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SYNTHESIS OF α-HETERO ATOM SUBSTITUTED β-KETO AND ENAMINE PHOSPHONATES

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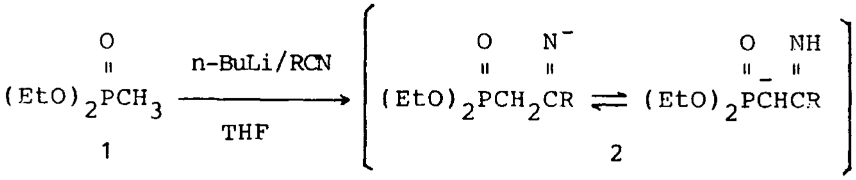
ABSTRACT: Various α-hetero atom substituted β-keto and enamine phosphonates are prepared by the nucleophilic addition of α-lithioanion of diethyl methylphosphonate to nitriles followed by subsequent addition of electrophiles.

β-Keto phosphonates bearing an α-hydrogen are valuable intermediates in organic synthesis, especially for the preparation of α,β-unsaturated ketones by the Wittig-Horner condensation.[1]

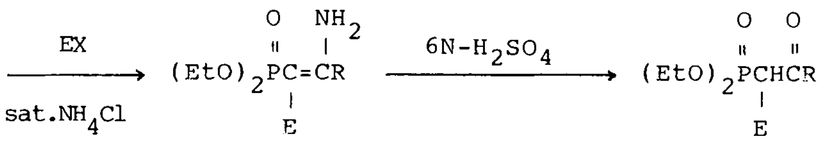
The most commonly used methods for preparing β-keto phosphonates are the classical Arbuzov reaction[2] and the elaboration of simpler alkyl phosphonate anions[3]. Recently developed reaction of dialkyl phosphorochloridites with α-hydroxy ketones in the presence of a Lewis acid is a good candidate for fully substituted β-keto phosphonates.[4] However, to the best of our knowledge, no practical procedure for the synthesis of α-hetero atom substituted β-keto phosphonates have been reported up to now.

Recently we presented some results for the preparation of β-keto phosphonates.[5] In an extension of this work we wish to report a convenient synthesis of various α-hetero atom substituted β-keto and enamine phosphonates. Our approach is based upon that α-lithioanion of diethyl methylphosphonate is allowed to react with a nitrile as an acyl cation equivalent, followed by treatment with various electrophiles such as PhSSPh, PhSCl, $MeSO_2SMe$, PhSeBr, and $PhSO_2Cl$.

Scheme



$$\underset{\mathbf{1}}{(EtO)_2\overset{O}{\overset{\|}{P}}CH_3} \xrightarrow[\text{THF}]{\text{n-BuLi/RCN}} \left[(EtO)_2\overset{O}{\overset{\|}{P}}CH_2\overset{N^-}{\overset{\|}{C}}R \rightleftharpoons (EtO)_2\overset{O}{\overset{\|}{P}}\overset{-}{C}H\overset{NH}{\overset{\|}{C}}R \right]_{\mathbf{2}}$$



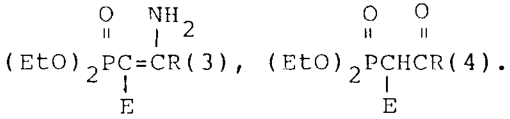
$$\xrightarrow[\text{sat.NH}_4\text{Cl}]{\text{EX}} (\text{EtO})_2\overset{\text{O}}{\overset{\|}{\text{P}}}\underset{\text{E}}{\underset{|}{\text{C}}}{=}\overset{\text{NH}_2}{\overset{|}{\text{C}}}\text{R} \xrightarrow{\text{6N-H}_2\text{SO}_4} (\text{EtO})_2\overset{\text{O}}{\overset{\|}{\text{P}}}\underset{\text{E}}{\underset{|}{\text{CH}}}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{R}$$

3 4

The general experimental procedure is as follows: To a stirred solution of diethyl methylphosphonate(1 mmol) in dry THF(5 mL) is added n-BuLi(1.1 mmol, 1.6 M in hexane) at -78 °C under nitrogen atmosphere. After being stirred for 1 hr at -78 °C, nitrile(1 mmol) is added and the reaction mixture is warmed to -5 °C for 2 hr. Electrophile(1.2 mmol) is added dropwise at -78 °C and stirred for 1 hr at same temperature. Usual work-up with sat.NH_4Cl gives the crude enamine phosphonates, which is purified by short-path column chromatography on silica gel(8/2 : hexane/ethylacetate). β -Keto phosphonates are obtained in quantitative yield by hydrolysis of corresponding enamine phosphonates with 6N-H_2SO_4 for 4 hr at room temperature.

The anion 2 is much more nucleophilic at carbon than it is at nitrogen, since a preponderance of the products is found to be derived from C-substitution rather than from N-substitution. As shown in Table, α-phenylthio and phenylseleno substituted β-keto and

Table. Preparation of



$(EtO)_2\overset{O}{\overset{\|}{P}}\underset{E}{C}=\overset{NH_2}{C}R$ (3), $(EtO)_2\overset{O}{\overset{\|}{P}}\underset{E}{C}H\overset{O}{\overset{\|}{C}}R$ (4).

Run	R	EX	E	Product(% Yield)[a]	
				3	4
1	Ph	PhSSPh	PhS	78	75
2	Ph	PhSCl	PhS	87	83
3	p-ClPh	PhSSPh	PhS	82	80
4	p-MePh	PhSSPh	PhS	82	80
5	Ph	MeSSMe	MeS	-	-
6	p-ClPh	$MeSO_2SMe$	MeS	66	50
7	Ph	PhSeBr	PhSe	88	85
8	i-Pr	PhSeBr	PhSe	74	73
9	Ph	$PhSO_2Cl$	Cl	84	80[b]
10	i-Pr	$PhSO_2Cl$	Cl	76	70

[a] Isolated yield based on nitrile.

[b] M.P.: 59-60 °C.

enamine phosphonates are easily obtained by treatment of 2 with phenyldisulfide, phenylsulfenyl chloride, and phenylselenyl bromide, respectively. However, a similar reaction with methyl disulfide did not afford α-methylthio substituted products (Run 5). This is probably due to the low reactivity of the anion toward the electrophilic sulfur moiety. When we change the methyl disulfide into the methyl methanethiosulfonate, the anion 2 could rapidly attack the sulfenyl sulfur, with loss of the sulfinate anion moiety. The reaction with benzenesulfonyl chloride afforded α-chloro substituted phosphonates(Run 9,10). Under this condition, we use the benzenesulfonyl chloride as a chlorenium ion source[6] and did not obtain any α-sulfonylated products.

All the products were characterized by their infrared, ^{1}H-nmr as well as GC-Mass. The infrared spectra of α-hetro atom substituted β-keto phosphonates indicate the products probably exist to some extent in the enol form.

We have examined the possibility for a preparation of α-sulfenylated β-keto phosphonates through the acylation of diethyl phenythiomethylphosphonate anion. However, this approach is not satisfactory because of a greater acidity of the initially formed product as compared with starting phosphonate.[7]

In summary, it is the principal advantages of the procedure described here that various β-keto and enamine phosphonates substituted with α-hetero atom can be easily prepared through one-pot procedure.

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