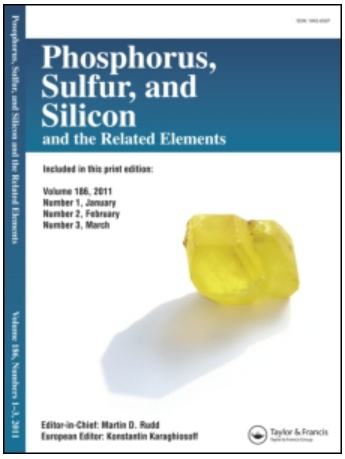

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SHORT COMMUNICATION
Phosphoric–Carboxylic Imides. V. Reaction with Grignard Reagents

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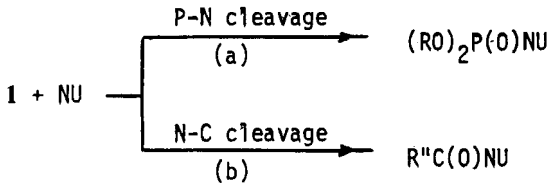
Mixed phosphoric–carboxylic imides were shown to react with Grignard reagents exclusively at the carbonyl centre.

Mixed phosphoric–carboxylic imides (**1**), $(RO)_2P(O)—NR'—C(O)R''$ combine two acyl groups in a single molecular system, thus providing two possible centres of attack by a nucleophilic reagent (Scheme 1).

Reactivity of system (**1**) towards a variety of nucleophiles (and the relation of this reactivity to that of the parent compounds—carboxylic and phosphoric amides) has been studied in this laboratory, and it has been found that the regioselectivity of the reaction depends upon the nature of the nucleophile. Neutral hydroxylic nucleophiles (water, alcohols) attack exclusively at the phosphoryl centre (Scheme 1a), and the typical half-life of (**1**) in alcohols at 25°C in ca 90 h.[1] Since both carboxylic[2] and phosphoric[3] amides are perfectly stable in hydroxylic solvents under neutral conditions (they are often recrystallised from aqueous alcohols), this result indicates much greater activation of the P—N than the N—C bond in (**1**) towards this type of nucleophilic reagent. Alkoxide ions, on the other hand, are highly selective towards the carbonyl carbon atoms in (**1**) (Scheme 1b).[4] Although no quantitative data on the relative reactivity of carboxylic and phosphoric amides towards alkoxide ions are available, the rates of their reactions with hydroxide ions are very similar.[5] Reaction of imides (**1**) with alkoxides[4] shows that in the case of this nucleophile the N—C bond of the mixed imide linkage has been activated to a much greater extent than the P—N bond. In this paper we report the reaction between imides (**1**) and Grignard reagents. The main purpose of this investigation was to establish whether new phosphorus–carbon or new carbon–carbon bonds are formed in reactions of (**1**) with carbon nucleophiles. Since the formation of the C—P or C—C bonds could be



SCHEME 1

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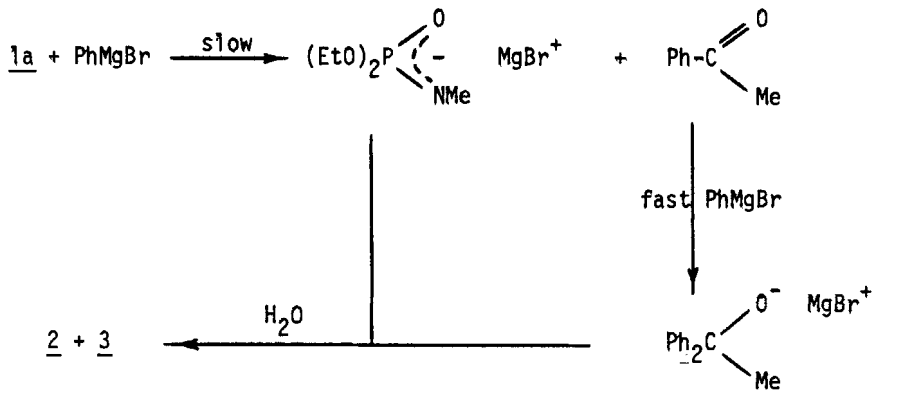
considered as irreversible, the product composition should be a direct measure of the regioselectivity of the attack of a carbanion precursor at the two acyl centres of (**1**). This regioselectivity could then be directly related to the reactivity of organometallic reagents towards carboxylic and phosphoric amides, i.e., parent structures for compounds (**1**). Reactions of Grignard reagents with carboxylic amides are known to produce ketones and to liberate amine molecules.[6] Although reactions between organometallic reagents and phosphorus compounds containing the P—Cl or P—OR functions represent the well established methods of the formation of the P—C bond,[7,7a] no reaction with Grignard reagents involving the phosphoramidate bond have been reported. We have found that *N*,*N*-dimethyl dimethylphosphoramidate, $(MeO)_2P(O)NMe_2$ is unreactive towards phenyl or methyl magnesium reagents and remains unchanged after the addition of Grignard reagent. This most likely results from the electron-donating effect of the NMe_2 group, reducing the electrophilicity of phosphorus to such an extent that no P—OMe cleavage[7] is observed.

