RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.3, No.4 (2010), 681-689
ISSN: 0974-1496
CODEN: RJCABP

COMMERCIAL SCALABLE PROCESS FOR THE PREPARATION OF IRBESARTAN INTERMEDIATE

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ABSTRACT

Development of efficient commercial process for the preparation of highly pure 4'-(2-Butyl-4-oxo-1,3-diaza-spiro[4,4]non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (**1**), an advanced intermediate of Irbesartan is described. The developed process minimizes the impurity formation and utilizes the simplified process to improve yield, throughput and is suitable for production on commercial scale.

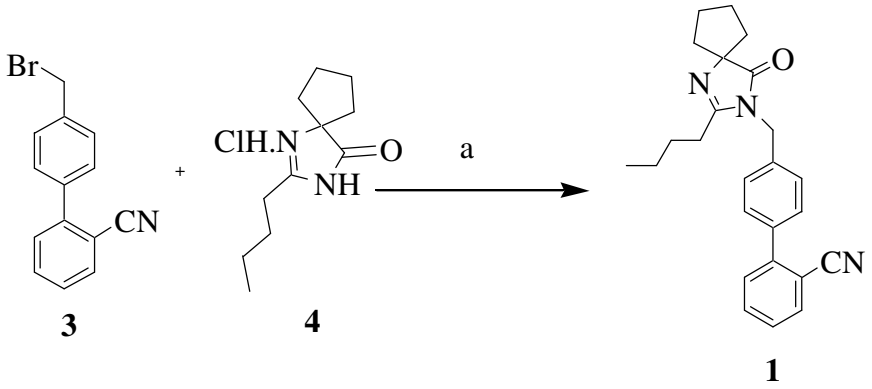
Keywords: Bromination, condensation, impurities, Irbesartan intermediate

INTRODUCTION

Irbesartan (Figure 1) is a non-peptide angiotensin II receptor antagonist useful in the management of hypertension, heart diseases, heart strokes, diabetic neuropathy and congestive heart diseases[1]. Irbesartan is currently available in the market as an antihypertensive drug under the brand name of Avapro[2]. Generally, Angiotensin II receptor blockers (ARBs) such as Irbesartan bind to the Angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to reduction in arterial blood pressure. The metabolism of Irbesartan, a highly selective and potent nonpeptide angiotensin II receptor antagonist, has been investigated in humans[3]. Irbesartan inhibits the activity of angiotensin II (AII) via specific, selective noncompetitive antagonism of the AII receptor subtype 1 (AT1) which mediates most of the known physiological activities of AII[4].

The angiotensin II type 1 (AT_1) receptor plays a pivotal role in the regulation of blood pressure and electrolyte balance, and is involved in the control of specific ingestive behaviours. Irbesartan is a recently developed angiotensin AT_1 receptor antagonist and displays higher affinity for its target receptor than other similar antagonists[5].

The first reported synthetic method[6,7] as shown in scheme-1 for the preparation of advanced intermediate (**1**) of Irbesartan consists of the condensation of 4'-Bromomethyl-biphenyl-2-carbonitrile (**3**) with 2-Butyl-1,3-diaza-spiro[4,4]non-1-en-4-one hydrochloride (**4**) using sodium hydride (NaH) as a base and dimethyl formamide (DMF) as solvent medium. When NaH is used as base in the process, utmost care should be taken to perform the reaction under inert atmosphere as it is an exothermic reaction, highly sensitive towards moisture, it is unsafe and not suitable for production on commercial scale. The DMF is readily bioabsorbed through the skin, highly irritant to skin and mucous membrane. Removal of high boiling solvents like DMF in the process is difficult and not economic. Moreover the product was purified through column chromatography which is not commercially viable and the reported reagent and solvent were not suitable for the large scale production.



Scheme-1: Reagents & conditions a) NaH, DMF, room temperature

Another procedure was described in the literature, as per which the condensation was performed in toluene and DMF mixture using different bases like sodium methoxide, sodium hydroxide, cesium carbonate, potassium carbonate and potatssium-t-butoxide, but the yields and purities have not been mentioned[8].

