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MICROWAVE-ASSISTED AROMATIZATION OF 1,3,5-TRISUBSTITUTED 2-PYRAZOLINES BY SILICA-SUPPORTED *N*-BROMOSUCCINIMIDE AS A USEFUL REAGENT UNDER SOLVENT FREE 'DRY' CONDITION

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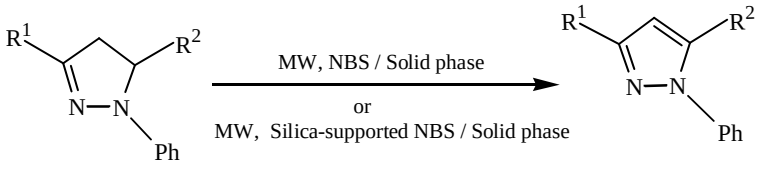
Abstract- An efficient aromatization of 1,3,5-trisubstituted 2-pyrazolines to their corresponding pyrazoles by NBS was carried out under microwave irradiation and solvent-free conditions in moderate yields. It has also been observed that, by activating the NBS reagent on silica gel as a support the reaction times can be dramatically reduced and good yields are obtained.

The use of microwave irradiation as a non-conventional energy source has become of considerable interest in organic chemistry. The frequency of publications and reviews during the last decade has substantiated 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 improved reaction yields.[1-4] The use of supported reagents has gained popularity because of the improved selectivity, reactivity and associated ease of manipulation.[5-8] Since only the polar reagents activated on the surfaces of various supporting minerals can efficiently absorb microwave energy, a variety of reagents supported on such surfaces can be utilized to enhance the organic reactions using a simple microwave (MW) oven.[1,3,9-13] Microwave-assisted chemical reactions, especially when activated on inorganic solid supports and conducted under solvent-free conditions,[11,12] have been of great interest to chemists. They offer several advantages over the conventional homogeneous and heterogeneous reactions in view of the rapid reaction rates and higher yields of the ensuing pure products. Solvent-free organic synthesis seems to be highly useful technique, especially when inorganic solid supports are employed.[10-12]

The oxidative aromatization of 1,3,5-trisubstituted 2-pyrazolines to pyrazoles is biologically important, since many pyrazole derivatives possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, antidiabetic and antibacterial activities.[14,15] 1,3,5-Trisubstituted 2-pyrazolines can be conveniently prepared from phenylhydrazine and chalcone intermediates.[16-18] Therefore, oxidative aromatization of 2-pyrazolines by oxidizing agents should provide an efficient method for the preparation of pyrazole derivatives. A variety of reagents such as $Zr(NO_3)_4$,[19] Pd/C,[20] oxygen activated on carbon,[21] Co(II) and oxygen,[22] iodobenzene diacetate,[23] lead tetraacetate,[24] MnO_2,[25] and $KMnO_4$,[26] have been previously reported most of which suffer from the use of excess reagent, longer reaction times, higher temperatures, acidity, formation of side products and toxicity due to the presence of toxic transition metal cations like Co(II), Pb(IV), Hg(II), Mn(IV and VII), Ag(I), Zr(IV) within the structural formula of the reagents used. Following our previously reported protocols on the oxidative aromatization of pyrazolines,[27-31] we report herein on a facile microwave-accelerated oxidation of 2-pyrazolines to pyrazoles by NBS under solvent-free condition using silica gel support.

Our objective in this work focused on some interesting features such as (a) the rapid reaction rates, higher yields and cleaner reaction conditions and (b) solvent-free condition which seems to be a highly useful technique, especially it is of many industrial advantages including reduced pollution, low costs, simplicity in processing and handling.[32,33]

The reaction of 1,3,5-trisubstituted 2-pyrazolines with NBS using silica gel under microwave irradiation afforded pyrazoles with no side products (Scheme **1**).



(1a-l) **(2a-l)**

Scheme 1

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

SiO_2 (g)	NBS (mmol)	Time (min)	Yield (%)
0.02	3.5	8	70
0.04	3.5	5	92
0.06	3.5	6	75

The results obtained from the conversion of various 1,3,5-trisubstituted 2- pyrazolines **(1a-l)** into their corresponding pyrazoles **(2a-l)** are recorded in Tables **2** and **3**.

