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o-Iodoxybenzoic acid (IBX): a versatile reagent for the synthesis of N-substituted pyrroles mediated by β-cyclodextrin in water

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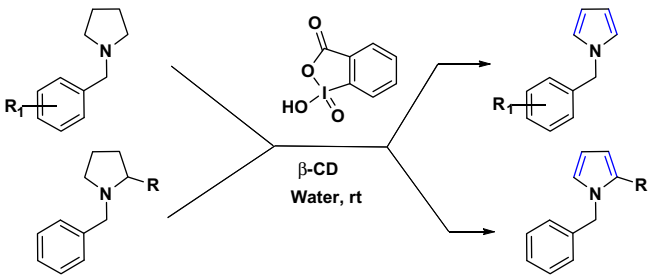
ABSTRACT

o-Iodoxybenzoic acid (IBX), a very mild and efficient hypervalent iodine(V) reagent, aromatizes diversely substituted 1-benzylpyrrolidines and N-substituted L-proline analogues to the corresponding substituted pyrroles in good to excellent yields under mild conditions mediated by β-cyclodextrin in water at room temperature. To the best of our knowledge, this is the first report on IBX, promoting complete aromatization leading to *N*-benzylpyrroles from the corresponding saturated five membered heterocyclic derivatives in water medium.

Hypervalent iodine reagents have attracted significant attention due to their mild and chemoselective oxidizing properties, as well as environ-friendly nature.[1] Due to enormous research work in the field of hypervalent iodine chemistry, a variety of polyvalent iodine reagents have been synthesized[2] for achieving novel and highly useful synthetic organic transformations, as iodine has low ionization potential and the ability to form coordination compounds. Since 1893, IBX was known[3a] as valuable synthetic reagent to carry out numerous selective oxidations such as oxidation of benzylic carbons, dehydrogenation of carbonyl compounds to the corresponding α,β-unsaturated analogues,[3b] oxidation of amines, dehydrogenation of N-heterocycles to the heteroaromatics, oxidative cleavage of dithioacetals and dithioketals,[4] and oxidation of alcohols to carbonyl compounds.[5a,b] Though, IBX is a valuable synthetic reagent to carry out wide organic transformation under impact or heating to >200 °C, it has been found to be explosive and confirmed by Plumb and Harper.[5c]

Pyrrole structural skeleton has gained prominence in heterocyclic chemistry,[6] due to associated applications. Pyrrole motif is also present as an important structural component in a wide variety of natural, biological and pharmacologically potent molecules such as porphyrins, bile pigments, coenzymes and alkaloids. Of these aforementioned classes of compounds, *N*-alkylpyrroles have been given special emphasis due to the widespread applications in the field of medicinal chemistry and material science. Even though, most of the poly *N*-alkyl pyrroles have tunable optoelectronic[7] and HMG-COA reductase inhibition properties,[8] their synthetic routes are limited. The traditional methods for the synthesis of *N*-alkylpyrroles involve robust reaction conditions such as reflux of amines and 2,5-dimethoxytetrahydrofuran in the presence of glacial acetic acid,[9] and conventional heating of pyrrole with benzyl/alkyl halides using ionic liquids in basic medium.[10] However, recently synthesis of *N*-alkylpyrroles is achieved via decarboxylative azomethine ylide generation by the reaction of 3-pyrroline with aldehydes.[11] Rao and co-workers elegantly employed *trans*-4-hydroxy-L-proline, a novel starting material for the synthesis of *N*-alkyl-pyrroles from aldehydes *via* the formation of oxazolidin-5-one from the initially formed imine adduct, followed by decarboxylation, elimination of water and redox isomerization[12a,b] and synthesis of pyrrole-substituted indolinones from the corresponding isatin derivatives.[12c] Owing to the broad spectrum of applications associated with *N*-alkyl pyrroles in various fields, evolving newer synthetic approaches is highly encouraged. As a part of our continuous explorations toward the development of novel methodologies for the synthesis of various heterocyclic compounds mediated by β-cyclodextrin,[13] we describe herein the synthesis of *N*-benzylpyrroles for the first time from the corresponding saturated analogues by the IBX oxidation mediated by β-cyclodextrin in aqueous medium at room temperature (Scheme 1).

Presently organic transformations in aqueous phase have attracted the global attention because of the added advantages of water as an environmentally benign and economically affordable



Scheme 1.