As per the process described in the patent, the condensation was performed using methyltributylammonium chloride as phase transfer catalyst in toluene as well as dichloromethane in the presence of different concentrations of aqueous sodium hydroxide. The drawbacks of these methods are multiple extractions, acid base treatment, lengthy and tedious isolation procedures[9].

A more recent procedure was disclosed in the literature in which the N-alkylation for the preparation of Irbesartan intermediate (**1**) was carried out in three steps[10]. These steps involve a) free base preparation of 2-Butyl-1,3-diaza-spiro[4,4]non-1-en-4-one hydrochloride (**4**) from its hydrochloride salt b) condensation with 4'-Bromomethyl-biphenyl-2-carbonitrile (**3**) using potassium carbonate/ potassium hydroxide in acetone medium c) purification of the crude residue in ethylacetate and n-hexane mixture to obtain the required product with the purity of ~98% and the yield of ~80%.

An improved process was disclosed in WO publication as per which the condensation reaction was performed in DMF medium using sodium hydroxide as base. As DMF is high boiling and water miscible solvent and considering the recovery and reuse aspects, it is not suitable on commercial scale. Moreover the process does not mention the impurity profile[11].

The process disclosed in our manuscript is affording the product with higher yield and purities than the reported processes with all potential impurities (Figure 2) in control.

An analogous synthetic approach for the preparation of 4'-(2-Butyl-4-oxo-1,3-diaza-spiro[4,4]non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile hydrochloride is reported in the literature[12] which involves the condensation of the compound **4** with compound **3**, which is having different ratios of dibromo and tribromo compounds. The reaction was carried out in the presence of diethyl phosphate as a reducing agent along with potassium hydroxide as a base in biphasic medium and Methyl tributyl ammonium chloride (MTBAC) as a phase transfer catalyst. However, the purity of the obtained in the above process for the intermediate is not mentioned. This process suffers from the disadvantages like use of expensive reducing agents and requires the purification of the crude product in mixture of solvents. There is no control on the formation of impurities for bromination of the intermediate.

Therefore, there is a need to have the process to produce high pure Irbesartan Intermediate (**1**) as it will impact on the yield and purity of the finished product. Herein, we report an economic, efficient and impurity free synthesis which will afford Irbesartan intermediate in higher yield (95%) with excellent quality.

EXPERIMENTAL

Solvents and Reagents were used as such without further purification. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker 400 MHz spectrometer. The chemical shift data was reported as δ (ppm) downfield from tetramethylsilane, which is used as an internal standard. The mass spectra were recorded using an HP 5989A LC-MS spectrometer. The FT-IR spectra were recorded in the solid state as a KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The chromatographic purity of the compounds was analyzed using Agilent 1200 series HPLC instrument under the following conditions:

Column : Symmetry C18, 4.6 × 75 mm, 3.5 µm
Mobile phase : Eluent A: Deionized water, Eluent B: HPLC grade Methanol

Chromatographic Conditions

a.	Column temperature	: Ambient
b.	Sample compartment	: Ambient
c.	Detector	: 225 nm
d.	Injection volume	: 10 µL
e.	Run time	: 45 minutes
f.	Flow rate	:1.0 mL/min
g.	Injector	:Auto sampler with variable volume injector
h.	Diluent	: HPLC grade Acetonitrile

4'-Bromomethyl-biphenyl-2-carbonitrile (3)

