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RESEARCH ARTICLE

LARGE SCALE SYNTHESIS OF HIGH PURITY IOPAMIDOL

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ABSTRACT

A commercial scale synthesis of ultra-pure Iopamidol **1** has been achieved using a simple protocol employing with a total of 9 steps and easily isolatable intermediates. The key intermediate (*S*)-1-((3,5-bis-(chlorocarbonyl)-2,4,6-triiodophenyl)amino)-1-oxopropan-2-yl acetate **7** has been synthesized with high purity. The main advantages of the route include readily available inexpensive starting materials and good overall yield of 78%. The process impurities including chiral analogue have been well controlled without using any resins or chiral separation techniques but with simple chromatographic grade silica treatment. The structures of all intermediates prepared were confirmed by NMR, IR and MS and HPLC analysis.

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INTRODUCTION

The Introduction of contrast media containing non-ionic iodinated compounds in X-ray diagnosis as *opacifying* agents represented a remarkable progress in the state of the technique, so far that, these media will eventually substitute the traditional iodinated ionic products (Lars-Göran *et al.,* 1996). The general chemical structure of these media is characterized by a 2,4,6 triiodo benzene substituted in 1, 3, 5 positions with nonionic highly hydrophilic arms containing *amido* linkages and hydroxyl residues which provides the enhanced contrast effect (Bonnemain *et al.,* 1990). The iodine atoms bound in the molecules are responsible for the absorption of X-rays. It has been estimated that more than 80 million contrast enhanced X-ray scans are performed worldwide each year, and this means that well above 5000 tons of iodinated contrast agents are manufactured (Krasuski and Sketch, 2000). Iopamidol 1, chemically known as 1-N,3-N-bis(1,3-dihydroxypropan-2-yl)-5- [[(2S)-2-hydroxypropanoyl] amino]-2,4,6-triiodobenzene-1,3-dicarboxamide is one of the oldest unbeaten contrast media, appeared in the literature in early sixties and was proposed as substitute of other troublesome candidates. wenty years later, clinical trials confirmed Iopamidol safety and diagnostic efficacy for myelography (Bonati *et al.,* 1980 and Drayer *et al.,* 1982). Iopamidol **1**, has been described for the first time in the British patent no. 1,472,050. It is used in diagnostics as an X-ray non-ionic contrast agent (Felder and Pitre, 1977) and administered at high doses and therefore it must have extremely high requirements of purity (Pitrè and Felder, 1997). It was the pioneer molecule in this field and still is one of the most employed worldwide (Felder *et al.,* 1988; Pitrè, and Felder, 1980 and Felder, and Pitre, 1975). Perusing the patent and academic literature revealed that the acetyl protected chiral alcohol *i.e* (*S*)-2-acetoxypropanoyl chloride **6** is the key intermediate used by many generic companies in their syntheses of Iopamidol (Anelli *et al.,* 1997; Clendinning, 1961; Felder and Pitre, 1977; Cannata *et al.,* 1996; Villa and Paiocchi, 2003; Lorenzini *et al.,* 2007; Doran *et al.,* 1993; Wang *et al.,* 2003 and Rangareddy and Vijayabhaskar Reddy, 2016). Recently Iopamidol synthesis by greener approaches *via* smiles rearrangement (Anelli *et al.,* 2012) and its thermal properties (Bellich *et al.,* 2017) atropisomerism (Fontanive *et al.,* 2015) and polymorphism, (Bellich *et al.,* 2017) impact on environment (Wendel *et al.,* 2014) have also been reported.

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Heterocyclic nonionic X-ray contrast agents also prepared (Pillai *et al.,* 1994). There are several published syntheses of the Iopamidol structure in both racemic and enantioenriched forms and many of these share the same common bond formations with a multistep process to achieve pure Iopamidol in pharmaceutical accepted forms.

