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# A novel use of the recyclable polymer-supported IBX: an efficient chemoselective and regioselective oxidation of phenolic compounds. The case of hydroxytyrosol derivatives.

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## ABSTRACT

A useful and novel application of polymer-supported IBX for the chemoselective and regioselective oxidation of phenolic compounds has been described. Hydroxytyrosol and carboxymethylated hydroxytyrosol have been prepared in good conversions and yields under green chemistry conditions in the presence of dimethyl carbonate as the solvent. Polymer-supported reagent has been recovered by simple filtration, regenerated and reused for more cycles of oxidation reactions without loss of efficiency.

Polymer-supported reagents are a useful tool in synthetic organic chemistry. An attractive feature deriving from their use is the easy work-up of the reactions. They can be separated from final products by simple filtration avoiding common procedures of extraction with toxic organic solvents. Additionally, polymer-supported reagents are generally reused for following reactions with economic and environmental benefits.[1]

In the last 10 years, hypervalent iodine reagents have experienced a wide development in organic chemistry. They have received a growing interest due to their mild and highly chemoselective oxidizing properties combined with the commercial availability.[2] The most important representative of pentavalent iodine heterocycles is 2-iodoxybenzoic acid (1-hydroxy-1-oxo-1H-1λ5-benz[*d*][1,2]iodoxol-3-one, IBX, Figure 1) firstly prepared by Hartmann and Mayer[3] and then by Santagostino et al. with a safe and convenient procedure.[4]

IBX is an excellent reagent utilized under homogeneous conditions for the oxidative conversion of phenols[5] and phenolic methyl aryl ethers into *ortho*-quinones.[6] When the oxidation reaction was followed by an in situ reduction, the catechol moiety was obtained.[5,6]

The presence of this functionality is essential to increase the biological activity of phenolic molecules, for example, the antioxidant activity.[7] Despite this peculiar capacity of IBX, only a few examples of catecholic compounds of biological interest have been prepared by this methodology. Between them, catecholestrogens[8] and (±)-brazilin, a tinctorial compound found in the alcoholic extracts of the Brazil wood showing antitumoral activities.[9]

Recently, we have been involved in the optimization and application of the IBX-oxidative procedure on a wide variety of natural organic compounds to obtain bioactive catechol derivatives and in the use of dimethyl carbonate as an ecofriendly solvent in alternative to common toxic reaction media.[10] For example, we utilized tyrosol **1** [2-(4-hydroxyphenyl)ethanol] and homovanillyl alcohol **2** [2-(4-hydroxy-3-methoxyphenyl)ethanol] as starting materials for the preparation of hydroxytyrosol **3** [2-(3,4-dihydroxyphenyl)ethanol, Figure 2] and several lipophilic derivatives.[11]

Hydroxytyrosol **3** is a natural bioactive molecule found in extra virgin olive oil[12] and wastewaters[13], which has been reported to exhibit antioxidant properties.[7a] Because of this, it is widely used in food[14] and cosmetic applications.[15] Hydroxytyrosol has also been found to exert several pharmacological properties including prevention and treatment of cardiovascular, hepatic, renal diseases and cancer.[16] Lipophilic derivatives are useful to extend the utilization of hydroxytyrosol in nonaqueous media, in particular for cosmetic applications.[17] Between them, we have recently introduced carboxymethylated hydroxytyrosol **4** [2-(3,4-dihydrophenyl)ethyl methyl carbonate, Figure 2].[10c,11] This new antioxidant exhibits attractive properties. Preliminary biological data showed its major effectiveness against the pulmonary carcinoma and melanoma compared to hydroxytyrosol.[18] Moreover, we described this

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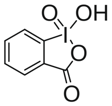


**Figure 1.** Chemical structure of 2-iodoxybenzoic acid (IBX).

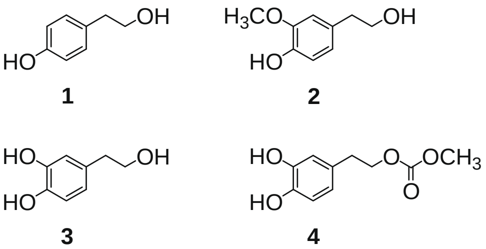


**Figure 2.** Chemical structures of some bioactive phenolic compounds.

compound as a precursor of hydroxytyrosol by hydrolysis under basic conditions[11] and of the new 2-arylhydroxytyrosol derivatives via Suzuki–Miyaura cross-coupling with arylboronic acids.[19]

Recently, various research groups have reported on the immobilization of IBX onto solid polymeric supports.[20] Between them, Rademann and co-workers[20a] employed 4-hydroxy-2-iodobenzoic acid and Merrifield resin as solid supports to prepare the corresponding supported-IBX derivative (Fig. 3). The periodinane reagent was immobilized to methyl polystyrene cross-linked with 1% divinylbenzene via an aryl ether linkage. Janda and co-workers used a similar procedure to attach 4-hydroxybenzoic acid to a set of soluble and insoluble polymer supports.[20b] These polymers were characterized by a loading factor defined as mmol of IBX per gram of resin.

