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A new entry to β-hydroxyphosphonates: the SmI_2-mediated reaction of diethyl iodomethylphosphonate with carbonyl compounds

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Abstract—In the presence of samarium iodide α-halophosphonates react with aliphatic carbonyl compounds (aldehydes and ketones) to afford β-hydroxyphosphonates in fairly good yields under neutral and mild conditions. Lower yields are obtained with aromatic carbonyl compounds.

Over the past decades there has been an increasing interest in lanthanides and their use in organic synthesis.[1] Of the low-valent lanthanides, samarium (usually as samarium iodide) has found the most widespread application in a variety of chemical transformations and carbon–carbon bond forming processes (radical cyclization, pinacol coupling reactions, ketyl–olefin coupling reactions, Reformatsky-type and aldol type reactions, conjugate additions).[2] Among them, the Reformatsky reaction,[3] historically involving an organozinc species, is a quite convenient way to produce β-hydroxy esters, very useful functional building blocks. To this concern SmI_2 can efficiently and advantageously substitute zinc metal, in particular in intramolecular asymmetric Reformatsky reactions.[4]

β-Hydroxy alkane phosphonates are also highly valuable compounds, due to their potential biological activities as stable biomimetics of the corresponding phosphates and to their ability to mimic their carboxylic counterparts. Moreover, they also serve as precursors for a variety of substituted phosphonates. Unfortunately, zinc does not efficiently promote the reaction between α-halophosphonates and carbonyl compounds to produce β-hydroxyphosphonates,[5] that are commonly prepared by reaction of α-metallated phosphonates (from α-lithiation of phosphonates[6] with lithium alkyls at low temperatures) with carbonyls[7] or epoxides (the latter in the presence of boron trifluoride).[8] They can also be prepared by addition of dialkyl phosphites to aldehydes,[9] reduction of β-ketophosphonates,[10] $TiCl_4$-catalyzed opening of 1,3-dioxane acetals with trimethyl phosphites.[11] Ether-soluble Co(0) complexes have been used to synthesise β-hydroxyphosphonates with advantages with respect to previous procedures.[12] More recently β-hydroxyphosphonates were prepared via a three-component coupling of acylphosphonate (from acyl chloride and triethyl phosphite) and two carbonyl compounds promoted by low-valent samarium (4 equiv.) in tetrahydrofuran–hexamethylphosphoramide solution.[13]

The aim of present work was to investigate the efficiency of samarium iodide in promoting reactions of α-halophosphonates and carbonyl compounds (aldehydes, ketones) to produce β-hydroxyphosphonates. The results are summarised in Table 1.

To investigate the ability of SmI_2 to promote these Reformatsky-type reactions, different experiments were performed using diethyl iodomethylphosphonate as a model for α-halophosphonate.

The best results have been obtained by the simultaneous addition of the organic reagents to a 0.1 M solution of SmI_2 (2.2 molar equivalents) in tetrahydrofuran. Although the mechanism of the above reaction has not been studied, the requirement of at least two molar equivalents of samarium iodide would suggest initial formation of a radical species and its further reduction to an organosamarium species by the second equivalent of samarium iodide.

Keywords: β-hydroxyphosphonates; samarium iodide.

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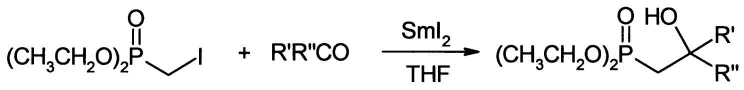
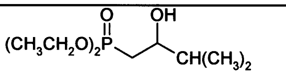
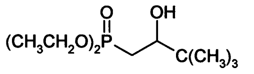
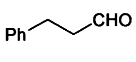
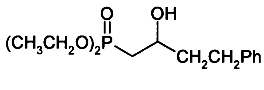
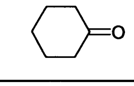
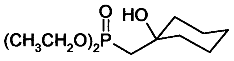
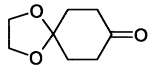
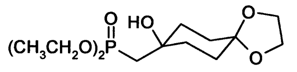
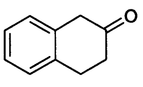
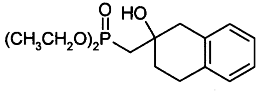
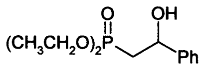
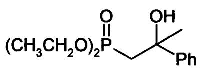
Table 1. Reactions between diethyl iodomethylphosphonate and aldehydes and ketones[a]



