Tetrahedron Letters 144 (2024) 155150

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

On the inconsistencies in previously reported protections of the catechol moiety of L-DOPA

Cliff Yang [a,1], Jinda Fan [a,b,2], Robert E. Maleczka Jr. [a,*,3]

[a] Department of Chemistry, Michigan State University, 578 South Shaw Lane, East Lansing, MI 48824, United States
[b] Institute for Qunatitative Health Science & Engineering, Michigan State University, 775 Woodlot Drive, East Lansing, MI 48824, United States

ARTICLE INFO

Keywords:
L-DOPA
Catechol
Acetonide
Tetrahydro-isoquinoline

ABSTRACT

Two reported methods for protecting the catechol moiety of L-DOPA as an acetonide have been compared. NMR spectral data and crystal structure analysis confirmed that in contrast to that indicated in *Greene's Protective Groups in Organic Chemistry* the conditions reported for the direct conversion of L-DOPA into its acetonide give instead, a Pictet-Spengler derived tetrahydroisoquinoline.

Introduction

L-DOPA and its derivatives have long been studied owing to their potential for a variety of medical applications [1,2]. Since L-DOPA is a catechol containing amino acid, the synthesis of L-DOPA derivatives almost always requires protection of the reactive catechol.

Formation of an acetonide is often used to protect catechols, including the catechol of L-DOPA. In the chapter on protection for phenols and catechols, the latest (2014) edition of *Greene's Protective Groups in Organic Chemistry*, lists three methods for the formation of acetonide derivatives (Scheme 1). The first method listed refers to the protection of dopamine and the second to forming the acetonide of benzene-1,2,4-triol [3]. Curiously, it is within this second method that readers are warned that the "*acetonide of dopamine is difficult to prepare because of Pictet–Spengler side reactions*" [3–5]. The third method is that published by Soloshonok and Ueki in 2008 [6]. The accompanying scheme shows their TsOH promoted reaction of the HCl salt of L-DOPA methyl ester with acetone to form the corresponding acetonide in "*>99 % yield.*"

While dopamine is not L-DOPA, it is reasonable to ask why acetonide formation of dopamine is complicated by Pictet-Spangler side rections when applying essentially the same reaction conditions to L-DOPA affords the acetonide in near quantitative yield? Indeed, also in 2008, Lui, Hu, and Messersmith noted that conditions like those of Soloshonok and Ueki resulted in "*an isoquinoline product*" (Scheme 1 note) [7]. However, that paper did not illustrate or provide compound characterization data on the isoquinoline product. While, those details were later provided in a patent application [8], they remain absent from the peer reviewed literature. Herein, we seek to change that and to provide the community additional information on the chemistry.

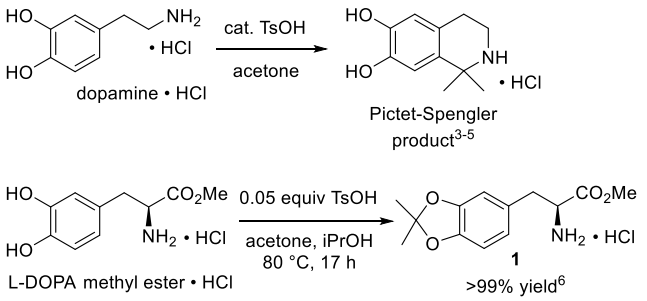
Results and Discussion

Through their independent routes Soloshonok[6] and Messersmith[7] both claimed to generate the acetonide of L-DOPA methyl ester (**1**). We repeated the Soloshonok method (Scheme 2) and compared the NMR data to those reported by Messersmith [7]. Interestingly, the respective ^{13}C NMR data were virtually identical to those reported by both Soloshonok[6] and Messersmith [7]. In contrast, the ^{1}H NMR spectra were not. For our product only two aromatic protons were observed (6.82 (s, 1H) and 6.71 (s, 1H)), instead of three aromatic signals (6.61–6.55 (m, 3H)) that Messersmith reported for **1** [7]. Our data were consistent with the formation of Pictet-Spengler derived tetrahydroisoquinoline **2a**. This structural assignment was confirmed by x-ray crystallography of the corresponding free base **2b** (see Fig. 1). These results confirm the Soloshonok procedure[6] affords **2a** and not **1**. (It remains unclear why they see three aromatic signals (6.50–6.80 (m, 3H) in their ^{1}H spectrum.).

