Synthesis of Phosphane Oxides and Phosphonates by Cerium-Mediated Addition of Organolithium Compounds to Chloro-Phosphorus Compounds

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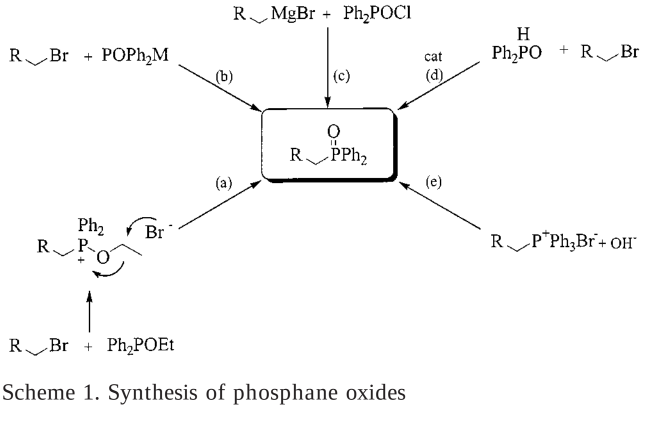
Keywords: Organocerium reagents / Phosphane oxides / Phosphonates / Electrophiles / Synthetic methods / Electrophilic Additions

The addition of organocerium reagents **2a–g** to phosphinoyl chloride **1a** or chlorophosphates **1b** leads to the synthesis of phosphane oxides **3aa–ag** and phosphonates **3bb**, **be** in good to high yield. The reaction can be extended to cerium enolates **4** (of ketones) and **6** (of nitriles) except when a benzyl group bound to the carbonyl moiety should be metallated. The latter reaction is the first reported synthesis of β-oxophosphane oxides by a simple reaction between enolates and a phosphorus(V) halide.

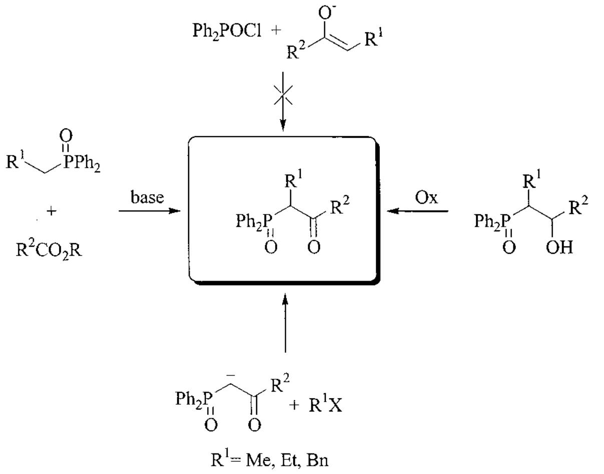
Introduction

New methods to prepare phosphane oxides are always welcome. In fact, these compounds are useful intermediates for the preparation of ligands for transition metal catalyzed reactions. They are also precursors for the Wadsworth−Emmons and Wittig−Horner olefin syntheses,[1] a cornerstone of laboratory and industrial practice. Many methods for the synthesis of phosphane oxides are known (Scheme 1): a) the Arbusov reaction of alkyl halides with a phosphinous ester,[2] b) the Michaelis−Becker reaction of alkyl halides with the sodium or lithium derivatives of a secondary phosphane oxide,[3] c) the reaction of phosphorus halides with organometallic reagents (mainly Grignard reagents),[4] d) the catalyzed coupling of secondary phosphane oxides with alkyl halides[5] and e) the hydrolysis of phosphonium salts.[6] Most of these reactions need high temperatures to occur; others are two-step procedures.



Scheme 1. Synthesis of phosphane oxides

A direct synthesis of β-oxophosphane oxides from enolates and phosphinoyl halides has not been reported so far. The most common methods to prepare them[2c,6,7] are two-step procedures, which require acylation of an alkyldiphenylphosphane oxide or oxidation of the β-hydroxy intermediate of a Wittig−Horner reaction (Scheme 2). Moreover, the introduction of an alkyl chain on the carbon atom between the phosphorus atom and the carbonyl moiety is restricted to short alkyl chains or benzyl groups.[8]



Scheme 2. Synthesis of β-oxophosphane oxides

We were recently interested in the reactivity of organocerium reagents with electrophiles.[9] These compounds are nonexpensive, highly efficient reagents for nucleophilic transfer of an alkyl group to electrophilic centres,[10] since side-reactions are almost completely suppressed. As a part of our research on the reactivity of organocerium compounds, we tested the reaction of these reagents with phosphorus halides. Until now only one method, which employs lanthanides in the synthesis of phosphane oxides, is known: the SmI_2-promoted coupling of alkyl halides and chlorophosphinites.[11] However, this procedure does not give high yields; nevertheless, it is a very simple method to prepare phosphane oxides.

