Addition of α-Lithioalkane Phosphonates to Nitriles, Synthesis of β-Keto Phosphonate and Enamine Phosphonates

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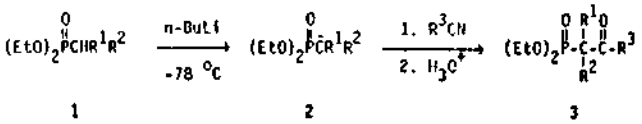
β-Keto phosphonates bearing a α-hydrogen are interesting for the conversion under Wittig-Horner condition into the corresponding α,β-unsaturated ketones.[1] β-Keto phosphonates fully substituted at the α-carbon do not find such frequent use as synthetic intermediates, but because the geometry and spatial demands of phosphorus group are comparable to those of quaternary carbon, the isosteric replacement of carbon with phosphorus has been studied in biologically active molecules.[2]

In marked contrast to a number of investigations that incorporate phosphonate reagents or focus on the biological activities of phosphonates, relatively little work has appeared describing general new synthesis of this functionality (particularly in case of fully substituted β-keto phosphonate).[3] Recently developed reaction of dialkyl phosphoro chloridites with α-hydroxy carbonyl compounds in the presence of a Lewis acid is a good candidate for fully substituted β-keto phosphonates.[4] However, its process is limited due primary to the availability of starting material.

Here we report a more convenient synthesis of various β-keto phosphonates and enamine phosphonates. Our approach is based upon that α-lithioalkane phosphonate is allowed to react with a nitrile as an acyl cation equivalent.[5]

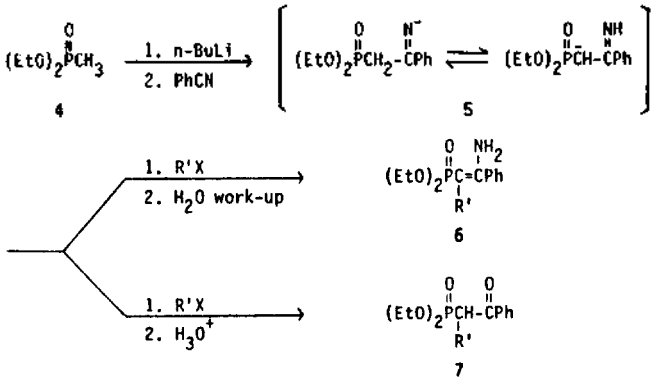
A diethyl alkanephosphonate **1** reacted with n-butyl lithium to give the corresponding dialkyl α-lithio alkane phosphonate **2** within 1 hr at -78 °C: reaction of the latter with nitrile and subsequently with hydrolysis gives the corresponding β-keto phosphonate **3** in good yields. Our results are summarized in the Table 1.

Aromatic nitriles were cleanly converted into ketones in high yields at rt within 3 hr. In the case of nitriles having a



1 2 3

Scheme 1



Scheme 2

α-hydrogen dimerized products were obtained as side products, as previously reported by G. Sumrell.[5a] In the case of an phenyl or thiophenyl substituent on the carbon to the phosphorus function, deoxybenzoin derivatives were obtained as a side product (Run 7,8,9). There was significant difference in the rate of deoxybenzoin formation in the hydrolysis (Run 7). The percent of deoxybenzoin formation after 2, 5 and 12 hr was 14, 27, 92%, respectively. Presently, we are investigating these results and will report shortly.

We also tried a tandem addition-alkylation-hydrolysis sequences as shown in Scheme 2.

To the best of our knowledge, this is the first example of the tandem addition to the nitrile followed by carbon-carbon bond formation. The anion **5** is much more nucleophilic at carbon than it is at nitrogen, since a preponderance of the products is found to be derived from C-alkylation rather than from N-alkylation. This method, which proceeds in one-pot, is very useful and practical in terms of the available starting material, and the versatility for the synthesis of various enamine phosphonates **6** and β-keto phosphonates **7**. These results are summarized in the Table 2.

