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Development of new and efficient polymer-supported hypervalent iodine reagents

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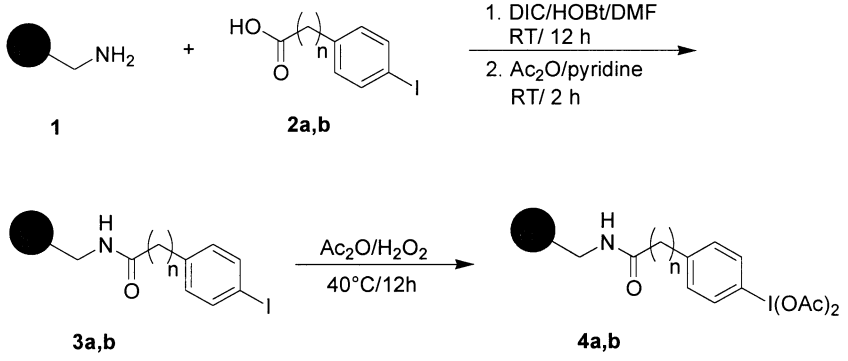
Abstract—The aminomethylpolystyrene-supported (diacetoxyiodo)benzene reagents **4a** and **4b** were prepared for the first time. Using these reagents several hydroquinones and phenols can be oxidized to the corresponding quinones. Spirocyclization of phenylacetic acid and of *N*-protected tyrosine derivatives could also be accomplished.

In the last 20 years, hypervalent organic iodine compounds have been used extensively for a variety of chemical transformations and particularly as reagents in several oxidation reactions.[1–7] For such reactions iodanes like (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene and periodanes like Dess–Martin reagent and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) have been widely used. The advantages of hypervalent organic iodine reagents and especially of those derived from iodobenzene are: ready availability, high efficiency, and (with some exceptions) stability towards atmospheric oxygen and moisture. Furthermore, they are environmentally safe and can be recycled. Therefore, the linkage of these properties with the advantages of solid phase organic synthesis should be an attractive target. Recently, two papers concerning the preparation and some synthetic applications of polymer-supported (diacetoxyiodo)benzene (PSDIB) appeared in the literature.[8,9] For example, this reagent was successfully used in oxidative 1,2-aryl migration of alkyl aryl ketones, in oxidation of different hydroquinones to the corresponding *p*-benzoquinones, in spirocyclization of tyrosine derivatives, and in α-hydroxylation of acetophenones. However, the wide use of PSDIB and related reagents has been limited by the expensive starting material as well as their tedious preparation. More importantly, due to the synthetic entry to PSDIB (electrophilic aromatic iodination of polystyrene) only iodophenyl-derived polymer-supported reagents are synthetically accessible at the present. In order to circumvent these problems we envisaged the preparation of alternative polymer-supported hypervalent iodine reagents, starting from inexpensive and commercially available prefunctionalized polymers. Polymers like aminomethylated polystyrene should be suitable for these purposes (Scheme 1).

Reaction of the aminomethylated polystyrene (**1**) (loading at



Scheme 1. (a) Series: n=0, (b) series: n=1.

Keywords: hypervalent iodine reagents; oxidation; quinones; spirolactones.
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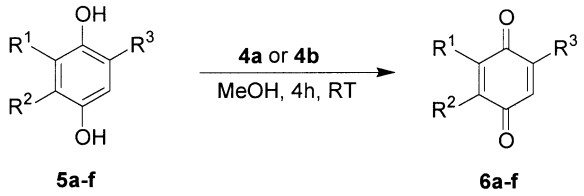
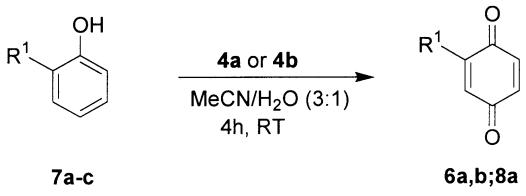
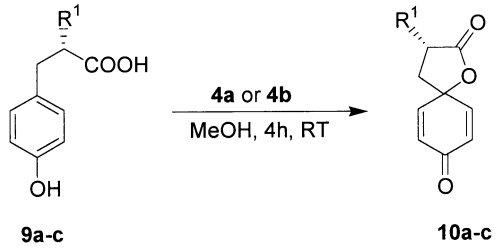


Scheme 2.



