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Green approaches to the production of iopamidol*

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Abstract: Iodinated contrast agents, such as iopamidol, are worldwide employed for performing a number of X-ray diagnostic procedures. Every year, thousands of tons of iodinated contrast agents are manufactured for the market with chemical processes that usually employ thionyl chloride. In this paper, we describe two new green approaches to iopamidol that avoid or reduce the use of this noxious reagent.

Keywords: green chemistry; imaging technology; iodinated contrast agents; iopamidol; thionyl chloride; X-ray contrast agents.

INTRODUCTION

Nowadays, the most commonly used iodinated contrast agents are non-ionic, water-soluble aromatic molecules containing three atoms of iodine, an element with high X-ray attenuation [1].

In particular, 5-acylamino-2,4,6-triiodo-1,3-benzenedicarboxamides are compounds widely employed in medicine as X-ray contrast agents since they are able to improve the images obtained with routinely used diagnostic procedures such as angiography, urography, and computed tomography [2–4]. These compounds have a very low toxicity, are not metabolized in humans, and are completely eliminated unchanged by renal excretion [5,6]. 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 [7].

Iopamidol **1** (Scheme 1), patented in 1974, was the first non-ionic X-ray contrast agent to give rise to stable aqueous formulations. It was the pioneer molecule in this field and still is one of the most employed worldwide [8–10].

The current manufacturing process for iopamidol **1** is shown in Scheme 1 and involves the iodination of 5-amino-1,3-benzenedicarboxylic acid **2** with a solution of iodine monochloride in hydrochloric acid [11]. The triododerivative **3** is then chlorinated with thionyl chloride to give, via the not isolated sulfinyl intermediate **4** [12], the acyl chloride **5**, which is reacted with (*S*)-2-acetoxypropanoyl chloride **6** [13] in *N*,*N*-dimethylacetamide. Derivative **7** is then amidated with an excess of 2-amino-1,3-propanediol (commonly named serinol) **8**, and the intermediate **9** is finally hydrolyzed with sodium hydroxide to give iopamidol **1**.

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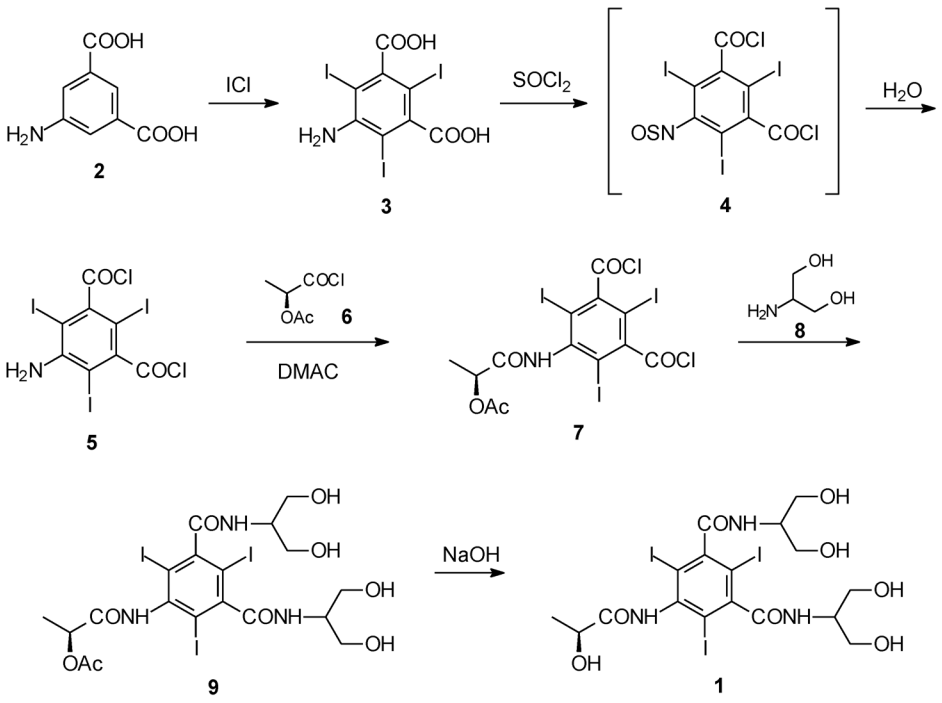
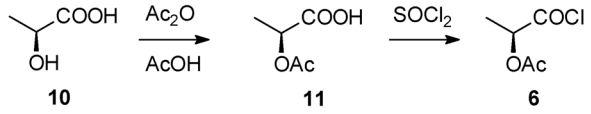


