Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(4):318-326

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Novel synthetic methodology for the synthesis of dibenzo azepines

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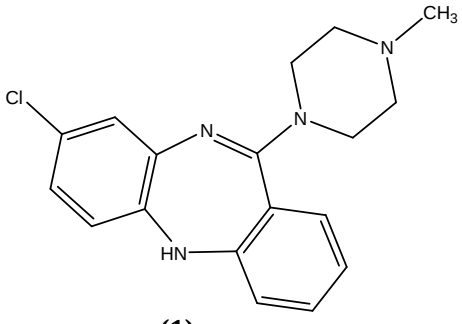
ABSTRACT

New synthetic methodology for the synthesis of dibenzo[b,e][1,4]diazepines, a key intermediates in the manufacturing of Clozapine which is indicated for use in therapy as dopamine receptor antagonist, Antipsychotic drug [1]. Synthesis of 2-(4-chloro-2-nitrophenylamino) benzoic acid methyl ester by simple rearrangement of2-[[2-(4-chloro-2-nitrophenoxy)acetyl]amino]benzoic acid methyl ester. The present work describes a novel, cost-effective and easily scalable process of dibenzo[b,e][1,4]diazepines.

Key words: Clozapine, Dopamine receptor antagonist, dibenzo[b,e][1,4]diazepines.

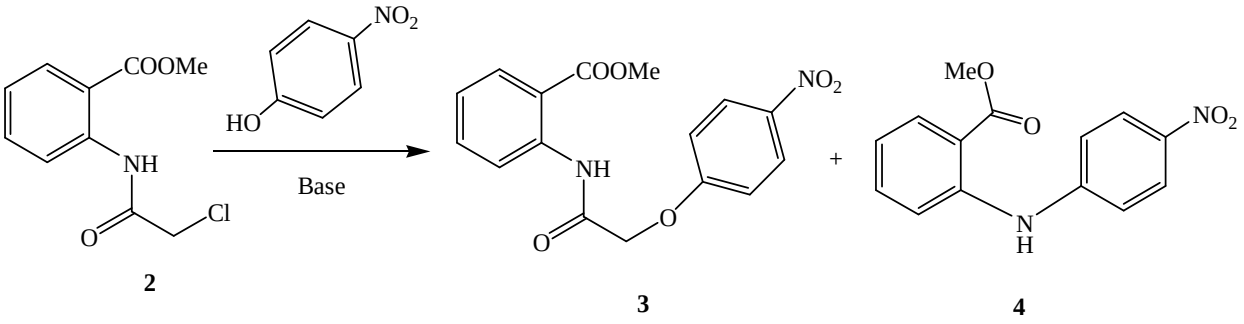
INTRODUCTION

Clozapine (**1**), is an antipsychotic drug mainly used for schizophrenia that does not improve by using of other antipsychotic medications. Clozapine was discovered in the 1960s and began being used in healthcare in 1971. It was the first atypical antipsychotic[1].It is on the World Health Organization's List of Essential Medicines, the most important medication needed in a basic health system. Clozapine was developed by Sandoz in 1961, and trials took place in 1972 and it was released in Switzerland and Austria. Early testing was performed in the United States around the same time[2].In 1975, clinical studies demonstrated that Clozapine was more effective against treatment-resistant schizophrenia thanother antipsychotics, the FDA and health authorities in most other countries approved its use only for treatment-resistant schizophrenia, and required Restricted Distribution. In December 2002, Clozapine was approved in the US for reducing the risk of suicide in schizophrenic or schizoaffective patients judged to be at chronic risk for suicidal behaviour.



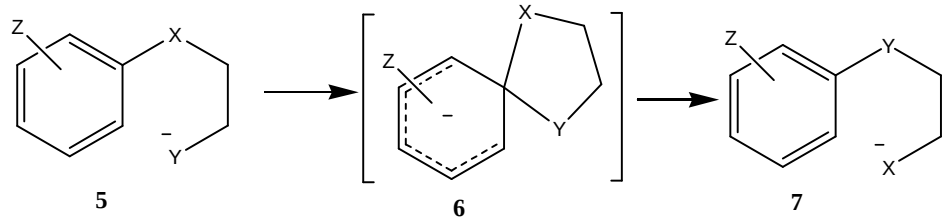
(1)

During ourresearch study of reaction between N-2-chloroacetyl methyl anthranilate**2**and nitrophenol, accidently it was observed that the expected product**3**was contaminated withone major unknown impurity, this impurity was isolated and characterized,and it was surprise to know that the isolated impurity was compound **4**.



