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Simple preparation of polymer supported IBX esters and amides and their oxidative properties

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Abstract—Novel polymer supported IBX esters and amides were prepared in two steps, which were the coupling of 2-iodobenzoic acid to a hydroxy or amino polystyrene followed by activation of the intermediate product. These polymer supported reagents were tested as oxidants by the conversion of a series of alcohols to the corresponding aldehydes or ketones. We found that the polymer supported IBX amides displayed excellent oxidative activity, in that they oxidized benzyl alcohol to benzaldehyde completely within 1 h at an oxidant to alcohol ratio of 2 to 1.

The hypervalent iodine reagent, 2-iodoxybenzoic acid (IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) has gained enormous interest as a highly efficient and mild oxidant which can be used for the conversion of alcohols to aldehydes or ketones.[1] However, IBX is insoluble in most organic solvents except DMSO, and this limitation has restricted the practical application of this reagent. Therefore, several research groups have tried to solve this problem by using an elevated reaction temperature,[2] adding a suitable catalyst,[3] performing the reaction in an ionic liquid and water,[4] or using the solid supported IBX.[5] Recently, Zhdankin et al. reported on the synthesis of novel IBX amides[6] and IBX esters,[7] which are stable and soluble reagents having oxidizing properties similar to IBX. They also reported that the pseudo-cyclic structure of the amides and esters, which arises from the intramolecular non-bonding iodine-oxygen interaction, partially replaces the intermolecular I···O secondary bonds that give rise to the polymeric structure of the IBX. In recent years, four research groups have reported on the synthesis of polymer-supported IBX reagents and their oxidative properties,[5] after being inspired by the many advantages of polymer supported reagents, including their easy work up and simple product isolation, which meet the industrial needs for environmentally friendly chemistry. As a rule, these research groups synthesized IBX precursors via several elaborate synthetic steps, starting from 2-amino-5-hydroxybenzoic acid, and then coupled them onto appropriately-functionalized supports such as silica gel, gel-type PS-based support, macroporous support, and several other soluble supports.[5a–c] Subsequent to the activation step, the supported IBX reagents brought about the fast and efficient conversion of alcohol to aldehyde or ketone. Most recently, Lei et al. reported an efficient synthesis of a polymer-supported IBX reagent that differs significantly from the previously reported ones.[5d] They prepared a polymer-supported IBX reagent through three-step reactions from macroporous poly(*p*-methylstyrene) beads, and then oxidized a range of alcohols to the corresponding aldehydes successfully using their polymer supported oxidants. However, the loading level of the oxidant was as low as 0.2∼0.5 mmol/g, due to the presence of undesired species generated during the iodination process, and the preparation of the polymer supported oxidants remained time-consuming (>2 days).

Here, for the first time, we propose a very simple method of preparing polymer supported IBX esters and amides, in two steps, involving the coupling of 2-iodobenzoic acid to a hydroxy or amino functionalized PS bead, followed by subsequent oxidation on the beads. Also, we proved that these polymer supported reagents were mild and efficient oxidants by the conversion of a series of alcohols to the corresponding aldehydes or ketones.

Synthesis of polymer supported IBX esters (Scheme 1-I). Hydroxyalkyl PS resin (BTCore EM OH bead,[8] 0.91 mmol/g, or 2.1 mmol/g, 1 mol% XL, 100–200 mesh)

