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Reformatsky-type Co-Mediated Synthesis of β-Hydroxyphosphonates

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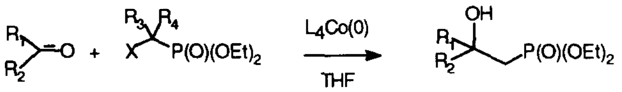
Abstract - Low-valent cobalt complexes were used in Reformatsky-type additions of α-halophosphonates to carbonyl compounds (ketones and aldehydes) to yield a variety of β-hydroxyphosphonates. © 1998 Published by Elsevier Science Ltd. All rights reserved.

We have previously reported that some low-valent cobalt-phosphine complexes are efficient mediators for one-pot Reformatsky-type reactions of halogen derivatives with carbonyl compounds, with several advantages over the classical zinc-mediated Reformatsky reaction.[1-3] The same cobalt complexes proved also effective in promoting aldol-type reactions of α-halo ketones with carbonyl compounds.[4]

We have now found that α-halo phosphonates react with carbonyl compounds (ketones and aldehydes) in the presence of low-oxidation-state cobalt complexes with phosphines to yield β-hydroxyphosphonates (Scheme 1).

Phosphonates, due to their stability toward the action of phosphatases, are of great biological interest as probes of enzyme active-sites, and may be used as analogues of naturally occurring phosphates in metabolic regulation or perturbation.

Scheme 1



R_1, R_2 = H, alkyl, aryl; R_3, R_4 = H, F; X = Cl, Br, I; L = Me_3P

The effectiveness of the reaction of α-halophosphonates with carbonyl compounds was tested as follows. For one model system - diethyl iodomethylphosphonate and benzaldehyde - the reaction was tested under a variety of experimental conditions (Table 1). The tetrakis(trimethylphosphine)cobalt(0), $[Co\{P(CH_3)_3\}_4]$ was selected first as cobalt complex because it is an easily available, well identified complex[5] that has been successfully used in Reformatsky-type and aldol-type reactions[1-4]. The stoichiometry of the reaction was investigated using different molar ratios of halophosphonate, benzaldehyde and cobalt(0)-complex. Highest yields of the β-hydroxyphosphonate were obtained with a "one-pot" procedure in which the two organic reagents were simultaneously added to the Co(0) complex with a iodomethylphosphonate/Co(0)-complex/benzaldehyde molar ratio ≥ 2.5/2.5/1[6].

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We also found that the β-hydroxyphosphonate was formed (albeit with lower yield) when the reaction was performed with a 10/1 molar ratio of organic reagents to cobalt, provided magnesium metal was present.[7] The substitution of bromine by chlorine was found to lower the yield and the rate of the reaction. Finally substitution of trimethylphosphine, as a ligand to cobalt, with the more convenient and less toxic triphenyl phosphine did not affect significantly the outcome of the reaction. In addition the phosphorus-to-cobalt molar ratio could be reduced from 4:1 to 2:1 without loss of effectiveness.

Table I. Co-mediated Addition of Diethyl α-Halomethylphosphonates to Benzaldehyde.

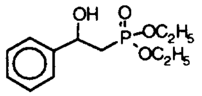
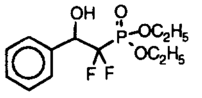
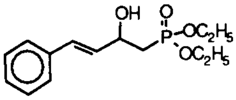
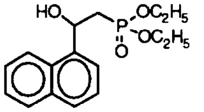
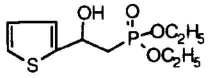
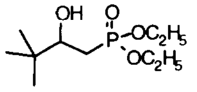
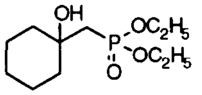
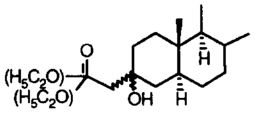
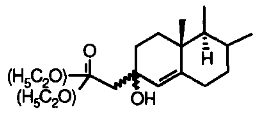
Halomethylphosphonate	Addition Product Yield (%)	Halocompound/Co/PhCHO	Ligand
Diethyl cloromethylphosphonate	33[a,b]	1.0:1.0:1.0	Me_3P
Diethyl iodomethylphosphonate	50[b]	1.0:1.0:1.0	Me_3P
	48 [traces][b,c]	1.0:1.0:1.0	Ph_3P
	50 [6][d]	2.0:2.0:1.0	Me_3P
	81 [15][b,c]	3.0:3.0:1.0	Me_3P
	80 [13][b]	3.0:3.0:1.0	Ph_3P
	75 [15][b]	2.5:2.5:1.0[e]	Ph_3P
	26 [15][d,f]	1.0:2.0:1.0	Me_3P
	50[d,g]	1.0:0.1:1.0	Me_3P

a) Dihydrobenzoin (5 %), benzyl alcohol (3%) and diethyl chloromethylphosphonate (18%) were recovered. b) Yields of isolated compounds. c) ACS reagent tetrahydrofuran from Aldrich was used as received. d) Yields determined by ^1H NMR. e) A phosphorus-to-cobalt molar ratio 2:1 was used. f) Benzyl alcohol (37%) and benzaldehyde (11 %) were recovered. g) Dihydrobenzoin (meso and racemate , 15 %) was detected.

