CONVENIENT METHOD FOR ONE-POT SYNTHESIS OF NOVEL *AMIDOTRIZOIC ACID* RADIOISOSTERES

Nadya Hadzhieva, Iliyan Kolev

Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna

ABSTRACT

INTRODUCTION: The present study presents an effective one-pot protocol for the synthesis of triiodosubstituted aromatic (benzoic) acids – radiopaque analogues of *amidotrizoic acid*. For the production of the acids intended, I_2/$AgNO_3$ couple was used as an effective iodinating reagent. Moreover, suitably substituted methoxybenzoic acid derivatives were selected as appropriate targets for iodination. The total iodine content in the final (crude) products was determined by Volhard's titrimetric method. Further details on the chemical structure of the reaction products were obtained by ATR-FTIR and ^{1}H NMR spectroscopy.

AIM: The aim of the present study is to evaluate the effectiveness of a new method proposed for the synthesis of triiodo-substituted aromatic acids – analogues of the X-ray contrast *amidotrizoic acid*.

MATERIALS AND METHODS: All necessary reagents and solvents for the study were purchased from Acros Organics, Fisher. The syntheses were performed under mild conditions using standard laboratory equipment. The infrared (IR) spectral instrument was a TENSOR II of Bruker (Germany), equipped with an ATR (Platinum) attachment. The total iodine content of the crude reaction products was assayed by a classical pharmacopoeial method.

RESULTS: All aromatic acids were successfully iodinated with the reagent couple used. Unfortunately, it was found that the reaction products were mixtures of several compounds – partially and completely iodinated products. The presence of 2,6-diiodosubstituted acids in them was established by the appearance of a v(C=O) band in the shortwave range (at over 1700 cm^{-1}). The total iodine content in the final (crude) products was determined by Volhard's back titration method.

CONCLUSION: The applied synthetic method allows the production of a mixture of partially and completely iodinated products, derivatives of the utilized aromatic acids – 3,4-dimethoxybenzoic (3,4-DMBA) and 3,5-dimethoxybenzoic acid (3,5-DMBA). The presence of 2,6-diiodosubstituted acids in the products' composition was determined using ATR-FTIR spectroscopy. The reduced yield of the totally substituted products was associated with the lower activity of the iodinating reagent. However, the iodine content of one of the products thus obtained was found to be close to the expected triiodine one.

Keywords: *aromatic iodination, I_2/$AgNO_3$, methoxy-substituted benzoic acids*

INTRODUCTION

Iodine-containing organic compounds are currently used both in organic synthesis and in medical practice. In the field of organic synthesis, they are mainly used as key intermediates in the production of more complex compounds (1). Most organoiodine substances used in medicine are antiseptics (2). However, there is also a class of organoiodine substanc-

es implemented as diagnostic contrast agents (CAs) (3). Contrast agents are classified mainly according to their ability to form ions into two groups: the so-called ionic (high-osmolar) and non-ionic (low-osmolar) radiopaque CAs (4). *Amidotrizoic* and *ioxaglic acid* (5) are amongst the iodine-containing ionic CAs utilized today.

Amidotrizoic acid

Ioxaglic acid
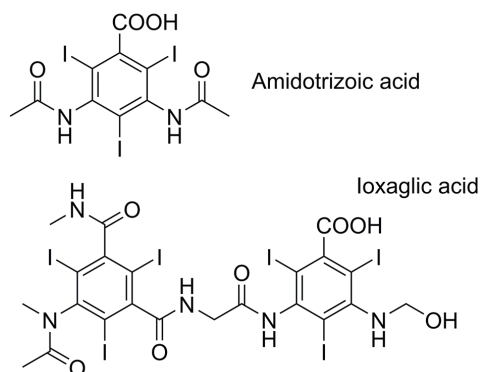
Preferred CAs should contain at least two, and more preferably, at least three iodine atoms per molecule or aromatic ring. Besides, an anthropomorphic phantom model (a physical model that mimics real human tissue) can be composed from each CA. Models are used to evaluate the characteristic related to signal exposure and noise response and the dynamic range of an image recording and detection system (6).