The ethyl ester of L-DOPA was also exposed to the Soloshonok conditions. Not surprisingly, compound **3a** was generated in 75 % yield

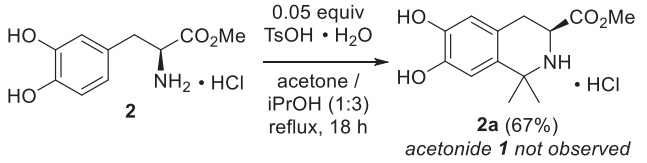
* Corresponding author.
E-mail address: maleczka@chemistry.msu.edu (R.E. Maleczka).
[1] orcid.org/0009-0000-9982-0858.
[2] orcid.org/0000-0003-3098-3397.
[3] orcid.org/0000-0002-1119-5160.

https://doi.org/10.1016/j.tetlet.2024.155150
Received 22 May 2024; Received in revised form 5 June 2024; Accepted 10 June 2024
Available online 14 June 2024



Note: These conditions have also been said to afford "an isoquinoline."[7]

Scheme 1. Examples from *Greene's Protective Groups in Organic Chemistry* [3].



Scheme 2. Repeating the Soloshonok procedure.

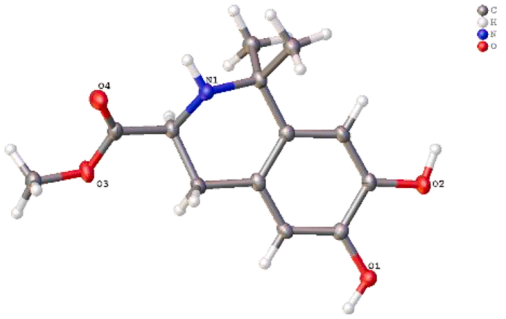


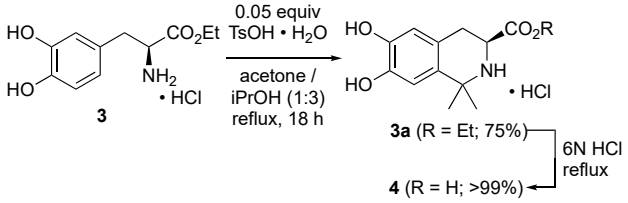
Fig. 1. Crystal structure of isoquinoline **2b**. Drawing of compound at 50 % ellipsoids showing the labeling of the hetero atoms.

(Scheme 3). An x-ray crystal structure of the free base of **3a** (**3b**) was also obtained (see Supporting information Fig. S2). To further confirm the presence of the tetrahydroisoquinoline, a solution of **3a** in 6 N HCl was heated to reflux. These conditions, which are known to deprotect acetonides [9], hydrolyzed the ester, but left the tetrahydroisoquinoline unchanged. Hydrolyzed product **4** allowed another point of comparison, as it is a known compound [10]. In fact, spectra of **4** were in agreement with those previously reported, confirming that the tetrahydroisoquinoline is being formed instead of the acetonide [11].

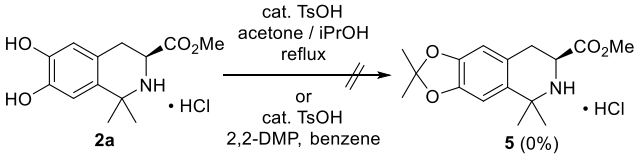
Lastly, we attempted to convert the catechol moiety of quinoline **2a** to acetonide **5** (Scheme 4). Somewhat surprisingly, no reaction was observed after extended exposure to the Soloshonok conditions or when 2,2-dimethoxypropane (2,2-DMP) was used in place of acetone. In both cases the starting tetrahydroisoquinoline was recovered.

