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An Efficient Straightforward Synthesis of Antidepressant Drug Moclobemide

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Asian Pub. Corp.

www.asianpubs.org

Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 2 Month: April–June
pp: 174–178
DOI: https://doi.org/10.14233/ajomc.2020.AJOMC-P268

Received: 26 April 2020
Accepted: 27 June 2020
Published: 2 July 2020

ABSTRACT

Efferent, new and simple synthesis for antidepressant drug moclobemide has been developed *via* two liner steps. Initially, morpholine was treated with 60% aqueous solution of 2-bromoethylamine hydrochloride under solvent and catalyst free condition leads to a key intermediate *N*-(2-aminoethyl)morpholine, which subsequently treated with *p*-chlorobenzoic acid in presence of commercially available solid catalysts, afforded moclobemide with good yield. Mild reaction conditions, short reaction time, easy workup, cost-effective, environment friendliness and high yields are attractive advantages of the present method, so our synthetic strategy was applicable to large scale manufacturing of moclobemide every conveniently.

KEYWORDS

N-(2-Aminoethyl)morpholine, Moclobemide, *N*-Alkylation, Direct amidation.

INTRODUCTION

Depression is a common but serious mood disorder. It causes several symptoms that affect how you feel, think and handle daily activity [1]. Biological differences, brain chemistry, hormones, inherited traits, are the major causes of depression. Obesity, pain, family conflicts, work problem, social isolation, and death are complications of depression [2,3]. Moclobemide is an antidepressant drug first marketed by Roche under trade names Manerix, Depnil, Aurorix, Clobemix, Moclamine, *etc*. [4-6]. It was first synthesized in the year 1972 as part of an effort to identify lipid-lower agents, later found to be effective as a monoamine oxidase inhibitor (MAOI). Moclobemide is a drug used to treat depression and social phobia [7-9].

When moclobemide is combined with pressor amine drugs or tyramine containing foods no significant rise in blood pressure occurs unlike with the old nonselective and irreversible monoamine oxidase inhibitors (MAOIs), which cause a drastic rise in blood pressure with such combination [10]. Due to the deficiency of cardiovascular, cognitive, anticholinergic and psychomotor impairments, moclobemide is useful in the elderly as well as those with cardiovascular disease.

N-(2-Aminoethyl) morpholine is a useful key intermediate in moclobemide synthesis, the majority of synthetic routes started with this intermediate. In the year 1940, Mason and Malkiel [11] introduced a synthesis of 2-morpholinoethylamine by

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amination of *N*-(2-chloroethyl)morpholine with ammonium hydroxide. After 40 years, Hultquis and Northey [12] by cyclization of *bis*(β-chlorethyl ether) with ethylenediamine is reported. Al_2O_3 catalyzed reaction of morpholine with monoethanol amide at a high temperature of 310 ºC was described by Liu *et al.* [13]. Amination of *N*-(hydroxyethyl)morpholine by phthalimide process is also reported for its preparation. Reaction of morpholine with solid 2-chloroethyl amine HCl salt in a ratio 1:1 using a base such as K_2CO_3, NaOH in solvent water or toluene is described in the literature [14-16], but in these conditions yield is only about 40%. However, all these methods reported are associated with limitations such as the use of hazardous raw material, catalyst and organic solvent, which are not suitable for large scale production. *N*-(2-Chloroethyl)morpholine is also the key raw material for another antidepressant drug minaprine [17] and antiparkinsonian drug moxiraparin and some clinically used drugs [18] (Fig. 1). Currently, the market price for this intermediate is very high hence the development of cost-effective, mild, efficient, high yielding rapid synthetic procedure for preparation of *N*-(2-chloroethyl)morpholine is desirable.