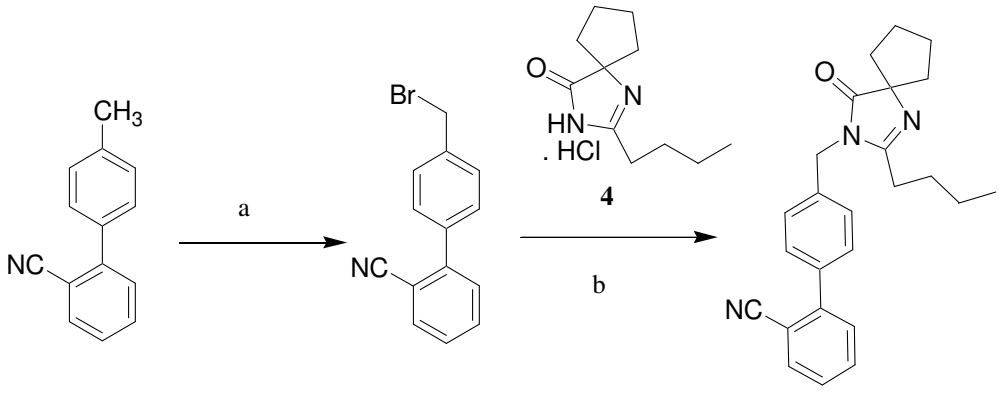
To a solution of compound **2** (100 g, 0.517 moles) in acetonitrile (500 mL) was added 1,3-dibromo-5,5-dimethylhydrantoin (DBDMH, 107.2 g, 0.72 moles) and 2,2'-Azobiisobutyronitrile (AIBN, 0.85 g, 0.005 moles). The contents were heated to reflux and maintained for 5-6 hours. Reaction progress could be monitored using Thin Layer Chromatography (TLC). After completion of the reaction, the solvent was distilled off, added water (500 mL) into the reaction mixture and maintained under stirring for 1 hour. The reaction mixture was cooled to 25-30°C and further maintained under stirring for 1 hour. Filtered the solid and washed with water (100 mL). To the wet compound, isopropanol (100 mL) was added and stirred for 1 hour at 25-30°C. Filtration followed by drying at 60-70°C afforded the title compound as a crystalline solid. Yield: 132 g, 93%. IR (KBr, cm^{-1}): 2220.71 (CN stretching), 1593.92,1560 (C=C aromatic stretching), 643.22 (aromatic substitution); Mass: 273.2 $(M+H)^{+}$; ^{1}H-NMR ($CDCl_3$) δ 4.56 (2H, s), 7.42-7.67 (3H, m), 7.52 (4H, s), 7.78 (1H, d, J=7 Hz).

4'-(2-Butyl-4-oxo-1, 3-diaza-spiro [4.4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (1)

To a solution of compound **4** (445 g, 1.93 moles) in dichloromethane (2500 mL) was added Triethyl benzyl ammonium chloride (13.18 g, 0.058 moles) under stirring. The contents were cooled to 5°C and aqueous solution of KOH (410 g, 7.32 moles, was dissolved in 880 mL of water) was added slowly during 30 minutes. Compound **3** (500 g, 1.83 moles) was added and reaction mixture was allowed to reach 25°C and maintained for 45 minutes. The completion of the reaction was confirmed by TLC, added water (2500 mL) by keeping the temperature at below 30°C and stirred for 20 minutes. The organic layer was separated, washed with water (1000 mL) followed brine solution (1000 mL) and dried over anhydrous sodium sulphate (50 g). The solvent was evaporated under vacuum to obtain crude product. The mixture of isopropanol (800 mL) and water (1200 mL) was added to the crude product, stirred for 1.5 hours at room temperature and stirred at 0-5°C for 30-45 minutes. The product was filtered and washed with the mixture of isopropanol (200 mL) and water (300 mL). The wet product was dried under vacuum at 40-45°C for 6 hours. Yield: 0.673 Kg, 95.4 %; IR (KBr, cm^{-1}): 2220.72 (CN stretching), 1720.08 (C=O amide stretching), 1628.73 (C=N stretching); Mass: HRMS(ES^{+}) calculated for C_{25} $H_{28}N_3O$ $(M+H)^{+}$: 386.22269, observed value : 386.22218 ; ^{1}H-NMR ($CDCl_3$) δ 7.77 (d, J=7.6 Hz, 1H), 7.65 (td, J=1.1, J=7.7 Hz,1H), 7.54 (J=4.1 Hz, 2H), 7.49 (d, J=7.6Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.28 (d, J=8.10Hz, 2H), 4.75 (s, 2H), 2.35 (t, J=7.8 Hz, 2H), 2.06-1.93 (m, 6H), 1.88-1.84 (m, 2H), 1.60 (quintet, J=7.4 Hz, 2H), 1.34 (sextet, J=7.4 Hz, 2H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 186.8, 161.5, 144.7, 137.7, 137.2, 133.8, 132.9,132.0, 129.4, 127.7, 127.1, 118.6, 111.2, 76.6, 43.3, 37.5, 28.8, 27.8, 26.1, 22.3, 13.7.

