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Methylation of Acids with Pentamethoxyphosphorane

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Several years ago it was reported that pentaethoxyphosphorane reacts with a variety of acidic materials to give the ethylated derivatives.[1] It has also been reported that triphenyldiethoxyphosphorane will effect cyclizations of various glycols and amino alcohols.[2] These reactants have some decided advantages over more common reagents. They do not require acids or bases as catalysts, nor are acids or bases generated during the course of their reactions. Another advantage of these reagents is that blocking groups are often not required. The major disadvantage that these reagents have had is their relative inaccessibility. They could only be prepared by allowing the appropriate trivalent phosphorus compound to react with diethyl peroxide. The prospect of working with large quantities of diethyl peroxide has successfully thwarted further development of these reagents.

Another approach has been to use the phosphorane formed from trimethyl phosphite and methyl vinyl ketone. This material has been shown to be an excellent methylating agent toward acids, phenols, and thiophenols.[3]

Recently a new route to phosphoranes has been developed, and it overcomes the problems associated with the diethyl peroxide route.[4] Pentamethoxyphosphorane (**1**) can be prepared by this method, which consists of allowing trimethyl phosphite (**2**) to react with 2 mol of methyl benzenesulfenate (**3**) at −78 °C in pentane.

$$\underset{\mathbf{2}}{(CH_3O)_3P} + 2\underset{\mathbf{3}}{C_6H_5SOCH_3} \rightarrow \underset{\mathbf{4}}{(CH_3O)_4PSC_6H_5}$$

$$\xrightarrow{3} \underset{\mathbf{1}}{(CH_3O)_5P} + \underset{\mathbf{5}}{(C_6H_5S)_2}$$

$$\underset{\mathbf{7}}{(CH_3O)_3P{=}O} + \underset{\mathbf{8}}{C_6H_5SCH_3} \leftarrow \underset{\mathbf{6}}{(CH_3O)_4P^+} + C_6H_5S^-$$

The reaction is rapid and leads to the production of **1** and diphenyl disulfide (**5**) along with trimethyl phosphate (**7**) and thioanisole (**8**). The contaminants most likely arise from dissociation of the first intermediate, the thiooxyphosphorane **4**, into the ion pair **6**.[5] The ion pair decomposes by S_N2 attack of thiophenoxide on carbon to give **7** and **8**.

Purification of **1** is effected by removing precipitated **5** by filtration at −78 °C. Extraction of the pentane solution with propylene carbonate removes more **5** and **7**. Distillation affords **1** (57%), which is usually contaminated with small amounts of **8** (3–7%). Pentamethoxyphosphorane is fairly stable thermally. After 71 h of heating at 80 °C, only a small amount of decomposition to trimethyl phosphate had occurred. After 184 h, 45% phosphate and 55% phosphorane were present. Pentamethoxyphosphorane is very hydrolytically unstable. It hydrolyzes immediately on contact with water.

Pentamethoxyphosphorane reacts with acids to give the permethylated products in the indicated isolated yields: benzoic acid, 90%; phenol, 92%; hydroquinone, 69%; salicylic acid, 85%; 2,4-dimethylphenol, 77%; and thiophenol, 90%. These reactions were conveniently conducted by adding **1** to the acid in methylene chloride, or in some cases no solvent was employed. In the case of thiophenol, the reaction is quite exothermic and the reactants were mixed at −78 °C and allowed to warm to room temperature. The products of the reactions are methanol, trimethyl phosphate, and the methylated compound. If the methylated compound is water insoluble, then trimethyl phosphate and methanol can be removed merely by washing with water.

Pentamethoxyphosphorane reacted slowly with 2,6-di-*tert*-butylphenol (7 days) at room temperature to produce 88% of 2,6-di-*tert*-butylanisole. At 80 °C, 86% of 2,6-di-*tert*-butylanisole was produced in 26 h.

Several nitrogen acids have been allowed to react with **1**; thus, succinimide and **1** reacted to give *N*-methylsuccinimide in 76% yield, phthalimide yielded 64% of *N*-methylphthalimide, and uracil gave 1,3-dimethyluracil in 88% yield.

The reactions of **1** with carbon acids are currently under study, and the results will be reported later. Earlier, it was shown that pentaethoxyphosphorane ethylates diethyl malonate on carbon and ethyl acetoacetate on oxygen.[1]

Experimental Section

All ^1H NMR spectra were recorded with a Varian T-60 NMR spectrometer. GLC analyses were conducted with F and M Model 700 and Varian 90-P gas chromatographs. Melting points were recorded with a Mel Temp apparatus and are uncorrected.

