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PREPARATION OF t-BUTYL 4-DIETHYLPHOSPHONO-3-OXOBUTANETHIOATE AND USE IN THE SYNTHESIS OF (E)-4-ALKENYL-3-OXOESTERS AND MACROLIDES

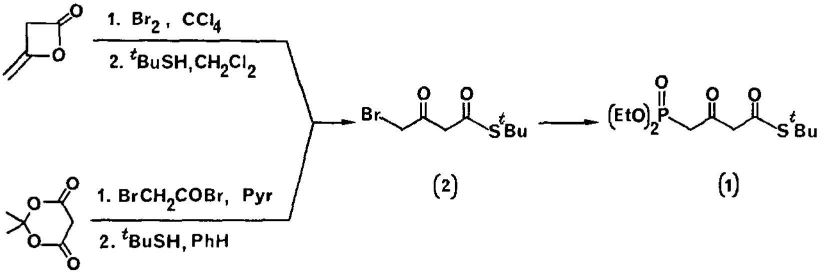
Steven V. Ley* and Peter R. Woodward

Department of Chemistry, Imperial College, London SW7 2AY

Abstract: *The preparation of t-butyl 4-diethylphosphono-3-oxobutanethioate (1) and Wadsworth- Emmons reaction with aldehydes and ketones is reported. Some of the products of these reactions were converted to unsaturated 3-oxomacrolides or 3-oxodiolides by transesterification in the presence of copper-(I)-trifluoroacetate.*

There is a need to develop synthetic units which will permit the ready preparation of 3-oxomacrolides, especially those containing additional double bonds. Several macrolides are known which contain these groupings, or their closely related structures, such as the cephalosporolides,[1a] diplodialides,[1b] irumamycin,[1c] venturicidin[1d] and kromycin.[1e] However, to date there is no single synthetic equivalent to these systems. Our interest in t-butylacetothioacetate and its use for tetronic acid[2] and 3-oxodiolide[3] synthesis prompted us to develop a related reagent, t-butyl 4-diethylphosphono-3-oxobutanethioate (1), the preparation and reactions of which we report here.

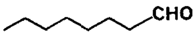
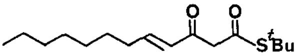
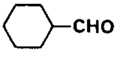
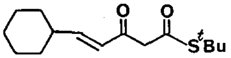
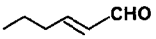
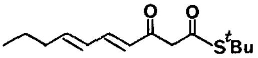
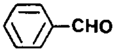
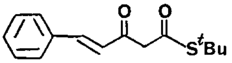
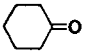
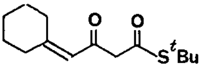
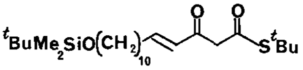
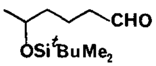
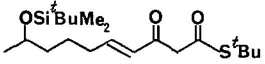
Compound (1) was formed in 85% yield by treatment of the monosodium salt of t-butyl 4-bromo-3-oxobutanethioate (2) with sodium diethylphosphite[4] in THF. The bromothioester (2) was readily available from diketene in 73% yield by bromination[5] and treatment with t-butanethiol. Acylation of Meldrum's acid[6] with bromoacetyl bromide followed by reaction with t-butanethiol also gave (2), in 76% overall yield.

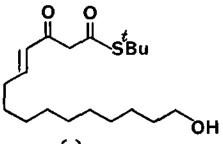


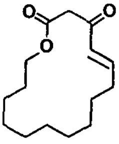
Reaction of (1) with 2 equivalents of sodium hydride in THF at room temperature and Wadsworth-Emmons coupling with various aldehydes and ketones gave moderate to good yields of unsaturated products (Table). In the case of the aldehydes the E-geometry of the products was clearly evident from the olefinic coupling constants of 15.5-18 Hz in the ^1H n.m.r. spectra. All products existed as a mixture of keto and enol tautomers.

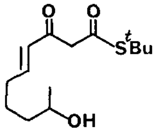
In order to examine the effectiveness of the t-butylthioester group in trans-esterification sequences, particularly for the proposed macrolide synthesis, the product of the reaction of entry 6 in the table was deprotected to the free alcohol (3) in 98% yield using HF in acetonitrile.[7] This was then treated with copper-(I)-trifluoroacetate in buffered (Na_2HPO_4) dichloromethane to give the required unsaturated 3-oxomacrolide (4) (35%). Deprotection of the (E)-3-oxothioester from entry 7 using tetra-n-butylammonium fluoride[8] gave (5) (85%) which upon treatment with copper-(I)-trifluoroacetate gave the diolide (6) in 35% overall yield.

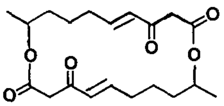
TABLE

Entry	Aldehyde/Ketone	Product	Yield%
1			58.3
2			81.0
3			49.5
4			54.4
5			67.2
6	^{t}BuMe$_2$SiO(CH$_2$)$_{10}$CHO		83.3
7			83.9


(3)


(4)


(5)


(6)

While the yields of the macrocyclic products in these reactions are not especially high, other methods were considerably poorer. Analogous chemistry using related phosphorane derivatives such as $Ph_3P{=}CHCOCH_2COS^tBu$, failed to afford useful yields of (E)-alkenyl-3-oxo products, like their oxygen counterparts.[4]

We now hope to extend the use of (1) to natural product syntheses.

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