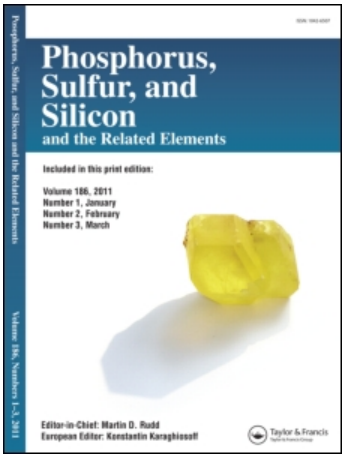

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PHOSPHORIC-CARBOXYLIC IMIDES. III. THE BENZOYLATION OF *N*-METHYLDIETHYL-PHOSPHORAMIDATE AND RELATED ANIONS

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The synthetic route to mixed phosphoric-carboxylic imides (**1**) *via* the *N*-acylation of phosphoramidates was investigated. The reaction of PhC(O)X (X = Br, Cl, F) with conjugate base of $(EtO)_2P(O)NHMe$ (**2**) yields three products: $PhCO_2Et$ (**3**), PhC(O)NHMe (**4**) and $(PhCO)_2NMe$ (**5**). (**4**) and (**5**) are formed via the initial rapid formation of (**1**), while (**3**) results from the ElcB reaction of (**2**). The attack of various nucleophilic species at mixed imide (**1**) was studied, and the possible mechanisms of the P—N bond cleavage, followed by the transfer of nitrogen from phosphoryl to the carbonyl centre, are discussed.

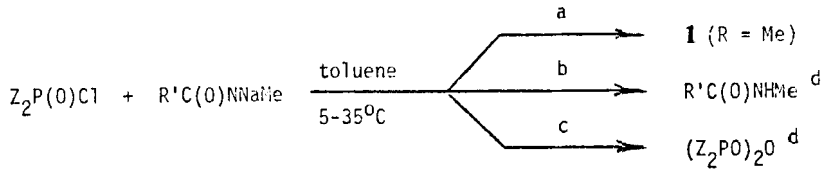
INTRODUCTION

Recent investigations of the structural,[1] solvolytic,[2] nucleophilic[3] and spectroscopic[4,5] properties of the mixed phosphoric-carboxylic imide system **1**, have revealed that in addition to the appearance of certain novel characteristics, this system succeeds in combining diverse features of both its parent phosphoric and carboxylic amide systems.

$$Z_2P(O)—NR—C(O)R'$$

1

Although secondary *N*-acylphosphoric amides (Z = RO; R = H) are readily accessible,[6] it has been found that the synthesis of their tertiary *N*-methyl analogues via the *N*-phosphorylation of a carboxamide anion is complicated by the side reactions indicated in Scheme 1:[4]



Z = MeO, EtO, R' = Ph, Me
CH_2O, Et

[d] Only observed for Z = MeO, EtO.

SCHEME 1

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The formation of the carboxamide and tetraalkylpyrophosphate products[7] leads to a lowering of the mixed imide yield to *ca.* 35%. As a result, the need to explore the possibility of synthesising **1** via the *N*-acylation of the corresponding phosphoramidate precursor arose.