Table 2. Substrates **(1a-l)** and their corresponding products **(2a-l)**.

Substrate	Product	R^1	R^2
1a	**2a**	2-Naphthyl	*o*-$CH_3C_6H_4$
1b	**2b**	Ph	Ph
1c	**2c**	*p*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$
1d	**2d**	*p*-$CH_3OC_6H_4$	*o*-$CH_3C_6H_4$
1e	**2e**	*p*-$CH_3OC_6H_4$	*m*-$CH_3C_6H_4$
1f	**2f**	*p*-$CH_3OC_6H_4$	Ph
1g	**2g**	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4
1h	**2h**	2-Naphthyl	*m*-$CH_3C_6H_4$
1i	**2i**	2-Naphthyl	*p*-ClC_6H_4
1j	**2j**	2-Naphthyl	*o*-ClC_6H_4
1k	**2k**	*m*-$CH_3C_6H_4$	*p*-$(CH_3)_2NC_6H_4$
1l	**2l**	*p*-$CH_3OC_6H_4$	*o*-ClC_6H_4

Table 3. Microwave-assisted aromatization of 1,3,5-trisubstituted 2-pyrazolines by NBS and silica-supported NBS under solvent-free condition[a]

Substrate	Product	NBS (mmol)	SiO_2 (g)	Time (min)	Yield (%)
1a	**2a**	3.50	0.040	10 (5)	60 (92)
1b	**2b**	3.25	0.037	7 (3)	58 (88)
1c	**2c**	4.75	0.054	10 (4)	49 (90)
1d	**2d**	5.50	0.078	9 (3)	64 (86)
1e	**2e**	5.25	0.060	8 (3)	54 (91)
1f	**2f**	4.25	0.048	7 (2)	60 (88)
1g	**2g**	4.75	0.054	10 (3)	58 (86)
1h	**2h**	5.00	0.057	8 (3)	52 (76)
1i	**2i**	5.00	0.057	10 (4)	56 (82)
1j	**2j**	4.75	0.054	7 (2)	54 (92)
1k	**2k**	4.25	0.048	8 (2)	46 (90)
1l	**2l**	3.50	0.040	8 (3)	58 (86)

[a]The reaction times and yields obtained using silica-supported NBS are shown in the parentheses.

EXPERIMENTAL

All melting points were determined on a Büchi 530 melting point apparatus, and reported uncorrected. IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using 90 MHz JEOL FT NMR spectrometer. The CHN analysis was carried out in Iranian Petroleum Research Center (Ray city, Tehran).

GENERAL PROCEDURE:
Oxidation of 1,3,5-trisubstituted 2-pyrazolines with NBS

The amounts of silica gel and NBS used for 1 mmol of the substrates (**1a-l**) in all the experiments are calculated (Table **3**) on the basis of the previously optimized amount of SiO_2 (0.04 g) for the substrate (**1a**) (1 mmol) and NBS (3.50 mmol) (Table **1**).
In a flask, a mixture of substrate (**1a-l**) (1 mmol) and the appropriate amount of NBS (Table **3**) was thoroughly mixed. The resulting mixture was then placed in an alumina bath inside a MW oven and irradiated (900 W) for 7-10 min in the solid state. After complete conversion of the substrate as monitored by TLC, the mixture was quenched with 5% $NaHCO_3$ solution and extracted with Et_2O. The organic layer was then separated, washed with H_2O, dried over anhydrous $MgSO_4$ and finally evaporated to give the products (**2a-l**), which were recrystalized from MeOH (Table **3**). In a separate set of experiments, these reactions were all repeated exactly under the same conditions in the presence of an appropriate amount of 70-230 mesh silica gel mixed with other components of the reaction and the results obtained are quoted in the parentheses in Table **3**.

3-(2-Naphthyl)-1-phenyl-5-*o*-tolylpyrazole (2a)
Yield: 332 mg (92%): yellow colored solid; mp 148-150 ºC. IR (KBr): υ1589, 1494 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 6.80 (s, 1H, C4 in pyrazole), 7.16-8.27 (m, 16H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 9.49 (CH_3), 96.51 (C5 in pyrazole), 95.12 (C4 in pyrazole), 149.28, 142.5, 138.92, 137.71, 133.21, 131.92, 120.86, 123.44, 124.56, 125.54, 126.23, 127.05, 127.69, 128.05, 128.46, 129.21, 129.95, 130.57. Anal. Calcd for $C_{26}H_{20}N_2$: C, 86.67; H, 5.56; N, 7.78. Found: C, 86.62; H, 5.54; N, 7.72.

