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Preparation and Reactivity of Polymer-Supported 2-Iodylphenol Ethers, an Efficient Recyclable Oxidizing System

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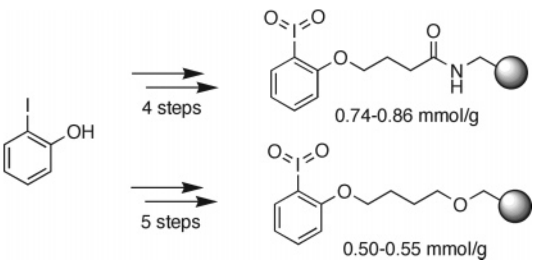
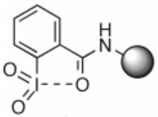


Preparation of new recyclable polymer-supported oxidizing reagents based on 2-iodylphenol ethers is described. The synthesis employs commercially available aminomethylated polystyrene or Merrifield resin and affords polymer-supported 2-iodylphenol ethers with loading up to 0.86 mmol/g with respect to IO_2 groups. The new reagents effect clean and efficient conversion of a wide range of alcohols, including heteroatomic and unsaturated structures, to the corresponding carbonyl compounds. Recycling of the resins is possible with minimal loss of activity after several reoxidations.

Hypervalent iodine(V) compounds, namely, 2-iodoxybenzoic acid (IBX) and its acetylation product, Dess−Martin periodinane (DMP), are now employed extensively in organic synthesis as highly selective reagents for the oxidation of alcohols to carbonyl compounds as well as for a variety of other synthetically useful oxidative transformations.[1] Despite their importance, IBX and DMP are not perfect reagents and have some disadvantages. IBX is potentially explosive and is insoluble in common organic solvents, while DMP is highly sensitive to moisture and decomposes upon prolonged storage with the formation of partially hydrolyzed insoluble products. Therefore, various derivatives of IBX, which are highly soluble and nonexplosive, have been developed recently.[2,3] Several variants of polymer-supported IBX-based reagents have also been prepared, and their usefulness as efficient oxidizing reagents was demonstrated by several research groups.[4,5] The polymer-supported IBX derivatives are especially attractive because of the low explosiveness and the preparative advantage of the attachment of a chemical reagent to a solid matrix.[5] Particularly promising oxidizing systems are represented by polymer-supported IBX amides[5d−f] **1** and *N*-(2-iodylphenyl)acylamides[5g,h] (NIPA resin, **2**).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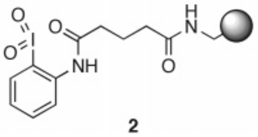
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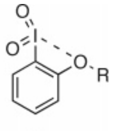
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Recently, we have reported the preparation, X-ray structure, and oxidative properties of 2-iodylphenol ethers **3**, which are readily available, soluble, and stable IBX analogues having a pseudocyclic four-membered ring motif.[6] Herein, we report the facile synthesis of polymer-supported 2-iodylphenol ethers and their reactivity toward oxidation of a broad range of alcohols.

To create a 2-iodylphenol ether scaffold and to ensure proper immobilization to resin through amide and ether bonds, 4-hydroxybutanoic acid and 1,4-butanediol moieties were chosen, respectively, as linkers. Preparation of these linkers was achieved through easy steps with excellent yields. Thus, reaction of commercially available 2-iodophenol **4** with ethyl 4-bromobutanoate gave ester **5**, which was afterward saponified to afford acid **6**. Acid **6** was subsequently coupled to aminomethylated polystyrene with HOBt/DIC to yield resin **8** (Scheme 1). To block any possible free amino groups the resin was treated with an excess of acetic anhydride and pyridine.

Since 2-iodophenol can be easily attached to the halomethylated polymers through a simple nucleophilic substitution, we

