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Reactions of (1-Chlorovinyl)diphenylphosphine Oxide with Organometallic Reagents

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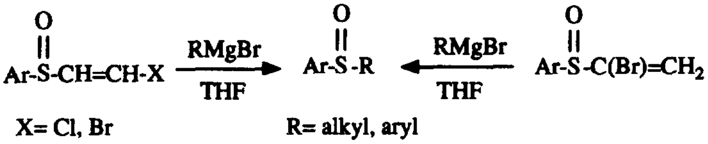
Abstract. Direct substitution of 1-chlorovinyl group by an aryl or an alkyl group in the reactions of (1-chlorovinyl)diphenylphosphine oxide with aryl and alkyl Grignard reagents was observed, whereas in its reactions with the corresponding cuprates addition across the double bond constituted the dominant reaction pathway.

We have recently reported the results of our studies on the reactions of halovinyl aryl sulfoxides with organocuprates, organomagnesium and organolithium compounds[1,2]. In particular[1], (*E*)- and (*Z*)-2-halovinyl phenyl sulfoxides were found to react with alkyl- or phenylmagnesium bromides at room temperature, leading to alkyl phenyl or diphenyl sulfoxides in good isolated yields (79-93%), and a similar behaviour was found for 1-bromovinyl sulfoxides,[2] according to Scheme 1.

SCHEME 1



$$\text{Ar-}\overset{\overset{\large O}{\|}}{\text{S}}\text{-CH=CH-X} \xrightarrow[\text{THF}]{\text{RMgBr}} \text{Ar-}\overset{\overset{\large O}{\|}}{\text{S}}\text{-R} \xleftarrow[\text{THF}]{\text{RMgBr}} \text{Ar-}\overset{\overset{\large O}{\|}}{\text{S}}\text{-C(Br)=CH}_2$$

X= Cl, Br R= alkyl, aryl

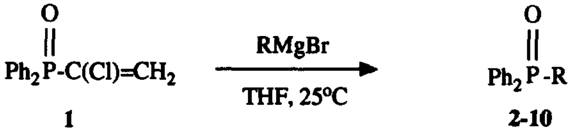
Optically active 1-bromovinyl and 2-bromovinyl aryl sulfoxides reacted enantiospecifically with Grignard reagents (e.e.≥98%).[2] Complete inversion of configuration was established for the reaction with the first type of substrate. This stereochemical evidence is consistent with the hypothesis of an attack of the Grignard reagent at the sulphur atom of the halovinyl sulfoxide with a concomitant expulsion of a two carbon fragment, which then decomposes to give acetylene.[1]

These results prompted us to investigate the reactions between organometallic reagents and (1-chlorovinyl)diphenylphosphine oxide **1**,[3] in order to compare the reactivity pattern between phosphorous and sulphur compounds and to verify the possibility of a new synthetic approach to phosphine oxides, a class of compounds of special interest due to their versatile use: *e.g.* as complexing agents,[4] in the synthesis of natural products[5] and in applied chemistry.[6]

Diphenylphosphinyl chlorides[7] and alkyl diphenylphosphinates[8] were reported to undergo a nucleophilic displacement with organomagnesium reagents, yielding alkyldiphenylphosphine oxides. The high enantiospecificity of this process was applied to the synthesis of optically active phosphine oxides, starting from menthyl phosphinates,[9] as a counterpart of the synthesis of optically active sulfoxides starting from menthyl sulfinate.[10] Furthermore, it has been recently reported[11] that some phosphine oxides react with organolithium or Grignard reagents with a ligand exchange or disproportionation, as it was reported for the analogous sulfoxides.[12]

We wish to report now that when (1-chlorovinyl)diphenylphosphine oxide **1** was reacted with Grignard reagents, an attack of the organometallic compound at the phosphorous atom with consequent formation of phosphine oxides **2-10** was observed (see Table).

Table. Reactions of (1-Chlorovinyl)diphenylphosphine Oxide **1** with Grignard Reagents



$$Ph_2P(=O)\text{-}C(Cl){=}CH_2 \xrightarrow[\text{THF, 25°C}]{\text{RMgBr}} Ph_2P(=O)\text{-}R$$

1 **2-10**

Entry	R	Product	Yield [a]
1	Me [b]	**2**	75
2	Et	**3**	34
3	*n*-Pr [c]	**4**	43
4	*n*-Bu [c]	**5**	32
5	Ph	**6**	71
6	*p*-Tol	**7**	74
7	*o*-Tol	**8**	28
8	*p*-Anisyl	**9**	78
9	2-Np	**10**	38

a) Yields refer to pure isolated products; b) methylmagnesium chloride was used;
c) reactions performed at 0°C did not show any significant difference on the products.

