Efficient and Practical Protection of the Catechol Residue of 3,4-Dihydroxyphenylalanine (DOPA) Derivative as Acetonide

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Abstract: The acetonide formation of 3,4-dihydroxyphenylalanine (DOPA) derivative was realized under efficient and practical reaction conditions: the reaction of the methyl ester of DOPA in acetone–*i*-PrOH in the presence of 5 mol% of TsOH afforded the catechol side chain protected DOPA as an acetonide in quantitative yield; the workup procedure is a simple evaporation of the solvents. This methodology allows an access to the reaction in large scale.

Key words: 3,4-dihydroxyphenylalanine (DOPA), protection, acetonide

The ubiquitous nature of the naturally occurring amino acid 3,4-dihydroxyphenylalanine (DOPA, **1**) ever fascinates scientists in biological and medicinal fields. One of the most successful cases is that DOPA is the most successful therapeutic agent in the treatment of Parkinson's disease.[1] In nature, DOPA is derived from post-translational modification of tyrosine, and is the biosynthetic precursor of dopamine. It is well known that DOPA is rarely included in proteins. However, it is detected in marine mussel adhesive proteins as well as egg-shell precursor proteins,[2] and it is postulated that the adhesive and cohesive properties of mussel adhesive proteins is attributable to the catechol side chain of DOPA residues.[3] On the other hand, it is well known that many biologically active natural products contain DOPA derivatives as a key structural unit.[4] Thus, not only in biological and medicinal fields but also in the field of synthetic organic chemistry, DOPA derivatives are regarded as a useful building block for design and synthesis of biologically active compounds, such as α-Me-DOPA, β^3-H-DOPA,[5] calpain I inhibitor,[6] ribasine alkaloids,[7] benzazepine derivatives,[8] pseudobactin,[9] piperonylsyndnone derivatives,[10] to mention just a few. However, DOPA (**1**) itself possesses a carboxyl group, an amino group, and a catechol moiety. To construct such desired useful compounds from DOPA, selective and efficient protection/deprotection steps are crucial. Furthermore, the physical and chemical properties of unprotected DOPA, which is hardly soluble in most of organic solvents and is oxidized readily under basic conditions, sometimes make it difficult for us to synthesize desired compounds. This is why the efficient and practical synthetic transformation methods of DOPA, including protection/deprotection, are highly demanded.

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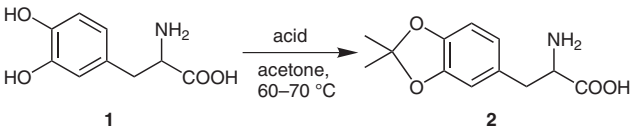


1 **2**

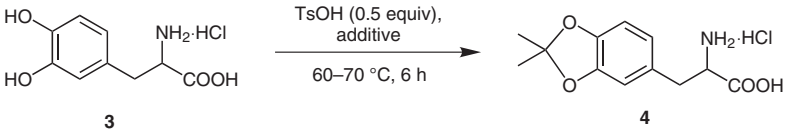
Scheme 1

In our laboratory, we have investigated the syntheses of tailor-made amino acids, utilizing alkylations, aldol additions, and Michael additions of glycine equivalents of Ni(II) complexes under operationally convenient conditions.[11] In the course of the study, we encountered the necessity of an efficient and practical protection method of the catechol residue of DOPA as an acetal or ketal. To our surprise, a literature search revealed that there is no efficient and practical method for the protection of the catechol residue of DOPA as an acetal or ketal. For instance, although they had attempted various standard methods, Sever and Wilker mentioned in their recent report[12] that '*Surprisingly, we were unable to prepare acetonide or diphenylmethylene ketal derivatives of DOPA*'. In this article, we would like to present an efficient protection method of the catechol residue of DOPA derivative as the acetonide under operationally convenient conditions.

As shown in Scheme 1, at first, we attempted to protect DOPA (**1**) in acetone under acidic conditions (e.g., TsOH). However, the conversion of the starting **1** was 27% at most. These poor yields could be attributable to the low solubility of DOPA in acetone. Therefore, we decided to use HCl salt of DOPA instead of DOPA itself. The HCl salt of DOPA **3** was prepared easily in quantitative yield by treatment of DOPA (**1**) with concentrated HCl.

However, the use of the HCl salt **3** did not improve the yield of the product **4** even after a long reaction time (Table 1, entries 1 and 2). To improve the solubility of compound **3**, the reaction was performed in MeOH (entry 3), but still low conversion was observed presumably due to the low reactivity of acetone and/or the evaporation of acetone at the reaction temperature. To overcome such drawbacks, we conducted a reaction using dimethoxypropane instead of acetone (entry 4). Although the yield of the product was improved, still it was not an acceptable yield. Therefore, we decided to run a reaction in MeOH using an excess amount of acetone, which functioned both as a reagent and solvent at the same time (entry 5). This mixed solvent system worked efficiently and improved

Table 1 Reaction Conditions Tested for the Acetonide Formation of the HCl Salt of DOPA



