One-Pot Pictet-Spengler Reaction and Esterification for the Preparation of a Key Tadalafil Synthetic Intermediate

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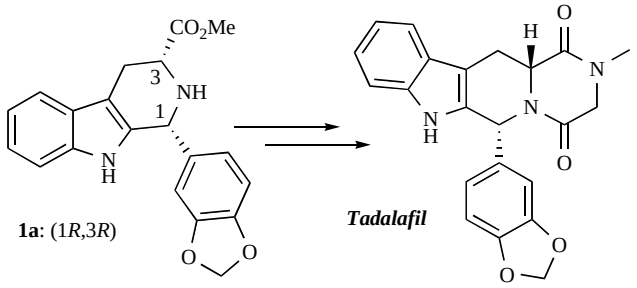
Abstract: A new method is reported for the preparation of 2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid methyl ester, a key intermediate in the synthesis of Tadalafil which is used for the treatment of male erectile dysfunction, *via* one-pot esterification and Pictet-Spengler reaction.

Keywords: Pictet-Spengler, esterification, isomerization, Tadalafil.

The synthesis of compound **1** (Scheme **1**) and its analogs have been recently studied extensively because of their importance as precursors to obtain pharmaceutical compounds such as alkaloids and drugs, the best and well-known being the Tadalafil (Scheme **1**) [1]. This compound, commercialized as Cialis™ (Icos/Lilly), was approved in 2003 by the FDA for the treatment of male erectile dysfunction (MED) and received much attention because of its decreased side effects and increased and effective duration when compared to Sildenafil (Viagra™, Pfizer). Only **1a**, i.e. the (1*R*,3*R*)- or *cis*-diastereoisomer, can be used in the synthesis of Tadalafil and in the literature, countless methods have been reported to obtain *cis*-**1a**, many of them are patented. Despite the fact that numerous methods have been published or patented, the interest in **1a** and Tadalafil is still high as observed by the continuous emergence appearance of new procedures for its preparation [2]. The reaction of **1a** with chloroacetyl chloride, followed by treatment with methylamine of the so formed *N*-chloroacetylcarboline, afforded the target compound Tadalafil [2, 3].



Scheme 1.

All of the methods published so far always employed D-tryptophan methyl ester as a precursor together with 3,4-(methylenedioxy)benzaldehyde (**3**, Scheme **2**), compound **1** being usually obtained as a 1:1 mixture of diastereoisomers by means of an acid-catalyzed Pictet-Spengler reaction [4]. The reaction conditions varied for solvent (chlorinated solvents [3], isopropyl alcohol [5], methanol [6], ethyl acetate [7], and *N*,*N*-dimethyl acetamide [8]), temperature (from 25 [3] to 80 °C [5]), reaction time (from 16 h [5] to 7 days [7]) and isolation of the desired *cis*-**1a** (preparative chromatography [3], fractioned crystallization [6]). The 1:1 diastereomeric mixture could be isomerized in good yield to *cis*-**1a** by heating in aqueous HCl for 2-3 days [3].

The method that we report here allows to obtain compound **1** starting from the amino acid D-tryptophan **2** (and aldehyde **3**) in methanol so that Pictet-Spengler reaction occurs concomitantly with the esterification of the carboxylic moiety, with further advantage in using the less expensive D-Trp-OH instead of its methyl ester.

We studied two different strategies. The first one employed $SOCl_2$ for the esterification, with the HCl that developed during the reaction acting as acid catalyst for the Pictet-Spengler reaction [9]. Although the yield was very good (92% in the final product as hydrochloride) with this procedure, the use of $SOCl_2$ as a reagent is not appealing for possible industrial purposes, and therefore, we decided to test some protic acids that could act as catalysts for both reactions.

Whereas H_2SO_4 proved to be efficient but afforded the final product with low purity grade, HCl gave the best results, both for yield (89%) and purity of the final product [10].

To drive the esterification to completion, the water formed had to be removed. The use of dehydrating agents, such as trimethyl orthoformate failed, mainly because the Pictet-Spengler reaction did not occur; moreover, both molecular sieves [6] and anhydrous sodium sulfate [8] were used in recent patented procedures and their use was not interesting for industrial scale-up. We therefore removed the water by a continuous stripping with methanol (i.e. removal of the solvent and its continuous replacement with fresh

