Organic Process Research & Development **2007**, *11*, 463–465

Improved and Practical Synthesis of 6-Methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride

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Abstract:

6-Methoxy-1,2,3,4-tetrahydroisoquinoline (1) or its hydrochloride salt (4) is an expensive chemical with limited commercial availability. We report an improved and practical synthesis of 4 from inexpensive 2-(3-methoxyphenyl)ethylamine (2) using a Pictet−Spengler condensation via a novel aminal intermediate. The synthesis significantly lowers the cost and provides easy access to 6-methoxy-1,2,3,4-tetrahydroisoquinoline or its HCl salt on a large scale.

Introduction

During the course of one of our recent projects we required substantial amounts of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (**1**) as a starting material. While it is commercially available, it is very expensive (>$400/g) and available only in milligram quantities as listed by a few chemical sources. Although several syntheses of this compound have been reported in the literature, none is convenient to carry out on a large scale. Among those approaches, the most direct method for synthesis of this tetrahydroisoquinoline is a Pictet−Spengler type condensation of 2-(3′-methoxyphenyl)ethylamine (**2**) with formaldehyde.[1] Several research groups have used this approach to obtain the target compound in small quantities. The product resulting from the direct condensation of 2-(3′-methoxyphenyl)ethylamine with formaldehyde is an oil making the isolation and purification process difficult for large-scale synthesis.[2] Bucks has reported a procedure for the direct isolation of the HCl salt of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**), but the procedure requires a time-consuming evaporation of aqueous HCl solution to dryness.[3] Ruchirawat and co-workers reported a direct synthesis of tetrahydroisoquinoline analogues using paraformaldehyde and formic acid.[4] Their workup involved a process-unfavorable step, distillation of formic acid to dryness, followed by isolation of the products as their oxalate salts. Although this approach represented the most practical synthesis of tetrahydroisoquinoline analogues, the methodology was not applied to the synthesis of our targeted molecule. In addition to the direct condensation of 2-(3′-methoxyphenyl)ethylamine with formaldehyde, other literature approaches required protection of the amine functionality prior to the acid-catalyzed condensation and a deprotection step after the condensation.[2a,5] An alternative approach, reported by Sall and Grunewald,[6] used a Friedel−Crafts type cyclization of methyl 2-(3′-methoxyphenyl)ethyl carbamate with polyphosphoric acid (PPA) to give a mixture of 6-methoxy- and 8-methoxy-3,4-dihydroisoquinolinones in a ratio of 2:1, respectively. Separation of the regioisomers by chromatography and subsequent reduction with lithium aluminum hydride yielded 6-methoxy- and 8-methoxy-1,2,3,4-tetrahydroisoquinolines. Although the procedure was recently utilized by Mewshaw and co-workers for their medicinal chemistry research,[7] the poor regioselectivity of cyclization and the harsh reaction conditions prevented its application in large-scale synthesis.

Results and Discussion

To fulfill our need of a large quantity of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (**1**), we evaluated the Pictet−Spengler condensation methodology starting from the commercially available 2-(3′-methoxyphenyl)ethylamine (**2**). The reaction of **2** with aqueous formaldehyde (37%) in 1 N aqueous HCl solution was found to be very slow at room temperature, resulting only in 50% conversion after 4 days. However, we discovered the reaction could be completed in just 1 h at 60 °C. After basification of the reaction mixture to pH ∼12 using 3 N aqueous NaOH solution, an off-white solid product was precipitated and isolated. Comparing this solid to an authentic sample of **1** (an oil) showed that the isolated solid product had the same HPLC retention time and LC/MS spectrum as that of the authentic sample. The ^{1}H NMR spectrum of the isolated solid product was similar but not identical showing only one set of peaks evidently from a single compound. However it contained two more nonexchangeable protons as compared to the authentic sample of **1**, which were found to be a CH_2 unit by ^{1}H NMR and ^{13}C NMR analyses. Apparently the isolated solid was not the desired product **1**. Based on the data, we concluded that the isolated solid was bis(6-methoxy-3,4-dihydroiso-

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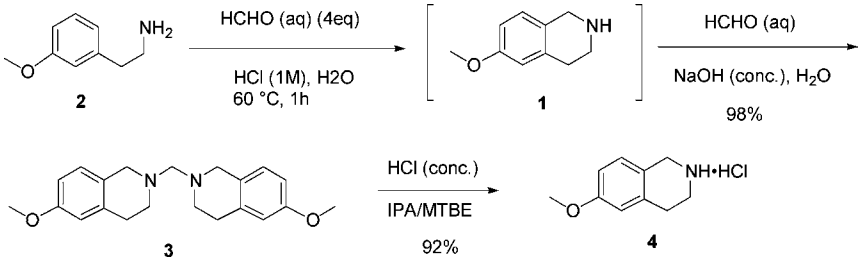
10.1021/op7000468 CCC: $37.00
Published on Web 04/25/2007

Scheme 1. **Improved synthesis of 6-methoxytetrahydroisoquinoline HCl salt**



quinolin-2(1*H*)-yl)methane (**3**), a novel compound resulting from the further reaction of amine **1** with excess formaldehyde as depicted in Scheme 1. Thus upon treatment of **3** with concentrated HCl in isopropanol (IPA), it was converted to the HCl salt of **1**, a solid with an identical melting point to that reported in literature.[3] We decided to take advantage of the easy isolation of bis(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methane (**3**) from the reaction mixture, knowing it could be directly converted to 6-methoxy-1,2,3,4-tetrahydroisoquinoline HCl salt **4**. During the scale-up, we used 50% of aqueous NaOH solution to minimize the reaction volume. In order to avoid the formation of oil product, we found it was important to basify the reaction mixture by addition of 50% of aqueous NaOH solution in several portions, as detailed in the Experimental Section, to produce solid aminal **3**. Upon treatment with concentrated HCl solution in IPA/MTBE, the HCl salt **4** precipitates from the reaction mixture and is isolated in excellent yield by simple filtration. This two-step process provides a simplified and practical access to this important material in large quantities utilizing inexpensive raw materials and easy isolation of solids.