Conclusion

This peer-reviewed work confirms that the method highlighted in *Greene's Protective Groups in Organic Chemistry* for the direct conversion of the catechol of L-DOPA into an acetonide fails. Instead, Pictet-Spengler cyclization gives a tetrahydroisoquinoline, which itself is difficult to derivatize as an acetonide.



Scheme 3. Generation and hydrolysis of Pictet-Spengler product **3a**.



Scheme 4. Additional attempts to install the acetonide.

CRediT authorship contribution statement

Cliff Yang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jinda Fan:** Writing – review & editing, Funding acquisition, Conceptualization. **Robert E. Maleczka:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

We thank Daniel Holmes and Li Xie of the Max. T. Rogers NMR Facility, Richard Staples for crystallographic analysis, TJ Delano and Selvan Demir for elemental analysis, and the MSU RTSF Mass Spectrometry Core for assistance in compound characterization.

Funding sources

We thank Michigan State University and the Department of Chemistry for financial support in the form of a Discretionary Funding Initiative Grant to REM. JF thanks the Departments of Radiology and Chemistry for startup funding.

Appendix A. Supplementary data

The Supporting Information is available online. Experimental procedures, including preparation of starting materials, compound characterization data, product spectra crystal reports (PDF), and crystal data for **2b** and **3b** (cif) are provided. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155150.

References

[1] O. Hornykiewicz, L-DOPA: from a biologically inactive amino acid to a successful therapeutic agent: historical review article, Amino Acids 23 (1–3) (2002) 65–70, https://doi.org/10.1007/s00726-001-0111-9.

[2] T. Nagatsua, M. Sawadab, L-dopa therapy for Parkinson's disease: past, present, and future, Park. Relat. Disord. 15 (1) (2009) 3–8, https://doi.org/10.1016/S1353-8020(09)70004-5.

[3] P.G.M. Wuts, Protection for catechols (1,2-dihyrdoxybenzenes), in: Greene's Protective Groups in Organic Chemistry, 2014, pp. 545–553.
[4] S. Morita, T. Ito, T. Tono, Syntheses of isoquinolines by condensation of dopamine with carbonyl compounds, Agric. Biol. Chem. 39 (2) (1975) 547–549, https://doi.org/10.1271/bbb1961.39.547.
[5] Z. Liu, B.H. Hu, P.B. Messersmith, Acetonide protection of dopamine for the synthesis of highly pure N-docosahexaenoyldopamine, Tetrahedron Lett. 51 (18) (2010) 2403–2405, https://doi.org/10.1016/j.tetlet.2010.02.089.
[6] V.A. Soloshonok, H. Ueki, Efficient and practical protection of the catechol residue of 3,4-dihydroxy-phenylalanine (DOPA) derivative as acetonide, Synthesis (Stuttg). 5 (2008) 693–695, https://doi.org/10.1055/s-2008-1032164.
[7] Z. Liu, B.H. Hu, P.B. Messersmith, Convenient synthesis of acetonide-protected 3,4-dihydroxyphenylalanine (DOPA) for Fmoc solid-phase peptide synthesis, Tetrahedron Lett. 49 (38) (2008) 5519–5521, https://doi.org/10.1016/j.tetlet.2008.07.052.
[8] P.B. Messersmith, B. Hu, Z. Liu, Method of Synthesizing Acetonide-Protected Catechol-Containing Compounds and Intermediates Produced Therein, US Patent Application 2010/0087622 A1, April 8, (2010).
[9] K. Ogura, G.I. Tsuchihashi, A versatile reagent for aldehyde synthesis. methyl methylthiomethyl sulfoxide, Tetrahedron Lett. 12 (34) (1971) 3151–3154, https://doi.org/10.1016/S0040-4039(01)97116-3.
[10] L. Misra, H. Wagner, Alkaloidal constituents of mucuna pruriens seeds, Phytochemistry 65 (18) (2004) 2565–2567, https://doi.org/10.1016/j.phytochem.2004.08.045.
[11] B. Frigadere, A. Maciuk, A. Harfouche, L.F. Evanno, Inhibiteurs de La Catechol-O-Methyl-Transferase (COMT), WO 2018/234333 A1, December 27, (2018).