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Preparation of Some Substituted Terephthalic Acids

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Abstract: The current article reports in detail the preparation of two substituted terephthalic acids: 2-Sulfomethylterephthalic acid (**1**) and 2-phosphonoterephthalic acid (**2**). Efficient, short syntheses have been developed for both compounds. They are potentially useful monomers for construction of acid-pendant polymer chains.

Keywords: terephthalic acids, arenesulfonic acids, arenephosphonic acids, acid-pendant polymers

Introduction

Substituted terephthalic acids, with pendant acidic functional group, have found increasing application in recent years. The best-known example among them is 2-sulfoterephthalic acid, which has been employed in the preparation of rigid-rod polymers^{1,2}, polymers with enhanced solubility³, dopants for electrically-conductive polymers⁴, enzyme inhibitors for glaucoma treatment.⁵

Our recent attempts at preparation of sulfonic acid-pendant poly(benzimidazole) (*SPBI*) demonstrated that conducting the polymerization at elevated temperatures, necessary for satisfactory chain length, triggers an adverse process of desulfonation and an accompanying loss of solubility of the resultant polymer. Consequently, we focused our attention on the preparation and employment of alternative acidic group-containing monomers. The current report details our efforts towards the synthesis and characterization of two particular compounds: 2-sulfomethylterephthalic acid (**1**) and 2-phosphonoterephthalic acid (**2**). The former is a new compound, whose synthesis and characterization we report for the first time, while 2-phosphonoterephthalic acid has been previously reported in two patent sources from 1998.^{6,7} For reasons, stated below, we found it necessary to develop a new synthetic protocol for the preparation of **2**, which is described in the current report.

Compounds **1** and **2**

Results and Discussion

Preparation of 2-sulfomethylterephthalic acid (1). The synthetic sequence employed in the preparation of compound **1** is shown in Scheme 1. The challenge in the preparation of this

material comes from the fact that of the three C-atoms connected to the benzene ring, two are in the form of carboxylic acid functional groups, while the third one is a benzylic type carbon, i.e. the third center has a different degree of oxidation. Therefore the carboxyl groups have to be introduced in the molecule as such, rather than being generated at a later stage. The preparation starts, therefore, with the dilithiation of 2,5-dibromotoluene with *t*-BuLi at $-78\text{ }^{\circ}\text{C}$, followed by reaction with dry ice and subsequent acidification, leading to the introduction of the two carboxyl groups.⁸ The resultant 2-methylterephthalic acid (**3**) is esterified⁹, then side-chain brominated with NBS, to produce dimethyl 2-bromomethylterephthalate (**4**).^{9,10} Compound **4** is then subjected to treatment with aqueous Na_2SO_3 , in the presence of Bu_4NBr as catalyst, in a process of nucleophilic replacement of bromine by a sulfonate anion.¹¹ The resultant sodium salt **5** is treated with conc. HCl to yield the target acid **1**.

Scheme 1

Preparation of 2-phosphonoterephthalic acid (2). In previously published patent literature the preparation of **2** is described, following two different methods. Method 1 relies 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.⁷ Such method is inherently complicated and difficult to apply in laboratory conditions, due to the character of the necessary equipment. Method 2 employs palladium- or nickel-catalyzed coupling of dimethyl 2-bromoterephthalate and triethyl phosphite, followed by acid hydrolysis.⁶ Our repeated attempts

to reproduce the latter chemistry led invariably to full recovery of the starting material. Hence we undertook the development of a new synthetic sequence, which would be easily applied in laboratory conditions, with reproducible results. The synthesis is presented in Scheme 2 and is based on the intermediate preparation of diethyl 2,5-dimethylbenzenephosphonate (**6**). Earlier preparations of **6**^{12,13}, described in literature, rely on the introduction of the phosphonate ester substructure *via* oxidative coupling of *p*-xylene with triethylphosphite or diethylphosphite. This methodology, however, requires substantial amounts of the relatively costly silver nitrate, and also leads to generation of polyphosphonated species, as well as arene self-coupling byproducts. We found that compound **6** could be conveniently prepared from 2-bromo-*p*-xylene.¹⁴ The latter can be either converted to the corresponding Grignard reagent (*Method A*) or lithiated derivative (*Method B*), followed by reaction of the corresponding organometallic intermediate with diethyl chlorophosphate. Compound **6**, upon oxidation with KMnO₄, yields the dipotassium salt of 2-(diethylphosphonyl)terephthalic acid (**7**). Salt **7** is treated with conc. HCl to yield the target compound **2**.

