Facile Preparation and Reactivity of Polymer-Supported *N*-(2-Iodyl-phenyl)-acylamide, an Efficient Oxidizing System
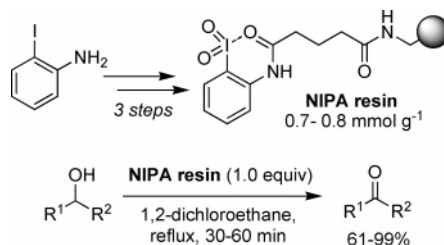
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ABSTRACT

A simple three-step preparation of polymer-supported *N*-(2-iodyl-phenyl)-acylamide (NIPA resin) starting from 2-iodoaniline is described. The resin was obtained with good loading levels (0.7–0.8 mmol g^{-1}) and has been successfully used for efficient oxidation of a diverse collection of alcohols. Thus, treating alcohols with 1.0 equiv of the resin in 1,2-dichloroethane under reflux for 30–60 min allowed rapid and in most cases complete conversion to the corresponding carbonyl compound.

Hypervalent iodine(V) compounds, namely, 1-hydroxy-(1*H*)-benzo-1,2-iodoxol-3-one (2-iodoxybenzoic acid, IBX) and its acetylation product, Dess–Martin periodinane (DMP), are now employed extensively in organic synthesis as mild and highly selective reagents for the oxidation of alcohols to carbonyl compounds as well as for a variety of other synthetically useful oxidative transformations.[1] However, the explosive character and low solubility of IBX in common organic solvents except DMSO, combined with the susceptibility of DMP to moisture and prolonged storage, restricts practical application of these reagents. Therefore, various derivatives of IBX, which are highly soluble and nonexplosive, have been developed recently.[2] The contributions from our group have also described the synthesis of IBX amides[3a]

and IBX esters[3b], which are stable and soluble reagents with oxidizing properties similar to those of IBX.[3c,d] To attain low explosiveness and to take preparative advantage of the attachment of a chemical reagent to a solid matrix, several polymer-supported IBX reagents have been prepared.[4a–e] More recently, the synthesis of various polymer-supported IBX amides and esters has been achieved by routes that are much shorter than the syntheses of solid-supported IBX

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reagents and has afforded resins that react with equal efficiency.[4f,g]

Recently, we reported the preparation and oxidative properties of *N*-(2-iodyl-phenyl)-acylamides **1**, which are soluble and stable IBX analogues having pseudo benziodoxazine structure (Figure 1).[5] These investigations, being
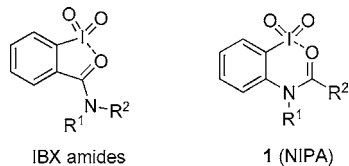
Figure 1. Amides of 2-iodoxybenzoic acid and *N*-(2-iodyl-phenyl)-acylamides (NIPA).

a logical extension of previous work on IBX amides, revealed that compounds **1** are able to oxidize either alcohols or sulfides, with their reactivity depending largely on the substitution pattern on the amide group adjacent to the iodyl moiety. In the context of these findings, we considered developing a polymer-supported *N*-(2-iodyl-phenyl)-acyl-amide reagent. Here we present the facile synthesis of such a hypervalent iodine derivative and show that it is a potent oxidant toward a broad range of alcohols.

To furnish a pseudo benziodoxazine scaffold and to ensure proper immobilization to the resin through an amide function, the carbamoylbutanoic acid moiety was chosen as a linker. Commercially available 2-iodoaniline **2** was reacted with glutaric anhydride to give acid **3**, which was subsequently coupled to aminomethylpolystyrene with HOBt/DIC to give resin **4**. To block any possible free amino groups, the resin was subsequently treated with an excess of acetic anhydride and pyridine.

The loading of the resin **4** was determined by elemental analysis and corresponded to 82% conversion when the mass increase is taken into account. Oxidation of **4** to NIPA resin **5** was initially performed with 3,3-dimethyldioxirane as was described for a solution-phase synthesis.[5] The obtained resin was characterized by IR spectroscopy and elemental analysis. Oxidizing activity of NIPA resin **5** was measured by GC−MS analysis with an excess of benzyl alcohol as a test substrate [1,2-dichloroethane (DCE), reflux, 60 min] and was found to be 0.31 mmol g^{-1} with respect to IO$_2$ groups. Moderate loading levels and utilization of unstable and not readily available 3,3-dimethyldioxirane prompted us to seek

a more convenient oxidation method. Since dioxirane oxidation was effective, it was decided to test the in situ generated dioxiranes as oxidizing agents.[6] However, these procedures yielded a lower resin activity of 0.08−0.14 mmol g^{-1}. The reaction with potassium monopersulfate triple salt (oxone)[7a] and sodium hypochlorite[3c] in aqueous medium also failed, resulting in a resin which exhibited virtually no oxidative activity.