To the best of our knowledge, the oxidation properties of these supported-periodinane reagents and their reuse have been investigated only for the conversion of benzylic, allylic, terpene alcohols and carbamate-protected aminoalcohols into respective carbonylic compounds.[20a,b]

Therefore, as another useful application of polymer-supported IBX, we describe here the first example of chemoselective and regioselective oxidation under green conditions (dimethyl carbonate as the solvent) of phenolic compounds to obtain bioactive catechol derivatives. In particular, we verified the efficiency of polymer-supported IBX as in Figure 3 in the oxidative insertion of a hydroxyl into tyrosol derivatives **1** and **5** as well as in the demethylation reaction of homovanillyl alcohol derivatives **2** and **6** to prepare hydroxytyrosol **3** and carboxymethylated hydroxytyrosol **4** through an one-pot procedure (Scheme 1). After the oxidation/reduction steps, the polymeric reagent was recovered, regenerated and reused for several oxidation reactions without lack of efficiency to give the final products in excellent yields. Cycles of polymer recycling are superior to those reported in the literature.[20a] It is remarkable that polymer-supported IBX oxidized directly tyrosol derivatives **1** and **5** into the corresponding hydroxytyrosol derivatives with a regioselectivity similar to those of enzymes.[21] At the same time, we have noticed an improvement as far as the yield is concerned compared to the only previous chemical procedure.[22] Similarly, homovanillyl alcohol derivatives **2** and **6** were demethylated with high regioselectivity. Moreover, polymer-supported IBX showed an excellent chemoselectivity not previously evidenced in the literature,[20] the free alcoholic chain present in compounds **1** and **3** was not oxidized.

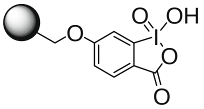
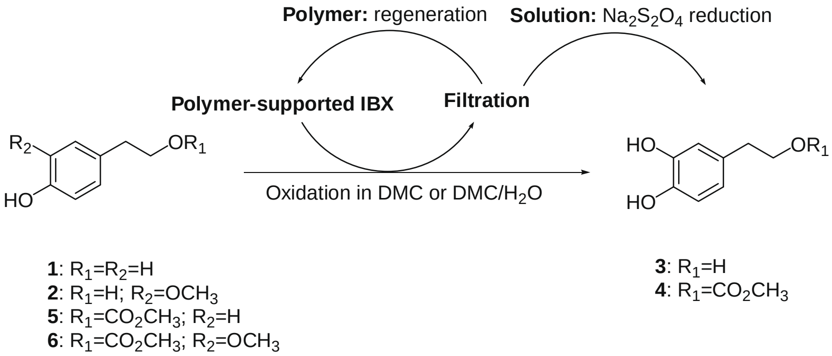


**Figure 3.** Polymer-supported IBX.[20a,b]

Tyrosol **1** or freshly prepared carboxymethylated tyrosol **5** (1.0 mmol)[10c] was solubilized in dimethyl carbonate (10 ml) at room temperature under magnetic stirring and then commercial polymer supported-IBX (2.1 mmol) was added.[23] When the substrate disappeared (1 h), the polymer was recovered by simple filtration and the remaining solution was treated with sodium dithionite ($Na_2S_2O_4$). After the work-up, hydroxytyrosol **3** and carboxymethylated hydroxytyrosol **4** were isolated. It is interesting to point out that under heterogeneous conditions, these compounds were obtained in quantitative yield and conversion. On the contrary, the direct oxidation of tyrosol **1** into hydroxytyrosol **3** under homogeneous conditions proceeded in only 30% yield. This was due to practical problems of extraction of the final products from the aqueous medium after the reductive step. Under these experimental conditions, a chemoselective esterification of the aliphatic chain of tyrosol **1** was necessary to diminish the hydrophilic character of the catecholic compounds.[11]