Scheme 2

Conclusions

In this work we have reported the preparation and characterization of two 2-substituted terephthalic acids, compounds **1** and **2**, which are potentially useful in the construction of functionalized polymer chains.

Experimental

^1H and ^{13}C 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; $\text{DMSO-}d_6$: 2.49 ppm and 39.5 ppm; D_2O : 4.76 ppm). ^{31}P NMR signals were indirectly referenced to 85% phosphoric acid ($\delta = 0.0$ ppm) *via* direct reference to $\text{P}(\text{OCH}_3)_3$ as an internal standard ($\delta = +141$ ppm relative to 85% H_3PO_4). Elemental analysis was provided by Atlantic Microlab, Norcross, GA. HRMS data was provided by the Mass Spectrometry and Proteomics facility at the Ohio State University. 2,5-Dibromotoluene was purchased from the Aldrich Chemical Co. Compounds **3** and **4** were prepared following previously published procedures.⁹ Compound **6**, although previously reported^{12,13}, was prepared following a new approach. Hence its synthesis and spectral data are reported in detail.

2-(Sulfomethyl)terephthalic acid (1). An aqueous solution of tetrabutylammonium bromide (0.008 g, 0.025 mmol in 4 mL of water) was added to a round-bottom flask containing dimethyl 2-bromomethylterephthalate (0.28 g, 0.98 mmol), Na_2SO_3 (0.15 g, 1.15 mmol) and ethanol (4 mL). The resultant mixture was stirred at reflux for 12 h, cooled to ambient temperature and the solvent removed under reduced pressure. Methylene chloride (10 mL) was added to the residual solid, the mixture was stirred for 15 min and then vacuum filtered. The solid was washed with methylene chloride and dried to yield the sodium salt **5** as white crystalline compound (0.20 g, 67%). ^1H NMR (D_2O) δ 3.90 (s, 3H), 3.91 (s, 3H), 4.64 (s, 2H), 7.89 (d, $J = 8.8$ Hz, 1H), 8.01 - 8.04 (m, 2H). Sodium salt **5** (0.20 g, 0.64 mmol) was added to 4.0 mL of concentrated hydrochloric acid and the resultant mixture stirred at reflux for 12 h. The mixture was then cooled to ambient temperature and left in a refrigerator for 18 h. The solid was vacuum filtered and dried in a drying pistol (60 °C at 1 mm Hg for 12 h) to yield 0.17 g (98%) of

acid **1**. Mp 290 – 292 °C. ¹H NMR (D₂O) δ 4.66 (s, 2H), 7.91 (d, J = 8.0 Hz, 1H), 8.00 - 8.04 (m, 2H); ¹H NMR (DMSO-*d*₆) δ 4.26 (s, 2H), 7.72 (d, J = 8.1 Hz, 1H), 7.84 (dd, J₁ = 8.1 Hz, J₂ = 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ¹³C NMR (DMSO-*d*₆) δ 54.1, 127.2, 129.6, 132.2, 133.4, 134.7, 136.7, 166.8, 168.6. HRMS (FAB⁺) *m/z* Calcd. for C₉H₈O₇S [M+Na]⁺ 282.9888, found 282.9893. Anal. Calcd. for C₉H₈O₇S · H₂O: C, 38.85; H, 3.62; S, 11.52. Found: C, 38.71; H, 3.72; S, 11.38.

