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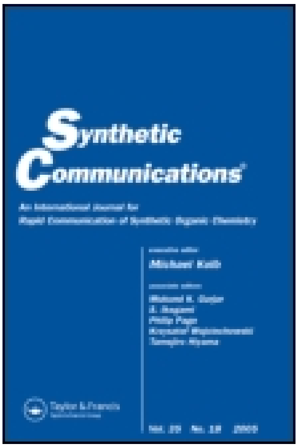

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 04 Jan 2013.Version of record first published: 04 Apr 2013.

To cite this article: Nathaniel Ivan , Vladimir Benin & Alexander B. Morgan (2013): Preparation of Phosphonoterephthalic Acids via Palladium-Catalyzed Coupling of Aromatic Iodoesters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:13, 1831-1836

To link to this article: http://dx.doi.org/10.1080/00397911.2012.673448

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Synthetic Communications®, 43: 1831–1836, 2013
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.673448

PREPARATION OF PHOSPHONOTEREPHTHALIC ACIDS VIA PALLADIUM-CATALYZED COUPLING OF AROMATIC IODOESTERS

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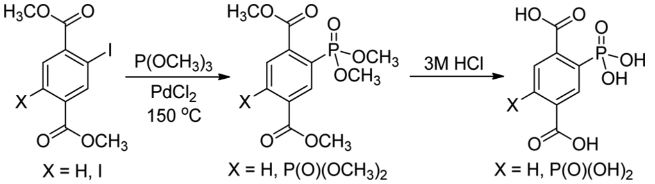
GRAPHICAL ABSTRACT



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.*

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Keywords Arenephosphonic acids; flame retardants; palladium-catalyzed coupling; phosphonates; phosphonoterephthalic acids

INTRODUCTION

Phosphonic acids have been the subject of increasing interest in recent years. They have been studied, both experimentally and theoretically,[1] for various applications, such as protogenic groups in proton exchange membrance (PEM) separator materials,[2,3] composite membranes,[4] and ologosiloxane-immobilized proton carriers.[5]

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 because of the steady reduction in use of halogenated compounds, driven by environmental and health concerns. Phosphorous-based

Received October 4, 2011.

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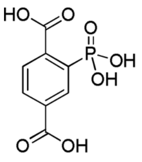
structures act as flame retardants both in the vapor phase, by a radical mechanism that interrupts the exothermic process and suppresses combustion, and in the condensed phase, by promoting char formation.[6,7] Most of the phosphorus-based structures that are commercially available are phosphate based, 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 P-C bonds rather than P-O-C bonds. Further, the more 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, which was subsequently reacted with diethyl chlorophosphate, followed by oxidation and hydrolysis.[10] In an effort to avoid the formation and use of organometallic intermediates, which demand inert conditions, we have developed a palladium-catalyzed coupling approach, which has been applied to the preparation of both the mono- and diphosphonoterephthalic acids (compounds **1** and **2**).



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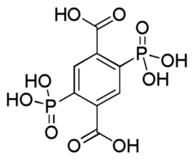

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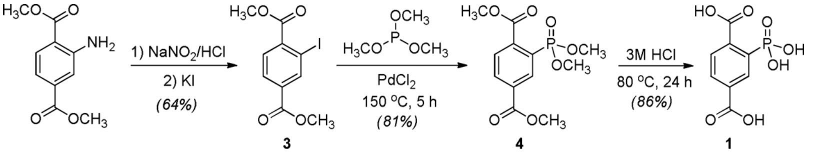
RESULTS AND DISCUSSION

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 a method is inherently complicated and difficult to apply in laboratory conditions, because of 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 $KMnO_4$.[13] The inherent drawbacks of such a method include incompatibility with certain functional groups,



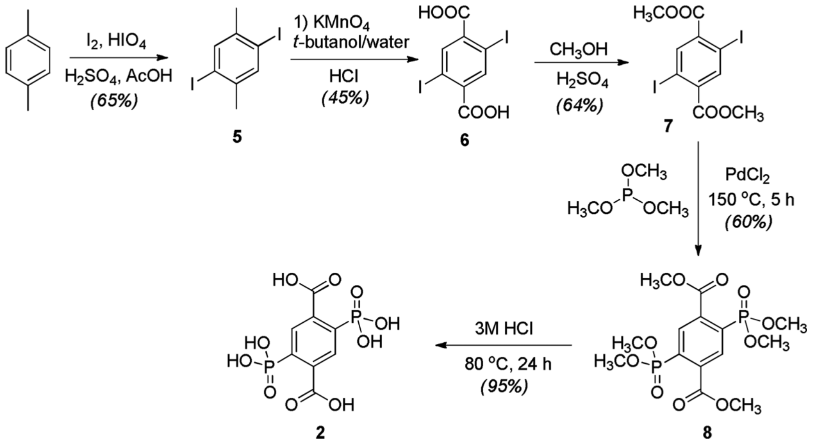
Scheme 1. Preparation of phosphonoterephthalic acid.

sensitive to Grignard or organolithium reagents, such 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 poly-Grignard reagent or lithio derivative.

