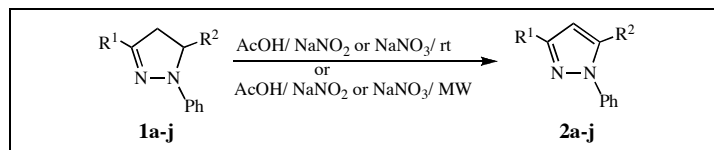


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Microwave-assisted aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles by *in-situ* generation of NO<sup>+</sup> and NO<sub>2</sub><sup>+</sup> respectively from sodium nitrite and sodium nitrate in acetic acid has been carried out efficiently under mild reaction conditions in good to excellent yields.

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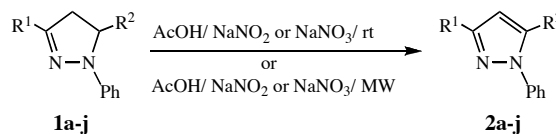
## INTRODUCTION

Application of microwave irradiation as a non-conventional energy source has found considerable interest in organic reactions including heterocyclic chemistry [1]. This has been substantiated by the appearance of many research publications and reviews in the literature during the last few decades [2]. The advantages of microwave irradiation over the classical thermal conditions probably stems from its simplicity in handling, increased reaction rates, and improved yields that render it a versatile technique in organic synthesis [3]. Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles, conveniently prepared from the reaction of appropriate chalcones with arylhydrazines [4], is of considerable synthetic and biological value [5]. The pyrazoles among other five-membered heterocycles often possess important biological and medicinal activities as analgesic, anti-inflammatory, antipyretic, anti-arrhythmic, psycho analeptic, antidiabetic and antibacterial agents [6]. A variety of oxidants such as zirconium nitrate [7], carbon-activated oxygen [8], Pd/C/acetic acid [9], cobalt soap of fatty acids [10], iodobenzene diacetate [11], lead tetraacetate [12], manganese dioxide [13], potassium permanganate [14], silver nitrate [15], mercury oxide [16], molecular oxygen in catalytic amount of *N*-hydroxyphthalimide (NHPI) and cobalt acetate [17], and iodine pentoxide or iodic acid/sodium bromide [18], have been previously reported; most suffer from the use of excess reagent, longer reaction times, higher temperatures, acidic media, side product formation and residual toxicity in the products due to the presence of toxic metal cations like Co(II), Pd(IV), Hg(II), Mn(IV and VII), Ag(I) and Zr(IV) added as catalysts. In the last few years, we have been interested to tackle the limitations and drawbacks allocated to above-mentioned previously reported protocols, by reporting more robust and readily

accessible reagents for the oxidative aromatization of 2-pyrazolines to 2-pyrazoles including 1,3-dibromo-5,5-dimethylhydantoin (DBH) [19], *N*-bromosulphonamides [20], silica-supported *N*-bromosuccinimide [21], trichloroisocyanuric acid [22], calcium hypochlorite [23], bismuth nitrate pentahydrate [24], and 4-(*p*-chlorophenyl)-1,3,4-triazole-3,5-dione [25].

In continuation of our studies in this regard, and also in light of our knowledge about sodium nitrite and successfully utilized in various organic reactions [26], we decided to examine a simple, cheap and efficient method for the conversion of a number of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles into the corresponding pyrazoles by NO<sup>+</sup> and NO<sub>2</sub><sup>+</sup> generated *in-situ* respectively from sodium nitrate as versatile and highly useful reagents sodium nitrite and sodium nitrate in acetic acid under microwave acceleration condition (Scheme 1).

**Scheme 1**



## RESULTS AND DISCUSSION

According to the experimental results collected in Tables 1 and 2, more efficient conversion of 2-pyrazolines occurred under microwave irradiation in acetic acid to yield the corresponding pyrazoles **2a-j** in shorter reaction times and higher yields (54-90%) when compared with conventional thermal condition. It is important to note that, when these reactions were conducted in other solvents such as methanol, acetonitrile or methylene chloride, no significant conversion was observed and

nearly all the starting pyrazolines remained unreacted. The unique role of acetic acid in promoting these conversions could be possibly attributed to: (i) higher solubility of sodium nitrite and sodium nitrate in acetic acid; (ii) acetic acid-assisted generation of  $\text{NO}^+$  and  $\text{NO}_2^+$  and (iii) deprotonation of the reaction intermediate ring systems by acetate anion produced in the reaction mixture, as shown in the suggested mechanism (Scheme 2). The application of microwave (MW) irradiation technique has profound effect for the acceleration of the reactions with providing short times, high conversions. The rate-enhancing role of microwave irradiation in Scheme 2 is now believed to be presumably due to the selective absorption of MW energy by polar acetic acid molecules that brings about rapid superheating of these molecules. Numerous repetitions of the reactions under different molar conditions indicated that, the most effective conversions occur when stoichiometric amounts of the sodium nitrite and sodium are taken in the reaction mixtures.

In conclusion, the advantages allocated to this method include: easy handling, low cost, easy accessibility, high stability and nontoxicity of the reagents used, mild reaction conditions and high yields of the products. These properties render this as efficient and convenient method to oxidize 2-pyrazolines to the pyrazoles.

Scheme 2

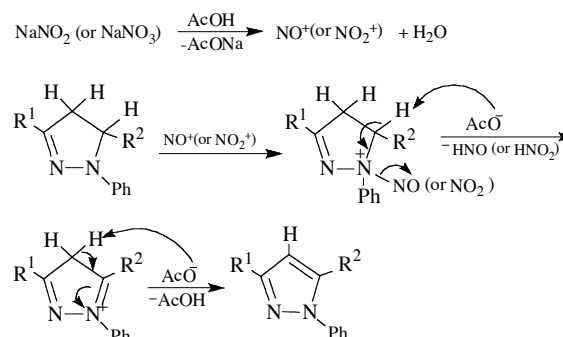


Table 1

Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **1a-j** (1 mmol) with sodium nitrite (1 mmol) at room temperature and under microwave irradiation conditions in acetic acid [a].

