

## One Pot Synthesis of Dibenzo [b,f][1,4]Thiazepine-11-(10H)-One

A.V.G.S. Prasad<sup>\*1</sup>, L. Rameswara Reddy<sup>1</sup> and P.V.Rao<sup>2</sup>

<sup>1</sup>R& D Department, Chiral Biosciences Ltd., Hyderabad-506 001, A.P (India)

<sup>2</sup>Department of Chemistry, Nizam College (Autonomous) Hyderabad-506 001, A.P (India)

\*E-mail: sivaprasad@chiralbiosciences.com

Article History:  
Received: 20 May 2013  
Accepted: 8 June 2013

### ABSTRACT

Dibenzo[b,f][1,4]thiazepine-11-(10H)-one is the key intermediate in the synthesis of antipsychotic agent Quetiapine and hence an improved method for synthesizing will be highly desired. A process was developed for synthesis of 2-(phenyl thio)-phenyl carbamate (4) from 2-nitro diphenyl sulphide (1) *via.*, in a single step synthesis of 2-nitro diphenyl sulphide (1) with an aqueous solution of Fe powder and NH<sub>4</sub>Cl then followed by treated with phenyl chloroformate. The ambient conditions, excellent product yields, easy work up procedure and short reaction time make this synthetic strategy a better protocol for the synthesis of an intermediate (4) and dibenzo[b, f][1,4]-thiazepine-11-(10H)-one (5). The structures of all the compounds were confirmed by their IR, <sup>1</sup>H NMR and mass spectral analysis.

**Keywords:** Iron powder, Ammonium Chloride, Phenyl Chloroformate and Poly Phosphoric Acid.

©2013 ijCEPr. All rights reserved

### INTRODUCTION

Medium sized heterocycles, especially seven and eight membered ring compounds are receiving significant attention because of the existence of their structural units in some natural products [1]. In particular, fused dibenzo-[b,f][1,4]-thiazepines are used in antihistaminic[2], potential high ceiling diuretics[3]. Dibenzo-[b,f][1,4]-thiazepine is a class of antipsychotic drug, 11-[4-[2-(2-Hydroxyethoxy)ethyl]-1-piperziny]dibenzo[b,f][1,4]thiazepin (trade name Quetiapine), a typical antipsychotic drug that is practiced for the treatment of schizophrenia and bipolar disorders for many years[4].

Aromatic amines are important starting materials and intermediates for the manufacture of a variety of chemicals such as dyes, photographic materials, surfactants, polymers, pharmaceutical products, agricultural chemicals and as antioxidants.

The reduction of aromatic nitro compounds is one of the most common methods for preparing the corresponding aromatic amines. Recently, many novel reducing agents have been reported in the literature. The most commonly used reagents are zinc, iron, or tin, in the presence of an acid, catalytic hydrogenation using Ni, Pd/C, and PtO<sub>2</sub>. Other reagents include sodium hydrosulfite, Sm, In, hydriodic acid, RhCl<sub>3</sub>, Au/SiO<sub>2</sub>, N<sub>2</sub>H<sub>4</sub>/Fe<sub>2</sub>O<sub>3</sub>/MgO, NaBH<sub>4</sub>/Pt-Ni, NaBH<sub>4</sub>/BiCl<sub>3</sub> and Al/NH<sub>4</sub>Cl.

Raymond. et., al discloses a method for the preparation of 2-aminodiphenyl sulphides involving the steps of reacting o-chloronitrobenzene with thiophenol to form 2-nitrodiphenylsulphide; reducing the nitro group to form corresponding amino compound using raney nickel, hydrazine and charcoal[5].

Schmutz, J.discloses a method for the preparation of 2-aminodiphenyl sulphides involving the steps of reacting o-chloronitrobenzene with thiophenol to form 2-nitrodiphenylsulphide; reducing the nitro group to form corresponding amino compound using raney nickel[6].

A.F. Thomas, B. Willhalm discloses a method for the preparation of 2-aminodiphenyl sulphides involving the steps of reacting o-chloronitrobenzene with thiophenol to form 2-nitrodiphenylsulphide; reducing the nitro group to form corresponding amino compound using iron powder in glacial acetic acid and water at reflux and in 12 hours[7].