2 **3** **4**

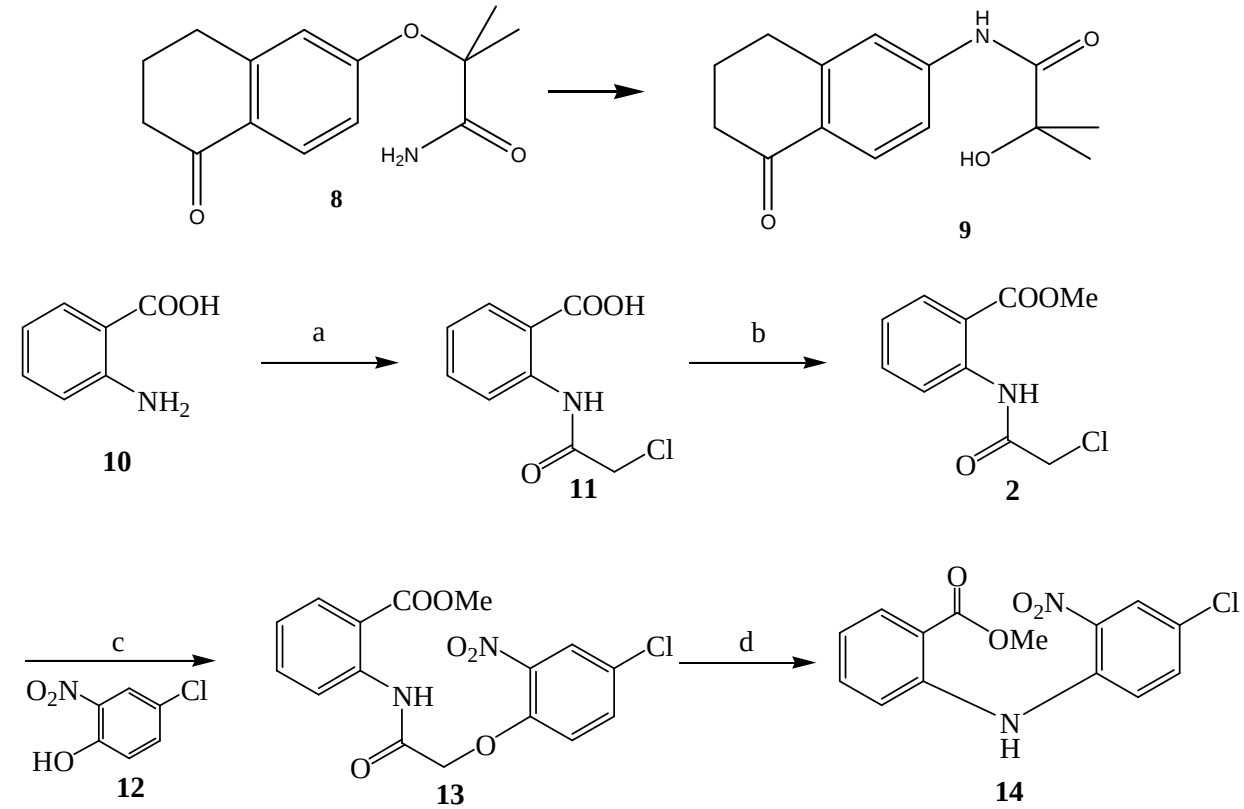
During the investigation for the formation of this impurity, in the literature we came across the well-known Smile rearrangement [3]which states the rearrangement reaction takes places in certain condition with the mechanism as shown below.



5 **6** **7**

T.N. Gerasimova demonstrated the reactions of polyfluoroaromatic compounds and smiles rearrangement of partly fluorinated o-aminodiaryl ethers [4].

Masahirao Mizuno et.al [5]also did the similar work where 2-methyl-2-[(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]propanamide **8** was rearranged to 2-hydroxy-2-methyl-N-(5-oxo-5,6,7,8-tetrahydro-2-naphthalenyl)propanamide **9.**



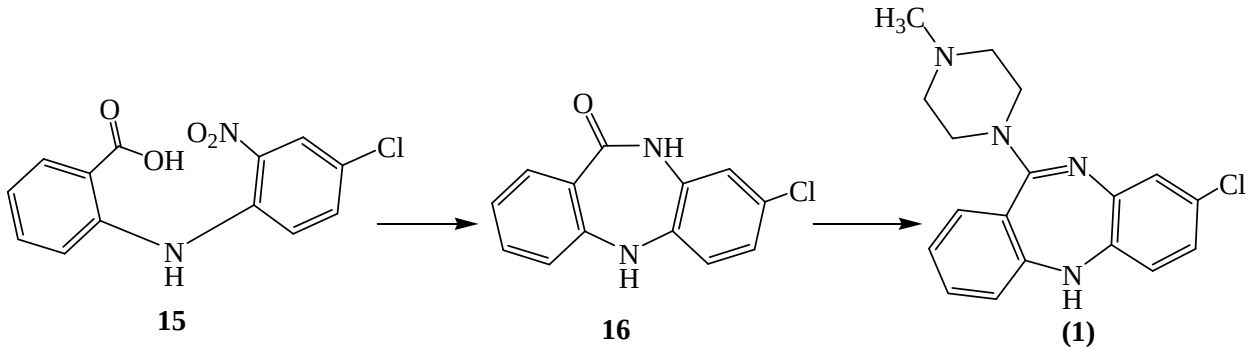
8 **9** **10** **11** **2** **12** **13** **14**

Scheme-1. Reagents and conditions:(a) Water, $NaHCO_3$, Chloroacetylchloride, 25-30°C; (b)Acetone, Dimethylsulphate, K_2CO_3, Hexanes, 35-40°C; (c) 4-Chloro-2-nitrophenol, DMF, K_2CO_3, 60-65°C; (d) Methanol, NaOMe, EtOAc 40-45°C;

In resemblance to the above examples,it indicates that the compound **3**was rearranged to compound **4** in alkaline medium. This kind of rearrangement is equivalent to Smile rearrangement.

To prove the above rearrangement following Scheme-1 was taken for the study. Anthranilic acid **10** was treated with chloroacetyl chloride to get N-chloroacetyl compound **11,**this N-chloroacetyl anthranilate**11**was esterified with Dimethyl sulphte (DMS) to get methyl ester compound **2**. This methyl ester compound was condensed with 4-chloro-2-nitrophenol **12** to get 2-[[2-(4-chloro-2-nitrophenoxy)acetyl]amino]benzoic acid methyl ester **13**. This compound **13** was rearranged in the presence of base to give product **14**.