RESULTS AND DISCUSSION

In our improved process, as shown in scheme-2, we explored the possibility of using commercially available 2-Butyl-1,3-diaza-spiro[4,4]non-1-en-4-one hydrochloride and 4'-methyl-biphenyl-2-carbonitrile as the intermediates for the preparation of 4'-(2-Butyl-4-oxo-1,3-diaza-spiro[4,4]non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile.



2 **3** **1**

Scheme-2: Reagents & conditions a) DBDMH/AIBN, acetonitrile and isopropanol b) KOH, dichloromethane, TEBAC, isopropanol and water.

Synthesis of 4'-bromomethyl-biphenyl-2-carbonitrile (3)

The reported processes [12] for the bromination using sodium bromate and aqueous hydrobromic acid gave different ratios of by products ranging from 10-20% under photolytic conditions. Diethyl phosphate is used as a reducing agent for the reduction of the dibromo and tribromo impurities formed in the process. The obtained crude is preceded to further stage without isolation of the product which is having different ratios of the impurities in the residue, which may effect on the yield and purity of the intermediates. We attempted to carry out the bromination with N-bromosuccinamide (NBS) using dibenzoyl peroxide as free radical initiator in different solvent mediums like carbon tetrachloride, chloroform, dichloromethane and acetonitrile. The product obtained with the yield of 70-80% and dibromo impurity formation was observed in each case.

To overcome these problems, we have chosen DBDMH (1,3-dibromo-5,5-dimethyl hydrantoin) as a reagent in the presence of AIBN (2,2'-Azobiisobutyronitrile) as a free radical initiator for bromination to minimize the formation of dibromo and tribromo impurities in the process. We have studied the effect of DBDMH equivalents and the solvent medium for this transformation (chloroform, dichloromethane, acetonitrile and ethyl acetate). The product was obtained with optimum yield and quality (dibromo impurity <0.5%) when DBDMH was used with 0.72 eq. and acetonitrile was used as solvent medium.

Condensation of 4'-bromomethyl-biphenyl-2-carbonitrile (3) and 2-Butyl-1, 3-diazaspiro [4, 4] non-1-en-4-one (4)

To improve the yield and quality of the desired product **1**, extensive optimization studies were taken up by the screening of reagents, solvents and reaction parameters. As per the basic patent route [6], sodium hydride was used to effect the transformation of compound **3** to compound **1.** Considering the cost factor and hazardous nature of the employed base (NaH) in combination with DMF, we intended to screen non-toxic and inexpensive bases in combination with different solvents to effect the transformation in an efficient manner. Among the screened bases, potassium hydroxide with dichloromethane indicated the best results. The data has been provided in the Table 1.

To find out the cumulative effect of the base and solvent on transformation in terms of yield and quality we optimized the base equivalents in the presence of dichloromethane quantity as 5.0 volumes. It turned out that 6.0 eq. of KOH is required for 1 mol of compound **3** (Table 2).

As the compound **4** is insoluble in dichloromethane, it required water in the reaction along with dichloromethane. The quantity of the water which plays a prominent role in the biphasic reaction was also optimized. The reaction homogeneity and better conversion was observed with 1.76 volumes of water with respect to compound **3**.