Scheme 1. Preparation of Polymeric Reagent **5**

HOBt = 1-hydroxy-*1H*-benzotriazole
DIC = diisopropylcarbodiimide
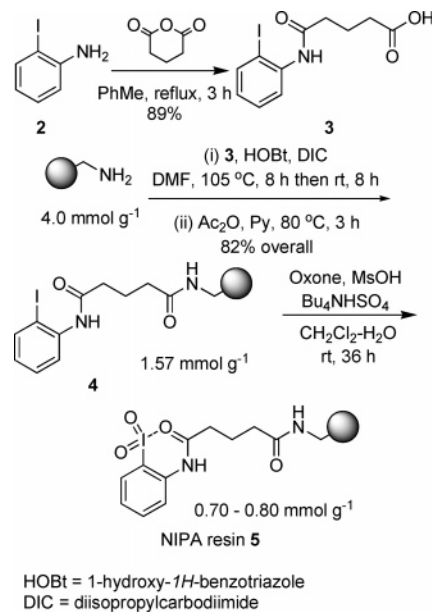
Finally, the oxidation with an equimolar mixture of tetrabutylammonium oxone[7b] with methanesulfonic acid (5.0 equiv, CH$_2$Cl$_2$, rt, 6 h)[4c−g] afforded the NIPA resin **5** with high loading levels (0.70−0.80 mmol g^{-1}). IR analysis of the prepared resin matched perfectly with the IR spectra of the resin **5** obtained by the 3,3-dimethyldioxirane oxidation. To avoid the supplementary preparation of tetrabutylammonium oxone, we have examined the oxidation of the polymer **4** in a CH$_2$Cl$_2$−H$_2$O biphasic system using oxone, Bu$_4$-NHSO$_4$, and CH$_3$SO$_3$H.

This modified protocol gave resin **5** with essentially the same loading levels and IR characteristics. As indicated by elemental analysis of resin **5**, only minor iodine loss (5−7% with respect to the initial iodine content) was observed under the strongly acidic reaction conditions.[8,9]

The oxidative properties of reagent **5** were evaluated by the reaction with various benzylic, allylic, primary and secondary alcohols, as well as a diol (Table 1). All employed alcohols were commercially available, as well as the respec-tive carbonyl compounds. Reactions were performed in DCE under reflux (30−60 min) since at room temperature long
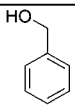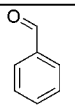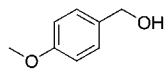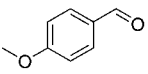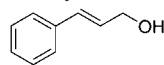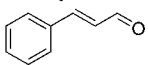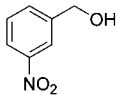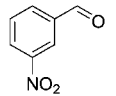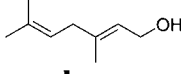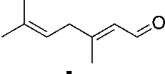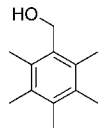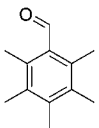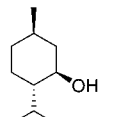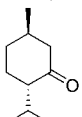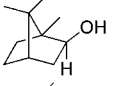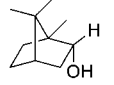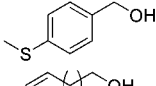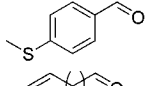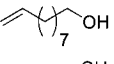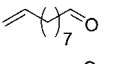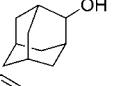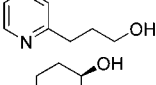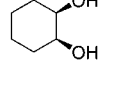
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Table 1. Oxidations of Alcohols with Reagent **5**

Entry	Alcohol	Product	Conversion, (%)[a]		Entry	Alcohol	Product	Conversion, (%)[a]
1	(structure)	(structure)	>99		11	(structure)	(structure)	>99
2	(structure)	(structure)	>99		12	(structure)	(structure)	>99[b]
3	(structure)	(structure)	>99		13	(structure)	(structure)	94[b, c]
4	(structure)	(structure)	98		14	(structure)	(structure)	61
5	(structure)	(structure)	>99		15	(structure)	(structure)	>99
6	(structure)	(structure)	>99		16	(structure)	(structure)	96
7	(structure)	(structure)	>99		17	(structure)	(structure)	85[d]
8	(structure)	(structure)	>99		18	(structure)	(structure)	>99 (89%)[e]
9	(structure)	(structure)	>99		19	(structure)	(structure)	>99 (86%)[e]
10	(structure)	(structure)	>99		20	(structure)	decomp	0[f]
					21	(structure)	(structure)	90[g]

[a] All oxidations were carried out with 1.0 equiv of NIPA resin **5** in dry DCE at reflux (85 °C) for 60 min, unless otherwise noted. The resin was removed by filtration and washed with dry DCE. The resulting filtrates were analyzed by GC–MS. For product isolation, combined filtrates from several resin washings were passed through a small pad of silica gel, the silica gel was washed with DCE, and the combined DCE fractions were evaporated to yield the respective carbonyl compound, pure by ^{1}H NMR. [b] Oxidation was performed for 30 min. [c] (Z)-Isomer (6%) was detected. [d] Oxidation was carried out with 0.5 equiv of NIPA resin **5**. 4-(Methylsulfinyl)benzaldehyde (7%) and (4-(methylthio)phenyl)-methanol (8%) were detected. [e] Isolated yields. [f] Insoluble black tar formed. [g] Oxidation was carried out with 2.0 equiv of NIPA resin **5** in dry DCE at 60 °C for 180 min.

reaction times (36–48 h) were required for complete conversion. Conversions were measured by GC–MS with a prior column calibration using authentic samples of reagents and products; yields were determined by weight. The reaction products were identified by direct comparison of the retention times and MS data with those obtained for authentic samples.