Entry	Substrate	Product	Product Yield % [b]	Recovery of R'R"CO %
1	$(CH_3)_2CHCHO$		79	21
2	$(CH_3)_3CHO$		89[c]	/
3			87	/
4			99[c]	/
5			24 [12][d]	21[e]
6			30 (25)[f]	65
7	PhCHO		35 [30][d] (23)[f]	{12}[g]
8	$PhCOCH_3$		45 [10][d] (39)[f]	{15}[g]

a) All compounds were fully characterised by 1H- and 13C-NMR and by MS spectroscopy.

b) Yields refer to % of isolated products, unless otherwise stated.

c) Yields determined by ^{1}H NMR.

d) Yields between [ ] refer to the product formed by water elimination from the hydroxylic function.

e) Along with some unidentified products.

f) Yields between ( ) refer to diethyl methanphosphonate formed under the reaction conditions.

g) Yields between { }refer to recovered pinacol product.

The reactions proceeded in good yields for aliphatic aldehydes (79–89%) and ketones such as cyclohexanone (99%), albeit in the latter introduction of a ketal function dramatically lowered the yields (entry 5).[†] Lower yields were also obtained with an easily enolizable ketone such as β-tetralone. Benzaldehyde and acetophenone, chosen as models for aromatic carbonyl compounds (that are more easily reduced to pinacols by samarium iodide than their aliphatic counterparts),[14] gave indeed modest yields of β-hydroxyphosphonate (35–45%), accompanied by the product formed by water elimination from the hydroxylic function. In these cases (entries 7 and 8) appreciable recovery of the corresponding pinacol (24–25%) and diethyl methane phosphonate (23–39%) was also observed. Aromatic α,β-unsaturated aldehydes such as cinnamaldehyde gave mixtures of many unidentified products (not reported in Table 1).

For one model system (diethyl iodomethylphosphonate and benzaldehyde) the reaction was also carried out using different ratios of organic reagents/samarium iodide (1/1; 1/2; 1/2.5); different orders of addition of the organic reagents to samarium iodide; and adding a co-solvent (DMF or DMPU). The results confirmed the requirement of 2 equivalents of samarium iodide: addition of diethyl iodomethylphosphonate to an equimolar amount of samarium iodide, followed by the carbonyl compound (about 10 min later) resulted in the produc-

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[†] Although no experimental evidence has been searched, hydrolysis of the ketal function followed by reaction of the resulting 1,4-cyclohexanedione to afford a water-soluble diphosphonate can be considered: the yield of the crude reaction mixture recovered from water was poor, and the monophosphonate obtained in the reaction is sparingly soluble in water.

tion of diethyl methane phosphonate (50%) and unreacted diethyl iodomethylphosphonate (50%), whereas the addition compound was not observed. Addition of diethyl iodomethylphosphonate to 2 equivalents of samarium iodide, followed by the carbonyl compound (about 10 min. later) gave comparable total yields (of addition and dehydration products) with respect to the simultaneous addition of the organic reagents. Addition of co-solvents did not improve the reaction.

In summary, the method outlined for the synthesis of β-hydroxyphosphonates represents a convenient approach with some advantages to known procedures: high yields (for aliphatic compounds), mild and neutral conditions (with no requirement of acid or base and anhydrous freshly distilled solvents) and easy work-up of the reaction and recovery of the products.

Typical procedure. In a typical procedure, a THF solution (2 mL) of diethyl iodomethylphosphonate (0.5 mmol) and carbonyl compound (0.5 mmol) was added dropwise over a 10 min period at room temperature to a stirred solution of SmI_2 in tetrahydrofuran (0.1 M, 12 mL). Soon after the addition, the original blue solution turned to a yellow suspension. The reaction was monitored by TLC (EtOAc/*n*-hexane). The reaction mixture was treated with aqueous HCl (0.1N solution, 3 mL) and extracted with ethyl acetate (3×4 mL); the organic layer was washed with a saturated Na_2SO_3 aqueous solution (2 mL), dried with sodium sulfate, filtered, the solvent evaporated and the crude purified by column chromatography.

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