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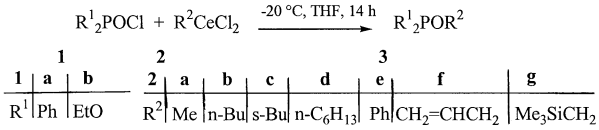
Table 1. Reaction of chloro derivatives of phosphorus(V) with organocerium compounds at −20°C in THF for 14 h



Entry	R^1	Substrate	R^2	Reagent	Product	Yield (%)
1	Ph	**1a**	Me[a]	**2a**	**3aa**	75
2	Ph	**1a**	Bu[a]	**2b**	**3ab**	80
3	Ph	**1a**	*s*Bu[a]	**2c**	**3ac**	40
4	Ph	**1a**	*n*-C_6H_{13}[a]	**2d**	**3ad**	85
5	Ph	**1a**	Ph[a]	**2e**	**3ae**	77
6	Ph	**1a**	$CH_2=CHCH_2$[b]	**2f**	**3af**	58
7	Ph	**1a**	Me_3SiCH_2[b]	**2g**	**3ag**	54
8	EtO	**1b**	Bu[a]	**2b**	**3bb**	60
9	EtO	**1b**	Ph[a]	**2e**	**3be**	70

[a] Organocerium reagent prepared from the corresponding organolithium compound. − [b] Organocerium reagent prepared from the corresponding Grignard reagent.

Results and Discussion

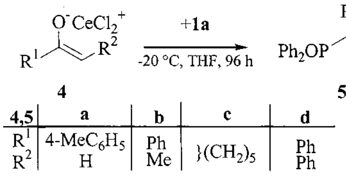
When organocerium compounds are allowed to react for about 14 h with chlorophosphates and phosphinoyl chlorides at −20°C, phosphonates and phosphane oxides, respectively, are obtained in good to high yields (Table 1).

The reaction can be applied to primary, secondary, allylic and silylated organocerium compounds both starting from Grignard and organolithium reagents. Substitution of a phenyl group can occur in the presence of a large excess of methylcerium.

Reaction times are quite long but comparable with those reported for the reaction with simple Grignard reagents,[12] but nevertheless yields are higher and the procedures simpler.

The reaction can be extended to dichlorophenylphosphane oxides and the reaction with butylcerium chloride led to dibutylphenylphosphane oxide in 69% yield.

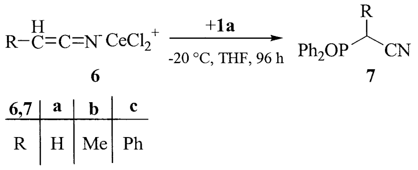
Table 2a. Reaction of diphenylphosphinoyl chloride (**1a**) with cerium enolates at −20°C in THF for 96 h; ketone enolates



Entry	R^2	R^1	Reactant	Product	Yield (%)
1	H	4-MeC_6H_4	**4a**	**5a**	77
2	Me	Ph	**4b**	**5b**	56
3	$[CH_2]_5$[a]	**4c**	**5c**	65	
4	Ph	Ph	**4d**	**5d**	0

[a] Cycloheptanone enolate.

Table 2b. Reaction of diphenylphosphinoyl chloride (**1a**) with cerium enolates at −20°C in THF for 96 h; nitrile enolates



Entry	R	Reactant	Product	Yield (%)
5	H	**6a**	**7a**	58
6	Me	**6b**	**7b**	64
7	Ph	**6c**	**7c**	0

The reaction was then extended to functionalized cerium compounds such as cerium enolates (Table 2). The most remarkable difference with respect to the reaction with nonfunctionalized cerium derivatives is the reaction time (96 h). Yields are good and the reaction can be applied to enolates generated from ketones (Table 2a, entries 1−3), and nitriles (Table 2b, entries 5, 6), but benzyl enolates did not react under these reaction conditions (Table 2, entries 4 and 7).

