Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 04 Sep 2009.

To cite this article: Jiang-Min Chen & Xiao-Mei Zeng (2009): β-Cyclodextrin-Catalyzed Mild Aromatization of Hantzsch 1,4-Dihydropyridines with o-Iodoxybenzoic Acid in Water/Acetone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:19, 3521-3526

To link to this article: http://dx.doi.org/10.1080/00397910902788133

Synthetic Communications®, 39: 3521–3526, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902788133

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β-Cyclodextrin-Catalyzed Mild Aromatization of Hantzsch 1,4-Dihydropyridines with *o*-Iodoxybenzoic Acid in Water/Acetone

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Abstract: Hantzsch 1,4-dihydropyridines undergo smooth aromatization oxidized by *o*-iodoxybenzoic acid (IBX) in water/acetone in the presence of β-cyclodextrin (β-CD) to afford the corresponding pyridine derivatives in excellent yields. The IBX and β-CD can be recycled and reused.

Keywords: Aromatization, β-cyclodextrin, Hantzsh 1,4-dihydropyridines, *o*-iodoxybenzoic acid (IBX), pyridine derivatives

Solvent usage is often an integral part of a chemical or manufacturing process. The unavoidable choice of a specific solvent for a desired chemical reaction can have profound economical, environmental, and societal implications. The pressing need to develop alternative solvents to some extent originates from these implications and constitutes an essential strategy in the emerging field of green chemistry.[1,2] The 12 principles are as follows: prevention, atom economy, less hazardous chemical synthesis, safer chemicals, safer solvents, energy efficiency, use of renewable feedstocks, reduction of derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, and inherently safer chemistry

Received August 6, 2008.
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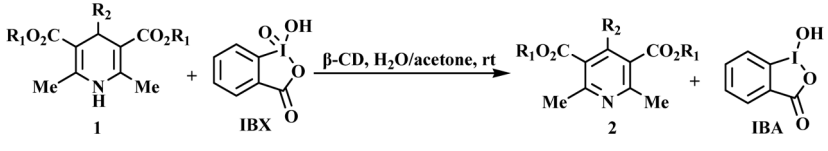
for accident prevention. To meet this end, organic reactions in aqueous medium could reduce the harmful effects of organic solvents. Supramolecule catalysts, such as β-cyclodextrin,[3] employed in this kind of reaction might become more sophisticated.

Hantzsch 1,4-dihydropyridines (**1**, Hantzsch 1,4-DHPs) are widely used as calcium-channel blockers for the treatment of cardiovascular disorder including angina, hypertension, and cardiac arrhythmias.[4] These compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver.[5] In this respect, a convenient preparation of pyridines from 1,4-DHPs is important for the identification of metabolites. Furthermore, the oxidation of Hantzsch 1,4-DHPs provides easy access to pyridine derivatives. Up to now, the aromatization of Hantzsch 1,4-dihydropyridines were well documented.[6] However, most of these reactions were completed in organic solvents or used metal salts in an aqueous medium at elevated temperatures.

o-Iodoxybenzoic acid (IBX), a well-known hypervalent iodine reagent, is stable against moisture and highly efficient. Even though it was discovered some time ago, its significant utilization as a reagent is of recent origin as a result of its insolubility in most solvents except dimethylsulfoxide (DMSO, the only solvent in which it does dissolve).[7] The limited solubility of IBX has also led to many variations.[8] Among these, the method developed by K. Surendra[3b] and coworkers, which includes the use of β-cyclodextrin, may be of most interest. In continuation of our study on the applications of hypervalent iodine reagents in organic synthesis,[9] herein we report a mild and efficient aromatization of Hantzsch 1,4-DHPs with IBX in the presence of β-cyclodextrin (Scheme 1). The present method has advantages such as mild reaction conditions, convenient manipulation, and good yields. The oxidation reagent and catalyst could be regenerated and reused.

The reactions were carried out by dissolving β-cyclodextrin in water at room temperature followed by the addition of Hantzsch 1,4-DHPs and then IBX. The mixture was stirred at room temperature overnight to give the corresponding pyridines. In all cases, excellent yields of pyridines **2** were obtained. 4-Aryl substrates **1a**–**g** (entries **1a**–**1g**) and 4-H-1, 4-DHP derivatives, where $R_2 = H$, **1h**–**i** respectively (entries **1h**–**1i**),



Scheme 1. Aromatization of Hantzsch 1,4-dihydropyridines with IBX in the presence of β-cyclodextrin.

Table 1. β-Cyclodextrin-catalyzed aromatization of Hantzsch 1,4-dihydropyridines with IBX in water/acetone

Entry	R_1	R_2	Product[a]	Yield (%)[b]	Mp (°C)[c]	Lit. Mp (°C)
1a	Et	C_6H_5	**2a**	90	62–63	61–62[6i]
1b	Et	2-Furyl	**2b**	89	Liquid	Liquid[6i]
1c	Et	4-$MeOC_6H_4$	**2c**	94	51–52	49–50[6i]
1d	Et	4-ClC_6H_4	**2d**	91	65–67	65–66[6i]
1e	Me	C_6H_5	**2e**	95	135–137	137[6h]
1f	Me	4-$MeOC_6H_4$	**2f**	93	114–116	115–117[6h]
1g	Me	4-ClC_6H_4	**2g**	90	137–139	138–140[6h]
1h	Et	H	**2h**	92	71–73	70–71[6i]
1i	Me	H	**2i**	96	100–102	101–103[6f]
1a[d]	Et	C_6H_5	**2a**	89	62–63	61–62[6i]

[a]All the products were characterized by melting points, ^{1}H NMR, and IR and compared with literature reports.
[b]Yields are isolated and unoptimized.
[c]Melting points are uncorrected.
[d]Recycled IBX was used.

gave the products of oxidative aromatization **2a**–**i**. This observation is in accord with the reported behavior of these derivatives under other oxidative conditions[6] (Table 1).

In these reactions, iodosobenzoic acid (IBA) obtained from the reduction of IBX has been recycled by oxidation to IBX.[10] Cyclodextrin has also been recovered and reused.

In conclusion, we have presented a mild and simple methodology for the oxidation of a variety of Hantzsch 1,4-DHPs using IBX at room temperature in water/acetone under supramolecular catalysis. The IBX and β-CD can be recycled and reused.

EXPERIMENTAL

Melting points were uncorrected. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ at 25°C using a Bruker Avance 400 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard and are reported in parts per million (ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ at 25°C using a Bruker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard and are reported in ppm. Infrard (IR) spectra were recorded on a Shimadzu IR-408 spectrometer. β-Cyclodextrin, a commercially available reagent, were used without further purification. IBX[10] and Hantzsch 1,4-DHPs[11] were synthesized

followed the methods in literature. ''In vacuo'' refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump. All the known products' physical and spectroscopic data were compared with those reported in the literature.

General Procedure for Aromatization

Hantzsch 1,4-DHP (1 mmol) in acetone (2 mL), was added to a solution of β-cyclodextrin (0.1 mmol) in distilled water (15 mL), followed by IBX (1.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then the product was extracted with ethyl acetate (3×15 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate/hexane (1:3) as eluent. After extraction with ethyl acetate, the reaction mixture was filtered to isolate IBA, and the aqueous phase was lyophilized to obtain the β-CD.

ACKNOWLEDGMENTS

We are grateful to the Foundation of Jiaxing University (Project No. 70105005).

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