Oxidizing Polymers: A Polymer-Supported, Recyclable Hypervalent Iodine(V) Reagent for the Efficient Conversion of Alcohols, Carbonyl Compounds, and Unsaturated Carbamates in Solution**

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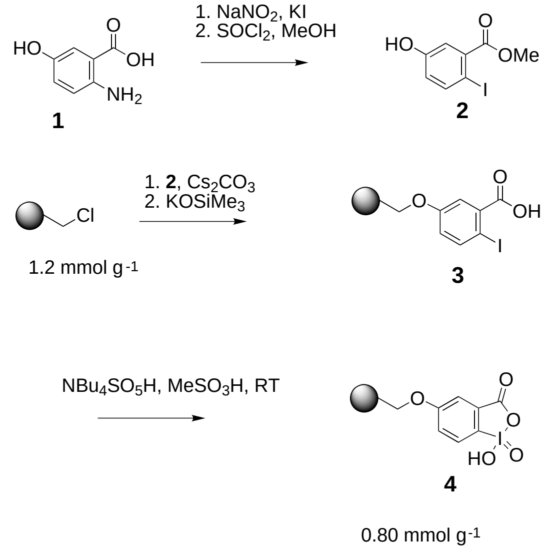
Polymer-supported reagents and reactive intermediates can be applied successfully to the parallel conversion of single compounds as well as for the construction of chemical libraries by exploiting the advantages of solution-phase synthesis in combination with those of synthesis on a solid phase.[1–3] The oxidation of alcohols to carbonyl compounds is one of the key transformations in organic synthesis because of the diversity of products that can be obtained from aldehyde and ketone precursors. Recently, polymer-supported oxoammonium salts were demonstrated to be reactive and versatile oxidation reagents.[3a] In contrast to previous methods, oxoammonium salts do not rely on heavy metal salts[3b,c] or on additional co-oxidants.[3d,e] The reactive intermediates derived from 4-alkoxy-2,2,6,6-tetramethylpiperidine-1-oxide (4-TEMPO) were used to oxidize a diverse collection of alcohols, mostly in excellent purity and yield. An extension to even more complex and sensitive substrates, preferably including those with nitrogen functionalities, would be highly desirable.

The chemistry of hypervalent iodine compounds has been reviewed extensively.[4] Iodinanes, that is, iodoso and iodine(III) reagents, have been prepared in a supported fashion by several research groups mainly as the bisacetoxyiodoso derivative[5] or as the respective dihalogeno compounds.[6] Iodoso reagents, however, cannot be used for a general transformation of alcohols to carbonyl compounds. On the contrary, periodinanes (namely, iodoxo and iodine(V) reagents) are widely employed in the oxidation of sensitive and complex alcohols, usually as the 1-hydroxy-(1*H*)-benzo-1,2-iodoxol-3-one 1-oxide (2-iodoxybenzoic acid, IBX)[7] or its acetylation product, the Dess–Martin reagent.[8] Periodinanes have not been prepared on a polymer support so far.