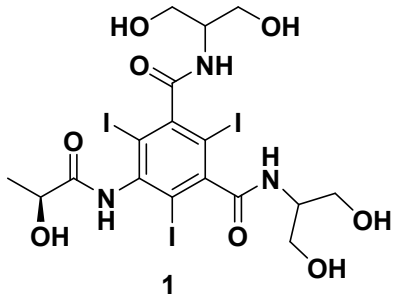


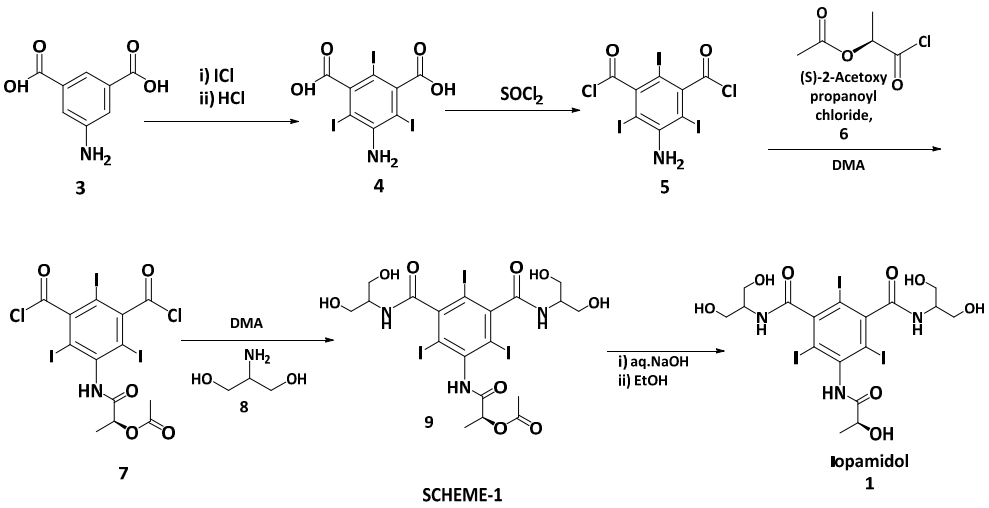
Figure 1. Iopamidol

The first generation manufacturing route (Scheme 1) for Iopamidol starts from the commercially available 5-amino isopthalic acid 3 iodination using a solution of iodine mono chloride in hydrochloric acid (Felder, 1984). The triodo derivative 4 is then chlorinated with thionyl chloride to give, via the not isolated sulfinyl intermediate 4(Gijsen *et al.,* 1999) acyl chloride 5 which is further react with (*S*)-2-acetoxypropanoyl chloride 6(Buisson and Azerad, 1999) in DMA. Derivative 7 is then amidated with an excess of 2-amino-1,3-propanediol (*Serinol*) 8, and the intermediate 9 is finally hydrolyzed with sodium hydroxide in presence of alcohol to give Iopamidol 1. A different process to produce Iopamidol was also studied by Bracco researchers (Felder *et al.,* 1992 and Musu *et al.,* 1990).

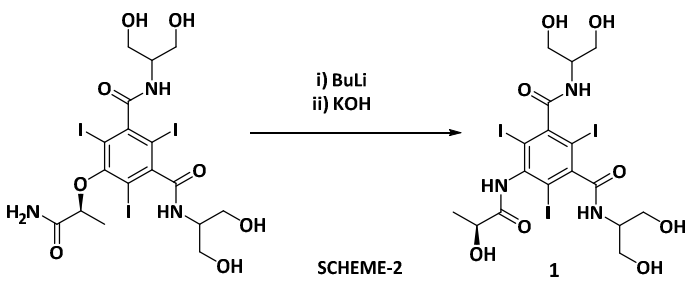
The crucial step is the final Smiles rearrangement, (Plesniak *et al.,* 2007; Truce *et al.,* 1970 and Anelli *et al.,* 1997) which consists of the migration of the substituted phenyl ring from one heteroatom (*O*) to the other (*N*), the latter being part of a secondary amide (Anelli *et al.,* 2001). An alternative process described by Bayer, (Rauchschwalbe *et al.,* 1999) wherein acyl chlorides eliminated in the preparation of carboxamide moieties. According to claim, 5-nitro-1,3-benzenedicarboxylic acid 3 can be esterified and amidated with *serinol*, 8, and then the nitro group reduced to amino to give the key intermediate 12 (Scheme-3) (Parady and Gelotte, 2000). A plurality of synthetic routes for preparing from lower alkyl esters of 5-nitro-isophthalic acid especially as methyl esters already known, (Ohen *et al.,* 1905) however, none of them are satisfactory. According to Clendinning, (1961) and others (Louis,1954) while nitrating dimethyl isophthalate using nitration mixture desired compound is obtained as main component, but considerable amount of monomethyl 5-nitroisophthalate (with our own observations) is formed by hydrolysis during work-up when the reaction mixture is discharged onto ice.

