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Preparation of Phosphonoterephthalic Acids *via* Palladium-catalyzed Coupling of Aromatic Iodoesters

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Abstract: The current article reports in detail the preparation of two phosphonoterephthalic acids: 2-Phosphonoterephthalic acid (**1**) and 2,5-diphosphonoterephthalic acid (**2**). Efficient, scalable syntheses have been developed for both compounds, based on Pd-catalyzed coupling reactions of iodinated terephthalate esters. Phosphonoterephthalic acids are potentially useful as flame retardant additives or as monomers for the construction of acid-pendant polymer chains.

Keywords: phosphonoterephthalic acids, flame retardants, phosphonates, arenephosphonic acids, palladium-catalyzed coupling

INTRODUCTION

Phosphonic acids have been the subject of increasing interest in recent years. They have been studied, both experimentally and theoretically¹, for various applications, such as protogenic groups in PEM separator materials^{2,3}, composite membranes⁴, oligosiloxane-immobilized proton carriers.⁵

On the other hand, phosphorous-based structures have found increasing use as both reactive and additive flame retardants. Their share in the world flame retardant market has been gradually increasing, partly due to the steady process of reduction in use of halogenated compounds, driven by environmental and health safety concerns. Phosphorous-based structures act as flame retardants both in the vapor phase, by a radical mechanism that interrupts the exothermic process and suppresses combustion, and in the condensed phase, by promoting char formation.^{6,7} Most of the phosphorus based structures that are commercially available are phosphate-based, and while those phosphates are easy to synthesize, they can have some hydrolytic instability and durability problems when exposed to high humidity or recycling conditions.⁸ Therefore, there is a real need to develop new phosphorus-based flame retardants, which have greater number of P-C bonds rather than P-O-C bonds. Further, a greater number of phosphorus present in a structure often translates into greater flame retardant activity per unit weight.⁹ To that end, we have been studying the synthesis of new phosphorus-based flame retardants with an emphasis on catalytic methods that may be industrially viable vs. traditional molar reagent processes.

In a recent publication, we described the preparation of 2-phosphonoterephthalic acid (**1**), through the intermediate formation of Grignard reagent (or organolithium reagent) from 2-bromoxylene, subsequently reacted with diethyl chlorophosphate, followed by oxidation and

hydrolysis.¹⁰ In an effort to avoid the formation and use of organometallic intermediates, demanding inert conditions, we have developed recently a palladium-catalyzed coupling approach, which has been applied to the preparation of both the mono- and diphosphonoterephthalic acids (Compounds **1** and **2**).

Structures 1 and 2

RESULTS AND DISCUSSION

The current report summarizes our efforts to develop a more general method for the introduction of phosphonic ester/phosphonic acid unit(s) onto an aromatic ring. The preparation of **1** has been described in two patent sources, following two different methods.^{11,12} Method 1 was based on the introduction of a phosphorus-containing moiety into the aromatic ring *via* aromatic electrophilic substitution process involving *p*-xylene and thiophosphoryl trichloride, followed by acid hydrolysis of the resultant 2,5-dimethylbenzenephosphonothioic dichloride and a high-pressure Co-catalyzed oxidation in an autoclave of 2,5-dimethylphosphonic acid.¹¹ Such method is inherently complicated and difficult to apply in laboratory conditions, due to the character of the necessary equipment. Method 2, on the other hand, employed palladium- or nickel-catalyzed coupling of dimethyl 2-bromoterephthalate and triethyl phosphite, followed by acid hydrolysis.¹² Our repeated attempts in the past, however, to reproduce the latter chemistry led invariably to full recovery of the starting material. Consequently, several years ago, we developed and published a protocol for the generation of **1**, based on the conversion of bromo-*p*-xylene into a Grignard (or organolithium) reagent, followed by reaction with diethylchlorophosphate, and a subsequent oxidation with KMnO₄.¹³ The inherent drawbacks of such a method include incompatibility with certain functional groups, sensitive to Grignard or

organolithium reagents, such as carbonyl or ester groups, as well as difficult polyfunctionalization, i.e. introduction of more than one phosphonate moiety, which would require the generation of di- or polyGrignard reagent or lithio derivative.

