

Macroporous Polystyrene-Supported (Diacetoxyiodo)benzene: An Efficient Heterogeneous Oxidizing Reagent

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Abstract: A heterogeneous, cross-linked macroporous polystyrene-supported (diacetoxyiodo)benzene reagent has been prepared. This reagent is completely insoluble in all solvents and has a rigid pore structure that allows it to function without the need for swelling. Its utility in a variety of oxidation reactions has been demonstrated.

Key words: (diacetoxyiodo)benzene, macroporous polystyrene, polymer-supported reagents, oxidation reactions

The hypervalent iodine reagent (diacetoxyiodo)benzene (**1**, Figure 1) is a powerful and versatile tool for organic synthesis,¹ and polymer-supported versions of it have been reported in the literature.² We have previously synthesized non-cross-linked polystyrene-supported (diacetoxyiodo)benzene **2**, and have used it for aromatic compound iodination,³ 1,2-aryl group migration reactions,³ α -hydroxylation of ketones,⁴ oxidation of dihydroquinones,⁴ oxidation of sulfides,⁴ oxidation of alcohols to either aldehydes or ketones,⁵ or carboxylic acids,⁶ and in sulfonamide⁷ and alcohol cyclization reactions.⁸ Reagent **2** has also been used in the synthesis of a variety of natural products,^{9,10} and isoflavones,¹¹ in ring-expansion reactions of 1-alkynylcycloalkanols,¹² and in C–H bond functionalization reactions.¹³

Our interest in multipolymer reactions, in which two or more polymer-supported reagents are used simultaneously,¹⁴ led us to use **2** in conjunction with a cross-linked polystyrene-supported TEMPO reagent for alcohol oxidation reactions.¹⁵ This work, combined with our multipolymer Mitsunobu reaction system¹⁶ has recently led us to design the first catalytic version of the Mitsunobu reaction, in which **1** is the stoichiometric oxidant and DEAD is a catalytic oxidant.¹⁷ One limitation of our methodology is that **1** is able to oxidize Ph_3P to $\text{Ph}_3\text{P}=\text{O}$. Thus, in some cases it was necessary to add Ph_3P slowly to the reaction mixture containing **1**, in order to keep these two reagents separated for as long as possible.

An alternative solution to this phosphine oxidation problem would be to separate **1** and Ph_3P by immobilizing them on separate, insoluble polymer supports. Such a

strategy has been previously reported to allow an oxidant and a reductant,¹⁸ and an acid and a base¹⁹ to coexist in the same reaction vessel. The key to this strategy is to have heterogeneous polymer-supported reagents. While we have previously reported the synthesis of various polymer-supported phosphines that could be used in our organocatalytic Mitsunobu reaction system,²⁰ **2** is non-cross-linked and becomes slightly soluble as the hypervalent iodine groups are reduced during the course of a reaction. Thus, we desired to have a cross-linked analogue of **2**, which would suit our needs for a multipolymer catalytic Mitsunobu reaction system, in which the oxidant and the phosphine are heterogeneous and phase-separated throughout the reaction. While such cross-linked reagents have been reported,^{21–24} we felt that they all suffered from various drawbacks (vide infra). Therefore, we designed macroporous polystyrene-supported (diacetoxyiodo)benzene **3** and herein report its synthesis and utilization.

Macroporous cross-linked polystyrene was chosen over the more common microporous (gel-type) cross-linked polystyrene since its rigid structure allows accessibility to the interior of the resin in all solvents, not just those it swells well in.^{25,26} Thus, we felt that a macroporous material would be an appropriate support for our studies since our experience indicated that the reaction conditions necessary to prepare **2** and **3** would not swell a microporous polymer support. Furthermore, the macroporous nature of **3** would allow it to be useful in oxidation reactions requiring solvents such as water, alcohols, acetonitrile, or DMF, all of which do not swell microporous polystyrene. In addition, we wanted a direct analogue of **2**, and did not want to use any potentially labile linker to attach the iodo groups to the polymer backbone, as has been done before.²³

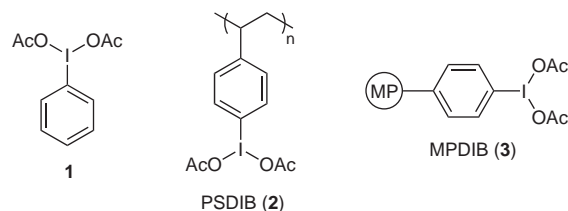
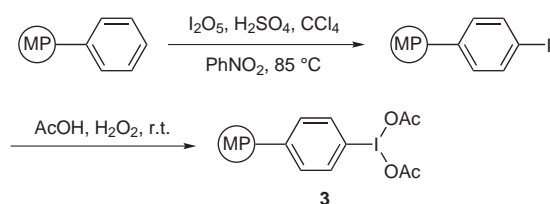


