The Synthesis and Oxidative Properties of Polymer-Supported IBX

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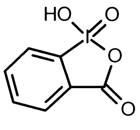
In the last 20 years hypervalent iodine reagents have enjoyed an increasing popularity in organic synthesis.[1–6] They can be used for a wide range of chemical transformations, especially as reagents for oxidations.[7–11] For these purposes iodinanes such as (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, the Dess–Martin periodinane (DMP), and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX, **1**) are particularly suitable. The advantages of these reagents are: high efficiency, easy availability, mild reaction conditions, and (with the exception of DMP) stability against moisture and oxygen. Furthermore, they are environmentally safe and can be regenerated. The combination of these properties with the advantages of polymer-supported reagents[12–15] is an attractive and worthwhile aim. Recently, we reported on the synthesis and oxidative properties of two aminomethylpolystyrene-bound (diacetoxyiodo)benzene derivatives.[16] In the context of these investigations we envisaged the development of a polymer-supported IBX reagent. Here we present the synthesis of such an IBX derivative and show that it is a powerful oxidant with broad applicability.



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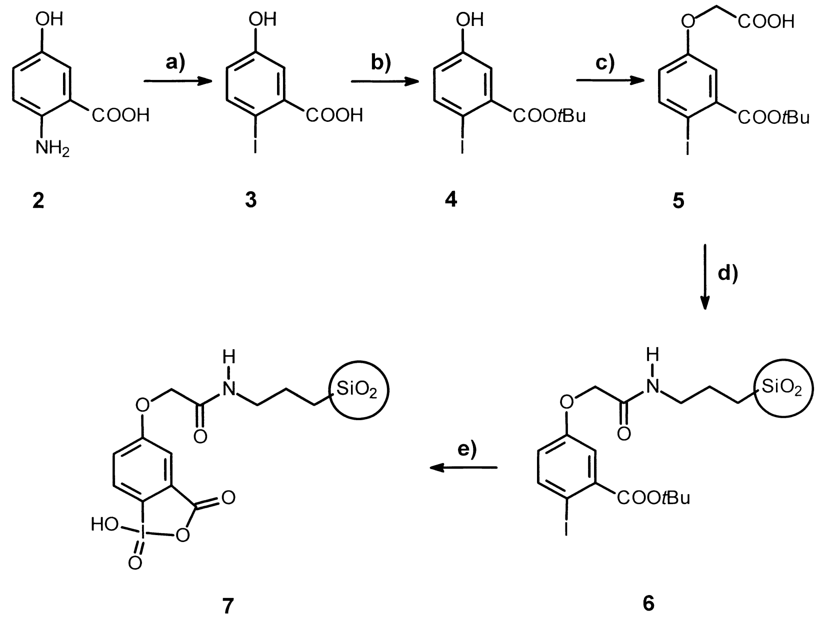

Scheme 1. Synthesis of **7**: a) $NaNO_2$, H_2SO_4, KI, 90 %; b) *N,N*-dimethylformamide di-*tert*-butyl acetal 50 %; c) NaH, $BrCH_2COOEt$, then NaOH; 84 %; d) aminopropylsilica gel, DIC, HOBt, 92 %; e) trifluoroacetic acid (10 %), then oxone; DIC = diisopropylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

The synthesis of reagent **7** was accomplished starting from commercially available 2-amino-5-hydroxybenzoic acid (**2**; Scheme 1). Treatment of compound **2** with $NaNO_2/H_2SO_4$ and excess KI afforded derivative **3**, which was transformed to the *tert*-butyl ester **4** using *N,N*-dimethylformamide di-*tert*-butyl acetal.[17] Compound **5** was obtained after alkylation of the phenolic hydroxy group with ethyl α-bromoacetate and subsequent hydrolysis with NaOH. This linker was subsequently coupled to aminopropylsilica gel with DIC/HOBt to give compound **6**. Cleavage of the *tert*-butyl ester with trifluoroacetic acid and oxidation with oxone[18] (potassium peroxymonosulfate) afforded the final reagent **7**.[19]

Various primary and secondary alcohols can be oxidized with **7** (Table 1). Whereas DMSO is indispensable as a solvent in the case of IBX, **7** also works in THF; in fact reactions proceed faster in THF than DMSO. Even the presence of water (1–10 %) has no negative influence on the yields and reaction times. The products are obtained with high purity and the yields are generally high to excellent. During the oxidation of primary alcohols to the corresponding aldehydes no overoxidation to the carboxylic acid was detected. It is particularly interesting that the oxidation of **4a** leads to **4b** with only the primary hydroxy group oxidized, even if **7** is added in threefold excess.[20] We tried to oxidize menthol and 3-methyl-2-butanol with **7** to get some clues of that remarkable selectivity. The yields of the corresponding ketones were poor (< 5 %) and cannot be increased even after longer reaction times (48 h). However, 2-methylcyclohexanol (**11a**) is oxidized easily and in high yield to 2-methylcyclohexanone (**11b**). The exact reason for this diverse reactivity is not yet fully understood and is the subject of current investigations.

