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Synthesis of 2-[2-(3,4,5-Trimethoxybenzoyloxy)ethyl]pyrrolidine Hydrochloride Controlled by GC-MS, ^{1}H and ^{13}C NMR Analyses

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The synthesis of 2-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]pyrrolidine hydrochloride was performed using 2-(2-hydroxyethyl)pyrrolidine as a starting material. Before the O-acylation reaction with 3,4,5-trimethoxybenzoyl chloride, the amino group was protected using benzyl chlorocarbonate. The removal of the blocking group was carried out in modified conditions, avoiding the alcoholysis of the ester bond. The final product was separated from its structural isomer by precipitation as its hydrochloride salt. Some steps of the synthesis were controlled by GC-MS. The identification of the respective compounds was performed by mass spectra analyses and confirmed by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses.

Key Words: 2-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]pyrrolidine hydrochloride, pyrrolidine derivatives, O-acylation of amino alcohols, removal of Cbz group.

Introduction

The pyrrolidine ring, which is present in a large number of compounds, is widely used in medicine. Among them, well known are tropane alkaloids (atropine, scopolamine)[1], their derivatives (eumydrin[2], ipratropium[3]), and antihistaminic agents (clemastine[4], acrivastine[5]). Biological activities exist in compounds with the 3,4,5-trimethoxybenzoyl group, used in cardio therapy (hexobendine[6], butobendine[7], dilazep[8]). The aim of this work was the synthesis of a new substituted pyrrolidine containing the 3,4,5-trimethoxybenzoyl group, with potential biological activity.

2-[2-(3,4,5-Trimethoxybenzoyloxy)ethyl]pyrrolidine hydrochloride was obtained in several steps (Scheme 1), and characterized by GC-MS, ^{1}H, ^{13}C NMR and IR analysis. The starting material, 2-(2-hydroxyethyl)-pyrrolidine (**1**), was synthesized previously in our laboratory[9]. The first step was the protection of the amino

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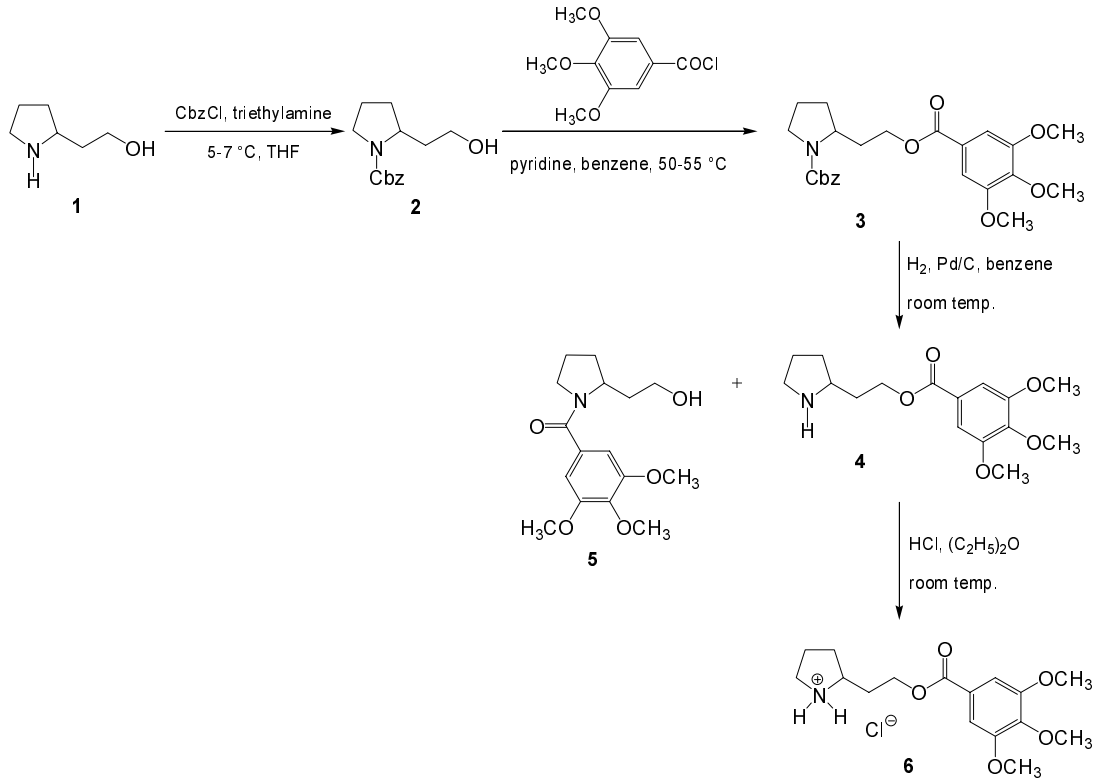
group using benzyl chlorocarbonate. The derivative **2** was then O-acylated with 3,4,5-trimethoxybenzoyl chloride. Finally, the hydrogenolysis of **3** was performed in order to remove the protection group, which yielded the expected product **4**, and its structural isomer **5**. The final product was isolated in the form of hydrochloride **6**.



