Silica-Supported 1,3-Dibromo-5,5-dimethylhydantoin (DBH) as a Useful Reagent for Microwave-Assisted Aromatization of 1,3,5-Trisubstituted Pyrazolines under Solvent-Free Conditions

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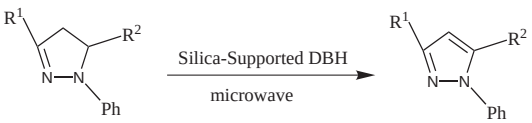
Abstract: 1,3,5-Trisubstituted pyrazolines are rapidly and conveniently oxidized to their corresponding pyrazoles by 1,3-dibromo-5,5-dimethylhydantoin (DBH) under microwave irradiation and solvent-free conditions. The presence of silica gel as a supporting agent is shown to be effective in reducing the reaction times and increasing the yields.

Key words: pyrazolines, 1,3-dibromo-5,5-dimethylhydantoin (DBH), 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 absorb microwave energy, a variety of reagents 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 to pyrazoles is biologically very important, since many pyrazole derivatives possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, antidiabetic and antibacterial activities.[4] 1,3,5-Trisubstituted pyrazolines can be easily prepared from phenylhydrazine and chalcone derivatives.[5] Therefore, oxidative aromatization of pyrazolines by oxidizing reagents should provide an efficient method for the preparation of pyrazole derivatives. 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] potassium permanganate[12] and *N*-bromsuccinimide (NBS)[13] have been previously reported, we report herein a facile microwave-accelerated oxidation of pyrazolines to pyrazoles by 1,3-dibromo-5,5-dimethylhydantoin (DBH) under solvent-free condition using silica gel.

Our objective in this work focussed on some interesting features such as (a) the rapid reaction rates, higher yields and cleaner reaction conditions and (b) solvent-free conditions which seems to be a highly useful technique, especially it has many industrial advantages including reduced pollution, low costs, simplicity in processing and handling.[1b,14] The reaction of 1,3,5-trisubstituted pyrazolines with DBH using silica gel under microwave irradiation afforded pyrazoles with no side products (Scheme 1). The reaction was first optimized for the substrate **1a** (Table 1).



1a–l **2a–l**

Scheme 1

Table 1 Optimization of Silica Gel for Substrate **1a** (1 mmol)

SiO_2 (g)	Time (min)	Yield (%)
0.01	5	80
0.02	2	90
0.03	3	84

The results obtained from the conversion of various 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles are recorded in Tables 2 and 3.

In conclusion, solvent-free microwave-assisted thermolysis proved to be a rapid oxidation of pyrazolines to pyrazoles 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.

IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained using 90 MHz Jeol FT NMR spectrometer.

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Table 2 Substrates **1a–l** and their Corresponding Pyrazoles **2a–l**

Substrate	Product	R^1	R^2
1a	**2a**	2-naphthyl	2-$CH_3C_6H_4$
1b	**2b**	Ph	Ph
1c	**2c**	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$
1d	**2d**	4-$OCH_3C_6H_4$	2-$CH_3C_6H_4$
1e	**2e**	4-$OCH_3C_6H_4$	3-$CH_3C_6H_4$
1f	**2f**	4-$OCH_3C_6H_4$	Ph
1g	**2g**	4-$OCH_3C_6H_4$	4-ClC_6H_4
1h	**2h**	2-naphthyl	3-$CH_3C_6H_4$
1i	**2i**	2-naphthyl	4-ClC_6H_4
1j	**2j**	2-naphthyl	2-ClC_6H_4
1k	**2k**	3-$CH_3C_6H_4$	4-$N(CH_3)_2C_6H_4$
1l	**2l**	4-$OCH_3C_6H_4$	2-ClC_6H_4

Table 3 Microwave-Assisted Aromatization of 1,3,5-Trisubstituted Pyrazolines by Silica-Supported DBH under Solvent-Free Conditions[a]

Substrate	Product[b]	Reagent/Substrate[c]	Time (min)	Yield (%)[d]
1a	**2a**	2.5	11 (2)	70 (90)
1b	**2b**	2.25	9 (1)	70 (82)
1c	**2c**	3.75	12 (4)	64 (76)
1d	**2d**	3. 5	15 (4)	74 (86)
1e	**2e**	3	13 (4)	62 (75)
1f	**2f**	3.5	9 (1)	76 (90)
1g	**2g**	4	10 (3)	62 (74)
1h	**2h**	3.75	15 (5)	70 (88)
1i	**2i**	3.75	10 (4)	68 (84)
1j	**2j**	3.5	8 (3)	74 (90)
1k	**2k**	3.25	8 (5)	70 (86)
1l	**2l**	3.5	8 (2)	68 (88)

[a] The reaction time and yields obtained using silica gel are shown in parentheses.
[b] Products were characterized by IR, ^{1}H NMR and by direct comparison with authentic materials.
[c] Molar ratio.
[d] Isolated yields.

