# Iodoxybenzoic Acid (IBX): An Efficient and Novel Oxidizing Agent for the Aromatization of 1,4-Dihydropyridines[1]

J. S.Yadav,* B. V. S. Reddy, A. K. Basak, G. Baishya, A. Venkat Narsaiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax yadavpub@iict.res.in; E-mail: +91(40)27160512

*Received 7 July 2005; revised 17 August 2005*

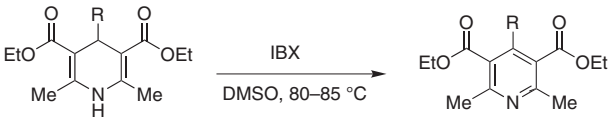
**Abstract:** Hantzsch 1,4-dihydropyridines undergo smooth aromatization catalyzed by iodoxybenzoic acid (IBX) to afford the corresponding pyridine derivatives in high yields. All the reactions were carried out in DMSO solvent at 80–85 °C for a period of two to four hours to complete conversion of the substrates.

**Keywords:** hypervalent iodine reagents, dihydropyridines, aromatization, DMSO, pyridine derivatives

Hypervalent iodine reagents have recently attracted much attention as powerful oxidants in organic synthesis because of their selective and mild oxidizing properties.[2] Among the various hypervalent iodine reagents, *o*-iodoxybenzoic acid (IBX) is a versatile oxidizing agent due to its high efficiency, ease of preparation, mild reaction conditions and its stability against moisture and air. A wide range of functional group tolerance and high-yielding reactions without over oxidation have made IBX very familiar for the oxidation of various alcohols. Recently, the use of IBX as a mild oxidant has been extended to many other elegant oxidative transformations by Nicolaou et al.[3]

Hantzsch 1,4-dihydropyridines are often regarded as the models of the naturally reduced nicotinamine adenine dinucleotide [NADH] co-enzyme which functions as redox reagent for biological reactions. 1,4-Dihydropyridines are rapidly emerging as the most important class of drugs for the treatment of cardiovascular disease.[4] These compounds generally undergo oxidative metabolism in the liver by the action of cytochrome p-450 to form the corresponding pyridine derivatives, which exhibit anti-hypoxic and anti-ischemic activities. Further, metabolism involves the cleavage of the ester groups. Some of the representatives of this class show acaricidal, insecticidal, bactericidal and herbicidal activities. On the other hand, these compounds are starting materials for the synthesis of antibacterial 1,6-naphthyridines and 1,2-benzisoazalenes.[5]

The oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous issues in organic chemistry. Generally, strong oxidants such as $CrO_3$, $HNO_3$, $KMnO_4$, cupric nitrate, ferric nitrate and CAN, and pyridinium chromate have been used to accomplish this oxidation.[6] However, many of these methods suffer from the use of strong acidic conditions and require extended reaction times or the need of excess oxidant and also the yields reported are far from satisfactory. Thus, there is a need for the development of novel reagents that provide beneficial levels of mildness and efficiency.

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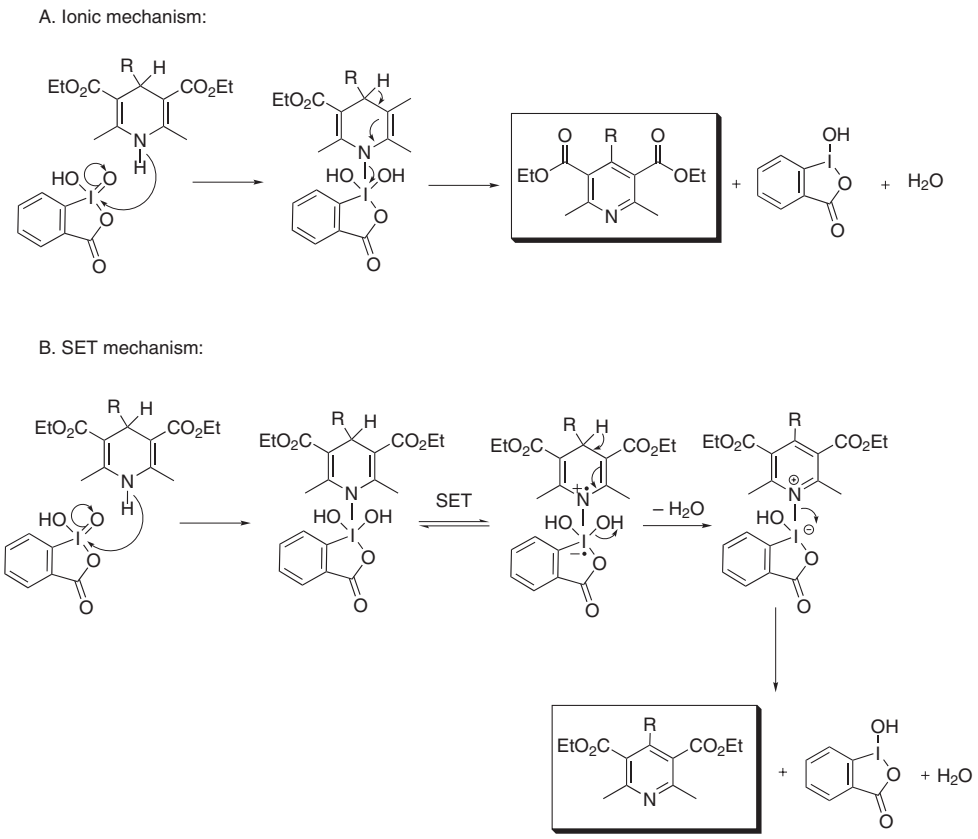
**Scheme 1**