Scheme 1

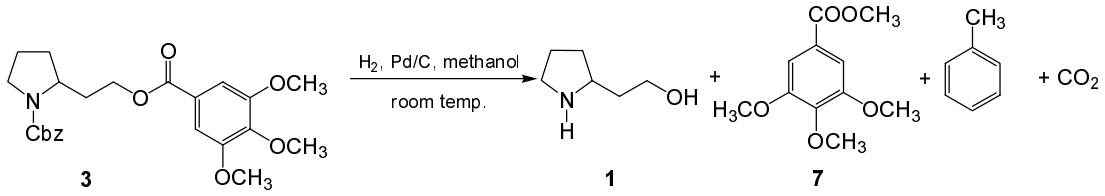
Results and Discussion

In order to protect the amino group in 2-(2-hydroxyethyl)pyrrolidine (**1**), benzyl chlorocarbonate was used. It allows blocking of only the nitrogen atom, leaving the hydroxy group free[10]. Usually this reaction is carried out in an aqueous solution of sodium hydroxide at room temperature with yields not exceeding 75% [10,11]. In this case, different conditions were applied due to expected difficulties with the product isolation from the aqueous solution. The reaction was carried out in THF in the presence of triethylamine at 5-10 °C. Under those conditions the N-Cbz-2-(2-hydroxyethyl)pyrrolidine (**2**) was obtained in 98% yield. Compound **2** was then O-acylated using 3,4,5-trimethoxybenzoyl chloride. The reaction, which was carried out in benzene in the presence of pyridine at 50-60 °C, gave N-Cbz-2-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]pyrrolidine (**3**) in 97.5% yield. The progress of the reactions was determined by GC-MS (Table 1). The structures of the compounds were confirmed by spectral analyses (Table 2).

The removal of the Cbz group was performed by the hydrogenolysis reaction using 5% Pd/C as catalyst [12,13]. The use of the classic solvent in this reaction – methanol[13] – led to alcoholysis of the ester bond and formation of methyl 3,4,5-trimethoxybenzoate (**7**) and the starting material **1** (Scheme 2). The course of this reaction was confirmed by the GC-MS analysis (data in Table 1).

Table 1. GC-MS data of compounds **1-5** and **7**.

Compound No.	Retention time (min.)	Mass/charge (relative intensity)
1	8.20	115(M^+, 2.0), 96(2.5), 70(100), 68(7.3), 56(12.6), 43(8.2).
2	20.17	249(M^+, 7.5), 204(21.5), 160(28.8), 114(13.4), 91(100), 79(4.2), 65(9.2), 41(4.9).
3	31.52	443(M^+, 14.1), 308(6.6), 239(2.5), 195(57.7), 160(13.6), 140(26.1), 96(71.2), 91(100), 77(3.4), 65(5.0), 41(2.3).
4	23.18	309(M^+, 1.8), 240(1.7), 212(13.2), 195(20.4), 114(2.7), 97(31.5), 70(100), 41(3.1).
5	24.38	309(M^+, 14.2), 265(21.2), 195(100), 168(4.4), 152(5.0), 122(3.1), 81(3.0), 41(1.3).
7	16.36	226(M^+,100), 212(5.6), 211(48.7), 195(28.6), 183(7.3), 155(23.6), 125(9.3), 81(4.0), 77(4.3), 66(6.6), 59(4.6).



