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An Improved Profess For Synthesis Of Dibenzo-[B,F][1,4]-Thiazepine-11-(10H)-One

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Abstract: 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_4Cl than 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, ^{1}H NMR and mass spectral analysis.

Key words: Iron powder, phenyl cloroformate, thiazepine and poly phosphoric acid.

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-piperzinyl]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]. As Horrom *et al.* disclosed that dibenzothiazeoine derivatives were useful for the antischizophrenics and also being useful for variety of medical application including as neuroleptic, antidepressant[2, 5]. Recently these drugs have been used to treat delirium and agitation[6]. The compound used as antipsychotic and neuroleptics have, however been plagued by the problems of undesired side effects, such as acute dyskinesias, acute dystopias, pseudo-parkinsonism and tardive dyskinesias [7]. Thus there still remains a need for compounds which exhibit antidopaminergic activity and pharmaceutical activity to overcome such undesired side effect. The synthesis of new derivatives possessing antibacterial activity has considerable attention owing to the continue increase in bacterial resistance. It has been reported that benzothiazepine and substituted benzothiazepine-2-one exhibited the strong antibacterial activity.[8, 9]. An improved process for preparing 11-chloro dibenzo-(*b, f*) (1, 5)-thiazepine has been reported by Joseph P.K. and et.al[10] G. Walther *et. al* [11] reported the synthesis of 4-substituted guanidine derivatives of dibenzo (*b, f*) (1, 5) oxazepines and dibenzo (*b, f*) (1,5) thiazepines which possess H_1-antihistaminic properties. Reduction of nitroarenes leading to aromatic amines is an important key step in the industrial syntheses of dyes, medicinal supplies and agricultural chemicals. Therefore, a variety of methods for the reduction of nitro groups have been developed. However, these reactions require an expensive and/or a moisture-sensitive reagent and an organic solvent, and for catalytic

hydrogenation, it is necessary to pressurize the reactor with hydrogen gas. In these methods, there is little consideration given to the environment, cost, safety, or simplicity of operation.

On the other hand, recently, 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.

Experimental:

Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on Schimadzu FTIR-8400 spectrometer using KBr pellets. ^{1}H NMR (300 MHz) spectra recorded in DMSO-d_6 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 sulfane (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 ^{0} 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^o C and stirred for 15-20 min, then added a solution of sodium carbonate at 50-55^{o}C than, the reaction mixture was heated at 60-65^o 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^{o}c with stirring. The reaction was heated to 100^o-105^{o}c for 6-8 h. The reaction mixture was cooled to about 80 ^{0} 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 ^{0}C, purity: 99.9% (HPLC); ^{1}HNMR (DMSO-d_6 300 MHz):7.02-7.8 (m, 8H, Ar-H), 10.5 (s, 1H, -NH); Mass (m/z): 227.9(M+1) Anal. Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.68; H, 3.92; N, 6.12.

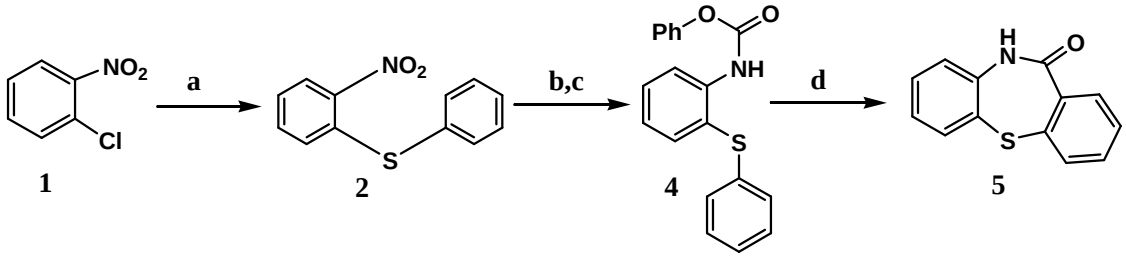
Results and discussion:

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_4Cl, 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.

We reported an improved and environmentally friendly process for synthesis of dibenzo [b, f] (1, 4) thiazepine-11-(10H)-one. Compound **1** was treated with thiophenol **2** in the presence of NaOH, in isopropyl alcohol as solvent to obtained compound **3**. The compound **3** was reduced with a mixture of iron powder, and ammonium chloride in aqueous solution at reflux condition to obtained the respective amine **3** which was converted to their corresponding 2-(phenylthio) phenyl carbamate with phenyl chloroformate than followed by cyclization with poly phosphoric acid. Here, we modified the process for first time to synthesis of 2-(phenyl thio)-phenyl carbamate **4** from 2-nitro diphenyl sulphide **1** in a single step to reduce the reaction time, purification process. According to this process, 99% of compound **4** was found after 6-7 h from a reaction of 2-nitro diphenyl sulphide **1** with a mixture of an aqueous solution of Iron powder, ammonium chloride, than followed by reaction with phenyl chloroformate with out purification. (Purity levels given in Table-1) Scheme1. Also the authors wish to reported that the reduction reaction with Fe/ NH_4Cl 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.

The structure of all the synthesized compounds was confirmed by their ^1H 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_4Cl in water; **c)** Ph0C0Cl / Na_2CO_3 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_4Cl before purification (%)	Iron with NH_4Cl 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

Conclusion:

In conclusion, we have demonstrated an environmentally friendly method for the synthesis of 2-(phenyl thio)-phenyl carbamate by the chemo selective reduction of nitro compound with iron metal with ammonium chloride as additive in water with good yields. We also reduced the number of reactions, time, and lower consumption of solvents and also reduced waste material quantity. All these advantages of result in considerable the reduction of manufacturing cost.

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