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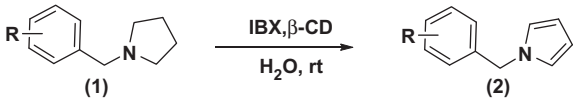
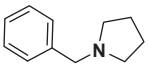
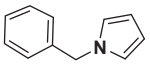
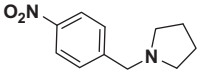
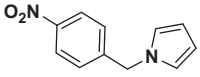
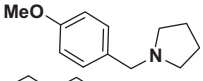
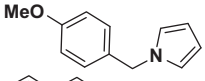
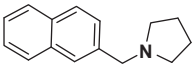
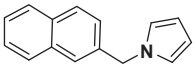
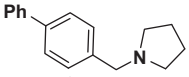
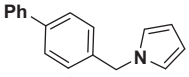
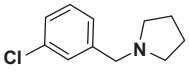
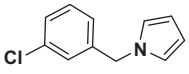
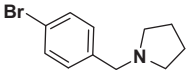
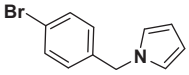
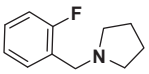
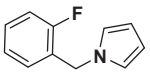
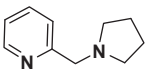
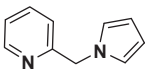
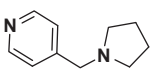
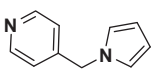
solvent. However the fundamental problem in performing the organic reactions in water is that many organic substrates are hydrophobic and are insoluble in water. This can be overcome by the use of an additive. Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities. They are torus-like macro rings consisting of six (α-CD), seven (β-CD), eight (γ-CD) 1,4-linked α-D-glucopyranose units. Cyclodextrins and modified cyclodextrins have attracted much attention as aqueous based hosts for the inclusion complex phenomenon with a wide variety of guests. Inclusion complex formation occurs as a result of interaction between hydrophobic cavity of CD and hydrophobic portion of guest. These bind the substrates selectively and catalyze the chemical reactions by supramolecular catalysis involving reversible formation of host-guest complex with the substrate by non-covalent bonding as seen in the enzyme complexation processes. These features of CDs attracted us to investigate varied organic transformations under biomimetic conditions. Since β-cyclodextrin is least expensive among the cyclodextrins, it has been utilized as a supramolecular catalyst in all our research endeavors.

In our initial study toward the development of this methodology, a model reaction was conducted by treating *N*-benzylpyrrolidine with 1 equiv of IBX in water under neutral reaction conditions. *N*-Benzylpyrrole was obtained in moderate yield (47%). Efforts were directed toward the yield optimization. During the exploratory studies conducted to optimize the reaction conditions and better the yields, several reactions were attempted by increasing the IBX quantity as well as by increasing the reaction times and temperatures. However these did not improve the yield. Introduction of β-CD as a supramolecular host in this reaction increased the yield to 86%.[15] The role of of β-CD in this reaction may be that it facilitates the solubility of IBX in water and conducts the reaction smoothly.[14] It is conclusively proved that in the absence of β-CD, these reactions did not result in satisfactory yields.

The scope of the present study was extended by reacting various diversely substituted *N*-benzylpyrrolidines, which were prepared from the corresponding pyrrolidines and benzyl bromides following reported literature methods, subjecting to the optimized reaction conditions. All the reactions were clean and gave corresponding *N*-benzylpyrroles in good to excellent yields. *N*-Benzylpyrrolidine bearing electron withdrawing group gave less yield of the *N*-benzylpyrrole (Table 1, entry 2) whereas the presence of electron releasing group on *N*-benzylpyrrolidine increased the yield relatively in shorter reaction times (Table 1, entry 3). Sterically hindered *N*-benzylpyrrolidine with an *ortho*-fluoro group (Ta-

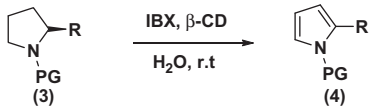
Table 1
Synthesis of *N*-benzylpyrroles from *N*-benzylpyrrolidines using IBX in presence of β-CD in water [a]

