Large Scale Synthesis of 5-amino-2,4,6-triiodoisophthalic Acid: A Key Intermediate for Iodinated X-ray Contrast Agents

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(Received on: February 13, 2018)

ABSTRACT

A commercial scale synthesis of 2,4,6-triiodoisophthalic acid 1, with high purity has been achieved using a highly convergent route employing with a total of three straight steps and easily isolated intermediates. The main advantages of the route include readily available starting materials and good overall yield of 81%. The structures of all intermediates were confirmed by ¹H-NMR, ¹³C-NMR, IR and MS and HPLC.

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Keywords: Large scale synthesis, 2,4,6-triiodoisophthalic acid derivatives, x-ray contrast agents.
INTRODUCTION

Contrast agents have long been used for the imaging of anatomic boundaries and to explore normal and abnormal physiologic findings. The introduction of increasingly faster and more discriminating radiographic imaging techniques has resulted in the need for radiation-attenuating contrast agents that can be used in traditional radiographic imaging or, more recently, in subtraction imaging, both of which can be projected and rotated in three dimensions.\(^{1a}\)

However, 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.\(^{1b}\) So far the most successful and widely applied contrast agents in use today are the iodinated contrast agents, first introduced into clinical practice in the 1950s. It is estimated that approximately 75 million doses of contrast agents are given worldwide each year.\(^{1c}\) The iodinated contrast agents fall into four broad groups, each possessing unique chemical, physical, and biologic properties to address the demands of a wide variety of imaging modalities. The iodinated contrast agents share a similar function group a tri-iodinated benzene ring (Figure 1). Iodine plays a key role in the attenuation of x-rays. The atomic radius of a covalently bonded iodine atom is approximately 133 pM, which falls within the range of the wavelengths of x-rays: 10 to 10,000 pM; thus, x-rays are easily attenuated by the iodine atoms.\(^{1d}\) Furthermore, three iodine atoms covalently bonded to a benzene ring offer couple of major advantages: (i) three large atoms located in such close proximity increase the effective molecular size, thus attenuating longer wavelength x-rays, and (ii) covalent bonding to a stable organic functional group reduces the risk of toxic effects from free iodide.

![Figure 1. 5-amino-2,4,6-triiodoisophthalic acid (1)](image)

Two major chemical variations result in four classes of iodinated contrast agents. Compounds consist of either one triiodinated benzene ring (monomers, Figure-2) or di-triiodinated benzene rings linked by an organic functional group (dimers, Figure-3).

![Figure 2. Some monomeric triiodinated contrast agents](image)
In addition, ionic tendency is governed by the presence (ex: ionic) or absence (ex: nonionic) of a carboxylate (-COO-) functional group contained on an organic side chain. Typically, because the carboxylate moiety adds a net negative charge to the molecule, these anionic agents are usually available as salts of sodium, calcium, or methyl glucamine cations. Hence, the four major classes of iodinated contrast agents are as follows:

1. Ionic monomer: single triiodinated benzene ring with a carboxylate-containing benzene substituent.
2. Ionic dimer: two linked triiodinated benzene rings in which at least one carboxylate-containing group is substituted on at least one benzene ring.
3. Nonionic monomer: mono triiodinated benzene ring without a carboxylate-containing benzene substituent.
4. Nonionic dimer: two linked tri-iodinated benzene rings that do not contain a carboxylate functional group within any benzene substituent.

![Figure 3. Some dimeric triiodinated contrast agents](image)

The general chemical structure of these media is characterized by a 2,4,6 triido benzene substituted in 1, 3, 5 positions with nonionic highly hydrophilic arms containing amido linkages and hydroxyl residues which provides the enhanced contrast effect. 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. However, all intravascular iodinated contrast agents are generally classified in to three major categories based on a tri-iodinated benzene ring.

i) **High-osmolar** contrast media (HOCM) are the oldest agents. They are relatively inexpensive, but their utility is limited. They are monomers (single benzene ring) that ionize in solution with a valence of -1. Their cation is either sodium or meglumine. (ex: Diatriazoic acid).

ii) A major advance was the development of nonionic compounds. They are monomers that dissolve in water but do not dissociate. Hence, with fewer particles in solution, they are designated **low-osmolar** contrast media (LOCM). (ex: iohexol and iopamidol).
The most recent class of agents is dimers that consist of a molecule with two benzene rings (again, each with three iodine atoms) that does not dissociate in water (nonionic). These compounds are designated iso-osmolar contrast media (IOCM). (ex: Iodixanol). Although there found to be a huge variation in efficacy of the contrast agents mentioned, typically majority are synthesize form a common key intermediate 1 (Scheme-1) which is an essential part of their structure. Hence, as part of our ongoing research, we have decided to make 5-amino-2,4,6-triiodoisophthalic Acid with commercially available raw materials with economically friendly route otherwise the commercial sources of this intermediate are sparse and highly expensive.

Scheme 1. Application of key intermediate 5-amino-2,4,6-triiodoisophthalic Acid in the synthesis of various contrast agents.
There are several published syntheses of this intermediate are available but all routes fail to establish a standard protocol for the synthesis of high pure material. A plurality of synthetic routes for preparing from lower alkyl esters of 5-nitro-isophthalic acid especially as methyl esters already known, however, none of them are satisfactory. According to Clendinning, and others, 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. This was modification of the early route, and although this approach successfully produced an API in few kilograms, but a number of drawbacks was associated following the first kilo-lab scale manufacturing campaign. Moreover, the resulting product is by no means pure enough for the above mentioned use in pharmaceutics with the obtained yield of around 35 to 38 % only.