RESULTS AND DISCUSSION

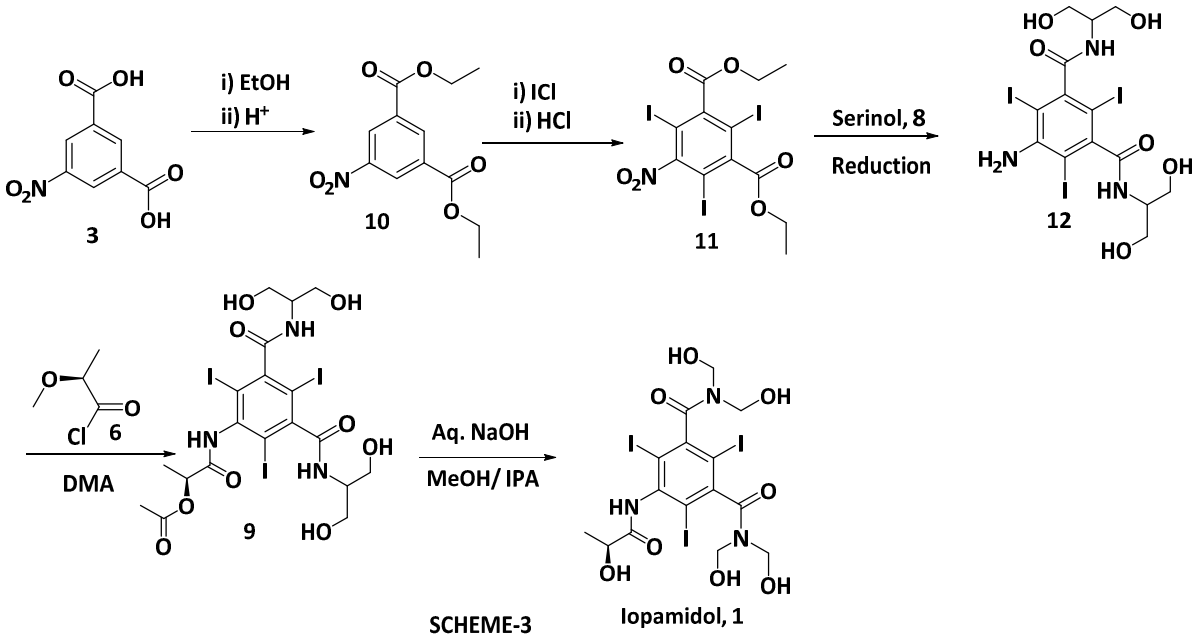
Despite of many synthetic methods are available from vast number of generic patents, (Felder and Pitre, 1977; Cannata *et al.,* 1996; . Villa, and Paiocchi, 2003; (Lorenzini *et al.,* 2007; Lorenzini *et al.,* 2007; Lorenzini *et al.,* 2006; Doran *et al.,* 1993 and Wang *et al.,* 2003) the synthetic routes starts from 5-amino-2,4,6-triiodoisopthalic acid. However, isopthalic acid **2** can be nitrated comfortably with nitration mixture but the reduction of Nitro acid 2A is bit tricky since reduction of aryl nitro compounds is known to proceed via the hydroxylamine, followed by azoxy and azo compounds to its corresponding aryl amine after a prolonged reaction time (Wang *et al.,* 2003).



