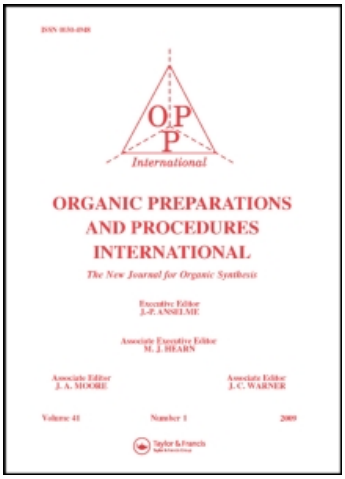

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A CONVENIENT SYNTHESIS OF DIETHYL (MERCAPTOMETHYL)PHOSPHONATE

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A CONVENIENT SYNTHESIS OF DIETHYL (MERCAPTOMETHYL)PHOSPHONATE

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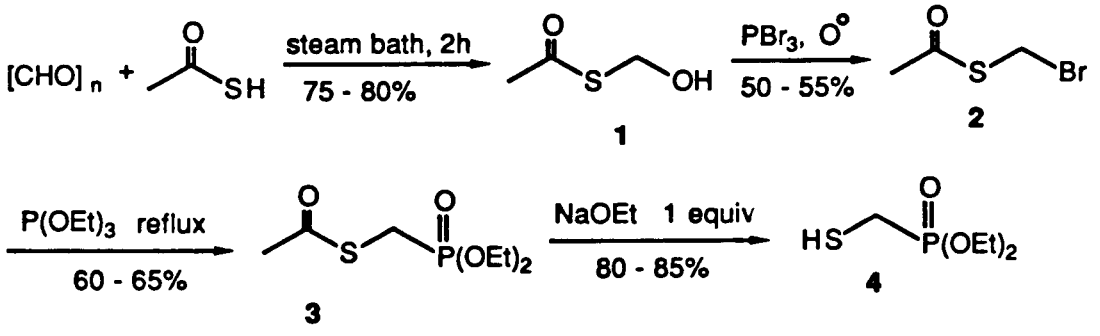
The design of α-thiomethylphosphonates as analogs of acylphosphates[1] and phosphate esters[2] has led to the development of a convenient new synthetic route to diethyl (mercaptomethyl)phosphonate (4). The synthetic scheme outlined below was developed because the previous synthesis[3] of 4 was found to be unreliable and difficult to scale up.



The previous synthesis of 4 was carried out by stepwise addition of the methylene and sulfur to the phosphorus. The design of the synthetic route above differs fundamentally, beginning with the sulfur (thiolacetic acid) and sequentially adding the methylene and the phosphorus. The desired product diethyl (mercaptomethyl)phosphonate (4) was found to be inherently unstable and underwent rapid oxidation and degradation to several products after

storage for several days. However, the acetylated diethyl (mercaptomethyl)phosphonate (3) may be stored at room temperature for an extended period of time with no apparent degradation. The acetylated reagent 3 may be conveniently deblocked when needed by treatment with one equivalent of freshly prepared sodium ethoxide in ethanol. Michael additions[1,2] and elimination reactions of alkyl halides[1] can be carried out in situ after allowing sufficient time for removal of the acetyl group. The yields of reactions carried out in situ are identical to those carried out with the purified thiol, but have the advantage of minimizing the handling of the thiol which has a potent stench! NMR spectra provide the structural proof for 1-4 and agree with the previously published spectra.[3]

EXPERIMENTAL SECTION

All compounds exhibited NMR spectra consistent with their respective structures. ^1H NMR spectra were determined with a Varian EM-360-A spectrophotometer at 60 MHz or with a 360 MHz Bruker spectrophotometer, using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (δ) downfield from Me_4Si. Thin layer chromatography was performed on Baker Si250 TLC plates. Distillations were carried out with a Kontes Short-path distillation apparatus. Chemical reagents and starting materials were obtained from Aldrich Chemical Co. or Alfa Products and were used without further purification, unless otherwise noted. All trialkyl phosphites were distilled from sodium prior to use

Hydroxymethyl Acetyl Sulfide[4] (1).- Thiolacetic acid (100 g, 1.3 mol) and paraformaldehyde (40.0 g) were heated on a steam bath for 2-3 hrs. The reaction mixture became clear light yellow in color which indicated completion of the reaction. The product was then distilled under reduced pressure to give 111 g (80%) of pure hydroxymethyl acetyl sulfide, bp. 35-36°/0.1 mm; NMR 60 MHz ($CDCl_3$): δ 2.38 (s, 3H, $CH_3C(O)S$), 4.2 (s, 1H, $HOCH_2S$), 5.0 (s, 2H, $HOCH_2S$).

