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# Synthesis of a Homologous Series of Trialkyl Arsines (C₃-C₁₂) and Applications of Arsenic Triiodide as a Synthetic Precursor

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This work presents some modifications in the post-synthetic processing for a classical arsenic reagent: $AsI_3$. In comparison with the widely used analog, the trichloride, arsenic triiodide presents several advantages such as low toxicity, air stability, and low volatility. It was used as a synthetic precursor in the preparation of a variety of arsenic(III) derivatives like arsines, arsenites, and thioarsenites. Besides that, $AsI_3$ was submitted to a diversity-oriented Grignard reaction in the preparation of a homologous series of trialkyl arsines ranging from $AsC_3H_9$ to $AsC_{12}H_{27}$. The series was analyzed by comprehensive two-dimensional gas chromatography coupled with time-of-flight mass spectrometry to provide a trialkyl arsines library that can be used for the direct analysis of natural samples.

**Keywords:** diversity-oriented Grignard, two-dimensional chromatography, trialkyl arsines, arsenic triiodide

## Introduction

Arsenic is a group XV element relatively abundant in the earth's crust. It is present in the constitution of a variety of minerals, such as arsenopyrites, realgar, and orpiment, and is found in seaborn organisms, in the form of arsenobetaine. Consequently, arsenic deposits in the environment and become integrated into the composition of fossil oils and their derivatives.[1-5] Furthermore, arsenic exhibit high toxicity and its permanence in the oil derivatives represents a problem to human health.[6]

The structure of arsenic contaminants in fossil oil derivatives is not exactly known, with existing relates of arsine ($AsH_3$) and alkylated derivatives, specially trimethyl arsine ($As(CH_3)_3$).[1-4] Other light trialkyl arsines, however, exhibit volatility compatible with lighter derivatives of fossil oil and can be considered as potential contaminants. Such compounds include from trimethyl $As(CH_3)_3$ to tributyl arsine $As(CH_2CH_2CH_2CH_3)_3$; or in the range: $AsC_3H_9$-$AsC_{12}H_{27}$ (120-246 g mol⁻¹).

Homoleptic trialkyl arsines are usually prepared through reacting Grignard (RMgX) or alkyl lithium (RLi) with arsenic trichloride (Scheme 1).[7]

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**Scheme 1.** Classic method for trialkyl arsine preparation.

Arsenic trichloride derivatives holding one or two As−Cl bonds and alkyl groups are known for their high toxicity and volatility. Illustratively, lewisite I, II, and III (general formula $(ClHC=CH)_nAsCl_{3−n}$, with n ranging from 1 to 3) has already been used as chemical warfare, due to its vesicant properties. Even arsenic trichloride, the precursor to these substances, is also listed as a toxic precursor by the Chemical Weapons Convention as a potent vesicant agent.[8] To avoid the toxicity of arsenic derivatives containing the As−Cl substructure, some different precursors have been related. Some examples are $AsN(Me_2)_3$, trialkyl arsenites ($AsOR_3$), or the cyclic arsenite $OCH_2CH_2OAsCl$.[9-11] Most of the methods, however, employ dangerous $AsCl_3$ as starting material in the preparation of the target molecules. Arsenic triiodide is an analog of $AsCl_3$ that exhibits interesting features, like low volatility, air, and water stability, and a synthetic method simple to be executed in the bench scale (Scheme 2).[12,13] Besides that, it is rarely related as starting material in the arsenic derivatives preparation.