Polymer-supported IBX was regenerated by treating the filtered resin with a solution of tetrabutylammonium oxone and methanesulfonic acid according to the procedure reported in the literature[20a] in the presence of dimethyl carbonate as the solvent



**1**: $R_1=R_2=H$
**2**: $R_1=H$; $R_2=OCH_3$
**5**: $R_1=CO_2CH_3$; $R_2=H$
**6**: $R_1=CO_2CH_3$; $R_2=OCH_3$

**3**: $R_1=H$
**4**: $R_1=CO_2CH_3$

**Scheme 1.** Conversion of phenolic compounds **1**, **2**, **5** and **6** into hydroxytyrosol derivatives **3** and **4** by polymer-supported IBX.

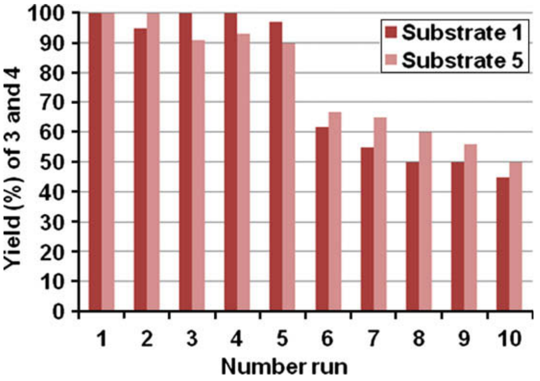


**Figure 4.** Yields of **3** and **4** after the recycling experiments of oxidation of tyrosol derivatives **1** and **5** by polymer-supported IBX.

instead of dry dichloromethane. As shown, polymer-supported IBX was used for at least five cycles of oxidation without loss of efficiency to give **3** and **4** (Graphic 1, runs 1–5). With the sixth recycling experiment, conversions and yields decreased, but no side-chain products were isolated demonstrating that the oxidations proceeded again with a high chemo- and regioselectivity (Fig. 4, runs 6–10).

Furthermore, we tested the efficiency of polymer-supported IBX in the oxidative demethylation of homovanillyl alcohol **2** and carboxymethylated compound **6** to obtain hydroxytyrosol derivatives **3** and **4**. We solubilized the substrates in dimethyl carbonate and then we added the oxidant as described above. Under these experimental conditions, final products **3** and **4** were isolated in low yields (38–40%). Moreover, adding a small amount of water, which acts as an oxygen source favouring the formation of the *ortho*-quinone,[6] substrates **2** and **6** disappeared in only 30 min to afford catechol derivatives **3** and **4** in quantitative conversion and yield after one-pot reduction with $Na_2S_2O_4$. Also, in this case we noted a remarkable increase of yield of the final product compared to the homogeneous conditions. As already reported, the resin was recovered by filtration and after regeneration, polymer-supported IBX was investigated for recycling experiments. Ten cycles of resin recycling were efficient (Fig. 5).

In conclusion, we have described the first application of the recyclable supported-IBX for the chemoselective and regioselective hydroxylation of tyrosol derivatives and oxidative demethylation of homovanillyl alcohol derivatives; a green solvent (dimethyl carbonate) was utilized. Hydroxytyrosol and carboxymethylated hydroxytyrosol are useful compounds in both cosmetic and pharmaceutical applications.

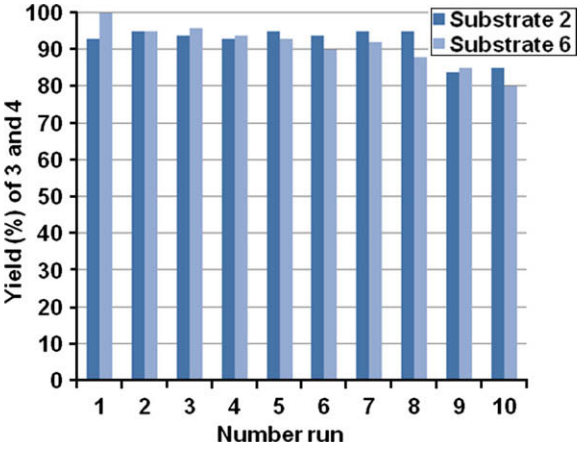


**Figure 5.** Yields of **3** and **4** after the recycling experiments of oxidation of homovanillyl alcohol derivatives **2** and **6** by polymer-supported IBX.

Works are in progress in our laboratory to apply this advantageous oxidative methodology to a wide number of phenolic compounds for the preparation of the corresponding bioactive catechol derivatives.

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