Bromomethyl Acetyl Sulfide[4] (2).- Phosphorus tribromide (94.8 g, 0.34 mol) was slowly added to the cooled neat hydroxymethyl acetyl sulfide (111 g, 1.05 mol) with stirring such that the temperature was not allowed to rise above 5-8°. An ice-salt mixture was used for cooling and the reaction was carried out in a nitrogen atmosphere. After the complete addition of the PBr_3, the reaction mixture was stirred for an additional 30 min at 5-8° and then allowed to come to room temperature. It was then poured over an ice-water mixture and extracted with ether (3 x 100 mL). The extracts were washed with water (2 x 100 mL), dried over anhydrous Na_2SO_4, and finally concentrated under reduced pressure to give the crude bromomethyl acetyl sulfide (2). Distillation of the crude product yielded 89.0 g (50%) of pure bromomethyl acetyl sulfide (2), bp. 53-55°/0.01 mm; NMR 60 MHz ($CDCl_3$: δ 2.38 (s, 3H, $CH_3C(O)S$), 4.68 (s, 2H, $BrCH_2S$).

(Diethylphosphono)methyl Acetyl Sulfide (3).- Bromomethyl acetyl sulfide (79.0 g, 0.47 mol) and triethyl phosphite (89.6 g, 0.54 mol) were combined together in a round-bottomed flask (250 mL) fitted with a Dean-Stark trap. The reaction was stirred at 130° and heated until ethyl bromide was no longer collected in the Dean-Stark trap (2-2.5 hrs). The product was distilled to give 63 g (60%) of a clear oil, bp. 105-106°/0.03 mm; NMR 360 MHz ($CDCl_3$): δ 1.27 (t, 6H, J = 7.0 Hz, $POCH_2CH_3$), 2.34 (s, 3H, $C(O)CH_3$), 3.18 (d, 2H, J_{H-P} = 14.0 Hz, PCH_2), 4.25 (dq, 4H, J_{H-P} = 7.1 Hz and J = 7.0 Hz, $POCH_2CH_3$).

Diethyl (Mercaptomethyl)phosphonate (4).- (Diethylphosphono)methyl acetyl sulfide (63 g, 0.28 mol) was added slowly to a solution of sodium ethoxide, freshly prepared from sodium (6.45 g, 0.28 mol) in 100 mL of absolute ethanol. The reaction mixture was stirred 1-1.3 hr at room temperature, followed by in vacuo removal of solvent. The residue was dissolved in water (75-100 ml), cooled and acidified to pH 2.0 with 2N HCl. The product was extracted with ether (3 x 150 ml); the organic layer was washed with water (2 x 100 ml), dried over Na_2SO_4 and filtered. The ether was removed in vacuo, and the remaining oil was distilled under vacuum to give 41 g (80%) of diethyl (mercaptomethyl)phosphonate (4) as a clear oil, bp. 69-71°/0.03 mm; NMR 360 MHz ($CDCl_3$): δ 1.31 (t, 6H, J = 7.1 Hz, $POCH_2\underline{CH_3}$), 1.83 (m, 1H, $J_{H\text{-}P}$ = 4.0 Hz and J = 8.1 Hz, $\underline{H}SCH_2P$), 2.64 (dd, 2H, $J_{H\text{-}P}$ = 13.3 Hz and J = 8.1 Hz, $HS\underline{CH_2}P$), 4.17 (dq, 4H, $J_{H\text{-}P}$ = 9.8 Hz and J = 7.1 Hz, $PO\underline{CH_2}CH_3$).

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