Microwave-assisted oxidation of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles to the corresponding pyrazoles with poly(*N*,*N*′-dibromobenzene-1,3-disulfonamide-1,2-ethanediyl)

Davood Azarifar,* Elahe Nadimi, Ramin Ghorbani-Vaghei and Behrooz Maleki

Department of Chemistry, School of Science, Bu Ali Sina University, 65174 Hamadan, Iran.
Fax: +98 811 827 2404; e-mail: azarifar@basu.ac.ir

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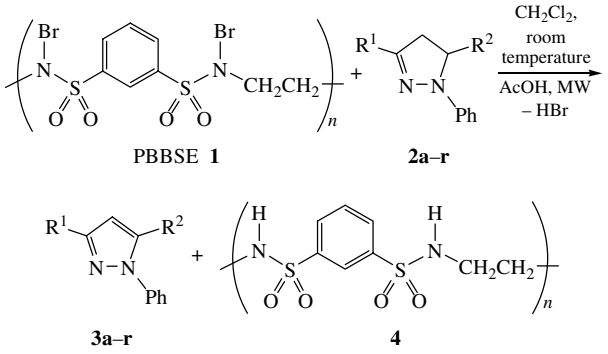
The title reaction gives pyrazoles in good yields under microwave irradiation when compared with conventional long-time conditions at room temperature.

The use of microwave irradiation in organic synthesis is of considerable importance.[1] The advantages of microwave irradiation as an energy source in organic reactions include increased reaction rates, improved yields, simplicity in handling and high-purity products.[2] 1,3,5-Trisubstituted 2-pyrazoles, which are of biological value as synthetic compounds of some medicinal interest,[3] can be obtained by the oxidative aromatization of corresponding 4,5-dihydro-1*H*-pyrazoles. 1,3,5-Trisubstituted 4,5-dihydro-1*H*-pyrazoles have been conveniently prepared by the cyclization of related chalcones with hydrazines.[4]

Reagents including Pd/C/AcOH,[5] $Zr(NO_3)_4$,[6] Co^{II}/O_2,[7] iodobenzene diacetate,[8] $Pb(OAc)_4$,[9] MnO_2,[10] $KMnO_4$[11] and $Ag(NO_3)_2$[12] have been reported to effect the oxidation of 2-pyrazolines to the corresponding pyrazoles. However, most of these require long reaction times and high temperatures and give by-products and low yields. Transition metal cations like Co^{II}, Pb^{IV}, Hg^{II}, Mn^{IV}, Mn^{VII}, Ag^{I} and Zr^{IV} added as catalysts leave residual toxicity in the products.

Previously, we developed more convenient and easily available reagents for the oxidative aromatization of 2-pyrazolines to the corresponding pyrazoles, including 1,3-dibromo-5,5-dimethylhydantoin (DBH),[13] trichloroisocyanuric acid,[14] *N*-bromosulfonamides,[15] *N*-bromosuccinimide/SiO_2,[16] 4-(4-chlorophenyl)-1,2,4-triazole-3,5-dione[17] and $Ca(OCl)_2$.[18]

In continuation of our research, we were prompted to examine the facile microwave-accelerated oxidation of substituted 4,5-dihydro-1*H*-pyrazoles **2a**–**r** to corresponding pyrazoles **3a**–**r** by poly(*N*,*N*′-dibromobenzene-1,3-disulfonamide-*N*,*N*′-1,2-ethanediyl) (PBBSE) **1** as an easily accessible reagent,[19] which can be conveniently recovered by the treatment of poly(benzene-1,3-disulfonamide-*N*,*N*′-1,2-ethanediyl) **4**, produced in the reaction, with bromine. The results are presented in Scheme 1 and Table 1.†



Scheme 1

References

1 (*a*) D. G. Yadav and N. M. Desai, *Catal. Commun*., 2006, **6**, 325; (*b*) A. Kaddouri and S. Ifrah, *Catal. Commun*., 2006, **2**, 109; (*c*) V. Polshettiwar and M. P. Kaushik, *Catal. Commun*., 2005, **3**, 191; (*d*) M. Adharvana Chari and K. Syamasundar, *Catal. Commun*., 2005, **1**, 67; (*e*) R. S. Varma, *Green Chem*., 1999, 43.

2 A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, 1213.

3 (*a*) S. G. Roelf Van, C. Arnold and K. Wellnga, *J. Agric. Food Chem*., 1979, **84**, 406; (*b*) H. Z. Katri and S. A. Vunii, *J. Ind. Chem. Soc*., 1981, **58**, 168.