CAUTION!
In view of the hazards associated with an active oxidant (DBH) due caution is recommended for its use at elevated temperatures; the localized temperature can be much higher than the bulk temperature of the bath in the microwave oven and we suggest the oven to be operated at a lower power and shorter reaction time.

Oxidation of 1,3,5-Substituted Pyrazolines 1 with DBH; General Procedure
A mixture of DBH (the molar ratios of DBH to substrate **1a–l** are given in Table 3) and the substrate **1a–l** (1 mmol), was thoroughly mixed with 70–230 mesh silica gel (8 mg per mmol of the reagent) and the mixture was placed in an alumina bath inside a MW oven and irradiated (900 W) for 1–5 min in the solid state. After complete conversion of the substrate 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, dried and evaporated to give the products **2a–l**.

2a
Yield: 324 mg (90%); yellow solid; mp 151–152 °C.

IR (KBr): 1589, 1494, 964 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): d = 2.22 (s, 3 H), 6.80 (s, 1 H), 7.16–8.27 (m, 16 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 19.49 (CH_3), 96.51 (C_4 in pyrazole), 95.12 (C_5 in pyrazole), 149.28 (C=N), 142.5, 138.92, 137.71, 133.21, 131.92 (C_{arom}), 120.86, 123.44, 124.56, 125.54, 126.23, 127.05, 127.69, 128.05, 128.46, 129.21, 129.95, 130.57 (CH_{arom}).

2b
Yield: 242 mg (82%); yellow solid; mp 136–138 °C (Lit.[9] mp 138–139 °C).

IR (KBr): 1582, 1491, 964 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): d = 6.93 (s, 1 H), 7.21–7.93 (m, 15 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 95.44 (C_4 in pyrazole), 90.79 (C_5 in pyrazole), 150.08 (C=N), 142.08, 138.80, 135.99 (C_{arom}), 121.21, 126.06, 128.06, 128.42, 128.71, 129.26, 129.86, 130.16, 131.99 (C_{arom}).

2c
Yield: 246 mg (76%); yellow solid; mp 95–98 °C.

IR (KBr): 1589, 1493 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): d = 2.20 (s, 6 H), 7.02 (s, 1 H), 7.25–7.61 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 21.35 (2 CH_3), 114.11 (C_4 in pyrazole), 111.61 (C_5 in pyrazole), 149.99 (C=N), 142.30, 138.134, 133.21, 131.89 (C_{arom}), 120.34, 122.97, 125.21, 126.31, 126.92, 127.71, 128.22, 129.32, 130.12 (CH_{arom}).

2d
Yield: 293 mg (86%); yellow solid; mp 70–72 °C.

IR (KBr): 1600, 1500 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): d = 2.19 (s, 3 H), 3.75 (s, 3 H) 6.72 (s, 1 H), 7.05–7.83 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 19.19 (CH_3), 55.08 (OCH_3), 113.42 (C_4 in pyrazole), 115.68 (C_5 in pyrazole), 150.86 (C=N), 160.92, 142.22, 140.06, 133.63, 130.12 (C_{arom}), 121.53, 122.12, 123.42, 125.14, 126.12, 127.28, 128.39, 129.20, 129.82 (CH_{arom}).

2e
Yield: 254 mg (75%); yellow solid; mp 84–86 °C.

IR (KBr): 1589, 1494 cm^{-1}.

^{1}H NMR (90 MHz, $CDCl_3$): d = 2.23 (s, 3 H), 3.85 (s, 3 H) 6.84 (s, 1 H), 7.06–7.85 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 21.09 (CH_3), 55.30 (OCH_3), 115.12 (C_4 in pyrazole), 112.45 (C_5 in pyrazole), 150.96 (C=N), 160.16, 146.87, 145.30, 139.87, 137.12 (C_{arom}), 123.12, 125.64, 126.12, 127.24, 127.92, 128.87, 129.12, 130.99, 131.42 (CH_{arom}).