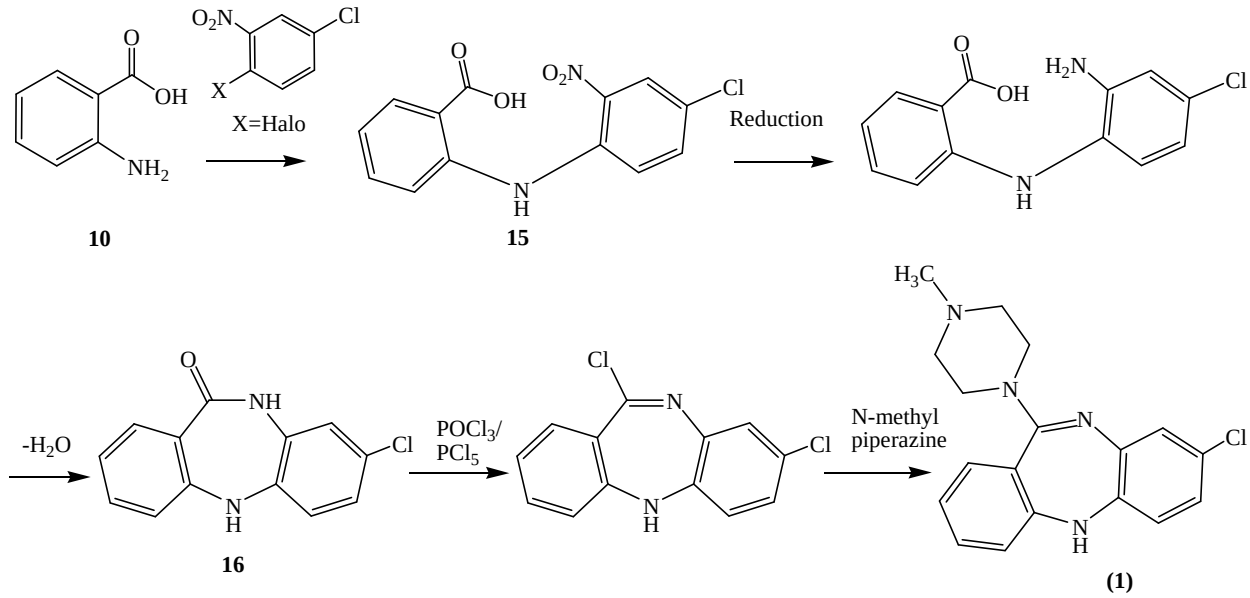
To find out the effective purpose and usage of this invention in the chemical or Pharmaceutical industry, further literature was collected and found out that this chemical reaction is of great importance in the synthesis of dibenzo[b,e][1,4]diazepines.Clozapine (**1**) is an Active Pharmaceutical intermediate (API) of this dibenzo-diazepine class.Main intermediateof Clozapine is 8-chloro-5,10-dihydro-dibenzo[b,e][1,4]diazepine-11-one i.e. compound **16**,This compound is synthesized from2-(4-chloro-2-nitrophenylamino)benzoic acid i.e. compound **15**and hence this compound **15** is an important key intermediate of Clozapine. As per the reported literature Leyva-Perez, Antonio et al [6]& Binaschi, Monica et al[7],compound **15** is reduced and cyclized to get compound **16** which was then converted to chloro-imine with chlorinating agent like $POCl_3$ or PCl_5 and then condensed with N-methylpiperazine to get Clozapine as depicted in the Scheme-2.



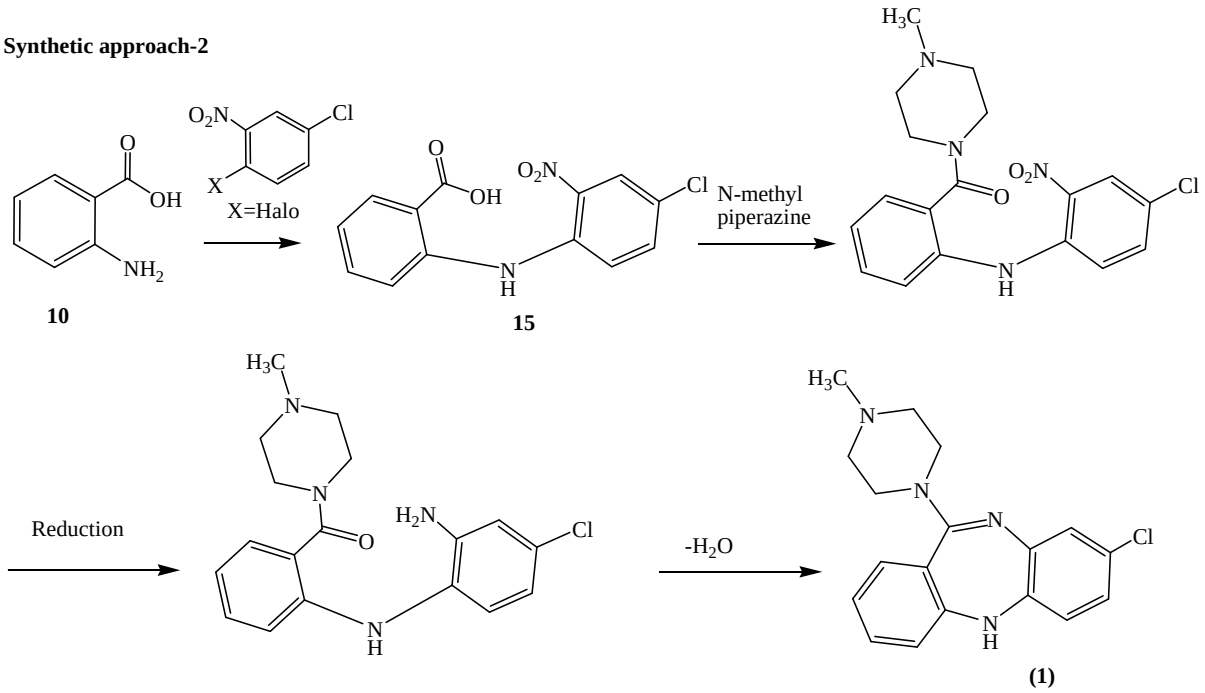
Scheme-2. Reported route of synthesis for Clozapine (**1**) from 2-(4-chloro-2-nitrophenylamino)benzoic acid **15**.

