Tetrahedron Letters,Vol.27,No.13,pp 1477-1480,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

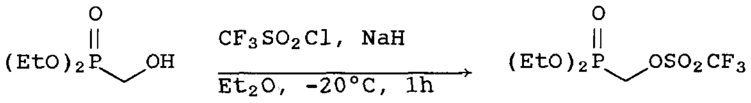
SYNTHESIS AND REACTIVITY OF DIETHYL PHOSPHONOMETHYLTRIFLATE

Dennis P. Phillion* and Steven S. Andrew
Monsanto Agricultural Products Company
Research Department, St. Louis, Missouri 63167

Diethyl phosphonomethyltriflate, prepared from diethyl hydroxymethylphosphonate, readily reacts in good to excellent yields with a variety of oxygen and nitrogen nucleophiles.

Currently, no mild method exists for effecting displacement reactions on the α-carbon of phosphonates. Such a reaction would be quite useful for synthesizing complicated phosphonates unavailable by other methods. For example, α-heterosubstituted methyl phosphonates can be prepared by displacement reactions on phosphonomethyl halides and sulfonates only with potent nucleophiles such as thiolates and selenates.[2] Other nucleophiles[3] react sluggishly or not at all. Since trifluoromethanesulfonate esters (triflates) show greatly enhanced leaving-group characteristics[4], it seemed plausible that diethyl phosphonomethyltriflate (2) would react with nucleophiles rapidly, in good yield, and at low temperature. Indeed, we have developed a straightforward synthesis of 2, utilizing NaH as the base, and found it to readily react at room temperature and in high yield with a variety of demanding oxygen and nitrogen nucleophiles.

Diethyl phosphonomethyltriflate (2) was synthesized from diethyl hydroxymethylphosphonate[5] (1) as depicted by the following equation:



1

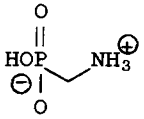
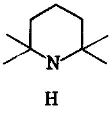
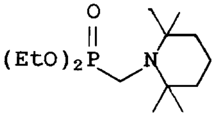
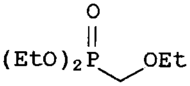
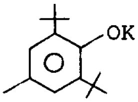
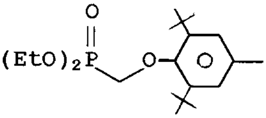
2

In a typical preparation of 2, CF_3SO_2Cl (38.06 mL, 356 mmol) was added in a single portion to a dry-ice/acetone cooled mixture of 99% granular NaH (9.28g, 386 mmol) in Et_2O (500 mL), and was followed immediately by the rapid dropwise addition of a solution of diethyl hydroxymethylphosphonate (50.0g, 297 mmol) in Et_2O (100 mL), maintaining an internal reaction temperature between -20°C and -15°C. After the resulting reaction mixture was stirred 1h at -20°C, H_2 evolution had almost ceased and the ^{31}P-NMR showed >99% conversion of diethyl hydroxymethylphosphonate to the corresponding triflate, so the mixture was rapidly filtered through celite to remove the remaining NaH, then was diluted with CH_2Cl_2 (1000 mL) and thoroughly extracted with saturated aqueous $NaHCO_3$ (3 X 35 mL), then was dried ($MgSO_4$) and concentrated to afford 71.36g (80%) of analytically pure 2 as a colorless oil.

If the reaction temperature was not maintained below -15°C, the ^{31}P-NMR spectrum showed bis(diethyl phosphonomethyl) ether (20.5 ppm) in addition to 2 (12.0 ppm). This mixture was easily separated by partitioning between Et_2O/H_2O. Other commercial forms of NaH (dry powder or oil dispersion) afforded less satisfactory results.[6] Impure preparations of 2 could also be easily separated by using the Waters Prep/LC system 500A (silica gel eluted with 3:2 cyclohexane/ethyl acetate). When LiH was used as base in Et_2O or toluene, initially formed 2 rapidly converted to diethyl chloromethylphosphonate under the reaction conditions. KH was also less effective than NaH as base; an unsatisfactory mixture of 2 and bis(diethyl phosphonomethyl) ether was formed. Diethyl phosphonomethyltriflate (2) was also found to be completely stable for long periods in the cold, and has been stored at -20°C for over 2 years with no decomposition. In addition, triflate 2 was stable for at least 3 days at room temperature, but slowly decomposed over several weeks.

A competition experiment demonstrated that iodide ion reacts significantly faster with diethyl phosphonomethyltriflate (2) than with allyl bromide. Thus, equal molar amounts of sodium iodide, triflate 2, and allyl bromide rapidly reacted in d_6-acetone solution. A 360 MHz ^{1}H-NMR spectrum showed complete consumption of 2 and a 5:1 ratio of diethyl iodomethylphosphonate/allyl iodide. Other reactions of diethyl phosphonomethyltriflate (2) with four demanding nucleophiles are summarized in the table. The amine and phenoxide nucleophiles (entries 1, 2, and 4) all rapidly reacted with 2. Excess ammonia reacted in <5 min at 0°C when the reaction was performed in EtOH solution (entry 1). The reaction of 2,2,6,6-tetramethylpiperidine with 2 in Et_2O was 100% complete within 30 minutes at 0°C. Both of these reactions afforded a single product by ^{31}P-NMR. Potassium 2,6-di-tert-butyl-4-methylphenoxide also reacted rapidly with 2 at 0 °C in THF solution, and within 1 h three products were observed by ^{31}P-NMR. The major product was isolated by chromatography (entry 4). Ethanol reacted very slowly with 2 and required 7 days at room temperature for complete reaction (entry 3).

