ACETONIDE PROTECTION OF DOPAMINE AND 3,4-DIHYDROXYPHENYLALANINE

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INTRODUCTION

As a member of the catecholamine family, 4-(2-aminoethyl)benzene-1,2-diol (dopamine), produced through decarboxylation of 3,4-dihydroxyphenylalanine (DOPA) in the nervous tissue, is an important neurotransmitter, essential to the normal functioning of the central nervous. The catechol of dopamine and DOPA is capable of chelating various metal ions, such as Fe^{3+} and Ti^{4+}, forming robust metal-organic coordination complex.[1] Dopamine and DOPA are readily oxidized, especially under basic conditions, to their quinone derivatives, which undergo self-polymerization or nucleophilic addition reactions with amino or sulfhydryl group. Chemical manipulation of dopamine, DOPA and their derivatives is often accompanied with suitable catechol protective groups, among which acetonide is well compatible with Fmoc solid-phase peptide synthesis.[2] Acetonide protected dopamine and its derivatives, are usually obtained in a build-up manner, involving constructing the target molecules from an acetonide protected subunit followed by nitration and reduction of the NO_2 group to NH_2.[3] Simply refluxing acetone with dopamine or DOPA hydrochloride in the present of *p*-toluenesulfonic acid (TsOH) does not result in acetonide protection of the catechol instead of a Pictet-Spengler isoquinoline (Scheme 1).[4-5] We designed a novel synthetic path to realize acetonide protection of the catechol of dopamine and DOPA.

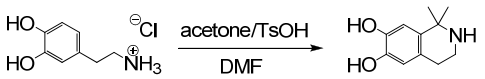
EXPERIMENTAL

Phthaloyl protecting group (Phth), which provides a full protection to primary amino groups and can be readily removed with hydrazine, was introduced to dopamine. The resulting Phth-dopamine was refluxed with 2,2-dimethoxypropane (DMP) and a catalytic amount of TsOH in anhydrous benzene. To shift the reaction equilibria, the reaction flask was equipped with a Soxhlet extractor, the thimble of which was filled with anhydrous $CaCl_2$ to trap byproducts. The reaction was monitored by the $FeCl_3$ test and was usually completed in 1.5–3 h. The isolated solid was identified to be Phth-dopamine-(acetonide) by MS and NMR spectra. After removal of the phthaloyl group, acetonide protected dopamine was obtained (Scheme 2). Applying this strategy, Phth protected DOPA methyl ester readily underwent acetonide cyclization and further reactions led to Fmoc-DOPA(acetonide)-OH, an intermediate to incorporate DOPA motif into synthetic peptides.[6]

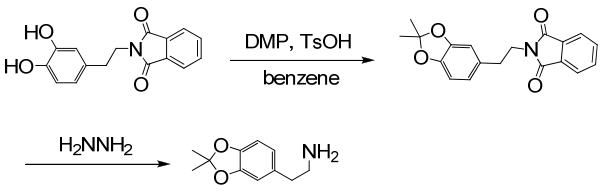
Since the cleavage of phthaloyl protecting group and the methyl ester protecting group are usually performed separately, other amino-protecting groups, carbamates (Boc, Fmoc) and amides (trifluoroacetyl (TFA-)), were evaluated using dopamine as a model of catecholamine. While Boc-dopamine failed, Fmoc and TFA- protected dopamine were successfully cyclized with DMP. Consequently, an improved synthetic method for Fmoc-DOPA(acetonide)-OH was accomplished by protecting the amino group of DOPA with TFA and the carboxyl group as a methyl ester followed by alkaline hydrolysis of the temporary protecting groups and introduction of Fmoc in a two-step one-pot synthesis (Scheme 3).

Kinetic study of acidic hydrolysis of acetonide was carried out using TFA-dopamine(acetonide) as a subject in a mixed solvent of TFA, water, and DMSO with a scavenger. The half-life of acetonide cleavage is ca. 6 h in 60% TFA, 19 min in 70% TFA, and 60 sec in 75% TFA solution.

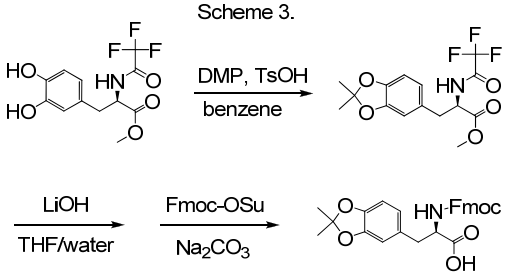
Scheme 1.



Scheme 2.



Scheme 3.



CONCLUSION

In summary, we have designed a highly efficient method to synthesize acetonide-protected DOPA based on the idea of refluxing its properly protected intermediate in anhydrous benzene followed by removal of the temporary amino and carboxyl protecting groups. The present strategy should be generally applicable to aldehydide and ketonide protection of dopamine, DOPA, and other catecholamines.

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