Process development of the synthesis of 2 ,3-dichlorophenylpiperazine

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Abstract : The new pathway for the synthesis of 2 ,3-dichlorophenylpiperazine from cheap raw material , 2 ,3-dichloroaniline is presented. The hydrogen sulphate salt of 2 ,3-dichloroaniline was converted to the corresponding Aryl Iodide in good yield of 81 % by reacting with conc. H_2SO_4 and $NaNO_2$ to form intermediate diazonium salt , which was further displaced by KI. The desired product was obtained by reacting Aryl Iodide and piperazine in the presence of CuI as catalyst , proline as ligand , K_2CO_3 as base and dimethyl sulfoxide as solvent with yield of 20 %. The method is simple , utilizes cheap catalyst and ligand , insensitive to moisture ; it is easy to separate the product , and can undergo large-scale production.

Key words : 2 ,3-dichlorophenylpiperazine ; 2 ,3-dichloroaniline ; diazonium salt ; 1 ,2-dichloro-3-iodobenzene
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Introduction

2 ,3-dichlorophenylpiperazine is a potential precursor in synthesizing potent drugs that target dopamine and serotonin receptor , such as aripiprazole[1] , NGB2849[2-3] and NGB2904[2-3]. Particularly , by being key intermediate in synthesis of aripiprazole , the latest schizophrenia drug[1,4-6] which posses both postsynaptic dopamine receptor and pre-synaptic auto-receptor , attracts special attention in its synthesis.

The current method of preparing 2 , 3-dichlorophenylpiperazine involves reaction between 1 , 2-dichloro-3-iodobenzene and piperazine in the presence of Pd (Palladium) catalyst , S-Binap as ligand , base and solvent like toluene[7-8]. This method which followed a breakthrough in development of C—N bond using palladium catalyst reported by Buchawald[9] in 1997 , has a yield between 50 % - 60 %. The industrial use of this method is hindered by high cost of Pd catalyst and relative ligands as well as air and moisture sensitivity[10]. Contamination of the product is another crucial problem , where it takes two days just to separate the product[8]. As a result , drugs containing 2 ,3-dichlorophenylpiperazine in its molecule are highly expensive on the market.

Yuan[2] and Robarge[3] reported another method that utilizes 2 ,3-dichloroaniline and diethanolamine as raw material and phosphorus pentoxide and triethylamine hydrochloride as catalyst. Again here , yield is low ; high operating temperature and large amount of catalyst are needed. This is still not an attractive method.

Zhang[10] reported that L-proline could be used as a promoter in CuI-catalyzed reaction of aryl halides with both aliphatic primary and aliphatic cyclic secondary amines at low temperature (40 - 110 °C) with good yield. Such information attracted our curiosity to study synthesis of 2 ,3-dichlorophenylpiperazine using this promising method. It is a simple mild method of forming C—N bond without complication in separation of product. Not only that , but also the procedure is relatively insensitive to moisture and can be performed under air atmosphere.

Diazonium salts are useful intermediates in synthesis of aromatic compounds because the diazonium group can be easily replaced by several atoms or

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groups such as —F, —Cl, —Br, —I, —CN, —OH and —H. Diazotization should be conducted below 5 ℃, because most of arene diazonium salts are unstable at temperature between 5 - 10 ℃. Replacement, which is accompanied by evolution of nitrogen gas can be easily achieved by adding another reagent like CuCl, CuBr, KI, etc to the mixture and followed by gently warming. This technique was used to synthesize precursor 1,2-dichloro-3-iodobenzene (Fig 1), from cheap raw material 2,3-dichloroaniline, through diazotization, followed by replacement with —I group while desired product, phenylpiperazine (Fig 2), was obtained by reacting good leaving group 1,2-dichloro-3-iodobenzene with piperazine in presence of CuI, ligand proline, solvent DMSO and K_2CO_3 as catalyst.

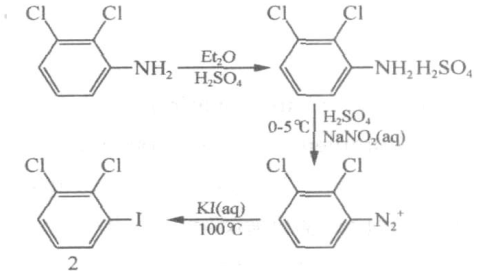

Fig. 1 Synthesis of 1,2-dichloro-3-iodobenzene

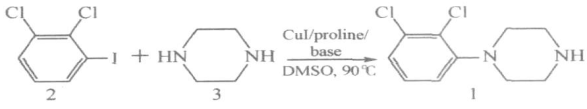

Fig. 2 Synthesis of 2,3-dichlorophenylpiperazine

1 Experimental section

1.1 Measurements

^{1}H-NMR was recorded with Varian AV 600 spectrometer. Melting points were measured by Micro melting point apparatus ST5A. Corresponding standard silica gel for column chromatography and TLC were used.

1.2 Synthesis of 1,2-dichloro-3-iodobenzene

Into a round bottom flask, 1.4 g (8 mmol) of 2,3-dichloroaniline was dissolved in 30 mL of Et_2O, followed by addition of 0.5 mL of conc. H_2SO_4. The mixture was sonicated for 10 s, and then the solvent was removed by vacuum to achieve 2,3-dichloroaniline hydrogen sulphate salt as white powder.