In summary, we have discovered a powerful and versatile oxidation system[21] which is particularly suitable for the oxidation of alcohols to the corresponding aldehydes and ketones under mild conditions. This method combines the advantages of polymer-supported reagents with the advantages of IBX, which is superior to the Dess–Martin reagent in terms of stability, efficiency, and versatility.[7] The reduced form of **7** is easily separated by simple filtration and can be regenerated by oxidation with oxone.[19] The products are obtained in high purity and side reactions were not detected. Finally our system could be suitable for the polymer-supported synthesis of amino sugars[22] and the cyclization of anilides.[23, 24]

Experimental Section

7: Compound **5** (1.28 g, 3.39 mmol) was dissolved in DMF (5 mL) and HOBt (0.57 g, 3.73 mmol) was added. This mixture was added to a suspension of aminopropylsilica gel (3.00 g, 2.7 mmol, ≈0.8 $mmol\,g^{-1}$ amino groups) in DMF (30 mL). Thereafter, DIC (0.52 mL, 3.39 mmol) was added and the mixture was stirred for 16 h. Pyridine (0.11 mL, 1.35 mmol) and acetic anhydride (0.13 mL, 1.35 mmol) were then added and the mixture was stirred again for 2 h to block any possible free amino groups. Polymer **6** was then filtered, thoroughly washed with DMF and

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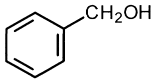
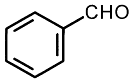
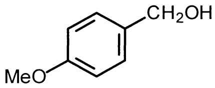
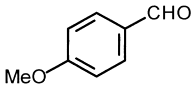
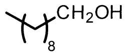
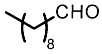
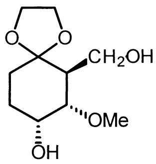
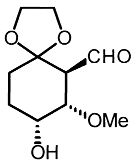
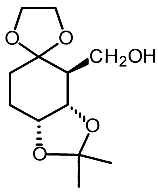
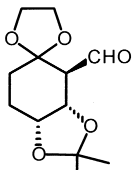
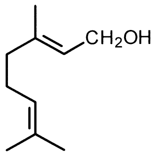
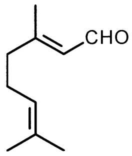
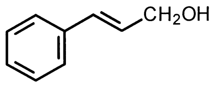
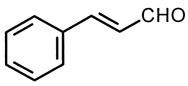
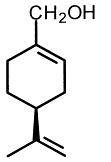
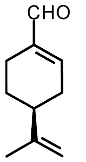
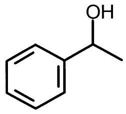
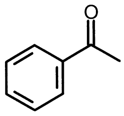
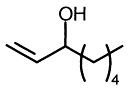
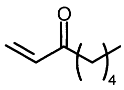
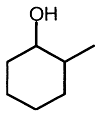
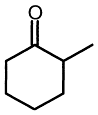
Table 1. Oxidation of alcohols with reagent **7**.

Entry	Substrate	Product	Purity [%][a]
1	 **1a**	 **1b**	quant.[b]
2	 **2a**	 **2b**	97
3	 **3a**	 **3b**	96
4	 **4a**	 **4b**	86[b]
5	 **5a**	 **5b**	84[b]
6	 **6a**	 **6b**	90[b]
7	 **7a**	 **7b**	94[b]
8	 **8a**	 **8b**	92[b]
9	 **9a**	 **9b**	83[b]
10	 **10a**	 **10b**	80
11	 **11a**	 **11b**	82

[a] Purity estimated by GC-MS. [b] Yield after flash chromatography on silica gel.

methanol, and then dried in vacuo to constant weight. Yield 3.68 g (92%). Derivative **6** was suspended in a mixture of dichloromethane and trifluoroacetic acid (9:1, 30 mL) and was agitated overnight at RT. The obtained compound was then washed thoroughly with methanol and dried in vacuo to constant weight. A solution of oxone (5.0 g, 8.1 mmol) in water (50 mL) was added to the dry polymer. This suspension was stirred at 70 °C for 3 h. The final product **7** was filtered off, washed with water, and dried in vacuo. To determine the activity, compound **7** (100 mg) was suspended in THF (0.5 mL) and benzylic alcohol (6.0 mg, 0.055 mmol) added and this suspension was agitated overnight. The activity was determined by the ratio of starting material to product and is normally in the range of 0.3–0.4 mmol g^{-1}.

IR (drift): $\tilde{\nu} = 3304$, 2941, 1661(br), 1573, 1462, 1424, 1100, 950, 799 cm^{-1}; elemental analysis (%) calcd for **7**: N 1.1, C 10.8, H 0.9; found: N 0.8, C 10.1, H 1.8.

Oxidation of alcohols: The alcohol was dissolved in THF (5 mL/1 g polymer) and 1.2 equivalents of polymer **7** were added. After agitating the mixture overnight at RT, the reaction mixture was filtered and washed. The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. If necessary, the products were purified by flash chromatography.

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[19] No remarkable loss of activity has been noticed after compound **7** was used four times.

[20] Substrates **4a** and **5a** were kindly provided by Dipl.-Chem. P. Baumhof and Dipl.-Chem. R. Mazitschek. Analytical data for **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.80$ (d, $J = 3.1$ Hz, 1 H, CHO), 4.21 (d, $J = 3.0$ Hz , 1 H, CH), 3.98–3.79 (m, 5 H, $2 \times CH_2 + CH$), 3.41 (s, 3 H, CH_3), 3.04 (dd, $J = 11$, 3 Hz, 1 H, CH), 2.29 (d, $J = 1.6$ Hz, OH), 1.97–1.85 (m, 2 H, CH_2), 1.62–1.50 (m, 2 H, CH_2); HR-MS (45 °C) calcd: 216.0997, found: 216.0983.

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