Most alcohols were oxidized to the respective aldehyde or ketone products in excellent purities and yields. As one exception, oxidation of 3-(pyridin-2-yl)propan-1-ol (Table 1, entry 20) led to the formation of a black tar, presumably due to the instability of the pyridinylpropanal toward heating. Interestingly, oxidation of *cis*-cyclohexane-1,2-diol yielded only the respective hydroxycyclohexanone, and in contrast to IBX amides,[3a] no C–C bond cleavage was observed.

(8) **Attachment of 3 to the Aminomethylated Polystyrene.** Compound **3** (9.990 g, 30 mmol) was dissolved in dry DMF (25 mL) and HOBt (1-hydroxy-*1H*-benzotriazole, 4.455 g, 33 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 (7.5 g, 30 mmol, 200–400 mesh, 2% cross-linked with divinylbenzene, loading 4.0 mmol g^{-1}) in 205 mL of dry DMF. Thereafter, DIC (diisopropylcarbodiimide, 4.5 mL, 30 mmol) was added, and the reaction mixture was heated to 105 °C and agitated at this temperature for 8 h. Then the reaction mixture was cooled to room temperature and was stirred for 8 h. Pyridine (4.9 mL, 60 mmol) and acetic anhydride (5.8 mL, 60 mmol) were then added and the mixture was agitated for 3 h at 80 °C. Polymer **4** was filtered, washed with DMF (6 × 10 mL), MeOH (6 × 10 mL), DMF (6 × 10 mL), MeOH (6 × 10 mL), and CH$_2$Cl$_2$ (6 × 10 mL) and dried in a vacuum to constant weight. Yield 13.425 g. IR: 1010, 1150, 1279, 1422, 1505, 1575, 1642, 2916, 3331 cm^{-1}. Iodine content: 19.94%. Loading: 1.57 mmol g^{-1} (82% conversion when the mass change is considered).

(9) **Preparation of NIPA Resin 5.** Polymer **4** (1.016 g, 1.6 mmol) and tetrabutylammonium hydrogensulfate (2.712 g, 8.0 mmol) were placed in a 100 mL round-bottom flask, and the resin was preswollen in CH$_2$Cl$_2$ (24 mL) for 1 h at room temperature. Then water (24 mL), oxone (9.832 g, 16.0 mmol) and MsOH (1.04 mL, 16.0 mmol) were added sequentially to the flask upon vigorous stirring. The reaction mixture was vigorously stirred at room temperature for 36 h. Thereafter, polymer **5** was filtered, washed with H$_2$O (6 × 15 mL), MeOH (6 × 10 mL), CH$_2$Cl$_2$ (3 × 10 mL), Et$_2$O (3 × 10 mL), CH$_2$Cl$_2$ (3 × 10 mL), Et$_2$O (3 × 10 mL), CH$_2$Cl$_2$ (3 × 10 mL), and Et$_2$O (3 × 10 mL) and agitated with 24 mL of CH$_2$Cl$_2$ for 6 h. The resin was filtered off and dried in a vacuum to a constant weight. Yield 0.998 g. IR: 696, 755, 1016, 1152, 1236, 1465, 1529, 1602, 1632, 2919, 3268 cm^{-1}. Iodine content: 17.58%. Loading (IO$_2$): 0.70–0.80 mmol g^{-1} based on BnOH oxidation (four resin batches were prepared).

The polymeric material, resulting from the reduction of NIPA resin **5** with alcohols, can be collected and reoxidized according to the procedure described above. A moderate decline in oxidative activity was observed after multiple recovery steps, putatively due to iodine loss in the course of resin reoxidation under acidic conditions.

In conclusion, we have prepared *N*-(2-iodyl-phenyl)-acylamide (NIPA) resin **5** as a first polymer-supported pseudo benziodoxazine. The synthesis employs commercially available aminomethylated polystyrene, includes three simple steps, and affords the resin with good loading of 0.70−0.80 mmol g^{-1}. The prepared resin effects fast and efficient conversion of a wide range of alcohols, including hetero-atomic and unsaturated structures. This new reagent can be regarded as a readily available alternative or as a complement to the known supported IBX reagents.

Supporting Information Available: Preparation procedure and spectroscopic data for compound **3** and IR spectra of resins **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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