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Tetrahedron Letters 49 (2008) 4026–4028
Tetrahedron Letters

Green iodination of pyrazoles with iodine/hydrogen peroxide in water

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Received 13 March 2008; revised 9 April 2008; accepted 14 April 2008
Available online 6 May 2008

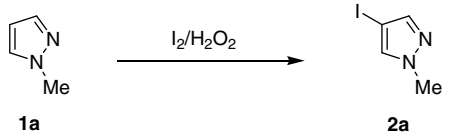
Abstract

In this Letter, we describe a practical, green iodination of pyrazoles to form the corresponding 4-iodopyrazole derivatives. The reaction takes place in water, using only 0.5 equiv of iodine and 0.6 equiv of hydrogen peroxide, a system that generates water as the only reaction by-product.

Pyrazole moieties, particularly those functionalized at the 4-position, are frequently found in biologically active compounds.[1,2] 4-Iodopyrazoles, which possess a useful functional handle at the 4-position, represent valuable intermediates toward the syntheses of these targets. For example, these compounds have been employed as participants in cross-coupling chemistry[3] and for halogen-metal exchange reactions.[4] Unfortunately, existing methodologies for the synthesis of 4-iodopyrazoles are not ideal for large scale processing.[5] The use of iodine with potassium iodide[6] or iodine monochloride[4a,7] to iodinate pyrazoles suffers from limited substrate scope and the use of excess reagent. Iodine, in addition to ammonium hydroxide[8] or HIO_3,[9] reacts unselectively with pyrazoles to form di- and tri-iodopyrazoles. The combination of iodine and diacetoxyiodobenzene provides a simple method for the regioselective synthesis of 4-iodopyrazoles, but requires chromatography to remove the reagent by-products.[10] *N*-Iodosuccinimide iodinates pyrazoles in a variety of solvents, but is expensive for use on scale.[11] The oxidative iodination of pyrazoles using only 0.6 equiv of iodine and 0.6 equiv of ceric ammonium nitrate (CAN) generates a large amount of cerium waste that can be difficult to remove.[12] These last three methods also suffer from problems of atom economy.

We sought to develop a process-friendly, efficient, and green procedure for the 4-iodination of pyrazoles. Despite the shortcoming of the I_2/CAN system mentioned above, this result provided the foundation for the development of our green iodination of pyrazoles. Additionally, it has been shown that stoichiometric iodine, aqueous hydrogen peroxide, and catalytic acid can be employed for the iodination of dimethoxy- and trimethoxy-substituted aromatic compounds.[13] The same group had earlier demonstrated that alkenes, later demonstrating the viability of a H_2O_2/I_2 system in water for similar iodinations[14] undergo Markovnikov iodo-alkoxylation in alcohol solvent, using 0.5 equiv of iodine and hydrogen peroxide.[15] The fusion of these concepts has enabled the development of an I_2/H_2O_2 system for the 4-iodination of pyrazoles (Scheme 1). In this Letter, we present the facile, green synthesis of 4-iodopyrazoles in water with additional water as the only reaction by-product. This technology has been employed on a large scale with minimal waste formation.

Initial efforts focused on the iodination of 1-methylpyrazole (**1a**). Iodination was attempted in a series of solvents



1a **2a**

Scheme 1.

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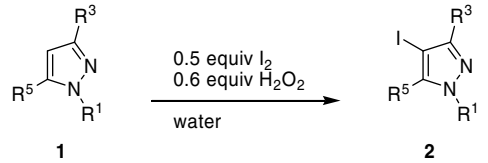
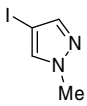
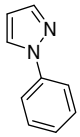
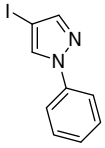
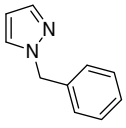
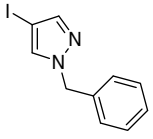
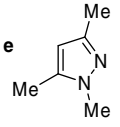
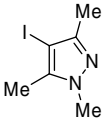
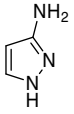
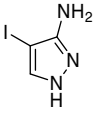
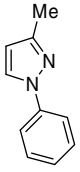
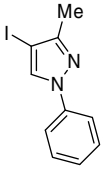
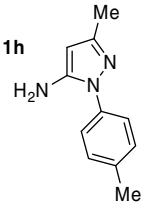
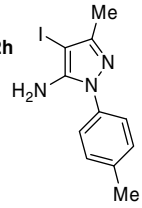
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.082

(water, methanol, ethanol, isopropanol, acetonitrile) using 0.5 equiv of iodine and 0.6 equiv of 30% hydrogen peroxide. Gratifyingly, all of these conditions afforded the desired 4-iodo-1-methylpyrazole (**2a**) in moderate to high conversions and high selectivity for mono-iodination at the 4-position. Optimal conversion was obtained in aqueous solution. 1-Methylpyrazole is water-soluble, but identical results were achieved for the iodination of more nonpolar substrates that are only sparingly soluble in water. The use of water as solvent offered two practical advantages: (1) most products could be isolated by direct crystallization from the corresponding reaction mixtures and (2) the aqueous waste stream and minimal organic content were easily discarded.