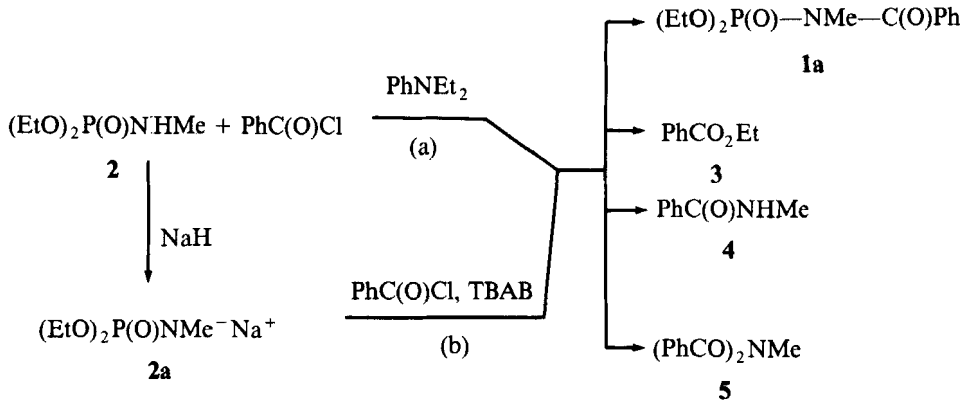
Although early literature reports claim facile *N*-acetylation[9] and *N*-benzoylation[10] of phosphoramidates under basic conditions, Edmundson and Moran[11] subsequently demonstrated the formation of *N*-substituted benzamides and dibenzamides by the benzoylation of a variety of phosphoramidate and phosphinamidate anions. The reaction appears to proceed via a nitrogen group transfer from phosphorus to carbon (Eq. (1)):

$$Z_2P(O)NR^- + PhC(O)X \xrightarrow[\text{reflux}]{\text{benzene}} PhC(O)NHR + (PhCO)_2NR$$
$$X = Cl, OC(O)Ph \qquad (1)$$

However, since no substantiated mechanistic proposals for the P—N cleavage reaction involved in Eq. (1) were given,[11] a re-examination of the benzoylation of diethyl-*N*-methylphosphoramidate under basic conditions was undertaken, with the aim of firstly, evaluating its potential as a synthetic route to the mixed imide $(EtO)_2P(O)$—NMe—C(O)Ph (**1a**), and secondly, elucidating the mechanism of the nitrogen group transfer reaction and the possible participation of (**1a**) therein.

RESULTS AND DISCUSSION

The initial attempts at benzoylating *N*-methyl diethylphosphoramidate (**2**) were modelled upon the procedure described by Alimov *et al.*[12] for the *N*-acylation of diethylphosphoramidate (which utilises *N*,*N*-diethylaniline as a base) and upon the reaction described by Edmundson and Moran,[11] involving sodium salt at (**2**) and benzoyl chloride. In the latter case a catalytic amount (5–10 mol%) of tetra-*n*-butylammonium bromide (TBAB) was added to the reaction mixture to enhance the nucleophilicity of the anion of (**2**). Reactions were carried out at temperatures of 8,



SCHEME 2

20, 55 and 75°C. Fractions of the reaction mixture obtained after filtration, washing with ether and evaporation were periodically monitored by TLC and ^{1}H NMR spectroscopy. Scheme 2 summarises the qualitative outcome of these reactions.

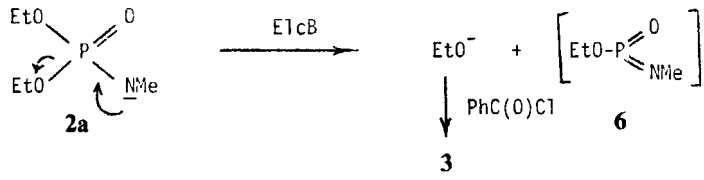
Since the ^{1}H NMR signal of the *N*-methyl group of substrate **2** occurs at high field (δ 2.58), the products **1a**, **4** and **5** were readily identified by their ^{1}H NMR *N*-methyl absorptions at δ 3.15 (d, $J_{H,P}$ = 8 Hz),[4] δ 2.96 (d, $J_{H,H}$ = 5 Hz) and δ 3.51 (s), respectively. Product **3** could only be identified by its OCH_2 absorption (δ 4.38, q, $J_{H,H}$ = 6 Hz) at relatively high concentrations, owing to a partial signal overlap with the methylene proton absorption of the phosphoramidate substrate and that of **1a**. Reaction (a) gives no detectable products after 1 h at 20°C; the reaction at 55°C yields 16% of **1a** after 1½ h. The concentration of the mixed imide increases to a maximum of 26% after 4 h at 55°C, whereafter it decreases with the concomitant increase in the concentrations of **3**–**5**. The final product mixture obtained after 20 h consists predominantly of **3** (*ca.* 40%) and **4** (33%). The outcome of the reaction conducted at 75°C is similar, yielding 27% **1a** after 1 h, with further heating (20 h) leading to the total disappearance of **1a** and the formation of **3**–**5** as the major reaction products. An obvious feature of the NMR spectrum of the product mixture obtained after 20 h at 75°C is the unusually low integration of the O—CH_2 protons, suggesting the participation of a de-ethylation reaction (not shown in Scheme 2).