Scheme 2

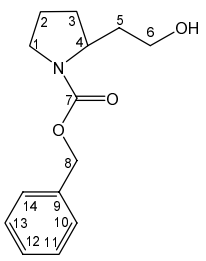
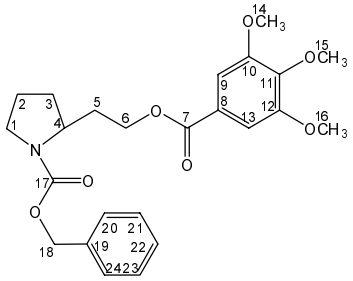
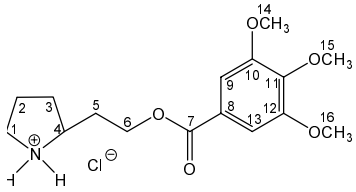
To avoid this undesirable reaction, the methanol was replaced with a non-protogenic solvent (benzene). The hydrogenolysis in benzene yielded the expected product, 2-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]pyrrolidine (**4**), and its possible structural isomer, 2-(2-hydroxyethyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidine (**5**). The probable reason for this fact is the intramolecular migration of the 3,4,5-trimethoxybenzoyl group from the oxygen to the nitrogen atom. The identification of those compounds was performed on the basis of the mass spectra analysis. The GC-MS data of **4** and **5** are summarized in Table 1.

All attempts to isolate the isomers by fractional crystallization were unsuccessful. Finally, these compounds were separated by converting the isomer **4** into hydrochloride. For this purpose the hydrogenolysis products in the diethyl ether solution were treated with dry hydrogen chloride. The product **6** was precipitated in the form of white crystals in 22.2% yield. The structure of this compound was confirmed by ^{1}H, ^{13}C NMR and IR analyses (Table 2).

Experimental

GC-MS analyses were carried out on a Hewlett-Packard HP 6890 capillary gas chromatograph equipped with a HP MSD 5973 mass selective detector. Compounds were separated on a fused silica capillary column HP-5MS (5% phenyl-methylpolysiloxane, 30 m x 0.25 mm I.D., film thickness: 0.25 μm). The column temperature was programmed: initial temperature, 60 °C (hold for 3 min); ramp rate, 10 °C/min; final temperature, 300 °C (hold for 10 min). Helium was used as a carrier gas at a flow of 1.2 mL/min. The injection port and transfer line temperatures were 280 °C. The instrument control and data handling were performed using HP ChemStation software.

Table 2. Spectral analyses data of the intermediates and final product.

Structure[a]	^{1}HNMR[b] ($CDCl_3$), δ (ppm)	^{13}C NMR ($CDCl_3$), δ (ppm)	IR, ν (cm^{-1}) (cm^{-1})
 **2**	1.54-1.99 (m, 6H, CH_2), 3.34-3.46 (m, 2H, CH_2-N), 3.60-3.68 (m, 2H, CH_2-O), 4.20-4.22 (m, 1H, CH), 5.10 (s, 1H, OH), 5.17 (s, 2H, OCH_2Ph), 7.30, 7.36 (2s, 5H, arom.).	C-2 (23.6), C-3 (31.2), C-5 (38.1), C-1 (46.5), C-4 (54,4), C-6 (59.1), C-8 (67.0), C-12 (127.8), C-11, C-13 (128.0), C-10, C-14 (128.5), C-9 (136.7), C-7 (156.6).	3500-3150, 3100, 3000-2800, 1740, 1660, 1480-1400, 1350, 1100, 870-770.
 **3**	1.82-2.03 (m, 6H, CH_2), 3.40-3.47 (m, 2H, CH_2-N), 3.86 (s, 9H, OCH_3), 4.06-4.08 (m, 1H, CH), 4.37-4.38 (m, 2H, CH_2-O), 5.09-5.15 (m, 2H, CH_2Ph), 7.27 (s, 2H, arom.), 7.32, 7.39 (2s, 5H, arom.).	C-2 (23.6), C-3 (31.1), C-5 (38.2), C-1 (46.3), C-4 (54.3), C-14, C-16 (56.1), C-6 (59,0), C-15 (60.9), C-18 (67.1), C-9, C-13 (106.8), C-22 (125.2), C-21, C-23 (127.8), C-11 (127.9), C-20, C-24 (128.0), C-19 (136.9), C-8 (155.0), C-10, C-12 (156.7), C-7 (166.2), C-17 (168.8).	3150-3100, 3000-2800, 1740,1660, 1570, 1480-1400, 1350,1100, 870-770.
 **6**	1.66-2.17 (m, 4H, $2CH_2$), 2.25-2.30 (m, 2H, CH_2), 3.35-3.43 (m, 2H, CH_2N), 3.68-3.73 (m, 2H, CH_2-O), 3.90 (s, 3H, 4-OCH_3), 3.92 (s, 6H, 3,5-OCH_3), 4.42-4.56 (m, 1H, CH), 7.29 (s, 2H, arom.).	C-2 (22.4), C-3 (22,5), C-5 (23.6), C-1 (44.6), C-14, C-16 (56.4), C-15 (57.7),C-4 (60.9), C-6 (61.9), C-9, C-13 (106.9), C-10, C-12 (124.7), C-11 (142.4), C-8 (153.0), C-7 (166.1).	2800-2550, 1715, 1590, 1500, 1470, 1410, 1330, 1220, 1130, 1000, 750.