Therefore, the present study was focused on the preparation of new triiodine-containing aromatic compounds – much cheaper analogues of *amidotrizoic acid*. The reactants for the present study were natural aromatic acids selected due to being the most environmentally friendly iodinating targets. Also, probably the most environmentally friendly iodinating reagent – $I_2/AgNO_3$ – was used. Given the short half-lives of the CAs used, the synthesis of the compounds in question needs to be simple, efficient, and reproducible. Therefore, a synthetic strategy that uses readily available substances and can be implemented by anyone has also been chosen here.

MATERIALS AND METHODS

All chemicals were of analytical grade and used as received: 3,4-dimethoxybenzoic acid (99+%, Acros Organics), 3,5-dimethoxybenzoic acid (99%, Acros Organics), iodine (99.8+%, ChemLab), silver nitrate (ACS, Fisher). The solvent methanol (99.9%, extra dry, AcroSeal®), was received from Acros Organics.

ATR-FTIR spectra were recorded using a Tensor II (Bruker, Germany) spectrometer, equipped with an ATR (Platinum) attachment. The spectra were collected within the range of 4000 to 400 cm^{-1}; in the absorbance mode and at a resolution of 4.0 cm^{-1}.

General procedure of aromatic iodination

All reactions were performed under ambient conditions utilizing standard 50 mL flat bottom flasks. For the iodination of both aromatic acids (1.5 g, 8.234 mmol), 3.1 equivalents of $AgNO_3$ and 3.1 equivalents of I_2 were used, respectively. The contents of each flask were dissolved in 30 mL of anhydrous MeOH. The reaction mixtures were allowed to stir magnetically at room temperature (21°C) for 24 hours. The flasks were pre-wrapped with aluminium foil to protect them from actinic light. The mixtures were then filtered and the obtained filtrates were concentrated under vacuum at 90°C. The crude residues thus obtained were subjected to spectral (FTIR and NMR) and titrimetric analysis. All syntheses were repeated three times to confirm the repeatability of the synthetic strategy chosen.

Caution!!!

All work with methanol, $AgNO_3$ and I_2 must be done under a well-ventilated hood using protective clothing and gloves.

Determination of total iodine content

Approximately 0.05 grams of crude reaction product were accurately weighed into a 15 mL pear-shaped flask. 1.7 mL of NaOH solution (15%), 7.0 mL of bidistilled water and 0.34 g of zinc powder were then added to the same reaction vessel. The resulting mixture was heated to reflux for 1.5 h and then allowed to cool to RT. The condenser used was rinsed gently with several portions of water (of 1.0 mL each). All rinsings were combined with the reaction solution. Then, the content of the flask quantitatively was transferred into a 25 mL volumetric flask. The content of the volumetric flask was brought to the mark with bidistilled water. The solution thus obtained (10 mL) was added to 2.5 mL of 0.1 N silver nitrate solution and 2.5 mL of diluted (1:1 v/v) HNO_3 solution. The excess $AgNO_3$ was titrated with 0.1 N ammonium thiocyanate solution using 0.2 mL of saturated solution of ferric alum as indicator. A 2.0 mL grad-

uated microburette (Herka® Intercolor) was used for the purpose. Titrations were done in triplicate. The results are expressed in molar equivalents.

RESULTS AND DISCUSSION

In the course of our previous researches, we were able to obtain two iodine-containing aromatic, derivatives of *eudesmic*, acids – 2-iodo-3,4,5-trimethoxybenzoic (ITMBA) and 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) (7,8). In both cases, however, the most aggressive iodinating reagent possible – $I_2/AgOOCCF_3$ couple – was used. Indeed, both acids were obtained in quantitative yields and of high purity (>98%). The applied method, although incomparable in its productivity, requires the usage of an extremely hazardous and corrosive reagent – trifluoroacetic acid (CF_3COOH). Therefore, in the present work, we had to develop a much safer method for iodinating the aforementioned aromatic acids. In this regard, the iodine-silver nitrate ($I_2/AgNO_3$) couple was chosen as a particularly suitable iodinating reagent (Scheme 1).