4 (*a*) D. Azarifar and M. Shaebanzadeh, *Molecules*, 2002, **7**, 885; (*b*) D. Azarifar and H. Ghasemnejad, *Molecules*, 2003, **8**, 642; (*c*) D. Azarifar and B. Maleki, *J. Heterocycl. Chem*., 2005, **42**, 157.

5 N. Nakamichi, Y. Kawashita and M. Hayashi, *Org. Lett*., 2002, **4**, 3955.

Table 1 Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **2a**–**r** (1 mmol) with PBBSE in CH_2Cl_2 at room temperature and under microwave irradiation in acetic acid.[a]

Substrate	Product[b]	R^1	R^2	Time/h	Yield (%)	Mp/°C	
						Found	Reported[c]
2a	**3a**	Ph	Ph	0.08 (10)	95 (78)	134–136	139–140
2b	**3b**	Ph	3-ClC_6H_4	0.08 (13)	85 (70)	116–118	112–114
2c	**3c**	Ph	4-$MeOC_6H_4$	0.08 (13)	82 (76)	80–82	78–80
2d	**3d**	Ph	4-$NO_2C_6H_4$	0.07 (10)	90 (69)	139–142	142–143
2e	**3e**	Ph	4-$Me_2NC_6H_4$	0.10 (15)	94 (58)	68–70	68–71
2f	**3f**	4-MeC_6H_4	3-MeC_6H_4	0.07 (13)	86 (62)	92–94	94–96
2g	**3g**	4-MeC_6H_4	2-Furyl	0.07 (10)	80 (70)	90–92	96–98
2h	**3h**	4-MeC_6H_4	4-$Me_2NC_6H_4$	0.12 (12)	98 (65)	117–120	118–120
2i	**3i**	3-ClC_6H_4	2-Thienyl	0.08 (10)	88 (79)	126–128	128–129
2j	**3j**	4-$MeOC_6H_4$	Ph	0.05 (15)	90 (70)	77–79	74–76
2k	**3k**	4-$MeOC_6H_4$	2-ClC_6H_4	0.05 (10)	95 (76)	69–71	66–68
2l	**3l**	2-Thienyl	4-ClC_6H_4	0.07 (12)	97 (78)	126–128	135–138
2m	**3m**	2-Thienyl	Ph	0.12 (13)	98 (76)	113–115	118–120
2n	**3n**	3-Thienyl	4-$Me_2NC_6H_4$	0.10 (11)	93 (75)	117–119	120–123
2o	**3o**	2-Naphthyl	2-MeC_6H_4	0.08 (10)	90 (70)	146–148	148–150
2p	**3p**	2-Naphthyl	3-Thienyl	0.07 (8)	85 (78)	125–127	128–132
2q	**3q**	4-MeC_6H_4	4-$Pr^iC_6H_4$	0.08 (10)	86 (70)	57–59	—
2r	**3r**	2-Thienyl	PhCH=CH	0.07 (13)	98 (85)	71–73	—

[a]The results under long-time conditions (room temperature) are shown in parentheses. [b]All the products were characterised by IR, ^1H and ^{13}C NMR spectroscopy and compared with authentic samples. [c]Published data.[6,17,18]

6 G. Sabitha, G. S. K. Reddy, C. S. Reddy, N. Fatima and J. S. Yadav, *Synthesis*, 2003, 1267.
7 J. N. Shah and C. K. Shah, *J. Org. Chem.*, 1978, **43**, 1266.
8 S. P. Singh, D. Kumar, O. Prakash and R. P. Kapoor, *Synth. Commun.*, 1997, **27**, 2683.
9 W. A. Gladstone and R. O. C. Norman, *J. Chem. Soc., Chem. Commun*., 1966, 1536.
10 I. Bhantnagar and M. V. George, *Tetrahedron*, 1968, **24**, 1293.
11 L. I. Smith and K. L. Howard, *J. Am. Chem. Soc.*, 1943, **65**, 159.
12 R. P. Dodwadmath and T. S. Wheeler, *Proc. Ind. Acad. Sci.*, 1935, **2A**, 438.
13 (*a*) D. Azarifar, M. A. Zolfigol and B. Maleki, *Bull. Korean Chem. Soc*., 2004, **25**, 23; (*b*) D. Azarifar, M. A. Zolfigol and B. Maleki, *Synthesis*, 2004, 1744.
14 (*a*) M. A. Zolfigol, D. Azarifar and B. Maleki, *Tetrahedron Lett*., 2004, **45**, 2181; (*b*) D. Azarifar and B. Maleki, *J. Chin. Chem. Soc*., 2004, **52**, 1215.
15 (*a*) R. Ghorbani-Vaghei, D. Azarifar and B. Maleki, *Bull. Korean Chem. Soc*., 2004, **25**, 953; (*b*) R. Ghorbani-Vaghei, D. Azarifar, A. Khazaei and B. Maleki, *Phosphorus Sulfur Silicon Relat. Elem.*, 2004, **179**, 1877; (*c*) R. Ghorbani-Vaghei, D. Azarifar and B. Maleki, *J. Chin. Chem. Soc.*, 2004, **51**, 1373.
16 D. Azarifar and B. Maleki, *Heterocycles*, 2005, **65**, 865.
17 M. A. Zolfigol, D. Azarifar, I. Mohammadpour-Baltork, S. Mallakpour, A. Forghaniha, B. Maleki and M. Abdollahi-Alibeik, *Tetrahedron Lett*., 2006, **47**, 833.
18 D. Azarifar and A. Gharshasebi, *Heterocycles*, 2006, **68**, 1209.
19 (*a*) R. Ghorbani-Vaghei and H. Jalali, *Synthesis*, 2005, **7**, 1099; (*b*) R. Ghorbani-Vaghei, H. Jalali, E. Shahbazee and H. Veisi, *J. Chin. Chem. Soc*., 2006, **53**, 379.