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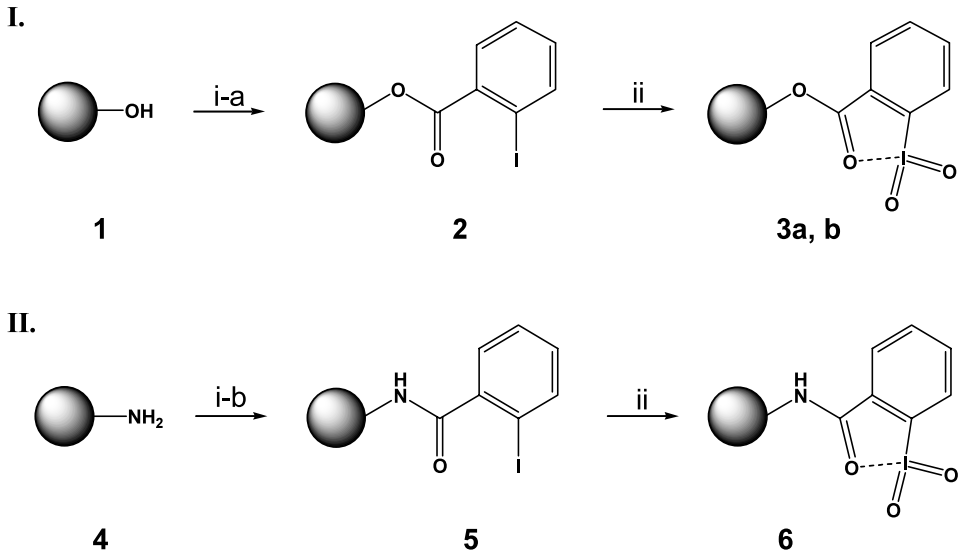


Scheme 1. Synthesis of polymer supported IBX esters and amides: (i-a) 2-iodobenzoic acid, DIC, DMAP, DMF, rt, 18 h; (i-b) 2-iodobenzoic acid, BOP, HOBt, DIEA, DMF, rt, 4 h; (ii) NBu_4SO_5H, $MeSO_3H$, DCM, rt, 18–20 h.

was pre-swollen with DMF at room temperature for 1 h. 2-Iodobenzoic acid was coupled to the resin by means of the standard DIC and DMAP coupling method (rt, 18 h) to afford 2-iodobenzoate resin. The resulting resin was oxidized successfully by reacting it with an equimolar mixture of tetrabutylammonium oxone[9] (5 equiv.) and methylsulfonic acid (DCM, rt, 18–20 h). The infrared spectra obtained from 2-iodobenzoate resin **2**, and the oxidant resin **3**, revealed that the strong carbonyl absorbance peaks of the ester linkage at 1728 cm^{-1} shifted to 1670 cm^{-1} after oxidation, which is the characteristic absorbance peak of an IBX ester.[7] The activation of 2-iodobenzoate resin **2**, was terminated when the initial carbonyl peak at 1728 cm^{-1} completely disappeared.

Synthesis of polymer supported IBX amides (Scheme 1-II). Aminoalkyl PS resin (BTCore EM NH_2 beads, 2.1 mmol/g) was prepared from BTCore EM OH beads (2.1 mmol/g, 1 mol% XL, 100–200 mesh) by converting the hydroxy group into an amino group via the Mitsunobu reaction followed by the Staudinger reaction.[10] The resin was pre-swollen with DMF solvent at room temperature for 1 h. 2-Iodobenzoic acid was coupled to the resin by the standard BOP, HOBt, DIEA (3 equiv. each) coupling method (rt, 4 h) affording 2-iodobenzamide resin. The resin was oxidized successfully by reacting it with an equimolar mixture of tetrabutylammonium oxone (5 equiv.) and methylsulfonic acid (DCM, rt, 18–20 h). The infrared spectra obtained from the 2-iodobenzamide resins **5**, and oxidant resins **6**, indicated that the strong carbonyl absorbance peak of the amide linkage at 1661 cm^{-1} shifted to 1618 cm^{-1} after oxidation, which is the characteristic absorbance peak of an IBX amide.[6] The activation of the 2-iodobenzamide resin was terminated when the initial carbonyl peak at 1661 cm^{-1} completely disappeared.

