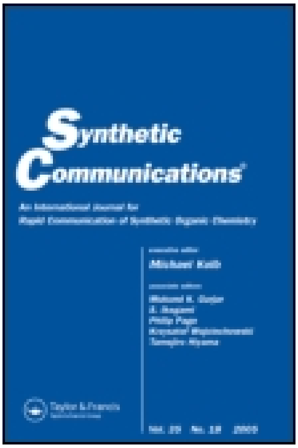

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Convenient Preparation of Diethyl (2-Thienyl)methanephosphonate

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Abstract: This article describes a convenient preparation of diethyl (2-thienyl)methanephosphonate in 88% overall yield.

Keywords: Arbuzov, chlorination, phosphite

As part of a program to develop optical devices composed of polymers, a consistent supply of diethyl (2-thienyl)methanephosphonate (**3**) was necessary. There are several reports of its preparation, and those[1–4] starting from the readily available 2-thiophenemethanol (**1**) were more attractive than others.[5–7] In general, these procedures start by chlorinating **1** to form 2-(chloromethyl)thiophene (**2**) and subsequently reacting it with triethyl phosphite in the classic Michaelis–Arbuzov condensation to form 3 (Scheme 1).

We began making **2** with concentrated hydrochloric acid.[8,9] We could obtain the product in moderate yield, but it came with a dark color, presumably from acid-catalyzed polymerization of **1**. This method required extractive workup followed by distillation. The noxious nature of **2** made us seek a method that would minimize postreaction processing.

The use of thionyl chloride for this transformation would be a simpler approach because the by-products generated in the reaction are gases: sulfur

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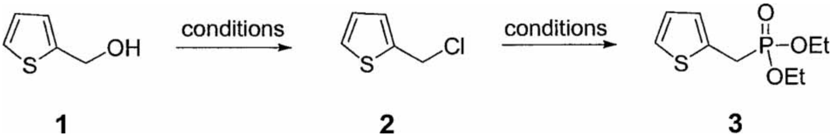

Scheme 1.

dioxide and hydrogen chloride.[3,4] Our first attempt was dropwise addition of thionyl chloride into a solution of **1**. Because this places **1** in direct contact with the hydrogen chloride generated, the formation of the dark color occurred rapidly at ambient or ice bath temperature. When the addition was reversed and the by-product gases were swept away by a steady flow of nitrogen, the chlorination ran cleanly. The alcohol (**1**) is immediately converted to the chlorosulfite ester, which rearranges to **2**.[10] The nitrogen flow protects **1** from the hydrogen chloride while in the addition funnel. It was easy to determine reaction completion by the evolution of gas from the reaction. The isolation and purification of **2** involved a simple fractional distillation directly from the reaction pot. The method provided **2** in high yield, and it could be stored at −20°C for one month without noticeable decomposition.[11]

For the Michaelis–Arbuzov reaction, the conditions reported by Zhang et al.[8] for the 5-bromo analog of **3** indicated it should be high yielding. However, triethyl phosphite was made the limiting reagent (slightly less than 1 equivalent) rather than **2** to capitalize on the boiling point difference between **2** and **3**: 130°C and 325°C at 760 torr, respectively. This method provided **3** in nearly quantitative yield with a simple isolation and purification by fractional distillation directly from the reaction pot.

In summary, the final conditions for the two-step transformation are shown in Scheme 2. Here is a convenient method to prepare diethyl (2-thienyl)methanephosphonate (**3**) in 88% overall yield starting from 2-(hydroxymethyl)thiophene (**1**). The method is robust and minimizes postreaction processing.

EXPERIMENTAL

Warning! The products **2** and **3** as well as triethyl phosphite, all have noxious odor and are most likely toxic. **All** of the unit processes described below should be performed in a well-ventilated fume hood. **All** the glassware

$$\mathbf{1} \xrightarrow[\text{a}]{91\%} \mathbf{2} \xrightarrow[\text{b}]{97\%} \mathbf{3}$$

Scheme 2. Optimized conditions. Reagents and conditions: a) $SOCl_2$, CH_2Cl_2, reverse addition, rt; b) 1 equiv. $P(OEt)_3$, 150°C.

employed in either preparation should be rinsed with organic solvents prior to removal from the fume hood. Chloroethane (ethyl chloride) appears on the list of hazardous air pollutants of the 1990 Clean Air Act of the U.S. Congress.[12] The chloroethane (bp 12°C) generated in the preparation of **3** can be condensed for safe disposal or stored for later use at 0°C or below.

NMR spectra were obtained on a Bruker AC-200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz, and ^{31}P at 81 MHz) and are referenced to solvent or tetramethylsilane. The 2-thiophenemethanol (**1**), triethyl phosphite (98%), and $SOCl_2$ (99%) were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). All other reagents were obtained commercially and used as received.