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† The IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets), and the NMR spectra were obtained using a 90 MHz JEOL FT NMR spectrometer. Microanalysis was carried out at The Iranian Petroleum Research Center (Tehran, Iran). All of the 2-pyrazolines and PBBSE were prepared according to published procedures (refs. 4 and 19, respectively). Microwave-assisted reactions were conducted in a Panasonic Model NNS59BH microwave oven.

Typical procedure for the oxidation of 1,3,5-trisubstituted 2-pyrazolines with PBBSE: long-time conditions at room temperature. PBBSE (2 mmol) was added to a solution of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **2a**–**r** (1 mmol) in CH_2Cl_2 (10 ml), 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 8–15 h (Table 1). After the complete conversion of the substrate, dry K_2CO_3 (0.5 g) was added to the reaction mixture, the mixture was stirred for 30 min, filtered to remove the insoluble polysulfonamide produced during the reaction, and extracted with CH_2Cl_2 (10 ml). The solvent was then evaporated from the extract to leave a crude solid product, which was further purified by recrystallization from ethanol to give pure pyrazoles **3a**–**r** in 58–85% yields (Table 1).

Microwave irradiation conditions. A mixture of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **2a**–**r** (1 mmol) and PBBSE (2 mmol) was dissolved in AcOH (15 ml), the solution was placed in an alumina bath inside a microwave oven and irradiated at 900 W for 0.05–0.13 h (Table 1). After the reaction was complete as indicated by TLC, the resulting mixture was treated with K_2CO_3 (0.5 g) and stirred for 0.6 h. The mixture was then filtered to remove the precipitated polysulfonamide, and the filtrate was evaporated under a reduced pressure to leave a crude product, which gave pure pyrazoles **3a**–**r** in 82–98% yields upon recrystallization from ethanol (Table 1). All the pyrazoles were characterised by IR, ^{1}H and ^{13}C NMR spectroscopy and compared with the literature data.[6,17,18]

3-(4-Methylphenyl)-1-phenyl-5-(4-isopropylphenyl)pyrazole **3q**: yield, 86%; yellow solid; mp 57–59 °C (from EtOH). IR (KBr, ν/cm^{-1}): 1597, 1498. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.22–7.90 (m, 14H, H_{Ar}), 2.93 (sept., 1H, CH), 2.40 (s, 3H, Me), 1.3 (d, 6H, Me). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 152.8 (C=N), 148.6, 139.5, 138.4, 130.3, 128.7, 127.4, 127.2, 126.7, 125.9. Found (%): C, 85.28; H, 6.78; N, 7.92. Calc. for $C_{25}H_{24}N_2$ (%): C 85.23; H, 6.82; N, 7.95.

1-Phenyl-5-(2-phenylethenyl)-3-(2-thienyl)pyrazole **3r**: yield, 98%; yellow solid; mp 71–73 °C. IR (KBr, ν/cm^{-1}): 1595, 1493. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.09–7.75 (m, 16H, H_{Ar}). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 151.5 (C=N), 144.3, 135.2, 130.5, 128.7, 128.12, 127.4, 127.3, 126.4, 125.6, 124.4, 123.2, 122.2, 117.4 (C-5 in pyrazole), 97.1 (C-4 in pyrazole). Found (%): C, 76.86; H, 4.82; N, 8.57. Calc. for $C_{21}H_{16}N_2S$ (%): C, 76.83; H, 4.88; N, 8.53.