Tremendous amount of research work was done on Clozapine. According to the literature Hunzikar et al [8] proposed following schemes for the synthesis of Clozapine.

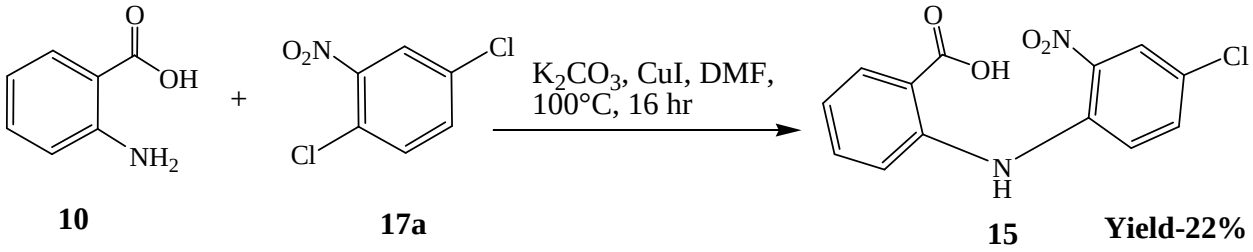
Synthetic approach-1



Synthetic approach-2

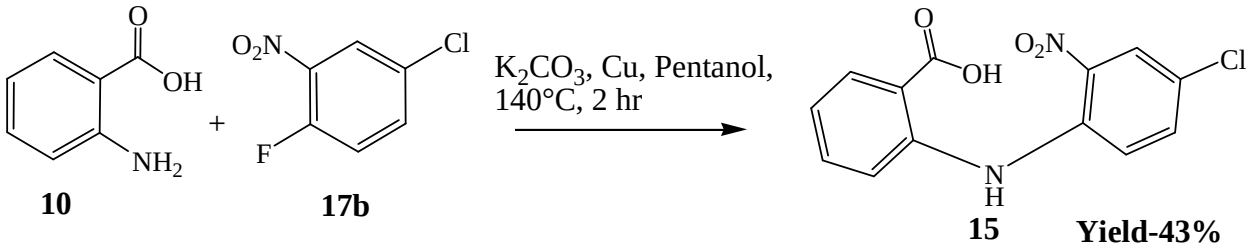


In the majority work of Clozapine synthesis, 2-(4-chloro-2-nitrophenylamino)benzoic acid **15**was synthesized by reaction of 2-aminobenzoic acid with 2-halo-5-chloronitrobenzene in the presence of a base and a reactionswere carried out at 100-140°C temperature.

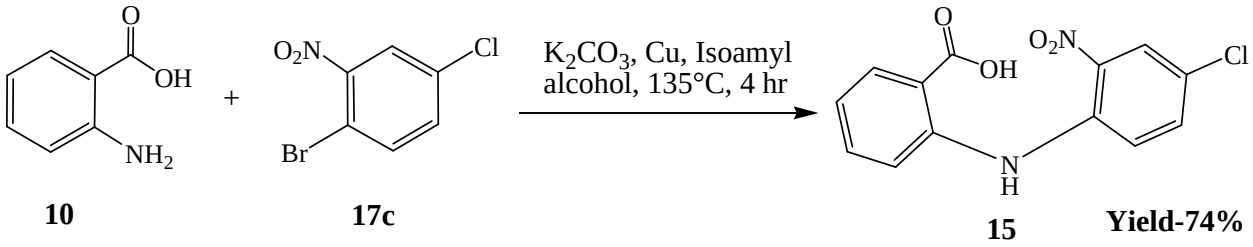


In Thomas G. Gant and his teams work [9] Anthranilic acid is reacted with 2,5-dichloronitrobenzene in the presence of DMF solvent and K_2CO_3 base at 100°C and the obtained yield was only 22%.

Similarly in the Hermkens Pedro work [10]2-fluoro-5-chloronitrobenzene was used along with anthranilic acid and the reaction was conducted in pentanol solvent and K_2CO_3 base with Copper as a catalyst and the reaction was conducted at 140°C, the obtained yield was 43%.