Diethyl 2,5-dimethylbenzenephosphonate (6). *Method A:* A suspension of Mg (1.42 g, 58.42 mmol) in anhydrous THF (100 mL) was brought to reflux. Several drops of 1,2-dibromoethane were added, followed by dropwise addition of 2-bromo-*p*-xylene (9.01 g, 48.68 mmol, 6.72 mL) at a rate to maintain reflux of the reaction mixture. When the addition was complete, the mixture was stirred for additional 1 h at 60 °C, cooled to ambient temperature and added dropwise to a stirred solution of diethyl chlorophosphate (8.40 g, 48.68 mmol, 7.00 mL) in anhydrous THF (20 mL) at 0 °C. The resultant mixture was stirred at ambient temperature for 1 h, followed by 12 h at 60 °C. It was then poured into aqueous solution of NH₄Cl and the organic layer separated. The aqueous fraction was saturated with NaCl and the organic layer separated. The combined organic fraction was dried (MgSO₄), the solvent removed under reduced pressure and the residue passed through a short silica gel column, which was eluted successively with Hexane : CH₂Cl₂ = 1 : 1 (400 mL), hexane : EtOAc = 1 : 3 (400 mL) and EtOAc (200 mL). The second and third fractions were combined, the solvent removed under reduced pressure, to yield the target as a colorless oil (7.10 g, 60%). ¹H NMR (CDCl₃) δ 1.32 (t, J = 7.5 Hz, 6H), 2.34 (s, 3H), 2.52 (s, 3H), 4.02-4.19 (m, 4H), 7.14 (dd, J₁ = 7.7 Hz, J₂ = 5.9 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.75 (dd, J₁ = 14.7 Hz, J₂ = 1.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 16.3 (d, J = 6.5 Hz), 20.6 (d, J = 3.4 Hz), 20.7 (s), 61.8 (d, J = 5.4 Hz), 126.4 (d, J = 182.6 Hz), 131.1 (d, J = 15.8 Hz), 133.1 (d,

J = 3.2 Hz), 134.5 (d, J = 10.5 Hz), 134.9 (d, J = 15.0 Hz), 138.5 (d, J = 9.9 Hz); ³¹P NMR (proton-decoupled)(CDCl₃) δ 19.9 (s).

Method B: *t*-BuLi (10.80 mmol, 6.36 mL of 1.7 M soln. in pentane) was added dropwise to a solution of 2-bromo-*p*-xylene (2.00 g, 10.80 mmol, 1.50 mL) in anhydrous THF (10 mL) at -78 °C (dry ice – acetone) in inert atmosphere. The reaction mixture was stirred for one hour at -78 °C then gradually warmed up to 0 °C over 0.5 h period. The resultant solution was added dropwise to a solution of diethyl chlorophosphate (1.86 g, 10.80 mmol, 1.55 mL) in anhydrous THF (5 mL) at 0 °C and stirring was continued for 12 h at ambient temperature. The resultant mixture was added to an aqueous solution of ammonium chloride (2.00 g in 50 mL water) followed by addition of ether (50 mL). After stirring for 5 min the layers were separated, the organic layer was dried (MgSO₄) and the solvent removed under reduced pressure. The crude product was further purified on a silica gel column (hexane : ethyl acetate = 1:1). The solvents were removed to yield the product as a clear oil (2.05 g, 78%). Spectral data of the product were analogous to those reported under **Method A**.

2-Phosphonoterephthalic acid (2). A mixture of compound **6** (5.40 g, 22.31 mmol), water (90 mL) and *t*-butanol (10 mL) was heated to reflux. Potassium permanganate (14.00 g, 89.16 mmol) was added in small portions and the mixture was left stirring at reflux for 2 hours. The temperature was then reduced to 80 °C and stirring continued for 12 h. The mixture was then cooled to ambient temperature and vacuum filtered on a fritted funnel. The filtrate was concentrated under reduced pressure and then acidified with concentrated hydrochloric acid, while controlling the temperature with an ice bath. The mixture was kept for an additional 3 h at 0 °C and the resultant precipitate was vacuum filtered. It was then suspended in water (10 mL), heated to reflux, cooled, vacuum filtered and dried to yield 3.33 g (61%) of white solid. Mp 295

- 297 °C (Lit.^{6,7} 298 °C, 288 – 290 °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); ¹H NMR (DMSO-*d*₆) δ 7.87 (dd, J₁ = 8.1 Hz, J₂ = 4.8 Hz, 1H), 8.02 (dt, J₁ = 8.1 Hz, J₂ = 1.5 Hz, 1H), 8.42 (dd, J₁ = 13.8 Hz, J₂ = 1.5 Hz, 1H); ¹³C NMR (DMSO-*d*₆) δ 130.8 (d, J = 11.6 Hz), 131.5 (s), 132.3 (d, J = 12.5 Hz), 133.6 (d, J = 12.1 Hz), 135.9 (s), 140.2 (d, J = 9.0 Hz), 167.0 (s), 169.4 (d, J = 5.0 Hz); ³¹P NMR (proton-decoupled) (DMSO-*d*₆) δ 10.8 (s). Anal. Calcd. for C₈H₇O₇P: C, 39.04; H, 2.87. Found: C, 39.31; H, 3.08.

