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An Efficient Procedure for the Demethylation of Aryl-Methyl Ethers in Optically Pure Unusual Amino Acids

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Abstract: An efficient procedure was developed for the removal of methyl groups from aryl methyl ethers, without racemization, in derivatives of unusual amino acids that are of significant importance in the design of highly selective peptide and protein ligands with specific conformational and topographical features. Demethylation of aromatic amino acids can result in an appreciable increase in receptor affinity, hence the new mild procedure which have been developed represents a facile and practical method for demethylation of Tyr (OMe) derivatives, including novel sidechain ring or C-3 modified analogs.

Ethers are among the most used protective groups in synthetic organic chemistry.[1] Methylation of a hydroxyl moiety is regarded as one of the most effective protection methodologies, due to its very high stability under numerous reaction conditions. However, it is this fact that makes it difficult to cleave the methoxyl group under many normal milder conditions,[2] especially when there exists an active hydrogen in the optically pure substrates. Some reagents developed for the demethylation of aromatic methyl ethers include Lewis acids, mixed mineral acids, oxidants, reducdants as well as silica & aluminum compounds.[3a-c] Very few methods are suitable for demethylation for aromatic amino acids for considering the solubility of amino acids and racemization problems encountered with the active hydrogens in the α positions.

We have successfully developed novel methodologies utilizing methylated phenolic hydroxy moieties which were used as the protecting group (directly from Aldrich) in the total procedure for the synthesis of four optically pure isomers of D- and L-*O*-Methyl-β-Methyl Tyrosine,[4] D- and L-*O*-Methyl-2',β-Dimethyltyrosine and a series of their precursors.[5] Obviously, the efficient/selective demethylation of the β-methyl tyrosine derivatives became crucial with respect to maintenance of optical purity in order to obtain the unusual Boc-amino acids for incorporation into polypeptide hormones. The complex of 48% hydrobromic acid and acetic acid[6] (v/v=5/1, reflux for 4 hrs) has been tried in our laboratories resulting in successful demethylation but with some observed racemization (about 30%) in optically pure special amino acids. It is for this reason we did not try other HX-HOAc (X= Cl, I) reagents, even though they have been used for the demethylation of 3,5 di-iodo-*p*-methoxyl-phenoxy-N-acetyl-L-phenylalanine ethyl ester (reflux 4-18 hrs).[7] Here we report a successful procedure in an acetic acid free aqueous phase for the demethylation of five *O*-methyl-β-methyltyrosine derivatives (Figure 1) with the corresponding results listed in Table 1. The reactions are demonstrated by the demethylation of (2R,3R)-2-Amino-3-(4'-methoxy-2'-methylphenyl) butanoic acid **1a**. A possible concerted bond formation and demethylation of a protonated substrate could be attributed to the mild demethylation conditions employed in the sealed reaction system (Figure 2).

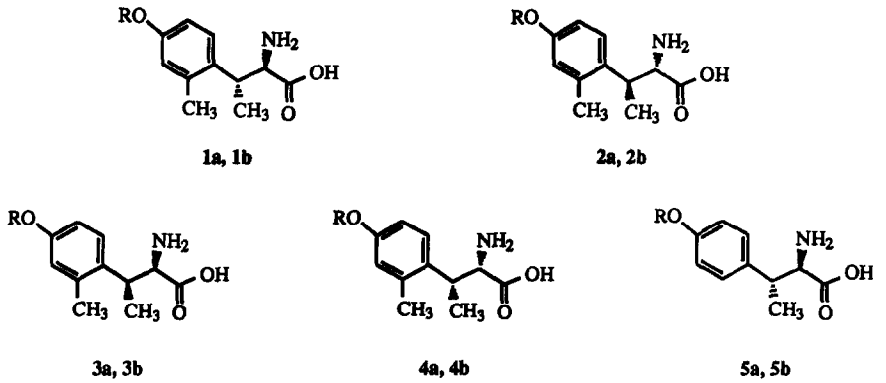

Figure 1. Methyl tyrosine derivatives examined in the demethylation study described (**a**, R=CH_3 **b**, R=H)

Table 1. Results of demethylation of the methyl tyrosine derivatives examined

substrates	purified yields %	resultant chirality (%) *	δ-OCH_3 of **a** (ppm)	δ-H's of **b** (ppm)		configurations	$[\alpha]_D^{25}$ of **b** (CH_3OH)
				α (d)	β (m)		
1a	90.2	>99	3.62	3.54	3.15	(2R, 3R)#	+30.4 (c=2.3)
2a	82.0	>99	3.62	3.54	3.15	(2S, 3S)	-31.0 (c=1.5)
3a	90.7	>99	3.59	3.60	3.51	(2R, 3S)	+21.0 (c=3.0)
4a	96.0	>99	3.59	3.60	3.51	(2S, 3R)	-22.4 (c=3.0)
5a	95.8	>99	3.60	3.51	3.01	(2R, 3R)	+40.8 (c=1.3)