Scheme 1

The above process, with some modifications, has been used since the early 1980s. Nevertheless, the replacement of some of the toxic and hazardous reagents with more benign ones would be important from an environmental point of view. The iodination reaction to give **3**, for example, is performed with ICl, which is obtained by direct oxidation of iodine with chlorine while the production of **5** needs thionyl chloride. The latter is also employed for the synthesis of **6** from lactic acid **10** (Scheme 2).



Scheme 2

Thionyl chloride is a low-cost and versatile reagent [14–19], widely employed in organic syntheses performed at laboratory or industrial scale. It is the reagent of choice for the preparation of acid chlorides [20], and the procedure usually involves heating the carboxylic acid with an excess of thionyl chloride neat or dissolved in an inert solvent. Usually, a catalyst, such as pyridine or *N*,*N*-dimethylformamide, is employed to promote the reaction. Heating at the boiling point of the solvent speeds the reaction to completion by removal of the volatile by-products, HCl and SO_2. For a laboratory preparation this is not a problem, provided that the reaction is performed under a well-ventilated fume cupboard. At industrial scale, this is a drawback since the gaseous stream must be efficiently treated in a scrubber with an alkaline solution, producing a consistent amount of salts.

Moreover, thionyl chloride has several safety problems because it is a very corrosive and reactive reagent. It causes severe skin burns, eye damage, and respiratory tract injury if the vapors are inhaled. It reacts violently with water, generating hydrogen chloride and sulfur dioxide, both irritating for the

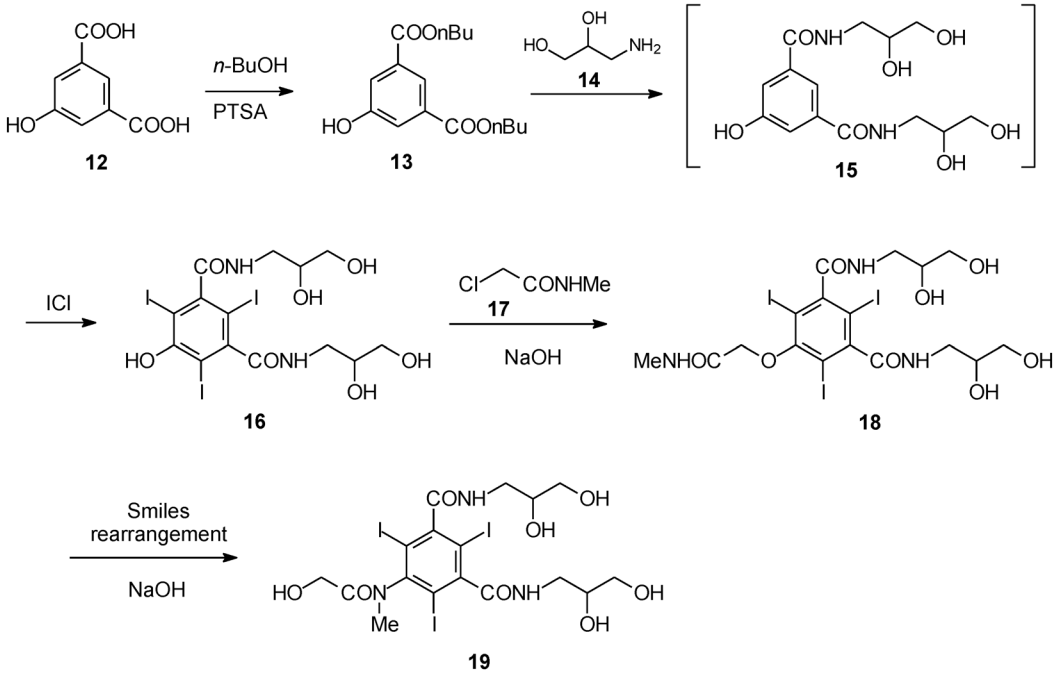
respiratory system. Since thionyl chloride is a precursor for a chemical weapon such as mustard gas, its production, commercial sale, and export are regulated under the international chemical weapons treaty [16].