Scheme 3.



Scheme 4.

least: 0.78 mmol/g) with 4-iodobenzoic acid (**2a**) or 4-iodophenylacetic acid (**2b**) using diisopropylcarbodiimide (DIC) in combination with 1-hydroxybenzotriazole (HOBt) followed by treatment with Ac_2O/pyridine (to acetylate possible remaining free amino groups) afforded conjugates **3a**,**b** in excellent yields. Subsequent oxidation to derivatives **4a**,**b** was accomplished using freshly prepared peracetic acid at 40°C overnight.[1,10] After filtration the resins were washed with methanol and dried. They should be protected from direct sunlight. The resins can be stored in a refrigerator although no appreciable decomposition was observed at room temperature. In order to test their activity a known excess of hydroquinone was converted to benzoquinone with a defined quantity of **4a** or **4b**. By comparing the integral of the ^{1}H NMR signals (in CD_3OD) of hydroquinone (6.5 ppm) and *p*-benzoquinone (6.7 ppm) the activity of the reagents **4a** and **4b** was determined. Both resins were equally active. Typically, 0.22–0.31 mmol hydroquinone can be converted to *p*-benzoquinone using one gram of conjugates **4a** or **4b**.

Subsequently several other mono-, di- and tri-substituted hydroquinones of the type **5a**–**f** were converted to the corresponding *para*-benzoquinones with excellent yields (Scheme 2 and Table 1). The yield of compound **6f** was moderate due to decomposition during the isolation procedure.

In order to test scope and limitations of our system several simple phenols like **7a**–**c** were subjected to oxidation with **4a** or **4b** using CH_3CN/H_2O as solvent (Scheme 3). In fact, *p*-benzoquinones **6a**,**b** and **8a** were obtained. On the other side, oxidation of derivatives of salicylic acid and salicylic acid methylester to the corresponding *p*-benzoquinone derivatives failed. However, it must be borne in mind that diacetoxy(iodo)benzene derivatives are not the reagents of choice for such transformations. [Bis(trifluoroacetoxy)-iodo]benzene is much more suitable for these oxidations.[1]

Finally, derivatives **9a**–**c** were subjected to oxidation and were converted to the corresponding spirolactones **10a**–**c** (Scheme 4) which are important as intermediates for the synthesis of the antitumor antibiotic Aranorosin and its analogues.[11–13] In all experiments, complete conversion was achieved. Whereas, compound **10a** was obtained in good yield, the *N*-protected spirolactones of tyrosine **10b** and **10c** were isolated only in low yields (Table 2). In the last two entries, significant decomposition was observed. Obviously, derivatives **10b** and **10c** are unstable under the reaction conditions. The reason for this instability may be due to the bulky substituent in the lactone moiety.

It is worth noting that after their use, resins **4a**,**b** can be regenerated without a measurable loss of activity. For this purpose, they are first washed with methanol to remove impurities and thereafter they are reoxidized as described above. Due to this fact, the ease of their preparation and their oxidative properties resins like **4a**,**b** can find broad application in organic synthesis and particularly in combinatorial chemistry. At the present, we investigate the transformation of reagents **4a**,**b** to the corresponding bis(trifluoroacetoxy)- or iodosyl derivatives in order to extend the scope of our system. Finally our results encourage us to prepare and to investigate the oxidative properties of further polymer-supported hypervalent iodine compounds starting

Table 1. Oxidations of hydroquinones and phenols to *p*-benzoquinones

Substrate	Product	R^1	R^2	R^3	Yield (%) with resin **4a**	Yield (%) with resin **4b**
5	**6a**	H	H	H	Quant.	Quant.
	6b	Cl	H	H	Quant.	Quant.
	6c	Me	H	H	Quant.	Quant.
	6d	Me	Me	H	Quant.	Quant.
	6e	Me	Me	Me	Quant.	Quant.
	6f	$NHCOC_9H_{19}$	H	H	52	50
7	**6a**[a]	H	H	H	81	80
7	**6b**	Cl	H	H	25[b,c]	24[b,c]
7	**8a**	CH_2OH	–	–	32[b]	33[b]

[a] Reactions were performed in CH_3CN/H_2O (3:1).
[b] Yield was determined by gas chromatography/mass spectroscopy (GCMS).
[c] Reaction was performed at 60°C.