1,3,5-Triphenylpyrazole (2b)

Yield: 260 mg (88%): yellow colored solid; mp 136-138 ºC (lit.,[19] mp 138-139 ºC). IR (KBr): υ1582, 1491 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 6.93 (s, 1H, C4 in pyrazole), 7.21-7.93 (m, 15H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 95.44 (C5 in pyrazole), 90.79 (C4 in pyrazole), 150.08, 142.08, 138.80, 135.99, 121.21, 126.06, 128.06, 128.42, 128.71, 129.26, 129.86, 130.16, 131.99. Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.00; H, 5.45; N, 9.20.

1-Phenyl-3-*p*-tolyl-5-*m*-tolylpyrazole (2c)
Yield: 291 mg (90%): yellow colored solid; mp 94-96 ºC. IR (KBr): υ1589,1493 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.20 (s, 6H, $2CH_3$), 7.02 (s, 1H, C4 in pyrazole), 7.25-7.61 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 21.35 ($2CH_3$), 114.11 (C5 in pyrazole), 111.61 (C4 in pyrazole), 149.99, 142.30, 138.134, 133.21, 131.89, 120.34, 122.97, 125.21, 126.31, 126.92, 127.71, 128.22, 129.32, 130.12. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.18; H, 6.17; N, 8.65. Found: C, 85.10; H, 6.00; N, 8.60.

3-*p*-Anisyl-1-phenyl-5-*o*-tolylpyrazole (2d)
Yield: 293 mg (86%): yellow colored solid; mp 73-75 ºC. IR (KBr): υ1600,1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.72 (s, 1H, C4 in pyrazole), 7.05-7.83 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 9.19, 55.08, 113.42 (C5 in pyrazole), 115.68 (C4 in pyrazole), 150.86, 160.92, 142.22, 140.06, 133.63, 130.12, 121.53, 122.12, 123.42, 125.14, 126.12, 127.28, 128.39, 129.20, 129.82. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.18; H, 5.89; N, 8.23. Found: C, 81.10; H, 5.90; N, 8.18.

3-*p*-Anisyl-1-phenyl-5-*m*-tolylpyrazole (2e)
Yield: 310 mg (91%): yellow colored solid; mp 82-85 ºC. IR (KBr): υ1589, 1494 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.84 (s, 1H, C4 in pyrazole), 7.06-7.85 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 21.09, 55.30, 115.12 (C5 in pyrazole), 112.45 (C4 in pyrazole), 150.96, 160.16, 146.87, 145.30, 139.87, 137.12, 123.12, 125.64, 126.12, 127.24, 127.92, 128.87, 129.12, 130.99, 131.42. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.18; H, 5.89; N, 8.23. Found: C, 81.00; H, 5.86; N, 8.20.

3-*p*-Anisyl-1,5-diphenylpyrazole (2f)
Yield: 287 mg (88%): yellow colored solid; mp 78-80 ºC. IR (KBr): υ1645, 1594 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.76 (s, 3H, OCH_3) 6.48 (s, 1H, C4 in pyrazole), 6.95-7.78 (m, 14H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 56.25, 111.85 (C5 in pyrazole), 106.42 (C4 in pyrazole), 148.30, 158.13, 136.36, 132.18, 131.02, 122.60, 127.21, 127.94, 128.62, 129.04, 129.79, 130.15, 130.73. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.98; H, 5.52; N, 8.59. Found: C, 80.96; H, 5.50; N, 8.57.

3-*p*-Anisyl-5-*p*-cholorophenyl-1-phenylpyrazole (2g)
Yield: 311 mg (86%): yellow colored solid; mp 99-102 ºC. IR (KBr): υ1612, 1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3) 6.98 (s, 1H, C4 in pyrazole), 7.26-7.91 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 54.92, 114.12 (C5 in pyrazole), 111.42 (C4 in pyrazole), 150.09, 159.91, 144.69. 140.95. 132.08, 130.51, 120.53, 121.96, 124.92, 126.82, 127.04, 128.79, 129.26. Anal. Calcd for $C_{22}H_{17}N_2OCl$: C, 73.13; H, 4.71; N, 7.75. Found: C, 73.10; H, 4.68; N, 7.72.