In continuation of our interest in developing new synthetic methodologies[7] herein, we wish to report an efficient protocol for the aromatization of Hantzsch 1,4-dihydropyridines using the inexpensive and readily available iodoxybenzoic acid (IBX) as the novel oxidant (Scheme 1). For instance the treatment of diethyl 2,6-dimethyl-4-(*p*-methoxyphenyl)pyridine-3,5-dicarboxylate with IBX (1.5 equiv) in DMSO at 80–85 °C for 2.5 hours afforded the corresponding pyridine derivative **2a** in 86% yield. In a similar manner, various Hantzsch 1,4-dihydropyridines were aromatized without any problem. To establish the generality of this method, various alkyl, aryl and heterocyclic substituents present on Hantzsch 1,4-dihydropyridines were oxidized under these reaction conditions. In all cases, the reactions proceeded readily with high efficiency. The influence of various solvents on the yield of the reaction was investigated using EtOAc, MeCN, $CH_2Cl_2$, $CHCl_3$, THF and MeOH. The oxidation reaction takes place smoothly in DMSO solvent and the products were obtained in very good yields. This can be attributed to the enhanced solubilizing power of the solvent for the oxidation as well as the substrate. In general, the reactions are very clean, high yielding and complete within two to four hours reaction time.

The possible mechanism for the oxidation reaction using IBX, proceed via an ionic, concerted pathway or by an ensuing single electron transfer (SET) from 1,4-dihydropyridine to the iodoxybenzoic acid to afford a nitrogen radical cation, followed by fragmentation (Scheme 2). Both of these processes consequently supply the desired pyridine derivatives along with *o*-iodosobenzoic acid (IBA). This method is very mild and tolerates several substituents present on alkyl, alkoxy, benzyl, cinnamyl and heterocyclic groups, which were in the 4-position of dihydropyridines. No debenzylation or dealkylation was ob-

**SYNTHESIS** 2006, No. 3, pp 0451–0454
Advanced online publication: 21.12.2005
DOI: 10.1055/s-2005-918519; Art ID: Z13405SS




**Scheme 2** Proposed ionic (A) and single-electron-transfer (B) mechanism leading to the formation of pyridine derivatives mediated by IBX.

**Table 1** Aromatization of Hantzsch 1,4-Dihydropyridines with IBX in DMSO

| Entry | Substrate | Product[a] | Reaction Time (h) | Yield (%)[b] | Mp[c] |
|---|---|---|---|---|---|
| a | 4-$MeOC_6H_4$ | **2a** | 2.5 | 86 | 51–52 |
| b | 4-$NO_2C_6H_4$ | **2b** | 3.5 | 88 | 112–113 |
| c | $C_6H_5$ | **2c** | 2.0 | 90 | 62–63 |
| d | $C_6H_5CH$=CH | **2d** | 3.0 | 83 | 161–162 |
| e | 2-Furyl | **2e** | 2.0 | 90 | – |
| f | $C_6H_5CH_2$ | **2f** | 4.0 | 84 | – |
| g | 4-$CH_3C_6H_4$ | **2g** | 3.5 | 89 | 71–72 |
| h | $CH_3(CH_2)_4CH_2$ | **2h** | 4.0 | 80 | – |
| i | 3,4$(OCH_3)_2C_6H_3$ | **2i** | 2.5 | 90 | 100–101 |
| j | $(CH_3)_2CH$ | **2j** | 3.5 | 83 | – |
| k | 4-$ClC_6H_4$ | **2k** | 3.0 | 88 | 69–72 |
| l | 2-Thienyl | **2l** | 3.5 | 82 | 79–80 |
| m | 2-$NO_2C_6H_4$ | **2m** | 4.0 | 84 | 73–75 |
| n | 3-Pyridyl | **2n** | 3.0 | 80 | 84–86 |
| o | $CH_3(CH_2)_8CH_2$ | **2o** | 4.0 | 82 | |