Moclobemide containing amide bond, common techniques to generate amide bond involves the reaction of a carboxylic acid with amine or converting carboxylic acid to derivatives such as acid halide, ester, anhydride or amide reacting with an amine using activating agents, additives or catalyst. The direct condensation of carboxylic acid and amine is highly desirable due to the easy availability of these compounds and the relative cleanliness of such process where side product is only being water. Typically, water is removed under the reaction condition to drive the equilibrium towards amide formation. The development of a novel process, which serves green chemistry purpose by maximizing efficiency and minimizing waste is currently in demand. There are some prior art procedures available in the literature for the synthesis of moclobemide. One of the most practical and widely used methods in industrial involve the reaction of *p*-chlorobenzoyl chloride with *N*-(2-aminoethyl)-morpholine strong basic solvents like triethylamine and pyridine [19]. $ZrCp_2Cl_2$ catalyzed amidation of *N*-(2-aminoethyl)morpholine with *p*-chlorobenzoic acid was reported by Allen *et al.* [20], however, $ZrCp_2Cl_2$ catalyst is expensive and the process requires 24 h for completion. In another procedure, where *p*-chlorobenzaldehyde was reacted with and *N*-(2-chloroethyl)-morpholine using catalyst $NiCl_2$ at 155 ºC [21]. Transamidation of *p*-chlorobenzamide with *N*-(2-aminoethyl)morpholine with catalyst Nb_2O_5 at 160 ºC is also reported [22]. Iron-catalyzed reaction of *p*-chlorobenzyl chloride with 2-chloroethylamine HCl followed by morpholine to form moclobemide has been reported [23]. The gas-phase reaction of carbon monoxide with *N*-(2-aminoethyl)morpholine and 1,4-dihalobenzene was also reported [24-26].

An extensive literature search reveals that these reported methods have some synthetic advantages individually, but still suffer from one or more disadvantages, such as (i) long reaction times, (ii) additional step required for the preparation of acid chloride and there is a stability issue with several of them, (iii) preparation of acid chloride involve use of hazardous reagents like thionyl chloride, oxalyl chloride in anhydrous conditions, which liberates corrosive by-products; (iv) toxic or expensive catalysts (v) harsh reaction conditions like high temperature; (vi) use of industrially undesired solvents (vii) tedious workup and most importantly unsatisfactory yields, all methods are reported on micro-scale. These directly impact the environment and economics on the industrial scale.

To circumvent such issues, there is a strong need to develop an ideal process for moclobemide with which is safe, economic and suitable for industrial production and meets the quality specifications. Retro-synthesis analysis of moclobemide, possible fragments are shown in Fig. 2. As per the retro-synthetic pathway, synthesis of moclobemide involves majorly two reactions *N*-alkylation of morpholine and carboxamide formation.

Based on the literature search and retrosynthetic analysis, a two-step commercially viable chemical protocol was designed and developed, which involves the synthesis of key intermediate *N*-(2-aminoethyl)morpholine followed by its direct catalytic amidation with *p*-chlorobenzoic acid to yield moclobemide.

EXPERIMENTAL

All chemicals and reagents, solvents were purchased from the commercial suppliers and used without further purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography

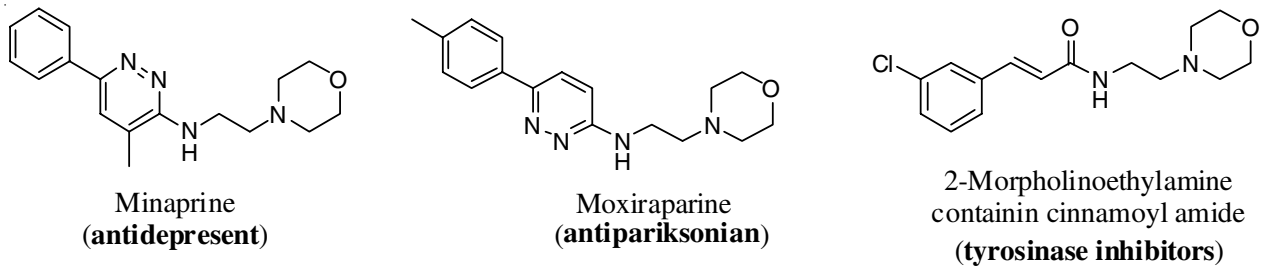


Fig. 1. Drug containing *N*-(2-aminoethyl)morpholine skeleton

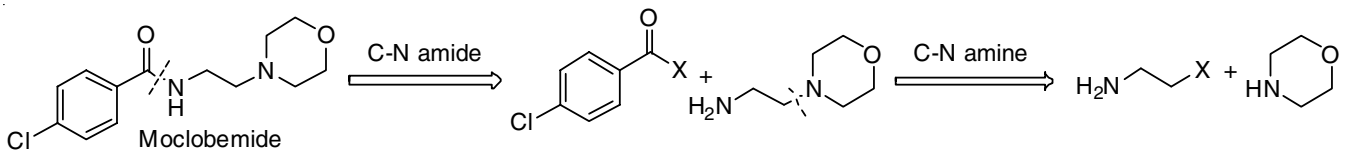


Fig. 2. Retro-synthetic analysis of moclobemide

(TLC) on Merck silica gel GF_{254} plates. Melting points of all the compounds were recorded by Analab ThermoCal melting point apparatus in the open capillary tube and are uncorrected. ^{1}H NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 or $CDCl_3$ as a solvent. The FTIR spectra (KBr) were recorded on Shimadzu FTIR Affinity-1 Fourier Transform Infrared spectrophotometer. Gas chromatography recorded on MICRO-9100, Netal (India) Make with FID detector, on Agilent CP-Sil8 CB method was set as initial temperature 100 ºC held for 5 min followed by the ramp at 20 ºC/min till 250 ºC and held for 15 min with injection port at 280 ºC and FID at 290 ºC. An injection volume of 2 µL was injected manually.