Conclusion

We have developed an improved and practical synthesis of 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4**) starting from inexpensive readily available 2-(3-methoxyphenyl)ethylamine (**2**). The process utilizes a Pictet−Spengler condensation to provide the novel solid intermediate bis(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methane (**3**) after basification of the reaction mixture. The isolated solid **3** is treated with HCl to provide the title compound **4** which is isolated by direct filtration from the reaction mixture in a pure form. Further studies on the application of this methodology to the synthesis of other tetrahydroisoquinoline derivatives will be reported in due course.

Experimental Section

General. All reagents and solvents were used directly as purchased from commercial suppliers. All reactions were conducted under nitrogen. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz using a Bruker Avance-300. Mass spectra were performed on Fannigan Navigator MS. Elemental analyses were provided by Robertson Microlit Laboratory, Inc.

Bis(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-methane (3). An aqueous solution of formaldehyde (416.5 g, 37 wt %, 5.13 mol) was added to a solution of 2-(3-methoxyphenyl)ethylamine (200.0 g, 1.28 mol) in aqueous 1 N HCl solution (1.92 L, 1.92 mol). The mixture was heated and stirred at 60 °C for 1 h. The reaction mixture was then cooled to room temperature and basified with 50% NaOH solution (174.4 g, 2.18 mol) as follows: (a) 40% of the total amount of NaOH solution was added slowly over 10 min and the internal reaction temperature was maintained at ∼25−30 °C by using an ice−water bath. The resulting light suspension was stirred at 25−30 °C for 1 h. (b) 15% of the total amount of NaOH solution was slowly added over 5 min while maintaining the internal reaction temperature around 25−30 °C. The resulting light suspension was stirred at 25−30 °C for 1 h. (c) 15% of the total amount of NaOH solution was added slowly over 5 min while maintaining the internal reaction temperature around 25−30 °C. The resulting light suspension was stirred at 25−30 °C for 1 h. (d) The remaining 30% of NaOH solution was added slowly over 5 min while maintaining the internal reaction temperature around 25−30 °C. After addition of all the NaOH solution, the resulting heavy suspension was stirred at 25−30 °C for 2 h. The solid product was collected by vacuum filtration, washed with H_2O (200 mL), and air-dried. The product (213.4 g, 98%) was obtained as a white solid. Mp: 121 °C (by DSC analysis). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, J = 8.4 Hz, 2H), 6.70 (dd, J = 8.4, 2.6 Hz, 2H), 6.65 (d, J = 2.5 Hz, 2H), 3.77 (s, 6H), 3.25 (s, 2H), 3.23 (s, 4H), 2.85 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.9, 136.0, 127.6, 127.3, 113.3, 112.0, 80.7, 55.2, 53.9, 49.0, 29.4. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.21. Found: C, 74.20; H, 7.95; N, 8.11.

6-Methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1). Aminal **3** (213.4 g, 0.63 mol) was suspended in IPA (1.06 L), to which a concentrated aqueous HCl solution (140.4 g, 36 wt %, 1.38 mol) was added slowly with a slight exotherm. Most of the solid was dissolved immediately following the addition of HCl, and then a solid reprecipitated in a few seconds. The resulting suspension was stirred at room temperature for 18 h. MTBE (0.53 L) was added, and the suspension was stirred at room temperature for an additional 4 h. The solid was collected by filtration, then was rinsed with a 1/1 mixture of MTBE/IPA (100 mL), and air-dried. The product (230.3 g, 92%) was isolated as a white solid. Mp: 239 °C (by DSC analysis). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.13 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4, 2.6 Hz, 1H), 6.79 (s, 1H), 3.77 (s, 6H), 4.14 (br s, 2H), 3.73 (s, 3H), 3.10 (br m, 2H), 2.50 (t, J = 1.6 Hz, 2H). ^{13}C NMR

(300 MHz, DMSO-d_6): δ 158.8, 133.7, 128.2, 121.2, 113.5, 113.4, 55.5, 43.4, 40.7, 25.3. Anal. Calcd for $C_{10}H_{14}NOCl$: C, 60.15; H, 7.07; N, 7.01; Cl, 17.76. Found: C, 60.23; H, 7.27; N, 6.88; Cl, 17.89.

Acknowledgment

We are grateful to Rekha Shah for analytical support and Steve Stefanick for the reaction safety evaluation. We further thank Ahmed Abdel-Magid, Steve Mehrman, Chris Teleha, and Jay Matthews for the fruitful discussions about the chemistry.

Supporting Information Available

Selected NMR spectroscopic data. This information is available free of charge via the Internet at http://pubs.acs.org.

Received for review February 21, 2007.

OP7000468