AN IMPROVED METHOD FOR THE SYNTHESIS OF METOCLOPRAMIDE

AZIM ZIYAEI HALIMEHJANI,A,* MOZHGAN AFRADI,B NAHID AFRADI

Faculty of Chemistry, Tarbiat Moallem University, 49 Mofateh St., Tehran, Iran, Department of Chemistry, Saveh branch, Islamic Azad University, Saveh, Iran. Email: ziyaei@tmu.ac.ir

Received: 27 July 2011, Revised and Accepted: 11 Nov 2011

ABSTRACT
An improved method for the synthesis of metoclopramide (MCP) is described by using a suitable solvent for the condensation step. The advantages of the present work are (a) using of low amount of the excess amine (b) low temperature and (c) high yield (96%). Also a new and simple method for the synthesis of MCP.HCl from MCP is presented.

Keywords: Metoclopramide, Antiemetic, Synthesis, Gastroprokinetic, Metoclopramide hydrochloride

INTRODUCTION
Metoclopramide (MCP) is a very useful compound with wide applications as a gastrointestinal prokinetic and antiemetic agent1-2. Its clinical application is because of possessing a dopamine D2 receptor antagonist and weak serotonin 5-HT4 receptor agonist activities3. Different routes for the synthesis of MCP have been described, almost exclusively in the patent literatures. One of the problems in the synthesis of MCP is concern to the condensation step. According to the report by Clinton et al. condensation of methyl 4-amino-5-chloro-2-methoxybenzoate with an excess of N,N-diethylethylenediamine gives low yield of MCP4. Thus, other authors use a Lewis acid (SiCl4, GeCl4, SnCl4 etc) as catalyst 5 or activate the amino group of the amine (using phosphorous trichloride) for the condensation step.6-7

MATERIALS AND METHODS
General
Industrial grade of reagents and solvents were used without further purification. Double distilled water was used in the reaction. The 1H and 13C NMR were measured in CDCl3, DMSO or D2O using a Bruker Avance-300 MHz spectrometer. The chemical shifts are reported in a ppm relative to TMS. FT-IR spectra were recorded using a Perkin-Elmer RX1 Fourier transformation infrared spectrometer with KBr plates.

Synthesis of MCP
In a 1 liter, 2 necked round bottom flask equipped with mechanical stirrer, 65.157 g (0.56mol) N,N-diethylethylenediamine, 50 g (0.194 mole) methyl 4-(N-acetyl amino)-5-chloro-2-methoxybenzoate, 6 mL acetic acid, and 57mL isopropanol was heated under stirring at 60-65 °C for 4h. Then, 270mL water and 27g NaOH was added and the mixture was stead distilled to remove excess amine. Next the mixture was cooled to room temperature and the precipitate was filtered and washed with water to give crude MCP (55.9g), m.p. 148.6, in a yield of 96%. Spectroscopic data: IR (KBr) υ(cm⁻¹) 3401, 3323, 3221, 1973, 1653, 1632, 1589, 1536, 1293, 1248, 1051, 994, 820; 1H NMR (300 MHz, CDCl3) δ (ppm) 8.24 (1H, br, -NH), 8.12 (1H, s), 6.29 (1H, s), 4.30 (2H, br), 3.89 (3H, s), 3.52 (2H, m), 2.56-2.67 (6H, m), 1.06 (6H, t, J = 7.2 Hz); 13C NMR (75 MHz, CDCl3) δ (ppm) 164.3, 157.5, 146.6, 132.8, 112.6, 111.2, 97.8, 55.8, 51.4, 46.6, 37.4, 12.0.

Synthesis of MCP, HCl
54.6 g of MCP was dissolved in 820 mL methanol, 13.5 mL H2O and treated with activated charcoal. The filtrated was cooled to room temperature and hydrochloric acid was added (pH 5.5-5.9). Then 150 mL acetone was added and the mixture was cooled to 0 °C. The precipitate was filtered and washed with acetone to give MCP.HCl (52.98g), m.p. 157.5-164.3 °C, 96% yield.

Scheme 1: The reaction route for the preparation of MCP, HCl
monohydrate of MCP hydrochloride (60.14 g), m.p. 183.2, in a yield of 93%. Spectroscopic data: IR (KBr) \( \nu(\text{cm}^{-1}) \): 3396, 3308, 3196, 2942, 2637, 1632, 1597, 1539, 1501, 1322, 1268, 1001, 913, 837, 680; \( ^{1}H \) NMR (300 MHz, DMSO-\( d_6 \)) \( \delta\) (ppm): 10.68 (1H, br, -NH), 8.34 (1H, t, \( J=5.8\) Hz), 7.68 (1H, s), 6.49 (1H, s), 6.00 (2H, br, NH\(_2\)), 3.83 (3H, s), 3.61 (2H, m), 3.11 (6H, m), 1.21 (6H, t, \( J=7.2\) Hz); \( ^{13}C \) NMR (75 MHz, DMSO-\( d_6 \)) \( \delta\) (ppm): 164.3, 157.6, 148.8, 131.6, 109.6, 108.8, 97.3, 55.8, 49.9, 47.1, 34.4, 8.5.

The synthesized MCP and MCP.HCl pass the tests mentioned in the USP and BP pharmacopoeia.

RESULTS AND DISCUSSIONS

Pakula et al.\(^8\) have reported an efficient method for condensation of methyl 4-(N-acetyl amino)-5-chloro-2-methoxybenzoate \(1\) and N,N-diethylethylenediamine \(2\) with using acetic acid as catalyst and in 86% isolated yield (Scheme 1). So, finding a simple method with higher yield is interesting for industry. For this purpose we have focused on the condensation method reported by Pakula by varying the parameters such as solvent, amount of materials, reaction time and temperature. We have found that by using isopropanol as solvent for the condensation of \(1\) and \(2\), the reaction condition was improved and made it possible to obtain a high purity product in an excellent yield (96%). Also the reaction temperature was decrease to 60-65 °C compare to the previously reported works (95-100 °C) that is very desirable for industrial use and energy saving. Furthermore, the amount of excess amine was decrease that is attracting for industry because of atom economy.

After improving the condensation process, we have tried to improve the condition for the acidification of MCP to obtain the MCP hydrochloride. Usually, this transformation was carried out in an anhydrous medium by using of gaseous HCl. Pakula et al. have reported a simple procedure for this process by using hydrochloric acid in water containing acetone in 76 % yield. We have established that hydrochloride of MCP can be obtained in excellent yield (93%) when MCP base was treated with hydrochloric acid in methanol and then the precipitation of the products with acetone. Excellent yields and elimination of the use of anhydrous solvents and gaseous HCl are the advantages of this new process.

CONCLUSION

In conclusion, we have found that by using isopropanol as solvent for the condensation step, the reaction condition was improved and an excellent yield of MCP was obtained. Also, by using methanol containing acetone in the acidification step, excellent yield of MCP.HCl was obtained in simple route that made it more economic.

AKNOWLEDGEMENT

We thank the faculties of Tarbiat Moallem University for financial support. We also thank to Behdasht Kar and Emad Darman Pars Drug Company for financial support. Many thank to Azad University of Saveh for supporting this project.

REFERENCES