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An expedient synthesis of diethyl diazomethylphosphonate

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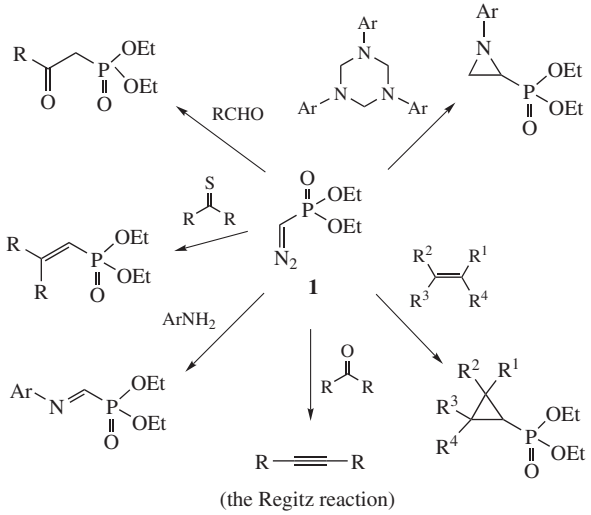
A simple three-step preparation of diethyl diazomethylphosphonate was performed from chloroacetone and triethyl phosphite in total yield 70%.

The phosphonate (PO_3^{2-}) moiety is a common structural fragment present in a wide range of biologically active compounds.[1,2] Despite structural and electronic differences between phosphonate and carboxylic functionalities the phosphonate one is regarded as a bioisostere of the carboxylic group.

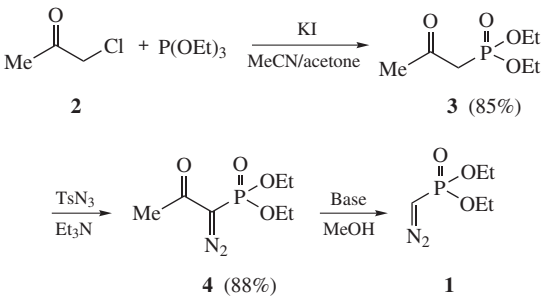
Diethyl diazomethylphosphonate **1** is widely used for preparation of various derivatives of phosphonic acids, such as cyclopropanes,[3] aziridines,[4] phosphonoketones,[5] imines[6] and α,β-unsaturated phosphonates[7] (Scheme 1). In addition, it is often used for the Regitz reaction, *i.e.* transformation of carbonyl compounds into acetylene derivatives.[8]



Scheme 1

The conventional method for preparation of diazo compound **1**[9] is based on diazotization of diethyl aminomethylphosphonate, which requires four labourious synthetic stages, the last diazotization step occurring with moderate yield of ~45%. An essential drawback of this approach is a vacuum distillation of the final product which makes this procedure rather dangerous especially in large scale preparations.

Here we describe an alternative efficient synthesis of diethyl diazomethylphosphonate from readily available chloroacetone **2** and triethyl phosphite (Scheme 2).† With the use of modified



Scheme 2

literature methodologies[10,11] diethyl 2-oxopropylphosphonate **3** and diethyl 2-oxo-1-diazopropylphosphonate **4** were obtained. Diazo grouping was introduced into keto phosphonate **3** by reacting with tosyl azide.

Analysis of literature data revealed that α-acetyl-α-diazomethylphosphonates can easily undergo deacetylation under basic methanolysis, *e.g.*, by treating them with K_2CO_3 in methanol (the Ohira's method).[12] However, this technique was not applied for obtaining these compounds in pure form. Conversion of **4** into

† NMR spectra were recorded on Bruker AV-300 and AV-400 spectrometers [300 and 400 (^{1}H), 75 and 100 (^{13}C), 121.5 and 162 MHz (^{31}P), H_3PO_4 as an external reference]. All solvents used in the reactions were dried with appropriate drying agents. The reaction progress was monitored by TLC (plates with silica gel Merck 60 F_{254}, UV irradiation or treating with cerium molibdate in 5% H_2SO_4 solution). The column chromatography was carried out on silica gel Merck 60 (230–400 ASTM).