It is well established fact that the temperature of the reaction plays the crucial role in the conversion of the starting material to the product. By keeping the other factors constant, we optimized the temperature of the reaction. It was observed that the optimum conversion without the side reaction can be achieved at 20-25^{o}C (Table 3).

In this transformation, the phase transfer catalyst plays the pivotal role. For this we have screened tetrabutyl ammonium bromide (TBAB), methyl tributyl ammonium chloride (MTBAC), triethyl benzyl ammonium chloride (TEBAC) and tetrabutyl ammonium chloride (TBAC) among which TEBAC has shown the superior results.

Once the highest conversion of the reaction was achieved in the optimized conditions (based on the HPLC purity of the reaction mass), different purification trials were attempted and a robust in situ purification method has been developed to remove all the impurities in the process by using isopropanol and water mixture as a medium for crystallization of the crude product. The purification trials details are provided in Table 4. The isopropanol and water mixture in 2:3 ratio was observed to be optimum to obtain the product with high purity with minimum yield loss.

After these systematic optimization studies, our attempts for the condensation of 2-Butyl-1, 3-diaza-spiro [4, 4] non-1-en-4-one hydrochloride (**4**) with bromo compound (**3**) was successful in affording the product (**1**) with high yield (95%) with all the possible potential impurities in control. Thus the process for the condensation of compound **3** and compound **4** was established by using potassium hydroxide as a base in dichloromethane and water mixture. TEBAC was used as phase transfer catalyst. The product was isolated by the insitu crystallization in isopropanol and water mixture. The present process produced the Irbesartan intermediate in high pure form (99.9%) with high yields (95%). The consistency and reproducibility were checked by performing the experiments on 500 g scale, the yields and purities are consistent and the data has been furnished in Table 5.

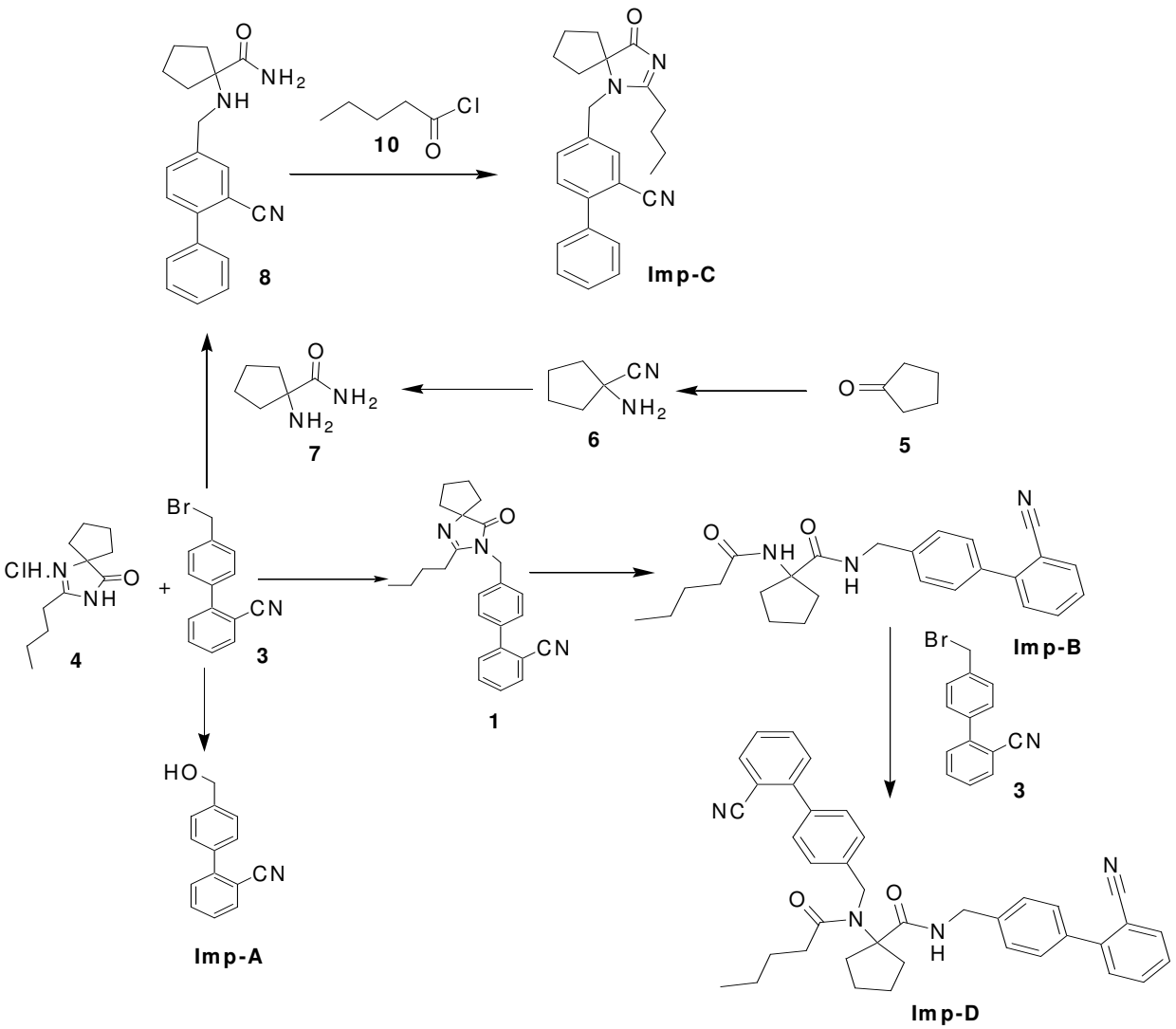
During the optimization studies and the screening of the various parameters, we have observed some impurities formation. These were identified by LCMS, isolated from the mother liquors and purified through different techniques like column chromatography, solvent washings and crystallizations. Total six impurities were identified and characterized by the spectroscopic methods (one of them is the starting material, **4** and another one is the intermediate, compound **3**). The impurities structures are shown in Figure 2 and synthetic schemes have been provided in Scheme-3. All these impurities were efficiently controlled in our improved process (Table 5).