In order to obtain a functional iodine(V) reagent a derivative of 2-iodobenzoic acid was required that was suitable for immobilization and that still retained similar oxidation properties as the parent compound. 4-Hydroxy-2-iodobenzoic acid esters permit efficient immobilization to chloromethyl polystyrene through a phenoxide linker. The alkoxy derivatives have thus been prepared and oxidized to the iodoso and not to the iodoxo derivative.[9] Methyl 5-hydroxy-2-iodobenzoate (**2**) was obtained in two steps from 2-amino-5-hydroxybenzoic acid (**1**) by a Sandmeyer reaction followed by esterification with thionyl chloride in methanol (Scheme 1).[10] Compound **2** was coupled to chloromethylpolystyrene cross-linked with 1% divinylbenzene (1.20 mmol g^{-1}) by using cesium carbonate as a base. The loading of the resin was determined by elemental analysis and was close to the theoretical loading (98%). Saponification to yield resin **3** was effected by treatment with potassium trimethylsilanoxide in THF.[11] Oxidation of **3** to resin **4** was investigated under various conditions; initial screening for oxidizing activity was conducted by HPLC analysis of the reaction with piperonyl alcohol (**5a**) as the test substrate. The reaction with potassium bromate[8] as well as potassium monopersulfate triple salt[12] (oxone) failed in aqueous solvent mixtures. Traces of the aldehyde **6b** were detected when the phase-transfer catalyst [18]crown-6 was used together with oxone in a triphase system. Tetrabutylammonium oxone[13] in dichloromethane (DCM) was used to avoid the presence of water and to assure proper swelling of the resin. This procedure yielded a low resin activity of 0.05–0.1 mmol g^{-1}. Peroxymonosulfonic acid (Caro's acid) is a stronger oxidant than its anion that is present in oxone and was therefore examined in further oxidation experiments. An equimolar mixture of tetrabutylammonium oxone with methylsulfonic acid (DCM, RT, 3 h) furnished resin **4** with a high activity of 0.8 mmol g^{-1}. Resin **4** was characterized by IR spectroscopy, elemental analysis, and MAS-NMR spectroscopy.[14] Elemental analysis indicated a loading of 0.84 mmol g^{-1}, which corresponded to a yield of 94% in respect to the initial loading and taking into account the mass increase of the resin. No loss of iodine was observed under the strongly acidic reaction conditions. The oxidizing polymer **4** was stable towards air and moisture and it could be stored without loss of activity.



Scheme 1. Preparation of polymeric iodine reagent **4**.

The oxidation properties of periodinane reagent **4** were investigated by reaction with a diverse collection of benzylic,

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allylic, primary as well as secondary alcohols **5a**–**22a**, including the terpene alcohols **11a**, **13a**, and **17a**–**19a**, and the carbamate-protected aminoalcohols **21a** and **22a** (Table 1). All reactions were followed by GC-MS (Figure 1) or by HPLC (214 and 280 nm). The products were identified by NMR spectroscopy and by mass spetrometry (EI, 70 eV); yields were determined by weight. Most alcohols were converted into the respective aldehyde or ketone products in good to excellent yields and purities. Resin **4** that had not been used at elevated temperatures could be recycled by repeated oxidation following extensive washings.

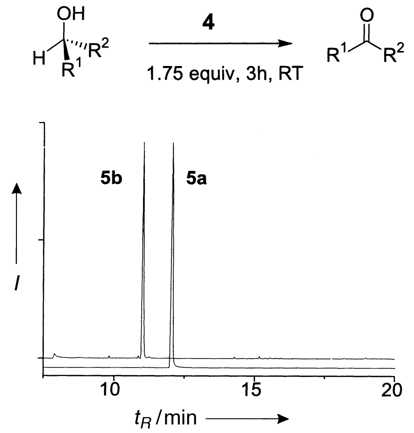


Figure 1. The oxidation of alcohols **5a**–**22a** by polymer **4** (0.8 $\text{mmol}\,\text{g}^{-1}$). The oxidative activity of the polymer reagent was determined using alcohol **5a** as a test substrate; see gas chromatograms.

In addition to the oxidation of alcohols, further important transformations effected by IBX were investigated with resin **4**.[15] Cyclohexanol (**16a**) reacted with **4** in a closed vessel (2.3 equiv, DCM, 2 h, 65 °C) to yield the α,β-unsaturated cyclohexenone **16c** via the cyclohexanone **16b** and a postulated iodine–enol ether intermediate.[15a] The unsaturated carbamate **23** was treated with reagent **4** (4 equiv, THF/DMSO (10/1), 90 °C, 16 h) to effect radical cyclization and afforded product **24** in 25 % yield.[15b] It should be noted that at elevated temperatures IBX can oxidize benzylic positions,[15c] which are abundant in the polystyrene backbone of **4** and might account for a competing reaction pathway.

In summary, we have prepared resin **4** as the first polymer-supported periodinane reagent. The resin was obtained with high loading (0.8 $\text{mmol}\,\text{g}^{-1}$) and was capable of converting a diverse collection of alcohols, including complex and sensitivestructures, efficiently and in good to excellent yields into the respective carbonyl compounds. In addition, the α,β-desaturation of carbonyl compounds and the radical cylization of an unsaturated carbamate were demonstrated. The novel reagent is likely to find broad application in polymer-assisted solution-phase synthesis. Furthermore, the new oxidizing resin should be suitable for integration into parallel polymer-supported reaction sequences and for the conversion of compound libraries.

