Indium-Mediated Allylation of β-Keto Phosphonates

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Phosphonates and their derivatives have attracted considerable interest in recent times because of their application as enzyme inhibitors and metabolic probes,[1] peptide mimetics,[2] and antibiotics and pharmacologic agents[3] in addition to their traditional roles as intermediates in organic synthesis.[4] β-Keto phosphonates which are easily accessible by a number of methods[5] are very useful intermediates in this family to be converted to many other structurally varied phosphonates. On the other hand, β-keto phosphonates are also interesting molecules containing an electrophilic phosphorus moiety as well as a carbonyl functionality. Thus, nucleophilic addition to the carbonyl group in the presence of relatively acidic hydrogens in β-keto phosphonate constitutes a challenging task. A recent report[6] shows that addition of allylmagnesium chloride and other Grignard reagents to β-keto phosphonate in absence of Lewis acid (BF_3−OEt_2) was not very successful, although allylic zinc reagent provides the corresponding β-hydroxy phosphonates in a number of cases without any additive. During past few years, indium metal has been used extensively in allylation of varieties of carbonyl compounds producing interesting results.[7] Our interest in organoindium reagent[8] as well as phosphonate derivatives[9] thus prompted us to explore addition of allylindium species to β-keto phosphonates, and we have discovered that allylindium derivatives add on to the carbonyl group of β-keto phosphonates easily without requirement of any Lewis acid (Scheme 1).

Scheme 1

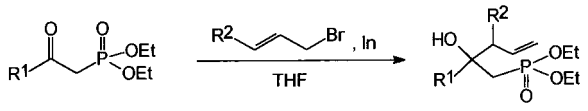
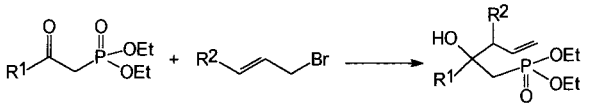
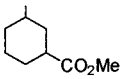
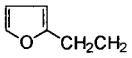
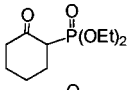
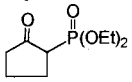


Table 1. Allylation of β-Keto Phosphonates



entry	R^1	R^2	time (min)	yield(%) [a]	ref
1	Me	H	35	93	6
2	Et	H	40	87	
3	$PhCH_2$	H	40	92	
4	$PhCH_2CH_2$	H	40	87	
5	Me_2CH	H	50	84	
6		H	40	81	
7		H	50	65	
8	*p*-(NO_2)-Ph	H	40	95	
9	*o*-(NO_2)-Ph	H	40	92	
10		H	45	81	
11	*p*-(NO_2)-Ph	Me	45	91 (9:1) [b]	
12	Me	Me	45	90 (1.2:1) [b]	6
13		H	60	69 (8.7:1) [b]	6
14		Me	70	67 (4.8:1) [b]	6

[a] Yields refer to pure isolated products. [b]Ratio of diastereoisomers were determined by NMR analysis (^1H and ^{13}C).

In a general experimental procedure, a solution of β-keto phosphonate in THF was added to allylindium bromide, formed in situ by reaction of allyl bromide and indium metal, at 0−5 °C, and the mixture was stirred at room temperature for 35 min (TLC). Quenching the reaction mixture with saturated aqueous ammonium chloride solution and extraction with ether furnished the crude product which was purified by column chromatography to give pure β-hydroxy phosphonate.

Several structurally varied β-keto phosphonates were subjected to allylations by this procedure to produce the corresponding β-hydroxy phosphonates. The results are summarized in Table 1. Open-chain phosphonates with alkyl, cycloalkyl, heterocycloalkyl, and aryl substitutions at β-position respond uniformly to this reagent giving a single product in each case. Cyclic β-keto phosphonates (entries 13, 14) also did not pose any difficulty in nucleophilic addition of allylindium reagent. Addition of crotylindium species to open chain as well as cyclic

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phosphonates proceeded smoothly providing only one regioisomer corresponding to γ-addition, although a mixture of diastereoisomers were obtained. Functionalities like carboxylic ester, nitro, and furan moiety are quite compatible with this reagent. In general, the reactions are very clean and reasonably fast. The yields are quite high with all substrates irrespective of variations in substitutions.