[a] All the products were characterized by $^1$H NMR, IR and mass spectroscopy and compared with literature reports.[5]
[b] Yields are isolated and unoptimized.
[c] Melting points are uncorrected.

served under the present reaction conditions, which are normally observed in aromatization of dihydropyridines by other oxidants. No side-products are formed during the aromatization by IBX while nitrated side-products are generally observed in the aromatization of dihydropyridines with metallic nitrates. The results obtained with various 4-substituted 1,4-dihydropyridines are summarized in the Table 1.

In summary, we showed that IBX could function as an efficient oxidant for the aromatization of Hantzsch 1,4-dihydropyridines. This method offers significant advantages such as the use of inexpensive, air- and moisture-stable oxidant, mild reaction conditions and compatibility with a variety of substituents present in the dihydropyridine skeleton, and easy workup procedure for the isolation of products.

1,4-Dihydropyridines were synthesized according to the reported procedure.[5e] Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1$H NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All the products physical and spectroscopic data were compared with those reported in the literature.

**General Procedure**

A mixture of Hantzsch dihydropyridine (2 mmol) and IBX (3 mmol) in DMSO (2 mL) was heated at 80–85 °C for 2–4 h (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water and extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography.

**Diethyl 1,6-Dimethyl-4-(*p*-methoxyphenyl)pyridine-3,5-dicarboxylate (2a)**

IR (KBr): 3069, 2984, 2843, 1736, 1559, 1441, 1372, 1231, 1176, 1015, 953, 867, 741 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.10 (t, *J* = 7.5 Hz, 6 H), 2.53 (s, 6 H), 3.78 (s, 3 H), 3.96 (q, *J* = 7.5 Hz, 4 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.2, 23.5, 56.1, 62.7, 114.6, 127.9, 128.5, 130.2, 146.4, 156.7, 160.2, 168.9.

EIMS: *m*/*z* (%) = 357 (26) [M$^+$], 299 (37), 268 (23), 180 (100), 141 (62), 88 (32), 51 (47).

**Diethyl 1,6-Dimethyl-4-cinnamylpyridine-3,5-dicarboxylate (2d)**

IR (KBr): 3074, 2961, 2836, 1731, 1596, 1552, 1468, 1381, 1241, 1109, 1053, 962, 836, 736 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.14 (t, *J* = 7.5 Hz, 6 H), 2.46 (s, 6 H), 4.08 (q, *J* = 7.5 Hz, 4 H), 6.65 (d, *J* = 15.8 Hz, 1 H), 7.21 (d, *J* = 15.8 Hz, 1 H), 7.32–7.60 (m, 5 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.8, 22.9, 62.3, 120.4, 122.9, 126.3, 127.1, 128.4, 136.2, 137.1, 142.9, 154.8, 168.6.

EIMS: *m*/*z* (%) = 353 (42) [M$^+$], 295 (24), 207 (19), 168 (78), 127 (100), 77 (65), 51 (31).

**Diethyl 1,6-Dimethyl-4-*n*-hexylpyridine-3,5-dicarboxylate (2h)**

IR (KBr): 2991, 2879, 1739, 1724, 1576, 1438, 1286, 1221, 1107, 1033, 923, 847, 759 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 6.5 Hz, 3 H), 1.28 (t, *J* = 6.8 Hz, 6 H), 1.33–1.43 (m, 8 H), 1.55 (t, *J* = 6.5 Hz, 2 H), 2.50 (s, 6 H), 4.17 (q, *J* = 6.8 Hz, 4 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.8, 23.2, 23.9, 32.3, 33.9, 62.8, 122.0, 126.9, 145.8, 155.6, 169.2.

EIMS: *m*/*z* (%) = 335 (41) [M$^+$], 277 (22), 189 (100), 150 (18), 109 (42), 71 (53), 43 (41).

## Acknowledgment

AKB and GB thanks to CSIR, New Delhi for the award of fellowship.

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