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http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 4: (3), 2014, 331-334

FORMAL SYNTHESIS OF QUETIAPINE: AN ANTIPSYCHOTIC DRUG

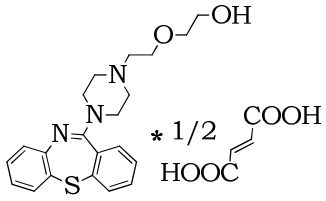
Venkata Ramana Kandula[a]*

[a] *Research and Development,Dr.Reddys Laboratories Ltd,Bollaram,Hyderabad,502325,India.*
E-mail: vrkandula416@gmail.com

ABSTRACT
Simple one pot synthetic pathway is described for Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one, a advanced intermediate in the synthesis of Quetiapine. The procedure starts from 2-(phenylthio) aniline and involves two simple insitu steps in one pot to give Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one in 80% overall yield with >99% purity.

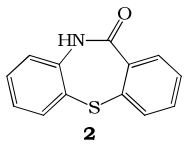
KEYWORDS: Dibenzothiazapine, onepot, Quetiapine, antipsychotic.

INTRODUCTION
Quetiapine hemifumarate (1)[i-ii] is chemically known as hemifumarate salt of 2-(2-(4-dibenzo [b,f] [1, 4] thiazepin-11-yl) piperazin-1-yl-ethoxy) ethanol which is marketed by AstraZeneca under the trade name 'seroquel'. Quetiapine is clinically effective for the treatment of Schizophrenia.



1

Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one which is a key intermediate for preparation of Quetiapine is represented by the Formula **2**.



2

From the literature precedents two formal approaches were reported, one is linear approach [iii-iv] and another one is convergent approach [v-vii], for the preparation of compound (**1**) from compound **(2)** as illustrated in Figure 1.

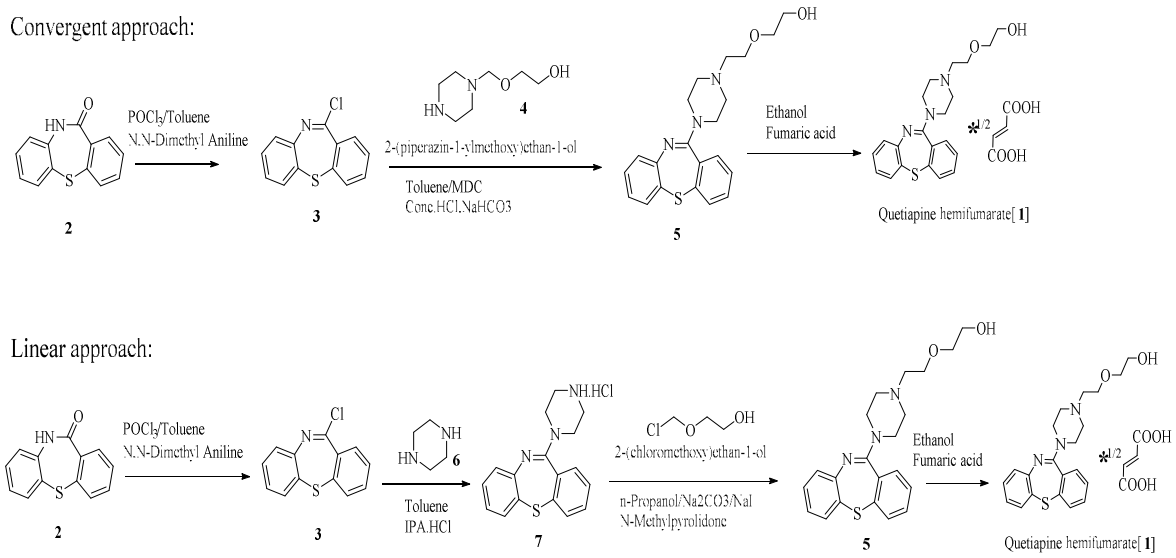


Figure 1: General synthetic routes to synthesis Quetiapine hemifumarate (I).

RESULTS AND DISCUSSION

A plethora of synthetic routes for the preparation of compound **2**.They were mainly starting from 2-aminobenzenethiol[viii-x],2-(phenylthio)aniline[xi-xii],Thiosalicycicacid[xiii-xv],2,2'-Dithiosalicylic acid[xvi] and 9H-thioxanthen-9-one[xvii].

The reported synthetic methods from literature for the synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (**2**) involve multistep synthesis with isolation of intermediates and repeated exchange of solvents. This is a disadvantage both from an ecological and economical point of view. Further, the reported schemes have various disadvantages such as low yield, use of high temperature and use of hazardous compounds. These disadvantages are unfavorable for the industrial scale synthesis. Thus there is an unmet need for an efficient method for synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (**2**). Herein, we report our efforts to develop an efficient synthesis to access compound **2** by utilizing one pot synthesis as illustrated in Figure 2 from commercially available 2-(phenylthio)aniline.

