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DIETHYL-1-MAGNESIUM CHLORIDE METHANEPHOSPHONATE, A NOVEL GRIGNARD REAGENT AND ITS USE IN ORGANIC SYNTHESIS

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Summary

Diethyl-1-magnesium chloride methanephosphonate was obtained by an exchange reaction between diethyliodo methanephosphonate and isopropylmagnesium chloride in THF at −70°C. Reactions of this novel Grignard reagent with various electrophiles are described, and compared with those of the analogous lithium or copper derivatives. Diethyl-1-magnesium chloride methanephosphonate is especially reactive towards phenylselenium halides and halogens.

Introduction

Diethyl-1-lithiomethanephosphonate (**1**) [1,2] or analogous reagents $(R^1O)_2P(=O)-CHLi(R^2)$ [3], and diethyl-1-cupromethanephosphonate (**2**) [4], are useful carbanionic reagents in organic synthesis. The lithium compound **1** is usually produced by deprotonation of diethylmethanephosphonate with n-butyllithium [1,2], and the 1-cupromethanephosphonate **2** [4,5] is generated from **1** by metal exchange.

We now report the efficient preparation of the novel Grignard reagent, diethyl-1-magnesium chloride methanephosphonate (**3**) (X = Cl) and its use as an alternative source of the diethoxyphosphinyl-stabilized carbanion for organic synthesis.

Results and discussion

It was not possible to obtain **3** (X = Cl) by direct metalation of diethyl chloromethanephosphonate with magnesium in tetrahydrofuran or diethyl ether.

Attempts to obtain **3** (X = Br) by lithium–magnesium exchange between diethyl-1-lithiomethanephosphonate and magnesium bromide gave only modest yields (45–55%). Iodolysis was used as the test reaction because 1-lithiomethanephosphonate (**1**) gives poor yields in iodolysis (5%) and because the reaction of Grignard

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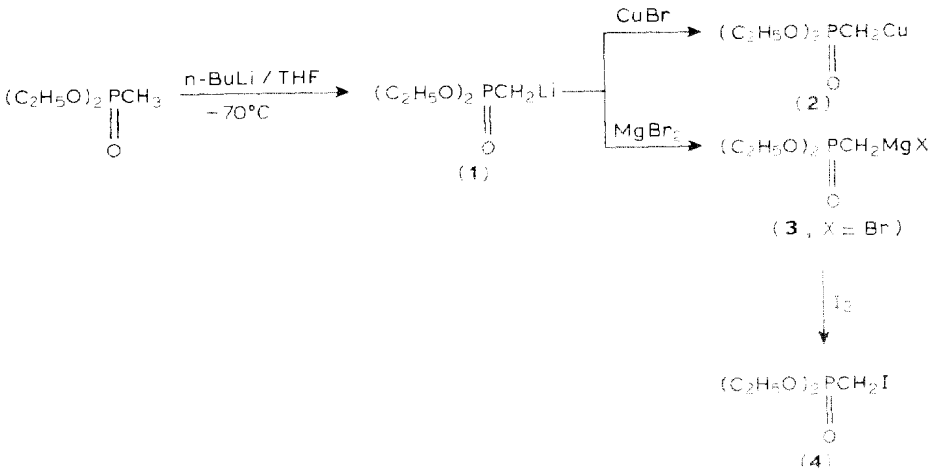
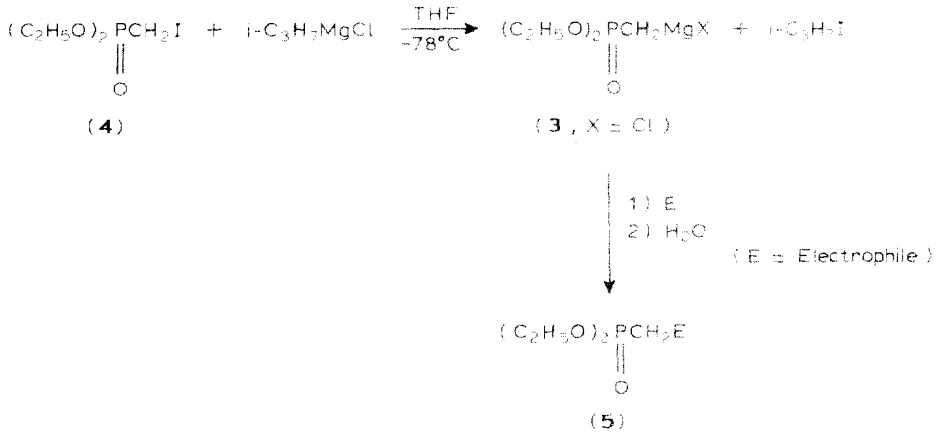


SCHEME 1

reagents with iodine is used in titration of the carbon–magnesium bond [6] (Scheme 1). The reason for the low yield of **3** (X = Br) seems to be that the exchange reaction is not complete even with two equivalents of magnesium bromide. The addition of more magnesium bromide, which should increase the yield of **3** (X = Br) produces difficulties, mainly because magnesium bromide is only slightly soluble in THF ether.