Synthesis of *N*-(2-aminoethyl)morpholine: To a stirring solution of 1,4-oxazinane (100 g, 1.16 mol), added 2-bromoethylamine·HBr (131 g, 0.387 mol) slowly by maintaining the temperature below 90 ºC in 1 to 2 h and the progress of the reaction was monitored by gas chromatography. After 6-8 h, the reaction mixture was cooled to room temperature and added 48% NaOH solution under stirring. Solid NaCl predicated was filtered under vacuum. The liquor containing water, morpholine and *N*-(2-aminoethyl)morpholine then distilled through 600 × 50 mm paced column. Initially, water is collected followed by 1,4-oxazinane was collected atmospherically at 120-130 ºC and finally 45 g (90% of theoretical) *N*-(2-aminoethyl)morpholine was distilled out at 130-150 ºC/50-80 mmHg as water white liquid (**Scheme-I**). Density: 0.990 g/mL at 25 ºC, b.p. 204 ºC (768 mm). IR (KBr, ν_{max}, cm^{-1}): 3272, 2970, 1634, 1541, 1513, 1237, 1089, 722. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86-3.56 (m, 4H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.44 (dd, *J* = 11.9, 5.6 Hz, 6H), 1.73 (s, 2H). Purity by GC: 99.04%.

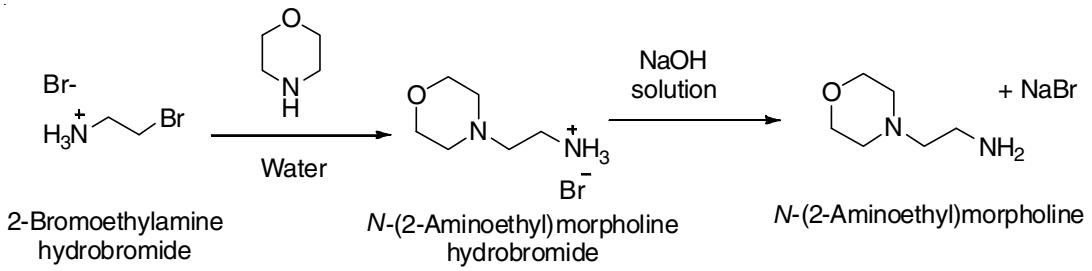
Synthesis of moclobemide: In 1 L reaction flask equipped with agitator, dean stark and reflux condenser, added 300 mL toluene, 2-morpholinoethylamine (45 g, 0.346 mol) and 4-chlorobenzoic acid (59.48 g, 0.380 mol) followed by boric acid catalyst (4.2 g, 20 mol %). The mixture heated up to 110 ºC and maintained for 20 h, progress of reaction was monitored by TLC using ethyl acetate:hexane (30:70). After complete water removal, solvent was removed under reduced pressure and the mixture was slowly cooled down to room temperature and added 400 mL acetone. The mixture was stirred for 30 min and then undissolved catalyst was removed by filtrating, while 70% of acetone was removed by distillation and the remaining solution cooled to 0 to 5 ºC stirred for 1 h and finally the product precipitated out. The solid was filtered, rinsed with little cold methanol to afford target compound moclobemide (70 g, 75 %) as white crystalline solid (**Scheme-II**). m.p.: 137 ºC (lit. 138 ºC). IR: (KBr, ν_{max}, cm^{-1}): 3272, 2970, 1634, 1541, 1513, 1237, 1089, 722. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.80 (s, 1H), 3.80-3.63 (m, 4H), 3.54 (dd, *J* = 11.1, 5.6 Hz, 2H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.51 (d, *J* = 4.0 Hz, 4H).

