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GREEN HIGH-YIELDING ONE-POT APPROACH OF ANTIPSYCHOTIC DRUG: ARIPIPRAZOLE

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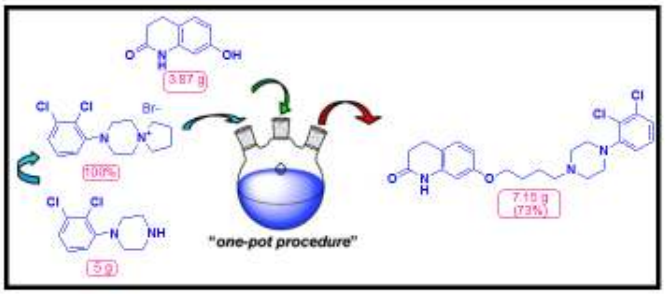
ABSTRACT
A simple, green and highly efficient approach was used to synthesize Aripiprazole, (7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril). We showed that the application of phase transfer catalyst-TBAHS (Tetrabutylammoniumhydrogensulphate) method with one pot reaction provides aripiprazole with excellent over all yields (>70%). In thiswe reported cost effective, high yielded, green methodology without formation of major impurities, Dehydro-Aripiprazole (*Metabolite*) and *Bis*-impurity (*EP-Impurity-D*). Thismethodology has several advantages over previously reported methods.

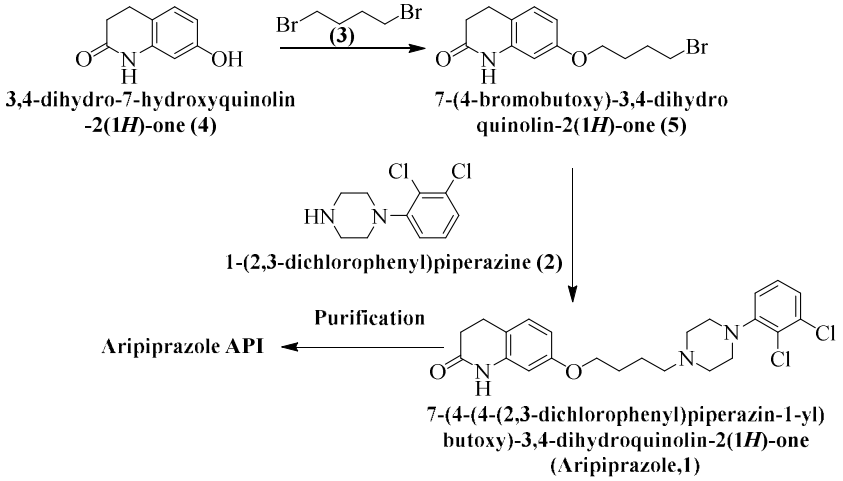


The synthesis of Aripiprazole (1) was achieved starting 1-(2,3-dichlorophenyl)piperazine(2) in one pot using TBAHS-Tetrabutylammoniumhydrogensulphate as a PTC &Quaternary Spiro ammonium salt (1A) as a in-situ intermediate. This approach could be useful for the preparation of pharmaceutically important moieties like Brexpiprazole,Lurasidoneand other drugs without formation of*Bis*- impurity.

KEYWORDS:EP-Impurity-D, Dehydro-Aripiprazole, One pot, PTC, Green methodology

INTRODUCTION
Aripiprazole, (7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy}-3,4-dihydrocarbostyril) belongs to the group of new antipsychotics. It is used in the treatment of schizophrenia, bipolar mania and some dementia related psychosis symptoms [I]. The drug was invented initially by the Otsuka Pharmaceutical Co., Ltd., Tokyo [OPC-14597 [II, III]] and co-marketed with Bristol-Myers Squibb [Abilify™, BMS-337039 [IV]]. Aripiprazole can form several inclusion compounds containing polar and protic species [V]. A series of experiments has been recently performed [VI,VII].

Several other methods have been reported in the literature for synthesis of aripiprazole. The innovator*Otsuka Pharmaceutical Co. Ltd*reported synthesis for Aripiprazole (**SCHEME-1, PATH-A**) as show below [VIII, IX]. Reaction of 1,4-Dibromo butane (**3**) with 7-hydroxy-3,4-Dihydrocarbostyril (**4**) yields 7-(4-bromobutoxy)- 3,4-dihydrocarbostyril (**5**) with 98% yield and ~25% *Bis*-impurity **(Fig: 1)** and the crude product react with 1-(2,3-dichloro phenyl)piperazine(**2**) yields required Aripiprazole**(1)** with *Bis* impurity ~25% remains unreacted in this stage but will be eliminated at final step by re-crystallization in aqueous alcoholic mixture followed several recrystallizationto get required aripiprazole **(1)** with API quality, but yields are very less due to ~25% *Bis* impurity in path-A (~50% over all yield).