Preparation of 1. A 2-L three-neck flask equipped with a dropping funnel and a mechanical stirrer was charged with 125.0 g (1.120 mol) of methyl benzenesulfenate[4b] and 700 mL of dry pentane. The flask was cooled in a dry ice–acetone bath under an atmosphere of argon. Over a period of 1.5 h, 69.50 g (0.560 mol) of freshly distilled trimethyl phosphite in 50 mL of dry pentane was added dropwise with vigorous stirring. An additional 75 mL of pentane was added to facilitate stirring of the heterogeneous reaction mixture; diphenyl disulfide precipitated from the pentane at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for an hour. The reaction mixture was cooled to −78 °C, and the pentane solution was separated from diphenyl disulfide by forcing it through a filter stick

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under an atmosphere of nitrogen. The precipitate was washed at −78 °C with 200 mL of pentane. The combined pentane solutions were washed twice with 100-mL portions of propylene carbonate, which removed phosphate and diphenyl disulfide.[4b] The pentane was removed in vacuo to afford 59.6 g (57% yield) of **1**. The ^1H and ^{31}P NMR spectra showed that the yellow oil contained pentane, diphenyl disulfide, and methyl phenyl sulfide.

In another experiment of about the same size, the product was distilled, bp 37 °C (0.07 mm), to give 34 g (57% yield) of **1** contaminated with 6% of thioanisole. More careful distillation afforded **1** essentially free of thioanisole. There was of course a diminution in yield. For the experiments being reported, **1** contaminated with thioanisole was used.

Reaction of 1 with Benzoic Acid. To a solution of 2.44 g (0.02 mol) of benzoic acid in methylene chloride (20 mL) was added 4.0 g (0.0215 mol) of **1** dropwise over a period of 10 min under an atmosphere of nitrogen. After the addition, the methylene chloride solution was washed with water to remove trimethyl phosphate. The methylene chloride solution was evaporated to give 2.48 g (90%) of essentially pure methyl benzoate. The ^1H NMR spectrum was identical with that of authentic material.

Reaction of 1 with Phenol. To a solution of 1.88 g (0.02 mol) of phenol in 20 mL of methylene chloride was added dropwise 4.0 g (0.0215 mol) of **1** under an atmosphere of nitrogen with stirring at room temperature. The ^1H NMR spectrum of the reaction mixture after the addition showed that all of **1** had reacted. The methylene chloride solution was washed with water and concentrated to give 2.0 g (90%) of anisole whose ^1H NMR spectrum was identical with that of authentic material.

Reaction of 1 with Hydroquinone. Hydroquinone (0.55 g, 0.0048 mol) was treated with 2.0 g (0.01 mol) of **1** at 5–10 °C with stirring. The reaction mixture was treated with 5 mL of water, and the crystalline product was isolated by filtration and dried to give 0.475 g (69% yield) of 1,4-dimethoxybenzene, mp 55–56 °C (lit.[6] mp 56 °C).

Reaction of 1 with Salicylic Acid. Salicylic acid (0.414 g, 0.003 mol) and 1.2 g (0.0064 mol) of **1** were mixed at room temperature and then heated at 70–75 °C for 1.5 hr. Distillation yielded 0.44 g (85%) of methyl *o*-methoxybenzoate, bp 245 °C (lit.[7] bp 228 °C). The ^1H NMR spectrum had absorptions for aromatic hydrogens (4 H) and overlapping singlets for the hydrogens of methoxy groups at δ 3.9 (6 H).

Reaction of 2,4-Dimethylphenol with 1. To 1.2 g (0.009 mol) of 2,4-dimethylphenol was added 2.1 g (0.0112 mol) of **1** at 5 °C. The reaction mixture was stirred at room temperature for 30 min and then washed with three 8-mL portions of water. The product was distilled, bp 192 °C, to give 1.0 g (77%) of 2,4-dimethylanisole. The ^1H NMR spectrum was identical with that reported.[8]

Reaction of 2,6-Di-*tert*-butylphenol with 1. Several reactions were conducted using 0.27 g (0.00131 mol) of 2,6-di-*tert*-butylphenol and 0.30 g (0.00161 mol) of **1** in deuterated benzene. The course of the reactions was followed by ^1H NMR spectroscopy and GLC. A sample of product was isolated, and its ^1H NMR spectrum was identical with that reported.[9]

Reaction of Thiophenol and 1. To 0.30 g (0.00161 mol) of **1** in an NMR tube at −78 °C was added 0.177 g (0.00161 mol) of thiophenol in methylene chloride. The reaction mixture was allowed to warm to room temperature slowly. The methylene chloride solution was washed with water and concentrated under vacuum. The ^1H NMR spectrum in benzene-d_6 was identical with that of a known sample of thioanisole. The yield was 87%.

