

ORIGINAL ARTICLES

ON THE IODINATION OF EUDESMINIC ACID WITH INO_3 IN AN AQUEOUS METHANOL MEDIUM

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ABSTRACT

INTRODUCTION: Both iodo-substituted aromatic hydrocarbons and their more complex derivatives (phenols, aromatic acids, carbaldehydes, and others) are currently being used with unquestionable success in organic and pharmaceutical synthesis. Rationally, the design of a wide variety of polysubstituted biphenyl, stilbene, and other derivatives can be successfully accomplished using these compounds. As a continuation of our previous work, we propose a much more convenient and feasible methodology for the synthesis of the polysubstituted diiodo-containing 2,6-diiodo-3,4,5-trimethoxybenzoic acid.

AIM: The aim of this article is to demonstrate the suitability of the used reagent pair, I_2/AgNO_3 , in the iodination of the natural 3,4,5-trimethoxybenzoic (eudesmic) acid in the presence of water.

MATERIALS AND METHODS: For the synthesis of the principal, a green strategy was applied, which used the commonly available and biocompatible reagents iodine, silver nitrate, methanol, and water. The suitability of the applied synthetic methodology was determined by the purity of the reaction product. The latter was established through Fourier transform infrared (FTIR) and ^1H nuclear magnetic resonance (NMR) analysis.

RESULTS: The presence of a small amount of water in the reaction mixture did not alter the yield and purity of the desired reaction product, 2,6-diiodo-3,4,5-trimethoxybenzoic acid. In all probability, the in situ formed iodine nitrate (INO_3) preserved its activity in an aqueous environment. The quantitative conversion of the organic reactant used can also be taken as indirect evidence of the stability of the thus obtained INO_3 .

CONCLUSION: The presented preparative methodology holds potential as an optimal choice in the synthesis of the target 2,6-diiodo-3,4,5-trimethoxybenzoic acid. Given its feasibility and use of commonly available reagents, the presented synthetic strategy can be easily implemented by novice chemists, including students.

Keywords: I_2/AgNO_3 , iodination, green synthetic strategy

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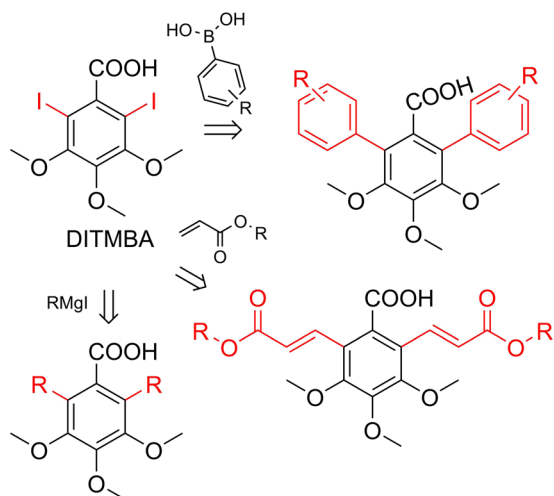
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INTRODUCTION

Both iodo-substituted aromatic hydrocarbons and their derivatives (phenols, aromatic acids, carbaldehydes, and others) are currently being used with unquestionable success in organic and pharmaceutical synthesis (1,2,3,4). They are primarily utilized as precursors in the synthesis of more structurally complex compounds, including biphenyl, stilbene, phenyl-substituted alkene, alkyne, and others (Scheme 1).





Scheme 1. Strategies illustrating the potential of the title acid in the synthesis of other classes of compounds.

Therefore, the synthesis of organoiodine compounds is of particular interest. Being photosensitive, the compounds in question are difficult to purify—a circumstance that must always be borne in mind when working with I-substituted compounds. Separately, any additional manipulation with this class of compounds can lead to further deterioration of their quality. That is why the choice of iodinating agents should be of paramount importance, especially while considering the quality and yield of the desired product. Whenever possible, the safest known reagents should be used—they should be safe for the user, the chemist, and the environment.

In this regard, we found that the *in situ*-prepared iodination reagent, INO_3 , exhibits significant activity against the title substrate, *eudesmic acid* (4). However, the experimental conditions we proposed may be regarded by most users as relatively difficult to reproduce. Therefore, we set out to investigate the potential of this reagent in the iodination of the title acid under much more synthetically friendly conditions—that is, in the absence of an argon atmosphere and an anhydride medium.