In this article, we describe two new approaches to iopamidol that have been developed with the aim to largely decrease the use of thionyl chloride and to reduce the amount of related wastes, according to the principles and the philosophy of green chemistry [21–23].

ALTERNATIVE PROCESSES

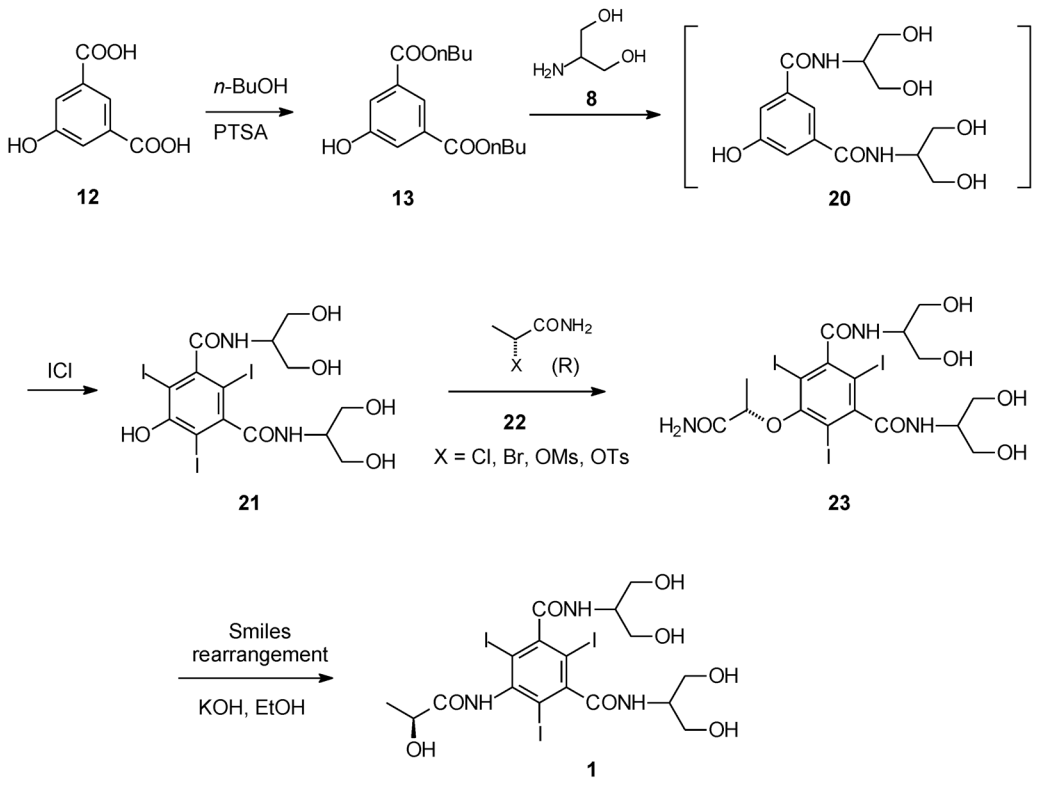
Smiles rearrangement

A different process for the production of iopamidol was studied and developed trying to mimic the synthesis of iomeprol **19** (Scheme 3), another X-ray contrast agent manufactured by Bracco [24,25]. It is worth briefly recalling the iomeprol synthetic path as it is a real green process. Indeed, apart from the first two steps performed in *n*-butanol, the rest of the synthesis is run in water. The crucial step is the final Smiles rearrangement [26–28], 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.



