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Preparation of Soluble and Insoluble Polymer Supported IBX Reagents

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Abstract—A series of soluble and insoluble polymer supported versions of the versatile oxidizing reagent IBX has been prepared. Each of the reagents were evaluated for their efficiency in the conversion of benzyl alcohol to benzaldehyde. Results from this study were that the soluble, non-crosslinked polystyrene supported IBX reagent gave the best rate of conversion to benzaldehyde, while the macroporous polymer supported IBX resin provided a superior rate of conversion to benzaldehyde when compared with a gel type resin. The macroporous IBX reagent was also shown to convert a series of alcohols to the corresponding aldehydes and ketones.

Introduction

Hypervalent iodine reagents are valuable tools in synthetic organic chemistry.[1] One important application of these reagents is the oxidation of alcohols to the corresponding carbonyls. In particular, Dess-Martin periodinane (DMP) has received much attention since it is efficient, mild reagent for this oxidation.[2] The precursor to DMP, *o*-iodosobenzoic acid (IBX) **1** has also been utilized for the conversion of alcohols to aldehydes and ketones. In fact, it is now preferred to DMP in many instances since it does not cleave 1,2-diols, is conveniently handled, and is stable to storage for prolonged periods.[3] Additionally, many new elegant oxidative transformations using IBX have been recently reported.[4] One drawback to the use of IBX is its solubility, IBX reactions are performed in either homogeneous DMSO solutions or heterogeneous slurries with other solvents. There is also an additional safety concern when using hypervalent iodine reagents in that they are potentially explosive and this may have precluded larger scale applications of IBX or related oxidants.[5]

Polymer supported reagents and catalysts are currently undergoing a renaissance in synthetic chemistry.[6] An attractive feature of polymer bound reagents is that they can be isolated from the reaction without work up using a simple filtration to yield a solution of pure product. This technology is now being used to great effect in the parallel synthesis of libraries of compounds for use in drug discovery programs. Additionally, the preparation of polymer bound reagents is important industrially since the spent reagent can be potentially reused after recovery and regeneration. Finally, many explosive reagents have been made safe by conversion into a resin bound version and notable examples include a polymer bound sulfonyl azide[7] reagent for diazotransfer reactions and an azodicarboxylate[8] reagent for Mitsunobu reactions. Because of the proven utility of IBX and its solubility and safety issues, it is an ideal candidate for the preparation of polymer bound analogues. Reported herein are our efforts for the preparation and application of both soluble and insoluble polymer supported IBX reagents.

Results and Discussion

The strategy for the preparation of a polymer bound version of the IBX reagent is outlined in Figure 1.

We envisaged that hydroxy-iodobenzoic acid **3** would be an ideal substrate to prepare a polymer bound IBX reagent, this through attachment via an aryl ether linkage.

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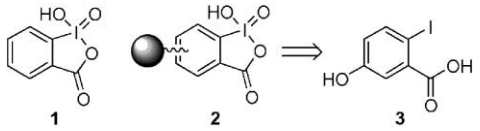
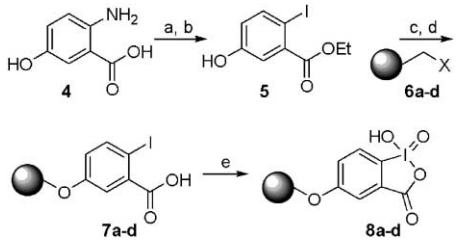


Figure 1. Strategy used to prepare polymer supported IBX reagents.

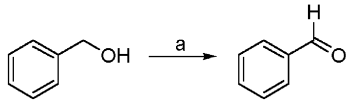
In our approach (Scheme 1), 5-hydroxy-2-anthranilic acid was converted to hydroxy-iodobenzoic acid **4** using a Sandmeyer reaction according to literature precedent.[9] Carboxylic acid **4** was then converted to the corresponding ester **5** in quantitative yield using a Fisher esterification reaction.

In search of an optimal polymer bound version of the IBX reagent, several different types of supports were investigated. These supports were an insoluble polystyrene gel-type *J*anda*J*el resin **6a**, a macroporous polystyrene ArgoPore resin **6b**, a soluble, non-crosslinked polystyrene resin **6c** and soluble poly(ethylene glycol) (PEG 3400) support **6d**. The common building block **5** was reacted with either chloromethyl functionalized polystyrenes **6a–c** or mesylate functionalized PEG 3400 **6d** in the presence of cesium carbonate in DMF to form the desired aryl ether. The corresponding polymer bound iodocarboxylic acids **7a–d** were then unmasked by barium hydroxide mediated hydrolysis. Each of the resins were found to be loaded in the following amounts **7a** (0.7 mmol g^{-1}), **7b** (0.9 mmol g^{-1}), **7c** (0.3 mmol g^{-1}), and **7d** (0.4 $mmol^{-1}$) as determined by either NMR (soluble resins) or elemental analysis of insoluble supports.