Experimental Section

Attachment of **2** to the Merrifield resin: A solution of **2** (500.4 mg, 1.8 mmol) in dry DMF (4 mL) was added to chloromethylated polystyrene

Table 1. Results of the treatment of various alcohols with polymeric reagent **4**.

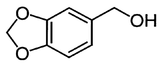
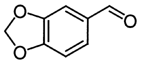
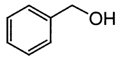
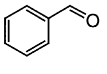
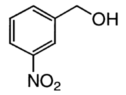
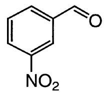
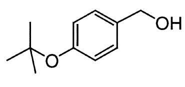
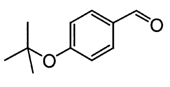
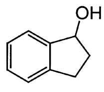
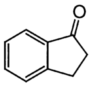
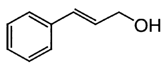
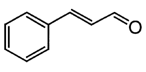
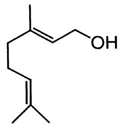
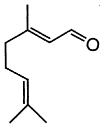
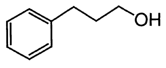
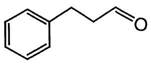
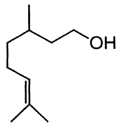
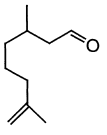
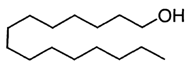
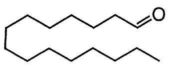
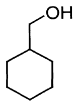
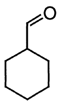
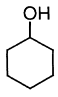
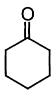
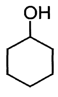
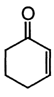
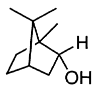
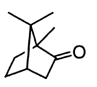
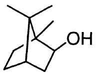
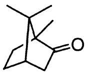
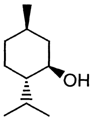
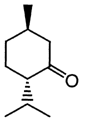
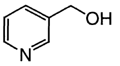
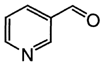
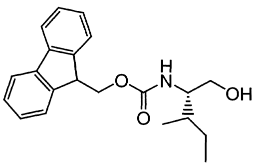
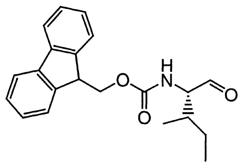
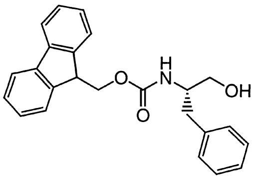
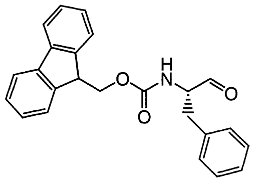
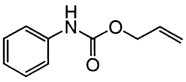
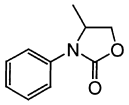
Starting material	Product	Purity [%][a]
 **5a**	 **5b**	> 95 (84)[e]
 **6a**	 **6b**	> 95
 **7a**	 **7b**	> 95
 **8a**	 **8b**	> 95
 **9a**	 **9b**	95
 **10a**	 **10b**	> 95
 **11a**	 **11b**	90[b]
 **12a**	 **12b**	70
 **13a**	 **13b**	56[c]
 **14a**	 **14b**	69
 **15a**	 **15b**	89
 **16a**	 **16b**	67
 **16a**	 **16c**	28[g]
 **17a**	 **17b**	> 95

Table 1. (Continued)

Starting material	Product	Purity [%][a]
 **18a**	 **17b**	> 95
 **19a**	 **19b**	26
 **20a**	 **20b**	66[d]
 **21a**	 **21b**	53[f]
 **22a**	 **22b**	> 95[f] (82)[e]
 **23**	 **24**	25[f, h]

[a] Determined by GC-MS. Reactions with 1.75 equiv of **4**, DCM, 2 h. [b] By-product: 7.5% *Z* isomer. [c] After reduced reaction time (30 min); 36% isopulegol is formed as major product after 2 h. [d] Obtained with 1 equiv of **4**. [e] Yield of isolated product. [f] Purity determined by HPLC. [g] 2.3 equiv of **4**, DCM, 65°C, 2 h; main product: cyclohexanone (**16b**, 78%). [h] 4 equiv of **4**, THF/DMSO (10/1), 90°C, 16 h.