Substrate	Product [b]	R <sup>1</sup>	R <sup>2</sup>	Time (min)	Yield [c] (%)	Mp (°C)	
						Found	Reported [d]
<b>1a</b>	<b>2a</b>	Ph	Ph	5 (0.17)	82 (90)	138-140	139-140
<b>1b</b>	<b>2b</b>	Ph	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	20 (0.34)	74 (80)	79-81	78-80
<b>1c</b>	<b>2c</b>	Ph	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	20 (0.5)	56 (74)	140-142	142-143
<b>1d</b>	<b>2d</b>	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	15 (0.34)	56 (84)	112-114	114-115
<b>1e</b>	<b>2e</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	Ph	20 (0.34)	68 (80)	76-78	77-79
<b>1f</b>	<b>2f</b>	2-naphthyl	4-ClC <sub>6</sub> H <sub>4</sub>	20 (0.34)	80 (80)	130-132	130-133
<b>1g</b>	<b>2g</b>	2-naphthyl	2-ClC <sub>6</sub> H <sub>4</sub>	20 (0.34)	56 (78)	68-70	67-70
<b>1h</b>	<b>2h</b>	2-naphthyl	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	10 (0.34)	78 (80)	146-148	148-150
<b>1i</b>	<b>2i</b>	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	20 (0.5)	72 (80)	128-130	126-128
<b>1j</b>	<b>2j</b>	Ph	3-ClC <sub>6</sub> H <sub>4</sub>	20 (0.34)	68 (78)	92-94	93-95

[a] The reaction times and yields obtained under microwave irradiation are given in parentheses. [b] All the isolated products were characterized on the basis of their physical properties and ir, <sup>1</sup>H nmr and <sup>13</sup>C nmr spectral analysis and by direct comparison with authentic materials. [c] Isolated yields. [d] Literature data, **2a-c** [7], **2d-j** [24].

Table 2

Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **1a-j** (1 mmol) with sodium nitrate (1 mmol) at room temperature and under microwave irradiation conditions in acetic acid [a].

Substrate	Product [b]	R <sup>1</sup>	R <sup>2</sup>	Time (min)	Yield [c] (%)	Mp (°C)	
						Found	Reported [d]
<b>1a</b>	<b>2a</b>	Ph	Ph	120 (0.34)	68 (72)	140-142	139-140
<b>1b</b>	<b>2b</b>	Ph	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	360 (0.67)	52 (70)	79-81	78-80
<b>1c</b>	<b>2c</b>	Ph	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	340 (0.67)	48 (62)	139-141	142-143
<b>1d</b>	<b>2d</b>	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	385 (0.83)	54 (70)	115-116	114-115
<b>1e</b>	<b>2e</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	Ph	300 (0.67)	62 (74)	78-80	77-79
<b>1f</b>	<b>2f</b>	2-naphthyl	4-ClC <sub>6</sub> H <sub>4</sub>	335 (0.67)	60 (70)	132-134	130-133
<b>1g</b>	<b>2g</b>	2-naphthyl	2-ClC <sub>6</sub> H <sub>4</sub>	345 (0.67)	60 (62)	69-71	67-70
<b>1h</b>	<b>2h</b>	2-naphthyl	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	150 (0.5)	74 (80)	149-151	148-150
<b>1i</b>	<b>2i</b>	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	200 (0.67)	56 (76)	126-128	126-128
<b>1j</b>	<b>2j</b>	Ph	3-ClC <sub>6</sub> H <sub>4</sub>	200 (0.5)	60 (70)	94-96	93-95

[a] The reaction time and yields obtained under microwave irradiation are given in parentheses. [b] All the isolated products were characterized on the basis of their physical properties and ir, <sup>1</sup>H nmr and <sup>13</sup>C nmr spectral analysis and by direct comparison with authentic materials. [c] Isolated yields. [d] Literature data, **2a-c** [7], **2d-j** [24].

## EXPERIMENTAL

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. Microwave-assisted reactions were conducted in a commercial Panasonic model MX30PG microwave oven (1000 Watt). 4,5-Dihydro-1H-pyrazoles were all prepared according to our previously reported procedure [4]. Pyrazoles were characterized on the basis of their melting points and ir,  $^1\text{H}$  nmr, and  $^{13}\text{C}$  nmr spectral analysis and compared with reported data.

**General Procedure for the Aromatization of 1,3,5-Trisubstituted Pyrazolines with Sodium Nitrite and Sodium Nitrate in Acetic Acid.** Crystalline sodium nitrite (or sodium nitrate) (1 mmol) was added to a flask containing 1,3,5-trisubstituted 2-pyrazolines **1a-j** (1 mmol) dissolved in glacial acetic acid (5 ml). The reaction mixture was stirred at room temperature for the time given in tables 1 and 2. After the complete conversion of the substrate as indicated by tlc analysis, the mixture was quenched with sodium bicarbonate solution (5%) and extracted with diethyl ether (10 mL). Then organic layer was dried over anhydrous sodium sulfate and concentrated to give the crude products **2a-j** which were purified by recrystallization from ethanol (96%). In a separate set of experiments, these reactions were all repeated under microwave irradiation condition in an alumina bath using a MX30PG1000 microwave oven.

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