Evaluation of polymer supported oxidants. Firstly, to determine the loading levels of the oxidants, excess benzyl alcohol (>3 equiv.) was oxidized in DCM with the oxidant beads (100 mg of beads/1 mL) for 18 h at 25°C, and the amount of benzaldehyde in the reaction mixture was measured by GC/MS. The typical loading levels of the oxidants, in the case of both the polymer supported IBX esters and amides, were 0.65 mmol/g (**3a**), 1.08 mmol/g (**3b**), and 0.98 mmol/g (**6**). The time courses of benzyl alcohol oxidation by the polymer supported oxidants were evaluated in a similar way. Under different oxidant to benzyl alcohol ratios, the conversion of benzyl alcohol to benzaldehyde was measured according to the reaction time (Fig. 1). We found that the polymer supported IBX amide **6**, gave the fastest oxidation of benzyl alcohol at an oxidant to benzyl alcohol ratio of 2:1 (100% conversion within 1

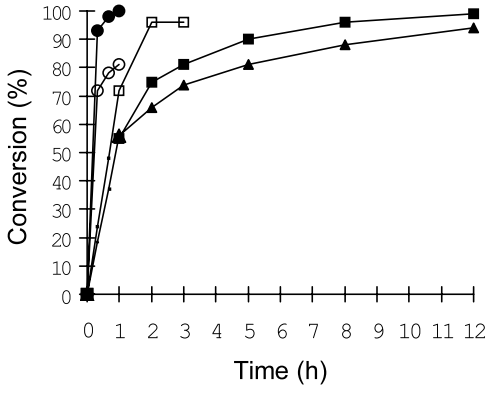


Figure 1. The time courses of benzyl alcohol oxidation by polymer supported IBX esters and IBX amides: using 2 equiv of oxidant **3a** (▲); 2 equiv of oxidant **3b** (■); 4 equiv of oxidant **3b** (□); 1.2 equiv of oxidant **6** (○); 2 equiv of oxidant **6** (●). All reactions were performed at 25°C in DCM (100 mg of bead/1 mL). Conversion (%) was determined by GC/MS analysis.

h), while the polymer supported IBX esters showed similar activities to those of the previously reported insoluble solid supported IBX reagents.

To explain the above results, we propose a mechanism for the oxidation of an alcohol by the supported IBX amide **6**, as shown in Figure 2. Compared with the IBX ester oxidant, the carbonyl oxygen of the IBX amide can enter into a stronger intramolecular nonbonding interaction with iodine. Consequently, this leads to the formation of a more favorable equilibrium state between **6**, and the cyclic IBX derivative **7**, and the same path of alcohol oxidation as that involving the common form of IBX is followed (i.e. ligand exchange and disproportionation),[11] affording an aldehyde and leaving the iodoso compound on the resins.

These results inspired us to investigate more thoroughly the oxidative properties of the polymer supported IBX amide **6**, with a series of additional alcohol substrates. Thus, 4-nitrobenzyl alcohol, 4-methoxybenzyl alcohol, 1-decanol, and cyclohexanol were oxidized by 2 equiv. of the polymer supported IBX amide **6**, in DCM, and the reaction mixtures were analyzed by GC/MS to measure the conversion yields of the alcohols to the corresponding aldehydes or ketones (Table 1).

The oxidation of the benzyl alcohol derivatives resulted in nearly complete conversion after only 1 h. Even the primary alkyl alcohol, 1-decanol, was converted to the corresponding aldehyde quantitatively after 14 h. These results demonstrate the very promising activity of the polymer supported IBX amide **6**. Normally, more than 2–5 h would be required to convert benzyl alcohol to benzaldehyde under similar reaction conditions, and the oxidation of the primary alkyl alcohol would not have resulted in more than 60% conversion, even after extending the reaction time,[5c] with the previously reported polymer supported IBX reagents. With cyclohexanol, the polymer supported IBX amide **6**, gave 40% conversion to cyclohexanone in 1 h. After extending the reaction time (14 h), it resulted in 81% conversion to cyclohexanone and an additional 8% conversion to α,β-unsaturated cyclohexenone, probably via the dehydrogenation of the first product, cyclohexanone.[5b,12]

In summary, we have prepared novel polymer supported IBX esters and amides in two simple steps. The oxidant resins were prepared with high loadings of $0.65 \sim 1.08$ mmol/g, and were evaluated with a series of alcohol substrates. The polymer supported IBX amide **6**, exhibited particularly fast and efficient oxidative activities toward a series of alcohols under mild reaction conditions. To the best of our knowledge, our polymer supported IBX amide **6**, resulted in the faster conversion of alcohols to the corresponding aldehydes than any other previously reported insoluble polymer supported IBX reagents.