3 4

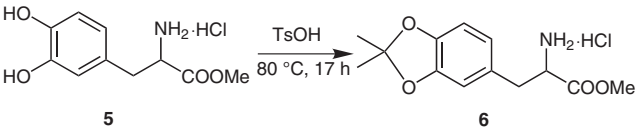
Entry	Additive	Solvent	Yield (%)
1	none	acetone	15
2[a]	none	acetone	27
3[b]	none	MeOH	26
4[c]	none	MeOH	46
5	none	acetone–MeOH (1:1)	71
6	$MgSO_4$	acetone	65
7	Na_2SO_4	acetone	78
8	4 Å MS	acetone	79

[a] The reaction was run for 15 h.
[b] The reaction was conducted with 2 equiv of acetone.
[c] The reaction was conducted with 2 equiv of dimethoxypropane.

the yield dramatically up to 71%. Presumably, the higher solubility of compound **3** in the co-solvent MeOH and the excess amount of 'reagent' acetone could have accelerated the reaction rate. As an alternative method, inspired by the report from Hu and Messersmith,[13] reactions were conducted in the presence of dehydrating reagents (entries 6–9). It was proved that dehydrating reagents worked as good as the mixed solvent system. However, we decided to keep optimizing the reaction conditions without dehydrating reagents since dehydrating reagents are not efficient and practical in large scale reaction. Unfortunately, in spite of numerous attempts, we could not obtain better results; for example, we have conducted several reactions with Dean–Stark device, but formation of unknown byproducts was observed. Therefore, we decided to modify the starting compound to the methyl ester of DOPA, and the HCl salt of methyl ester of DOPA **5** was prepared by treatment of unprotected DOPA (**1**) with $SOCl_2$ in MeOH (isolated yield: >99%).

Since this reaction is controlled by equilibria, we conducted the reaction with a Dean–Stark device. To our satisfaction, the application of the methyl ester **5** improved the yield of compound **6** up to >99%, even in the presence of the smaller amount of the acid catalyst (Table 2, entry 1). The workup procedure is quite simple: just removal of solvents afforded the desired product (any further purification step is not necessary), and it allows us to access the reaction in larger scale. To make the reaction system simpler and more practical, the reaction was preformed using *i*-PrOH as a co-solvent, and it furnished the desired product in quantitative yield (entry 2). Next, we investigated the effect of the amount of the acid catalyst TsOH. The decreasing of the catalyst to 5 mol% did not effect on the complete consumption of the starting compound (entry 3),

Table 2 Reaction Conditions Tested for the Acetonide Formation of the HCl Salt of DOPA Methyl Ester[a]



5 6

Entry	TsOH (equiv)	Solvent	Solvent[b]	Yield (%)
1	0.1	acetone–MeOH (1:1)	MeCN	>99
2	0.1	acetone	*i*-PrOH	>99
3	0.05	acetone	*i*-PrOH	>99
4	0.01	acetone	*i*-PrOH	86

[a] All reactions are conducted with Dean–Stark device. The purity of the product is >90%.
[b] For the purpose of azeotropic removal of water.

while the deceleration of the reaction rate was observed in the case of the reaction with 1 mol% TsOH (entry 4).

In summary, a very simple, efficient and practical protection method of DOPA has been developed. Especially, we have realized the first simple, efficient and practical protection method of catechol side chain of DOPA. The formation of the acetonide of methyl ester of DOPA was realized in acetone–*i*-PrOH in the presence of 5 mol% of TsOH. The workup procedure is a simple evaporation of the solvents. The purity of the product is enough high to use for further reaction without any purification step. This method does not require any special technique and/or reaction conditions, and allows us to conduct the reaction in large scale for practical purpose. Also, this efficient cate-

chol residue protection of DOPA would help the synthetic chemists in the preparation of many biologically active compounds.

General laboratory techniques used in this study were as previously reported.[11i] The new compound was characterized by ^{1}H NMR and ^{13}C NMR (300 MHz and 75.4 MHz, respectively) (Varian-300), and HRMS (Micromass, ESI Q-TOF). The melting point (mp) is uncorrected and was obtained in an open capillary. All reagents and solvents, unless otherwise stated, are commercially available and were used as received.

Acetonide of DOPA Methyl Ester (6)

To a flask attached with a Dean–Stark device containing DL-3-(3,4-dihydroxyphenyl)alanine methyl ester hydrochloride (**5**; 4.95 g, 20 mmol) and acetone (20 mL) acetone was added *p*-toluenesulfonic acid monohydrate (0.19 g, 1.0 mmol) and an excess amount of *i*-PrOH for azeotropic removal of H_2O. The mixture was stirred at 80 °C for 17 h. After removal of the solvents under vacuum, the desired product **6** was obtained in quantitative yield (the purity of the product is >95%, since they contain a small amount of TsOH); mp 227.6 °C (dec.).

^{1}H NMR (D_2O): δ = 1.49 (3 H, s), 1.66 (3 H, s), 3.00 (1 H, dd, *J* = 17.0, 12.5 Hz), 3.14 (1 H, dd, *J* = 17.0, 5.28 Hz), 3.81 (3 H, s), 4.41 (1 H, dd, *J* = 12.4, 5.28 Hz), 6.50–6.80 (3 H, m).

^{13}C NMR (CD_3OD): δ = 28.0, 28.8, 29.8, 52.3, 54.1, 60.3, 112.6, 116.0, 121.0, 129.5, 146.5, 146.7, 170.3.

HRMS: *m*/*z* calcd for $C_{13}H_{18}NO_4$ [M – Cl^-]: 252.1236; found: 252.1143.

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