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A novel and efficient synthesis of DOPA and DOPA peptides by oxidation of tyrosine residues with IBX

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ABSTRACT

An efficient route to 3,4-dihydroxylphenylalanine (DOPA) and DOPA peptides was described by oxidation of L-tyrosine and L-tyrosine derivatives with 2-iodoxybenzoic acid (IBX). DOPA was obtained after an situ reduction of the corresponding *ortho*-quinone with sodium dithionite. Oxidation reactions proceeded in good yields and high chemo- and regio-selectivity. The chirality of the DOPA residue was retained under the reaction conditions. The efficiency and the selectivity of the reaction were successfully tested using recyclable polymer-supported IBX.

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The synthesis of unnatural amino acids and peptides is of pivotal importance for the development of a selective chemical engineering of proteins.[1] According to general methods employed for these transformations, the amino acids and peptides can be modified at the backbone of the molecule as well as in their side chains. Backbone modifications include changes at any one of the three repeating moieties, that are NH, CO, and α-CH bonds.[2] Side chain modifications are in general performed by the oxidation of low redox potential residues.[3–7] In this latter case, a different selectivity is observed depending on the nature of the oxidant. As for example, the selective oxidation of methionine (Met), cysteine (Cys), and tryptophan (Trp) in the presence of other potentially oxidizable residues has been performed with the methyltrioxorhenium (MTO)/hydrogen peroxide catalytic system.[8] High redox potential residues, aliphatic side-chain amino acids, require most powerful oxidants. Thus, leucine (Leu) and leucine residues are oxidized by dimethyldioxirane (DMD) at γ-CH bond to obtain the corresponding 4,4-dimethyl-4-butanolide derivatives without backbone modifications.[9]

Recently, Harding and co-workers reported the oxidation of threonine (Thr) residues with 1-hydroxy-1-oxo-1*H*-1λ5-benz[*d*]-[1,2]iodoxol-3-one (2-iodoxybenzoic acid, IBX) as a synthetic strategy to incorporate an aldehyde or ketone moiety into a peptide chain.[10] The oxidation of alcohols to corresponding aldehydes and ketones with IBX reagents has been also described in the case of primary and secondary alcohols,[11] benzyl alcohols,[12] and β-amino alcohols.[13] Among other possible applications of IBX,[14] the *ortho*-hydroxylation of phenols to catechol derivatives performs with a regioselectivity similar to that of natural polyphenol oxidases.[15] In the last few times, we were involved in the utilization of IBX for the synthesis of bioactive catechol derivatives, such as 2-(3′,4′-dihydroxyphenyl)ethanol (hydroxytyrosol) and its lipophilic derivatives, useful molecules for cosmetic and pharmaceutical applications.[16] In a similar way, guaiacyl lignans were converted to the corresponding catechol derivatives with significative antioxidant activity.[17] Tyrosine (Tyr) is the only α-amino acid bearing the phenolic moiety. The catechol derivative of Tyr is 3,4-dihydroxyphenylalanine (DOPA). DOPA is an unusual amino acid derived from post-translational modification of tyrosine.[18] It is well known that DOPA is rarely included in proteins. However, it is found in marine biological tissues, including coral reef structures,[19] eggshells,[20] seashells[21] and adhesives produced by mollusks.[22] It has been postulated that the adhesive and cohesive properties of mussel adhesive proteins in sea water is due to the catechol moiety present into DOPA and DOPA residues.[23] Cross-linked structures having DOPA residues create hardened matrices useful as biomaterials.[24] Since the late 1960s, DOPA is the most successful therapeutic agent in the treatment of Parkinson's disease.[25] It is the building block for design and for the synthesis of biologically active compounds.[26] Thus, research in the design of novel synthesis of DOPA peptides is a high priority. The recent Letter of Harding prompted us to describe the efficient and selective *ortho*-hydroxylation of Tyr and Tyr-containing peptides to corresponding DOPA derivatives with IBX.

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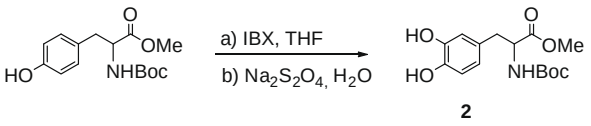


Scheme 1. Oxidative conversion of Boc-Tyr-OMe **1** into Boc-DOPA-OMe **2** with IBX/$Na_2S_2O_4$ system.

