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Macroporous polystyrene-supported IBX amide: the improved oxidative properties in various solvents

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Abstract—In this study, macroporous polystyrene-supported IBX (MPS-IBX) amides were prepared in two simple steps, and the polymeric reagent was then evaluated for its efficiency in converting a range of alcohols to the corresponding carbonyl compounds in various solvents. The results indicated that the MPS-IBX amides were compatible with a variety of solvents, and had a more efficient oxidation activity toward alkyl alcohols than the gel type polystyrene-supported IBX amides. Finally, the resin that was consumed in the oxidation reaction was regenerated to give a restored loading level of 0.44–0.54 mmol/g.

The oxidation of alcohols to ketones or aldehydes is an important organic reaction that provides useful intermediates for the preparation of other organic compounds.[1] In particular, the hypervalent iodine reagent 2-iodoxybenzoic acid (IBX) has attracted much attention due to its stability, high selectivity, low toxicity, and easy availability.[2,3] Despite its numerous advantages, IBX is potentially explosive and insoluble in most common organic solvents.[4] Therefore, several research groups have tried to synthesize IBX derivatives that are stable and soluble.[5] For example, Zhdankin et al. have reported several stable and soluble IBX amides. The increased stability and solubility of the IBX amides are the results of their pseudo-cyclic structure.[7] Recently, solid-supported IBX reagents have been studied extensively due to such advantages as an easy workup and simple isolation. Therefore, silica gel, polystyrene (PS) beads, and several other soluble solid supports have been applied.

Previously, our group reported a simple two-step method of preparing a polymer-supported IBX amide using a gel type PS-support.[5e] We then proved this polymer-supported reagent was a mild and efficient oxidant due to the successful conversion of a series of alcohols to the corresponding carbonyl compounds. However, the oxidation activity of the gel type PS-supported reagent was strongly dependent on the solvents we employed because the PS resin had different swelling properties, which were the result of its gel type and the hydrophobic nature of the polymer backbone. In addition, the oxidation of the long chain alkyl alcohol took a long time to complete, and we presumed that the alcohols diffused slowly to the inner reactive sites of the resin. Therefore, to improve on the properties of the IBX resin, we synthesized macroporous polystyrene-supported IBX (MPS-IBX) amide and investigated the reactivity differences between the gel type resin and this macroporous resin.

We prepared the MPS-IBX amide in two simple steps as follows: 2-iodobenzoic acid was coupled to the aminomethyl MPS resin[6] by the standard DIC/HOBT coupling method for 4 h at rt. The completion of the coupling step was determined by the Kaiser test.[12] Then the resin was oxidized by tetrabutylammonium oxone[11] (5 equiv) with methanesulfonic acid for 10–12 h at rt in dichloromethane (DCM). The infrared spectra that we obtained from the 2-iodobenzamide resin and the oxidant resins indicated that the strong carbonyl absorbance peak of the amide linkage at 1659 cm^{-1} was shifted to 1618 cm^{-1} after oxidation, which was the characteristic absorbance peak of an IBX amide.[7] To determine the loading level of the oxidant resin, excess benzyl alcohol (>3 equiv) was oxidized in DCM along with the oxidant resin (100 mg of bead/1 mL) for 24 h at rt. The amount of benzaldehyde in the reaction

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Keywords: Macroporous polystyrene-supported IBX amide; MPS-IBX resin; Polymer-supported reagent; Oxidation.

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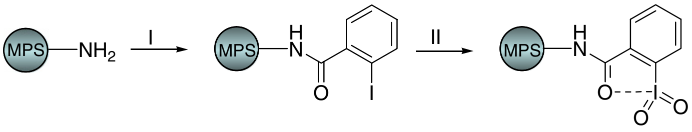


Scheme 1. Synthesis of MPS supported IBX amides. Reagents and conditions: (i) 2-iodobenzoic acid, DIC, HOBT, DIEA, DMF, rt, 6 h; (ii) NBu_4SO_5H, $MeSO_3H$, DCM, rt, 10–12 h.

mixture was measured by 300 MHz ^{1}H NMR spectroscopy. The loading level of the MPS-IBX amide was determined to be in the range of 0.44–0.54 mmol/g (see Scheme 1).