**Scheme 2.** Synthesis of AsI₃. Arsenic trichloride is made *in situ* during the synthesis.

The synthesis of arsenic(III) derivatives such as arsines ($AsR_3$), arsenites ($As(OR_3)$), and thioarsenites ($As(SR_3)$) involves the attack of a nucleophilic agent to the arsenic center, with the elimination of a leaving group. In $AsCl_3$, the arsenic atom is bonded to three electron-withdrawing chlorides (electronegativity, $\chi_{Cl}$ 3.16; $\chi_{As}$ 2.18). When chlorides are replaced by iodides, arsenic becomes less electrophilic ($\chi_I$ 2.66). The As–I (195 kJ mol$^{-1}$), bond, however, is weaker than As–Cl (306 kJ mol$^{-1}$). Besides that, iodide is larger and more polarizable than chlorine and it is a more efficient leaving group.[14]

One of the problems with arsenic triiodide use, as obtained from the classical method of preparation (Scheme 2), is its low purity and high-water content, which is not compatible for direct use with organometallics such as Grignard reagents. The purification and drying of such material proved tedious and complicated. Aiming to enable the wide use of $AsI_3$ as a safer and more convenient precursor for the preparation of organoarsines and derivatives, some post-synthetic processing modifications are presented here. The objective is the development of a method that demands smaller direct human manipulation, with the simplicity of execution and scalability. Furthermore, recrystallization with highly flammable and stinky carbon disulfide was eliminated.

Arsenic triiodide was used in the preparation of some light trialkyl arsines. Recent literature presents sparse publications about alkyl arsines, especially in the case of the heteroleptic ones. The lack of the description of arsines in the literature and the inherent difficulties in handling such a class of compounds induce us to develop a simple and safe way to access the series of alkylarsines. To generate a library for chromatographic identification of such class of compounds, a diversity-oriented synthesis was performed, intending to obtain a homologous series of trialkyl arsines, employing a mixture of Grignard reagents from 1 to 4 carbons (Scheme 3).

Comprehensive two-dimensional gas chromatography coupled with mass spectrometry detectors emerged as a fundamental tool for the analysis of complex mixtures. This technique is frequently used in the geochemical characterization of crude and distilled petroleum and also for the identification of contaminants from sources as diverse as petrochemical, food, waters, air, soil, and pesticides. In this context, the development of new analytical standards for plausible classes of contaminants is essential, for it allows the direct qualitative analysis of the arsenic derivatives in natural samples without derivatization.[15,16]

## Experimental

Arsenic derivatives are toxic and should be manipulated in an efficient fume hood. Ether and tetrahydrofuran were purified by distillation over sodium and dried over 3 Å molecular sieves. All arsenic residues were converted to the stable and less toxic arsenic sulfide by its reaction with $H_2S$ in aqueous acid media or with thioacetamide.[17] Other experimental details can be found in the Supplementary Information.

### Arsenic triiodide

To a 1 L beaker equipped with efficient magnetic stirring, 28 g (0.14 mol) of arsenic(III) oxide ($As_2O_3$) were added in 400 mL of $HCl_{aq}$ (37%) at 100 °C. The mixture was stirred until complete dissolution of the oxide. Separately, a solution of 140 g (0.84 mol, 6 eq.) of potassium iodide (KI) was prepared and slowly added to the reaction media at 100 °C and under stirring for 30 min. The pale-yellow solution immediately became orange with the formation of a copious amount of precipitate. After 1 h of reaction, an orange-red wet solid was collected by filtration and washed with HCl. The solid was dried by azeotropic distillation with cyclohexane using a Dean-Stark apparatus. The dry solid was then packed in a cellulose capsule or paper sachet that was transferred into a Soxhlet apparatus. $AsI_3$ is slightly soluble in boiling chloroform. Reflux with chloroform extracted the $AsI_3$ from the paper sachet and, after cooling, furnished large crystals of highly pure $AsI_3$, that was collected by filtration. This method provided crystalline arsenic iodide as orange-red with hexagon-like shape (67.24 g, 0.1477 mol, 54% yield, melting point 144-145 °C (lit.[12] 149 °C)).



