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Facile preparation and reactivity of polystyrene-supported (dichloroiodo)benzene: a convenient recyclable reagent for chlorination and oxidation

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ABSTRACT

A facile one-pot preparation of polystyrene-supported (dichloroiodo)benzene (loading of $-ICl_2$ up to 1.35 mmol/g) from polystyrene, iodine, and bleach has been developed. This recyclable reagent is useful for efficient chlorination of organic substrates and selective oxidation of various alcohols to the corresponding carbonyl compounds in high yields under mild conditions. The final products are conveniently separated from the polymeric byproduct by simple filtration and isolated in good purity after evaporation of solvent.

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In recent years, hypervalent organoiodine compounds have emerged as reagents of choice for a variety of synthetically useful oxidative transformations.¹ (Dichloroiodo)arenes belong to the oldest and best investigated class of hypervalent iodine reagents, particularly useful for chlorination or oxidation of diverse organic and organometallic substrates, including industrial applications.^{2,3} For example, the chlorination of 4-aminoacetophenone with PhICl₂ to give 4-amino-3-chloroacetophenone, which is a common intermediate to many of the COX-II (cyclooxygenase-2) selective inhibitors, has been successfully scaled up in a pilot plant.³ Despite the synthetic importance of (dichloroiodo)benzene, its broader application has been restricted due to the low atom economy, because stoichiometric amount of iodobenzene as a waste product is produced. This represents a major drawback from the green chemistry viewpoint.⁴ A possible solution would be the application of recyclable reagents, whose byproducts can be efficiently separated from reaction mixtures and reused. Accordingly, several approaches to recyclable monomeric analogues of (dichloroiodo)benzene, such as, 4,4'-bis(dichloroiodo)biphenyl, 3-(dichloroiodo)benzoic acid, and several fluorous and nonfluorous aryl and alkyl iodine(III) dichlorides have been developed.⁵ However, from practical viewpoint these recyclable reagents are not very attractive because of their generally high cost, incomplete recovery of the aryliodide

* Corresponding authors. E-mail address: vzhdanki@d.umn.edu (V.V. Zhdankin). (85–91%) after each reaction cycle, and complicated work-up involving fluorous techniques or acid-base biphasic protocols.

Compared to the corresponding monomeric analogues, an attractive feature of polymer-supported hypervalent iodine reagents is that their recyclable byproducts can be easily separated from the reaction mixture without the complicated workup just using a simple filtration to yield a solution of the pure product. The advantages of polymer-supported hypervalent iodine reagents are now widely recognized by organic chemists, and increasing exploitation of these systems is occurring both in academic and industrial laboratories.^{6,7} Polymer-supported versions of various hypervalent iodine reagents have been developed and practically used, including polystyrene-supported analogues of (diacetoxyiodo)benzene,^{7a-c} [bis(trifluoroacet-oxy)iodo]benzene,^{7d} halogen-ate(1) complexes,^{7e} [hydroxy(tosyl-oxy)iodo]benzene,^{7f} iodosylbenzene sulfate,^{7g} 2-iodoxybenzoic acid (IBX),^{7h} and several non-cyclic IBX derivatives.⁷ⁱ⁻¹ Surprisingly, but despite the synthetic importance of (dichloroiodo)benzene, the polymer-supported version of this reagent has not received much attention. A brief description of the preparation of polymer-supported (dichloroiodo)benzene by chlorination of iodinated polystyrene using chlorine gas was reported in 1984.⁸ This method, however, involves the initial preparation of iodinated polystyrene under harsh conditions (160 h, 110 °C), requires the use of hazardous chlorine gas, and affords polystyrene-supported (dichloroiodo)benzene with a relatively low loading of active chlorine.





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We wish to report a new, convenient one-pot procedure for the preparation of polystyrene-supported (dichloroiodo)benzene (PS-DCIB, **2**) from polystyrene (PS, **1**), iodine, and bleach (5% aqueous NaOCI) as the chlorinating agent.⁹ In this procedure, PS **1** is first oxidatively iodinated using I_2/I_2O_5 reagent system in the presence of sulfuric acid in nitrobenzene–carbon tetrachloride mixture under reflux conditions. Next, to the cooled reaction mixture containing a solution of polystyrene-supported iodobenzene (PS-IB), solutions of commercial bleach and then concentrated hydrochloric acid are added drop wise resulting in the precipitation of PS-DCIB **2** (Scheme 1).

