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A facile route to a polymer-supported IBX reagent

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Abstract—A three-step preparation of a polymer-supported IBX reagent from poly(p-methylstyrene) is reported. This reagent has been used successfully for the efficient oxidation of a series of alcohols to the corresponding aldehydes. © 2003 Elsevier Science Ltd. All rights reserved.

In 1983 Dess and Martin first introduced the use of hypervalent compounds to facilitate the oxidation of alcohols.¹ They demonstrated successfully that periodinane (DMP) 1, prepared in two steps from o-iodobenzoic acid, could be used to oxidise primary and secondary alcohols to the corresponding aldehydes and ketones. Subsequently, this reagent found widespread use in synthetic organic chemistry and is renowned for its mild reactivity and chemoselectivity. Unfortunately, however, periodinane 1 is unstable to prolonged storage and is thus best synthesised immediately prior to use. In 1994 Frigero and Santagostino reported that the precursor to DMP 1, 1-hydroxy-1,2-benziodoxole-3(1H)one-1-oxide (IBX) 2 could also be utilised in the oxidation of alcohols.² The mildness of this reagent was further demonstrated by the finding that IBX could also be employed in the oxidation of 1,2-diols to 1,2diketones without the unwanted cleavage of the C-C bond associated with the use of DMP 1,3 tetrapropylammonium perruthenate⁴ (TPAP) or pyridinium chlorochromate⁵ (PCC) reagents. IBX 2 is still continuing to find new and varied applications in organic synthesis.6



Keywords: polymer-supported reagents; iodoxybenzoic acid (IBX); oxidation; alcohols.

Polymer-supported reagents have found widespread utility in organic synthesis.⁷ Their use is especially relevant in automated high through-put applications since attachment of a chemical reagent to an insoluble polymer matrix enables easy reaction work-up. A simple filtration process allows the product to be recovered and moreover recovery of the spent reagent enables it to be recycled, thus meeting the requirements of environmentally friendly chemistry. Three syntheses of solid-supported IBX have been published recently.8 Each of these routes commenced with a solution phase synthesis employing 2-amino-5-hydroxybenzoic acid as a starting material. In each case, after elaboration, this molecule was coupled to an appropriately-functionalised solid support, either an aminopropyl silica gel,^{8a} or a polystyrene based support^{8b,c} or else to soluble non-crosslinked polystyrene or PEG-based supports.^{8c} However, difficulties were encountered in isolating the supported reagent when attached to non-crosslinked supports and, in every case, attachment to non-soluble supports involved the formation of potentially labile amide and benzyl ether bonds.

We wished to develop a synthesis of a solid-supported IBX reagent that did not require a late stage linkage step and thus the incorporation of potentially labile covalent bonds into the supported reagent. We therefore elected to carry out a synthesis of IBX that was totally solid support-based. Moreover, by using a crosslinked support, this strategy would also avoid the difficulties encountered in handling non-crosslinked soluble supports Reported herein is the synthesis of the reagent and an evaluation of its utility for the oxidation of a series of alcohols.

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Scheme 1. Synthesis of polymer-supported IBX reagent 6. Reagents and conditions: (i) suspension polymerisation, AIBN, PVA (87–89% hydrolysed), 2-ethyl-1-hexanol, Δ ; (ii) I₂, NaIO₄, H₂SO₄, Ac₂O, CH₃COOH, CH₂Cl₂, rt, 24 h; (iii) KMnO₄, methyltri-*n*-octylammonium chloride, H₂O, CH₂Cl₂, Δ , 24 h; (iv) NBu₄SO₅H, MeSO₃H, CH₂Cl₂, rt, 5 h.

Synthesis of polymer-supported IBX. Macroporous poly(p-methylstyrene) resin beads 3 were prepared from *p*-methylstyrene and divinylbenzene (8 mol%) using standard suspension polymerisation techniques with 2ethyl-1-hexanol being used as the porogen (Scheme 1). The poly(*p*-methylstyrene) resin was then iodinated by treatment with sodium periodate and iodine in a mixture of acetic acid, sulfuric acid, acetic anhydride and dichloromethane to give iodinated poly(p-methylstyrene) 4.9 On the basis of steric grounds and literature precedence,¹⁰ we believe that iodinated product 4 consists of a major component, the desired ortho-iodinated species (ortho to the methyl group) and a minor component the undesired *meta*-iodinated species (*meta* to the methyl group). Iodinated polymer 4 was then oxidised successfully by reaction with potassium permanganate in the presence of methyltri-n-octylammonium chloride (Aliquat[®]) in a mixed solvent system of water and dichloromethane to give polymer 5.11 Polymer-supported oxidant 6, of which the major component is polymer-supported IBX, was obtained by the oxidation of **5** by treatment with tetrabutylammonium oxone¹² in dichloromethane containing a small amount of methanesulfonic acid.^{8b} The infrared spectrum obtained