Fortunately we were able to develop a more convenient method starting from the easily available compound **4** [7]: isopropylmagnesium chloride reacted with this compound with complete halogen–metal exchange and quantitative formation of the Grignard reagent **3** (X = Cl) (Scheme 2).

The conversion of **4** into **3** (X = Cl) was confirmed by hydrolysis of aliquot portions of the reaction mixture. After extraction of these aliquot portions with



SCHEME 2

dichloromethane the organic layer was evaporated and analyzed by ^1H NMR: after 45 min the substrate **4** had totally disappeared and diethyl methanephosphonate **5a** (E = H) was the only product visible in the NMR spectrum.

To examine the synthetic utility of **3** (X = Cl) thus obtained, reactions with various electrophiles were investigated. Reactions of **3** (X = Cl) with halogenated derivatives, with carbonyl compounds, or with carbon dioxide gave **5b–5g**, in moderate yields. Towards these electrophiles the Grignard reagent **3** (X = Cl) was obviously less reactive than diethyl-1-lithiomethanephosphonate (**1**).

Two reactions clearly distinguished the reactions of the Grignard reagent **3** (X = Cl) from those of the corresponding lithium compound **1** or cupro compound **2** and illustrated its synthetic value, viz.:

(a) The reagent **3** (X = Cl) reacted with phenylselenium chloride or phenylselenium bromide to give the interesting Wittig–Horner reagent diethyl-phenylselenomethanephosphonate **5h** [8] in good yield (70–85%). With the lithium reagent **1** or copper reagent **2** the corresponding reactions gave poor yields of **5h** (10 and 30%, respectively).

(b) The bromolysis of **3** (X = Cl) gave diethylbromo methanephosphonate (**5i**), a compound rather difficult to obtain by other routes [7,9]. In this case again the Grignard reagent **3** (X = Cl) gave much better yields of **5i** than 1-lithio or 1-cupro phosphonates **1** or **2**.

These routes to diethyl-phenylseleno methanephosphonate **5h** and diethyl-bromo methanephosphonate **5i** represent a good alternative to the existing synthetic methods [7–9], and provide an easy and convenient method of making these compounds in small quantities.

In conclusion, it has been shown that diethyl-1-magnesium chloride methanephosphonate **3** (X = Cl), a novel Grignard reagent derived from the more easily available diethyl iodomethanephosphonate, can be employed advantageously in certain organic syntheses. It complements diethyl-1-lithio and diethyl-1-cupro methanephosphonates, (**1** and **2**) as a source of the diethoxyphosphinyl carbanion.

Experimental

Diethyl iodomethanephosphonate (**4**) was synthesized by a published procedure from diiodomethane and triethylphosphite [7]. Solvents were dried and distilled before use and all reactions were carried out under nitrogen or argon. Silica gel 60 (Merck) was used for column chromatographic procedures. Analytical data for the products **5** are listed in Table 1. IR spectra were recorded on a Perkin–Elmer 580B spectrometer and NMR spectra on a Perkin–Elmer R12 spectrometer. Microanalyses were performed by the Microanalytical Laboratory CNRS.

*Preparation of diethyl-1-magnesium chloride methanephosphonate (**3**, X = Cl) and reaction of **3** with electrophiles: preparation of **5a–5f**, **5h**, **5i**. General procedure*

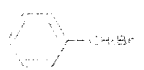
A solution of diethyl iodomethanephosphonate (**4**) (10 mmol) in tetrahydrofuran (10 ml) was added dropwise at −70°C to a solution of isopropylmagnesium chloride which had been freshly prepared in tetrahydrofuran (11 mmol, 1.5 *M*) then diluted with 40 ml of tetrahydrofuran. Stirring for 45 min at −70°C gave a solution of **3**.