**Scheme 3.** Synthesis of the trialkyl arsines homologous series.

## Trialkyl arsine homologous series

To a two-neck round bottom flask equipped with efficient magnetic stirring and a condenser, under an argon atmosphere, metallic magnesium (2 g, 83 mmol) was added to 100 mL of dry tetrahydrofuran. Then, ethyl bromide (2.2 mL, 30 mmol) was slowly added to the suspension, with a syringe. After the start of the reaction, noticed by the warming and the greyish color of the mixture, other alkyl halides were added: 1.8 mL (20 mmol) of propyl bromide, 2.2 mL (20 mmol) of butyl bromide and 1.9 mL (30 mmol) of methyl iodide. After the Grignard mixture was prepared, a total of 15 g (33 mmol) of arsenic triiodide were added portionwise. The argon atmosphere was maintained, and the reaction was stirred for 12 h at ambient temperature. When the orange precipitate was replaced by a pale yellow solid, a saturated aqueous solution of ammonium chloride was added to the reaction media. The mixture was extracted with 3 × 30 mL of tetrahydrofuran. Organic fractions were combined and dried over magnesium sulfate. The ethereal solution containing the homologous series was diluted with dichloromethane (10 μL of the solution to 1 mL of dichloromethane) and submitted to analysis with comprehensive two-dimensional chromatography coupled with time of flight mass spectrometry (GC × GC-TOFMS). MS spectra were attributed based on the fragmentation pattern. Fragmentograms and proposed attributions are presented in the Supplementary Information.[18]

## Results and Discussion

### Arsenic triiodide

The synthesis of AsI$_3$ was performed by the method described by Bailar Jr. in 1939.[12] Proposed modifications involve the processing of solid material isolated from the reaction. The purification process proved essential to the success of the posterior synthetic steps, notably in the case of trialkyl arsines via Grignard reaction. Drying of arsenic triiodide was performed in a closed system by azeotropic distillation with cyclohexane in a Dean-Stark apparatus (Figure 1). Dry solid recovered from this process proved impure and was recrystallized from a warm chloroform solution. To avoid manipulation of arsenic derivatives during the recrystallization, a Soxhlet apparatus in a closed system was used. No decomposition of the crystalline AsI$_3$ was observed along with one year of storage without special care.

### Arsenic triiodide as a precursor

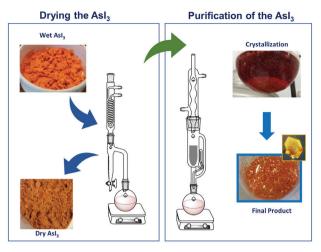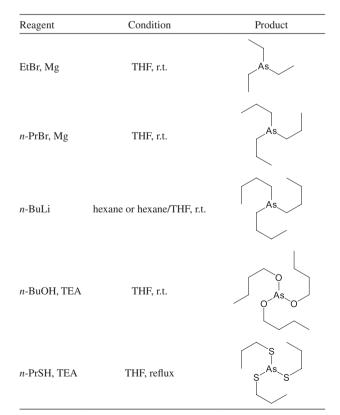To evaluate the efficiency of arsenic triiodide as a



**Figure 1.** Purification of AsI$_3$.

synthetic precursor, some tests were conducted with nucleophilic reagents (Table 1).[19,20] AsI$_3$ reacted readily with all tested nucleophiles at room temperature and was completely consumed after some hours (depending on the scale of the reaction). The end of the reaction was determined by the replacement of orange crystals by a white to pale yellow precipitate. Products were identified by gas chromatography coupled with mass spectrometry (GC-MS)

**Table 1.** Use of AsI$_3$ in the preparation of homoleptic arsenic(III) derivatives

| Reagent | Condition | Product |
|---|---|---|
| EtBr, Mg | THF, r.t. |  |
| *n*-PrBr, Mg | THF, r.t. |  |
| *n*-BuLi | hexane or hexane/THF, r.t. |  |
| *n*-BuOH, TEA | THF, r.t. |  |
| *n*-PrSH, TEA | THF, reflux |  |

THF: tetrahydrofuran; r.t.: room temperature; TEA: triethylamine.

and more details are displayed in the Supplementary Information. By this method, it was possible to prepare arsines ($AsR_3$), arsenites ($As(OR)_3$) and thioarsenites ($As(SR)_3$).