Table 2. Spirocyclizations

Substrate	Product	R^1	Yield (%) with resin **4a**	Yield (%) with resin **4b**
9	**10a**	H	82	80
	10b	Cbz-NH	25	26
	10c	Boc-NH	24	25

from other commercially available functionalized polymers and trisubstituted iodophenyl derivatives.

1. Experimental

^{1}H NMR (and ^{13}C NMR) spectra were recorded on a Bruker AC-250 (DRX-500) spectrometer with the solvent residual peak as internal standard. The GCMS spectra were recorded on a HP 5890 Series II Gas Chromatograph coupled with HP 5972 Series Mass Selective Detector (specifications of the column: Macherey Nagel Optima 1/20 μm, 25 m×0.2 mm ID). Iodometric analysis was performed in the Institut für Anorganische Chemie, Universität Karlsruhe, Germany. Merck silica gel 60 for column chromatography and Merck precoated TLC plates, silica gel F_{254} for TLC were used. Compounds **1**, **2**, **5**, **7** and **9** are commercially available and were used without further purification. All solvents were purified and, when necessary, dried in the usual way.

1.1. General preparation of the aminomethylpolystyrene derivatives 3a,b

Aminomethylpolystyrene **1** (5.0 g, loading at least 0.78 mmol/g) was suspended in dry DMF (50 mL). Subsequently, 2 equiv. (relative to the loading of the resin) of either 4-iodobenzoic acid (**2a**) or (4-iodophenyl)-acetic acid (**2b**) as well as 2.1 equiv. of HOBt were added to the mixture above. After addition of 2 equiv. of diisopropylcarbodiimide the suspension was stirred overnight at room temperature. Thereafter, 0.5 equiv. of pyridine and 0.5 equiv. of acetic anhydride were added, and the suspension was stirred for 2 h. The resin was filtered in a glass funnel, washed thoroughly with DMF and methanol and then dried.

1.1.1. Poly[styrene-*co*-4-iodo-*N*-(4′-vinyl-benzyl)-benzamide] (3a). Obtained 5.92 g, expected 5.90 g. Iodometric analysis: calcd I 8.4; found I 8.9.

1.1.2. Poly[styrene-*co*-2-(4′-iodo-phenyl)-*N*-(4″-vinyl-benzyl)-acetamide] (3b). Obtained 6.11 g, expected 5.95 g. Iodometric analysis: calcd I 8.3; found I 8.8.

1.2. Synthesis of the aminomethylpolystyrene-supported (diacetoxyiodo)benzenes 4a,b

Acetic anhydride and hydrogen peroxide solution (35%) were mixed in a 4:1 ratio at 0°C and stirred for 6 h. Thereby the solution was slowly warmed up to room temperature. This peracetic acid solution was added to the iodinated polystyrene **3a** or **b** (about 10 mL per gram resin) at exactly 40°C and stirred at this temperature overnight. Thereafter, the resin was filtered in a glass funnel and washed thoroughly with methanol. After washing, the resins **4a**,**b** were dried in vacuo to a constant weight. Their activity was determined by dissolving 20 mg of hydroquinone in methanol and adding 200 mg of the resin **4a** or **4b**. This suspension was stirred for 4 h at room temperature. The resin was filtered with a glass funnel and washed well with methanol. The combined organic layers were evaporated in vacuo. From the residue a ^{1}H NMR spectrum was taken. The activity of the resin was determined by comparison of the integrals of the singlets at 6.5 ppm (hydroquinone) and 6.7 ppm (*p*-benzoquinone).

1.3. General procedure for the oxidation of hydroquinones 5a–f

Hydroquinones **5a**–**f** (0.15 mmol) were dissolved in methanol (5 mL). To this solution 2 equiv. of the resin were added and the resulting mixture was stirred for 4 h at room temperature. Thereafter, the suspension was filtered and the resin was thoroughly washed with methanol. The combined organic layers were evaporated in vacuo to afford the pure benzoquinones **6a**–**e**; compound **6f** was obtained after column chromatography (silica gel, hexane/ethyl acetate 6:1). For yields see Table 1.

1.3.1. *p*-Benzoquinone (6a). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=6.7 (s, 4H); GCMS: calcd *m*/*z* 108; found *m*/*z* 108.