Figure 1

Thus, reagent **3** was prepared by a procedure analogous to that used for the preparation of **2**.²⁷ Unfunctionalized macroporous cross-linked polystyrene was iodinated with I_2 , I_2O_5 and H_2SO_4 at $85\text{ }^\circ\text{C}$ in CCl_4 and $PhNO_2$, and the resulting iodo groups were oxidized with in situ generated peracetic acid, generated from H_2O_2 and Ac_2O (Scheme 1). The level of iodine incorporation (45% of the theoretical maximum) and oxidation (100%) were determined by elemental analysis.²⁸ The loading level of **3** was found to be 1.3 mmol/g. The oxidation of the iodine groups was confirmed by the appearance of a broad signal in the IR spectrum at 1630 cm^{-1} . This corresponds to the carbonyl stretching frequency observed in **1**. Furthermore, it should be noted that the IR spectrum recorded for **3** was very similar to what was previously observed for **2**.³



Scheme 1 Synthesis of reagent **3**

With reagent **3** in hand, we examined its utility in a variety of oxidation reactions (Table 1). Depending upon the reaction conditions, alcohols were selectively oxidized to the corresponding aldehyde (entries 1–4), ketone (entries 5 and 6), or carboxylic acid (entries 7 and 8). In addition, dihydroquinones were cleanly oxidized to the corresponding quinones (entries 9 and 10) and a sulfide selectively formed the expected sulfoxide (entry 11). Even $AsPh_3$ afforded the corresponding oxide upon treatment with **3** (entry 12),²⁹ and most importantly with regards to our interest in organocatalytic Mitsunobu reactions, both Ph_3P and diethyl 1,2-hydrazinedicarboxylate³⁰ were cleanly oxidized (entries 13 and 14). In these reactions, the only contaminant, if any, of the product was unreacted starting material, and the product was isolated in a pure state after several filtration and concentration operations, except for the carboxylic acids, which required an acidification step. The identity of all products was confirmed by comparison of 1H NMR spectra with those of commercially available samples. Importantly, the reaction conditions and yields for entries 1–10 of Table 1 are all similar to when **2** was used as the oxidant.^{4–6}

It should be noted that in all of the reactions, except for acid synthesis and hydrazine oxidation, only 1.3 equivalents of **3** were necessary to achieve high yields. Thus, even though **3** is a heterogeneous reagent, most, if not all, of the oxidizing equivalents on the polymer support are accessible to the homogeneous oxidation substrate in these reactions. This accessibility and reactivity validates our choice of polymer support, and operationally, it eliminates the need to add a large excess of **3**, which is often required when using heterogeneous, polymer-supported reagents.

Table 1 Oxidation Reactions Using **3**³¹

Entry	Substrate	Product	Yield (%) ^a
1			96
2			86
3			88
4			83
5			95
6			90
7			94 ^b
8			96 ^b
9			96
10			95
11			92
12			96
13			96
14			77 ^c

^a Isolated yield of reaction using 1.3 equiv of **3** at r.t.

^b Reaction using 2.6 equiv of **3**.

^c Reaction using 1.5 equiv of **3**.

In summary, we have synthesized a heterogeneous, macroporous cross-linked polystyrene-supported (diacetoxiodo)benzene reagent **3**, that is capable of efficiently and selectively oxidizing a range of substrates. It is anticipated that the rigid macroporous structure of the polymer support will allow this reagent to find wide use in reactions in which a completely insoluble, heterogeneous reagent is desired and that require solvents that do not swell microporous (gel-type) cross-linked polystyrene.

One such application would be the high-throughput, parallel oxidation of primary alcohols to the corresponding carboxylic acids. Furthermore, the use of this new reagent in conjunction with cross-linked polystyrene-supported triphenylphosphine in organocatalytic Mitsunobu reactions is currently under investigation.