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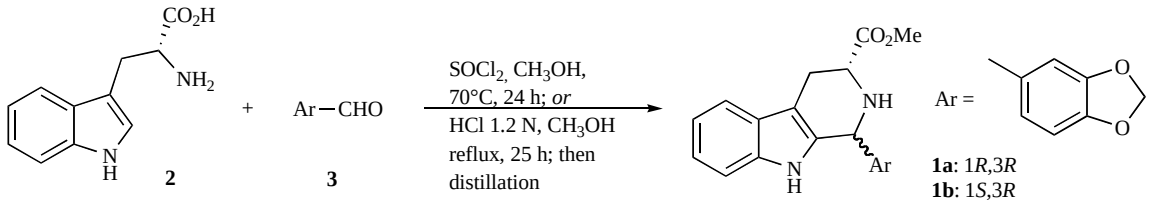

Scheme 2.

methanol, see ref. [10]; water is driven off under non-equilibrium conditions) until the final ester percentage reached the desired value (usually 90-95%). The residual carboxylic acid could be isolated and separated from the corresponding ester by treatment with aqueous $NaHCO_3$. As for the diastereomeric ratio, we always obtained an approximately 1:1 mixture of **1a** and **1b**, which completely isomerized to **1a** under the patented conditions [3]. It should be highlighted that no hydrolysis occurred during the isomerization.

The method was studied and fine-tuned for possible industrial applications too, aiming at obtaining a reproducible synthetic protocol that was tested up to 100 g of reagents.

With the method reported herein, scaled up to 50 g of starting D-Trp-OH, compound **1a** was obtained in 67% yield (I cycle, after isomerization), that increased in the subsequent recycling steps from 84% (II cycle) onwards [11].

In the process herein described two reactions occurred in the same reactor without any separation of the intermediates, i.e. the Pictet-Spengler reaction and the esterification of the carboxylic group. The process uses an inorganic acid such as hydrochloric acid which is easily available, low cost, industrially applicable and easily handling. Furthermore, D-Trp-OH is less expensive than its methyl ester so that the entire process results as economically interesting and promising for possible industrial applications.

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REFERENCES

[1] (a) Gresser, U.; Gleiter, C.H. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors Sildenafil, Vardenafil and Tadalafil. *Eur. J. Med. Res*. **2002**, *7*, 435; (b) Brock, G.; McMahon, C.G.; Chen, K.K.; Costigan, T.; Shen, W.; Watkins, V.; Anglin, G.; Whitaker, S. Efficacy and safety of Tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J. Urol*. **2002**, *168*, 1332.

[2] (a) Xiao, S.; Lu, X.; Shi, X. X.; Sun, Y.; Liang, L. L.; Yu, X. H.; Dong, J. Syntheses of chiral 1,3-disubstituted tetrahydro-β-carbolines *via* CIAT process: highly stereoselective Pictet–Spengler reaction of D-tryptophan ester hydrochlorides with various aldehydes. *Tetrahedron: Asymmetry* **2009**, *20*, 430; (b) Kumpaty, H. J.; Van Linn, M. L.; Kabir, M. S.; Forsterling, F. H.; Deschamps, J. R.; Cook, J. M. Study of the cis to trans isomerization of 1-phenyl-2,3-disubstituted tetrahydro-β-carbolines at C(1): evidence for the carbocation-mediated mechanism. *J. Org. Chem*. **2009**, *74* , 2771; (c) Zhang, Y.; He, Q.; Ding, H.; Wu, X.; Xie, Y. Improved synthesis of Tadalafil. *OPPI* **2005**, *37*, 99.

[3] (a) Daugan, A. C. M. Tetracyclic derivatives, process of preparation and use. U.S. Patent 5,859,006, January 12, 1999; (b) Daugan, A. C. M.; Gellibert, F. Tetracyclic cyclic GMP-specific phosphodiesterase inhibitors, process of preparation and use. U.S. Patent 6,143,746, November 7, 2000; (c) Daugan, A. C. M.; Labaudinière, R. F. Chemical compounds. U.S. Patent 6,143,757, November 7, 2000; (d) Daugan, A.; Grondin, P.; Rualt, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. The discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor. 2: 2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione Analogues. *J. Med. Chem*. **2003**, *46*, 4533.

[4] For a review on the Pictet-Spengler reaction see: Coz, E. D.; Cook, J. M. The Pictet-Spengler condensation: a new direction for an old reaction. *Chem. Rev*. **1995**, *95*, 1797. For recent examples of P.S. reactions in aqueous medium see: (a) López-Rodríguez, M. L.; Morcillo, M. J.; Garrido, M.; Benhamú, B.; Pérez, V.; de la Campa, J. G. Stereospecificity in the reaction of tetrahydro-β-carboline-3-carboxylic acids with isocyanates and isothiocyanates: kinetic vs thermodynamic control. *J. Org. Chem*. **1994**, *59*, 1583; (b) Herraiz, T.; Galisteo, J.; Chamorro, C. L-tryptophan reacts with naturally occurring and food-occurring phenolic aldehydes to give phenolic tetrahydro-β-carboline alkaloids: activity as antioxidants and free radical scavengers. *J. Agric. Food Chem*. **2003**, *51*, 2168; (c) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. Water as an efficient medium for the synthesis of tetrahydro-β-carbolines *via* Pictet-Spengler reactions. *Tetrahedron Lett*. **2007**, *48*, 1379.