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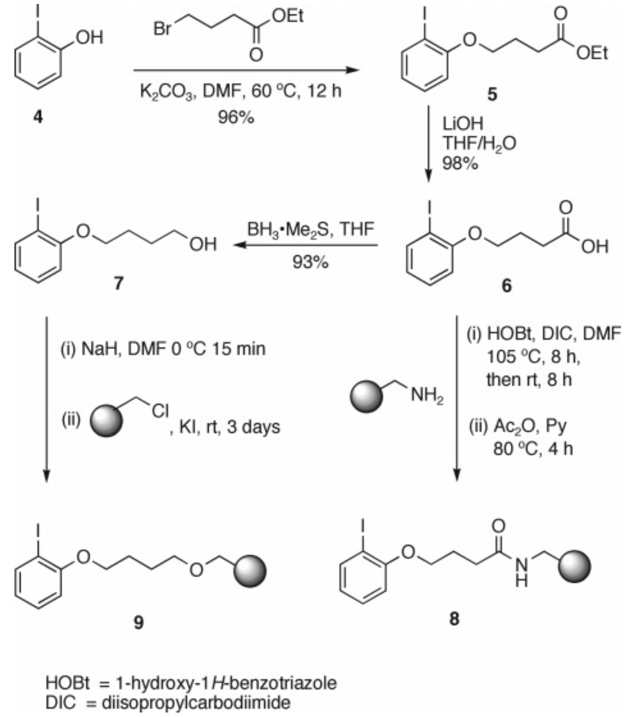
SCHEME 1. Synthesis of Polymer-Supported 2-Iodophenol Ethers 8 and 9



SCHEME 2. Oxidation of Resins 8 and 9

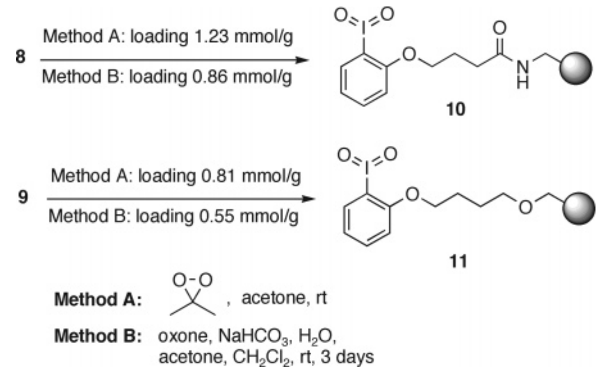
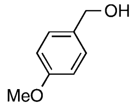
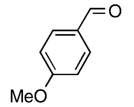
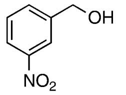
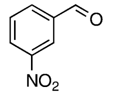
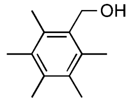
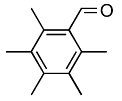
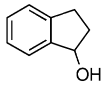
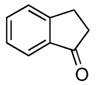
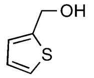
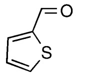
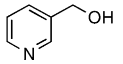
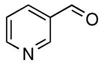
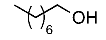
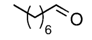
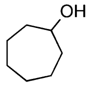
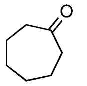
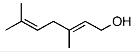
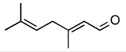
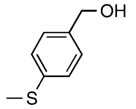
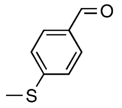


TABLE 1. Oxidation of Alcohols with Reagents 10 and 11[a]

Entry	Reagent	Substrate	Product	Conversion(%)	Time (h)
1a 1b	**10** **11**			>99 >99	0.7 3
2a 2b	**10** **11**			>99 >99	1.5 3
3a 3b	**10** **11**			>99 >99	3 6
4a 4b	**10** **11**			>99 >99	5 1.5
5a 5b	**10** **11**			>99 >99	1 2.5
6a 6b	**10** **11**			>99 >99	1.5 3
7a 7b	**10** **11**			>99 >99	4 6
8a 8b	**10** **11**			>99 >99	4 6
9a 9b	**10** **11**			96[b] 97[c]	2 3.5
10a 10b	**10** **11**			77[d,e] 75[d,f]	3 3

[a] All oxidations were carried out with 1 equiv of reagents **10** or **11** in dry DCE under reflux for specified time, unless otherwise noted. The resin was removed by filtration and washed with dry DCE. The resulting filtrates were analyzed by GC−MS. [b] (*Z*)-Isomer (4%) was also detected as a side product. [c] (*Z*)-Isomer (3%) was also detected. [d] Oxidation was carried out with 0.5 equiv of resins **10** and **11**. [e] 4-(Methylsulfinyl)benzaldehyde (13%), [4-(methylthio)phenyl]methanol (7%), and [4-(methylsulfinyl)phenyl]methanol (3%) were detected. [f] 4-(Methylsulfinyl)benzaldehyde (11%), [4-(methylthio)phenyl]methanol (9%), and [4-(methylsulfinyl)phenyl]methanol (5%) were detected.

have also investigated Merrifield resin as a solid support. This resin is cheaper than aminomethylated polystyrene and is more stable to the typical acidic oxidation conditions that have previously been used for the oxidation of known polymer-supported reagents.[5] Although direct attachment of 2-iodophenol **4** to Merrifield resin was unsuccessful, the readily available alcohol **7** was successfully coupled to the Merrifield resin via ether link to yield polymer **9** (Scheme 1).