RESULTS AND DISCUSSION

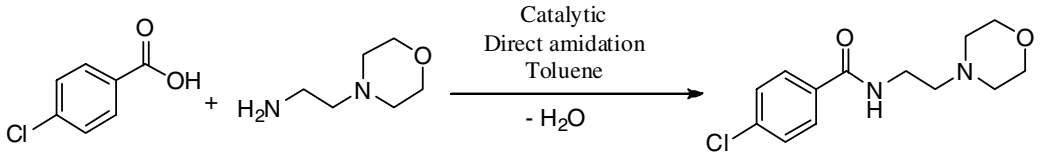
Accordingly, our priority was to optimize the process for the key intermediate *N*-(2-aminoethyl)morpholine. Initially, direct *N*-alkylation of morpholine with monoethanolamine was planned. Morpholine and monoethanolamine are refluxed neat or in toluene in presence of catalysts such as MnO_2, activated fuller's earth, but in all cases no or trace amount of product formation was observed as indicated by GC analysis even after 24 h of reflux condition. Due to costly catalyst and longer reaction time (48 h), it was decided to activate OH group of ethanolamine. Using an active derivative of monoethanolamine, 2-bromoethylamine·HBr as starting material was synthesized by the bromination of monoethanolamine [27].

Initially, we focused on a 1:1 mole ratio of morpholine to 2-bromoethylamine·HBr. We conducted the experiment in the absence of base, presence of strong base NaOH and toluene, alcoholic medium but in all cases marginally lower yield was observed. These results shown in Table-1, it is clearly observed that in the synthesis of *N*-(2-aminoethyl)morpholine, no role of solvent and base is effective. Morpholine it self acting as reactant as well as solvent and 2-bromoethylamine·HBr is highly reactive, no requirement of an additional base catalyst, thus better results were observed in absence of solvent and base (Table-2).

In the next stage, we examined the reaction by increasing the mole ratio of morpholine with respect to 2-bromoethylamine·HBr in absence of NaOH. When 2-bromoethylamine·HBr added to morpholine, an exothermic reaction up to 90 ºC was observed. Complete conversion of 2-bromoethylamine·HBr



Scheme-I: Synthesis of *N*-(2-aminoethyl)morpholine



Scheme-II: Synthesis of antidepressant drug moclobemide

TABLE-1
STUDY OF THE EFFECT OF TEMPERATURE AND BASE CATALYST AND SOLVENT

[a]Mole ratio	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1:1	Solvent free	–	90-95	2	35
1:1	Solvent free	NaOH	90-95	2	30
1:1	Methanol	NaOH	90-95	2	25
1:1	Toluene	NaOH	90-95	2	30

Reaction conditions: [a]Mole ratio of morpholine:2-bromoethylamine·HBr

TABLE-2
OPTIMIZATION OF THE MOLE RATIOS

Entry	[a]Mole ratio	Temp. (°C)	Time (h)	Yield (%)
1	1: 2	90-95	2	40
2	1: 2.5	90-95	2	60
3	1: 3	90-95	2	90
4	1: 4	90-95	2	90

Reaction conditions: [a]Mole ratio of morpholine:2-bromoroethylamine·HBr

practically requires minimum 3 equiv. moles of morpholine (Table-2).

Maximum yield up to 90% obtained with 3 or 4 equivalent moles of 1,4-oxazinane. No major difference yield observed when 4 equivalents morpholine was used. Hence for the synthesis of *N*-(2-aminoethyl)morpholine, the reaction condition with three equivalent moles of morpholine without any solvent and base was optimized for next study.

Based on the literature review, solid heterogeneous catalysts boric acid [28] was chosen for the direct amidation of *p*-chloro benzoic acid and *N*-(2-aminoethyl)morpholine to get moclobemide. The effect of solvent was ascertained by conducting a reaction of *p*-chlorobenzoic acid with *N*-(2-aminoethyl)morpholine in different organic solvents over catalyst boric acid. The organic solvents such as THF, ethyl acetate, 1,4-dioxane, toluene, DMF were examined, where toluene stood out as an excellent solvent for direct formation of amide. Moreover, toluene is industrially acceptable and Class-II organic solvent according to ICH guidelines is a beneficial advantage.

To establish the role of solvent and catalyst, initially neat reaction of *p*-chlorobenzoic acid with *N*-(2-aminoethyl)morpholine was conducted in the absence of solvent and catalyst, the reaction did not proceed even after 24 h of reflux. In the presence of toluene, an uncatalyzed reaction affords only 10% yield even after 24 h of reflux (Table-3, entries 1 and 2).The reaction was carried out in the presence of catalysts boric acid. The effect of catalyst loading on the reaction yield was ascertained. As catalyst loading increased, the yield of the product increased, thus revealed that catalyst boric acid works well for this reaction. Typically, in the presence of 15 mol% catalyst, the reaction proceeds smoothly to afford corresponding product amide in excellent yield (Table-3, entry 5).

