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Selective solid-phase iodination of phenolic groups with *bis*(pyridine)iodonium (I) tetrafluoroborate

Gemma Arsequell,[a] Gemma Espuña,[a] Gregorio Valencia,[a,*] José Barluenga,[b,*] Raquel Pérez Carlón,[b] and José M. González[b]

[a]*Unit for Glycoconjugate Chemistry, I.I.Q.A.B.-C.S.I.C., Jordi Girona 18-26, E-08034 Barcelona (Spain);*

[b]*Instituto Universitario de Química Organometálica "Enrique Moles"-Unidad Asociada al C.S.I.C., Universidad de OviedoE-33071, Oviedo (Spain)*

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Abstract: Selective direct aromatic electrophilic iodination of target phenol groups can be performed by the IPy_2BF_4 reagent on multiple phenol containing substrates while anchored on solid supports. The tactics make use of orthogonal protecting groups capable of inhibiting the reaction of the untargeted phenol. Suitable groups are of ether and silyl type. The methodology has been demonstrated on a biomolecule such as dermorphin where the integrity of one of two phenol functions is crucial for its biological activity. © 1999 Elsevier Science Ltd. All rights reserved.

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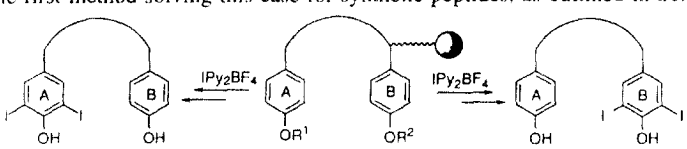
Aromatic iodides have long been used in organic synthesis as versatile intermediates that can be transformed to a variety of functional groups.[1] However, not many methods are available for the mild introduction of iodine into aromatic molecules.[2] Rather less extensive is the repertoire allowing direct iodination of labile molecules that can be further functionalized as to lead to new pharmacologically active entities. The extensive experience in the use of the solid, stable in air, reagent bis(pyridine)iodonium (I) tetrafluoroborate (IPy_2BF_4) that usually renders iodinated arenes at room temperature with excellent regioselectivity and yields,[3] has allowed us to directly iodinate the phenol groups of tyrosine residues in peptides, either in solution[4] or on solid-phase[5] under very mild, clean and quick reaction conditions.[6]

Phenol is one of the functional groups frequently found in pharmacophores. In more complex examples, such as the case of the isodityrosine natural products involving vancomycin-glycopeptide antibiotics,[7] the diaryl ether formation is the foremost synthetic challenge where selective halogenated phenols[8] are important synthetic precursors. Accordingly, the possibility of synthesizing, modifying or labelling these groups is of interest in medicinal chemistry.

A still unresolved case in multiple phenol presenting biomolecules, is the specific direct iodination of one among the various identical functionalities. Herein we present, to the best of our knowledge, the first method solving this case for synthetic peptides, as outlined in Scheme 1.



Scheme 1. Targeted synthetic transformations

A key finding was recorded after attempting the iodination of a series of commercially available or known phenol protected tyrosine derivatives in absence of an external source of acid.[3] All were Fmoc derivatives of general formula, FmocTyr(OR)OH, having an ether type (R being Me, *t*-Bu, Bn and 2-ClTr) or a related silyl derivative[9] (R being TBDMS). Two sets of experiments

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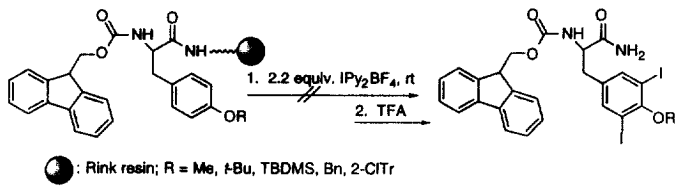
were conducted depending if the substrate was in solution or linked to a Rink resin under reaction conditions as to quantitatively prepare the di-iodinated species.[10] All phenol masking groups assayed prevented IPy_2BF_4 mediated iodination, either in solution or on a solid support (Scheme 2).



Scheme 2. Inhibition of iodination reaction on phenol derivatives upon masking the phenol functionality