The reaction between equimolar proportions of phenylmagnesium bromide and *N*-methyl-*N*-acetyldiethylphosphoramidate (**1a**, R = Et; R′ = R″ = Me) was carried out in ether at room temperature, followed by quenching with aq. ammonium carbonate solution,[8] and the reaction product, after removing ether was examined by ^{1}H NMR spectroscopy and separated by column chromatography (Silica gel 40, Merck, chloroform–ethyl acetate, 9 : 1). The outcome of the reaction is summarized in Eq. (1).

$$\underset{\mathbf{1a}}{(EtO)_2P(O)—NMe—C(O)Me} + PhMgBr \rightarrow \tfrac{1}{2}(\mathbf{1a}) + \underset{\mathbf{2}}{\tfrac{1}{2}(EtO)_2P(O)NHMe} + \underset{\mathbf{3}}{\tfrac{1}{2}Ph_2C(OH)Me} \quad (1)$$

Unreacted (**1a**) and phosphoramidate (**2**) were identified by comparison of their ^{1}H NMR spectra with those of genuine samples; diphenylmethyl carbinol (**3**) was characterised by its m.p., ^{1}H NMR spectrum and elemental analysis.[9] The proportions of all three products shown in Eq. (1) supports Scheme 2 for their formation.



SCHEME 2

The absence of acetophenone in the product mixture implies that second attack of Grignard reagent is much faster than the first, which is in agreement with the greater electrophilicity of the carbonyl centre in acetophenone than that in (**1a**).[11] When substrate (**1a**) was treated with two molar equivalents of phenylmagnesium bromide, (**1a**) disappeared completely from the reaction mixture and only products (**2**) and (**3**) were obtained in high yields. The results discussed above were paralleled by the results of reaction between *N*-methyl-*N*-acetyldimethylphosphoramidate (**1b**, R = R′ = R″ = Me) and two molar equivalents of methylmagnesium iodide.

$$\underset{\mathbf{1b}}{(MeO)_2P(O)—NMeC(O)Me} + 2MeMgI \rightarrow \underset{\mathbf{2b}}{(MeO)_2P(O)NHMe} + \underset{\mathbf{4}}{Me_3COH} \quad (2)$$

Also in this case nucleophilic substitution takes place at the carbonyl group yielding acetone, which then reacts with the excess of Grignard reagent to give the final product, tert-butanol (**4**). In order to determine whether the reaction of (**1b**) with MeMgI involves any other pathways than that represented by Eq. (2), one of the experiments was carried out without subsequent aqueous work-up. After the reaction was completed, the products were allowed to hydrolyse by exposure to atmospheric moisture, ether evaporated, residue extracted with chloroform, and the composition of the chloroform solution was examined by ^1H NMR spectroscopy and TLC. Apart from products (**2b**) and (**4**),[14] the only product observed in low concentration was acetone presumably formed in the first step of the reaction. We were particularly interested in the possibility of the competitive attack of the relatively non-bulky organomagnesium reagent at the phosphoryl centre:

$$\mathbf{1b} + MeMgI \xrightarrow{\text{attack at P}} \underset{\mathbf{5}}{Me—P(O)(OMe)_2} + MeC(O)NHMe \quad (3)$$

Analysis of the reaction product gave no indication of the formation of even small quantities of dimethyl methylphosphonate (**5**).[15] It seems therefore that mixed imides (**1**) behave with respect to Grignard reagents exclusively as carbonyl, not phosphoryl substrates. The low susceptibility of phosphorus to the nucleophilic attack (both in terms of the P—N and the P—O bonds cleavage) observed for simple phosphoramidates is retained in imides (**1**). On the other hand the carbonyl carbon in (**1**) undergoes nucleophilic addition easily in a manner analogous to that of other carbonyl derivatives. In conclusion, with respect to organomagnesium reagents, both acyl centres in mixed imides (**1**) retain the reactivity patterns of their respective parent amide systems.

ACKNOWLEDGMENT

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7. D. E. C. Corbridge, Phosphorus, Elsevier, Amsterdam, 1980, Chapter 4; (a) L. Maier reports the following reaction: $3(Me_2N)_2P(S)Cl + Et_3Al \rightarrow 3(Me_2N)_2P(S)Et + AlCl_3$, yield; 80.2% (*Helv. Chim. Acta*, **47**, 27 (1964)).
8. If aqueous-acidic work-up is used, phosphoramidate (**2**) hydrolyses rapidly to the methylammonium salt of diethylphosphate. This salt is well soluble in water, hence the analysis of the etheral layer does not provide with the full outcome of the reaction.
9. (**3**), yield 50%; m.p. 80–81°C (lit.[10] m.p. 80–81°C); ^{1}H NMR ($CDCl_3$): δ 1.93 (3 H, s, Me); δ 2.73 (1 H, broad s, OH); δ 7.2–7.6 (10 H, m, 2Ph); (Found: C, 84.51; H, 7.01%. Calc. for $C_{14}H_{14}O$: C, 84.85; H, 7.07%).
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11. As measured by their resonance substituent constants σ_R^0, (diethylphosphoryl) amino group is a much stronger electron-donor than the phenyl group ($\sigma_R^0 = -0.40$[12] and -0.11,[13] respectively).
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14. ^{1}H NMR ($CDCl_3$). (**2b**): δ 2.55 (3 H, d of d, $J_{H,H}$ 6 Hz, $J_{H,P}$ 12 Hz, NMe); δ 3.69 (3 H, d, $J_{H,P}$ 11 Hz, OMe); δ 4.00 (1 H, broad s, NH). (**4**): δ 1.30 (9 H, s, 3 Me); δ 1.80 (1 H, broad s, OH).
15. The independently prepared[16] (**5**) shows in the ^{1}H NMR spectrum a characteristic doublet (δ 1.53, $J_{H,P}$ 18 Hz) of the P—Me group.
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