The critical oxidation of the support bound iodoacids **7** to the corresponding polymer supported IBX reagent **8** proved difficult to optimize. Initial attempts centered around the macroporous resin supported iodoacid **7b** and the PEG supported iodoacid **7d** since the preparation of IBX is commonly accomplished in aqueous conditions and these supports are well known to work well in water. Unfortunately, neither the traditional conditions of potassium bromate in sulfuric acid[2] nor the recently described Oxone oxidation procedure[10] gave the desired oxidants **8**. We were aware of a recent report where tetrabutylammonium hydroxide had been used in place of sodium hydroxide with great effect for the reaction of a polystyrene bound substrate.[11] This led us to examine the use of the tetrabutylammonium salt of Oxone[12] in organic solvents for the oxidation of **7a** to **8a**, however, these conditions also failed to provide the desired oxidant. After further experimentation, we found that addition of one equivalent of methane sulfonic acid[13] to the oxidation reaction enabled conversion to the desired polymer bound oxidant as estimated by IR spectroscopy.[14] Using these conditions, each of the polymer supported iodoacids **7a–d** were converted to the corresponding oxidants **8a–d**. The insoluble polymer bound oxidants were easily isolated by simple filtration, however, the soluble polymer supported reagents were more difficult to isolate cleanly. For example, the non-crosslinked polystyrene supported oxidant **8c** required extraction into methylene chloride and washing with brine to remove unwanted oxone



Scheme 1. (a) (i) $NaNO_2$, aqueous H_2SO_4, 0 °C; (ii) KI, 90 °C, 57%; (b) EtOH, HCl, reflux; (c) Cs_2CO_3, DMF, 70 °C, 14 h; (d) $Ba(OH)_2{\cdot}8H_2O$, MeOH rt, 12 h; (e) Bu_4N-Oxone, 5 equiv, $MeSO_3H$ 5 equiv, CH_2Cl_2, 2 h.



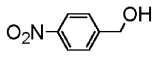
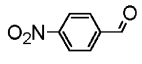
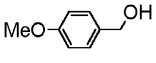
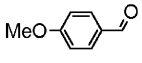
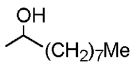
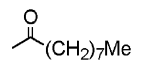
Scheme 2. (a) **8a–c**, CH_2Cl_2.

salts, since isolation of the polymer by precipitation from methanol would have quenched the freshly generated reagent. The PEG bound oxidant **8d** also proved troublesome, precipitation of the polymer from diethyl ether was accompanied by co-precipitation of the oxone salts, because of this the PEG oxidant **7d** was dropped from the study.

With the synthesis of three polystyrene supported reagents **8a–c** in hand, a comparison of their activity in the oxidation of benzyl alcohol to benzaldehyde was examined. Here, two equivalents of the support bound oxidants **8a–c** were shaken with a solution of benzyl alcohol in methylene chloride (Scheme 2).

Homogenous non-crosslinked polystyrene supported reagent **8c** was superior with 100% conversion to product (determined by GC) after only 1 h. For the insoluble polymers, the macroporous ArgoPore supported reagent proved best, and thus oxidation of benzyl alcohol gave 93% conversion to benzaldehyde after 2.5 h that rose to 100% after 4 h. The gel-type polymer supported reagent, however, only gave 75% conversion after 2.5 h and failed to increase after extended reaction time.

Table 1.

Alcohol	Product	% Conversation[a]
		99
		50, 78[b]
		45[c]
		99

[a]% Conversion estimated by GC after 4 h.
[b]After 6 h.
[c]No further increase in yield was observed.

From these findings a series of oxidations of additional substrates using the macroporous polymer supported oxidant **7b** were also examined (Table 1). A solution of each alcohol was shaken with 2 equiv of **7b** and the conversion to product was estimated after 4 h by GC. *p*-Nitrobenzyl alcohol gave complete conversion after 4 h, however, the less reactive *p*-methoxybenzylalcohol was only converted to 50% yield after 4 h. 2-Decanol was converted to 2-decanone in 45% yield after 4 h, however, no further conversion to product was observed even after extending the reaction time. Finally, cyclohexanol was smoothly converted to cyclohexanone in excellent yield.

Conclusion

In summary,[15] we have developed a series of polymer supported IBX reagents. Our findings were that: (1) The soluble, non-crosslinked polystyrene supported reagent gave the greatest rate of conversion of alcohol to aldehyde. (2) The macroporous ArgoPore reagent was superior to the gel supported reagent for this same reaction. (3) The macroporous reagent was found to convert a series of alcohols to the corresponding aldehydes and ketones in good to excellent yields. Investigations of alternative supported versions of IBX and applications of the polymer supported IBX reagents reported is ongoing in our laboratory and will be reported in due course.

Acknowledgements

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13. The addition of methane sulfonic acid forms Caro's acid (monoperoxysulfuric acid) in situ, which is a stronger oxidant than Oxone alone.
14. The progress of oxidation was measured by a disappearance of the acid carbonyl at 1710 cm^{-1} and the appearance of a broad carbonyl peak at approximately 1630 cm^{-1}.
15. (a) Note added to proof: After submission of our manuscript the following papers appeared describing similar approaches to polymer supported IBX reagents. Mülbaier, M.; Giannis, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4393. (b) Sorg, G.; Mengei, A.; Jung, G.; Rademann. *J. Angew. Chem., Int. Ed.* **2001**, *40*, 4395.