### Homologous series of trialkyl arsines

This series was prepared by way of a diversity-oriented Grignard reaction. Figure 2 displays predicted trialkyl arsines by the random combination of the four linear alkyl fragments (methyl, ethyl, propyl, and butyl) and the three positions available in arsenic(III). The series was analyzed with GC × GC-TOFMS and fragmentograms were obtained. From all predicted species, just methyldipropylarsine (MDPAs) was not identified, probably because of co-elution with an isomer.

The current chromatogram can be employed as a library in the directed analysis of complex samples with volatile arsenic as a contaminant, such as oil and its derivatives.

## Conclusions

Modifications in the post-synthetic processing facilitate the use of $AsI_3$ as a synthetic precursor in the
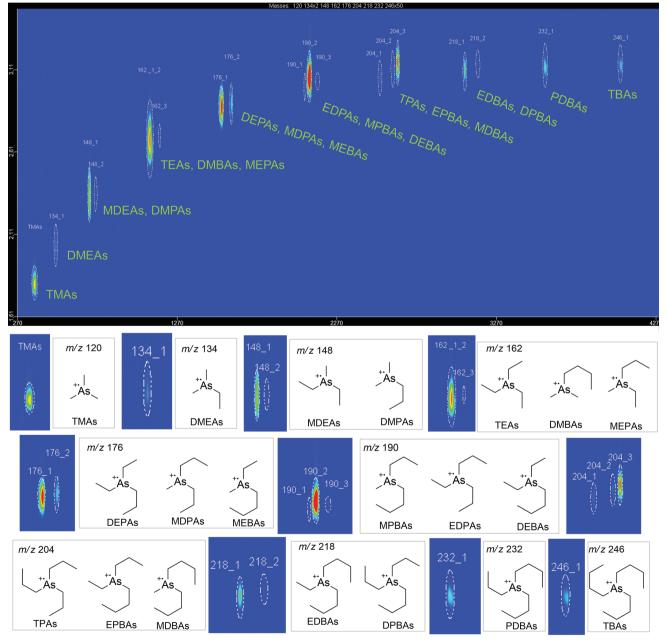


**Figure 2.** Homologous series of linear trialkyl arsines (GC × GC-TOFMS). Capital letters indicate the substitution pattern, where M: methyl; E: ethyl; P: propyl; B: butyl; D: di; T: tri.

preparation of different classes of As$^{III}$ derivatives, such as arsines, arsenites, and thioarsenites. The proposed method decreased operator exposition while processing the material, especially in higher scales. Besides that, an air-stable product was isolated in a crystalline and pure form.

Arsenic triiodide was also submitted to a diversity-oriented Grignard reaction used in the preparation of a homologous series of linear trialkyl arsines ranging from AsC$_3$H$_9$ to AsC$_{12}$H$_{27}$. Nineteen arsines were analyzed by GC × GC-TOFMS and the fragmentograms were obtained.

## Supplementary Information

Experimental description, X-ray powder diffraction of AsI$_3$, NMR spectra and fragmentograms can be found in the Supplementary Information, which is available free of charge at http://jbcs.sbq.org.br as PDF file.

## Acknowledgments

## Author Contributions

Carolina B. P. Ligiero and Marcos A. S. Francisco were responsible for the synthesis, conceptualization, data curation, formal analysis, investigation, methodology, writing original draft, review, and editing; Michelle S. Gama, and Carlos A. Carbonezi were responsible for the GC × GC-TOFMS analysis; Isabela C. L. Leocadio and Wladmir F. de Souza were responsible for funding acquisition, conceptualization and project administration; Pierre M. Esteves was responsible for resources, supervision, project administration, conceptualization, funding acquisition, methodology, writing review, and editing.

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