Table. Reaction of Diethyl Phosphonomethyltriflate (2) with Nucleophiles.

Entry	Nucleophile (equivalents)	Isolated Product	time/temp	% Isolated Yield[b]
1	NH_3 (20)		<5 min/0 °C	70[a]
2	 (3)		30 min/0 °C	86
3	EtOH (20)		7 days/25 °C	89
4	 (1.2)		1 h/0 °C	56

(a) The initially formed product was hydrolyzed with refluxing 48% HBr to facilitate isolation.

(b) Yields are not optimized.

These results demonstrate the high reactivity and excellent stability of diethyl phosphonomethyltriflate (2). A study of the scope and limitations of this, and related reactions is currently underway.[7,8]

References and Notes

1. B. A. Arbuzov and N. P. Bogonostseva, J. Gen. Chem. of the USSR, 27 2419 (1957); K. A. Petrov, V. A. Chauzov, and I. V. Pastukhova, Zh. Obshch. Khim., 46, 1413 (1976).
2. J. V. Comasseto and N. Petragnani, J. Organomet. Chem., 152, 295 (1978).
3. K. A. Petrov, L. V. Treshchalina, and V. M. Chizhov, Zh. Obshch. Khim., 47, 2741 (1977); A. Holy and I. Rosenberg, Nucleic Acids Symp. Ser., 9, 145 (1981); A. Holy and I. Rosenberg, Collect. Czech. Chem. Commun., 47, 3447 (1982); I. Rosenberg and A. Holy, Ibid, 48, 778 (1983).

4. P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 85 (1982).
5. Adapted from Chemical Abstracts 72:21745y. Thus, a mixture of diethyl phosphite (50 g, 362 mmol), paraformaldehyde (11.1 g, 362 mmol), and triethylamine (5.0 mL, 36 mmol) was slowly heated to 50 °C to initiate the reaction. Within 3-5 minutes the reaction had exothermed to 130 °C (refluxing), and the resulting solution showed >95% pure diethyl hydroxymethylphosphonate (**1**) by ^{31}P-NMR (24.5 ppm downfield from 85% phosphoric acid). This material was suitable for further use although analytically pure material was obtained in 90% yield by silica gel chromatography on the Water's Prep/LC System 500A (eluted with 3.5% ethanol in ethyl acetate).
6. In a typical preparation of **2** using these high surface area forms of NaH, a mixture of **1** (20.0g, 119 mmol) and NaH (3.71g, 155 mmol) in Et_2O (200 mL) was mechanically stirred for 4 hours at room temperature. This suspension of sodium alkoxide was slowly added dropwise over 40 minutes to a -78°C cooled solution of CF_3SO_2Cl (19.8 mL, 178 mmol) in Et_2O (200 mL). The resulting solution was stirred an additional 10 minutes at -78°C, then slowly warmed to -5°C to afford >99% of **2** by ^{31}P-NMR. After filtration to remove excess NaH, the filtrate was diluted with CH_2Cl_2 (800 mL) and extracted with saturated aqueous $NaHCO_3$ (2 x 100 mL), then was dried ($MgSO_4$) and concentrated to afford 23.25g of an oil. The ^{31}P-NMR showed bis(diethyl phosphonomethyl)ether (20.5 ppm) in addition to **2** (12.0 ppm) in a ratio of 1:10, respectively. This mixture was easily separated by partitioning between Et_2O/H_2O, affording purified triflate **2** in an overall isolated 50% yield.
7. All new compounds were completely characterized and gave satisfactory analytical and spectral data. Selected data for compound **2**: colorless oil, ^{1}H NMR ($CDCl_3$) δ 1.38 (6H, t, J = 7 Hz), 4.02-4.50 (4H, m), 4.65 (2H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$, ^{1}H decoupled) 16.06 ppm (d, $J_{(^{13}C,\,^{31}P)}$ = 5.1 Hz), 63.69 (d, $J_{(^{13}C,\,^{31}P)}$ = 5.9 Hz), 66.32 (d, $J_{(^{13}C,\,^{31}P)}$= 168.5 Hz), 118.40 (d of quartets, $J_{(^{13}C,\,^{31}P)}$ = 320.2 Hz, $J_{(^{13}C,\,^{31}P)}$ = 1.9 Hz). Anal. Calcd for $C_6H_{12}F_3O_6PS$: C, 24.01; H, 4.03; F, 18.99; P, 10.32; S, 10.68. Found: C, 23.74; H, 4.04; F, 18.72; P, 10.44; S, 10.53.
8. Recently the triflate derivative of diethyl 1-hydroxyethylphosphonate was prepared for a solvolysis study. See X. Creary and T. L. Underiner, *J. Org. Chem.*, *50*, 2165 (1985).

(Received in USA 31 December 1985)