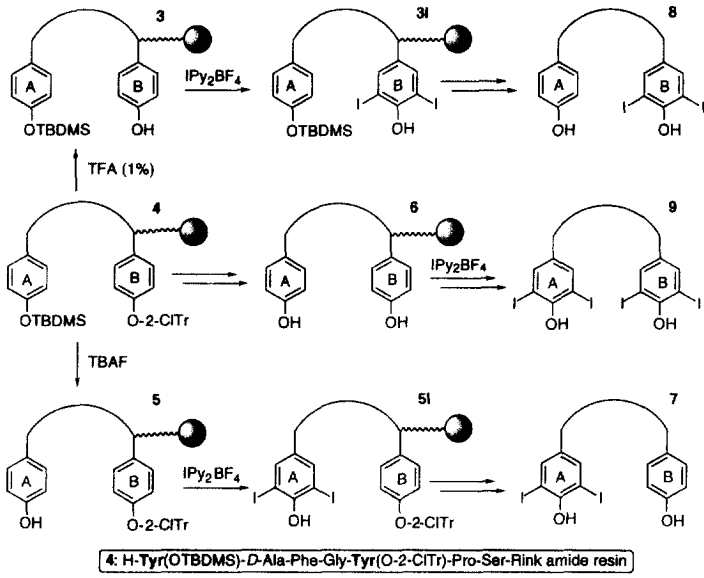
Consequently, it seemed clear that the chemoselective iodination of a free phenol group could be conducted by judiciously masking others on the same molecule. To prove this concept, we have chosen a relevant case taken from peptide chemistry. It is well known that the two tyrosine residues on the analgesic peptide dermorphin[11] (DER: H-Tyr-*D*-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2) contribute differently to its biological activity. Thus, similarly to other opioid peptides, the *N*-terminal Tyr residue seems to be an essential component for the recognition of the peptide by μ- and δ-opioid receptors. Therefore, any changes on the phenol groups are detrimental when applied to tyrosine in position 1 but not in position 5. In accordance, we have devised a strategy to chemoselectively iodinate this latter position without introducing any further step or additional synthetic burden.[12] This method simultaneously renders a whole series of dermorphin derivatives having either one or both Tyr residues in protected, free or iodinated forms which are presented in Table 1.

Table 1. (H-AA_1-D-Ala-Phe-Gly-AA_2-Pro-Ser-Rink amide resin)[a]

Resin	*AA1*	*AA2*	Resin	*AA1*	*AA2*
1	Tyr(O-Bu^t)	Tyr	**4**	Tyr(O-TBDMS)	Tyr(O-2-ClTr)
1I	Tyr(O-Bu^t)	Tyr(*I,I*)	**5**	Tyr	Tyr(O-2-ClTr)
2	Tyr(O-2-ClTr)	Tyr	**5I**	Tyr(*I,I*)	Tyr(O-2-ClTr)
2I	Tyr(O-2-ClTr)	Tyr(*I,I*)	**6**	Tyr	Tyr
3	Tyr(O-TBDMS)	Tyr	**6I**	Tyr(*I,I*)	Tyr(*I,I*)
3I	Tyr(O-TBDMS)	Tyr(*I,I*)			

[a]See Scheme 3 for an overall chemoselective iodination of the phenolic groups of dermorphin onto solid-phase

To achieve this goal, different combinations of protecting phenol groups of both Tyr were assayed. The most versatile is exemplified by the peptidyl resin **4**. As seen in Scheme 3, a single peptidyl resin batch provides a selective entry to the di-iodinated derivatives of dermorphin either at Tyr in position 1 or 5 (di-I-DER **7** and di-I-DER **8**, respectively).[13] This synthetic manifold relies on the orthogonality[14] of the 2-ClTr and TBDMS groups combined with an efficient solid-phase IPy_2BF_4 iodination.[15] Moreover, this resin can be also used to yield either dermorphin itself or, alternatively, a tetra-iodinated derivative, tetra-I-DER **9**. In fact, upon conversion of resin **4** into **6**, subsequent iodination with IPy_2BF_4 affords resin **6I**, and further cleavage yields the tetra-iodinated peptide **9**. The di-iodinated derivatives have also been synthesized from peptidyl resins bearing other combinations of Tyr protecting groups[17] (see Table 1).



Scheme 3. Chemoselective iodination of phenolic residues on dermorphin (see Table 1, for labelling codes)

In conclusion, by using common and orthogonal protecting groups of the phenol group of tyrosine, a simple and versatile global strategy is proposed for chemoselectively iodinating a target Tyr residue in a multiple Tyr containing peptide sequence, thus, solving the need to preserve the integrity of other Tyr residues that are essential for maintaining the biological activity of the peptide sequence. This strategy may also allow the preparation of multiply iodinated peptide analogues[18] and the generation of peptidomimetic libraries[19] by chemical transformation of existing iodinated peptides. These findings open the door for designing similar solutions for pharmacophores of non peptidic nature.

Acknowledgements

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14. Cleavage of TBDMS group in front of 2-ClTr group, was done using TBAF in DMF and cleavage of the 2-ClTr in front of TBDMS was done using 1% TFA in CH_2Cl_2.
15. Iodination occurred quantitatively only on the unprotected Tyr residue as examined by HPLC, MALDI-TOF-MS and ^{1}H-NMR, thus confirming the observation that protected Tyr residues are unreactive.
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