SCHEME-1 (PATH-A): MANUFACTURING OF ARIPIPRAZOLE IN PRODUCT PATENT ROUTE

In this process, it is observed that formation of impurity *Bis* (Dimer) is about ~25% of in reaction mixture.In order to avoid the formation of*Bis* impurity, Our research group has been extensively working on identifying and improving new synthetic methods specially alter the reaction intermediate instead of reaction of 7-hydroxy-3,4- Dihydrocarbostyril**(4)** with 1,4-dibromo butane**(3)** reaction with 1-(2,3-dichloro phenyl)piperazine**(2)** to prepare spiro quaternary ammoniumsalt intermediate **(1A)** by using less mole equivalence of dibromo butane**(PATH-B)**. Reaction of Spiro quaternaryintermediate **(1A)** with carbostyrile**(4)** established a new green and efficient method for the synthesis of aripiprazole**(1)**using PTC (TBAHS), which can be more effective and one pot approach without formation of*Bis* and dehydro impurity.

Advantages in this one pot synthesis for Aripiprazole is **(A)** we can avoid isolation of highly Lacrometric intermediate (7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1H)-one) **(B)** Avoid Intermediate(s) Isolation and purification **(C)** Minimize batch cyclic time **(D)** Atom economy and minimizing effluent for green approach **(E)** Improve overall yield by decreasing number of steps **(F)** Avoid formation of reported impurity's like metabolite Dehydro-Aripiprazole&*Bis*impurity (EP- Impurity- D).

TBAHS as the phase transfer catalyst, being acidic in nature and it performs many organic transformations under mild conditions. It has been used for various synthesis and it is easy to handle, inexpensive, water soluble and thermally stable.[X]

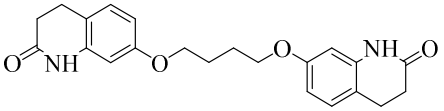


FIGURE -1: Aripiprazole Bis Impurity (EP- Impurity- D)
Bis-(3,4 dihydrocarbostyril-7-oxy) 1,4 butane

The formation of *Bis*impurity (which is formed due to the side reaction of (**5)**with**(4)**) is one of the major concerns while synthesizing Aripiprazole **(1)** in this sequence of path-A. It can be possible to reduce the formation of *Bis* impurity by using less mole equivalent of 1,4-Dibromo butane **(3)**and spiro quaternary intermediate**(1A)**in the reaction path-B.

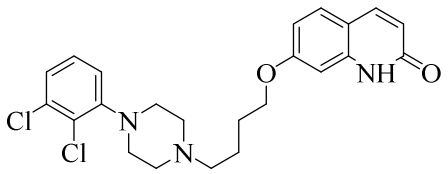


FIGURE-2: Dehydro Aripiprazole (Metabolite)
7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-2(1H)-quinolinone

The formation of Dehydro impurity (which is formed due to the side reaction of Aripiprazole **(1)** byoxidation during reaction longer time maintenance under heating) is one of the major concerns while synthesizing Aripiprazole **(1)** in this path-B.

Herein, we have chosen Aripiprazole **(1)** as a model to improve its synthesis via reducing the formation of impurities including *Bis* impurity (also known as EP impurity D, Figure-2) and dehydroimpurity (also known as MetaboliteAripiprazole) in path-B.

MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400MHz spectrometer using DMSO-d6, CDCl3 as solvent and tetra methylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turbo ion spray interface at 375 °C. All the organic extracts were dried over sodium sulfate after work-up. The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated

Procedure for preparation of Aripiprazole, (7-(4-(4-(2,3dichlorophenyl) piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one),1 in green high-yielding one-pot approach: To a suspension of 1-(2, 3-dichlorophenyl)piperazine,**2**(5.0 g, 0.021 mol) in MIBK (100 mL) added 1, 4-dibromobutane,**3** (5.12 g,0.023 mol)and potassium iodide (6.86 g, 0.049 mol).The resulting mixture was refluxed under vigorous stirring for 30 hr. after completion of reaction, to the quaternary spiro ammonium salt (8-(2,3-Dichlorophenyl-8-aza5-azoniaspiro(4,5) decane Bromide), (**1A**) added 7-hydroxy-4,5-dihydrocarbostyry, **4** (3.87 g,0.023mol) and TBAHS (1.46 g,0.0043mol). The resulting mixture was refluxed under vigorous stirring for48 hr. The reaction temperature was then adjusted in a manner to distil under a water pump vaccum 800 mL of MIBK with a column-head temperature ranging from 60-70 ° after cooling to room temperature water (100 mL) and hexane (100 mL) were added, and the suspension was stirred for 30 min. The medium was filtered and the filter cake washed 4 times with 20 mL water and suctioned to give 7.15 g (73%) Aripiprazole,**1**.

