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Working with Hazardous Chemicals

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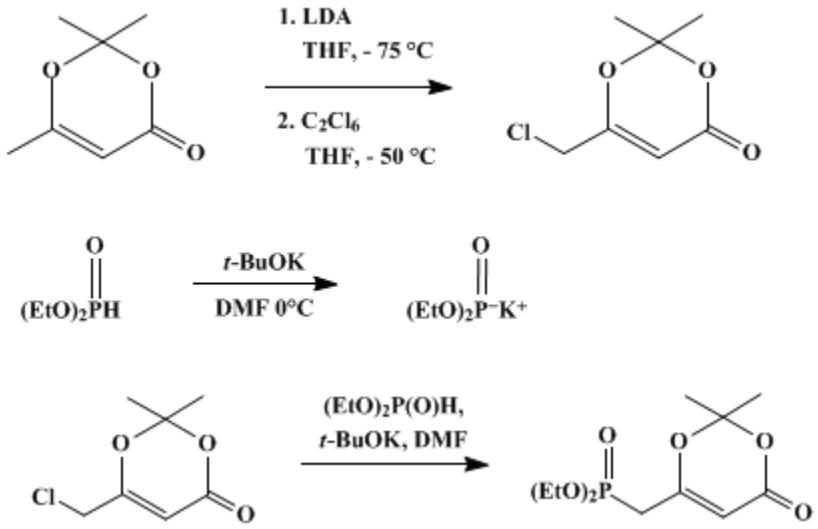
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.066.0194

Organic Syntheses, Coll. Vol. 8, p.192 (1993); Vol. 66, p.194 (1988).

6-DIETHYLPHOSPHONOMETHYL-2,2-DIMETHYL-1,3-DIOXEN-4-ONE

[Phosphonic acid, [(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl]-, diethyl ester]



Submitted by Robert K. Boeckman, Jr., Robert B. Perni, James E. Macdonald, and Anthony J. Thomas[1].
Checked by Stacey C. Slater and James D. White.

1. Procedure

A. *6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one.* A three-necked, 500-mL, round-bottomed flask is fitted with a nitrogen inlet, a rubber septum, and a 125-mL dropping funnel. The flask is flame-dried, flushed with nitrogen and charged with diisopropylamine (22.0 mL, 0.16 mol) and 100 mL of tetrahydrofuran (THF) (Note 1). This solution is cooled in an ice bath, and the dropping funnel is charged with a solution of butyllithium (80.0 mL of a 1.88 *M* solution in hexane, 0.15 mol), which is added dropwise over 15 min (Note 2). The resulting solution is cooled to approximately −75°C in a dry ice–acetone bath and treated with a solution of 2,2,6-trimethyl-1,3-dioxen-4-one[2] (16.0 g, 0.11 mol) in tetrahydrofuran (20 mL) dropwise over 20 min (Note 3). During the addition, a fine yellow suspension forms. The enolate solution is stirred at −75°C for an additional 15 min and then transferred via cannula to a 1-L flask containing hexachloroethane[3] [4]; [5] (39.0 g, 0.16 mol) (Note 4) in tetrahydrofuran (150 mL) at −50 to −55°C (dry ice–acetone bath) over 30 min. When the addition is complete, any residual enolate is transferred with an additional portion of tetrahydrofuran (20 mL). The resulting reaction mixture is allowed to warm slowly to −25°C over 30 min and poured into ice-cold aqueous 10% hydrochloric acid (200 mL), and the mixture is briefly shaken to discharge the red color. The organic layer is separated, and the aqueous layer is extracted with ether (2 × 100 mL). The combined organic extracts are washed with saturated aqueous sodium bicarbonate solution (100 mL), saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford 31.50–35.50 g of an oily solid. Column chromatography on Florisil (100–200 mesh, 400 g) (Note 5) and elution with hexane (1 L) and 20% ethyl acetate–hexane (2 L), gives 12.17–12.67 g (63–65%) of the desired product as a yellow oil (Note 6),(Note 7),(Note 8).

B. *6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one.* A 500-mL, three-necked flask is outfitted as above, flushed with nitrogen, and charged with potassium *tert*-butoxide (21.0 g, 0.187 mol) and dimethylformamide (200 mL) (Note 9). The stirring mixture is cooled in an ice bath and treated with diethyl phosphite (26.7 g, 0.193 mol). The resulting solution is stirred in the ice bath for 20–40 min and then treated dropwise with a solution of 6-chloromethyl-2,2-dimethyl-1,3-dioxen-4-one (11.00 g,