Table 2. Evaluation of time course for the oxidation ofbenzyl alcohol by polymer-supported oxidant 6

Entry	Time / h	Conversion ^a (%)	Selectivity ^a (%)
1	1	44	100
2	2	66	100
3	3	72	100
4	4	81	100
5	5	86	98
6	7	98	97

All reactions were carried out at 25°C. ^aPercentage conversion and reaction selectivity were determined by GC analysis.

from polymer **6** had three strong absorbances at 1555, 1603 and 1657 cm⁻¹ which are characteristic of IBX¹³ and polymer-supported IBX.^{8a,b}

Evaluation of polymer-supported IBX 6. Initially, the loading of polymer-supported oxidant **6** was determined by oxidising benzyl alcohol to benzaldehyde in CH_2Cl_2 and analysing the reaction mixture by GC. In this way the loadings of two separate batches of polymer-supported oxidant **6** were determined to be 0.2 and 0.5 mmol/g. The higher of these values is in good agreement with loadings obtained previously for polymer-supported IBX.⁸ We next set out to determine the optimum solvent in which to study the reaction and also to investigate the effect of differing oxidant:alcohol ratios. The results obtained from this study are summarised in Table 1.

Similarly, the time course of benzyl alcohol oxidation by polymer-supported IBX **6** was evaluated. Table 2 shows the effect upon yield and purity of benzaldehyde production at various time intervals. These results led to all subsequent work adopting a 5 h reaction protocol employing CH_2Cl_2 as the solvent and a ratio of oxidant:alcohol of 2:1.

Having established an effective oxidation protocol a series of alcohols were treated with polymer-supported IBX 6. Benzyl alcohol, 4-methoxybenzyl alcohol, 4-mitrobenzyl alcohol, octanol and 3,4-(methylenedioxy)benzyl alcohol were all oxidised to the corresponding aldehydes in 5 h by treatment with reagent 6 at room temperature in dichloromethane. The results obtained from this study are shown in Table 3 and indicate that polymer-supported IBX 6 oxidises effectively both electron rich and electron deficient benzyl alcohols to the corresponding benzaldehydes in

Table 1. Evaluation of reaction conditions for the oxidation of benzyl alcohol by polymer-supported oxidant 6

Entry	Oxidant:alcohol (mmol:mmol)	Solvent	Conversion ^a (%)	Selectivity ^a (%)
1	1:1	CH ₂ Cl ₂	66	100
2	2:1	CH_2Cl_2	86	98
3	2:1	DMSO	44	100
4	2:1	THF	50	96
5	2:1	CHCl ₃	75	100

All reactions were carried out at 25°C. "Percentage conversion and reaction selectivity were determined by GC analysis.

Table 3. Oxidation of a series of alcohols using polymer-supported IBX reagent $\mathbf{6}$

Entry	Alcohol	Aldehyde	Conversion ^a /%	Selectivity ^a /%
1	ОН	S	86	98
2	ОН	Š	100	100
3	OMe OH	OMe	100	100
4			o ⁵²	82
5	СССОН		Sin 100 €	100

All reactions were carried out at 25° C in CH₂Cl₂ (1ml/100 mg of 6) for 5 h and employed a polymer-supported IBX 6:alcohol ratio of 2:1. Active oxidant 0.2 mmol/g polymer. ^aPercentage conversion and reaction selectivity were determined by GC analysis.

excellent yields and purity. However, oxidation of a primary alkyl alcohol proved to be more difficult and a lower yield was obtained. This finding is again in agreement with previous studies.^{8b,c}

In summary a short efficient synthesis of a polymersupported IBX reagent that differs significantly from previously reported syntheses⁸ has been developed. This reagent has been used successfully for the oxidation of a range of alcohols under very mild conditions to furnish the corresponding aldehydes. Currently, we are evaluating the use of reagent **6** in a flow through reactor system and will report our findings in this area in due course.

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