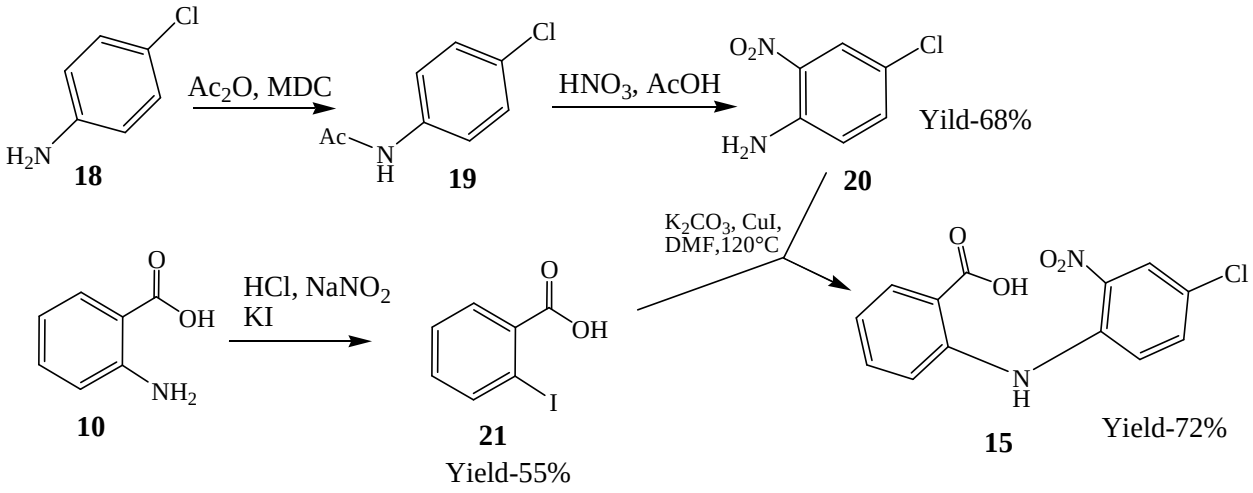


In the Monica Binaschi, et al [7]& Shen Jianhua team [11]they used 2-bromo-5-chloronitrobenzene and iso-amyl alcohol as a solvent with copper catalystto get 74% yield, but typically this type of reaction require higher temperature around 140°C.



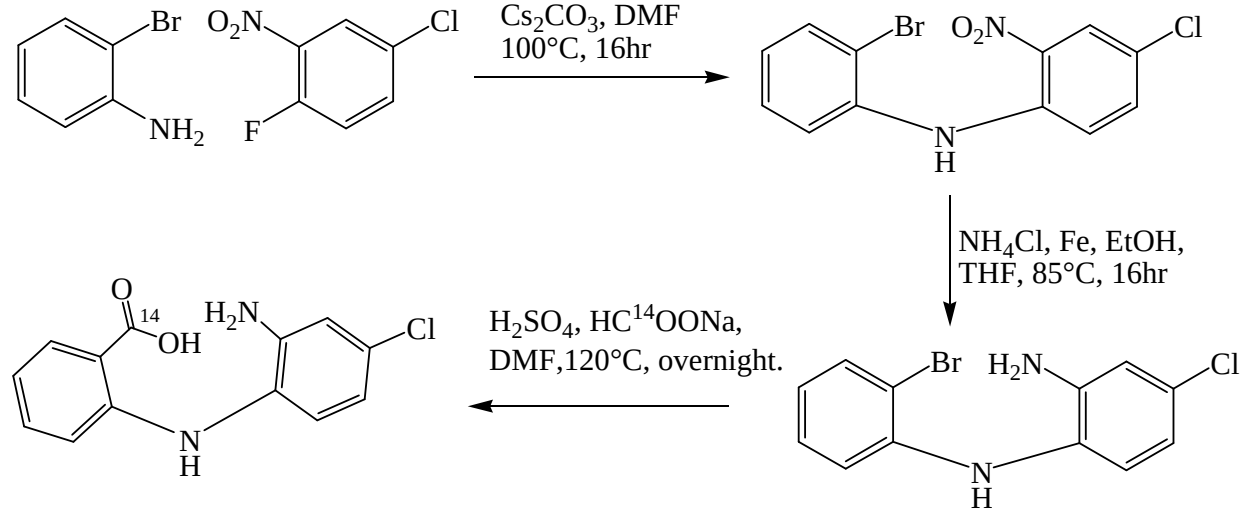
10 **17c** **15** **Yield-74%**

Team of Wu, Yong et al [12] synthesized the compound **15** by reacting 2-iodobenzene **21** with 2-nitro-4-chloroaniline**20** in DMF at 120°C gave 72% yield.Though the yield of the condensation stage is 72% but preparation of 2-Iodobenzoic acid from anthranilic acid gave 55% yield and 2-nitro-4-chloroaniline **20** preparation from 4-chloroaniline **18** gives 68% yield and hence overall cost is increased.