Scheme 1. Commercial scale synthesis of Iopamidol



Scheme 2. Iopamidol synthesis *via* Smiles rearrangement



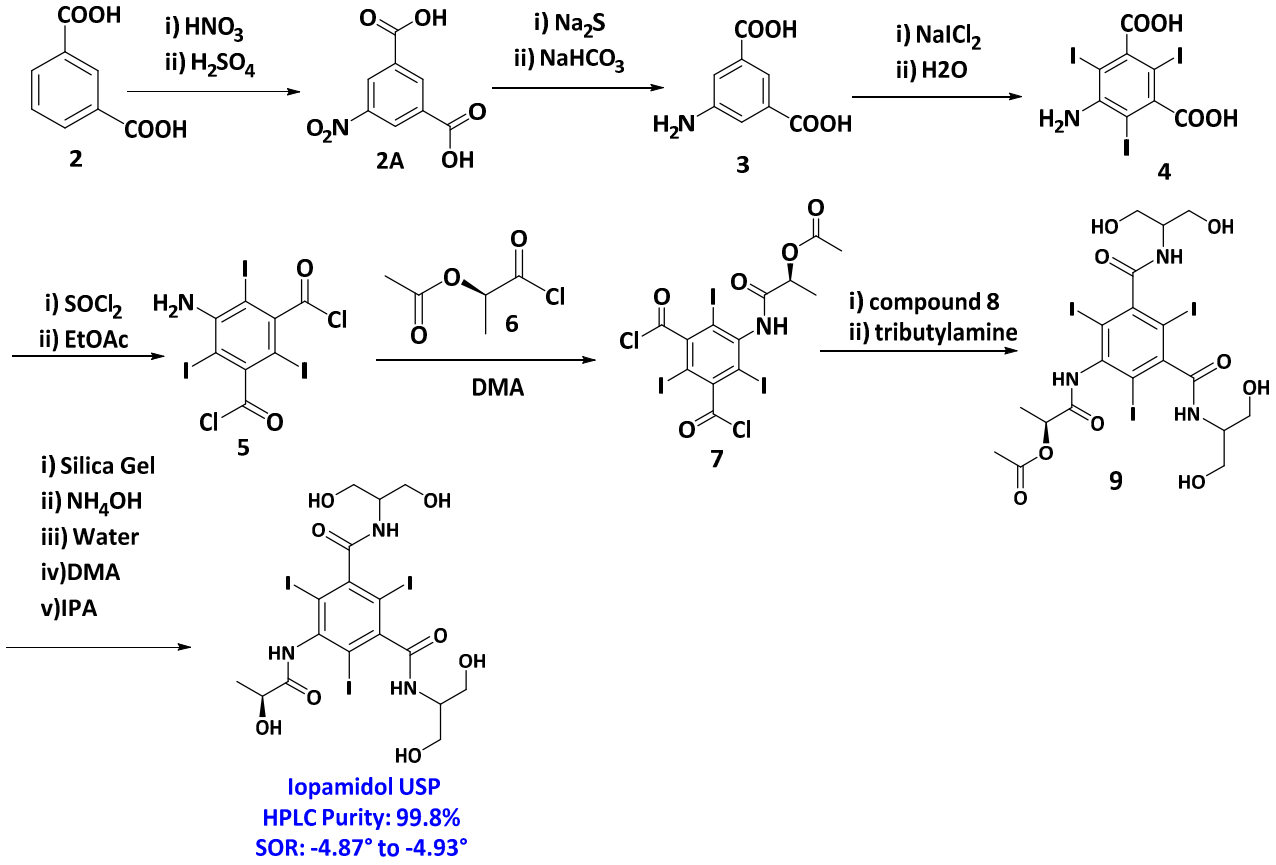
Scheme 3. Synthesis of Iopamidol via Alkyl Esters

Therefore, the ability of reaction conditions lies to accelerate and reduce the reaction time and also the amount of intermediates isolated, increasing the yield of aryl amine. Fe/HCl, Fe/Acetic Acid, Raney Nickel, Pd/C(Behrens and Dahl, 1999; Tafesh and Weiguny, 1196) Sn/HC[l](Beyer,1882) and Lewis Acid $AlCl_3$ (Reinsch *et al.,* 2013) have been used to reduce 5-nitro isophthalic acid. Nevertheless, either of the conditions were found to be suitable in the reduction stage, though yields are moderately good, due to the temperature and time of reaction required for the complete conversion were notably higher and longer. In addition, cleansing of the metal especially iron sweeps reactive intermediates or products from the surface making way for subsequent reactions (Hung *et al.,* 2000). To avoid these difficulties, we have eliminated metal mediated reduction instead used a simple and eco-friendly method by using sodium sulphide/sodium bicarbonate (Hartman and Silloway, 1955 and Rangareddy and Vijayabhaskar Reddy, 2016) mixture to reduce 5-nitroisophthalic acid to 5-aminoisopthalic acid 3 in 89% yield. Available synthetic protocols, (Felder and Pitre, 1977; Cannata *et al.,* 1996; . Villa, and Paiocchi, 2003; (Lorenzini *et al.,* 2007; Lorenzini *et al.,* 2007; Lorenzini *et al.,* 2006) suffers from a wide variety of insufficiencies in preparing 1 are (i) using metal for reduction (ii) using high concentrated resins for purification and (iii) no control over process impurities generated during the linear synthesis. Therefore, these approaches cannot be used in large-scale manufacturing. In spite the route shown in Scheme 3. gave an efficient process that can deliver several grams of pure material, ultimately this process was still far from ideal in a manufacturing setting in the long term. Since X-ray contrast agents generally administered intravenously hence ultra-purity and regulatory prescribed standard material (*USP* Monographs, 2017; *EP* monographs, 2017) are highly required. However, the present available routes are highly suffering of delivering several kilograms of pure material. At this juncture, while developing the commercial scale synthesis of Compound 1 as per regulatory requirement (*USP* Monographs, 2017; *EP* monographs, 2017) we have found solutions (Scheme 4) (Rangareddy and Vijayabhaskar Reddy, 2016) for drawbacks in the current available synthetic routes.