The oxidation reaction was also performed in various solvents such as acetonitrile (ACN), THF, acetone, and diethyl ether (100 mg of bead/1 mL) at 25 °C. As was expected, the MPS-IBX amides were compatible with all the solvents since the solvents could easily diffuse into the MPS resin. However, GC/MS analysis indicated that lactol and lacton were formed with the MPS-IBX amide when THF was used as the solvent. This was probably due to the oxidation reaction of THF by the MPS-IBX amide, and for this reason it could not be used as a solvent. We employed 300 MHz ^{1}H NMR spectroscopy to determine the conversions. The profiles of benzyl alcohol oxidation reaction in several solvents were compared between on the gel type PS-IBX amide resin and on the MPS-IBX amide resin. Both resins in DCM were shown similar oxidative properties (Fig. 1). However, in acetone, diethyl ether, and THF, only the MPS-IBX amide resin revealed strong oxidative properties toward benzyl alcohols. The reduced MPS-IBX amide resin was regenerated by oxidation with tetrabutylammonium oxone, and we observed no loss of activity after five regenerations.

These results inspired us to investigate further the MPS-IBX amide's oxidative properties using an additional series of alcohols. As shown in Table 1, the alcohols were oxidized in DCM, ACN, acetone, and diethyl ether. The reaction mixtures were analyzed by 300 MHz ^{1}H NMR spectroscopy to measure the conversion of the alcohols to the corresponding aldehydes or ketones (Table 1).

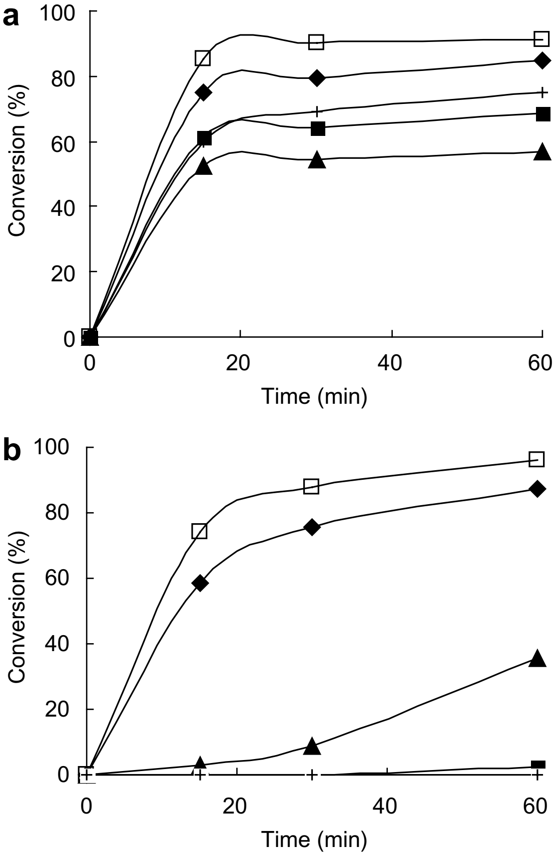
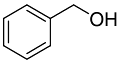
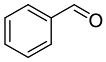
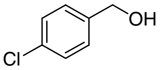
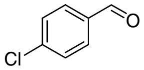
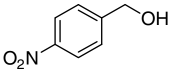
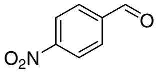
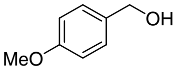
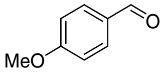
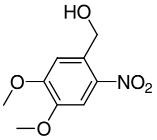
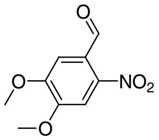
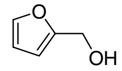
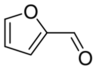
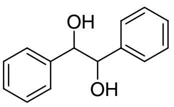
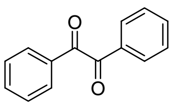
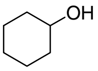
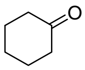
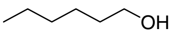
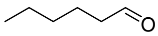
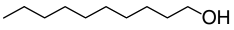
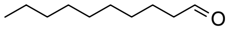