Scheme 3

The initial part of the iopamidol synthesis via Smiles rearrangement (Scheme 4) exactly follows Scheme 3, provided that serinol **8** is used in place of isoserinol **14** [29]. In comparison with the synthetic path of Scheme 1, there are two advantages: (i) the elimination of thionyl chloride since the carboxamide moieties are prepared through ester groups and (ii) the iodination in a later stage, which allows a significant saving of the expensive iodine monochloride.



Scheme 4

As iopamidol is an optically active compound and the Smiles rearrangement takes place without involving the stereogenic carbon atom, accordingly, the intermediate **23** must be the (*S*) enantiomer. The latter derives from **21** through a reaction taking place with inversion of configuration, which brings two problems: (i) compound **22** must be synthesized from the unnatural and less accessible (*R*) lactic acid, and (ii) the leaving group X in **22** must guarantee a complete inversion of configuration. Among several tested leaving groups (halides, mesylate, tosylate), the tosylate proves to be the most valuable one as it allows one to obtain **1** with e.e. >98 % working in ethanol/water. Chloride too is quite interesting as the related compound **22** could be obtained from natural (*S*) ethyl lactate through a chlorination with thionyl chloride taking place with inversion of configuration followed by amidation. Unfortunately, its reaction in water with **21** afforded **1** whose optical purity resulted slightly below the specification limit. The results are summarized in Table 1.

An additional problem had to be solved in the final Smiles rearrangement, which could not be performed under the harsh conditions (aq. NaOH, 90 °C) used for the synthesis of iomeprol. In that case, the secondary amide proves stable and the main reaction is the rearrangement while the primary amide of **23** largely undergoes hydrolysis to the corresponding acid. Accordingly, we turned to milder conditions (KOH in MeOH or EtOH, 50 °C) which allows one to obtain iopamidol **1**.

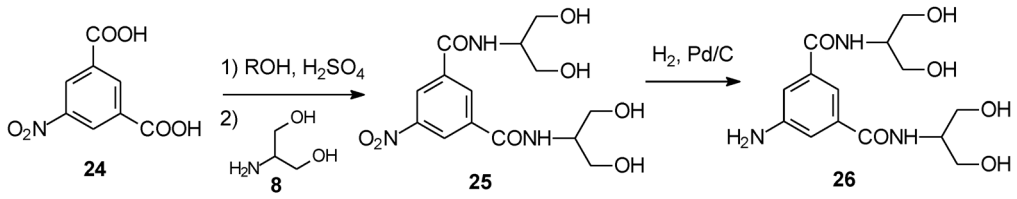
Table 1 Results of alkylation and Smiles rearrangement with different leaving groups in **22**.[a]

X in **22**	Solvent	Yield of **1** (two steps)	Optical purity	Chemical purity
TsO	DMA	40	67	96
TsO	$MeOCH_2CH_2OH$	40	96	99
TsO	H_2O/EtOH	56	98	99
MsO	$MeOCH_2CH_2OH$	30	84	98
MsO	$EtOCH_2CH_2OH$	42	88	98
MsO	H_2O/EtOH	40	94	97
MsO	H_2O	56	94	98
Cl	$MeOCH_2CH_2OH$	33	20	98
Cl	H_2O	40	88	99

[a]Ratio **22/21** = 2 mol/mol.