The process disclosed in this communication covered by our patent (Rangareddy and Vijayabhaskar Reddy, 2016) (Scheme-4) and starts with a nitration of isophthalic acid 2A whose reduction with sodium sulphide in presence of sodium bicarbonate give 5-amino isophthlicacid 3 in about 92% yield and around 99% of HPLC purity (Table-1). Then compound 3 iodinated with $KICl_2$ or $NaICl_2$ in water and converted to 5-amino-2,4,6-triiodoisophthalic acid 4 which subsequently converted to triiodo isophthalyl dichloride 5 by means of thionyl chloride in ethyl acetate. The dichloride 5is then allowed to react with compound 6 using DMA to give 7 in very high purity and yield.

Then compound 7 converted to diamide by reacting with 2 equivalents of 2-amino-1,3-dihydroxypropane (*Serinol*) 8 in the presence of tributylamine as a base. Thus formed chiral amide 9 is hydrolyzed with an aqueous NH4OH in presence of Silica Gel. The crude product is treated with silica gel to remove the *o*-acetyl and *N*-acetyl impurities (Figure-3). Due to Silica high specific surface area (around 800 m2/g) and works as mild Lewis acid makes as a primary choice of interest to adsorb hydroxyl analogues of Iopamidol during the hydrolysis over resins. The final recrystallization is performed by using water and IPA to provide ultra-pure lopamidol1 (Rangareddy and Vijayabhaskar Reddy, 2016). Although, triiodination of 5-amino-1,3-dibenzoic acid with ICl and its derivatives are well documented in the literature, (Parkesh *et al.,* 2006; Pillai *et al.,* 1994) those methods suffer from major drawbacks mainly due to the corrosive properties of the iodinating agents and to their limited storage life.

As such, particularly when considering large amounts of reactants and substrates to be employed, for instance on an industrial scale, the need of preparing the iodinating agent before usage and its storage may become particularly troublesome. In addition, the presence of chlorine atoms within the iodinating agents themselves may lead to side-reactions and, thus, to the undesired formation of chlorine side-products as pharmacopeias listed impurities, (Parkesh *et al.,* 2006) which may affect reaction yields and purity of the final compounds. Thus, attempts have been devoted to address iodination methods comprising the use of iodinating agent's alternative to iodine chloride or derivatives thereof.