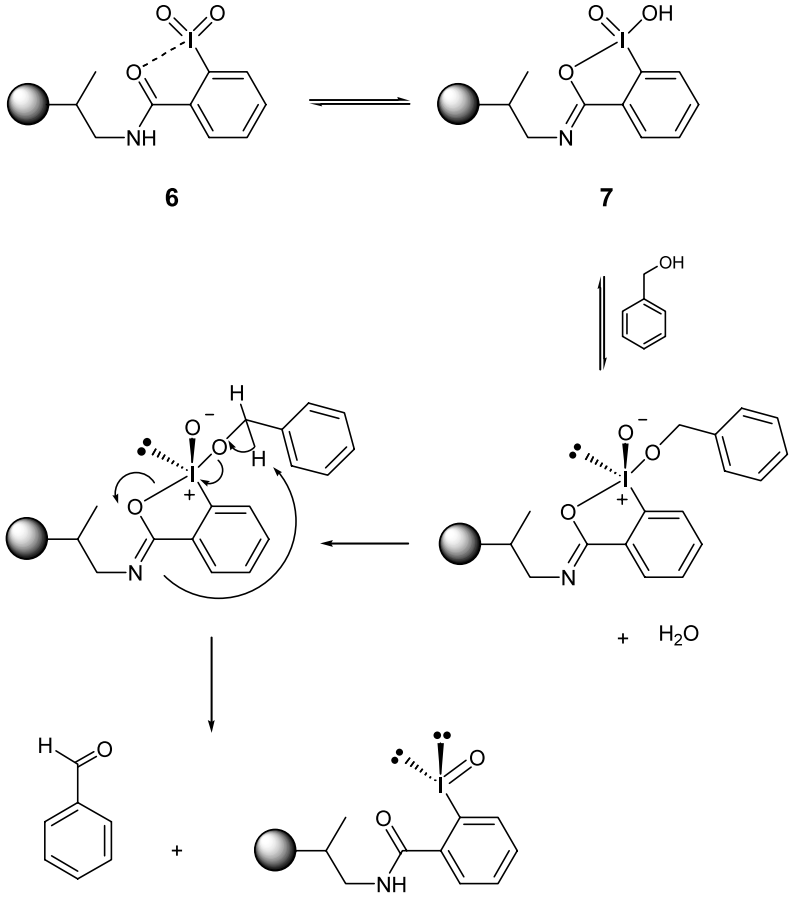
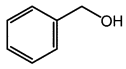
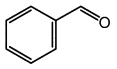
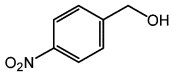
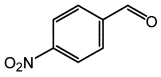
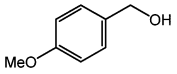
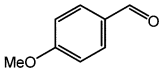
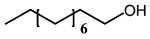
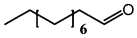
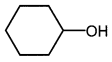
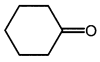


Figure 2. Suggested mechanism of benzyl alcohol oxidation with polymer supported IBX amide.

Table 1. Results of alcohol oxidation using the polymer supported IBX amide **6**

Entry	Alcohol	Aldehyde	Conversion[a] (%)
1			>99
2			>99
3			>99
4			56, >99[b]
5			40, 81[b, c]

All reactions were performed at 25℃ in DCM (100mg of **6**/1mL) for 1h. The ratio of **6**:alcohol was 2:1. [a]Determined by GC/MS analysis. [b]after 14h, [c]2-Cyclohexen-1-one (8% conversion) was detected.

Acknowledgements

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