Reaction of Succinimide with 1. To a solution of 0.46 g (0.00465 mol) of succinimide in 5 mL of methylene chloride at 5 °C was added 1.01 g (0.00567 mol) of **1** over 10 min. The trimethyl phosphate and methanol were distilled at 40–65 °C (0.15 mm), and the residue was recrystallized from methanol to give 0.405 g (76%) of *N*-methylsuccinimide, mp 66–68 °C (lit.[10] mp 71 °C).

Reaction of Phthalimide with 1. Phthalimide (0.10 g, 0.00068 mol) and 0.235 g (0.0012 mol) of **1** were mixed at −78 °C. After standing at room temperature overnight, a solid formed which was separated by centrifugation, washed with water, and dried to give 0.70 g (64%) of *N*-methylphthalimide, mp 132–134 °C (lit.[11] mp 134 °C).

Reaction of Uracil with 1. Uracil (0.064 g, 0.00057 mol) and 0.230 g (0.0012 mol) of **1** were mixed at 0 °C. A solid formed on standing. Trimethyl phosphate was removed at 80 °C (0.1 mm) to give 0.65 g (88%) of 1,3-dimethyluracil, mp 120–121 °C (lit.[12] mp 120–121 °C).

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Registry No.—**1**, 1455-07-8; **2**, 121-45-9; **3**, 28715-70-0; **8**, 100-68-5; anisole, 100-66-3; 1,4-dimethoxybenzene, 150-78-7; methyl *o*-methoxybenzoate, 606-45-1; 2,4-dimethylanisole, 6738-23-4; methyl benzoate, 93-58-3; *N*-methylsuccinimide, 1121-07-9; *N*-methylphthalimide, 550-44-7; 1,3-dimethyluracil, 874-14-6; benzoic acid, 65-85-0; phenol, 108-95-2; hydroquinone, 123-31-9; salicylic acid, 69-72-7; 2,4-dimethylphenol, 105-67-9; 2,6-di-*tert*-butylphenol, 128-39-2; thiophenol, 108-98-5; succinimide, 110-14-5; phthalimide, 85-41-6; uracil, 66-22-8; 2,6-di-*tert*-butylanisole, 1516-95-6.

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Heteroatom-Substituted Butadienylphosphonium Salts as Reagents. A New Synthesis of 2-Ethoxycyclohexadienes and Cyclohexenones

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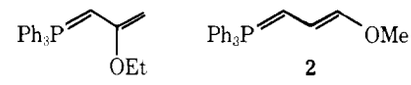
In connection with a general research program designed to discover and develop new methodology for annelation and homologation operations, we have examined the synthetic utility of several functionalized allylidenetriphenylphosphoranes, and some of our efforts have been duly rewarded. For example, (2-ethoxyallylidene)triphenylphosphorane (**1**)



1 **2**

was found to react smoothly with α,β-unsaturated ketones to produce 2-ethoxy-1,3-cyclohexadienes which could be converted to substituted cyclohexenones by subsequent acid-catalyzed hydrolysis.[1] In another investigation, (3-methoxyallylidene)triphenylphosphorane (**2**) was found to be a highly effective reagent for the facile three-carbon homologation of aldehydes and ketones to α,β-unsaturated aldehydes via intermediate 1-methoxy-1,3-butadienes.[2] These results have naturally stimulated further studies to ascertain whether other unsaturated, heteroatom-substituted phosphoranes or phosphonium salts might also be useful as synthetic reagents.

The important discovery that butadienyltriphenylphosphonium salts[3] **3** (X = H) and diethyl butadienylphosphonates[4] **4** (X = H) undergo reactions with the enolates of carbonyl compounds **5** to produce cyclohexadienes **6** (X = H) suggested to us that the placement of a heteroatom group onto

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