Scheme 4. Commercial Synthesis of Iopamidol via Isolated itermediates

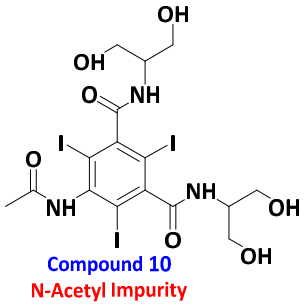


Figure 2. N-Acetyl impurity

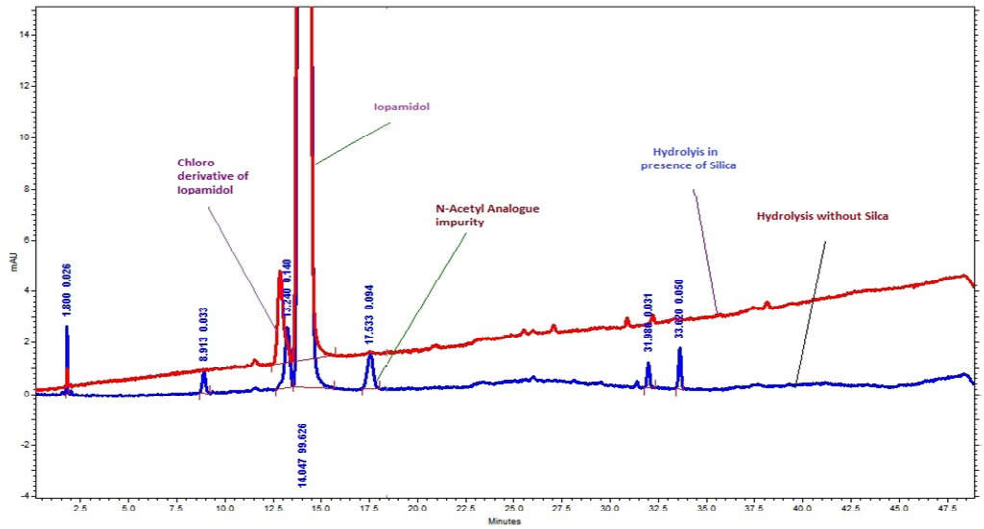


Fig. 3. HPLC chromatogram of Hydrolysis of compound-9 with Silica gel

Among them are, for instance, the electrochemical iodination of 3,5-disubstituted anilines or of given 3,5-disubstituted phenols, as disclosed, respectively, in WO 1996/37461 in pending, and still unpublished. Beside the above electrochemical synthetic approaches, the iodination of phenol derivatives, referred to as ortho hydroxyl substituted aromatic carbonyl compounds, in the presence of molecular iodine suitably activated with a strong oxidizing agent, including iodic acid, has been described by Patil (Massa *et al.,* 2005; Patil *et al.,* 2006). In this respect, it is worth noting that the use of strong oxidizing agents with aniline or even halogenated anilines is known to lead to the formation of mixtures of colored by-products, mainly azo-compounds deriving from oxidative coupling reactions involving the aromatic amino group (Baer and Tosoni, 1956; Cross and Chapman, 1991; Malthe-Sorenssen *et al.,* 2001).

In spite of this major drawback, we have observed that the triiodination of suitable 3,5-disubstituted anilines can be advantageously carried out in high yields and purity by using a pre prepared $NaICl_2$ in Water. The iodination reaction of compound **3** was more easily processed in a very good yield due to high activity of $NaICl_2$ (Baer and Tosoni, 1956; Cross and Chapman, 1991). Although the reaction observed to be taken longer hours than expected due to slow conversion of mono to di and to triiodinated compound, but the yield is good at the given reaction conditions to >70% after a smooth work up. The triiodo derivative 4 is then chlorinated with thionyl chloride and compound 5 has been isolated in moderate yield of 87%. Compound 5 is observed to be light and temperature sensitive hence the 5-amidation with 2-(*S*)-acetoxy propionyl chloride carried out at 0 to 5°C by using DMA as a base and solvent.

Impurity

While scaling up batches, it was found with HPLC analysis an impurity at the level of 1.3% by area with RRT of 0.96 (Table-2, Figure-3). An attempt to identify the impurity by LC-MS failed as no molecular ion was observed. A sample of impurity was isolated by chromatography and its mass spectrum (EI) was characteristic of acetyl moiety. Suspicion was immediately directed at (*S*)-2-acetoxy propionyl chloride as the source of the problem. As commercial (*S*)-2-acetoxy propionyl chloride comes with a slight excess of acetyl chloride in it which generating this impurity. However, this impurity is very detrimental and difficult to eliminate and will appear considerable amount in Iopamidol.

Control of the Impurity:

Reasons for variations in batches and previous non-detection of *N*-acetyl impurity were sought, and clues were found in the hydrolysis step. There was a high chance of acetyl radical may be generated while de-acetylation of hydroxyl group in the presence of alcohol. However, this possibility can be very much emphasized with HPLC where the impurity is only generating during the hydrolysis step in methanol or ethanol where as in aqueous ammonia mediated hydrolysis ultimately controls this impurity.

Conclusion

In summary, we have developed a simple protocol for the preparation of Iopamidol and its intermediates for commercial synthesis with very high purity (Rangareddy and Vijayabhaskar Reddy, 2016). The reduction of 4 to 5 was carried out without metal or heterogeneous catalysts and the high purities of all the intermediates achieved using eco-friendly solvents like IPA/acetonitrile/methanol mixtures in presence of Silica Gel by eliminating the so called anionic resins. In addition, the synthesis, is now free of any toxic metals, has simple solid isolations directly from the reaction mixtures producing an API of high purity for requirement of X-ray contrast agents.

Experimental Section: General. Compounds 2, 6, 8 and solvents were obtained from commercial suppliers and used without further purification. IR spectra were recorded Shimadzu FT-IR instrument. Melting points were obtained with Mettler Toledo and uncorrected. NMR spectra were recorded using a Bruker DPX-300 MHz instrument.