We propose an addition-elimination reaction mechanism. The cerium atom coordinates the oxygen atom, thus enhancing the electrophilic character of the phosphorus atom. Then the carbanion moiety of organocerium compounds can migrate and attack the phosphorus atom leading to a pentacoordinated intermediate. Finally, ejection of a chloride ion gives the product.

An alternative ^{s}N2 mechanism is discarded, since, at the present time, displacements of halide ions by means of cerium compounds are unknown.[10]

In conclusion, the reaction of organocerium compounds with chloro derivatives of phosphorus(V) is feasible and is competitive with respect to the known synthetic methods, which employ organometallic reagents, most of which require a two-step procedure. Moreover, organocerium derivatives allow the first reported one-step synthesis of β-oxophosphane oxides, bypassing the known three-step procedures.

Experimental Section

General Remarks: THF was dried by reflux over sodium wire until the blue color of benzophenone ketyl persisted and then distilled into a dry receiver under nitrogen. − All compounds were fully characterized by NMR and IR spectroscopy and mass spectrometry. − Commercial cerium(III) chloride heptahydrate was placed in a flask with a stirring bar. The flask was heated in vacuo in an oil bath to 140°C/0.2 Torr for 2 h. Nitrogen was introduced while the flask was still hot. The flask was cooled in an ice bath and dry THF was introduced by syringe. The suspension was stirred overnight at room temperature. The resulting white slurry was then cooled at −78°C and the titrated commercial organolithium reagent (or allylmagnesium bromide prepared by standard procedure from allyl bromide and magnesium turnings) was added dropwise by syringe. Cerium enolates were prepared by transmetallation according to literature procedures.[13]

General Procedure: A THF solution of compounds **1a,b** (5 mmol) was added dropwise to the organocerium reagent **2a**−**g**, **4a**−**g** (12.5 mmol) with stirring at −20°C under nitrogen. The reaction mixture was allowed to stand in the freezer for about 14 h for simple organocerium compounds (Table 1) and for 96 h for cerium enolates (Table 2), and then it was quenched with 3% HCl solution, extracted with diethyl ether, and washed with water. The dried (Na_2SO_4) extracts were concentrated under reduced pressure and purified by flash chromatography on a silica-gel column (chloroform/ethyl acetate, 9:1, as eluant). − Methyldiphenylphosphane oxide (**3aa**),[14] butyldiphenylphosphane oxide (**3ab**),[6] (1-methylpropyl)diphenylphosphane oxide (**3ac**),[15] hexyldiphenylphosphane oxide (**3ad**),[16] triphenylphosphane oxide (**3ae**),[17] allyldiphenylphosphane oxide (**3af**),[18] diphenyltrimethylsilylmethylphosphane oxide (**3ag**),[18] butyldiethylphosphonate (**3bb**),[19] phenyldiethylphosphonate (**3be**),[20] 2-(diphenylphosphinoyl)-1-(4-methylphenyl)ethanone (**5a**),[21] 2-(diphenylphosphinoyl)-1-phenylpropan-1-one (**5b**),[22] 2-(diphenylphosphinoyl)cycloheptanone (**5c**),[23] diphenylphosphinoylacetonitrile (**5e**),[24] and 2-(diphenylphosphinoyl)propanenitrile (**5f**),[25] showed physical data identical to those reported in the literature.

Reaction of Dichlorophenylphosphane Oxide with Butylcerium Chloride: A THF solution of dichlorophenylphosphane oxide (5 mmol) was added dropwise to butylcerium chloride (17.5 mmol) with stirring at −20°C under nitrogen. The reaction mixture was allowed to stand in the freezer for about 14 h before it was quenched with a 3% HCl solution. The mixture was then extracted with diethyl ether, and washed with water. The dried (Na_2SO_4) extracts were concentrated under reduced pressure and purified by flash chromatography on a silica-gel column (chloroform/ethyl acetate, 9:1, as eluant). Dibutylphenylphosphane oxide showed physical data identical to those reported in ref.[26]

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Received February 16, 1999
[O99091]