Iodination of aromatic residues in peptides by reaction with IPy_2BF_4

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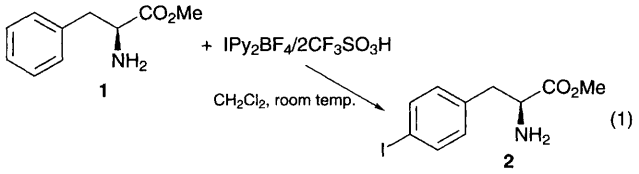
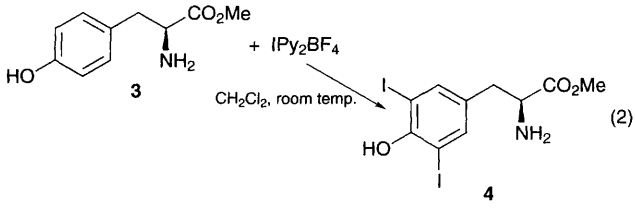
A simple and straightforward approach to selectively iodinate Tyr residues on peptides using IPy_2BF_4 is described which is compatible with Met residues on the side chain; preliminary studies reveal that the method is also suitable to iodinate Phe derivatives.

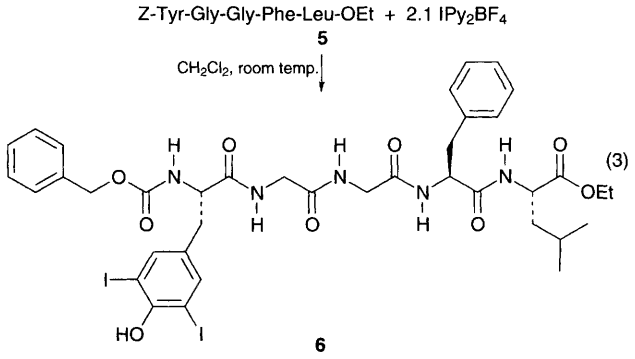
Iodine isotopes are routinely employed in medical nuclear imaging and radioimmunoassays.[1] Single photon emission computed tomography (SPECT) is a useful technique for brain studies[2] and relies mainly upon Tc-99m labelled agents,[3] although I-123 is also well suited for this purpose.[4] Peptides are ligands of potential interest for this computerized clinical procedure, however their labelling by electrophilic iodination[5] requires an oxidizing agent that can be harmful to the peptide; thus, indirect[6] and conjugation based[7] approaches have become very popular.

We have previously reported that IPy_2BF_4 efficiently iodinates arenes under mild conditions, a process that shows wide scope.[8] Here we report preliminary results concerning the use of this reagent in the iodination of the aryl residues of some amino acids, and the selectivity observed for its reaction with small peptides that could lead to a convenient approach for their direct labelling. First, we established suitable conditions to iodinate amino acid derivatives. The methyl ester of phenylalanine **1** was ring iodinated at room temperature in CH_2Cl_2 by treatment with IPy_2BF_4 and CF_3SO_3H (1 : 1.1 : 2.2 molar ratio, where acid is added to formally liberate I^+ in solution by precipitation of PyH^+), furnishing the 4-iodophenylalanine methyl ester **2** in 70% isolated yield [eqn. (1)]. Minor amounts of the corresponding *ortho*-isomer are also formed, as evidenced by ^1H and ^{13}C NMR analyses of the crude reaction mixture prior to purification. Importantly, this fact proves that iodination of phenylalanine can be directly accomplished without requiring previous activation of the C-4 ring position.[9] Tyrosine **3** can also be easily iodinated using this approach and, remarkably, without the need for addition of triflic acid to liberate the electrophile. In this regard, the reaction of equimolar amounts of IPy_2BF_4 and **3** furnishes mixtures of the mono- and di-iodinated derivatives; moreover, the diiododerivative **4** is quantitatively obtained after mixing the reagents in CH_2Cl_2 at room temperature, but using 2 : 1 molar ratio of IPy_2BF_4 and **3** respectively, [eqn. (2)].

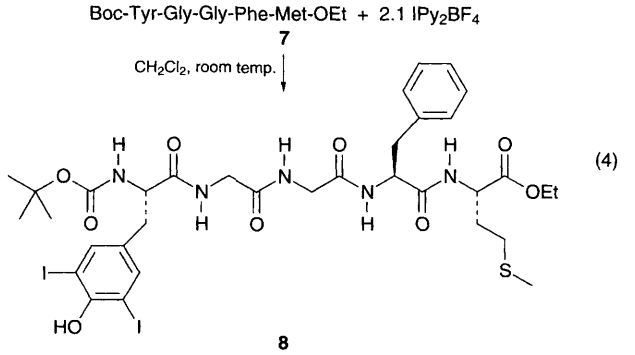




Furthermore, iodination of a Leu-enkephalin derivative **5** (Z-Tyr-Gly-Gly-Phe-Leu-OEt) follows the same pattern as the amino acids, with either CH_2Cl_2 or Me_2SO as solvent. Z-Leu-enkephalin-OEt reacts at room temperature with IPy_2BF_4 (molar ratio 1 : 2.1, respectively) giving instantaneously the diiodo peptide **6**,† in quantitative yield [eqn. (3)]. Starting from



a $[^2H_6]Me_2SO$ solution of **5** of known concentration, adding gradually weighed amounts of IPy_2BF_4 into the NMR tube, and analysing changes of diagnostic aryl signals allows the progress of the reaction to be monitored by ^1H NMR. With a 1 : 1 molar ratio peptide : iodinating reagent, a mixture containing unreacted starting material (13%) and the mono- and di-iodinated (68 and 19% respectively) compounds was formed. Nevertheless, the starting material essentially disappeared after addition of 1.4 equiv. of IPy_2BF_4, giving rise to the formation of the mono- and di-iodinated compounds. Parallel results were found using HPLC analysis for this clean transformation. Finally, the iodination of the related Boc-Met-enkephalin-OEt derivative **7** (Boc-Tyr-Gly-Gly-Phe-Met-OEt) with IPy_2BF_4 was examined to analyse the effect of the reagent upon a side chain containing a sensitive amino acid [eqn. (4)]. Using a



2.1 : 1 excess of IPy_2BF_4 with respect to the peptide furnishes **8**,‡ corresponding again to the diiodination of the aryl residue of tyrosine, in 73% yield (recovered starting material accounted for the remainder of the material). The formation of by-products arising from oxidation of sulfur on the Met residue was ruled out by HPLC analysis of an oxidized sample obtained after treatment of the peptide with H_2O_2.

Footnotes

† Compound **6** was purified by HPLC. MS analysis for **6** (MALDI TOF) shows m/z = 992 for $[M + Na]^+$, in agreement with the proposed structure.

‡ Compound **8** was purified by HPLC. ESI-MS for **8** shows m/z = 954, $[M + H]^+$, accounting well for the proposed structure.

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