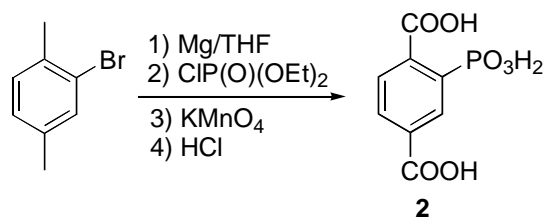
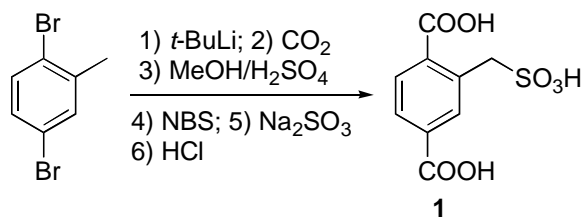
Acknowledgements.

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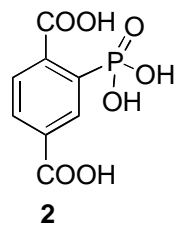
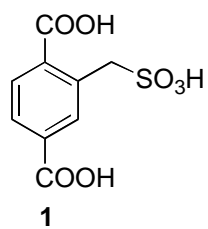
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Graphical Abstract

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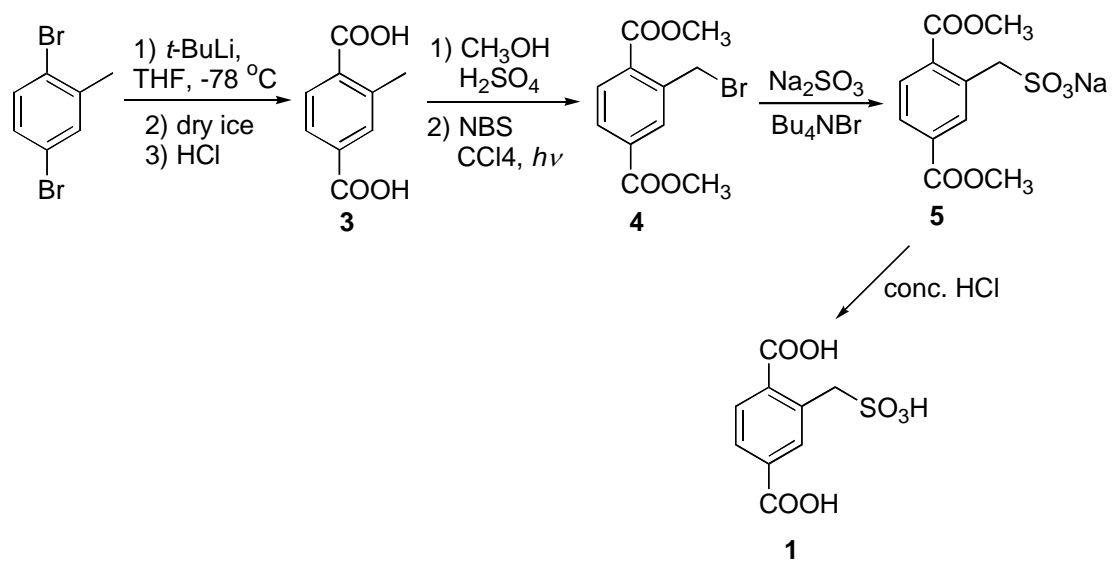
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Compounds **1** and **2**

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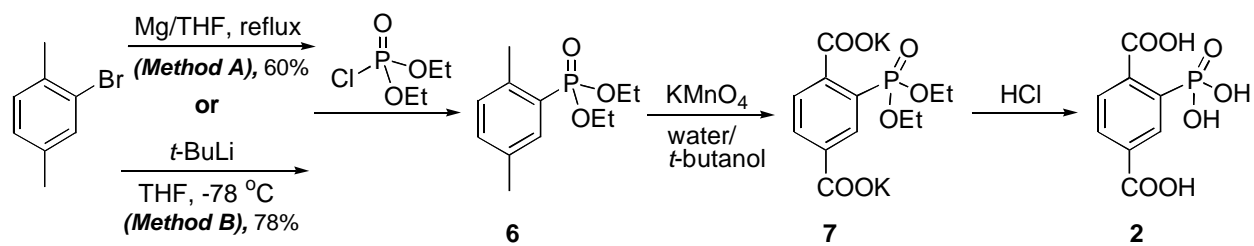
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Scheme 1

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Scheme 2

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