* > 99% indicates no minor isomer observed

the X-ray structure has been determined for the key precursor[5b]

A representative procedure is illustrated by the synthesis of (2R,3R)-2-Amino-3-(2'-methyl-4'-hydroxylphenyl) butanoic acid **1b**. Into a 1-neck 250 ml round bottomed flask with a stirbar was placed sodium iodide (2.29g, 15.3 mmol, 1.1eqv) and hydrobromic acid (48%, 156 ml). To the stirring solution was added (2R,3R)-2-Amino-3-(4'-methoxyl-2'-methylphenyl) butanoic acid **1a** (3.10g, 13.9 mmol) in one portion. The flask was sealed tightly with a septum fastened by rubber rings, before being immersed into a 90-94°C water bath. The reaction mixture was stirred at this temperature for 2 hours. The flask was removed from the water bath and cooled down to room temperature before being opened, (while the flask was still hot a syringe needle

was inserted through the septum to equilibrate the pressure on the inside of the flask prior to being opened). The resulting mixture was evaporated *in vacuo* to yield a crude yellow solid which was evaluated by H^1-NMR. The crude product was used directly as it bromide to form the N^{α}-Boc derivative.

A small scale demethylation reaction was performed in order to determine the yields of the free amino acids, utilizing ion-exchange chromatography to obtain the free acids. The crude product (from 0.39g **1a**) was purified by Amberlite IR-120-plus exchange resin (25g) to yield 0.33g **1b** (90.2%). (Table 1)

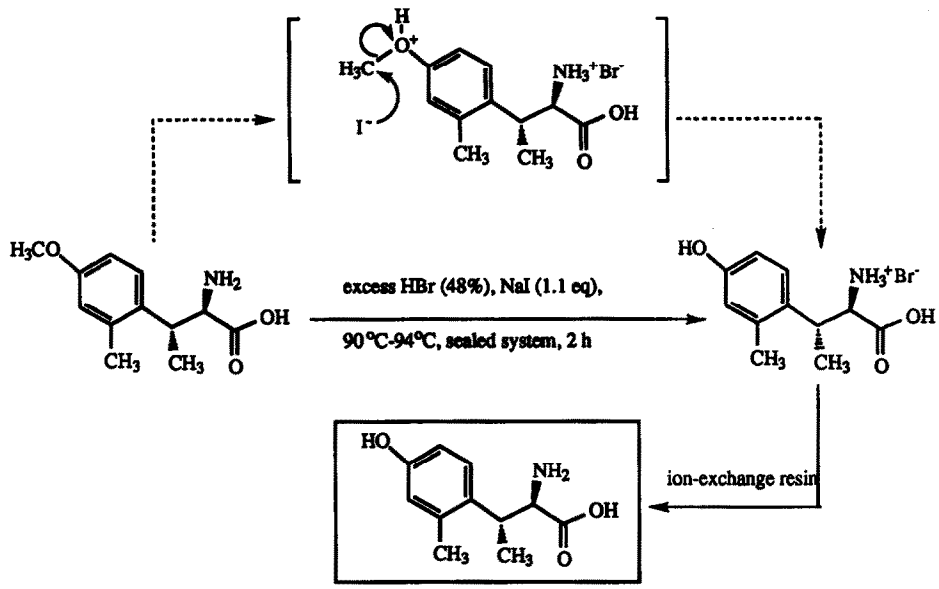

Figure 2. Demethylation utilizing acetic acid free aqueous phase and mild sealed reaction conditions

H^1-NMR (250MHz) was used to monitor the reaction process and evaluate the resulting chirality. The disappearance of the methoxyl group signal from substrate **a** (as the bromide salt - sampled from the continuing reaction) or the upfield shift of hydrogen signals on the aromatic ring as the reaction proceeded, indicated the progress of the demethylation reaction. The chemical shifts of the α and β hydrogens of the diastereomeric isomers of the bromide salts being considerably different, makes them convenient for the determination of the resulting chirality.

In summary, the newly established method provides a convenient and efficient demethylation for aromatic methyl ethers of optically pure special amino acids. The application of this method to the demethylation of methoxy and polymethoxy moieties in other tyrosine derivatives will be exploited in the near future.

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