Polymer **2** was isolated from the reaction mixture as a yellow solid by filtration and purified by washing with water and then diethyl ether. Based on the previous reports on oxidative iodination of polystyrene using I_2/I_2O_5 reagent system,^{7b,c} we assume that this is a regioselective reaction leading exclusively to the *para*-substituted dichloroiodo derivative **2**. The loading of the – ICl₂ groups in PS-DCIB **2** was 1.35 mmol/g as determined by titration of the iodine liberated from a solution of KI, which is substantially higher compared to the previously reported loading of 1.1 mmol/g.⁸ Nearly 40% of the phenyl rings in resin **2** are loaded with –ICl₂ according to the titration results. Resin **2** was also characterized by IR spectroscopy. PS-DCIB is sensitive to heat and sunlight and noticeably decomposes after one week at room temperature. It should be used as freshly prepared or stored away from direct sunlight in a refrigerator.

PS-DCIB **2** is a convenient chlorinating reagent with a reactivity pattern similar to (dichloroiodo)benzene. Several representative chlorination of organic substrates are shown in Scheme 2.

In particular, alkenes, such as cyclopentene 3 and cyclohexene 5, react with PS-DCIB in dichloromethane at room temperature to afford the respective trans-1,2-dichlorocycloalkanes 4 and 6. Similarly to the previously reported reactions of cycloalkenes with ArICl₂,^{5b} the chlorination affords the products of *anti*-addition, as confirmed by comparison of ¹H NMR spectra of products **4** and **6** with data available in the literature. 1.3-Diphenylpropane-1.3dione 7 reacts with PS-DCIB under similar conditions in the presence of pyridine to afford 2-chloro-1.3-diphenylpropane-1.3-dione 8. PS-DCIB can also chlorinate activated aromatic substrates, such as 4-iodoanisole 9 and 4-aminoacetophenone 11 giving the corresponding monochlorinated products 10 and 12 (Scheme 2). 4-Amino-3-chloroacetophenone hydrogen chloride salt 12 was previously prepared in 87% yield of 94% purity in a pilot plant by chlorination of 4-aminoacetophenone **11** with PhICl₂.³ Our protocol, however, has the advantage of convenient separation of product 12 from the byproduct, polystyrene-supported iodobenzene (PS-IB), by simple filtration followed by regeneration of PS-DCIB from PS-IB by treatment with aqueous NaOCl/HCl. Pure product 12 was obtained from the organic solution after treatment with HCl/dioxane as a hydrogen chloride salt whose melting point, ¹H NMR and ¹³C NMR spectra (see Supplementary data) were in agreement with the previously reported data³ and demonstrated high purity of the sample.

It was recently reported that (dichloroiodo)benzene can serve as an efficient stoichiometric oxidant for the oxidation of alcohols in the presence of catalytic amounts of TEMPO (2,2,6,6-tetrameth-







Scheme 2. Representative chlorinations of organic substrates using PS-DCIB 2.

ylpiperidine-1-oxyl).⁹ Taking into account the synthetic importance of oxidation of alcohols, we have investigated the use of PS-DCIB in this reaction. First, we have searched for optimized reaction conditions using benzyl alcohol as a model substrate and PS-DCIB in the presence of TEMPO in different solvents. Results of this study are summarized in Table 1.

As it can be seen from Table 1, dichloromethane, chloroform, and aqueous acetonitrile are the best solvents for these oxidations. However, the polymeric byproduct of the reaction, PS-IB, is partially soluble in dichloromethane or chloroform, which complicates recycling of the reagent and isolation of the products. Furthermore, these two solvents are not environmentally benign. Among the solvents examined, aqueous acetonitrile was superior to other solvents in terms of the reaction time, conversion, yield, and work-up.

The results of oxidations of several alcohols **13** of different types using PS-DCIB under optimized conditions are summarized in Table 2. The reactions were performed in aqueous acetonitrile in the presence of catalytic amount of TEMPO (0.1 equiv) at 50 °C using excess of PS-DCIB **2** (1.5 equiv). Conversions were measured by GC–MS with a prior column calibration using authentic samples of reactants and products. The corresponding aldehydes and ketones **14** formed from the oxidation of each alcohol **13** were further converted into the 2,4-dinitrophenylhydrazone derivatives and identified by comparison of their ¹H NMR or melting points with the literature data.