More recently, in our efforts to incorporate a phosphonate or boronate moiety into an aromatic ring, we discovered that while transition-metal-catalyzed coupling reactions of trialkyl or dialkyl phosphites with aromatic bromoesters did not take place (as noted previously), 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 diazotozation of dimethyl 2-aminoterephthalate, following a literature protocol,[14] followed by a reaction with aqueous KI. Compound **3** was then reacted with excess trimethylphosphite, in the presence of $PdCl_2$, at elevated temperature, yielding the phosphonate ester **4**.[12] The latter was successfully hydrolyzed to the target acid **1**, using 3 M HCl at 80 °C.



Scheme 2. Preparation of 2,5-diphosphonoterephthalic acid.

Preparation of 2,5-Diphosphonoterephthalic Acid (2)

p-Xylene was diiodinated 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 $KMnO_4$ 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 consequently very poor 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 $PdCl_2$. The resultant diphosphonic ester **8** was hydrolyzed in conditions analogous to the ones described for the preparation of **1**.

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 ^{13}C NMR spectra of intermediate and target compounds were recorded at 300 MHz and 75 MHz respectively and referenced to the solvent ($CDCl_3$: 7.27 ppm and 77.0 ppm; D_2O: 4.76 ppm). ^{13}C NMR spectra in D_2O were indirectly referenced to acetone-d_6 in D_2O (literature chemical shift value δ 33.0 ppm for the $\underline{C}D_3$ signal).[16] Elemental analysis was provided by Atlantic Microlab, Norcross, GA. Dimethyl aminoterephthalate was purchased from Acros Organics.

Preparation of Phosphonoterephthalic Esters (4, 8)

A mixture of iodoester (**3** or **7**) (1 eqv.), trimethyl phosphite (4 eqv. per iodine site), and $PdCl_2$ (0.1 eqv. per iodine site) was purged with nitrogen and then stirred for 5 h at 150 °C in a nitrogen atmosphere. Water and 1,2-dichloroethane were added after cooling to ambient temperature. The organic layer was separated, washed two times with water, and dried ($MgSO_4$), and the volatile components were removed under reduced pressure.

Dimethyl (dimethylphosphono)terephthalate (4)[12]. Purified on a silica-gel column, using methylene chloride, followed by CH_2Cl_2–EtOAc = 3:1, followed by pure EtOAc. Colorless oil (81% yield). ^1H NMR ($CDCl_3$) δ 3.83 (d, $J = 11.4$ Hz, 6H), 3.96 (s, 3H), 3.97 (s, 3H), 7.79 (dd, $J_1 = 4.9$ Hz, $J_2 = 8.0$, 1H), 8.25 (dt, $J_1 = 1.5$ Hz, $J_2 = 8.0$ Hz, 1H), 8.56 (dd, $J_1 = 1.6$ Hz, $J_2 = 14.3$ Hz, 1H).

Dimethyl 2,5-bis(dimethylphosphono)terephthalate (8). Purified by recrystallization from toluene. White solid (60% yield). Mp 129–131 °C. ^{1}H NMR ($CDCl_3$) δ 3.84 (d, $J = 11.3$ Hz, 12H), 3.98 (s, 6H), 8.28 (dd, $J_1 = 13.5$ Hz, $J_2 = 5.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 53.3 (s), 53.5 (t, $J = 2.9$ Hz), 131.2 (dd, $J_1 = 187.8$ Hz, $J_2 = 2.9$ 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 $C_{14}H_{20}O_{10}P_2$: C, 40.99; H, 4.91. Found: C, 41.12; H, 4.93.

Preparation of Phosphonoterephthalic Acids (1, 2)

The phosphonoterephthalate ester (**4** or **8**) (1.50 mmol) was suspended in 30 mL of 3 M HCl. The resultant mixture was stirred at 80 °C for 24 h. The solution was concentrated to dryness and tetrahydrofuran (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). ^{1}H NMR (D_2O) δ 7.67 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 7.93 (dt, $J_1 = 8.0$ Hz, $J_2 = 1.0$ Hz, 1H), 8.27 (dd, $J_1 = 15.0$ Hz, $J_2 = 1.0$ Hz, 1H).

2,5-Diphosphonoterephthalic acid (2). Yield: 95%. Mp 310 °C (dec). ^{1}H NMR (D_2O) δ 8.27 (dd, $J_1 = 13.0$ Hz, $J_2 = 5.0$ Hz, 2H); ^{13}C NMR (D_2O, indirectly referenced to acetione-d_6 in D_2O) δ 136.0 (t, $J = 10.4$ Hz), 137.6 (dd, $J_1 = 176.2$ Hz, $J_2 = 2.7$ Hz), 139.4 (t, $J = 10.6$ Hz), 173.5 (t, $J = 2.7$ Hz). Anal. calcd. for $C_8H_8O_{10}P_2 \cdot H_2O$: C, 27.92; H, 2.93. Found: C, 27.76; H, 3.17.

Complete experimental details are available online in the Supporting Information.

ACKNOWLEDGMENTS

Funding for this project was provided by the National Institute of Standards and Technology, Building and Fire Research Laboratory (NIST-BFRL), Fire Research Grant No. 70NANB9H9183. Nathaniel Ivan thanks the Department of Chemistry at the University of Dayton for summer financial support.

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