0.062 mol) in tetrahydrofuran (50 mL) over 20 min. The resulting purple solution is stirred for an additional 15 min at 0°C and treated with concentrated hydrochloric acid dropwise until the purple color is discharged (ca. 6 mL). The resulting mixture is filtered by suction through Celite (Note 10), and the collected solids are washed with tetrahydrofuran (50 mL). The combined organic portions are treated with several grams of anhydrous potassium carbonate and filtered, and the tetrahydrofuran is removed with a rotary evaporator. Dimethylformamide and excess diethyl phosphite are removed by distillation at 0.4 mm with the bath temperature maintained below 50°C (Note 11). The residue is diluted with ethyl acetate (200 mL) and placed in the refrigerator at 0°C overnight. The solid that precipitates is removed by filtration, and the filtrate is concentrated under reduced pressure to ca. 75 mL and purified by flash chromatography (Note 12) and (Note 13) on 700 g of Florisil (9 × 22-cm column). Elution with 3 L of 1 : 1 ethyl acetate–hexane, 3 L of 3 : 1 ethyl acetate–hexane, and then 3 L of 100% ethyl acetate affords 8.30–8.56 g (48–50%) of 6-diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one (Note 14) and (Note 15). Mixed fractions may be rechromatographed to afford an additional 2–4% of product.

2. Notes

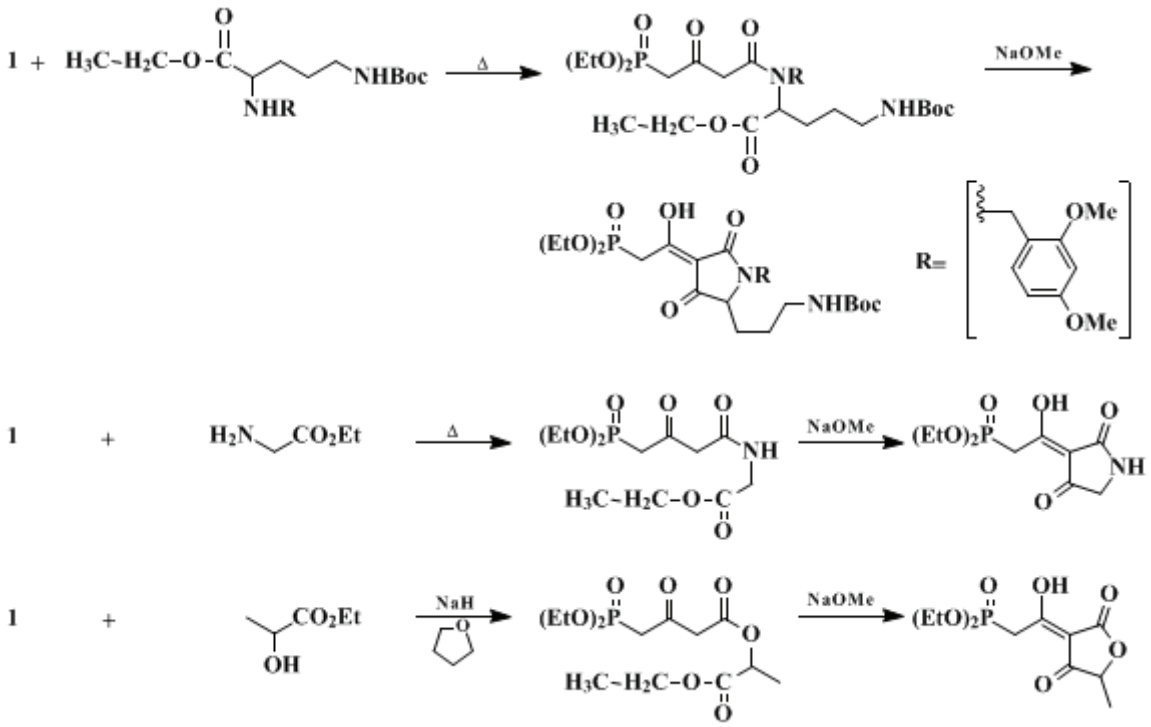
1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Diisopropylamine was distilled under a nitrogen atmosphere from calcium hydride.
2. A solution of butyllithium in hexane (ca. 1.8 *M*) was obtained from Lithcoa and standardized by titration against 2,5-dimethoxybenzyl alcohol.[6]
3. 2,3,6-Trimethyl-1,3-dioxen-4-one is commercially available from the Aldrich Chemical Company, Inc. and may be used without further purification.
4. Hexachloroethane was obtained from the Aldrich Chemical Company, Inc. and used without further purification.
5. Florisil is a magnesium silicate adsorbent obtained from the Floridin Company.
6. Substantial amounts of unreacted hexachloroethane may be recovered from early fractions.
7. The reaction may be carried out equally well on a 32-g scale.
8. The NMR and IR spectral data of the chloride are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.74 (s, 6 H), 4.02 (s, 2 H), 5.53 (s, 1 H), IR (film) cm^{-1}: 2970, 1730, 1640, 1390, 1280, 1210, 1024.
9. Dimethylformamide (DMF) was distilled under reduced pressure (20 mm) from calcium hydride. Diethyl phosphite may be used directly from a freshly opened bottle or redistilled before use.
10. This filtration is very slow, and a wide sintered-glass funnel is recommended.
11. The product phosphonate decomposes to diethylphosphonoacetone above 50°C, and care must be taken during the distillation and concentration of chromatography fractions that heating baths do not exceed this temperature.
12. The procedure of W. C. Still was utilized.[7]
13. Chromatographic fractions were analyzed by TLC by elution with ethyl acetate, and were visualized with a permanganate spray. The phosphonate had R_f = 0.35.
14. The NMR and IR spectral data of the phosphonate are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 6 H), 1.72 (s, 6 H), 2.81 (d, 2 H), 4.16 (m, 4 H), 5.40 (d, 1 H); IR (film) cm^{-1}: 2980, 1720, 1630, 1370, 1255. The absence of residual hexachloroethane was confirmed by ^{13}C NMR spectroscopy.
15. The phosphonate should be stored at 0°C. Under these conditions the purified product is stable for at least several months.