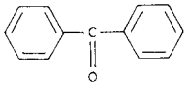
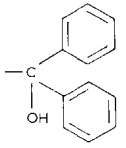
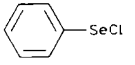
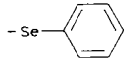
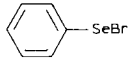
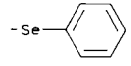
A solution of the relevant electrophilic reagent (10 mmol) in tetrahydrofuran (10

(Continued on p. 18)

TABLE 1

REACTION OF DIETHYL-1-MAGNESIUM CHLORIDE METHANEPHOSPHONATE (3) WITH ELECTROPHILES

(5): $(C_2H_5O)_2P(O)CH_2E$	Electrophile	E	Yield (%)	B.p. or m.p. (°C/Torr)	Empirical [a] formula or lit. m.p. or b.p. (°C/Torr)	^{1}H NMR (CCl_4/TMS int.) δ(ppm)
5a	H_2O	H	85 (100) [b]	87/17	64–65/2 [10]	1.25 (t, 6H); 1.3 (d, 3H); 4.0 (dq, 4H)
5b	$CH_2{=}CHCH_2Br$	$-CH_2CH{=}CH_2$	60	70/1	$C_8H_{17}O_3P$ [11]	1.3 (t, 6H); 1.6–2.7 (m, 4H); 3.8–4.4 (m, 4H); 4.8–6.2 (m, 3H)
5c			52	125/0.5	140–141/1 [12] 144–147/2.3	1.2 (t, 6H); 1.6–3.1 (m, 4H); 3.7–4.3 (m, 4H); 7.2 (s, 5H)
5d			75 [b]	oil	$C_{12}H_{19}O_4P$ [13]	1.15 (t, 6H); 1.6–2.4 (m, 2H); 3.4–4.3 (m, 4H); 4.7–5.4 (m, 2H); 7.0–7.5 (m, 5H)
5e			66 [c]	95	$C_{12}H_{18}NO_6P$	1.2 (dt, 6H); 2.0–2.7 (dd, 2H); 3.5–4.5 (m, 5H); 4.8–5.4 (m, 1H); 7.5–8.5 (dd, 4H)

5f			54 [d]	88	$C_{18}H_{23}O_4P$ [14]	1.05 (t, 6H); 2.7 (d, 2H); 3.1–4.1 (m, 4H); 5.6 (s, 1H); 7.0–7.8 (m, 10 H)
5g	CO_2		(60) [a]	oil	$C_6H_{13}O_5P$ [2]	1.3 (t, 6H); 2.9 (d, 2H); 4.1 (dq, 4H); 11.5 (s, 1H)
5h			70–85	145/0.2	135/0.05 [8]	1.25 (t, 6H); 2.9 (d, 2H); 3.7–4.4 (dq, 4H); 7.1–7.3 (m, 3H); 7.4–7.7 (m, 2H)
			70	150/0.2		
5i	Br_2		64	86/0.1	99/1 [15]; 121/15 [7] 56/0.25	1.35 (t, 6H); 3.3 (d, 2H); 3.8–4.5 (m, 4H)

[a] Yield of pure isolated product or, in parentheses, of crude product. [b] Yield after chromatography on silica gel. [c] Yield after recrystallization from hexane/ethyl-acetate (5/2). [d] Yield after recrystallization from pentane/ether (1/1). [e] The microanalyses showed the following maximum deviations from the calculated values C, ±0.36; H, ±0.20; Br, ± 0.44, except for **5h**, Found: C, 43.81; H, 6.01. $C_{11}H_{17}O_3PSe$ (307.2) calcd.: C, 43.01; H, 5.58%. [f] ^1H NMR spectrum (DMSO-d_6/sodium trimethylsilylpropionate).

ml) was added dropwise at −70°C. In the preparation of **5a, 5h, 5i** the mixture was allowed to warm to room temperature then immediately hydrolyzed (40 ml of H_2O), but for **5b–5f**, it was stirred for 2–4 h at room temperature before the hydrolysis. The aqueous layer was extracted with dichloromethane or chloroform (3 × 50 ml). The extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure to leave the crude **5** as an oil, which was purified by distillation in vacuo or by chromatography on silica gel.

Preparation of diethylcarboxy methanephosphonate (5g)

The solution of the diethyl-1-magnesium chloride methanephosphonate **3** (X = Cl) was prepared as described above then poured with stirring into a Dewar vessel containing dry-ice/ether solution. After a few minutes the mixture was poured into a beaker and allowed to warm to room temperature with stirring. Water (50 ml) was added, the organic layer was washed with 10% aqueous sodium carbonate solution (2 × 25 ml), and the aqueous layers were combined and washed with ether (2 × 50 ml). The aqueous layer was then acidified to pH = 1 with 2 *M* sulfuric acid, saturated with sodium chloride, and extracted with dichloromethane (3 × 30 ml). After drying with magnesium sulfate the solvent was removed under vacuum to leave crude **5g** as an oil.

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