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- (27) **Preparation of 3**
A solution of I₂ (22.40 g, 88.20 mmol) in nitrobenzene (250 mL) and CCl₄ (40 mL) was added to macroporous cross-linked polystyrene (20.00 g), followed by a solution of I₂O₅ (8.76 g, 27.56 mmol) in 50% H₂SO₄ (44 mL). The reaction mixture was stirred for 4 d at 85 °C. The reaction mixture was then cooled to r.t., diluted with CHCl₃-MeOH (1:15, 300 mL), and filtered. The collected polymer was washed sequentially with H₂O (3 × 200 mL), AcOH (2 × 200 mL), CHCl₃ (3 × 200 mL) and MeOH (3 × 200 mL) and dried in vacuo to afford iodinated polymer (27.64 g). IR: 2932, 1526, 1340, 1184, 999, 819, 812, 703 cm⁻¹. Elemental analysis of the product showed the iodine content to be 24.63%, which corresponds to a loading of 1.9 mmol/g.
The iodinated macroporous cross-linked polystyrene (27.0 g) was added to a solution of peracetic acid generated by the dropwise addition of H₂O₂ (30%, 136 mL) dropwise to Ac₂O (500 mL) at 0 °C, which was then allowed to warm to r.t. The suspension was stirred at 40 °C for 16 h and then filtered. The collected polymer was washed with Et₂O (3 × 200 mL) and dried in vacuo to afford **3** (33.0 g). IR: 2930, 1630, 1587, 1483, 1234, 818, 812, 702 cm⁻¹. Elemental analysis of the product showed the iodine content: 16.68%, which corresponds to a loading of 1.3 mmol/g. The decrease in loading level from 1.9 mmol/g to 1.3 mmol/g indicates essentially quantitative oxidation of the iodine groups on the polymer and both loading levels indicate that approximately 45% of the aryl rings of the polymer were functionalized.
- (28) This was calculated by determining the ratios of the iodine content of the iodinated polymer (24.63%) to that of 4-ethyliodobenzene (54.69%), and the iodine content of **3** (16.68%) to that of 4-ethyl(diacetoxyiodo)benzene (36.24%). The first ratio (0.45:1) indicates that approximately 45% of the aryl rings of the starting material polymer were iodinated and the second ratio (0.46:1) indicates that essentially all of the iodo groups were oxidized.
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- (31) **Oxidation of Alcohols to the Corresponding Aldehydes and Ketones (Table 1, Entries 1–6)**
Reagent **3** (0.5 g, 0.65 mmol) was added to a solution of alcohol (0.5 mmol) and TEMPO (9.4 mg, 0.06 mmol) in acetone (3 mL) and the mixture was stirred at r.t. for 2 h. The reaction mixture was then filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was poured into H₂O (10 mL), and extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered,

and concentrated in vacuo. The pure product was obtained by filtration of the crude product through silica gel.

Oxidation of Primary Alcohols to the Corresponding Carboxylic Acids (Table 1, Entries 7 and 8)

Reagent **3** (1.0 g, 1.3 mmol) was added to a solution of alcohol (0.5 mmol) and TEMPO (39 mg, 0.25 mmol) in acetone (3 mL) and the mixture was stirred at r.t. for 2 h. Then, H₂O (2 mL) was added to the mixture, and the suspension was stirred for an additional 24 h. The reaction mixture was then diluted with Et₂O (5 mL), and HCl (1 N, 3 mL) was added. After stirring for 10 min more, the mixture was filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was extracted with Et₂O (3 × 10 mL). A sat. Na₂CO₃ solution was added to the combined organic layer and then separated. The aqueous layer was neutralized by 1 N HCl and extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give pure product.

Oxidation of Dihydroquinones to the Corresponding Quinones (Table 1, Entries 9 and 10)

Reagent **3** (0.5 g, 0.65 mmol) was added to a solution of dihydroquinone (0.5 mmol) in MeOH (3 mL) and the mixture was stirred at r.t. for 4 h. The reaction mixture was then filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was concentrated in vacuo and pure quinone was obtained by filtration of the crude product through silica gel.

Oxidation of Diphenyl Sulfide to Diphenyl Sulfoxide (Table 1, Entry 11)

Reagent **3** (0.5 g, 0.65 mmol) was added to a solution of PhSPh (0.5 mmol) in CHCl₃-H₂O (99:1, 3 mL) and the mixture was stirred at 40 °C for 72 h. The reaction mixture was then filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was concentrated in vacuo and pure sulfoxide was obtained by filtration of the crude product through silica gel.

Oxidation of AsPh₃ and PPh₃ to the Corresponding Oxides (Table 1, Entries 12 and 13)

Reagent **3** (0.5 g, 0.65 mmol) was added to a solution of AsPh₃ or PPh₃ (0.5 mmol) in THF (3 mL) and the mixture was stirred at r.t. for 4 h. The reaction mixture was then filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was concentrated in vacuo and the pure oxide was obtained by filtration of the crude product through silica gel.

Oxidation of Diethyl 1,2-Hydrazinedicarboxylate to DEAD (Table 1, Entry 14)

Reagent **3** (0.58 g, 0.75 mmol) was added to a solution of diethyl 1,2-hydrazinedicarboxylate (0.5 mmol) in THF (8 mL) and the mixture was stirred at r.t. for 17 h. The mixture was then filtered to remove the polymer, which was washed with Et₂O (5 mL). The filtrate was concentrated in vacuo and pure DEAD was obtained by filtration of the crude product through silica gel.