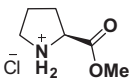
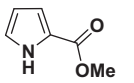
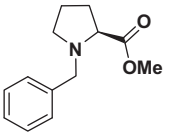
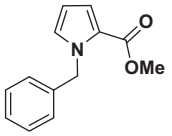
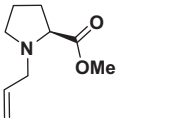
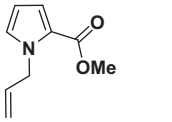
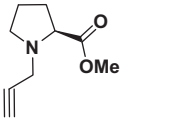
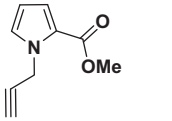
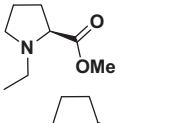
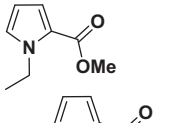
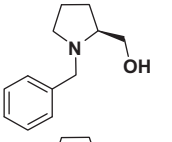
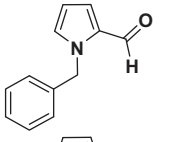
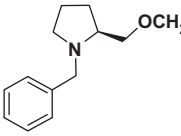
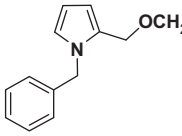


Entry	*N*-Benzylpyrrolidine (**1**)	*N*-Benzylpyrrol (**2**)	Time (h)	Yield[b] (%)
1			4	86, 52[c]
2			7	80
3			5	89
4			8	82
5			6	72
6			9	76
7			7	73
8			8	70
9			9	79
10			8	82

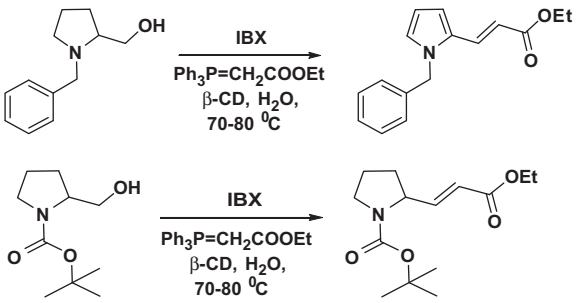
[a] Reactions and conditions: *N*-benzylpyrrolidine (1.0 mmol), IBX (2.0 mmol), β-CD (1.0 mmol), Water (5 mL).
[b] Isolated yield.
[c] In the absence of β-CD.

Table 2
Synthesis of *N*-protected methyl pyrrole-2-carboxylate derivatives from the corresponding *N*-protected L-proline esters using IBX in presence of β-CD in water[a]



Entry	**3**	**4**	Time (h)	Yield[b] (%)
1			4	89
2			6	84
3			7	73
4			5	68
5			6	71
6			5	75
7			6	78

[a] Reaction and conditions: *N*-benzylpyrrolidine (1.0 mmol), IBX (2.0 mmol), β-CD (1.0 mmol), Water (5 mL).
[b] Isolated yield.



Scheme 2.

ble 1, entry 8) did not hamper the reaction and gave corresponding *N*-benzylpyrrole in moderate yield.

While applying this interesting research work toward the naturally occurring L-proline derivatives, L-proline ester hydrochloride was subjected to the IBX oxidation reaction in water medium mediated by β-CD under optimized reaction conditions, resulting in methyl 1*H*-pyrrole-2-carboxylate in 89% (Table 2, entry 1). Encouraged by this result this reaction was extended to prepare a wide variety of *N*-protected L-proline derivatives such as *N*-benzyl, *N*-ethyl, *N*-propargyl, *N*-allyl-L-proline methyl esters and the reactivity pattern was examined toward this novel transformation. The corresponding results were tabulated (Table 2, entries 2, 3, 4, 5). In L-proline methyl ester, when N-was protected with Boc anhydride, acetic anhydride, the corresponding *N*-protected pyrrolidines failed to undergo aromatization to give pyrrole derivatives, instead starting materials were recovered.

When *N*-benzyl-L-prolinol was treated with IBX under optimized reaction conditions. 1-benzyl-1*H*-pyrrole-2-carbaldehyde was obtained in moderate yield (Table 2, entry 6). However, the same *N*-benzyl-L-prolinol was subjected to Wittig's reaction with ylide ($Ph_3P{=}CH_2COOEt$) in presence of IBX and β-cyclodextrin in water which resulted in (*E*)-ethyl 3-(1-benzyl-1*H*-pyrrol-2-yl) acrylate in excellent yield (Scheme 2). Moreover, the corresponding *N*-Boc-protected L-prolinol failed to undergo aromatization and instead gave only the Wittig product (Scheme 2). All the products were characterized by ^1H, ^{13}C NMR, mass spectra and compared with authentic samples.[16]

In conclusion, we have demonstrated for the first time a mild and highly efficient protocol for the synthesis of *N*-benzylpyrroles under neutral conditions, using IBX as an oxidizing agent mediated by β-cyclodextrin in water. To the best of our knowledge, this is the first report on the synthesis of *N*-benzylpyrroles under supramolecular catalysis in water medium. This simple, convenient and practical approach may have wide applicability in both synthetic and medicinal chemistry.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.077.

