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Addition of allylindium reagents to acyl phosphonates: synthesis of tertiary α-hydroxy alkylphosphonates

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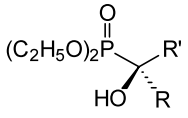
Abstract—Treatment of acyl phosphonates with allylindium reagents in the presence of acetic acid afforded the corresponding α-hydroxy alkylphosphonates in good yields under mild conditions. © 2003 Elsevier Science Ltd. All rights reserved.

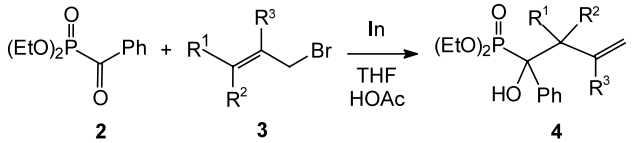
α-Hydroxy alkylphosphonates (**1**) have received attention both as substrates for the preparation of other α-substituted phosphonates,[1] and because of their potential biological activity. For example, representatives of this class act as inhibitors of farnesyl protein transferase (FPTase),[2] renin,[3] HIV protease,[4] and 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase.[5] If the α carbon bears a hydrogen (**1a**), synthetic methods are known for preparation of this functionality through final formation of any one of the four bonds.[1f] Although certainly some are known,[6] examples where the α carbon is fully substituted (**1b**) are less common and methods for the synthesis of such compounds may be more limited.



1a R = H; R' = alkyl or aryl
1b R, R' = alkyl or aryl

Recently we have reported studies on isoprenoid metabolism and the process of protein prenylation that have employed phosphonate analogues of farnesyl pyrophosphate,[7] and these studies have led to an interest in preparation of fully substituted α-hydroxy alkylphosphonates. Addition of organometallic nucleophiles to the carbonyl group of β-keto phosphonates has been reported[8] and parallel reactions of α-keto or acyl phosphonates were attractive because they promised efficient synthesis of the desired compounds. Acyl phosphonates can differ in reactivity from the β-keto isomers because of the ability of the phosphorus to function as a leaving group upon treatment with organometallic reagents that are strong nucleophiles.[6b] Because allylindium reagents have emerged as particularly mild organometallic reagents, and because indium-mediated Barbier type reactions of a variety of functional groups have been reported,[9] these reagents appeared likely to favor addition over displacement. In this paper, we wish to report the synthesis of α-hydroxy phosphonates through indium-mediated allylation of acyl phosphonates.

As shown in Scheme 1, addition of an allyl indium reagent to an acyl phosphonate would be expected to proceed with allylic transposition.[9] To test the feasibility of this process with an accessible acyl phosphonate, the known phosphonate **2** was prepared through reaction of benzoyl chloride and triethyl phosphite.[10] When phosphonate **2** was treated with allyl bromide (**5**) and indium metal in water, or in mixtures of water and an organic co-solvent, the desired α-hydroxy phosphonate **6** was isolated in moderate to low yield. Under these conditions significant amounts of benzoic acid sometimes were observed, presumably formed by hydrolysis of the acyl phosphonate. In anhydrous THF, the



2 **3** **4**

Scheme 1.

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desired reaction proceeded slowly with little apparent hydrolysis. However, the phosphonate product ultimately was obtained only in low yield and significant amounts of the ketone formed by displacement of phosphorus often were observed.[6b] When phosphonate **2** was treated with allyl bromide and indium metal in THF in the presence of acetic acid,[11] the desired α-hydroxy phosphonate was obtained in high yield after one hour at room temperature (Table 1).

As shown in Table 1, high yields of the allyl adducts also were obtained with several other allylic bromides under these reaction conditions.[11] Methallyl bromide (**7**) reacted in a parallel fashion and gave phosphonate **8** in a similar yield. The more functionalized bromides **9** and **11** also gave good yields of the corresponding products, phosphonates **10** and **12**, respectively, indicating that these mild reaction conditions will tolerate some additional functionality. Finally, upon reaction with prenyl bromide (**13**), phosphonate **14** was obtained as a single regioisomer and the expected[9,12] allylic transposition was apparent from the ^{1}H NMR spectrum of the product.

The success of these allylation reactions as shown above encouraged exploration of this strategy with other acyl phosphonates. As shown in Table 2, allylation of some representative acyl phosphonates proceeded in very good yields. The aliphatic phosphonates **15**, **17**, **19** and **21** were selected to gauge the impact of steric hindrance on the allylation reaction. Because both the acetyl and trimethylacetyl phosphonates (**15** and **21**, respectively) gave the desired products in nearly identical yields, the impact of branching appears to be minimal. Phosphonate **23** also gave the 1,2-adduct **24** in very good yield, and no trace of the product of conjugate addition was observed. While allylindium reagents generally favor 1,2-addition in other conjugated systems,[13] this example shows that 1,2-addition can be accomplished in conjugated acyl phosphonates.