In conclusion, the present procedure provides a very efficient addition of allyl and crotyl moieties to carbonyl group of β-keto phosphonates through the corresponding allyl indium reagents. The notable advantages of this procedure are mild conditions (room temperature), fast reaction (35−70 min), operational simplicity, no requirement of a Lewis acid, and high yields. We believe this will find useful applications in the growth of phosphonate chemistry.

Experimental Section

General Methods. Tetrahydrofuran was distilled from potassium−benzophenone immediately prior to use. Indium (Ingot, SRL, India) was used as such without any treatment. Allyl bromide and all liquid chemicals were distilled before use. β-Keto phosphonates were prepared following reported procedures.[5b,d] ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively. IR spectra were taken as thin films. Elemental analyses were performed on a Perkin-Elmer autoanalyzer 2400 II at our Institute.

General Procedure for Allylation of β-Keto Phosphonates. Representative Procedure for Diethyl [2-Oxopropyl]phosphonate (entry 1). A solution of diethyl [2-oxopropyl]-phosphonate (194 mg, 1 mmol) in THF (2 mL) was added to a cooled (0−5 °C) solution of allylindium bromide in THF, prepared in situ by stirring allyl bromide (302 mg, 2.5 mmol) with indium metal (cut into small pieces, 115 mg, 1 mmol) in THF (2 mL) for 5 min at room temperature. The reaction mixture was then stirred at room temperature for 35 min (monitored by TLC) after which it was quenched with saturated aqueous ammonium chloride solution. The mixture was extracted with ether, and the ether extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product which was purified by column chromatography over silica gel to furnish pure diethyl [2-methyl-2-hydroxy-pent-4-enyl] phosphonate (220 mg, 93%) whose ^{1}H and ^{13}C NMR spectra are in full agreement with those reported.[6]

This procedure has been followed for allylation of all phosphonates listed in Table 1. Spectral (IR, ^{1}H and ^{13}C NMR) and analytical data for all new β-hydroxy phosphonates are presented below in order of their entries in Table 1.

Diethyl [2-ethyl-2-hydroxy-pent-4-enyl]phosphonate (entry 2): IR 3427, 1639 cm^{-1}; ^{1}H NMR δ 5.77−5.92 (m, 1H), 5.09−5.14 (m, 2H), 4.04−4.21 (m, 4H), 3.89 (s, 1H), 2.36 (d, J = 7.20 Hz, 2H), 1.98−2.04 (m, 2H), 1.52−1.71 (m, 2H), 1.34 (t, J = 7.20 Hz, 6H), 0.92 (t, J = 7.50 Hz, 3H); ^{13}C NMR δ 133.5, 118.2, 72.4 (d, J_{CP} = 4.5 Hz), 61.6 (d, J_{CP} = 6.37 Hz) (2C), 43.9 (d, J_{CP} = 10.35 Hz), 34.5 (d, J_{CP} = 135.9 Hz), 32.7 (d, J_{CP} = 9 Hz), 16.1 (d, J_{CP} = 6.22 Hz) (2C), 7.83 (d, J_{CP} = 10.50 Hz). Anal. Calcd for $C_{11}H_{23}O_4P$: C, 52.80; H, 9.20. Found: C, 52.33; H, 8.78.