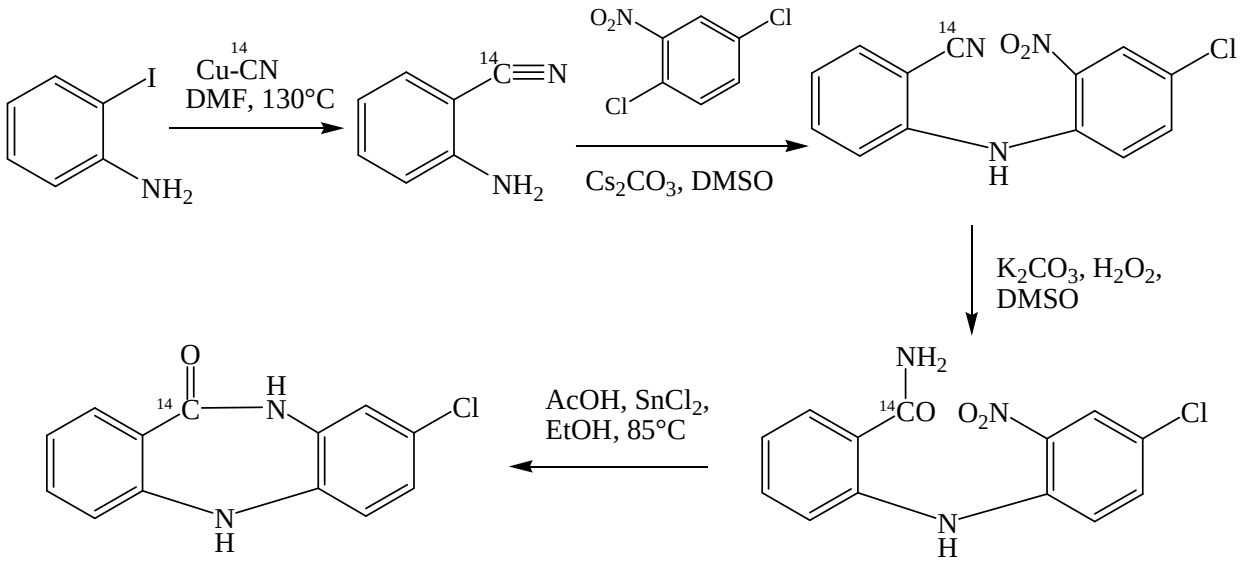


18 **19** **20** **10** **21** **15**

Elmore Charles S. et al [13] proposes two different routes for the synthesis of Labelled compound. In their first route, 2-bromoaniline is condensed with 2-fluoro-4-chlronitrobenzene in DMF at 100°C, subsequently nitro group is reduced to amine and then bromo group was replaced tocarboxylic acid group by reacting with sulfuric acid and labelled sodium formate, however this route did not mentioned yields but clearly statedabout poor yields.

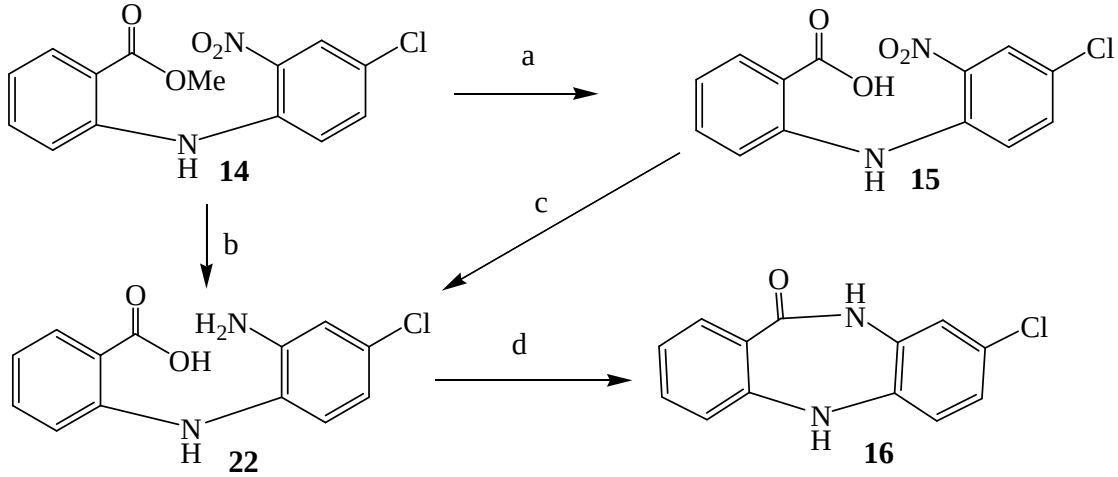


In the second route of work from this team, synthesis started with 2-Iodoaniline reacted with labelled copper cyanide to get labelled 2-cyano aniline which on reaction with 2,5-dichloronitrobenzene gave condensed product which was converted to amide using hydrogen peroxide and finally nitro group was reduced to amino and cyclized subsequently, overall yield of the labelled 8-chloro-5,10-dihydro-dibenzo[b,e][1,4]diazepine-11-one was 47%.



Drawbacks from the above reported literature schemes of 2-(4-chloro-2-nitrophenylamino)benzoic acid **15** gives an attention to the new synthetic method which is cost-effective and easily scalable.

In our research study (Scheme-3) the rearranged compound **14** was converted to compound **16** either by hydrolysis of ester to acid **15** followed by reduction using sodium dithionite to get compound **22**or first reduction by Sodium dithionite and insitu hydrolyzing amino-ester to amino-acid **22**. Reported literature for synthesis of 8-chloro-5,10-dihydro-dibenzo[b,e][1,4]diazepine-11-one i.e.**16**from compound **22**by refluxing in Xylene [11] for 96 hrs to get 79% yield, heating **22**in the solvent diphenylether at 175°C [14] for 2hrs and isolation through column chromatography gave 76% yield, cyclization using EDC.HCl, HOBt in MeCN solvent [7] to get 98% yield. We have conducted cyclization of **22**using Ethyl chloroformate, triethylamine and the reaction was conducted at room temperature.



Scheme-3. Reagents and conditions:(a) Methanol, NaOH, 40-50°C; (b)Acetone, Na_2CO_3,$Na_2S_2O_4$, NaOH, 35-40°C; (c)Acetone, $Na_2S_2O_4$, $NaHCO_3$, 60-65°C; (d) Dichloromethane, Ethyl chloroformate,Triethylamine, 30-35°C;

EXPERIMENTAL SECTION

The IR spectra were recorded using a Perkin-Elmer spectrum one FT-IR spectrometer instrument by using 1% potassium bromide pellet technique. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6& $CDCl_3$ at 300 MHz & 75 MHz respectively on Bruker 300 MHz Avance NMR spectrometer using Tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on Agilent 1100 Series LC-MSD-TRAP-SL instrument.

Reactions were monitored by thin layerchromatography on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-gradechemicals are commercially available and were used without further purification.

In this new synthetic methodology (Scheme-1) of compound **15**synthesis, Anthranilic acid **10**was chloroacetylated to get N-chloroacetyl compound **11**in the range of 98-99% yield,which was esterified with Dimethyl sulfate (DMS) to get compound **2**with the yield range of 95-97%. Compound **2** was condensed with 4-chloro-2-nitrophenol **12** to get **13**with quantitative yield of 92-96%and itwas rearranged in the presence of sodium methoxide to give product **14**with the excellent yield of 92-95% and the overall yield is 80-88%. This compound **14** was reduced with sodium dithionite and hydrolyzed in the presence of base to get compound **22**, which was cyclized using ethyl chloroformate and Triethyl amine to get 8-chloro-5,10-dihydro-dibenzo[b,e] [1,4]diazepine-11-one i.e. **16** a key intermediate in the synthesis of Clozapine.