RESULTS AND DISCUSSION

Despite of many synthetic methods are available from vast number of generic patents, the all available synthetic routes starts from commercially available isophthalic acid. However, isophthalic acid can be nitrated comfortably with nitration mixture but the reduction of Nitro acid is 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. 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, Sn/HCl and Lewis Acid AlCl3 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. To avoid these difficulties, we have eliminated metal mediated reduction instead used a simple and eco-friendly method by using sodium sulphide/sodium bicarbonate mixture to reduce 5-nitroisophthalic acid to 5-aminoisophthalic acid in 89% yield.

In spite the route shown in Scheme 2 gave an efficient process that was capable of delivering 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 are highly required. However, the present available routes are highly suffering of delivering several kilograms of pure material.

Scheme 2. Synthesis of 5-amino-2,4,6-triiodoisophthalic Acid via Alkyl Esters.
After considering all, a commercial route was hence designed and developed that consists of a total 4 synthetic steps with all isolated intermediates starting with readily available isophthalic acid. All the intermediates prepared in house with high purity and characterized which otherwise very difficult to obtain from the commercial sources for low cost.

The process disclosed in this communication covered by our patent and starts with a nitration of isophthalic acid 2 leads to compound 3 whose reduction with sodium sulphide in presence of sodium bicarbonate give 5-amino isophthalic acid 4 in about 93% yield and around 99% of HPLC purity (Table-1).

Table 1. HPLC parameters for the analysis of 5-amino-2,4,6-triiodoisophthalic acid

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Then compound 4 iodinated with either KICl2 or NaICl2 in water and converted to compound 1 which further may be converted to triiodoisophthaloyl esters 7 by means of thionyl chloride in ethyl acetate followed by treating with appropriate alcohols.

Although, triiodination of 5-amino-1,3-dibenzoic acid with ICl and its derivatives are well documented in the literature, those methods suffer from major drawbacks mainly due to the corrosive properties of the iodinating agents and to their limited storage life. Thus, attempts have been devoted to address iodination methods comprising the use of iodinating agent’s alternative to iodine chloride or derivatives thereof. 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.

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. 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 NaICl2 in Water.

The iodination reaction of compound 4 was more easily processed in a very good yield due to high activity of NaICl2. Although the reaction observed to be slow than expected, it
could be understood that, due to slow conversion of mono to di and finally to triiodinated compound as observed in HPLC. But the yield is good at the given reaction conditions to >70% after a smooth work up.


EXPERIMENTAL SECTION

General. Compound 2 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; $^1$H-NMR spectra were measured with reference to an internal standard of TMS at 0 ppm and $^{13}$C-NMR spectra measured with DMSO signal at 39.5 ppm. The HPLC analysis was performed with an Agilent 1100 instrument with DAD detector. The processes described below are taken from the laboratory process descriptions used as for pilot plant manufacture. A description of the scale on which these processes were operated is given for each stage.

Example 1: Preparation of 5-nitroisophthalic acid (3):

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 3 as white powder (116.3 Kg, 91.5%). m.p: 258.7°C; 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-aminoisophthalic acid (4):

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 4 as an off-white powder (92.78 kg, 93%). m.p.: >300 °C; HPLC purity: 98.90%, MS (M+H) 182.5; IR (KBr, cm\(^{-1}\)): 3500, 3020, 1715; \(^1\)H-NMR: (300 MHz, DMSO-\(d_6\)), \(\delta\) 7.70 (s, 1H), 7.34 (s, 2H); 6.23 (br, 2H); \(^13\)C-NMR (300 MHz, DMSO-\(d_6\)), \(\delta\) 168.90, 149.02, 134.11, 118.52, 118.2.

Example 3: Preparation of 5-amino-2,4,6-triiodoisopthalic acid (1):

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 1 as brown powder (201 kg, 71%). m.p.: 268 °C; HPLC purity: 99.67%, MS (M+H) 559.84; IR (KBr, cm\(^{-1}\)): 3500, 3020, \(^1\)H-NMR: (300 MHz, DMSO-\(d_6\)), \(\delta\) 13.80 (br, 2H), 5.58 (s, 2H); \(^13\)C-NMR (300 MHz, DMSO-\(d_6\)), \(\delta\) 169.94, 148.32, 147.89, 78.29, 70.58.

![Figure 4. \(^1\)H-NMR spectrum of 5-amino-2,4,6-triiodoisopthalic acid.](image)
Figure 5. $^{13}$C-NMR spectrum of 5-amino-2,4,6-triiodoisopthalic acid.

Figure 6. HPLC spectrum of 5-amino-2,4,6-triiodoisopthalic acid.
CONCLUSION

In summary, we have developed a highly efficient general approach for the preparation of 5-amino-2,4,6-triiodoisophthalic acid, a key intermediate in the preparation of so many triiodinated x-ray contrast agents, which represents a significant improvement over existing protocols, advantageous to the scientific community. This approach offers many benefits, including higher overall yields, simpler purification operations, considerable reduction time, while avoiding the need for additional steps. Furthermore, it has the potential to be successfully used for the synthesis of analogues and any number of iodinated contrast agents.

ACKNOWLEDGMENTS

We would like to thank the management and the broader team based in Saraca Laboratories, Hyderabad, India for all the work and effort put in by all on the commercial development of iodinated contrast agents over its varied and lengthy history.

REFERENCES