Firstly we turned our attention on the oxidation of Boc-Tyr-OMe derivative **1**.[27] THF appeared to be the most useful solvent. The oxidation of **1** (1.0 mmol) with a small excess of the oxidant (1.2 equiv) in THF (8.0 mL) at room temperature followed by in situ reduction with sodium dithionite ($Na_2S_2O_4$, 2.0 equiv) in water (8.0 mL), afforded a quantitative conversion of substrate after 40 min. Boc-DOPA-OMe derivative **2** was obtained in 95% yield as the only product (Scheme 1; Table 1, entry 1). No chromatographic purifications were needed. The structure of **2** was unambiguously assigned by comparison with an authentic sample.[28] Compound **2** showed a value of the optical rotatory power $[\alpha]_D$ +7.0 (methanol, *c* 1.0, *T* = 22 °C) according to an authentic L-enantiomer.[28]

In order to further confirm the chirality of Boc-DOPA-OMe derivative **2**, it was deprotected by HCl-saturated ethyl acetate and 10% KOH solution in methanol to give free DOPA which was subjected to chiral HPLC analysis (CHIROBIOTIC T, Aldrich) using commercial L-DOPA and D,L-DOPA as previously reported.[29] The presence of the peak attributable to L-DOPA and the absence of the D-DOPA in the HPLC profile of the sample prepared according to our procedure confirmed the chirality of the product**.** These experimental data demonstrated that the stereochemical integrity of the final product was not compromised during the oxidative/reductive step of Boc-L-Tyr-OMe **1**.

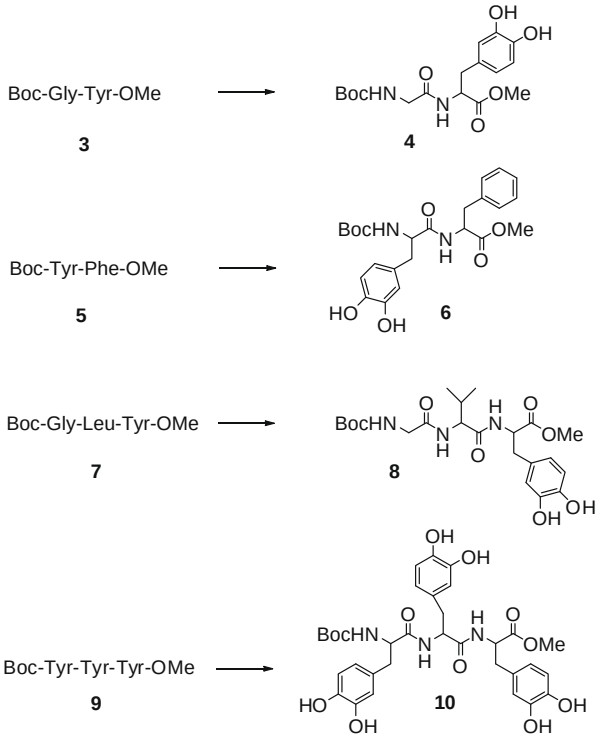
According to the previously reported mechanism, the oxidation reaction with IBX probably proceeded with an ionic pathway.[15b,c] In particular, the regioselectivity of the *ortho*-hydroxylation of **1** is a consequence of an intramolecular delivery of an oxygen atom from the iodine(V) center of the λ^5-iodanyl intermediate to the most nucleophilic and congested *ortho*-site on the phenol with concomitant reduction into a more stable λ^3-iodanyl orthoquinol monoketal. It is interesting to note that the IBX/$Na_2S_2O_4$ system mimed the activity of naturally occurring mushroom tyrosinase (EC 1.14.18.1).[30]

On the basis of the efficiency observed in the oxidation of **1,** we extended the IBX procedure to a panel of selected Tyr-containing dipeptides and tripeptides bearing amino acids with different aliphatic or aromatic side-chain residues (Scheme 2).

The oxidation of Boc-Gly-Tyr-OMe **3** with IBX afforded Boc-Gly-DOPA-OMe **4** in good conversion and yield (Table 1, entry 2), besides a low amount of unreacted substrate. In a similar way, treatment of Boc-Tyr-Phe-OMe **5** gave the corresponding Boc-DOPA-Phe-OMe **6** in satisfactory conversion and yield (Table 1, entry 3). The transformations reported were found to be selective, and the possible oxidation of the benzylic position[31] in phenylalanine (Phe) residue as well as that of the amide group[32] in the backbone were not observed in our experimental conditions. Finally,

Table 1
Experimental data of oxidations depicted in Schemes 1 and 2

Entry	Substrate	Product	Conv. (%)	Yield (%)
1	**1**	**2**	>98	95
2	**3**	**4**	90	85
3	**5**	**6**	88	84
4	**7**	**8**	85	80
5	**9**	**10**	80	75



Scheme 2. Oxidative modification of dipeptides **3**, **5** and tripeptides **7**, **9** with IBX/$Na_2S_2O_4$ system.

