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A Novel Carbon Leaving Group in the Reaction of Organometallic Compounds with Phosphine Oxides

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Abstract. The reaction of diphenyl(methoxymethyl)phosphine oxide **1** with organometallic reagents was found to lead to substitution of the methoxymethyl group. The P-phenyl substituent showed a lower propensity to undergo a displacement. © 1999 Elsevier Science Ltd. All rights reserved.

In recent work we have reported synthetic, mechanistic and stereochemical features concerning the use of carbon leaving groups in the reactions of organometallic reagents with sulfoxides[1-5] and phosphine oxides.[6-7] It was demonstrated that the halovinyl[1, 2, 6, 7] or the phosphonylmethyl moiety[3-5] could be successfully and stereospecifically[2-5, 7] displaced in the reaction between Grignard reagents and sulfoxides or phosphine oxides bearing these groups.

This displacement procedure appeared as a novel and versatile strategy[4-5] for the transformation of a chiral nonracemic compound into a variety of sulfoxides or phosphine oxides. Therefore, in order to further expand its synthetic potential, we have evaluated the possibility of enlarging the list of carbon leaving groups which could effectively be used for similar displacements.

We wish to report now the results that we have obtained by testing diphenyl(methoxymethyl)-phosphine oxide **1** as a substrate. This compound has been used previously as a convenient

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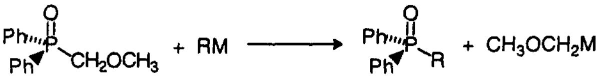
reagent in natural product chemistry[8] to perform the Horner-Wittig synthesis[9] of vinyl ethers under strictly controlled reaction conditions.[10] In these methods, the carbanion derived from **1** is usually generated by treatment of **1** with a strong base, such as LDA.

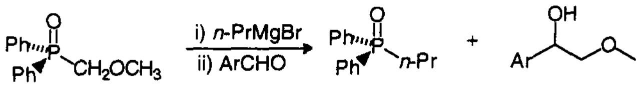
In contrast, we have found that treatment of **1** with Grignard reagents or organolithium compounds elicits a completely different behaviour from the substrate, leading to a facile nucleophilic substitution, with the methoxymethyl anion acting as a leaving group (Equation 1).



1

Equation 1

The relevant results from the reaction of compound **1** with selected organometallic reagents are reported in the Table. The reactions were performed in THF at room temperature and with 1.5:1 organometallic reagent: substrate ratio, and resulted in a practically complete conversion of **1**. In all the cases studied, nucleophilic substitution leading to the formation of product **a** was by far the main reaction path. The nature of the leaving carbanionic species was established by quenching the reactions with aryl aldehydes. Thus, when the reaction of **1** with *n*-PrMgBr was quenched with aryl aldehydes (Ar = *p*-chlorophenyl, *o*-anisyl), the corresponding methoxymethyl aryl carbinol was identified in the reaction mixture by GC-MS, confirming unequivocally that a methoxymethyl carbanionic species was indeed released during the course of the substitution process (Equation 2).



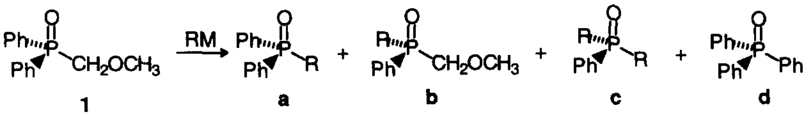
1

Equation 2

The release of the phenyl rather than the methoxymethyl moiety as a leaving group accounts for the formation of small amounts of products **b**. Products **c** could arise from a double substitution of **1**, with the methoxymethyl and the phenyl moieties both behaving as leaving groups. The presence of the phenyl nucleophile in the reaction mixture could be considered responsible for the observed formation of triphenylphosphine oxide (product **d**). The detection of small amounts of ArCH(OH)Ph in the reactions quenched with aryl aldehydes further corroborates this conclusion. As expected, only triphenylphosphine oxide was obtained in the reaction of diphenyl(methoxymethyl)phosphine oxide with phenylmagnesium bromide and phenyllithium (entries 7-8). In general, organolithium compounds (entries 8-10) offered no advantage over Grignard reagents in these substitution reactions.

Table:

Reaction of diphenyl(methoxymethyl)phosphine oxide with organometallic compounds[a]



Entry	R	M	Reaction Time (h)	a	b	c	d
1	Me	MgCl	2	96 (51)[b]			4
2	Et	MgBr	15	88 (42)[b]	4		8
3	*n*-Pr	MgBr	3	70 (40)[b]	18		12
4	2-Np	MgBr	40	63	4	10	23
5	*p*-Tol	MgBr	15	69	7	9	15
6	*p*-An	MgBr	15	63	18		19
7	Ph	MgBr	5	100 (65)[b]			
8	Ph	Li	40	100[c]			
9	Me	Li	2	60			40
10	*n*-Bu	Li	2	67		33	

[a] The representative relative ratios of the most relevant products deriving from a ligand exchange reaction at the phosphorus centre are reported in the respective columns. [b] Isolated yield of product **a**. [c]A 20% amount of the starting material was recovered unchanged. However, it should be noted that in this entry the starting material is identical with product **b**.

In conclusion, the methoxymethyl moiety emerged from this study as a suitable leaving group in the chemistry of phosphine oxides. Furthermore, side products detected in the reactions indicated also a propensity of the P-phenyl substituent to undergo a displacement with organometallic species. The full scrambling of ligands reported for the reaction of tri(*p*-tolyl)phosphine oxide with phenyllithium[11] should be connected with this property. However, at variance with the methoxymethyl moiety, the leaving group ability of the phenyl group does not seem to be amenable to synthetic use. The higher leaving group ability of the methoxymethyl moiety, which is rather unexpected,[10] could be tentatively considered as an effect of the coordination between the oxygen atom and the metal cation present in, or originating from, the organometallic reagent.

Reaction of diphenyl(methoxymethyl)phosphine oxide (1) with ethylmagnesium bromide. Synthesis of diphenylethylphosphine oxide. A solution of 2.6 mL of ethylmagnesium bromide (0.7 N in THF) was added dropwise to a stirred solution of 0.3 g of **1** in 5 mL of anhydrous THF at rt under a N_2 atmosphere. After 15 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted three times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude reaction mixture was subjected to a column chromatography (silica gel, eluent methanol/ethyl acetate 1:9). 0.116 g of ethyldiphenylphosphine oxide were obtained (42% yield). mp 119-121 °C (ethyl acetate/petroleum ether) (lit[12] 120-121 °C). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.77-7.68 (m, 4 H), 7.52-7.43 (m, 6 H) 2.30-2.23 (m, 2 H) 1.18 ppm (dt, J= 17.4, J=7.6 Hz, 3 H). MS 70 eV m/e (relative intensity) 229 (10), 202 (72), 201 (100).

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