As per the process disclosed in US and EP patents, 2-nitrodiphenylsulphide is reduced with iron powder in HCl to form corresponding amino compound. The synthesis carried out according to procedures described above requires isolation and extensive purification of intermediates. Starting from o-chloronitrobenzene the total yield of the final product 11-(1-piperaziny) dibenzo [b, f] [1, 4] - thiazepine does not exceed 50%[8].

Each of the above methods has at least one of the following drawbacks:

1. Harsh reaction condition
2. Significant limitations based on safety and handling considerations,
3. Destroy many sensitive functional groups,
4. Expensive and/or moisture-sensitive reagents,
5. A high-pressure hydrogen reactor and

6. Non-chemoselectivity in reduction reaction.

In view of lack of process, which is avoiding all the shortcomings an alternative improved one pot process for the preparation of dibenzothiazepine derivative is highly desired.

**NH<sub>4</sub>Cl as the hydrogen donor**

Rahat H. Khan treated a wide range of aromatic nitro compounds with tellurium powder in aqueous methanolic ammonium chloride and resulted in selective reduction of the nitro groups. The reactions were typically completed within 2-5 h, and gave the corresponding aniline in good to excellent yield [9].

Takehito Tsukinoki and Hirohisa Tsuzuki demonstrated an environmental friendly method for the synthesis of anilines by the chemoselective reduction of nitroarenes with zinc metal and NH<sub>4</sub>Cl in water[10].

D. G. Desai et al and Yugang Liu et al also reported the reduction of nitroarenes with FeS-NH<sub>4</sub>Cl-CH<sub>3</sub>OH-H<sub>2</sub>O and Fe-NH<sub>4</sub>Cl system respectively, and had a satisfying yield[11,12].

Considering that iron powder is oxidized to FeCl<sub>2</sub> and FeCl<sub>3</sub> in the presence of HCl, we want to determine if the Halide (X) salt additives are merely promoting the formation of FeX<sub>2</sub> in the reaction mixture, with FeX<sub>2</sub> as the active reductant. We suggest that the halide salts are serving a similar function here, accelerating the transfer of iron into solution and renewing the available source of Fe (O).

Looking for “cleaner” alternatives to classical syntheses and in developing green chemistry and also in pursuing our new interest in developing inexpensive and non polluting reagents

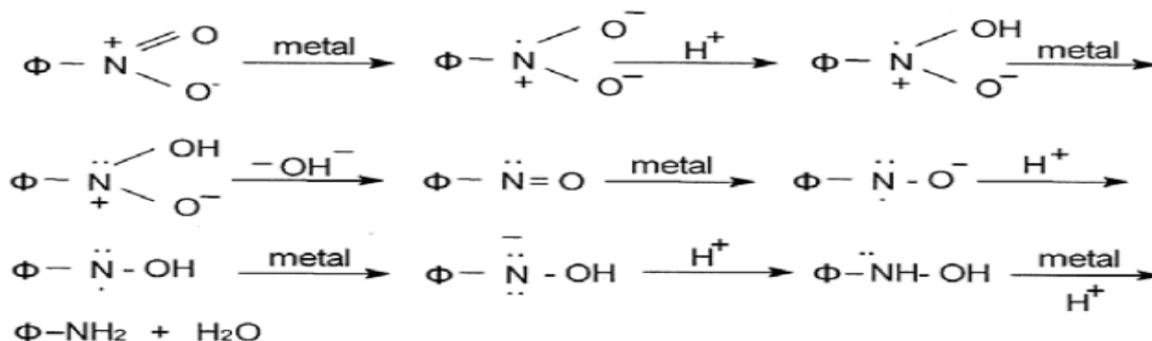
**Green Context**

In view of human health and environmental concerns, much attention is being paid to ‘Green Chemistry’, which is a chemical methodology to decrease or eliminate the use or generation of hazardous substances in the design, preparation and application of chemical production.

As per pharmacopeias and drug master file requirement, the impurity level limit is very stringent. This incomplete reaction gave a challenging task to obtain 100% conversion. Further purification, incurring heavy losses of the product is difficult due to the similar properties of the product and the starting material. Therefore, it seems desirable to develop a low cost effective, environmentally friendly high yield and commercially viable method.

We found NH<sub>4</sub>Cl, which has broader functional-group compatibility, to be suitable alternative to aqueous HCl. We elected to use iron as the reducing agent because it is cheap and readily available, and known to tolerate a variety of functionalities.