1.3.2. Chloro-*p*-benzoquinone (6b). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=7.1 (m, 1H); 6.9 (m, 1H); 6.7 (m, 1H); GCMS: calcd *m*/*z* 142; found *m*/*z* 142.

1.3.3. Methyl-*p*-benzoquinone (6c). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=6.9 (s, 1H); 6.7 (m, 2H); 2.2 (s, 3H); GCMS: calcd *m*/*z* 122; found *m*/*z* 122.

1.3.4. 2,3 Dimethyl-*p*-benzoquinone (6d). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=6.6 (s, 2H); 1.9 (s, 6H).

1.3.5. Trimethyl-*p*-benzoquinone (6e). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=6.5 (s, 1H); 1.9 (3×s, 9H); GCMS: calcd *m*/*z* 150; found *m*/*z* 150.

1.3.6. 2-Decanoylamino-*p*-benzoquinone (6f). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=8.02 (br, 1H, NH); 7.57 (d, *J*=2.4 Hz, 1H); 6.70–6.77 (m, 2H); 2.42 (t, *J*=7.6 Hz, 2H); 1.64–1.70 (m, 2H); 1.24–1.34 (m, 12H); 0.85 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm)=188.0; 182.8; 172.5; 138.2; 133.1; 114.7; 37.9; 31.8; 29.3; 29.2; 29.1; 25.0; 22.6; 14.1; MS (HR-EI, 80°C) calcd *m*/*z* 277.2; found *m*/*z* 277.2, mp 85°C.

1.4. General procedure for the oxidation of phenols

Phenols **7a**–**c** (0.15 mmol) were dissolved in acetonitrile/

water (3:1, 5 mL). To this solution 4 equiv. of the resin were added. The resulting mixture was stirred for 4 h at room temperature and then filtered and thoroughly washed with acetonitrile. Evaporation of the solvent in vacuo afforded the benzoquinones **6a**,**b** and **8a**. For yields see Table 1.

1.4.1. Hydroxymethyl-*p*-benzoquinone (8a). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=6.5–6.7 (m, 3H); 4.2 (s, 2H, CH_2).

1.5. General procedure for spirocyclizations

Derivatives **9a**–**c** (0.15 mmol) were dissolved in methanol (5 mL). After addition of 2 equiv. of the resin, the resulting mixture was stirred for 4 h at room temperature. The suspension was filtered and washed with methanol. The combined organic layers were evaporated in vacuo to afford the corresponding spirolactones **10a**–**c**. Analytical pure compounds were obtained after column chromatography (silica gel, hexane/ethyl acetate 1:1). For yields see Table 2.

1.5.1. 1-Oxaspiro[4.5]deca-7,10-diene-2,8-dione (10a). ^{1}H NMR (250 MHz, CD_3OD): δ (ppm)=7.0 (d, 2H); 6.2 (d, 2H); 2.7 (t, 2H); 2.3 (t, 2H); GCMS: calcd *m*/*z* 165; found *m*/*z* 165.

1.5.2. (*S*)-[(Benzyloxycarbonyl)amino]-1-oxaspiro[4.5]-deca-7,10-diene-2,8-dione (10b). $[\alpha]_D^{20}=-16.3$ (c=0.6, CH_2Cl_2), (lit.[14], $[\alpha]_D^{21}=-14.3$, c=2.62, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm)=7.3 (s, 5H); 6.8 (d, 2H); 6.3 (2×d, 2×1H); 5.4 (d, 1H); 5.1 (s, 2H); 4.4–4.6 (m, 1H); 2.7 (dd, 1H); 2.3–2.5 (m, 1H); GCMS: calcd *m*/*z* 313; found *m*/*z* 313.

1.5.3. (*S*)-[(*tert*-Butoxycarbonyl)amino]-1-oxaspiro[4.5]-deca-7,10-diene-2,8-dione (10c). $[\alpha]_D^{20}=-17.5$ (c=0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=6.83–6.88 (m, 2H); 6.32 (d, 1H, J=8.3 Hz); 6.30 (d, 1H, J=8.3 Hz); 5.16 (b, 1H); 4.53 (b, 1H); 2.76 (dd, 1H); 2.45 (dd, 1H); 1.62 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm)=183.9, 173.3, 155.2, 146.0, 143.9, 129.3, 129.0, 81.3, 50.3, 39.1, 34.5, 28.2; GCMS: calcd *m*/*z* 279; found *m*/*z* 279.

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