CONCLUSION

In conclusion, we have established the optimized conditions for the bromination on compound **2** and systematically studied the effect of base, catalyst, solvent volume and temperature for the condensation of compound **3** with compound **4.** We have developed an improved, high yielding, eco friendly and industrially feasible process for Irbesartan intermediate with all the potential impurity levels in control.

ACKNOWLEDGMENTS

We thank the management of Srini Pharmaceuticals Ltd for supporting this work. Cooperation from the colleagues from the analytical research and development is highly appreciated.



Scheme-3: Synthetic pathways for the impurities

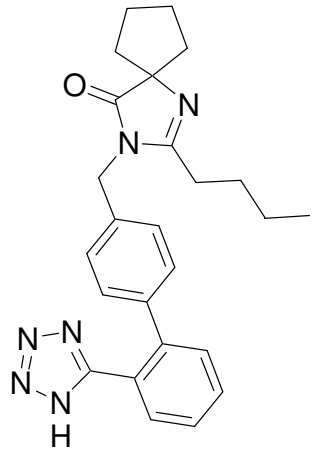
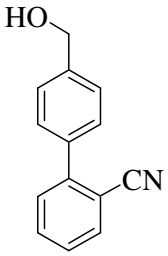
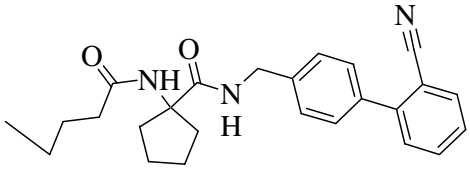