Table 1
Iodination of pyrazoles **1a**–**h**



1 **2**

Entry	Substrate	Product	Isolation method[a]	Isolated yield[b] (%)
1	**1a** 	**2a** 	A	91
2	**1b** 	**2b** 	A	63
3	**1c** 	**2c** 	A	94
4	**1d** 	**2d** 	B	67
5	**1e** 	**2e** 	A	95
6	**1f** 	**2f** 	A	82
7	**1g** 	**2g** 	B	100
8	**1h** 	**2h** 	A	75

[a] Method A: Isolated by direct crystallization from the reaction mixture following treatment with 5% $NaHSO_{3(aq)}$. Method B: isolated by work-up in EtOAc, followed by column chromatography.

[b] Product purity was confirmed by ^1H NMR spectroscopy.

The reaction conditions employed for the regioselective 4-iodination of 1-methylpyrazole were applied to a series of pyrazole derivatives **1a**–**h**, leading to the isolation of 4-iodo compounds **2a**–**h** in 63–100% yield (Table 1). All starting material substitution patterns allowed for the regioselective formation of the corresponding 4-iodopyrazole products. The reaction proceeded well for substrates without substitution on nitrogen and with *N*-alkyl (entries 1, 4 and 5) and *N*-aryl substituents (entries 3, 7, and 8). Substitution was also tolerated at both the 3- and 5-positions. Electron-rich pyrazoles underwent rapid iodination (<1 h, entry 6), while other substrates required extended reaction times (24–72 h). Most products crystallized directly from the reaction mixture and were isolated as pure after treatment of the suspension with 5% $NaHSO_{3(aq)}$ (method A).[16] Those products that failed to crystallize were isolated by work-up and silica gel chromatography (method B).[17]

The utility of this green iodination procedure was demonstrated on a large scale; 7.0 kg of 1-methylpyrazole (**1a**) was subjected to the optimized reaction conditions affording 16.4 kg (91% yield) of 4-iodo-1-methylpyrazole (**2a**). Each iodine atom of I_2 was incorporated into the product, meaning that the primary by-product from this procedure was the water formed by the reduction of H_2O_2. As such, the filtrate and subsequent water washes were easily disposed of as neutral aqueous waste.

We have developed a green procedure for the regioselective 4-iodination of pyrazoles using only 0.5 equiv of iodine and 0.6 equiv of hydrogen peroxide in water. This protocol was successful for a series of differentially substituted pyrazole starting materials to afford the corresponding 4-iodopyrazole products in good to excellent yields. In many cases, the product crystallized directly from the reaction mixture, resulting in water as the only significant reaction by-product. Efforts are underway to identify other heterocycles that also undergo this green iodination chemistry.

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16. *Method A. 4-Iodo-1-methylpyrazole* (**2a**): To a solution of 1-methylpyrazole (20.0 mL, 0.241 mol) and iodine (30.7 g, 0.121 mol) in water (85.0 mL) was added 30% $H_2O_{2(aq)}$ (16.4 mL, 0.144 mol). The reaction mixture was stirred for 24 h at room temperature. At this time, the reaction was complete, and a cold solution of 5% $NaHSO_{3(aq)}$ (50.0 mL) was added to the mixture, affording an off-white slurry. The product was filtered and washed with water to provide **2a** as an off-white crystalline solid (45.6 g, 91%). The material was purified by ^{1}H NMR spectroscopy.
17. *Method B. 4-Iodo-3-methyl-1-phenylpyrazole* (**2g**): To a mixture of 3-methyl-1-phenylpyrazole (3.00 g, 18.6 mmol) and iodine (2.36 g, 9.29 mmol) in water (12.8 mL) was added 30% $H_2O_{2(aq)}$ (1.14 mL, 11.2 mmol), and the reaction mixture was stirred for 52 h at room temperature. At this time, the reaction was complete, and a cold solution of 5% $NaHSO_{3(aq)}$ (10.0 mL) was added to the mixture. The biphasic mixture was extracted with ethyl acetate, washed with water, and evaporated under reduced pressure to afford a yellow oil. This material was purified by silica gel chromatography to afford **2g** as a light yellow oil (5.27 g, 100%). The material was purified by ^{1}H NMR spectroscopy.