**Mechanism**



**MATERIALS AND METHODS**

Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 spectrometer using KBr pellets. <sup>1</sup>H NMR (300 MHz) spectra recorded in DMSO-*d*<sub>6</sub> on a Bruker AVANCE 300 instrument with the TMS as an internal standard. All the chemical shifts values were recorded as δ ppm. Mass spectra (EI-MS) were taken on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV. CHN analysis was carried out on Carlo Erba E A 1108 automatic analyzer. The progress of each reaction was monitored and purity of the compounds was checked by thin layer chromatography.

**Synthesis of (2-nitrophenyl) phenyl sulfide (2)**

To thiophenol (150g) and NaOH (60g) in isopropyl alcohol (500 m L) was added slowly 1-chloro-2-nitro benzene (1) (250 g) and the solution was refluxed for 6 h (monitored by TLC). After the completion of reaction, the reaction

mixture was cooled and added water (1000 mL) than, the compound was extracted with toluene and evaporated under vacuum to obtained the compound (2). Yield: 294 - 296 g.

#### Synthesis of phenyl-2-(phenylthio)-phenylcarbamate (4)

To aqueous solution of iron powder (300 g) and ammonium chloride (40g) added slowly a solution of compound (2) in water. The reaction mixture was refluxed at 85-95 °C for 3-4 hrs (monitored by TLC). After completion of reaction, the mixture was cooled to room temperature, filtered to remove metal catalyst and the compound 3 was extracted with toluene (3x 150 mL).Yield: 282-284 g.

To this, phenyl chloroformate (270 mL) in toluene was added over a period of 30-40 min at 50-55°C and stirred for 15-20 min, then added a solution of sodium carbonate at 50-55°C than, the reaction mixture was heated at 60-65°C for 2 h (monitored by TLC). After cooling to room temperature, the toluene layer was collected and dried over anhydrous sodium sulphate, evaporated under reduced pressure to get crude, phenyl-2-phenyl thiophenylcarbamate (4) which can be subjected to cyclization without purification. Yield: 365-385 g.

#### Synthesis of dibenzo [b, f][1,4] thiazepine-11(10H)-one (5)

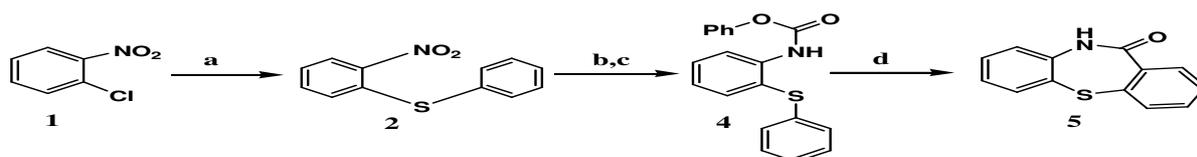
Compound (4) was added slowly to a solution of polyphosphoric acid (1520g) at 65°C with stirring. The reaction was heated to 100°-105°C for 6-8 h. The reaction mixture was cooled to about 80 °C, than added ice cold water slowly. After cooling to ambient temperature the product was filtered off as an off-white solid, washed sparingly with acetone and dried.

Yield: 99 %; m. p: 265-266 °C, purity: 99.9% (HPLC); <sup>1</sup>HNMR (DMSO-d<sub>6</sub> 300 MHz):7.02-7.8 (m, 8H, Ar-H), 10.5 (s, 1H, -NH); Mass (m/z): 227.9(M+1) Anal. Calcd for C<sub>13</sub>H<sub>9</sub>NOS: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.68; H, 3.92; N, 6.12.

### RESULTS AND DISCUSSION

In continuation of our progressive investigation, there is growing interest in synthetic reactions in environmentally friendly water. We are strongly interested in the development of the chemo selective reduction of nitro groups using a cheap reagent with easy operation in water without any organic solvent, a methodology which would have some advantages in terms of cost, safety, simple operation, human health and environmental concerns as compared with use of an organic solvent. Here, we wish to report that in water without any organic solvent, aromatic amines can be obtained in high yields by an operationally easy chemo selective reduction of aromatic nitro compounds. We found NH<sub>4</sub>Cl, which has broader functional-group compatibility, to be suitable alternative to aqueous HCl. We selected to use iron as the reducing agent because it is cheap and readily available, and known to tolerate a variety of functionalities.

