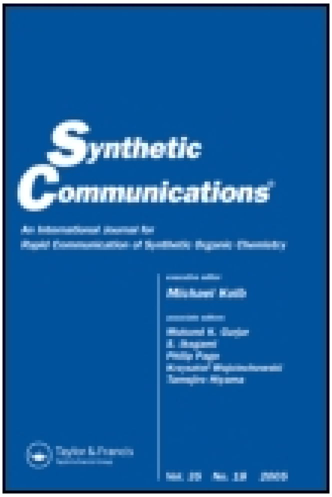

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Microwave-Assisted Aromatization of 1,3,5-Trisubstituted 2-Pyrazolines by $Bi(NO_3)_3 \cdot 5H_2O$, as a Novel and Convenient Oxidizing Agent

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Microwave-Assisted Aromatization of 1,3,5-Trisubstituted 2-Pyrazolines by $Bi(NO_3)_3 \cdot 5H_2O$, as a Novel and Convenient Oxidizing Agent

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Abstract: Bismuth(III) nitrate pentahydrate, $Bi(NO_3)_3 \cdot 5H_2O$, has been used as a mild, efficient, and inexpensive oxidant for the oxidative aromatization of several 1,3,5-trisubstituted 2-pyrazolines to pyrazoles in acetic acid under microwave irradiation with good to excellent yields.

Keywords: Aromatization, $Bi(NO_3)_3 \cdot 5H_2O$, bismuth(III) nitrate pentahydrate, microwave irradiation, 1,3,5-trisubstituted pyrazolines

During the past few decades, a considerable portion of research publications and reviews have been allocated to the application of microwave technology in organic synthesis.[1] Microwave irradiation has received much attention because it requires short reaction times and provides simplicity in handling, enhanced reaction yields, and high-purity products. Furthermore, the oxidative aromatization of 1,3,5-trisubstituted 2-pyrazolines to pyrazoles is of great biological importance because of their analgesic, antiinflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, antidiabetic,

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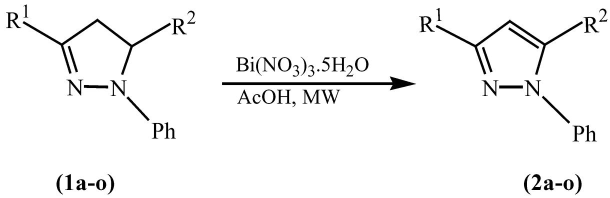
and antibacterial activities.[2,3] We have previously reported on the convenient preparation of 2-pyrazolines from reactions between hydrazines and chalcone intermediates, which can be generated from reactions of aromatic ketones with aldehyeds.[4–6] In view of the simple preparation of 2-pyrazolines, their aromatization by suitable oxidants should provide a convenient approach to pyrazoles. In this regard, a variety of oxidizing agents such as $Zr(NO_3)_4$,[7] Pd/C,[8] Co(II) and oxygen,[9] MnO_2,[10] iodobenzene diacetate,[11] and lead tetraacetate[12] have been reported. However, most of these reagents present several disadvantages including long reaction times, unavailability of the reagents, toxicity because of the presence of certain toxic elements in these reagents, hard workup, and unsatisfactory yields of the products. Thus, in view of these drawbacks, there is a need to search for new high-yielding, environmentally safe, and cheaply available reagents for conversion of 2-pyrazolines to pyrazoles. In continuation of our ongoing research on oxidation of 1,3,5-trisubstituted 2-pyrazolines,[13–19] herein we report an efficient oxidative aromatization of 1,3,5-trisubstituted 2-pyrazolines to their corresponding pyrazoles using crystalline $Bi(NO_3)_3 \cdot 5H_2O$ under microwave irradiation (Scheme 1).

Because of the versatility of $Bi(NO_3)_3 \cdot 5H_2O$ as a useful reagent in organic synthesis,[20–23] we examined the aromatization of 1,3,5-trisubstituted 2-pyrazolines **(1a–o)** to their corresponding pyrazoles **(2a–o)** under microwave irradiation using this reagent and found it to be an effective oxidant with high yields of products (92–99%) and very short reaction times (35–60 s) (Tables 1 and 2).

EXPERIMENTAL

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



Scheme 1.

Table 1. Substrates (**1a–o**) and their corresponding products (**2a–o**)

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**	p-$CH_3OC_6H_4$	o-ClC_6H_4
1l	**2l**	Ph	p-$CH_3OC_6H_4$
1m	**2m**	Ph	p-$NO_2C_6H_4$
1n	**2n**	Ph	m-ClC_6H_4
1o	**2o**	Ph	p-BrC_6H_4

Table 2. Microwave-assisted aromatization of 1,3,5-trisubstituted 2-pyrazolines by $Bi(NO_3)_3 \cdot 5H_2O$

				Melting point (°C)	
Substrate	Product[a]	Time (s)	Yield (%)[b]	Found	Literature[c]
1a	**2a**	40	99	148–150	151–152
1b	**2b**	35	98	139–141	136–138
1c	**2c**	55	96	100–102	95–98
1d	**2d**	50	98	73–76	70–72
1e	**2e**	60	95	82–84	84–86
1f	**2f**	45	99	77–79	75–77
1g	**2g**	40	97	102–104	101–103
1h	**2h**	60	99	79–81	75–78
1i	**2i**	50	94	127–130	130–133
1j	**2j**	45	96	70–72	72–75
1k	**2k**	45	94	66–69	63–65
1l	**2l**	50	98	75–77	77–78
1m	**2m**	50	94	139–141	143
1n	**2n**	55	92	93–95	91
1o	**2o**	55	95	126–128	131

[a] All the isolated products were characterized on the basis of their physical properties and ^1H NMR, ^{13}C NMR, and IR spectra and by direct comparison with authentic compounds.

[b] Isolated yields.

[c] Literature data, **2a–k**,[17] **2l–m**,[11] and **2n–o**.[10]

Oxidation of 1,3,5-Trisubstituted 2-Pyrazolines with $Bi(NO_3)_3 \cdot 5H_2O$: General Procedure

Crystalline $Bi(NO_3)_3 \cdot 5H_2O$ (1.2 mmol) was added to a flask containing 1,3,5-trisubstituted 2-pyrazolines **(1a–o)** (2 mmol) dissolved in glacial AcOH (10 ml). The resulting mixture was then placed in an alumina bath inside a microwave oven (900 W) and irradiated for 30–60 s. After complete conversion of the substrate as monitored by TLC using a mixture of ethyl acetate and n-hexane (1 : 9), the mixture was quenched with $NaHCO_3$ solution (5%) and extracted with CH_2Cl_2 (2 × 10 ml). Then, the organic layer was dried over anhydrous $MgSO_4$ and evaporated to leave an oily residue, which, upon crystallization from aqueous EtOH (96%), gave yellow crystalline products **(2a–o)** in 92–99% yield (Table 1).

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