More recently, in our efforts to incorporate phosphonate or boronate moiety into an aromatic ring, we discovered that while transition metal-catalyzed coupling reactions of trialkyl or dialkyl phosphates with aromatic bromoesters did not take place (as noted above), the corresponding reactions with iodoesters were quite facile. The reported preparations of compounds **1** and **2** are based on the latter strategy.

Preparation of 2-phosphonoterephthalic acid (1). The synthetic sequence employed in the preparation of compound **1** is shown in Scheme 1. Dimethyl iodoterephthalate **3** was generated by diazotization of dimethyl 2-aminoterephthalate, following a literature protocol¹⁴, followed by a reaction with aq. KI. Compound **3** was then reacted with excess trimethylphosphite, in the presence of PdCl₂, at elevated temperature, yielding the phosphonate ester **4**.¹² The latter was successfully hydrolyzed to the target acid **1**, using 3M HCl, at 80 °C.

Scheme 1

Preparation of 2,5-diphosphonoterephthalic acid (2). *p*-Xylene was diiodinated by using periodic acid/iodine, in a mixture of acetic acid, sulfuric acid and water, to yield 2,5-diiodo-*p*-xylene **5** (Scheme 2).¹⁵ Compound **5** was subjected to oxidation, using KMnO₄ in a *t*-butanol/water solvent mixture, followed by acidification, to yield 2,5-diiodoterephthalic acid **6**. Attempts to conduct the oxidation in purely aqueous medium were not successful, as they led to the partial sublimation of **5** and consequent very low yields of the acid **6**. The published

literature protocol suggested conversion of the diiodoacid **6** into the dimethyl ester **7** in a two-step sequence, involving the intermediate generation of the diacid chloride. We managed to accomplish the synthesis of **7** in a single step, employing Fischer esterification of the acid **6** in excess methanol, with sulfuric acid as a catalyst. Compound **7** was then subjected to a reaction with trimethyl phosphite in the presence of PdCl₂. The resultant diphosphonic ester **8** was hydrolyzed in conditions analogous to the ones described for the preparation of **1**.

Scheme 2

CONCLUSIONS

In this work we have reported the preparation and characterization of two phosphonoterephthalic acids, compounds **1** and **2**, using Pd-catalyzed coupling to prepare the corresponding phosphonate esters. This protocol could be extended further, and utilized as a general methodology in the preparation of other aromatic phosphonic acids, potentially useful as either flame retardants or for other chemical research and synthetic needs.

EXPERIMENTAL

¹H and ¹³C NMR spectra of intermediate and target compounds were recorded at 300 MHz and 75 MHz respectively and referenced to the solvent (CDCl₃: 7.27 ppm and 77.0 ppm; D₂O: 4.76 ppm). ¹³C NMR spectra in D₂O were indirectly referenced to acetone-*d*₆ in D₂O (literature chemical shift value δ 33.0 ppm for the CD₃ signal).¹⁶ Elemental analysis was provided by Atlantic Microlab, Norcross, GA. Dimethyl aminoterephthalate was purchased from the Acros Organics.

General Procedure for the Preparation of Phosphonoterephthalic Esters (4, 8). A mixture of iodoester (**3** or **7**) (1 eqv.), trimethyl phosphite (4 eqv. per iodine site) and PdCl₂ (0.1 eqv. per iodine site) was purged with nitrogen, and then stirred for 5 h at 150 °C, in nitrogen atmosphere. Water and 1,2-dichloroethane were added after cooling to ambient temperature. The organic layer was separated, washed two times with water, dried (MgSO₄) and the volatile components removed under reduced pressure.

Dimethyl (dimethylphosphono)terephthalate (4).¹² Purified on a silica gel column, using methylene chloride, followed by CH₂Cl₂ : EtOAc = 3 : 1, followed by pure EtOAc. Colorless oil (81% yield). ¹H NMR (CDCl₃) δ 3.83 (d, J = 11.4 Hz, 6H), 3.96 (s, 3H), 3.97 (s, 3H), 7.79 (dd, J₁ = 4.9 Hz, J₂ = 8.0, 1H), 8.25 (dt, J₁ = 1.5 Hz, J₂ = 8.0 Hz, 1H), 8.56 (dd, J₁ = 1.6 Hz, J₂ = 14.3 Hz, 1H).