The loadings of the resins **8** and **9** were determined by elemental analysis and corresponded to 89% and 70% conversion, respectively, when the mass increase is taken into account. Oxidation of polymers **8** and **9** was initially performed with 3,3-dimethyldioxirane (Scheme 2, method A), as described for the solution-phase synthesis of the monomeric 2-iodylphenol ethers **3**.[6] Obtained resins **10** and **11** were characterized by IR spectroscopy and elemental analysis. Oxidizing activity of reagents **10** and **11** was measured by GC−MS analysis using an excess of 4-methoxybenzyl alcohol as the test substrate under reflux in 1,2-dichloroethane (DCE) for 3 h. Based on these measurements, the loadings of resins **10** and **11** were found to be 1.23 mmol/g and 0.81 mmol/g correspondingly with respect to the IO$_2$ groups. Since the dioxirane oxidation was effective, but not very practical (3,3-dimethyldioxirane is unstable and not readily available), we have tested the in situ generated dioxirane as the oxidizing agent. The modified protocol (Scheme 2, method B) consists of treatment of resins **8** and **9** with oxone, NaHCO$_3$, and acetone at room temperature and affords resins **10** and **11** with only slightly lower loading levels (0.74−0.86 mmol/g for polymer **10** and 0.50−0.55 mmol/g for polymer **11**). We have used this practical procedure (method B) for the preparation of numerous batches of resins **10** and **11** in gram quantities.

The oxidative properties of resins **10** and **11** were evaluated by the reaction with various benzylic, allylic, primary, and secondary alcohols (Table 1). All employed alcohols and the samples of the respective carbonyl compounds were commercially available. Reactions were performed in DCE under reflux until complete disappearance of alcohol (monitored by TLC). Conversions were measured by GC−MS with a prior column calibration using authentic samples of reagents and products. The reaction products were identified by direct comparison of the retention times and MS data with those obtained for authentic samples.

Although both reagents gave corresponding carbonyl compounds with high conversion and purity, resin **10** performed these oxidations faster in most cases. Both reagents showed good selectivity toward oxidation of an alcohol group in the presence of a sulfide group in 4-(methylthio)benzyl alcohol (entry 10). The oxidizing reactivity of resins **10** and **11** is generally similar to the monomeric 2-iodylphenol ethers **3**,[6] with noticeable improvement in the selectivity of oxidation of 4-(methylthio)benzyl alcohol.

The reduced polymeric materials formed in the reaction of resins **10** and **11** with alcohols can be collected and reoxidized according to the procedure described above. A slow decline in oxidative activity was observed after multiple recovery steps, possibly due to iodine loss in the course of resin reoxidation.

In conclusion, we have prepared polymer-supported analogues of 2-iodylphenol ethers. The synthesis of these reagents employs commercially available aminomethylated polystyrene and Merrifield's resin, includes four or five simple steps, and affords the resins **10** and **11** with good loadings of 0.74−0.86 and 0.50−0.55 g/mmol, respectively. Reagents **10** and **11** effect clean and selective oxidation of a wide range of alcohols, including heteroatomic and unsaturated structures.

Experimental Section

Experimental details, analytical data, and spectra of compounds **5**−**7** can be found in the Supporting Information.