Mixed process

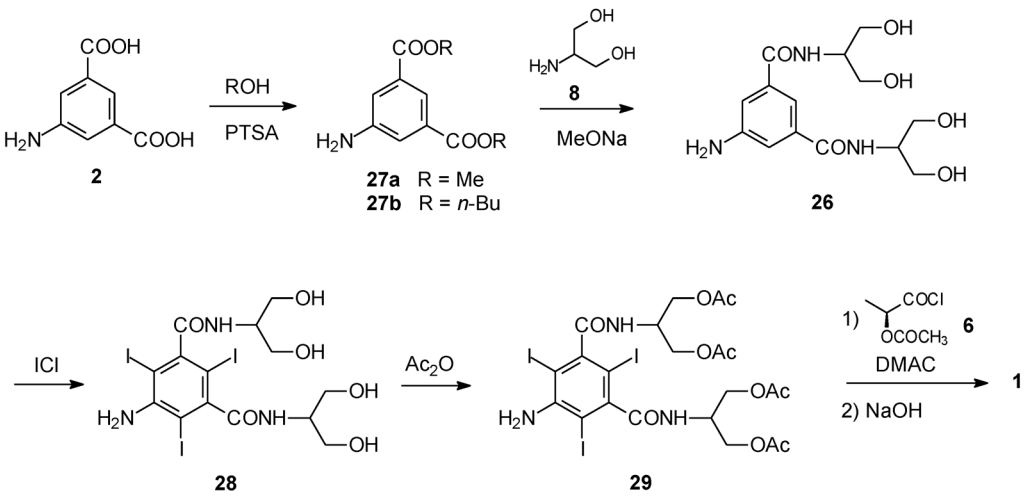
Again, the crucial point for a new process was the elimination of the acyl chlorides in the preparation of the carboxamide moieties. According to the literature, 5-nitro-1,3-benzenedicarboxylic acid **24** can be esterified, amidated with serinol, and then the nitro group reduced to amino to give the key intermediate **26** (Scheme 5) [30,31].



Scheme 5

Safety studies performed by us showed that the intermediate nitroamide **25** has some stability problems when heated at a temperature near the one of reaction, and, for this reason, we decided to still rely on 5-amino-1,3-benzenedicarboxylic acid **2** (Scheme 6).

The carboxylic groups of **2** are transformed into either methyl **27a** or *n*-butyl **27b** diesters by esterification with the corresponding alcohol and *p*-toluenesulfonic acid (PTSA). Diester **27b** is preferred because the water formed in the reaction can be easily removed by distillation of the azeotrope with *n*-butanol. The subsequent amidation to **26** is performed in methanol using sodium methoxide as the catalyst and close to stoichiometric amounts of serinol. This is a great advantage in comparison with the current process where serinol is also used as the proton acceptor in the amidation step, thus making recovery of excess serinol compulsory due to the high cost of such starting material. Diamide **26** nicely crystallizes from the reaction mixture. The iodination of the aromatic ring in **26** is performed as in the current process with a solution of iodine monochloride in hydrochloric acid. Again, the introduction of iodine in a late stage of the synthesis allows a significant saving of this expensive starting material. The selective acylation of the aniline group of **28** with compound **6** was unsuccessful due to similar reactivity of the hydroxy groups. Accordingly, the latter are selectively protected as acetates by reaction with acetic anhydride using 4-dimethylaminopyridine (DMAP) as the catalyst [32], followed by acylation of the aniline group with **6**. The final hydrolysis with NaOH of all the acetoxy groups affords iopamidol **1** with good yield (Scheme 6) [33].



Scheme 6

CONCLUSION

The synthesis of iopamidol involves the use of large amounts of thionyl chloride every year. With the aim to eliminate this noxious reagent, two new synthetic processes have been developed. With the Smiles process, the elimination of thionyl chloride was complete even though an effective recycle of tosylate is necessary for economical reasons. In the mixed process, the amount of thionyl chloride employed was significantly reduced, greater than 70 %, but not totally eliminated because it was also needed for the synthesis of intermediate **6**.

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