[a]Structures and carbon numbering system used in ^{13}C NMR analyses.
[b]Abbreviations used: s, singlet; m, multiplet; arom., unsaturated aromatic protons.

^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker DPX 400 MHz spectrometer with tetramethylsilane as an internal standard at 400 MHz (^{1}H) and 100 MHz (^{13}C), at room temperature. Chemical shifts are given in ppm.

IR spectra were recorded on a Zeiss Specord 80IR spectrophotometer using NaCl plates or KBr pellets and reported in wave numbers (cm^{-1}).

Elemental analyses were carried out on a Heraeus EuroEA Elemental Analyzer.

N-Cbz-2-(2-hydroxyethyl)pyrrolidine (2): 2-(2-Hydroxyethyl)pyrrolidine **1** (0.025 mol) and triethylamine (0.025 mol) was dissolved in THF (20 cm^3) and cooled to 4 °C. To the stirred mixture was

added a solution of benzyl chlorocarbonate (0.025 mol) in 20 cm^3 THF dropwise over ca. 1 h. The mixture was stirred for 1 h at 4-7 °C, and then filtered to remove triethylamine hydrochloride. The filtrate was concentrated by vacuum evaporation to give **2** (6.1 g, 98%) in the form of a viscous liquid. Anal. Calcd. for $C_{14}H_{19}NO_3$: N, 5.62. Found: N, 5.38. GC-MS data are collected in Table 1. ^1H, ^{13}C NMR and IR data are given in Table 2.

N-Cbz-2-[2-(3,4,5-trimethoxybenzoyloxy)ethyl]pyrrolidine (3): To a stirred mixture of **2** (0.02 mol) and pyridine (0.02 mol) in 20 cm^3 of dry benzene was added a solution of 3,4,5-trimethoxybenzoyl chloride (0.02 mol) in dry benzene (30 cm^3) dropwise over 45 min. The mixture was stirred at room temperature for 2 h and then at 45-50 °C for 2 h. After cooling to 20 °C, pyridine hydrochloride was separated and the solvent was removed under vacuum. The compound **3** (8.45 g, 97.5%) was obtained as a pale yellow oily liquid, which was analyzed and used without further purification. n_D^{25}=1.5296. GC-MS data are collected in Table 1. ^1H, ^{13}C NMR and IR data are given in Table 2.

2-[2-(3,4,5,-Trimethoxybenzoyloxy)ethyl]pyrrolidine hydrochloride (6): A solution of **3** (0.0045 mol) in 50 cm^3 of dry benzene and 0.1 cm^3 of glacial acetic acid were added to the reaction flask, containing 1 g of activated 5% Pd/C in 60 cm^3 of dry benzene. Hydrogen was passed through the mixture at room temperature until barium carbonate had disappeared at a control bulb (ca. 12 h). The mixture was filtered and benzene was removed in vacuo. The crude product, obtained as a pale yellow oily liquid, was placed into a vacuum desiccator with paraffin flakes to remove the benzene residue. The diethyl ether solution of the product containing **4** and **5** was saturated with dry hydrogen chloride and then left at room temperature for 24 h. The crystalline precipitate was collected by filtration, washed with dry diethyl ether and recrystallized from acetone, affording **6** (0.35 g, 22.2%) in the form of white crystals. M.p. 137-139 °C. Anal. Calcd. for $C_{16}H_{24}ClNO_5$: C 55.36, H 7.01, N 4.05. Found C, 55.16, H, 7.29, N, 4.06. ^1H, ^{13}C NMR and IR data are compiled in Table 2.

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