Diethyl [2-benzyl-2-hydroxy-pent-4-enyl]phosphonate (entry 3): IR 3423, 1639 cm^{-1}; ^{1}H NMR δ 7.14−7.22 (m, 5H), 5.79−5.90 (m, 1H), 5.03−5.13 (m, 2H), 4.00−4.11 (m, 4H), 3.74 (br s, 1H), 2.78−2.91 (m, 2H), 2.29 (d, J = 7.02 Hz, 2H), 1.90−1.99 (m, 2H), 1.15−1.35 (m, 6H); ^{13}C NMR δ 137.3, 134.1, 131.2 (2C), 128.5 (2C), 126.9, 119.5, 72.9, (d, J_{CP} = 4.50 Hz), 62.5 (d, J_{CP} = 6.52 Hz) (2C), 46.7 (d, J_{CP} = 9.75 Hz), 45.2 (d, J_{CP} = 8.25 Hz) 35.0 (d, J_{CP} = 136.35 Hz), 16.7 (d, J_{CP} = 5.40 Hz) (2C). Anal. Calcd for $C_{16}H_{25}O_4P$: C, 61.54; H, 8.01. Found: C, 61.89; H, 7.73.

Diethyl [2-hydroxy-2-(2′-phenylethyl)pent-4-enyl]phosphonate (entry 4): IR 3411, 1634, 1604 cm^{-1}; ^{1}H NMR δ 7.14−7.29 (m, 5H), 5.84−5.93 (m, 1H), 5.14−5.19 (m, 2H), 4.05−4.40 (m, 5H), 2.69−2.74 (m, 2H), 2.47 (d, J = 7.20 Hz, 2H), 2.05 (dd, J_{HP} = 20.40 Hz, 15.90 Hz, 2H), 1.88−1.94 (m, 2H), 1.26−1.36 (m, 6H); ^{13}C NMR δ 142.6, 133.9, 128.9 (2C), 128.7 (2C), 126.6, 119.1, 72.5 (d, J_{CP} = 4.57 Hz), 62.2 (d, J_{CP} = 6.52 Hz) (2C), 45.1 (d, J_{CP} = 9.97 Hz), 42.6 (d, J_{CP} = 9.45 Hz), 35.5 (d, J_{CP} = 153.30 Hz), 30.3 (d, J_{CP} = 3.37 Hz), 16.76 (d, J_{CP} = 6.07 Hz) (2C). Anal. Calcd for $C_{17}H_{27}O_4$: C, 62.58; H, 8.28. Found: C, 62.97; H, 8.19.

Diethyl [2-hydroxy-2-isopropyl-pent-4-enyl]phosphonate (entry 5): IR 3431, 1639 cm^{-1}; ^{1}H NMR δ 5.86−6.00 (m, 1H), 5.07−5.13 (m, 2H), 4.03−4.21 (m, 4H), 3.84 (s, 1H), 2.23−2.47 (m, 2H), 1.89−2.09 (m, 3H), 1.34 (t, J = 7.50 Hz, 6H), 0.87−0.96 (m, 6H); ^{13}C NMR δ 133.9, 117.8, 74.3 (d, J_{CP} = 4.95 Hz), 61.5 (d, J_{CP} = 7.45 Hz) (2C), 41.5 (d, J_{CP} =8.25 Hz), 35.5 (d, J_{CP} =10.5 Hz), 31.4 (d, J_{CP} =139.8 Hz), 16.9, 16.6, 16.2 (d, J_{CP} = 6.22 Hz) (2C). Anal. Calcd for $C_{12}H_{25}O_4P$: C, 54.55; H, 9.47. Found: C, 54.09; H, 9.31.

Diethyl [2-cyclohexyl-2-hydroxy-pent-4-enyl]phosphonate (entry 6): IR 3433, 1639 cm^{-1}; ^{1}H NMR δ 5.80−5.89 (m, 1H), 5.00−5.09 (m, 2H), 4.02−4.13 (m, 4H), 3.77 (s, 1H), 2.29−2.37 (m, 2H), 1.55−2.07 (m, 7H), 1.30 (t, J = 7.05 Hz, 3H), 1.29 (t, J = 7.05 Hz, 3H), 0.98−1.20 (m, 6H); ^{13}C NMR δ 130.0, 117.8, 74.0 (d, J_{CP} = 5.02 Hz), 61.5 (d, J_{CP} = 6.60 Hz) (2C), 46.1 (d, J_{CP} = 9.30 Hz), 41.8 (d, J_{CP} = 9.30 Hz), 32.0 (d, J_{CP} = 135.50 Hz), 27.23, 26.6, 26.5 (2C), 26.4, 16.3 (d, J_{CP} = 6.30 Hz), 16.2 (d, J_{CP} = 5.55 Hz). Anal. Calcd for $C_{15}H_{29}O_4P$: C, 59.21; H, 9.54. Found: C, 58.75; H, 9.41.