From a preparative point of view, this is an especially attractive reagent for large-scale applications, due to its non-toxic and environmentally-friendly nature. Moreover, the spent silver reagent may be recovered for reuse.

The potential of the $I_2/AgNO_3$ reagent in the iodination of aromatic hydrocarbons has been already demonstrated in several scientific reports (9,10). In others, details about the interaction of $AgNO_3$ with I_2 were presented (11). So far, only the syntheses of mono-iodosubstituted compounds have been completed with this reagent. In the present report, however,
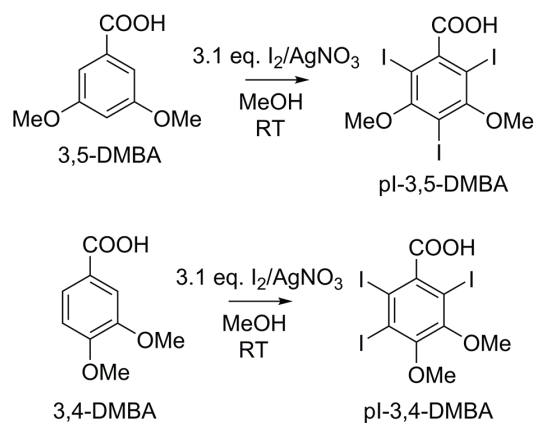
Scheme 1. Syntheses of pI-3,4-DMBA and pI-3,5-DMBA.

it was used for the first time in an attempt to synthesize triiodosubstituted products (Scheme 1).

For the purposes of the study, the synthetic method described by Hathaway et al. (12) was applied in general. Only slight modifications were imposed to the unreacted iodine removal procedure. In the light of experimental simplicity and the imposed goal of obtaining an organoiodine product, an imitator of *amidotrizoic acid*, we analysed the reaction products in their crude form. No technique was used to separate the resulting products as a whole. This, of course, would increase the costs and complicate the whole process.

The performed NMR analysis did not allow us to determine the exact composition of the products thus obtained due to the presence of several positional isomers of partially iodinated acids. Contrary to expectations, however, through this technique we
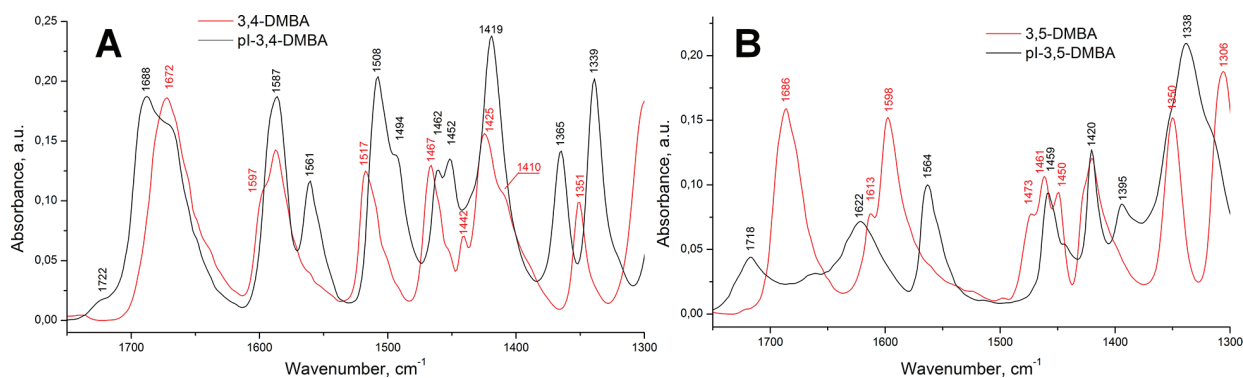

Fig. 1. ATR-FTIR spectra of (A) 3,4-DMBA (black curve), pI-3,4-DMBA (red curve), (B) 3,5-DMBA (black curve), and pI-3,5-DMBA (red curve) in the 1750 ÷ 1300 cm⁻¹ region.

were able to establish only the full consumption of the used organic precursors.