The flask was then placed in a magnetic stirrer with ice, where 6 mL of H_2O in 1.96 mL of conc. H_2SO_4 were added. A pre-cooled solution of $NaNO_2$ (950 mg) in 17 mL of H_2O were added over 15 min, stirred further for 30 min at 0 ℃. Then KI (2.7 g) in 17 mL of H_2O were added over 5 min, followed for further stirring at 0 ℃ for 1 h.

A condenser was installed to the flask and the mixture was heated at 100 ℃ for 2 h. Reaction was stopped and contents were cooled to room temperature. After cooling, 30 mL of hexane was added through a reflux condenser to rinse off the sublimed material, the resulting bi-phasic layer was stirred rapidly for 1h; the organic layer was separated, washed with 5 % $NaHSO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuum to form a pink liquid. Silica gel column chromatography was used to separate the product, using hexane as eluent solvent. Concentration in vacuum distillation, afforded 1,2-dichloro-3-iodobenzene (1.8 g, 81 %) as white crystal; TLC (hexane) Rf = 0.6; mp :35 - 36 ℃.

1.3 Synthesis of 2,3-dichlorophenylpiperazine

Into a 3-neck round bottom flask, the mixture of 1,2-dichloro-3-iodobenzene (1.4 g, 5.1 mmol), piperazine (2 g), K_2CO_3 (2 g), proline (0.17 g), CuI (0.15) was dissolved in 30 mL of DMSO and placed under N_2 gas, temperature was raised to 90 ℃ and maintained there with stirring for 72 h.

After cooling, the organic compound was extracted by partition with 30 mL of EA and 30 mL of H_2O for 3 times, further washed with brine, dried by Na_2SO_4 and concentrated in vacuum to form brown liquid, which was chromatographed by using mixture of dichloroethane and methanol in the volume ratio of 10 ∶1 and concentrated by vacuum distillation to get a semi-solid, 0.23 g. HCl gas in MeOH was added, sonicated for 10 s to form a correspond hydrogen chloride salt, which was further purified through recrystallization by slowly adding isopropanol in reflux temperature until all contents dissolved and then slowly adding hexane until first crystal commence, after cooling into room temperature, the contents were

kept in 0 ℃ overnight. 0.26 g of 2,3-dichlorophenylpiperazine hydrochloride with overall yield of 20 % was obtained after filtration, mp: 239 - 241 ℃ [239 - 242 ℃][3]. ^{1}H-NMR (δ, CD_3Cl) 3.37 - 3.43 (m, 8H), 6.97 (m, 1H), 7.16 - 7.2 (m, 2H).

2 Results and Discussion

1,2-Dichloro-3-iodobenzene was prepared from corresponding aniline through diazotization in good yield of 81 %. Purification by column chromatography was performed to obtain pure white crystal, mp: 35 - 36 ℃.

1,2-Dichloro-3-iodobenzene was coupled with piperazine in the presence of CuI as catalyst and proline as ligand. This is Ullmann Copper Mechanism[10-11] which traditionally uses high temperature and often require the use of stoichiometric amounts of copper reagents which leads to problems of waste disposal. However, the presence of proline ligand, solves these problems. According to Zhang[10] the coupling reaction of secondary amino acids with aryl halides occurred best at temperature between 60 - 95 ℃, and proline serves as the best additive. The amount of CuI and proline used are 0.1 and 0.2 equivalents respectively that means the problems of handling CuI disposal is reduced tremendously.

The target product was easily separated by chromatography and further purified by conversion to corresponding hydrogen chloride salt followed by recrystallization, to afford pure light brown crystal in overall yield of 20 %. However, two by-products were noticed which are un-reacted precursor and over reacted product on both sides of piperazine, diphenylpiperazine. The weight ratio between the desired product to over reacted one is 1∶2; this is good clue in finding improved high yield method, which could be done through protecting one side of piperazine. The next work is to study appropriate method for protecting one side of piperazine.

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Two-level implementation method for converting STEP-NC into XML

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Abstract: A two-level implementation method, based on a study of the STEP-NC information model and XML, is proposed to convert STEP-NC into XML. In the first level, STEP-NC is divided into a series of interconnected modules. In each small module, the object serialization early binding maps each STEP-NC instance into an XML instance as attribute data using JDOM. Using XML, STEP-NC data can be shared for networked manufacturing and cooperative manufacturing in different places. In the second level, STEP-NC data is shown by a tree and some tables, such that it is easily used by the operator. Furthermore, an interface from STEP-NC files to traditional CNC files has been developed so that using STEP-NC a component can be processed directly in a CNC machine tool.

Key words: STEP-NC; XML; JDOM; CNC

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2,3-二氯苯基哌嗪合成方法的改进

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摘要: 2,3-二氯苯胺硫酸盐经重氮化,再与 KI 置换生成相应的芳基碘化物,产率 81 %。芳基碘化物与哌嗪在二甲基亚砜中反应,CuI 和脯氨酸为催化剂,收率 20 %。该方法操作简单,对湿不敏感,产物易于分离,具有一定的实用价值。

关键词: 2,3-二氯苯基哌嗪; 2,3-二氯苯胺; 重氮化; 1,2-二氯-3-碘苯

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