3. Discussion

This procedure is a modification of the previously-published procedure by Boeckman and Thomas.[8] The acetone diketene adduct serves as a versatile, activated β-keto ester equivalent.[2,3,4,5,9] Conversion of this material to the phosphonate by the procedure described above affords an even more versatile synthon that is useful for the preparation of protected analogues of the Nazarov reagents by means of a Wadsworth–Emmons olefination.[10,11]

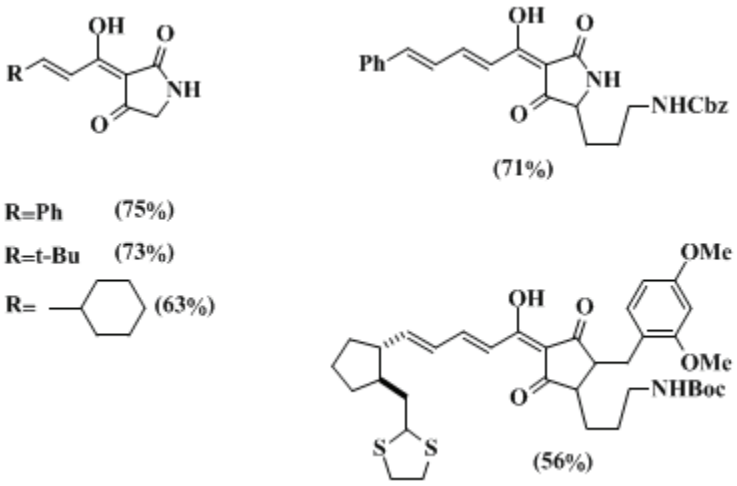
The title phosphonate and related substances undergo thermal decomposition to β-acyl ketenes at

temperatures in excess of 50°C.[12] Thus thermolysis in the presence of alcohols, amines, α-hydroxy esters, and α-amino esters affords the corresponding β-keto esters and amides; the latter two classes can be cyclized upon subsequent base treatment to unsaturated tetronic and tetramic acids and the related phosphonate reagents.[8,13]



For sensitive amino acids prone to thermal dimerization to the related diketopiperazines, the reaction can be conducted in refluxing tetrahydrofuran solution in the presence of *p*-toluene- or camphorsulfonic acid as catalyst. Where possible the non acid-catalyzed thermal procedure is preferred since it generally provides cleaner products in higher yields.

The resulting tetramic and tetronic acid phosphonate reagents undergo the Wadsworth–Emmons olefination[11] with a variety of aldehydes to afford (*E*)-α,β-unsaturated and diene acyl tetramic and tetronic acids in good to excellent yields on treatment with potassium *tert*-butoxide (2 equiv) in tetrahydrofuran. For readily enolizable substrates use of the *N*-protected systems is generally required. The following compounds have been prepared, in the indicated yields, in this manner:



Two alternative methods for the preparation of phosphorus-activated tetramic acid reagents have recently been described.[14] [15] These reagents have served to provide a workable solution to the problem

of construction of the dienoyl tetramic acid unit required for the synthesis of tirandamycin-A.[16,17,18,19].

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium benzophenone ketyl

6-Diethylphosphonomethyl-2,2-dimethyl-1,3-dioxen-4-one

6-Chloromethyl-2,2-dimethyl-1,3-dioxen-4-one

2,2,6-trimethyl-1,3-dioxen-4-one

2,3,6-Trimethyl-1,3-dioxen-4-one

tetramic and tetronic acid phosphonate

tirandamycin-A

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

p-toluene (108-88-3)

permanganate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

diethyl phosphite (762-04-9)

camphorsulfonic acid (5872-08-2)

hexachloroethane (67-72-1)

diisopropylamine (108-18-9)

2,5-dimethoxybenzyl alcohol (33524-31-1)

magnesium silicate

diethylphosphonoacetone (1067-71-6)

potassium tert-butoxide (865-47-4)

Phosphonic acid, [(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl]-, diethyl ester (81956-28-7)