References and notes

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15. *General procedure for the synthesis of N-benzylpyrroles.* To an aqueous solution of β-cyclodextrin (1.0 mmol of β-CD in 5 mL of water), IBX (2.0 mmol), *N*-benzylpyrrolidine (1.0 mmol) was added while stirring, and stirring was continued for the stipulated reaction time as shown in the Table at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3 × 5 mL), the combined organic layers were washed with saturated brine solution, dried and concentrated in vacuum. The crude product was purified by column chromatography on Silica gel using hexane/ethyl acetate (9:1) as an eluent.
16. *Data for the representative examples of synthesized compounds.* 1-Benzyl-1*H*-pyrrole[4] (entry 1, Table 1): 86 %, light yellow oil, ^1H NMR (300 MHz; $CDCl_3$; TMS) 5.27 (s, 2H, CH_2), 6.38 (t, 2H, *J* = 2.0 Hz, CH), 6.89 (t, 2H, *J* = 1.8 Hz, CH), 7.29–7.39 (m, 2H, Ph), 7.44–7.55 (m, 3H, Ph). ^{13}C NMR (75 MHz; $CDCl_3$; TMS) 53.30, 108.45, 121.12, 126.95, 127.59, 128.67, 138.10.
Methyl 1H-pyrrole-2-carboxylate (entry 1, Table 2): 89 %, pale yellow solid, ^1H NMR (300 MHz; $CDCl_3$; TMS) 3.85 (s, 3H, OMe), 6.19–6.22 (m, 1H), 6.83–6.85 (m, 1H), 6.91–6.93 (m, 1H), 9.53 (br s, 1H, NH). ^{13}C NMR (75 MHz; $CDCl_3$; TMS) 51.45, 110.45, 115.74, 122.35, 123.39, 162.18.
Methyl 1-benzyl-1H-pyrrole-2-carboxylate (entry 2, Table 2): 84 %, pale yellow oil, ^1H NMR (300 MHz; $CDCl_3$; TMS) 3.74 (s, 3H, OMe), 5.53 (s, 2H), 6.10–6.12 (m, 1H), 6.81 (t, 1H, *J* = 2.2 Hz, CH), 6.91–6.92 (m, 1H), 7.04–7.09 (m, 2H), 7.18–7.28 (m, 3H). ^{13}C NMR (75 MHz; $CDCl_3$; TMS) 50.83, 51.97, 108.53, 118.35, 121.98, 126.95, 127.40, 128.58, 138.27, 161.13.
Methyl 1-allyl-1H-pyrrole-2-carboxylate (entry 3, Table 2): 73 %, yellow oil, ^1H NMR (300 MHz; $CDCl_3$; TMS) 3.78 (s, 3H, OMe), 4.93–4.98(m, 3H), 5.10 (d, 1H, *J* = 10.1 Hz), 5.91–6.04 (m, 1H), 6.09 (t, 1H, *J* = 2.6 Hz), 6.78 (t, 1H, *J* = 1.8 Hz), 6.87–6.89 (m, 1H). ^{13}C NMR (75 MHz; $CDCl_3$; TMS) 50.80, 50.91, 108.28, 116.54, 118.10, 121.67, 128.13, 134.76, 161.10.
(E)-ethyl 3-(1-benzyl-1H-pyrrol-2-yl)acrylate: 88 %, yellow oil, ^1H NMR (300 MHz; $CDCl_3$; TMS) 1.27 (t, 3H, *J* = 6.7 Hz), 4.14 (q, 2H, J_1 = 14.3 Hz,

J_2 = 6.7 Hz), 5.18 (s, 2H), 6.09 (d, 1H, 4.36 (q, 2H, J = 15.8 Hz), 6.17 (t, 1H, J = 3.7 Hz), 6..64–6.66 (m, 1H), 6.75 (t, 1H, J = 1.5 Hz), 7.00(d, 2H, J = 6.7 Hz), 7.20–7.31(m, 3H), 7.48(d, 1H, J = 15.8 Hz). ^{13}C NMR NMR (75 MHz; $CDCl_3$; TMS) 14.37, 50.59, 60.27, 109.90, 111.85, 113.31, 126.08, 126.39, 127.71, 128.81, 129.05, 131.96, 137.22, 167.29.