Dimethyl 2,5-bis(dimethylphosphono)terephthalate (8). Purified by recrystallization from toluene. White solid (60% yield). Mp 129 – 131°C. ¹H NMR (CDCl₃) δ 3.84 (d, J = 11.3 Hz, 12H), 3.98 (s, 6H), 8.28 (dd, J₁ = 13.5 Hz, J₂ = 5.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 53.3 (s), 53.5 (t, J = 2.9 Hz), 131.2 (dd, J₁ = 187.8 Hz, J₂ = 2.9 Hz), 134.4 (t, J = 10.7 Hz), 137.9 (t, J = 11.0 Hz), 166.7 (t, J = 3.1 Hz). Anal. Calcd. for C₁₄H₂₀O₁₀P₂: C, 40.99; H, 4.91. Found: C, 41.12; H, 4.93.

General Procedure for the Preparation of Phosphonoterephthalic Acids (1, 2). The phosphonoterephthalate ester (**4** or **8**) (1.50 mmol) was suspended in 30 mL of 3M HCl. The resultant mixture was stirred at 80 °C for 24 h. The solution was concentrated to dryness and THF (10 mL) was added to the solid. The resultant suspension was stirred for 10 min and vacuum filtered to yield the product as a white solid.

2-Phosphonoterephthalic acid (1).¹¹⁻¹³ Yield: 86%. Mp 296 - 298 °C (Lit.¹² 298 °C).

¹H NMR (D₂O) δ 7.67 (dd, J₁ = 8.0 Hz, J₂ = 4.0 Hz, 1H), 7.93 (dt, J₁ = 8.0 Hz, J₂ = 1.0 Hz, 1H), 8.27 (dd, J₁ = 15.0 Hz, J₂ = 1.0 Hz, 1H).

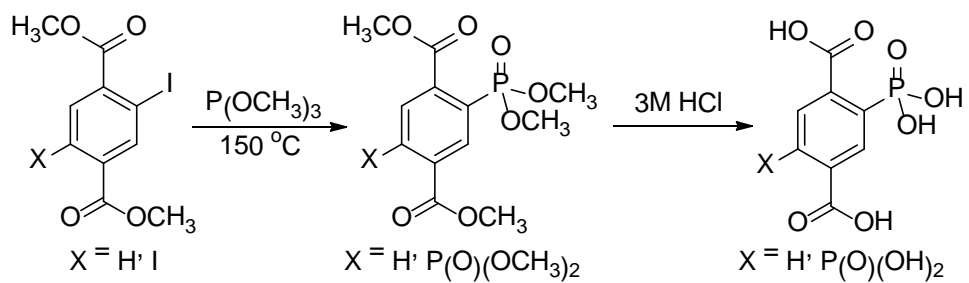
2,5-Diphosphonoterephthalic acid (2). Yield: 95%. Mp 310 °C (dec). ¹H NMR (D₂O) δ 8.27 (dd, J₁ = 13.0 Hz, J₂ = 5.0 Hz, 2H); ¹³C NMR (D₂O, indirectly referenced to acetone-*d*₆ in D₂O) δ 136.0 (t, J = 10.4 Hz), 137.6 (dd, J₁ = 176.2 Hz, J₂ = 2.7 Hz), 139.4 (t, J = 10.6 Hz), 173.5 (t, J = 2.7 Hz). Anal. Calcd. for C₈H₈O₁₀P₂·H₂O: C, 27.92; H, 2.93. Found: C, 27.76; H, 3.17.