As expected, the reactivity of PS-DCIB in TEMPO-catalyzed oxidation of alcohols is similar to the monomeric PhICl₂, and the

Table 1
Effect of solvent on TEMPO-catalyzed oxidation of benzyl alcohol to benzaldehyde

Entry	Solvent	Time (h)	Conversion ^b (%)	Yield ^c (%)
1	CH ₂ Cl ₂	2	>99	92
2	CHCl ₃	2	>99	90
3	hexane	12	>99	89
4	MeCN-H ₂ O (1:1)	3	>99	92
5	H ₂ O	12	90	63
6	MeOH	12	70	30

 ^a Reactions of PhCH₂OH (0.2 mmol) were performed at 50 °C in the presence of TEMPO (0.1 equiv), pyridine (3 equiv) and PS-DCIB (1.5 equiv) in 2 mL of solvent.
 ^b Conversions were determined by GC analysis.

^c Isolated yields of benzaldehyde as the 2,4-dinitrophenylhydrazone derivative.

0

1	9	5	4

Table 2

2, Py, TEMPO (0.1 equiv)

ОН

	$R^1 \xrightarrow{I} R^2$ MeCN-H ₂ C	D(1:1, v/v), 50 °C	► _{R1} 儿	R ²		
	13a-k	14a-k				
(isolated as 2,4-dinitrophenylhydrazones)						
Entry	Alcohol 13	Product ^b	Time (h)	Yield ^{c,d} (%)		
1	Рh ОН 13а	14a	3	92		
2	Ph OH 13a	14a	3	91, 90, 90 ^e		
3	O ₂ N 13b	14b	2	90		
4	MeO U 13c	14c	2.5	88		
5	S OH 13d	14d	12	20 ^f		
6	Ph OH 13e	14e	12	85		
7		H 14f	12	82		
8		14g	2	92		
9	ОН	14h	3	85		
10	OH Ph 13i	14i	3	90		
11	Ph OH 13j	14j	3.5	83		
12		14k	3	83		

^a All reactions of alcohols **13** (0.2 mmol) were performed at 50 °C in the presence of TEMPO (0.1 equiv), pyridine (3 equiv) and PS-DCIB (1.5 equiv) in MeCN-H₂O (1:1, v/v) (2 mL).

^b All carbonyl compounds were identified as 2,4-dinitrophenylhydrazone derivatives by comparison of their ¹H NMR spectra and melting points with literature data.

^c Conversions for all reactions were above 99% unless noted otherwise.

 $^{\rm d}\,$ Isolated yields of the 2,4-dinitrophenylhydrazone derivatives.

^e Yields after first, second and third regeneration of PS-DCIB 2.

^f Reaction mixture contains 60% of unreacted alcohol according to GC data.

polymer-supported reagent **2** can be used for efficient oxidation of various alcohols to the corresponding carbonyl compounds under mild conditions. Benzylic alcohols are oxidized to the corresponding aldehydes with 100% conversion after 2–3 h (Table 2, entries 1–4), while 2-thiophenemethanol shows much lower reactivity (entry 5). Primary aliphatic alcohols, 1-octanol and 3-phenyl-1-propanol are smoothly oxidized to the corresponding aldehydes in excellent yields (entries 6 and 7), and secondary alcohols (entries 8–12) are oxidized to the respective ketones in good yields. The byproduct, polystyrene-supported iodobenzene (PS-IB), is

separated from the reaction mixtures by simple filtration and converted back to PS-DCIB by treatment with aqueous NaOCl/HCl in about 90% overall yield. The recycled PS-DCIB does not show any significant loss of activity in oxidation of benzyl alcohol to benzaldehyde after three regeneration cycles (Table 2, entry 2).

In summary, we have developed a facile one-pot procedure for the preparation of a recyclable polymer-supported hypervalent iodine reagent, PS-DCIB, from polystyrene, iodine, and bleach under mild condition. The synthesis of PS-DCIB employs commercially available chemicals and affords PS-DCIB with high loading level of active chlorine (loading of -ICl₂ up to 1.35 mmol/g). PS-DCIB selectively oxidizes primary and secondary alcohols to the respective carbonyl compounds in the presence of catalytic amount of TEMPO in aqueous acetonitrile, and selectively chlorinates various organic substrates, including α -chlorination of carbonyl compounds, electrophilic chlorination of electron-rich arenes, and the chlorination of alkenes under mild conditions with easy work-up. The reduced form of PS-DCIB, PS-IB can be separated from the reaction mixtures by simple filtration and converted back to PS-DCIB by treatment with bleach and aqueous HCl in about 90% overall yield.

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Supplementary data

Supplementary data (experimental procedures and ¹H and ¹³C NMR spectra for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.065.

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