Figure 1. The time course for the oxidation of alcohol to aldehyde using MPS-IBX amide (a) and gel type polystyrene-supported IBX amide (b) in different solvents: using 2 equiv of oxidant at rt and methoxybenzyl alcohol as the substrate; DCM (□), ACN (◆), THF (■), acetone (▲) and diethyl ether (+). Conversion (%) was determined by 300 MHz ^{1}H NMR spectroscopy.

In our previous studies with the gel type PS-IBX amide, we noticed that the oxidation of both the primary and long chain alkyl alcohols took at least 12 h at rt for more than a 98% conversion toward the quantitative aldehydes.[5e] The PS-IBX amide in particular gave a conversion of only 40% for cyclohexanol to cyclohexanone in 1 h. After extending the reaction time to 14 h, we obtained an 81% conversion to cyclohexanone and an additional 8% conversion to α,β-unsaturated cyclohexenone, probably via the dehydration of cyclohexanone.[5e,8] However as shown in Table 1, the MPS-IBX amide resin offered good conversion rates in DCM (4 h) for the oxidizations of long chain alkyl alcohols and cyclohexanol to the corresponding aldehydes and ketones. We also found that MPS-IBX amide resin had excellent properties for oxidizing benzyl alcohols to the corresponding aldehydes in acetone and diethyl ether. Based on these results, we can confirm that the diffusion of alcohols may be an important factor in determining the oxidation power of the IBX resin. When the gel type PS-IBX resin is not fully solvated, the alcohols may experience diffusion resistance and, therefore, slowly diffuse into the inner reactive sites of the resin. Moreover, in a poor solvent system the polymer matrix of the gel type PS-supports could collapse and block the internal reactive sites. In the case of the MPS-IBX resin, however, high levels of internal crosslinking can create a rigid porous structure, which may neither collapse nor swell in various solvents.[9] In addition, the internal reactive sites of macroporous resins are freely accessible across a broad spectrum of solvent polarities,[10] and the alcohols are free to move into the resin reaction sites. Therefore, the MPS-IBX amide resin can be used for oxidizing alcohols in a variety of solvents, as long as the solvents themselves are not oxidized.

Table 1. Results of alcohol oxidation using MPS-IBX amide

Entry	Alcohol	Product	Solvent	Reaction time[a] (h)	Yield (%)
1			Acetone	1	99[c]
2			Diethyl ether	1	96[b]
3			DCM	1	99[b]
4			Acetone	1	92[b]
5			ACN	4	96[b]
6			Diethyl ether	4	98[c]
7			ACN	4	58[b] 99[c]
8			Diethyl ether	4	92[c]
9			ACN	4	84[b]
10			DCM	4	86[b]

[a] All reactions were performed with 2 equiv of MPS-IBX amide resin at room temperature.

[b] Isolated yields.

[c] Conversion yields were determined by 300 MHz ^{1}H NMR spectroscopy.

In summary, we prepared an MPS-IBX amide resin by a simple two-step process and showed that the resin had no problem with diffusion when oxidizing alcohols. In the various solvents we studied, all benzyl alcohol derivatives were easily converted to benzaldehydes. Even long chain alkyl alcohols and primary alcohols were rapidly converted to the corresponding aldehydes and ketones by the MPS-IBX amide resin. Based on these results, the MPS-IBX amide may solve the solvent limitation problem that occurs when oxidizing alcohols to corresponding carbonyl compounds. Finally, we expect this solvent-friendly MPS-IBX resin to expand the overall scope of the IBX resin's application.

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