HPLC at 215 nm (Waters Model Alliance 2695-separation module, Inersil ODS C18, 250mm long, 4.6mm i.d., and 5-m particle diameter column, Mobile phase A was Phosphate buffer (pH 3.0±0.05) and acetonitrile in the ratio of 80:20 [buffer (pH 6.0)], prepared by dissolving 2.72 g of KH_2PO_4 in 1000 ml of water, pH adjusted to 3.0±0.05 with dilute ortho phosphoric acid. Mobile phase B was acetonitrile and methanol in the ratio of 8:2 (v/v) ,flow rate 1.0 ml/min ,45 min, gradient pump, retention time 15.23 min.; 99.0%). Mp: 136-137.6 oC; IR (KBr) 3434, 1677, 1234, 1034 cm^{-1}; ^1H NMR (DMSO-d_6, 400MHz) δ 10.0 (s, 1H), 7.3 (s, 1H), 7.2 (d, 1H), 7.1 (t, 1H), 7.05 (d, 1H), 6.5 (d, 1H), 6.4 (d, 1H), 4.3 (t, 2H), 3.9 (t, 2H), 2.97 (b, 2H), 2.9 (b, 2H), 2.7 (t, 2H), 2.4 (t, 2H), 2.4 (b, 2H); 2.4 (b, 2H), 1.7 (m, 2H), 1.5 (m, 2H). ES-MS m/z 448.4 (M^++1, 100%).

RESULTS AND DISCUSSIONS:

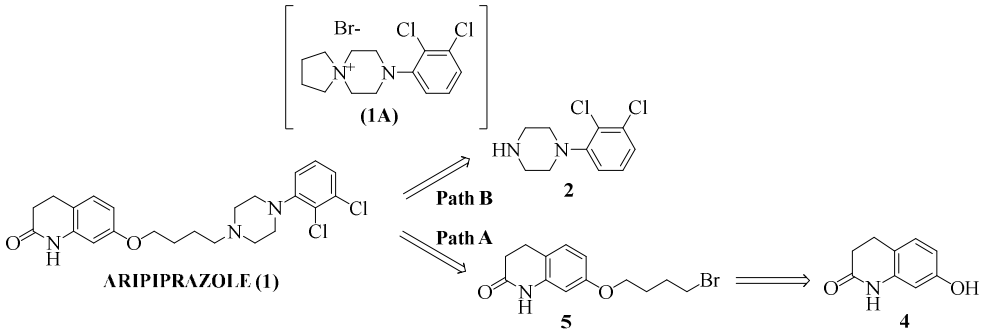


FIGURE-3: Retrosynthetic analysis of Aripiprazole (1)

Several methods for syntheses of aripiprazole (**1**) have been reported [11]. In many of these routes including innovators approach **(Path-A)**, 3,4-dihydro-7-hydroxyquinolin-2(1H)-one (**4**) is reacted with 1, 4-dibromo butane (**3**) in solvent Acetone and base potassium carbonate used catalyst to improve the rate of reaction sodium iodide, reaction mass heated to reflux after 25-30 hour, Checked TLC, Distil off Acetone completely, crude 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1H)-one (**5**) isolated from n-hexane/water mixture with 98 % yield and 25% *Bis* impurity.

7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1H)-one (75% Purity with *Bis* impurity 25%) taken in acetone solvent with sodium iodide and 1-(2, 3-dichlorophenyl) piperazine**(2)** refluxed for 12 h after completion of reaction crude aripiprazole isolated in n-hexane/ water mixture and wet material recrystalized with 20% aqueous ethanol/ IPA to get API quality aripiprazole and Dimer impurity washed completely, Yield: 50 % yield (Path-A overall yield to get API quality aripiprazole is50% only)