AIM

The aim of this article is to provide a much more convenient method for the synthesis of diiodo-substituted eudesmic acid – 2,6-diiodo-3,4,5-trimethoxybenzoic acid.

MATERIALS AND METHODS

All chemicals were of analytical grade and used as received: 3,4,5-trimethoxybenzoic acid (99+%; Alfa Aesar, Ward Hill, MA, USA), iodine (99.5+%; Fisher Chemical, Hampton, MA, USA), silver nitrate (certified ACS; Fisher Chemical), and methanol (99.9%, extra dry, AcroSeal®; Acros Organics, Veneto, Italy). Double-distilled and deionized water was used throughout the study.

Attenuated total reflectance (ATR)-Fourier transform infrared (FTIR) spectra were recorded using an FTIR spectrometer (model Tensor II; Bruker, Billerica, MA, USA), equipped with an ATR module. The spectra were collected within the $4,000 \div 400 \text{ cm}^{-1}$ range at a resolution of 4.0 cm^{-1} .

^1H nuclear magnetic resonance (^1H NMR) spectra were recorded at 250 MHz on a Bruker Avance DRX 250 spectrometer using CDCl_3 as a solvent and $(\text{CH}_3)_4\text{Si}$ as an internal standard.

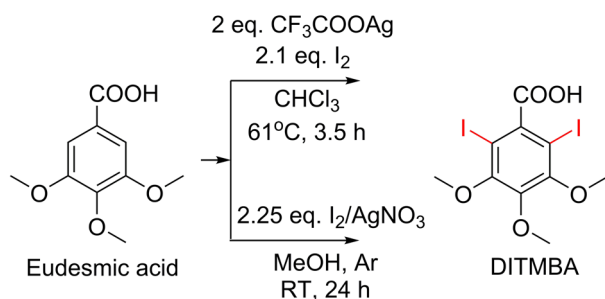
Synthesis of 2,6-Diiodo-3,4,5-Trimethoxybenzoic Acid

Synthesis was performed under ambient conditions (using air-dry laboratory glassware and an air-conditioned workroom) utilizing a standard 50 mL single-neck, flat-bottom flask. The latter was wrapped with aluminum foil and charged with 1 g of 3,4,5-trimethoxybenzoic acid (4.7 mmol), 1.76 g of AgNO_3 (2.2 eq.; 10.34 mmol), 2.64 g of I_2 (2.2 eq., 10.34 mmol), 25 mL of methanol, and 0.1 mL of water. The reaction mixture was allowed to stir magnetically at room temperature (21°C) for 24 hours. The resulting mixture was filtered, and the obtained filtrate was transferred to a 0.5 L beaker (equipped with a magnetic stirrer) loaded with 0.1 g of NaHSO_3 , and 300 mL of water. The separated product was collected by suction filtration and repeatedly washed with water. The isolated solid was allowed to dry in a vacuum desiccator (over activated silica gel) for 24 h (yield $\geq 95\%$). The identity and purity of the crude product was analyzed by ATR-FTIR and ^1H NMR spectroscopy. The synthesis process was repeated three times to confirm the repeatability of the chosen methodology.

RESULTS AND DISCUSSION

Throughout the course of our previous research, we were able to obtain the acid in question—2,6-diiodo-3,4,5-trimethoxybenzoic (DITMBA)—using two

radically different approaches (5,6). In one instance, iodine-silver trifluoroacetate reagent ($I_2/AgOOC-CF_3$) was used, while the $I_2/AgNO_3$ iodinating reagent was used in the other (Scheme 2).



Scheme 2. Approaches used for the synthesis of DITMBA.

Undoubtedly, the choice of the latter method should, from a manipulation safety perspective, be preferred. The interaction between the specified reagents inevitably leads to the formation of the actual iodinating reagent, iodine nitrate, INO_3 (7). Given that INO_3 solutions are not stable on standing, they should be prepared *in situ* in the presence of the organic target/reactant (7,8,9). In most known methodologies, the work with this reagent has been conducted under strictly anhydride conditions (7). For one approach, however, the reagent in question was obtained by manually mixing its two precursors in a mortar (10)—i.e., under solid-phase conditions. With this in mind, it seems logical to assume that even in the presence of moisture/water, the reagent's activity is fully preserved.