The structure of all the synthesized compounds was confirmed by their <sup>1</sup>H NMR, Mass and elemental analysis data. The physical data of the synthesized compounds were given in experimental section.



Scheme-1 : (a) Thiophenol, NaOH in IPA (b) Fe powder + NH<sub>4</sub>Cl in water; (c) PhOCOCl / Na<sub>2</sub>CO<sub>3</sub> solution in TL (d) PPA

Table-1: Purity levels of dibenzo - [b, f] (1, 4)-thiazepine-11-(10H)-one

Exp. No	Iron with HCl before purification (%)	Iron with HCl after purification (%)	Iron with NH <sub>4</sub> Cl before purification (%)	Iron with NH <sub>4</sub> Cl after purification (%)
1	97.70	99.50	99.30	Not required
2	95.90	99.74	99.90	Not required
3	96.80	99.80	98.80	Not required

4	97.50	99.90	99.80	Not required
5	96.80	99.60	99.50	Not required

- Reduction with Iron with HCl requires isolation of Dibenzo [b,f][1,4]Thiazepine-1 l-(10H)-One and extensive purification with acetone and Poly phosphoric acid ( PPA ).
- Reduction with Iron with NH<sub>4</sub>Cl requires only isolation of Dibenzo [b,f][1,4]Thiazepine-1 l-(10H)-One with high purity of above 99.0% .
- Reduction in number of operations and time ( repurification ), higher total yield, lower consumption of solvents, reduction of waste material quantity; All these advantages result in considerable reduction of manufacturing costs and highlight the favor Philosophy of ‘Green Chemistry’..

## CONCLUSIONS

In conclusion, we have demonstrated an environmentally friendly method for the synthesis of anilines by the chemoselective reduction of nitroarenes with iron metal with ammonium chloride as additive in water.

We also reduced the number of steps, time, and lower consumption of solvents and also reduced waste material quantity. All these advantages result in considerable the reduction of manufacturing cost.

Also the authors wish to reported that the reduction reaction with Fe/ NH<sub>4</sub>Cl is a mild compared to iron-acid reduction, can be done in stain less steel vessel and also scale up to 100 kg batches. This offers great advantages in industrial scale preparations.

## REFERENCES

1. (a.)Geronikaki A. A., Dearden J. C., Filimonov D., Galaeva I., Garibova T. L., Glorizova T., Krajneva V., Lagunin A., Macaev F. Z., Molodavkin G., Poroikov V. V., Pogrebnoi S. I., Shepeli F., Voronina T. A., Tsitlakidou M., Vlad L., J. Med. Chem., **47**(2004) 2870; (b.) Cutignano A., Tramice A., De Caro S., Villani G., Cimino G., Fontana A., Angew. Chem., Int. Ed, **42** (2003), 2633; (c.) Renneberg D., Dervan P. B., J. Am. Chem. Soc., **125** (2003) 5707.
2. Horrom B. W., Minard F. N., Zaugg H.E., U S Appl, **4** (1978) 097,597.
3. Richard C.A. , Philip A. R. and Hansjorg U., J.Med.Chem, **21**(1978)838
4. The Merck Index 13<sup>th</sup> Edn. P. 1439.
5. Raymond. et. al, Journal of Organic Chemistry, **21** (1956)138
6. Schmutz, J., Helv. Chim. Acta, **48**(1965)336
7. Thomas A.F., Willhalm B., Tetrahedron Letters, **21** (1965) 1309
8. US 3,050, 524/1962 as well as EP 1660469/2007
9. Rahat H. Khan, J. Chem. Research (S) (2000)290
10. Takehito Tsukinoki and Hirohisa Tsuzuki., Green Chemistry,**3** (2001)37.
11. Desai D. G. et al ., Synthetic Communications,**31**(8) (2001) 1249
12. Yugang Liu et al., Adv. Synth. Catal.,**347** (2005)217

[ijCEPr-264/2013]

Adopt **GREEN CHEMISTRY**  
Save Our Planet.  
We publish papers of Green Chemistry on priority.

If you think that you may be a potential reviewer in field of your interest, write us at [rasayanjournal@gmail.com](mailto:rasayanjournal@gmail.com) with your detailed resume and recent color photograph.