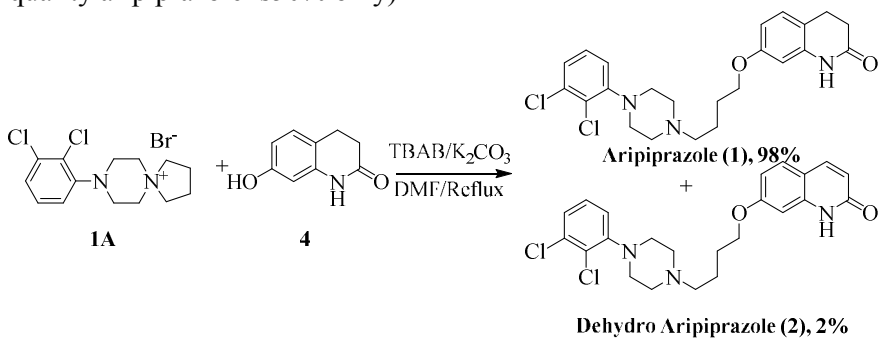
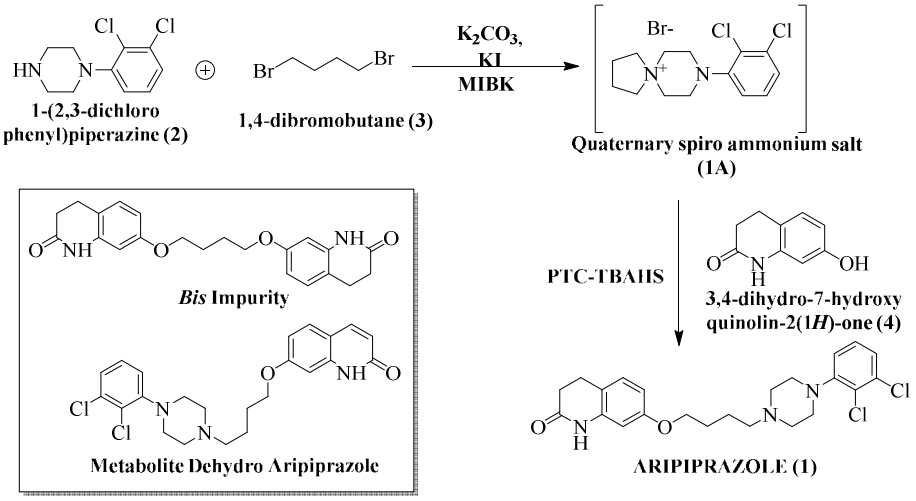


FIGURE -4: SYNTHESIS OF ARIPIPRAZOLE (1) USING PTC-TBAB WITH ISOLATED SPIRO QUATERNARY AMMONIUM SALT (1A)

To avoid *Bis* impurity, researchers selected corresponding spiro intermediates such as 8-(2,3-Dichlorophenyl)-8-aza-5azoniaspiro [4,5] decane Bromide (**1A**) instead of 7-(4-bromo butoxy)-3,4-dihydroquinolin-2(1H)-one (**5**) intermediate.

Path-B was selected to prepare Aripiprazole,**1** by avoiding the major impurity *Bis*(Fig: 1) and dehydroaripiprazole (Fig: 2) formation and to improve the yield of API. Here we designed and improved process by proceeding with spiro quaternary ammonium salt,**1A** without isolation and purification. Lot of effluent, process time, drying of intermediates atom economy is advantage in this present route.Herein, we have chosen Aripiprazole to improve its synthesis via reducing the formation of impurities including *Bis* impurity &Dehydro impurity. During the preparation of Aripiprazole in our lab path-B [12] by isolation of spiro intermediate **(1A)** using PTC-TBAB **(Figure-4)**

One unknown impurity was detected in HPLC analysis at levels ranging from 0.5- 2.0 %. The impurity was isolated, purified, characterized as dehydro impurity. The dehydro impurity formed from product aripiprazole due to very high temp and PTC-Tetra-n-butyl ammonium bromide (TBAB). We are unable to purify the product to achieve API quality, so we selected path-B without isolation one pot method using new PTC-TBAHS and it reduced the formation of dehydro impurity from 0.02%. This impurities formations avoided by one pot method path-B



SCHEME-2 (PATH-B): ONE POT SYNTHESIS OF ARIPIPRAZOLE USING TBAHS

As a part of the one pot **(Path-B)**synthesis 1-(2, 3-dichlorophenyl)piperazine**(2)** is reacted with 1,4-dibrobutane **(3)** in MIBK, potassium carbonate as a base at reflux temp under catalyst sodium iodide yields Spiro quaternary ammonium salt **(1A)** without isolationin one pot by charging3,4-dihydro-7-hydroxy quinoline-2(1H) **(4),** Tetrabutylammonium Hydrogen Sulphate (TBAHS)at reflux temperature for longer time (48hr). The API quality of aripiprazole obtained after ethanol recrystalization with more than 70% over all yield.

CONCLUSIONS: Addressed here is a scalable process for the synthesis of Aripiprazole,**1** in one pot method using TBAHS as catalyst with more than 70% over all yield and with API quality. The followed synthetic sequence avoids the formation of Bis impurity and Dehydro impurity successfully.

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