Therefore, we decided to modify/simplify our previously reported methodology by removing the need to observe strictly anhydride conditions. In this regard, the reaction was not conducted under an argon atmosphere. Therefore, in this work, 100 μ L of water was intentionally introduced into the reaction medium (as reflected in the experimental section).

Contrary to expectations, at the end of the stipulated 24-hour reaction period, the quantitative depletion of the introduced iodine was seemingly registered—a sign that carries information about the quantitative progress of the planned reaction. Convincing analytical/instrumental evidence for the same has also been obtained.

Indeed, as can be seen in Fig. 1, the profiles (or spectral fingerprints) of the resulting and previously reported FTIR spectra completely coincide—a circumstance that can only be perceived as proof of the identity of the obtained product.

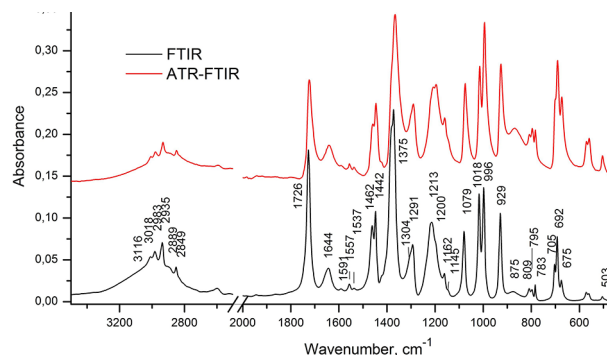


Fig. 1. FTIR spectra of DITMBA obtained in anhydrous methanol (black line) and water-methanol (red line) media.

Since the analysis in question could not provide us with information about the purity of the reaction product, conducting additional research proved imperative. In order to obtain objective information about this parameter, the crude product was subjected to additional 1H NMR analysis (Fig. 2).

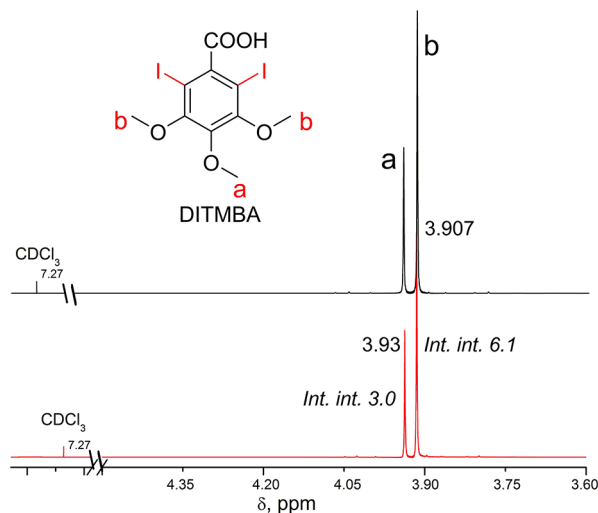


Fig. 2. 1H NMR spectra of DITMBA obtained in anhydrous methanol (black line) and water-methanol (red line) media.

¹A circumstance that is accepted to be used for identification purposes only.

In the recorded NMR spectrum (Fig. 2), the presence of unreacted eudesmic acid was *de facto* not detected. The same applied to the monoiodo-substituted acid. Furthermore, the number and position of all registered resonance signals matched those reflected in (6).

The presence of a small amount of water in the reaction mixture did not alter the yield and purity of the desired DITMBA. Therefore, with full justification, it can be claimed that under the imposed experimental circumstances, the intended goal was successfully achieved.

Moreover, the obtained results serve as a testament to the fact that even in an organized water-methanol medium, the *in situ*-formed INO_3 retains its activity. In parity, as an additional but indirect proof of the same, the quantitative conversion of the implemented organic reactant can be presented as well.

CONCLUSION

The presented preparative methodology holds potential as an optimal approach in the synthesis of the target 2,6-iodo-3,4,5-trimethoxybenzoic acid. As a feasible method that can be performed with commonly available reagents, the presented synthetic strategy can easily be performed by novice chemists, including students.

Acknowledgements

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