Diethyl 2-oxopropylphosphonate **3**.[10] A solution of chloroacetone **2** (5.33 g, 57.6 mmol) and KI (9.4 g, 56.6 mmol) in 16 ml of dry acetone was stirred at room temperature for 2 h, then triethyl phosphite (9.25 g, 55.6 mmol) in 16 ml of dry diethyl ether was added, and the solution was refluxed for 2 h. The mixture was cooled to room temperature and the precipitate was filtered off. After evaporation of the solvent under reduced pressure the crude product **3** was distilled *in vacuo*. Yield 9.19 g (85%), colourless liquid, bp 101–105 °C (1.5 Torr) [lit.,[14] bp 75 °C (0.2 Torr)]. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 6H, Me, ^3J 7.1 Hz), 2.33 (s, 3H, Me), 3.07 (d, 2H, CH_2, $^2J_{HP}$ 24 Hz), 4.17 (m, 4H, OCH_2). ^{31}P NMR ($CDCl_3$) δ: 19.75.

Diethyl 1-diazo-2-oxopropylphosphonate **4**.[11] A mixture of **3** (7.74 g, 40 mmol), tosyl azide (7.88 g, 40 mmol) and triethylamine (40 ml) was stirred at room temperature for 18 h. After evaporation of triethylamine under reduced pressure the residue was dissolved in minimal amount of MTBE and 100 ml of light petroleum was added. The precipitate was filtered off, the filtrate was evaporated and the residue was purified by column chromatography on silica gel [ethyl acetate–hexane (1:2), then pure ethyl acetate]. Yield 7.39 g (88%), yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 6H, Me, ^3J 7.1 Hz), 2.27 (s, 3H, Me), 4.25 (m, 4H, OCH_2). ^{31}P NMR ($CDCl_3$) δ: 11.3.

Diethyl diazomethylphosphonate **1**. A solution of **4** (4.0 g, 18 mmol) in 50 ml of MeOH was stirred with sodium phosphate (1.29 g, 13.3 mmol) at room temperature for 15 min [during this time the starting compound completely disappeared (TLC control)]. The precipitate was filtered off. After evaporation of the solvent under reduced pressure MTBE was added and the precipitate was filtered off again. Solvent was removed on rotary evaporator and compound **1** was obtained essentially pure. Yield 3.0 g (93%), yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 6H, Me, ^3J 7.0 Hz), 3.7 (d, 1H, CH, $^2J_{HP}$ 12 Hz), 4.15 (m, 4H, OCH_2). ^{31}P NMR ($CDCl_3$) δ: 19.2.

Table 1 Methanolysis of compound **4**.

Entry no.	Base	*T*/°C	Time	Yield of **1** (%)[a]
1	Et_3N	20	24 h	traces
2	Et_3N	50	8 h	traces
3	Et_3N	64 (reflux)	10 h	40[b]
4	NaOH	20	15 min	—[c]
5	NaOEt	20	10 min	—[c]
6	K_2CO_3	20	30 min	85
7	Na_2CO_3	20	30 min	75
8	DBU	20	1 h	83
9	Na_3PO_4	20	15 min	100 (93[d])

[a]Yield based on ^{31}P NMR. [b]Large quantity of by-products. [c]No product. [d]Isolated yield.

1 by using mixture methanol/triethylamine was also described,[13] however, the product was not purified and its formation was confirmed by NMR and IR spectra only. Following the mentioned procedure we have revealed that treatment of compound **4** with Et_3N/MeOH at 20 or 50 °C led to trace amount of **1** after 24 h. Under reflux conditions, diazophosphonate **1** was formed in 40% yield along with large quantity of by-products. Therefore, additional study for optimization was performed. It was found that strong bases like sodium hydroxide and sodium ethoxide induced fast decomposition of starting material without formation of desired product. In case of sodium hydrogen carbonate starting compound remained without change, whereas sodium or potassium carbonates as well as DBU appeared to be effective bases affording the desired diazophosphonate **1** in 75–85% yield. Finally, sodium phosphate (Na_3PO_4) has proved to be the most perspective base leading to almost quantitative formation of **1** without any impurities. After simple filtration and removal of solvent diethyl diazomethylphosphonate **1** was obtained pure (^{1}H, ^{13}C and ^{31}P NMR data) and did not require distillation.

In conclusion, we elaborated an efficient and convenient three-step protocol for the preparation of diethyl diazomethylphosphonate. An essential advantage of Na_3PO_4 over other bases during deacetylation of diazo compound **4** was discovered, leading to the desired product quantitatively, which gives advantage of large scale preparations without dangerous distillation.

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