2-[(2-chloroacetyl)amino]benzoic acid (11)
Sodium bicarbonate (27.5 g, 0.328 mol) was taken into flask and dissolved in water (600 ml). Anthranilic acid (30.0 g, 0.219 mol) was added slowly and stirred till complete dissolution at room temperature. Chloroacetyl chloride (29.6 g, 0.262 mol) was slowly added to the solution, material was precipitated during the addition, reaction mass was stirred for 2 hrs and the progress of reaction was monitored by TLC, after reaction completion, reaction slurry was filtered and washed with water (100 ml).Filtered material was dried to get 46.1 g of **11**,98% yield. Melting range 182-184°C;^{1}H NMR ($CDCl_3$,300 MHz) (δ, ppm): 4.23 (s, 2H), 7.19 (t, 1H,*J* = 6.0 Hz), 7.62 (dt, 1H,*J* = 6.0, 1.2 Hz), 8.15 (dd, 1H, *J* = 6.0, 1.2 Hz), 8.73 (d, 1H, *J* = 6.0 Hz), 11.77 (bs, 1H);^{13}C NMR (DMSO-d_6,75 MHz) (δ, ppm): 43.4, 116.8, 119.8, 123.5, 131.2, 134.2, 139.9, 165.2, 169.3; Mass (m/z): 214 (M+H).

Methyl, 2-[(2-chloroacetyl)amino]benzoate (2).
Compound **11** (30.0 g, 0.14 mol) was charged to the flask along withAcetone (300 ml), Potassium carbonate (20.3 g, 0.148 mol) was added and stirred for 15 minutes. Dimethyl sulphate DMS (26.6 g, 0.211 mol) was added slowly drop wise to the reaction mass at room temperature allowing it to rising to 38°C and maintained for 2 hrs. Progress of reaction was monitored by TLC, after completion of the reaction, acetone was distilled out under vacuum, water (150 ml) Ethyl acetate (150 ml) was charged to the reaction mass and layers were separated, aqueous layer was back extracted with ethyl acetate (60 ml). Both the Ethyl acetate layers were mixed and concentrated under vacuum at 45-55°C, Hexane (150 ml) was charged to the residue and gradually cooled to 10-15°Cand filtered off, washed with chilled Hexanes (30ml). Filtered material was dried under vacuum at 40-45°Cto get 31.4 g of compound **2**, 98.2% yield. Melting range 96-98.5°C;^{1}H NMR ($CDCl_3$,300 MHz) (δ, ppm): 3.96 (s, 3H), 4.21 (s, 2H),7.16 (dt, 1H, *J*=8.1, 0.6 Hz), 7.57 (dt, 1H,*J*=8.7, 1.8 Hz), 8.06 (dt, 1H, *J*=8.1, 1.5 Hz),8.69 (d, 1H, *J*=8.7),11.87 (bs, 1H); ^{13}C NMR ($CDCl_3$,75 MHz) (δ, ppm):43.2, 52.5, 115.8, 120.4, 123.4, 130.9, 134.5, 140.2, 165.2, 168.2; Mass (m/z): 228 (M+H), 250(M+Na).

Methyl, 2-[[2-(4-chloro-2-nitrophenoxy)acetyl]amino]benzoate (13).
To a stirred solution of DMF (100 ml) and 4-chloro-2-nitrophenol **12** (16.0 g, 0.092 mol), Potassium carbonate (18.2 g, 0.132 mol) was added and heated 55-60°C. Compound **2** (20.0 g, 0.088 mol) was dissolved in DMF (100 ml) and slowly added to the above reaction mass at 60-65°C and then maintained for 6 hours. Reaction was monitored by TLC and after reaction completion temperature reduced to 30°C. In another flask water (1200 ml) was taken and the above reaction mass was slowly quenched to it. Precipitated material was filtered off and washed with water (50ml) and material was dried under reduced pressure at below 55 °C to get lemon colored powder30.4 g of **13**, yield 95%. Melting range166.5-169.5°C.^{1}HNMR(DMSO-d_6,300 MHz) (δ, ppm): 3.82 (s, 3H), 5.02 (s, 2H), 7.25 (t, 1H,*J* = 6.1 Hz), 7.43 (d, 1H, *J* =6.8 Hz), 7.64 (t, 1H, *J* =6.8 Hz), 7.74 (dd, 1H, *J* =6.8, 2.0 Hz),7.93 (dd, 1H, *J* =6.1, 1.1 Hz),8.09 (d, 1H, *J* =1.9 Hz), 8.39 (dd, 1H, *J* = 6.6, 0.45 Hz), 11.20 (bs, 1H);^{13}C NMR ($CDCl_3$, 75 MHz) (δ, ppm): 52.9, 69.1, 117.5, 118.2, 121.3, 124.2, 125.4, 125.7, 131.1, 134.6, 134.7, 139.4, 140.5, 149.5, 166.3, 167.7; Mass (m/z): 365 (M+H).

