g**	4-$CH_3C_6H_4$	2-Furyl	5	0.2	0.083	80	72	89	90–92	96–98
1h	**2h**	4-$CH_3C_6H_4$	4-$(CH_3)_2NC_6H_4$	5	0.16	0.05	82	76	87	118–120	118–120
1i	**2i**	3-ClC_6H_4	2-Thienyl	4.5	0.16	0.06	73	68	78	126–128	128–129
1j	**2j**	4-$CH_3OC_6H_4$	Ph	5.7	0.25	0.05	75	62	95	77–79	74–76
1k	**2k**	4-$CH_3OC_6H_4$	2-ClC_6H_4	5.5	0.25	0.083	88	87	87	69–71	66–68
1l	**2l**	2-Thienyl	4-ClC_6H_4	4	0.16	0.083	95	90	89	126–128	135–138
1m	**2m**	2-Thienyl	Ph	4.5	0.2	0.05	98	95	80	113–115	118–120
1n	**2n**	3-Thienyl	4-$(CH_3)_2NC_6H_4$	5	0.25	0.083	98	85	79	117–119	120–123
1o	**2o**	2-Naphthyl	2-$CH_3C_6H_4$	5	0.18	0.06	97	86	77	146–148	148–150
1p	**2p**	2-Naphthyl	3-Thienyl	4.5	0.16	0.06	86	89	90	125–127	128–132
1q	**2q**	4-$CH_3C_6H_4$	4-i-PrC_6H_4	4.7	0.16	0.083	80	68	76	57–59	–
1r	**2r**	2-Thienyl	$C_6H_5CH{=}CH$	5	0.13	0.06	78	78	86	71–73	71–73

[a] All the products were characterized on the basis of their IR, ^1H NMR and ^{13}C NMR spectral analysis and compared with the literature data [18–21].
[b] Isolated yields.



Scheme 2.

1. Experimental

Aldehydes, ketones, acetic acid and 1,3-dichloro-5,5-dimethylhydantoin (DCH) were obtained from Fluka and were used without further purification. 2-pyrazolines **1** was prepared by known methods [5]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N and S were performed using a Heraeus CHN–O-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were measured with a Bruker DRX-300 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. The microwave oven used for this work was an ETHOS-MR (800W, 180 °C) operating at 2450 MHz.

*1.1. General procedure for the preparation of **2** in AcOH*

To a solution of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **1a-r** (1 mmol) in AcOH (10 mL) was added DCH (4 mmol), and the mixture was stirred vigorously at room temperature. The progress of the reaction was monitored by TLC using EtOAc/*n*-hexane (1/4). The reactions completed in 4–5 h (Table 1). After complete conversion as indicated by TLC, the mixture was quenched with an aq $NaHCO_3$ solution and extracted with Et_2O. The organic layer washed with H_2O, derived and evaporated to give the products **2a-r** in 73–98% yields (Table 1).

*1.2. General procedure for the preparation of **2** using microwave irradiation in AcOH*

A mixture of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **1a**–**r** (1 mmol) and DCH (4 mmol) was dissolved in AcOH (15 ml), the solution was placed in an alumina bath inside a MW oven and irradiated at 300 W for 0.2–0.183 h (Table 1). After complete conversion as indicated by TLC, the mixture was quenched with an aq $NaHCO_3$ solution and extracted with Et_2O. The organic layer washed with H_2O, derived and evaporated to give the products **2a**–**r** in 62–95 yields (Table 1). All of the isolated products except **2q** are known compounds and their spectra and physical data have been reported in the literature [18–21].

*1.3. General procedure for the preparation of **2** using microwave irradiation under solvent-free (silica-supported)*

In solvent-free (silica-supported) a mixture of DCH (the molar ratios of DCH to substrate **1a**–**r** are 4/1) and the substrate **1a**–**j** (1 mmol), was thoroughly mixed with 70–320 mesh silica gel (9 mg per mmol of the reagent) and the mixture was placed in an alumina bath inside a MW oven and irradiated (300 W) for the time given in Table 1. After complete conversion as indicated by TLC, the mixture was quenched with an aq $NaHCO_3$ solution and extracted with Et_2O. The organic layer washed with H_2O, and evaporated to give the products **2a**–**r**.

3-(4-Methylphenyl)-1-phenyl-5-(4-i-propylphenyl)pyrazole (**2q**): yellow solid; mp: 57–59 °C; yield: 0.30 g (86%); IR (KBr) (ν_{max}/cm^{-1}): 1597 (C=N), 1498 (C=C); Anal. Calcd. (%) for $C_{25}H_{24}N_2$ (352.47): C, 85.19; H, 6.86; N, 7.95.

Found: C 85.28; H, 6.78; N, 7.92; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, 6H, $^{3}J_{HH}$ = 7.0 Hz, 2 Me), 2.40 (s, 3H, Me), 2.89 (m, 1H, CH), 7.22–7.90 (m, 14H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (Me), 23.9 (2 Me), 33.7 (CH), 106.4(CH), 125.9 (2 CH), 126.3 (CH), 126.7 (2 CH), 127.2 (2 CH), 127.4 (2 CH), 128.5 (2 CH), 128.7 (2 CH), 130.0 (C), 130.3 (C), 138.4 (C), 139.5 (C), 144.5 (C=N), 148.6 (C), 152.8 (C=N).

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