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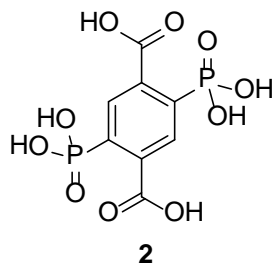
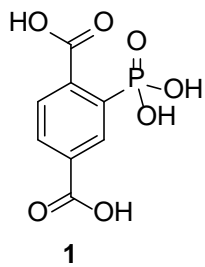
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Graphical Abstract

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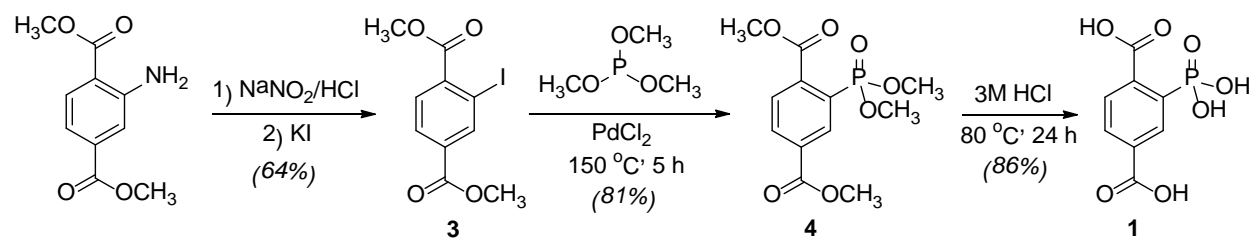


Structures 1 and 2

Ivan, N.; Benin, V.; Morgan, A. B.

Preparation of Phosphonoterephthalic Acids via Palladium-catalyzed Coupling of Aromatic Iodoesters

Scheme 1

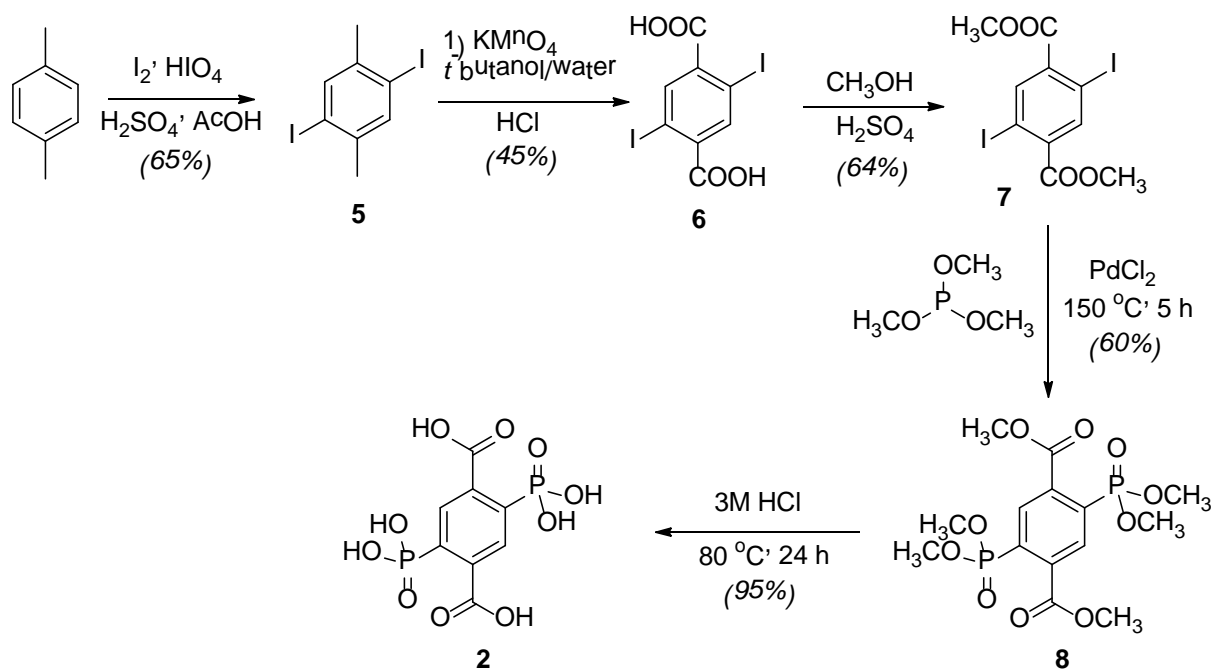


Scheme 1

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Preparation of Phosphonoterephthalic Acids via Palladium-catalyzed Coupling of Aromatic Iodoesters

Scheme 2



Scheme 2

Ivan, N.; Benin, V.; Morgan, A. B.

Preparation of Phosphonoterephthalic Acids via Palladium-catalyzed Coupling of Aromatic Iodoesters