In a second series of experiments, the investigation was extended to several carbonyl compounds, aldehydes and ketones, to test the effectiveness and the applicability of the method (Table II). In each case the main product was the 1,2-addition compound to the carbonyl; reasonable to good yields were obtained, depending on both the halophosphonate and the carbonyl compound, as well as on the ratio of the organic reagents to the cobalt-complex. Diethyl methylphosphonate and the product formed by water elimination from the hydroxilic function were present in variable amounts as byproducts. The effectiveness of triphenylphosphine as a ligand-to-cobalt was confirmed.

In a typical procedure, a solution containing diethyl iodomethylphosphonate (1.5 mmol) and benzaldehyde (0.5 mmol) in tetrahydrofuran (3 mL) was added dropwise at room temperature to a solution of the Co-phosphine complex[1] (1.5 mmol) in tetrahydrofuran (12 mL) . The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane 70/30). The solution was diluted with ethyl acetate, poured into crushed ice/0.1 N HCl, and extracted with ethyl acetate (3 x 15 mL). The combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude material was dissolved in ethyl acetate, washed with a saturated solution of ethylenediaminetetraacetic acid, disodium salt, till colourless, dried and evaporated to dryness. Chromatography over silica gel (ethyl acetate/n-hexane 50/50 and ethyl acetate/methanol 95/5) yielded **1a** (0.61 g, 81 % yield) accompanied by the product formed by water elimination from the hydroxilic function (15 % yield).

Table II. Co-mediated Addition of Diethyl α-Halomethylphosphonates to Carbonyl Compound.

Carbonyl compound	α-Halomethylphosphonate	Addition Product	Yield (%)	Procedure[a]
Benzaldehyde	Diethyl iodomethylphosphonate	 **1a**	81 [15]^{b,c,d}	B
"	Diethyl (bromodifluoromethyl) phosphonate	 **1b**	45^{b,e} 60^{b,e}	A B
trans-Cinnamaldehyde	Diethyl iodomethylphosphonate	 **1c**	40^{b} 70 [16]^{b,d,f}	A B
1-Naphthaldehyde	"	 **1d**	52^{b,h}	A
2-Thiophene-carboxaldehyde	"	 **1e**	48^{b,g}	A
Pivalaldehyde	"	 **1f**	30^{b,e} 83 [12]^{d,f}	A B
Cyclohexanone	Diethyl cloromethylphosphonate	 **1g**	25^{b}	A
"	Diethyl iodomethylphosphonate	"	40^{b} 85 [9]^{b,d}	A B
5-α-Cholestan-3-one	"	 **1h**	40^{b,i}	A
4-Cholesten-3-one	"	 **1i**	22^{b} 56^{b,l}	A B

a) Procedure A: the halocompound and the carbonyl compound were added to the Co-complex, $[Co\{P(CH_3)_3\}_4]$, in a 1:1:1 molar ratio at room temperature, if not otherwise stated. Procedure B: similar to procedure A, except that the halocompound /carbonyl compound/Co-complex molar ratio was 2.5:2.5:1.0, if not otherwise stated. In both procedures the phosphorus-to-cobalt molar ratio was 4:1. b) Yields of isolated compounds. c) The yields in brackets refer to the product formed by water elimination from the hydroxilic function: such product was observed in significant amount when procedure B was used. d) Procedure B: halocompound /carbonyl compound/Co-complex molar ratio 3.0:3.0:1.0. e) Triphenylphosphine was used as a ligand-to-cobalt. f) Yields determined by ^1H NMR. g) Starting carbonyl compound was recovered (20 %). h) Starting carbonyl compound was recovered (25 %). i) Starting carbonyl compound was recovered (38 %). l) Starting carbonyl compound was recovered (30 %).

The synthesis of β-hydroxyphosphonates has been reported by reaction of α-metallated phosphonates (from α-lithiation of phosphonates[8] with lithium alkyls at low temperatures) with carbonyl compounds[9] or epoxides[10] (the latter in the presence of boron trifluoride).

Zinc-mediated, Reformatsky reactions of halophosphonates with carbonyl compounds are limited only to specific cases.[11,12]

The cobalt-mediated synthesis of β-hydroxyphosphonates proceeds smoothly under mild and neutral conditions and do not require freshly dried solvents. The fact that triphenylphosphine can be used as a ligand-to-cobalt, that the phosphine-to-cobalt ratio can be reduced to 2:1, and that the reaction can be performed under substoichiometric conditions with respect to cobalt (albeit in lower yield) are added advantages. The method therefore represents a valid supplement to the existing procedures.

References and Notes.

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6. In the cobalt-mediated Reformatsky-type reaction of α-haloesters with carbonyl compounds the best results were obtained with a 1:1:1 molar ratio of haloester:carbonyl compound:Co(0)-complex.
7. To investigate whether an organomagnesium compound might be involved, a parallel experiment was performed adding the diethyl iodomethylphosphonate and benzaldehyde to magnesium alone in tetrahydrofuran. The amount of diethyl iodomethylphosphonate, benzaldehyde and magnesium were the same in both experiments and so were the other experimental conditions (temperature, time of reaction, speed of stirring). In the absence of cobalt a significant amount of starting material was recovered unchanged: the chief reaction product was dihydrobenzoin, accompanied by a smaller amount of β-hydroxyphosphonate.
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11. Collard, J. N.; Benezra, C. *Tetrahedron Lett.* **1982**, *23*, 3725-3728.
12. Classical "one-pot" Reformatsky reaction of diethyl iodomethylphosphonate with benzaldehyde in dry tetrahydrofuran in the presence of activated zinc turnings failed to give the β-hydroxy phosphonate.