3-(2-Naphthyl)-1-phenyl- 5-*m*-tolylpyrazole (2h)
Yield: 274mg (76%): yellow colored solid; mp 80-82 ºC. IR (KBr): υ1612, 1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3) 6.98 (s, 1H, C4 in pyrazole), 7.26-7.91 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 54.92, 114.12 (C5 in pyrazole), 111.42 (C4 in pyrazole), 150.09, 159.91, 144.69. 140.95. 132.08, 130.51, 120.53, 121.96, 124.92, 126.82, 127.04, 128.79, 129.26. Anal. Calcd for $C_{22}H_{17}N_2OCl$: C, 73.13; H, 4.71; N, 7.75. Found: C, 73.10; H, 4.68; N, 7.72.

5-*p*-Cholorophenyl-3-(2-naphthyl)-1-phenylpyrazole (2i)
Yield: 313 mg (82%): yellow colored solid; mp 134-137 ºC. IR (KBr): ∪1600,1500 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.03 (s, 1H, C4 in pyrazole), 7.25-8.29 (m, 16H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 116.46 (C5 in pyrazole), 112.11 (C4 in pyrazole), 150.08, 144.43, 139.12, 133.18, 132.08, 130.42, 123.31, 124.11, 126.33, 126.92, 127.12, 127.42, 127.95, 128.42, 129.12, 129.98. Anal. Calcd for $C_{25}H_{17}N_2Cl$: C, 78.74; H, 4.46; N, 7.35. Found: C, 78.72; H, 4.42; N, 7.20.

5-*o*-Cholorophenyl-3-(2-naphthyl)-1-phenylpyrazole (2j)
Yield: 350 mg (92%): yellow colored solid; mp 77-79 ºC. IR (KBr): ∪1599,1491 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.00 (s, 1H, C4 in pyrazole), 7.30-8.51 (m, 16H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 115.32 (C5 in pyrazole), 110.80 (C4 in pyrazole), 151.82, 136.08, 134.77, 134.26, 133.24, 132.12, 123.88, 125.05, 125.58, 126.23, 126.80, 127.19, 127.74, 128.12, 128.52, 129.12, 129.91, 130.61. Anal. Calcd for $C_{25}H_{17}N_2Cl$: C, 78.74; H, 4.46; N, 7.35. Found: C, 78.72; H, 4.44; N, 7.00.

5-*p*-Dimethylaminophenyl-1-phenyl-3-*m*-tolylpyrazole (2k)
Yield: 318 mg (90%): yellow colored solid; mp 68-72 ºC. IR (KBr): ∪1590, 1520 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.87 (s, 6H, NMe_2), 7.00 (s, 1H, C_4 in pyrazole), 7.24-7.74 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 19.47, 42.10 (2C), 111.34 (C5 in pyrazole), 106.82 (C4 in pyrazole), 151.22, 165.09, 144.21, 142.17, 136.42, 132.12, 124.32, 125.10, 126.06, 127.12, 127.99, 128.09, 128.92, 129.82, 130.12. Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.59; H, 6.51; N, 11.90. Found: C, 81.52; H, 6.40; N, 11.86.

3-*p*-Anisyl-5-*o*-cholorophenyl-1-phenylpyrazole (2l)
Yield: 310 mg (86%): yellow colored solid; mp 60-62 ºC. IR (KBr): ∪1590,1490 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.78 (s, 3H, OCH_3), 6.87 (s, 1H, C4 in pyrazole), 6.97-7.85 (m, 13H, arom). ^{13}C-MNR (22.5 MHz, $CDCl_3$): δ 54.97, 112.42 (C5 in pyrazole), 110.02 (C4 in pyrazole), 149.46, 161.12, 144.87, 139.14, 131.22, 130.72, 120.23, 121.82, 124.42, 126.96, 127.04, 128.79, 128.86, 129.20, 129.94. Anal. Calcd for $C_{22}H_{17}N_2OCl$: C, 73.13; H, 4.71; N, 7.75. Found: C, 73.14; H, 4.66; N, 7.35.

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