resin (0.5 g, 0.6 mmol, 200–400 mesh, cross-linked with 1% divinylbenzene, loading 1.2 mmol g^{-1}). Cs$_2$CO$_3$ (390 mg, 1.2 mmol) was added and the reaction mixture was agitated for 3 h at 80°C. The resin was washed with DMF, THF/AcOH (1/1), MeOH, DCM, MeOH, DCM, Et$_2$O (six times each) and dried in vacuo. IR: $\tilde{\nu}$ = 1111, 1213, 1244, 1288, 1378, 1561, 1588, 1733 cm^{-1}. Iodine content: 11.73%. Loading: 0.92 mmol g^{-1}. This value corresponds to 98% conversion when the mass increase is taken into account.

Ester hydrolysis: Potassium trimethylsilanoxide in dry THF (4 mL, saturated solution) was added to the resin product (ca. 0.6 mmol). After shaking the resin for 1 h at room temperature and washing with MeOH (5 times), a mixture of THF/AcOH (9/1, 4 mL) was added and the suspension was agitated for 5 h at RT. Finally, the resin was washed (THF, DCM, MeOH, and Et$_2$O, seven times each) and dried to yield product **3**. IR: $\tilde{\nu}$ = 1707 cm^{-1}, the ester band completely disappeared.

Oxidation of **3**: Resin **3** (100 mg, 0.092 mmol) was treated with a solution of tetrabutylammonium oxone (460 mg, 0.46 mmol, active oxygen ca. 1.6%) and methylsulfonic acid (30 µL, 0.46 mmol) in dry DCM (1.2 mL), and agitated for 3 h at RT. The product was washed thoroughly with DCM, Et$_2$O, DCM, Et$_2$O, DCM, and Et$_2$O (seven times each). The product was dried to yield resin **4**. IR: $\tilde{\nu}$ = 1578, 1602, 1655 cm^{-1}. Iodine content: 10.8%. Loading: 0.85 mmol g^{-1}. This value corresponds to 93% conversion of the chloromethyl groups over three steps when the mass increase is taken into account. The oxidative activity of resin **4** (0.8 mmol g^{-1}) was determined by converting an excess of test substrate **5a**.

Oxidation of alcohols: Solutions of **5a**–**22a** (1 equiv) in dry DCM (15 mM) were treated with resin **4** (1.75 equiv) for 3 h at RT. The resin was filtered off and washed with dry DCM. The volatile compounds in the filtrate were analyzed by GC-MS. The nonvolatile compounds were analyzed by HPLC-MS. For product isolation, the collected filtrates of several washings (DCM, 3 × 2 mL) were evaporated to yield, for 5 mg of starting alcohols **5a** and **22a**: **5b** (4.2 mg, 84%) and **22b** (4.1 mg, 82%), respectively. The purity and identity of the products were determined by GC or HPLC and by NMR spectroscopy.

5b: ^{1}H NMR (400 MHz, CD$_3$CN): δ = 9.81 (s, 1H, CHO), 6.8–7.5 (m, 3H, aromatic protons), 6.01 (s, 2H, CH$_2$); ^{13}C NMR (100.6 MHz, CD$_3$CN): δ = 190.2, 153.6, 148.5, 131.7, 128.2, 108.0, 105.2, 102.3. **22b**: ^{1}H NMR, ^{1}H COSY (400 MHz, [D$_6$]DMSO): δ = 9.65 (s, 1H, CHO), 7.0–8.0 (m, 13H, aromatic protons), 7.90 (d, ^3J = 7.8 Hz, 1H, NH), 4.3–4.4 (m, 3H, Fmoc-9-H, Fmoc-CH$_2$), 4.25 (m, 1H, α-CH), 3.25 (dd, ^3J = 6.8, ^2J = 13.9 Hz, 1H, β-CH), 2.82 (dd, ^3J = 10.4 Hz, 1H, β-CH).

Resin recycling: The resin consumed in oxidations was collected, washed, and dried. Oxidation following the procedure described above yielded resin **4** with a restored oxidation activity of 0.8 mmol g^{-1}. Three cycles of resin recycling were investigated.

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