Table 1. Allylation of benzoyl phosphonate **2**

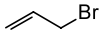
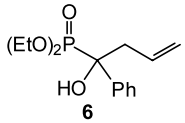
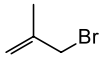
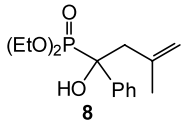
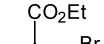
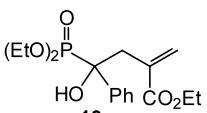
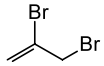
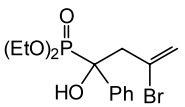
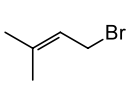
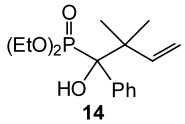
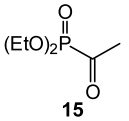
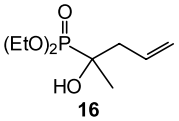
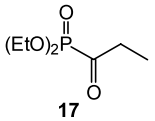
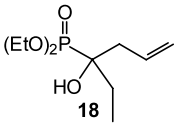
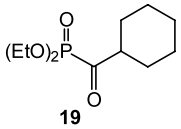
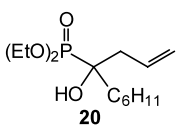
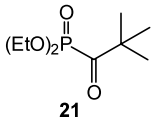
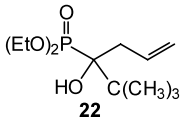
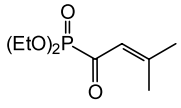
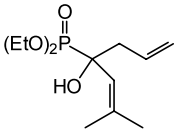
allyl bromide	product	yield (%)
 **5**	 **6**	82
 **7**	 **8**	84
 **9**	 **10**	81
 **11**	 **12**	87
 **13**	 **14**	82

Table 2. Indium-mediated allylation of acyl phosphonates

acyl phosphonate	product	yield (%)
 **15**	 **16**	80
 **17**	 **18**	88
 **19**	 **20**	91
 **21**	 **22**	80
 **23**	 **24**	93

In conclusion, these studies have shown that it is possible to prepare tertiary α-hydroxy phosphonates from acyl phosphonates in high yield through an indium-mediated allylation. The process works well with several different allylic bromides, and does not appear to be sensitive to steric hindrance at the β carbon. Future work will focus on synthesis of tertiary α-hydroxy phosphonates with greater potential for biological activity.

Acknowledgements

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11. *General procedure for allylation of acyl phosphonates*: To a stirred suspension of indium (41 mg, 0.36 mmol) and allyl bromide (**5**, 44 mg, 0.36 mmol) in THF (1 mL) were added successively to a solution of acyl phosphonate **2** (73 mg, 0.3 mmol) in THF (0.5 mL) and acetic acid (17.2 μL, 0.3 mmol) at room temperature. The reaction mixture was stirred for 1 h, quenched by addition of saturated aqueous NH_4Cl (0.5 mL), and extracted with ethyl ether (2×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (EtOAc:hexane, 1:1; silica gel) to afford the α-hydroxy phosphonate **6** (67 mg, 82%) as a white solid: mp 72–74°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.58 (m, 2H), 7.39–7.33 (m, 2H), 7.30–7.24 (m, 1H), 5.69–5.55 (m, 1H), 5.18–5.09 (m, 2H), 4.17–4.08 (m, 2H), 3.99–3.70 (m, 2H), 3.20 (d, J=7.2 Hz, 1H), 3.02–2.93 (m, 2H), 1.28 (t, J=7.2 Hz, 3H), 1.16 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 131.4 (d, J_{CP}=11.2 Hz), 128.0 (d, J_{CP}=2.2 Hz, 2C), 127.3 (d, J_{CP}=3.0 Hz), 126.2 (d, J_{CP}=4.2 Hz, 2C), 120.1, 75.2 (d, J_{CP}=160.8 Hz), 63.4 (d, J_{CP}=7.2 Hz), 63.1 (d, J_{CP}=8.3 Hz), 42.3 (d, J_{CP}=4.5 Hz), 16.4 (d, J_{CP}=5.7 Hz), 16.2 (d, J_{CP}=5.1 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 22.65. Anal. calcd for $C_{14}H_{21}O_4P$: C, 59.15; H, 7.45. Found: C, 59.18; H, 7.35.
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