In order to obtain more information on the composition of the reaction products, an additional ATR-FTIR spectral analysis was performed. In general, IR analysis was interpretively focused on changes in the C=O stretching vibration zone (from 1650 to 1750 cm^{-1}).

Certainly, the arguments presented here must be considered qualitative in nature. The observed ν(C=O) frequency shift to higher wavenumbers in pI-3,4-DMBA (from 1672 to 1688 cm^{-1}) is thought to be associated with the presence of an *ortho*-positioned iodine atom. Similar spectral behaviour was also observed in the case of ITMBA (7). At this stage, however, we cannot confirm the presence of a second iodine atom in the vacant *meta* position of the aromatic 3,4-DMBA nucleus. In the same spectrum (Fig. 1A), the presence of a low-intensity band with a maximum at 1722 cm^{-1} was also observed. Undoubtedly, the appearance of this absorption is associated with the presence of an *ortho*-diiodosubstituated functional moiety (8). The pronounced shoulder with a maximum at about 1672 cm^{-1} in the composition of the main band should be attributed to the *ortho*-unaffected carboxyl functional. Of course, that does not mean that the most preferred position for iodination, *meta*, is not affected. As well, the changes that occurred throughout the IR spectral range were used as further evidence of complete consumption of the starting acid.

Significant spectral changes in the frequency region of carbonyl vibrations of iodinated 3,5-DMBA were also observed (Fig. 1B). In the indicated area, a clearly distinguishable band with a maximum at 1718 cm^{-1} was registered too. Doubtless, the appearance of the band in question is associated with the presence of a 2,6-diiodosubstituted product (8). To determine whether the complete iodination of the acid in question has occurred, we performed an additional titrimetric analysis.

A classic pharmacopoeial method was chosen to assess the total iodine content (13). The chosen method is complex and time-consuming. The initially applied sample preparation reaction aims at converting quantitatively the covalently bound iodine into its traceable ionic form. Methodologically, Volhard's classical titrimetric course was then followed.

In brief, the measured average iodine content in pI-3,4-DMBA and pI-3,5-DMBA was found to be 2.1±0.12 and 2.8±0.09, respectively.

In fact, the information presented herein complements the content of the aforementioned spectral findings. It seems logical that the expected *ortho*-diiodine spatial interaction will most likely prevent the successful introduction of a third iodine atom into the aromatic 3,4-DMBA nucleus. That is why the preferred synthesis of a diiodo-substituted product was carried out in this case (Fig. 2). As far as the pI-3,5-DMBA product is concerned, it is safe to say that the acid in question was obtained in almost quantitative yield.
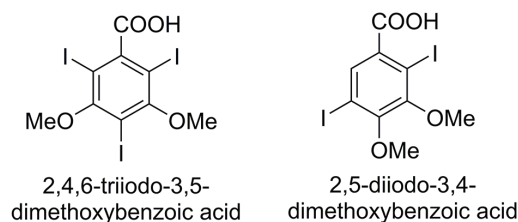

2,4,6-triiodo-3,5-dimethoxybenzoic acid   2,5-diiodo-3,4-dimethoxybenzoic acid

Fig. 2. The main reaction products of the conducted interactions.

CONCLUSION

The present invention relates to a method for the preparation of polyiodinated aromatics. In particular, it relates to a process including the direct iodination of 3,4- and 3,5-dimethoxy-substituted aromatic acids to its corresponding iodosubstituted derivatives.

In general, however, this methodology proved to be suitable only for the synthesis of 2,4,6-triiodo-3,5-dimethoxybenzoic acid.

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