Example 1: Preparation of 5-nitroisopthalic acid (2A)

To a stirred solution of sulfuric acid (459.89 kg, 4.692 Kmol) was added 73% nitric acid (207.8 kg, 3.298 Kmol) over the period of 1 h at 0 to 5°C. Then isothalic acid **2** (100 kg, 0.602 Kmol) was added lot wise to reaction mixture under 5°C and agitated for 1 h at same temperature. Then temperature increased to 60 to 65°C and stirred for 3 h. After that, the reaction temperature was further increased and maintained at 80 to 85°C and stirred for 9 h. Then the reaction mass was cooled to 30 to 35°C and charged into ice cold water and stirred for 1h at 5 to 10°C. The solid thus precipitated was filtered off and washed with100 L chilled water. The resultant solid dried at 70°C for 4 h to give 2A as white powder (116.3 Kg, 91.5%). HPLC Purity: 99.68%, MS (M+H): 212.23; IR (KBr, cm^{-1}): 3500, 1720, 1360, 1290, ^{1}H-NMR: (300 MHz, DMSO-d_6), δ 12.978 (s, 2H), 8.74 (s, 3H); ^{13}C-NMR (300 MHz, DMSO-d_6), δ 164.95, 148.16, 135.19, 133.35, 127.28.

Example 2: Preparation of 5-aminoisopthalic acid (3)

A solution of sodium sulphide (193 kg, 2.474 Kmol), sodium bicarbonate (208 kg, 2.476 Kmol) in 697 L of DM Water was added compound 2A (116.3 kg, 0.5518 Kmol) followed by 233 L of methanol at 30°C and stirred. Then the temperature was raised to 80 to 85°C and stirred over 5 h. Then the reaction was cooled to 30°C and mass was filtered off. The filtrate pH was adjusted to 1.1 with conc. HCl and stirred for 1 h at 5 to 10°C. The resultant solid was filtered and washed with 100 L of DM water. The solid dried at 75°C give 3 as an off-white powder (92.78 kg, 93%). HPLC purity: 98.90%, MS (M+H) 182.5; IR (KBr, cm^{-1}): 3500, 3020, 1715; ^{1}H-NMR: (300 MHz, DMSO-d_6), δ 7.70 (s, 1H), 7.34 (s, 2H); 6.23 (br 2H); ^{13}C-NMR (300 MHz, DMSO-d_6); δ 168.90, 149.02, 134.11, 118.52, 118.2.

Example 3: Preparation of 5-amino-2,4,6-triiodoisopthalic acid (4)

A stirred mixture of 3036 L of DM water and compound **3** (92 kg, 0.5082 Kmol) at 50 to 55°C with constant stirring was added $NaICl_2$ (403 kg, 1.825 Kmol) in 3 h. The homogeneous reaction mixture was stirred for 24 h at ambient temperature. After that, the reaction mixture was cooled to 0 to 5°C. The resulted solid was filtered off and washed with 150 L of DM water. The solid dried to give 4 as brown powder (201 kg, 71%). HPLC purity: 99.67%, MS (M+H) 559.84; IR (KBr, cm^{-1}): 3500, 3020, ^{1}H-NMR: (300 MHz, δ, DMSO-d_6), δ 13.80 (br, 2H), 5.58 (s, 2H); ^{13}C-NMR (300 MHz, DMSO-d_6), δ 169.94, 148.32, 147.89, 78.29, 70.58.

Example 4: Preparation of 5-amino-2,4,6,-triiodo isopthaloyl dichloride (5)

A stirred solution of 5-amino-2,4,6-triiodoisopthalic acid 4 (201 kg, 0.359 Kmol), tertiary butyl ammonium bromide (200 g) in 2 L of ethyl acetate was slowly added thionyl chloride (222 kg, 1.865 Kmol) at room temperature. Then the temperature of mass increased to 75° C and stirred for 20 h. The reaction was cooled to 10°C and added 150 L of DM water. Then the ethyl acetate layer was washed with 50 L of sodium bicarbonate (2%) solution followed by 50 Lt of saturated ammonium chloride solution. The organic layer thus collected and evaporated to gives off compound **5 (**182 kg, 85%). HPLC purity: 97.97%, MS (M+H): 596.9; IR (KBr, cm -1): 3500, 3020, 1725; ^{1}H-NMR: (300 MHz, DMSO-d6), δ 6.11 (s, 2H); ^{13}C-NMR (300 MHz, DMSO-*d6*), δ 169.55, 149.06, 148.92, 78.39, 66.17.