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2f
Yield: 294 mg (90%); yellow solid; mp 75–77 °C.

IR (KBr): 1645, 1594 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 3.76 (s, 3 H) 6.48 (s, 1 H), 6.95–7.78 (m, 14 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 56.25 (OCH_3), 111.85 (C_4 in pyrazole), 106.42 (C_5 in pyrazole), 148.30 (C=N), 158.13, 136.36, 132.18, 131.02 (C_{arom}), 122.60, 127.21, 127.94, 128.62, 129.04, 129.79, 130.15, 130.73 (CH_{arom}).

2g
Yield: 266 mg (74%); yellow solid; mp 101–103 °C.

IR (KBr): 1612, 1500, 964 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 3.87 (s, 3 H) 6.98 (s, 1 H), 7.26–7.91 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 54.92 (OCH_3), 114.12 (C_4 in pyrazole), 111.42 (C_5 in pyrazole), 150.09 (C=N), 159.91, 144.69, 140.95, 132.08, 130.51 (C_{arom}), 120.53, 121.96, 124.92, 126.82, 127.04, 128.79, 129.26 (CH_{arom}).

2h
Yield: 317 mg (88%); yellow solid; mp 75–78 °C.

IR (KBr): 1651,1596 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 2.51 (s, 3 H), 7.07 (s, 1 H), 7.37–8.50 (m, 16 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 21.47 (CH_3), 97.12 (C_4 in pyrazole), 95.96 (C_5 in pyrazole), 150.09 (C=N), 145.07, 142.80, 138.93, 134.47, 131.24 (C_{arom}), 122.86, 123.04, 123.062, 125.09, 126.14, 127.09, 127.86, 129.18, 129.94, 130.06 (CH_{arom}).

2i
Yield: 320 mg (84%); yellow solid; mp 130–133 °C.

IR (KBr): 1600,1500 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 7.03 (s, 1 H), 7.25–8.29 (m, 16 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 116.46 (C_4 in pyrazole), 112.11 (C_5 in pyrazole), 150.08 (C=N), 144.43, 139.12, 133.18, 132.08, 130.42 (C_{arom}), 123.31, 124.11, 126.33, 126.92, 127.12, 127.42, 127.95, 128.42, 129.12, 129.98 (CH_{arom}).

2j
Yield: 343 mg (90%); yellow solid; mp 72–75 °C.

IR (KBr): 1599, 1491, 968 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 7.00 (s, 1 H), 7.30–8.51 (m, 16 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 115.32 (C_4 in pyrazole), 110.80 (C_5 in pyrazole), 151.82 (C=N), 136.08, 134.77, 134.26, 133.24, 132.12 (C_{arom}), 123.88, 125.05, 125.58, 126.23, 126.80, 127.19, 127.74, 128.12, 128.52, 129.12, 129.91, 130.61 (CH_{arom}).

2k
Yield: 304 mg (86%); yellow solid; mp 67–70 °C.

IR (KBr): 1590, 1520, 980 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 2.43 (s, 3 H), 2.87 (s, 6 H) 7.00 (s, 1 H), 7.24–7.74 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 19.47 (CH_3), 42.10 [2 C, $N(CH_3)_2$], 111.34 (C_4 in pyrazole), 106.82 (C_5 in pyrazole), 151.22 (C=N), 165.09, 144.21, 142.17, 136.42, 132.12 (C_{arom}), 124.32, 125.10, 126.06, 127.12, 127.99, 128.09, 128.92, 129.82, 130.12 (CH_{arom}).

2l
Yield: 317 mg (88%); yellow solid; mp 63–65 °C.

IR (KBr): 1590,1490 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): d = 3.78 (s, 3 H), 6.87 (s, 1 H), 6.97–7.85 (m, 13 H).

^{13}C NMR (90 MHz, $CDCl_3$): d = 54.97 (OCH_3), 112.42 (C_4 in pyrazole), 110.02 (C_5 in pyrazole), 149.46 (C=N), 161.12, 144.87, 139.14, 131.22, 130.72 (C_{arom}), 120.23, 121.82, 124.42, 126.96, 127.04, 128.79, 128.86, 129.20, 129.94 (CH_{arom}).

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