2-(Chloromethyl)thiophene (2)

A dry, 500-mL, two-necked, round-bottomed flask was equipped with a magnetic stirring bar, thermometer, 250-mL pressure-equalizing dropping funnel, and gas adapters on both the flask and top of the dropping funnel (see Figure 1). The flask was charged with 250 mL of CH_2Cl_2 followed by 41.5 mL of $SOCl_2$ (67.68 g, 569 mmol, 1.1 equiv). The funnel was charged with 59 g of 2-thiophenemethanol (**1**) (49.2 mL, 517 mmol). A source of dry

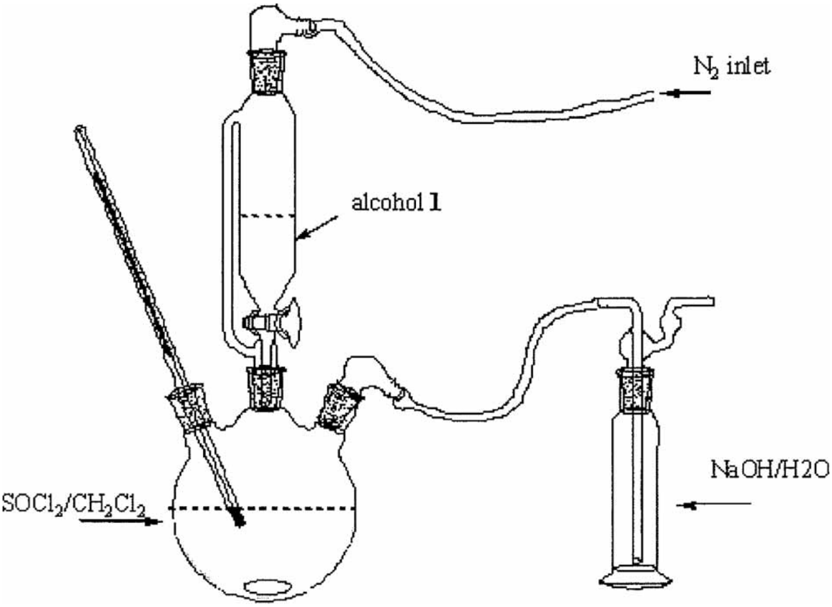

Figure 1. Apparatus for transformation of **1** into **2**.

N_2 was connected to the-gas adapter on the dropping funnel. The gas adapter on the flask was connected with tubing to a gas-washing bottle containing 1 L of 1 M aqueous NaOH. The reaction flask was placed in a 25°C water bath and vigorously stirred, and the N_2 flow was started at a moderate rate. The alcohol was added dropwise over 30 min. The temperature within the reaction climbed to 28°C after one third of the alcohol had been added and gradually fell to 25°C by the end of the addition. The water in the bath was replaced with warm water (32°C) to facilitate completion. After 30 min, no further gas evolved and the solution was golden yellow. The thermometer, addition funnel, and gas inlet adapter were removed from the reaction flask. A short-path, vacuum still head was equipped to the center neck and the other necks were glass-stoppered. The CH_2Cl_2 was evaporated under reduced pressure (8 Torr) and the remaining oil was distilled (55–75°C, 8 Torr) into a 500-mL, round-bottomed flask to give **2** as a colorless liquid (62.1 g, 91%). The compound was stored at −20°C. ^{1}H NMR ($CDCl_3$) δ 7.3 (d, $J = 1.3$ and 5.1 Hz, 1H), 7.08 (d, $J = 3.6$ Hz, 1 H), 6.95 (dd, $J = 3.6$ and 5.2 Hz, 1H), 4.79 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.21, 127.83, 127.04 (two overlapping resonances), 40.51.

Diethyl (2-Thienyl)methanephosphonate (3)

To a 500-mL, round-bottomed flask containing 62.1 g of **2** (468 mmol) was added a magnetic stirring bar followed by 80.2 mL of triethyl phosphite (77.7 g, 468 mmol, 1 equiv). A Claisen adapter equipped with a thermometer (for monitoring internal reaction temperature) and reflux condenser was attached to the flask. A gas adapter was used to connect the condenser through tubing to a 0°C trap then onto an N_2 bubbler. The flask was heated to 160°C with a heating mantle. After 7 h, analysis of the reaction mixture by ^{1}H NMR showed complete consumption of the starting materials. A short-path, vacuum distillation head was attached to the reaction flask and the mixture was distilled (1 Torr, 130–145°C) to obtain 106.3 g of **3** as a colorless liquid (97%). ^{1}H NMR ($CDCl_3$) δ 7.18 (dt, $J = 1.5$ and 5.1 Hz, 1 H), 7.01–6.92 (m, 2H), 4.08 (dq, $J = 7.1$ and $^3J_{POCH}$ 7.8 Hz, 4H), 3.36 (d, $^2J_{PCH} = 21$ Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 132.32 (d, $J_{P\text{-}C} = 10.2$ Hz), 127.19 (d, $J_{P\text{-}C} = 8.9$ Hz), 126.89 (d, $J_{PC} = 3.8$ Hz), 124.61 (d, $J_{PC} = 3.8$ Hz), 62.23 (d, $^2J_{POC} = 7.0$ Hz), 27.78 (d, $J_{PC} = 144.8$ Hz), 16.24 (d, $^3J_{POCC} = 6.4$ Hz); ^{31}P NMR ($CDCl_3$) δ 23.75 (s). Anal. calcd. for $C_9H_{15}O_3PS$: C, 46.15; H, 6.45; S, 13.69. Found: C, 46.00; H, 6.28; S, 13.56.

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