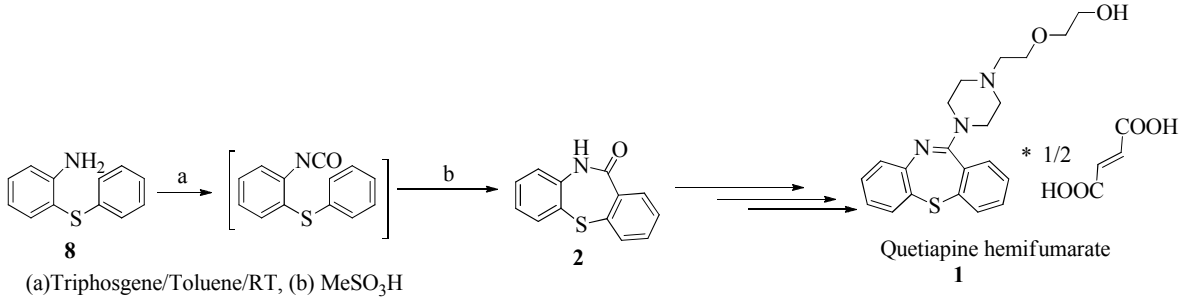


Figure 2: One pot synthetic route to synthesis Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (II) and formal syntheis of Quetiapine salt

The present synthesis provides simple one-pot process for the preparation of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one of the compound **2** which process overcomes the shortcomings of the prior art processes by reaction of 2-(phenylthio)aniline of Compound **8** with triphosgene

followed by cyclization in the presence of methanesulfonic acid, to afford compound of formula **2**.

CONCLUSIONS

In summary, a simple, atom economic and convenient one pot synthetic method has been developed for the preparation of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one utilizing easily accessible and inexpensive starting materials. This synthetic approach includes some important aspects such as high yields and mild reaction conditions, which make this synthetic protocol a useful and an attractive procedure for the industrial synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one thus producing block buster antipsychotic drug Quetiapine.

EXPERIMENTAL SECTION

General Methods

^{1}H NMR spectra were recorded on a 400-MHz Varian Gemini FT NMR spectrometer, and ^{13}C NMR spectra were recorded using a 200-MHz Varian Gemini FT NMR spectrometer. The chemical shifts are reported in ð ppm relative to TMS. The Fourier transform infra red (FT-IR) spectra were recorded using a Perkin-Elmer 16650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on a HP-5989A LC-MS spectrometer. The melting points were determined using the capillary method on a Polmon (model MP-96) melting-point apparatus and are uncorrected. The solvents and reagents were used without further purification.

Synthesis of Dibenzo [b, f] [1, 4] thiazepin-11[10H]-one (2)

In a round bottom flask, triphosgene (14.6 g,0.099 mol) was dissolved in toluene (100 mL) and the mixture was cooled to -10 to 0°C followed by slow addition of 2-(phenylthio)aniline(20 g, 0.049 mol) in toluene(200 mL) at the same temperature over a period of about 3 hours. On complete addition, the temperature of the reaction mass was raised to 20-30°C and mixture was maintained at the same temperature for about 4 hours, completion of the reaction was monitored by TLC. After completion of reaction, 10% aqueous solution of sodium bicarbonate (10 g in 100 mL of water) was added to reaction mass and stirred for 2 hours. The organic layer was separated and washed with water (60 mL) followed by separation and distillation of solvent from the organic layer under vacuum at below 65°C followed by addition of methanesulfonic acid (60 g) . The temperature of reaction mass was raised to 100-105°C and maintained at the same temperature for completion of reaction as monitored by TLC. The temperature of the reaction mass was lowered to 25-30°C followed by slow addition of pre-cooled water (180 mL) at the same temperature to precipitate the solid. The solid obtained was isolated by filtration and washing of solid with water (20 mL) followed by washing of solid with acetone (20 mL) and subsequent drying of solid at 55-60°C to afford the desired compound in 80%yield. Melting range: 259-260°C. MS (m/z): 228.2 (M+H). ^{1}H NMR (400MHz, $CDCl_3$) 7.1 (t, J = 7.5 Hz, 4H), 7.21(d, J = 7.8 Hz, 1H), 7.31-7.36 (m, 1H), 7.41-7.55 (m, 1H), 7-65-7.67 (m, 1H), 10.7 (br s, 1H). ^{13}C NMR (200MHz, $CDCl_3$), 122.2, 126.0, 128.3, 129.4, 130.2, 131.8, 131.9, 132.2, 133.0, 137.0, 137.2, 139.2, 169.4.

Acknowledgements

The authors thank the management of Dr. Reddy's Laboratories Ltd. for supporting this work.

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Received on April 14, 2014.