TABLE-3
DIRECT AMIDATION OF *p*-CHLOROBENZOIC ACID WITH *N*-(2-AMINOETHYL) MORPHOLINE OVER A CATALYST BORIC ACID

Entry	Catalyst/solvent	Catalyst loading (mol%)	Time (h)	Yield (%)
1	None/solvent free	0	24	0
2	None/Toluene	0	24	10
3	Boric acid	5	20	50
4	Boric acid	10	20	70
5	Boric acid	15	20	75

Reaction condition: *p*-Chlorobenzoic acid (1.1 equiv.), *N*-(2-aminoethyl)morpholine (1 equiv.), reflux in toluene with azeotropic removal of water.

A plausible mechanism for boric acid catalyzed moclobemide synthesis is depicted in Fig. 3, where *p*-chlorobenzoic acid might have reacted with boric acid to form a mixed anhydride intermediate. This intermediate might have attacked by strong nucleophile *N*-(2-aminoethyl)morpholine to form moclobemide and regenerates the catalytically active boric acid [29,30].

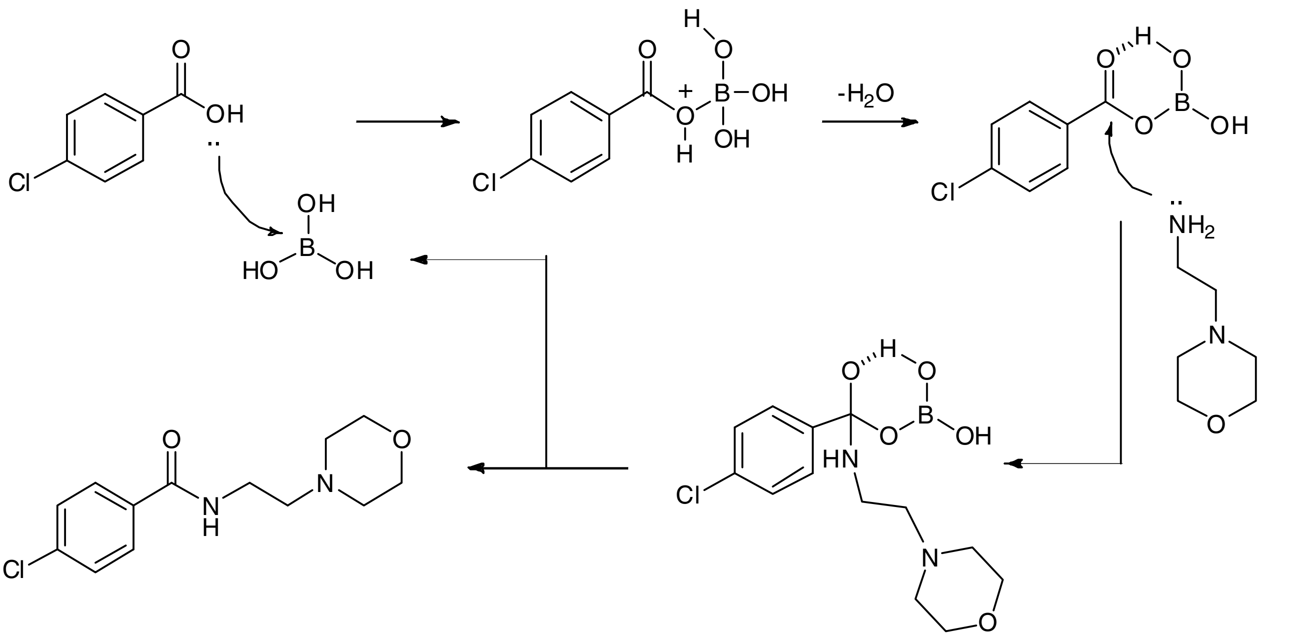


Fig. 3. Catalytic cycle for the boric acid catalyzed amidation reaction

Conclusion

A solvent-free, catalyst-free new protocol for the synthesis of intermediate *N*-(2-aminoethyl)morpholine using cheaper and easily available 60% aqueous solution of 2-bromoethylamine·HBr is reported. Synthesis of the anti-depressant drug moclobemide was achieved by direct amidation of *N*-(2-aminoethyl)morpholine with *p*-chlorobenzoic acid in presence of commercially available boric acid catalyst in short reaction period with excellent yield.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. G.U. Chaturbhuj, Department of Pharmaceutical Science and Technology, Institute of Chemical Technology, Mumbai, India for analytical supports.

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