A general experimental procedure is as follows: To a stir-

Table 1. Preparation of β-keto Phosphonates **3**

Run	R^1	R^2	R^3	Yield(%)[a]	Run	R^1	R^2	R^3	Yield(%)
1	H	H	Ph	95	8	H	Ph	P-Me-Ph	80(10)[b]
2	H	H	P-me-Ph	89	9	H	SPh	Ph	76(16)[b]
3	H	H	O-Cl-Ph	95	10	Me	Me	Ph	87
4	H	H	Me	32	11	Et	Ph	Ph	80
5	H	H	Et	42	12	Et	Ph	O-Cl-Ph	84
6	H	Et	O-Cl-Ph	86	13	Hex	Ph	Ph	76
7	H	Ph	Ph	80(14)[b]					

[a]Isolated yield. [b]The numbers in parenthesis indicate the yield of deoxybenzoin derivatives, $PhC(O)CH_2Ph$, $P\text{-}Me\text{-}PhC(O)CH_2Ph$, and $PhSCH_2C(O)Ph$, respectivley.

Table 2. Preparation of β-keto and enamine phosphonates.

Run	R'X	Method[b]	Reaction Products	Yield (%)[a]
14	$CH_2=CHCH_2Br$	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_2CH=CH_2$	62
15	CH_3I	A	$(EtO)_2P(O)CH(C(=O)Ph)CH_3$	86
16	CH_3I	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_3$	82
17	$PhCH_2Br$	A	$(EtO)_2P(O)CH(C(=O)Ph)CH_2Ph$	62
18	$PhCH_2Br$	B	$(EtO)_2P(O)C(=NH_2)C(Ph)CH_2Ph$	67

[a]Isolated yield. [b]Method A: hydrolysis, Method B: H_2O work up.

red solution of diethyl alkanephosphonate (1 mmol) in dry THF (5 m*l*) was added n-butyllithium (1.1 mmol, 1.6 M in hexane) at -78 °C under nitrogen atmoshere. After being stirred for 1 hr at -78 °C, nitrile (1.1 mmol) was added and the reaction mixture was warmed to rt and stirred for an additional 2 hr. Hydrolysis was accomplished by addition of 5 N sulfuric acid (1 m*l*) for 2 hr at rt. Normal work up gave the β-keto phosphonate, which was purified by short-path column chromatography on silica gel (8/2: ethylacetate/ether).

Tandem addition-alkylation is as follows: After the similar treatment of nitrile (1.1 mmol) at -78 °C, the mixture was warmed slowly to -20 °C for 3 hr. Alkyl halide (1.1 mmol) was added dropwise, the mixture was warmed up to rt. usual H_2O work up gave the crude enamine phosphonate and hydrolysis described above gave the β-keto phosphonate.

All the products were characterized by their infrared, ^{1}H-nmr, ^{31}p-nmr spectra as well as GC-Mass.[6] The infrared spectra of β-keto phosphonates indicate that the products probably exist to some extent in the enol form. In summary, we have discovered a convenient procedure for the preparation of β-keto phosphonate and enamine phosphonates. This method is complementary to the existing procedures (especially fully substituted β-keto phosphonates) and sometimes could be the method of choice because of its simplicity and high yield.

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6. Spectral data for compound (Run 1): ^{1}H nmr ($CDCl_3$) 8.18(m, 2H), 7.60(m, 3H), 4.21(m, 4H), 3.65(d, J = 22Hz, 2H), 1.40(t, 6H); ^{31}P nmr($CDCl_3$) +22.8; IR(neat) 1690(C = O), 1270, and 1030 cm^{-1}; Mass (70 eV), *m/z* (%) 256(M^+, 2), 77(40), 105(100), spectral data for compound (Run 18): ^{1}H nmr($CDCl_3$) 7.18-7.20(m, 10H), 5.80(s, 2H, NH_2), 4.00(m, 4H), 3.40(d, =J18Hz, 2H), 1.22(t, 6H); IR(neat) 3200-3500(NH_2), 1620, 1400, 1210 and 1030 cm^{-1}; Mass (70 eV), *m/z* (%) 345(M^+, 1), 77(85), 91(67), 208(100).

Synthesis of some novel 3-substituted pyridazin-6-ones and Pyridazine Nucleosides

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The synthetic method and reactivity of pyridazine were investigated during few decades.[1-3] However, pyridazine derivatives have not been studied extensively compared with other diazines because they do not occur as natural products. Recently, some pyridazines were found to possess biological activity.[1] Townsend and his coworkers[4] have designed and synthesized some polysubstituted pyridazine nucieosides by the exchange or interchange of carbon and nitrogen atoms on the heterocyclic base portion of the nucleosides such as uridine, 6-azauridine and 3-deazauridine.

In the course of our studies on some biologically active pyridazine nucleosides, we have attempted the synthesis of