Example 5: Preparation of (*S*)-1-((3, 5-bis(chlorocarbonyl)-2,4,6-triiodophenyl) amino-1-oxopropan-2-yl acetate (7)

Compound 5 (182 kg, 0.305 Kmol) dissolved in 364 L of DMA and added *(S*)-2-acetoxypropionyl chloride 6 (116.48 kg, 0.7739 Kmol) at 0 to 5°C about 1 h. Then reaction mass kept with stirring for 16 h at 30 to 35°C. Then 100 L of DM water and 1092 L of chloroform were simultaneously added to reaction mixture. The organic layer thus separated was washed with 50 L of sodium bicarbonate (2%) solution. The organic layer was evaporated to give 7 (196 kg, 90.5%). HPLC Purity: 98.35%, MS (M+H): 710.4; IR (KBr, cm^{-1}): 3100, 3020, 1725, 1685*;* ^{1}H-NMR: (300 MHz, DMSO-d_6), δ 10.34 (s, 1H), 5.27-5.20 q, 1H), 2.14 (s, 3H), 1.55-153 (d, 3H); ^{13}C-NMR (300MHz, DMSO-d_6) , δ 169.51, 169.28, 169.04, 168.66, 168.49, 149.89, 144.07, 143.28, 99.91, 85.94, 69.43, 20.80, 17.56.

Example 6: Preparation of (*S*)-1-((3, 5-bis ((1, 3-dihydroxypropan-2-yl) carbamoyl)- 2, 4, 6-triiodophenyl) amino-1-oxopropan-2-yl acetate (9)

Compound 7 (196 kg, 0.276 Kmol) dissolved in 196 L of DMA and 588 L of MeCN and was added tributylamine (112.58 kg, 0.6069 Kmol) at 45°C with constant stirring. Then added 8 (58.8 kg, 0.646 Kmol) along with 196 L of DMA at ambient temperature over 2 h. Mass temperature was increased to 100°C and stirred for 5 h. Then reaction mixture cooled to 30°C and added DM water (65 L) and DCM (350 L) simultaneously to reaction mixture. The collected organic layer was evaporated to gives 9 (163 kg, 72 %). HPLC purity 97.14%, MS (M+H): 820.9*;* ^{1}H-NMR: (300 MHz, DMSO-d_6*),* δ: 10.11 (s 1H), 8.20 (s, 2H), 4.68-4.48 (q, 1H), 4.36-4.35 (m, 2H), 3.53-3.51 (d, 8H), 2.11 (s, 3H), 1.53-1.50 (d, 3H); ^{13}C-NMR (300 MHz, DMSO-d_6), δ 169.57, 169.10, 168.90, 168.12, 168.06, 150.11, 149.89, 142.18, 98.70, 98.48, 69.52, 69.47, 62.16, 59.22, 58.93, 53.22, 53.07, 52.83, 37.53, 34.64, 25.54, 21.49, 20.94, 20.88, 17.67, 17.64.

Example 7: Preparation of Iopamidol (1)

Compound 9 (163 kg, 0.199 Kmol) dissolved in aqueous ammonia (652 Kg, 18.6 kmol) containing silica gel (50 Kg, *60-120* mesh). The temperature of mass was raised to 40° C and stirred at ambient temperature for 4 h. Then pH was adjusted to 5 with con. HCl and cooled to 5°C. . Then the mass was filtered off on celite bed, washed with 25 L of DM water and collected filtrate was distilled out to get 1 (127kg, 82.5%). HPLC purity : 99.0%. MS (M+H) : 778.4; ^{1}H-NMR: (300 MHz, D_2O), δ, 4.50-4.43 (q, 1H), 15-3.79 (m, 2H), 3.18-3.79 (d, 8H), 1.54-1.51 (d, 3H), ^{13}C-NMR (300MHz, DMSO-d_6), δ 169.1, 168.9, 168.12, 150.11, 150.01, 149.89, 142.18, 98.83, 98.7, 90.48, 69.52, 69.47, 62.16, 59.32, 58.93, 53.22, 53.07, 52.83, 37.59, 34.64, 25.54, 21.49, 20.94, 20.88, 17.66.

Purification of Iopamidol in Presence of Silica Gel

Crude Iopamidol **1** (127 Kg) was dissolved in DMA at 30°C and stirred for 1 h. Then 100 kg of Silica gel (60-120 *mesh*) charged with stirring for 2 hrs. Then filtered the reaction mass at through Celite bed and washed with another 50 L of DMA. The collected filtrates were heated 50°C and added 1216 L of IPA and stirred for 5 h at same temperature. The resultant solid cooled to 30°C and filtered. The white wet cake obtained was dried under vacuum to yield high pure Iopamidol (111.76 kg, 88%). HPLC purity: 99.83%, SOR: $[\alpha]^{D}_{20}$ -4.89°, c= 40% in water, λ=436 nm).

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