Attachment of 4-(2-Iodophenoxy)butanoic Acid to Aminomethylated Polystyrene (Resin 8). 4-(2-Iodophenoxy)butanoic acid (10.000 g, 32.5 mmol) was dissolved in dry DMF (25 mL), and HOBt (1-hydroxy-1*H*-benzotriazole, 4.845 g, 35.75 mmol) was added. The resulting mixture was stirred vigorously until all of the solid material dissolved. The resulting solution was added to a suspension of aminomethylated polystyrene (8.1 g, 32.5 mmol, 200−400 mesh, 2% cross-linked with divinylbenzene, loading 4.0 mmol/g) in 205 mL of dry DMF. Thereafter, DIC (diisopropylcarbodiimide, 4.9 mL, 32.5 mmol) was added, and the reaction mixture was heated to 105 °C and was agitated at this temperature for 8 h. Then the reaction mixture was cooled to rt and additionally stirred for 8 h. Pyridine (5.5 mL, 67 mmol) and acetic anhydride (6.5 mL, 67 mmol) were then added, and the mixture was agitated for 2 h at 80 °C. Polymer **8** was filtered, washed with DMF (6 × 10 mL), MeOH (6 × 10 mL), DMF (6 × 10 mL), MeOH (6 × 10 mL), and CH_2Cl_2 (6 × 10 mL), and dried in vacuum to constant weight. Yield: 14.126 g. IR: 1012, 1046, 1177, 1238, 1272, 1458, 1513, 1642, 2364, 2908, 3402 cm^{-1}. Anal. Found: I, 21.04. Loading: 1.66 mmol/g (89% conversion when the mass change is considered).

Attachment of 4-(2-Iodophenoxy)butan-1-ol to Merrifield Resin (Resin 9). To a solution of 4-(2-iodophenoxy)butan-1-ol (4.48 g, 15.3 mmol) in dry DMF (50 mL) under nitrogen was added NaH (0.450 g, 18.8 mmol) and the mixture stirred for 15 min at 0 °C. Then a suspension of Merrifield resin (loading 3.8 mmol/g, 4.0 g, 15.3 mmol) in 100 mL of dry DMF was added followed by KI (0.200 g, 1.2 mmol). The resulting mixture was stirred for 3 days at room temperature. Solids were filtered off, washed with DMF (3 × 25 mL), MeOH (3 × 25 mL), water (3 × 25 mL), MeOH (3 × 25 mL), and CH_2Cl_2 (3 × 25 mL), and dried in vacuum to constant weight. Yield: 4.1 g. IR: 1010, 1088, 1243, 1269, 1458, 1577, 1654, 2922, 3398 cm^{-1}. Anal. Found: I, 18.64. Loading: 1.47 mmol/g (70% conversion when the mass change is considered).

General Procedure for the Oxidation of Resins 8 and 9 (Method B). In a 1000 mL flask were mixed $NaHCO_3$ (15 g), acetone (50 mL), and H_2O and the mixture cooled to 5−7 °C with ice. Then Oxone (30 g) was added in three portions over 15 min and the mixture stirred at that temperature for an additional 40 min. Appropriate resin (∼1 g; preswollen in 25 mL of CH_2Cl_2 for 1 h) was then added. An additional 25 mL of CH_2Cl_2 was used to completely transfer the resin. The resulting mixture was mixed for 3 days. Thereafter, polymer was filtered, washed with H_2O (6 × 50 mL), MeOH (6 × 10 mL), CH_2Cl_2 (3 × 10 mL), Et_2O (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), Et_2O (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), Et_2O (3 × 10 mL), and agitated with 25 mL of CH_2Cl_2 for 6 h. The resin was filtered off and dried in vacuum to a constant weight.

Polymer 10. Oxidation of resin **8** (1.011 g, 1.68 mmol) according to the general procedure afforded 0.992 g of polymer **10**, isolated as off-white powder. IR: 752, 1027, 1117, 1156, 1231, 1267, 1453, 1542, 1642, 2364, 2917, 3393 cm^{-1}. Anal. Found: I, 21.66. Loading (IO_2): 0.74−0.86 mmol/g based on 4-methoxybenzyl alcohol oxidation (5 resin batches were prepared).

Polymer 11. Oxidation of resin **9** (1.000 g, 1.47 mmol) according to the general procedure afforded 0.890 g of polymer **11**, isolated as off-white powder: IR 744, 1015, 1095, 1243, 1269, 1460, 1576, 1654, 1700, 2364, 2917, 3407 cm^{-1}. Anal. Found: I, 16.43. Loading (IO_2): 0.50−0.55 mmol/g based on 4-methoxybenzyl alcohol oxidation (four resin batches were prepared).

General Procedure for the Oxidation of Alcohols with Polymers 10 and 11. To a vigorously stirred mixture of polymer (0.02 mmol) in dry dichloroethane (DCE) (1 mL) was added the appropriate alcohol (0.02 mmol), and the solution was refluxed until complete disappearance of alcohol (monitored by TLC). Thereafter, polymer was filtered and washed with dry DCE (3 × 2 mL). The resulting filtrates were analyzed by GC−MS.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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