Diethyl [2-(3′-carbomethoxycyclohexyl)-2-hydroxy-pent-4-enyl]phosphonate (entry 7): IR 3427, 1732, 1639 cm^{-1}. ^{1}H NMR δ 5.86−5.92 (m, 1H), 5.06−5.11 (m, 2H), 4.06−4.16 (m, 4H), 3.91 (s, 1H), 3.66 (s, 3H), 1.56−2.38 (m, 10H), 1.34 (t, J = 7.20 Hz, 6H), 1.16−1.27 (m, 4H); ^{13}C NMR δ 176.3, 133.6, 118.2, 73.9 (d, J_{CP} = 4.8 Hz), 61.7 (d, J_{CP} = 6.37 Hz) (2C), 51.5, 45.2 (d, J_{CP} = 2.77 Hz), 43.3 (d, J_{CP} = 4.05 Hz), 41.8 (d, J_{CP} = 9.37 Hz), 31.9 (d, J_{CP} = 135.67 Hz), 29.0, 28.9, 25.7, 25.4, 16.3 (d, J_{CP} = 6.30 Hz), 16.2 (d, J_{CP} = 6.30 Hz). Anal. Calcd for $C_{17}H_{31}O_6P$: C, 56.35; H, 8.56. Found: C, 55.85; H, 8.17.

Diethyl [2-hydroxy-2-(4′-nitrophenyl)pent-4-enyl]phosphonate (entry 8): IR 3384, 1639, 1600 cm^{-1}; ^{1}H NMR δ 8.20 (d, J = 8.85 Hz, 2H), 7.64 (d, J = 8.85 Hz, 2H), 5.61−5.75 (m, 1H), 5.22 (s, 1H), 4.98−5.02 (m, 2H), 4.02−4.12 (m, 2H), 3.69−3.77 (m, 1H), 3.44−3.57 (m, 1H), 2.59 (d, J = 7.20 Hz, 2H), 2.43 (dd, J_{HP} = 18.30 Hz, 16.80 Hz, 2H), 1.32 (t, J = 7.05 Hz, 3H), 0.97 (t, J = 7.05 Hz, 3H); ^{13}C NMR δ 152.9, 146.7, 132.1 (d, J_{CP} = 1.5 Hz), 126.6 (2C), 123.0 (2C), 119.2, 73.8 (d, J_{CP} = 4.8 Hz), 61.9 (d, J_{CP} = 6.45 Hz), 61.7 (d, J_{CP} = 6.67 Hz), 48.9 (d, J_{CP} = 15.3 Hz), 36.8 (d, J_{CP} = 136.57 Hz), 16.2 (d, J_{CP} = 6.07 Hz), 15.9 (d, J_{CP} = 6.00 Hz). Anal. Calcd for $C_{15}H_{22}O_6PN$: C, 52.48; H, 6.41; N, 4.08. Found: C, 52.86; H, 6.23; N, 3.91.