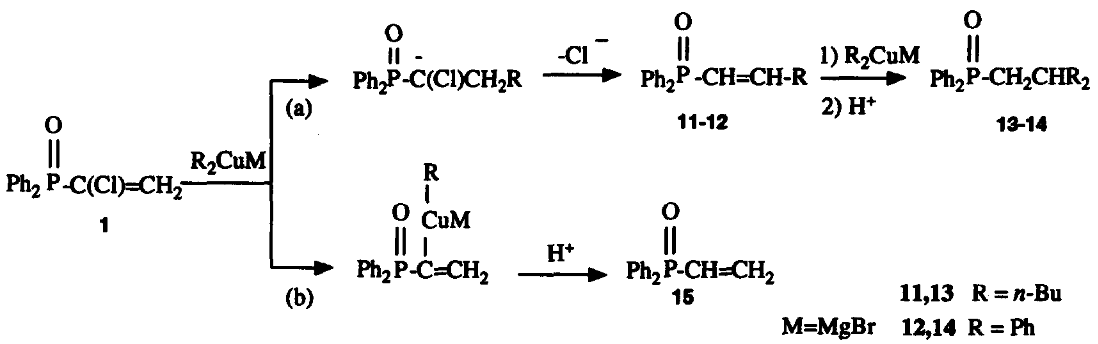
As reported in the Table, good yields were obtained when **1** reacted with methylmagnesium chloride and with some aryl Grignard reagents (entries 1, 5, 6 and 8). If other alkylmagnesium reagents were used (entries 2-4), lower isolated yields of **3-5** were obtained, due to the formation of minor quantities of several by-products, presumably originated by metalation[5] and further reaction of the alkyldiphenylphosphine oxide **3-5** obtained in the first displacement reaction.

Moderate yields were also obtained with *o*-tolylmagnesium and 2-naphthylmagnesium bromide (entries 7 and 9), probably owing to steric reasons. A similar argument was used to explain some unsuccessful reactions of hindered Grignard reagents with menthyl phosphinates.[8,9,13]

On the whole, the observations made with the Grignard reagents indicate a close analogy with the behaviour of the sulfoxides. The presented results confirm clearly the quality of the chlorovinyl group as a viable leaving group in heteroatom chemistry. It seems likely that, as in the sulfoxides, also in this case the fate of the two-carbon fragment is the decomposition to acetylene.

A more complex pattern was observed when (1-chlorovinyl)diphenylphosphine oxide **1** reacted with cuprates in THF at 0°C (Scheme). Using a 1.5:1 cuprate:substrate ratio, compound **1** was completely consumed. Among the examined organocuprates, *n*-$Bu_2CuMgBr$ and $Ph_2CuMgBr$ gave the phosphine oxides **13** (isolated yield 49%) and **14** (yield 63%) as the main isolated products. Gas-chromatography/Mass Spectrometry analysis of both reaction mixtures revealed minor quantities of the vinylphosphine oxides **11** (R= *n*-Bu, 35% of the reaction products), **12** (R= Ph, 5%) and diphenylvinylphosphine oxide **15** (less than 5% in both reactions). On the other hand, *n*-Bu_2CuLi and *n*-$Bu_2Cu(CN)Li_2$ caused mainly reduction of the substrate (*i.e.* formation of **15**), while Ph_2CuLi gave the same products of $Ph_2CuMgBr$, although in lower yields (**14** was isolated in 47% yield) due to the formation of a greater amount of side-products. Although a deeper investigation would be necessary for the rationale of these observations, the formation of the above products could be tentatively explained according to the following Scheme.[14]

SCHEME 2



(a) The main pathway should be represented by an addition process leading to a species from which products **11-12** are originated.[15] These undergo a further addition of cuprate to give **13** or **14**. (b) The formation of vinyldiphenylphosphine oxide **15** should be the result of a metal-halogen exchange followed by the final neutralization.

In conclusion, the results of the present investigation suggest that synthetically useful reactions can be performed reacting 1-halovinylphosphine oxides with organometallic reagents. Carbon-phosphorous or carbon-carbon bond can be formed depending upon the nature of the reagents, thus permitting to obtain different types of phosphine oxides from a common precursor.

Reaction of (1-Chlorovinyl)diphenylphosphine Oxide 1 with Grignard Reagents. Synthesis of Diphenylmethylphosphine Oxide 2.

A solution of 2.2 mmol of methylmagnesium chloride in THF was added dropwise to a stirred solution of 0.3 g (1.1 mmol) of 1 in 12 mL of THF, under N_2. After 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The combined organic extracts were washed with an aqueous solution of NaOH 1 N and with water, and dried (Na_2SO_4). Then the solvent was removed *in vacuo*. The residue was eluted through a very short column of basic aluminum oxide (eluent ethyl acetate). After vacuum distillation of the solvent, the residue was purified by crystallization (benzene/petroleum ether, mp 109-110 °C, lit.[16] 111.5-112 °C). Yield 75%.

Reaction of (1-Chlorovinyl)diphenylphosphine Oxide 1 with Organocuprates. Synthesis of (2,2-diphenylethyl)diphenylphosphine Oxide 14.

A solution of 3.3 mmol of freshly prepared phenylmagnesium bromide in THF was added dropwise to a stirred slurry of 0.314 g (1.65 mmol) of CuI in 5 mL of THF at 0°C. After 10 min, a solution of 0.3 g (1.1 mmol) of **1** in 6 mL of THF was added dropwise. The reaction mixture was stirred at 0°C for 1 h and then was quenched with a saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried (Na_2SO_4) and the solvent was removed *in vacuo*. (2,2-Diphenylethyl)diphenylphosphine oxide **14** was purified by crystallization (ethyl acetate, mp 221-222 °C). Yield 63%. ^{1}H NMR (500 MHz) δ 7.99-7.95 (m, 2 H), 7.58-7.03 (m, 16 H), 6.81-6.79 (m, 2 H), 3.64 (ddd, J=3.5, 7.6, 11.0 Hz, 1 H), 3.32 (ddd, J= 5.7, 11.0, 14.1 Hz, 1 H), 3.26 (ddd, J=3.5, 9.0, 14.1 Hz, 1 H). MS (70 ev): *m/e* (relative intensity) 382 (M^+,4), 202 (100), 180 (16), 165 (12).

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