Methyl, 2-(4-chloro-2-nitrophenylamino)benzoate (14).
Compound**13** (22.0 g, 0.0603 mol), Methanol (154 ml) and Toluene (4ml) was charged to the flask under nitrogen atmosphere. Sodium methoxide (3.6 g, 0.067 mol) was added to it and heated 55-65°C and maintained the reaction mass temperature for 6 hours. Reaction was monitored by TLC and after reaction completion, mass was concentrated under reduced pressure, Ethyl acetate (150 ml) was charged and filtered through paper. Red colored filtrate was concentrated to get red solid material, it was slurried in hexane and filtered off and dried to get reddish colored powder 16.6 g of **14**, yield 90%. ^{1}H NMR ($CDCl_3$, 300 MHz) (δ, ppm): 3.96 (s, 3H), 7.06-7.10 (m, 1H), 7.38 (dd, 1H, *J* = 6.8, 1.9 Hz), 7.46 (d, 2H, *J* = 2.7 Hz), 7.54 (d, 1H, *J* =6.8 Hz), 8.05 (d, 1H, *J* =6.0 Hz), 8.18 (d, 1H, *J* =1.9 Hz), 11.13 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) (δ, ppm): 52.4, 118.9, 119.1, 119.8, 122.3, 124.4, 126.0, 132.1, 133.5, 134.8, 137.1, 137.9, 141.8, 167.3; Mass (m/z): 307 (M+H).

2-(2-amino-4-chloro-phenylamino)benzoic acid (22).
Compound **14** (15.0 g, 0.0534 mol) andAcetone (150 ml) was charged to the flask, solution ofsodium carbonate (28.3 g, 0.267 mol) in water (60 ml) was added to it. Sodium dithionite (46.5g, 0.267 mol) was added in 10 lots at

35-40°C and maintained the reaction mass temperature for 2 hours. Reaction was monitored by TLC and after reaction completion, reaction mass was filtered and washed with acetone (50ml), the filtrate was concentrated under reduced pressure, Methanol (45ml) was added to the residue and Sodium hydroxide (4.3g, 0.1068 mol) was added to the reaction mass and heated to 55-60°C. Progress of reaction was monitored by TLC, after completion of reaction,mass was concentrated to half and pH of reaction was adjusted to 3-4 using HCl to get precipitated compound. Material was filtered off and dried to get 13.2 g of 22, yield 95%. ^{1}H NMR (DMSO-d_6, 300 MHz) (δ, ppm): 5.23 (br s, 2H), 6.53-6.63 (m, 2H), 6.70 (dd, 1H, *J* = 6.8, 8.1 Hz), 6.83 (d, 2H, *J* = 2.1 Hz), 7.04 (d, 1H, *J* = 8.1 Hz), 7.30 (dd, 1H, *J* =6.9, 9.0 Hz), 7.87 (dd, 1H, *J* = 2.1, 8.1 Hz), 8.97 (s, 1H); Mass (m/z): 263 (M+H).

8-Chloro-5,10-dihydro-dibenzo[b,e][1,4]diazepine-11-one (16).
Compound **22** (10.0 g, 0.038 mol) and Dichloromethane (200 ml) was charged to the flask, Triethyl amine (3.1 g, 0.031 mol) was added to it. Ethyl chloroformate (5.0g, 0.046 mol) was added slowly to the reaction mass at 25-30°C and maintained the reaction mass temperature for 1 hours. Reaction was monitored by TLC and after reaction completion, reaction mass was concentrated under reduced pressure, Water (80 ml) was added to the residue and stirred for 1 hr. Ash to black colored Material was filtered off and dried to get 8.3 g of 16, yield 89%. ^{1}H NMR ($CDCl_3$, 300 MHz) (δ, ppm): 6.88-7.0 (m, 5H), 7.35 (td, 1H), 7.67 (dd, 1H), 7.98 (s, 1H), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) (δ, ppm): 119.1, 120.5, 120.9, 121.1, 122.4, 123.9, 126.4, 131.2, 132.2, 133.45, 138.72, 149.8, 167.7; Mass (m/z): 263 (M+H).

RESULTS AND DISCUSSION

New synthetic method of 2-(4-chloro-2-nitrophenylamino)benzoic acid has an added advantage over the existing methods though the number of steps are more in the route. It is cost-effective and environment friendly reaction compared to the other reported literature methods. Existing methodsshowed lower yield from 22-43%. Best observed yield from the existing method was 74% where the Anthranilic acid is reacted with 2-bromo-5-chloro nitrobenzene [7], but this reaction needs 135-140°C temperature which is of a great concern interms of safety. 135-140°C temperature for industrial scale-up needs special dedicated reactors with special utility to attain this temperature and hence contribute additional cost in to the product. 2-bromo-5-chloro nitrobenzene is also costlier compared to the 4-chloro-2-nitrophenol. The new proposed synthetic method does not require more than 70°C temperature and all the chemicals used are easily & commercially available. The development of alternate route is useful in the synthesis of pharmaceutical product provides means to find methods which are advantageous in an economic sense, from the technical point of view or otherwise, in particular for large scale manufacture.

CONCLUSION

In summary, we have demonstrateda new and simple synthetic methodology for manufacturing of 2-(4-chloro-2-nitrophenylamino) benzoic acid methyl ester which is a key intermediate in the synthesis of Clozapine. Though the number of steps are more but it is cost effective compared to the reported methods as the 4-chloro-2-nitro phenol is cheap compared to 2-bromo-5-chloro nitrobenzene. The methodology is not only efficient and practical but also useful for industrial scale up as it is cost effective and it does not require any special utility of higher temperature. Similarly the same Smile rearrangement can be of great help for the synthesis of dibenzo[b,e][1,4]thiapinnes or oxapines too.

Acknowledgements
The author express special thanks to Dr. R. P. Phalak Principal of PG Department of Chemistry, Dadasaheb D. N. Bhole College Bhusawal & Dr. A V Reddy, Suven Life Sciences for his extended guidance and support.

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