Diethyl [2-hydroxy-2-(2′-nitrophenyl)pent-4-enyl]phosphonate (entry 9): IR 3348, 1639, 1604 cm^{-1}; ^{1}H NMR δ 7.66 (d, J = 8.1 Hz, 1H), 7.36−7.54 (m, 3H), 5.68−5.78 (m, 1H), 5.04−5.11 (m, 3H), 4.00−4.09 (m, 2H), 3.81−3.89 (m, 1H), 3.65−3.73 (m, 1H), 2.81 (d, J = 7.20 Hz, 2H), 2.65−2.76 (m, 1H), 2.37−2.48 (m, 1H), 1.28 (t, J = 7.20 Hz, 3H), 1.07 (t, J = 7.20 Hz, 3H); ^{13}C NMR δ 149.7, 137.0 (d, J_{CP} = 6.9 Hz), 132.6, 130.6, 129.0, 128.1, 123.9, 119.1, 74.0 (d, J_{CP} = 4.5 Hz), 61.9 (d, J_{CP} = 65.2 Hz), 61.9 (d, J_{CP} = 6.67 Hz), 46.8 (d, J_{CP} =12.3 Hz), 35.9 (d, J_{CP} =135.6 Hz), 16.1 (d, J_{CP} = 6.22 Hz), 15.5 (d, J_{CP} = 6.15 Hz). Anal. Calcd for $C_{15}H_{22}O_6PN$: C, 52.48; H, 6.41; N, 4.08. Found: C, 52.15; H, 6.60; N, 3.71.

Diethyl [2-(ethyl-2′-furyl)-2-hydroxy-pent-4-enyl]phosphonate (entry 10): IR 3435, 1639 cm^{-1}; ^{1}H NMR δ 7.16 (d, J = 1.47 Hz, 1H), 6.14 (dd, J_1 = 1.92 Hz, J_2 = 2.1 Hz, 1H), 5.85 (d, J = 3 Hz, 1H), 5.65−5.79 (m, 1H), 4.98−5.03 (m, 2H), 3.93−4.05 (m, 5H), 2.57−2.65 (m, 2H), 2.29 (d, J = 6.99 Hz, 2H), 1.73−1.98 (m, 4H), 1.21−1.29 (m, 6H); ^{13}C NMR δ 156.2, 141.2, 133.8, 119.2, 110.5, 105.0, 72.2 (d, J_{CP} = 4.5 Hz), 62.3 (d, J_{CP} = 6.52 Hz), 62.2 (d, J_{CP} = 6.52 Hz), 45.0 (d, J_{CP} = 10.12 Hz), 38.6 (d, J_{CP} = 9.37 Hz), 35.3 (d, J_{CP} = 135.5 Hz), 30.1, 16.8 (d, J_{CP} = 6.15 Hz), 16.7 (d, J_{CP} = 6.15 Hz). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.96; H, 7.91. Found: C, 56.73; H, 7.65.

Diethyl [2-hydroxy-3-methyl-2-(4′-nitrophenyl)pent-4-enyl]phosphonate (major diastereoisomer) (entry 11): IR 3384, 1639, 1604 cm^{-1}; ^{1}H NMR δ 8.13−8.19 (m, 2H), 7.58−7.63 (m, 2H), 5.85−5.97 (m, 1H), 5.22 (s, 1H), 4.94−5.14 (m, 2H), 3.93−4.94 (m, 2H), 3.51−3.59 (m, 1H), 3.21−3.38 (m, 1H), 2.25−2.55 (m, 3H), 1.24 (t, J = 7.5 Hz, 3H), 0.91 (d, J = 9 Hz, 3H),

0.81 (t, J = 7.50 Hz, 3H); ^{13}C NMR δ 152.8 (d, J_{CP} = 2.7 Hz), 146.7, 139.4, 127.1 (2C), 122.8 (2C), 116.9, 75.4 (d, J_{CP} = 4.95 Hz), 61.8 (d, J_{CP} = 6.30 Hz), 61.4 (d, J_{CP} = 6.9 Hz), 50.7 (d, J_{CP} = 17.32 Hz), 36.1 (d, J_{CP} = 137.1 Hz), 16.1 (d, J_{CP} = 6.15 Hz), 15.7 (d, J_{CP} = 6.07 Hz), 14.6 (d, J_{CP} = 2.32 Hz). Anal. Calcd for $C_{16}H_{24}O_6N$: C, 53.78; H, 6.41; N, 3.92. Found: C, 53.27; H, 6.43; N, 3.71.

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