the oxidation of tripeptides Boc-Gly-Leu-Tyr-OMe **7** bearing one reactive Tyr residue, and Boc-Tyr-Tyr-Tyr-OMe **9** bearing three reactive Tyr residues, was studied. In the case of **7** the Tyr residue was selectively oxidized to give Boc-Gly-Leu-DOPA-OMe **8** in good conversion and yield (Table 1, entry 4). The treatment of Boc-Tyr-Tyr-Tyr-OMe **9** with 1.2 equiv of IBX afforded a complex mixture of reaction products probably due to a low selectivity in the oxidation of different Tyr residues. According to this hypothesis, the reaction repeated in the presence of a large excess of IBX (4.0 equiv) gave the highly functionalized tripeptides Boc-DOPA-DOPA-DOPA-OMe **10**, in which all Tyr residues are functionalized, in satisfactory yields (Table 1, entry 5). The shifts of the absorptions of the nine aromatic protons at 6.26–6.62 ppm in the ^{1}H NMR spectrum of **10** compared to the absorptions of the twelve aromatic protons at 6.56–6.86 ppm of **9** and the appearance of three new quaternary carbon atoms in the ^{13}C NMR spectrum of **10** confirmed the assigned structure.[33]

As selected examples, the stereochemical integrity of peptides **4** and **10** was confirmed by comparison of the optical rotatory power with authentic samples after the deprotection procedure described above [Gly-L-DOPA: found $[\alpha]_D$ +46.0, reported +46.07°; L-DOPA-L-DOPA-L-DOPA: found $[\alpha]_D$ +13.7, reported +13.76 (1 M HCl, *c* 1.0, *T* = 25 °C).[34]

In view of the technological applications of the IBX procedure for the oxidative conversion of tyrosine derivatives into DOPA residues, we worked under heterogeneous conditions using polymer-supported IBX, specifically IBX polystyrene already applied successfully by us for the synthesis of hydroxytyrosol.[35] We tested the oxidation of Boc-Tyr-OMe derivative **1, the** selected model compound. Good results in terms of conversion of substrate and yield of **2** were obtained with an excess of the oxidant (2.1 mmol, conversion: 95%, yield: 90%). Recycling experiments proceeded with success. When the substrate disappeared (1 h), the polymeric reagent was recovered by filtration and the remaining solution was treated with $Na_2S_2O_4$. IBX polystyrene was regenerated as was pre-

Table 2
Experiment of recycling of IBX polystyrene in the oxidation of **1**

Entry	Run	Conv. (%)	Yield (%)
1	1	95	90
2	2	95	88
3	3	95	90
4	4	94	89
5	5	95	88
6	6	75	72
7	7	72	70
8	8	70	68
9	9	72	70
9	10	70	68

viously reported[35] and reused in oxidations after adding fresh substrate. As shown, IBX polystyrene was used for at least five cycles of oxidation without loss of efficiency to give **2** (Table 2, 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 an high chemo- and regio-selectivity (Table 2, runs 6–10).

In summary, IBX and IBX polystyrene were efficient reagents in the oxidative conversion of tyrosine and tyrosine derivatives into DOPA and DOPA residues. The stereochemical integrity of the final product was not compromised during the reactions. Usually, DOPA peptides are prepared under solid phase synthesis that sometimes requires complex reaction conditions. To the best of our knowledge this is the first example of an one-pot synthesis of DOPA peptides starting from already available substrates. This procedure opens a novel way for the synthesis of modified proteins having DOPA residues in their structure.

Acknowledgments

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33. *Spectroscopic data of Boc-DOPA-DOPA-DOPA-OMe* **10**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (9H, s, $(CH_3)_3C$), 2.67–2.82 (6H, m, ArCH_2), 3.56 (3H, m, COOCH_3), 4.21–4.52 (3H, m, CH_2CHNH), 6.26–6.62 (9H, m, Ar-*H*). ^{13}C NMR (200 MHz, $CDCl_3$): δ 28.0 $(CH_3)_2CH$), 36.6 (CH_2), 36.9 (CH_2), 37.1 (CH_2), 52.2 (*C*H), 53.6 (CH), 54.3 (OCH_3), 60.5 (CH_3CHCH_2), 80.64 ($C(CH_3)_3$), 115.2 (Ar), 115.8 (Ar), 116.1 (Ar), 120.7 (Ar), 127.3 (Ar), 127.7 (Ar), 127.9 (Ar), 129.6 (Ar), 143.6 (Ar), 144.1 (Ar), 144.3 (Ar), 144.4 (Ar), 155.9 (NHCOOCH), 170.8 ($NHCOCH_2$), 171.5 ($NCOCH_2$), 172.2 (CO).
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