[5] Orme, M. W.; Martinelli, M. J.; Doecke, C. W.; Pawlak, J. M.; Chelius, E. C. Modified Pictet-Spengler reaction and products prepared therefrom. PCT WO2004/011463 A1, February 5, 2004.

[6] Lohray, B. B.; Lohray, V. B.; Patel, S. I. Process for preparing Tadalafil and its intermediates. PCT WO2005/068464 A2, July 28, 2005.

[7] Dolitzky, B. Z.; Diller, D. Preparation of Tadalafil intermediates. PCT WO2006/110893 A2, October 19, 2006.

[8] Deshpande, P. B.; Boda, B. B.; Surti, S. S.; Shah, P. P. Process for preparing Tadalafil and its intermediates. U.S. Patent 2006/0258865 A1, November 16, 2006.

[9] D-Trp-OH (511 mg, 2.5 mmol) was added to a solution of $SOCl_2$ (274 μL, 3.75 mmol) in methanol (15 mL) cooled at 0°C. Piperonal (375 mg, 2.5 mmol) was added after 10 min and the ice bath removed. The resulting solution was then heated at 70 °C for 24 h. After cooling at r.t., the solvent was evaporated to dryness and the residue washed with Et_2O (2 x 10 mL) and suspended into aqueous satd $NaHCO_3$ (40 mL). The product was extracted with $CHCl_3$ (3 x 25 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, compound **1** - a pale yellow solid - was obtained (806 mg, 92%) as a 1:1 diastereomeric mixture.

[10] To a suspension of D-tryptophan (5.10 g, 25.0 mmol) in methanol (22.5 mL), an aqueous solution of HCl 37% (2.5 mL) was added. Piperonal (3.75 g, 25.0 mmol) was then added to the resulting solution, which was allowed to react at reflux temperature for 25 h. The solvent was removed by distillation and continuously replaced with fresh methanol up to a total volume of 400 mL of the distilled. The methanol was evaporated to dryness and the residue washed with Et_2O (10 mL) and suspended into aqueous satd $NaHCO_3$ (20 mL). The product was extracted with EtOAc (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, compound **1** - a pale yellow foam - was obtained (7.80 g, 89%) as a 1:1 diastereomeric mixture. **1a**: ^{1}H NMR (200 MHz, DMSO-d6) δ (ppm): 10.84 (s, 1 H), 7.54 (d, *J* 6.7 Hz, 1 H), 7.29 (d, *J* 7.4 Hz, 1 H), 7.17-6.99 (m, 5 H), 6.10 (s, 2 H), 5.87 (s br, 1 H), 4.73 (s br, 1 H), 3.84 (s, 3 H), 3.38-3.26 (m, 2 H).

^{13}C NMR (50.33 MHz, DMSO-d6) δ (ppm): 168.5 (s), 148.5 (s), 147.1 (s), 136.7 (s), 128.9 (s), 127.0 (s), 125.4 (s), 125.0 (d), 122.0 (d), 119.2 (d), 118.2 (d), 111.6 (d), 110.4 (d), 108.3 (d), 106.3 (s), 101.5 (t), 57.6 (d), 55.2 (d), 53.0 (q), 22.2 (t).

[11] Borzatta, V.; Scarpi, D.; Guarna, A.; Occhiato, E.G. Process for the preparation of 2,3,4,9-tetrahydro-1H-beta-carboline-3-carboxylic esters. PCT WO2009/103787 A1, August 27, 2009. The procedure differs from the one reported in ref. 10, because compound **1** was not isolated but directly isomerized to **1a** by treatment with aqueous 1.0 N HCl (see Ref. 3 for experimental conditions of the isomerization). The product was recovered by filtration (I cycle yield: 67% in **1a**). The residue, resulting from the mother liquor and containing a mixture of **1a**, **1b** and their corresponding carboxylic acids, was added to fresh reagents (i.e. D-Trp-OH and piperonal) in the next process, allowing the recovery of **1a** in 84% yield (II cycle only). The experiments stopped with the second cycle, but we believe that following cycles could further improve the overall yield.