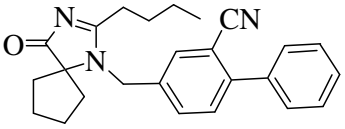
Fig.-1: Structure of Irbesartan



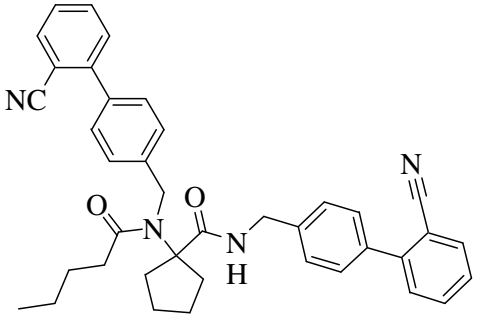
Imp-A



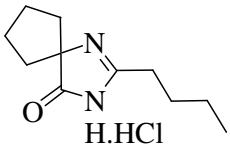
Imp-B



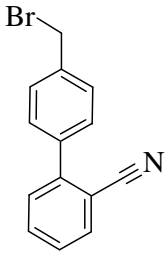
Imp-C



Imp-D



Imp-E



Imp-F

Fig.-2: Structures of impurities

Table-1: Screening of different bases and solvents

Expt No	Base	Solvent medium	Reaction temperature	Reaction time	Yield (%)	Purity by HPLC
01	Sodium hydroxide	DMF	25-30^{o}C	6 hours	62.9%	94.5%
02	Sodium hydroxide	Toluene + water	30-35^{o}C	2.2 hours	85.7%	96.3%
03	Sodium hydroxide	Dichloromethane + water	25-30^{o}C	1.5 hours	80.1%	99.2%
04	Potassium carbonate	DMF	40-45^{o}C	8.5 hours	73.7%	93.1%
05	Potassium carbonate	Toluene + water	91-95^{o}C	15 hours	77.6%	98.17%
06	Cesium carbonate	DMF	25-30^{o}C	4.5 hours	74.5%	94.3%
07	Sodium methoxide	DMF	25-30^{o}C	2.5 hours	72%	95.3%
08	Potassium tertiary butoxide	DMF	25-30^{o}C	1.5 hours	6.3.7%	93.7%
06	Potassium Hydroxide	Dichloro methane + water	25-30^{o}C	45 min	95.3%	99.9%

Table-2: Optimization of the equivalents of base

Expt No	KOH equivalents	Reaction time	Reaction temperature	Yield (%)	Purity by HPLC	Remarks
01	2.0	10 hours	25-30^{o}C	--	--	Reaction was not proceeded for completion. ~45% conversion observed by HPLC
02	4.0	6 hours	25-30^{o}C	--	--	Reaction was not proceeded for

						completion. ~75% conversion observed by HPLC
03	6.0	45 min	25-30°C	95%	99.8%	Reaction was proceeded for completion.
04	8.0	30 min	25-30°C	91%	97.8%	Reaction was proceeded for completion.

Table-3: Effect of temperature on the reaction progress

Expt No	Reaction temperature	Reaction time	Yield (%)	Purity by HPLC	Remarks
01	0-5°C	24 hours	--	--	Reaction conversion was observed as ~33% by HPLC
01	10-15°C	15 hours	--	--	Reaction conversion was observed as ~54% by HPLC
02	15-20°C	4.5 hours	--	--	Reaction conversion was observed as ~79% by HPLC
03	20-25°C	45 min	95.2%	99.87%	Reaction was proceeded for completion.
04	40-45°C	30 min	92.7%	98.1%	Reaction was proceeded for completion.

Table-4: Effect of isopropanol and water ratio on yield and quality

Expt No	Isopropanol : water	Yield (%)	Purity by HPLC (%)
01	0:5	98.1	96.5
02	1:4	97.3	99.05
03	2:3	95	99.95
04	3:2	93	99.95

Table-5: Yield and purities data for the purification in mixture of isopropanol and water

Expt No	Yield (%)	Purity by HPLC (%)						
		Total purity	Imp-A	Imp-B	Imp-C	Imp-D	Imp-E	Imp-F
01	95.4	99.95	0.01	ND	0.01	ND	ND	ND
02	96.0	99.93	0.03	ND	0.02	ND	ND	ND
03	94.8	99.95	0.01	ND	0.01	ND	ND	ND

***** ND= Not detectable

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