The reaction (b) carried out at 8°C yields *ca.* 10% of **1a**; warming to room temperature results in the gradual appearance of **3** and **4**. Heating at 75°C leads to an increase in the concentrations of **3**–**5**, at the expense of both **1a** and **2a**.[13] Prolonged heating (> 40 h) results in the complete disappearance of **1a** and increase in the concentration of imide **5**. In addition, the ^{1}H NMR spectrum of the final product mixture (46 h at 75°C) revealed a 30% loss of ethyl groups, as indicated by the integration ratio of the total methylene protons/total aromatic proton absorptions.

The qualitative outcome of the benzoylation of **2** is clearly independent of the type of base employed ($PhNEt_2$ or NaH). However, the reaction temperature is of prime importance in determining the relative concentrations of the four products. The nature of the reaction products indicates that the base catalysed benzoylation of **2** follows two essentially independent pathways. The first, accounting for the formation of the ester **3**, involves a P—OEt cleavage reaction, whereas the second, accounting for the formation of the amide and imide products **1a**, **4** and **5**, involves an *N*-benzoylation reaction. The mechanisms of these two reaction pathways are discussed individually.

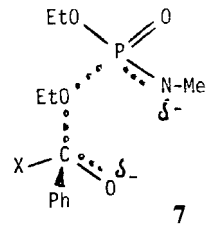
1. Ester Formation

The formation of **3** indicates that under basic conditions, **2** is capable of expelling ethoxide ion, which is benzoylated to yield **3**. The unimolecular elimination mechanism shown in Eq. (2) (ElcB) parallels the mechanism that has been proposed to operate in the base-catalysed solvolysis of certain phosphoramidic chlorides, in order to explain the considerable rate differences observed between substrates bearing an abstractable hydrogen at nitrogen and those in which the nitrogen is fully substituted.[14]



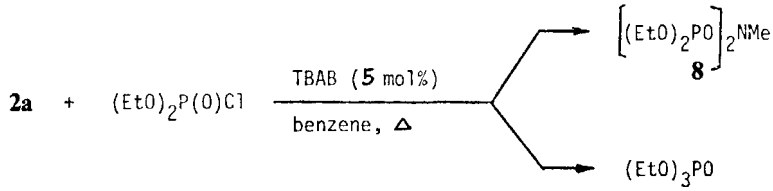
(2)

However, Hamer and Tack[15] have shown that in systems bearing poorer leaving groups than chloride ion (eg. RO^-, ArO^-), the base-catalysed solvolysis proceeds via a BAc2 rather than an ElcB mechanism. The observation that the formation of **3** from the conjugate base **2a** occurs in media that are deficient in nucleophiles capable of effecting P—O cleavage of the latter, excludes the participation of a BAc2 mechanism, thus indicating an elimination-type mechanism. In view of the poor leaving ability of EtO^- ($pK_a \sim 16$),[16] it is unlikely that the mechanism is purely unimolecular, but rather involves electrophilic assistance by the benzoylating agent in the rate-determining P—O cleavage step (structure **7**).



7

Evidence in favour of the proposed participation of an electrophile in the EtO^- expulsion reaction was obtained by firstly conducting a control experiment. In the absence of benzoyl chloride, prolonged heating of **2a** (sodium salt) in benzene under reflux, leads to no detectable (^{1}H NMR) dealkylation. Secondly, the reaction was repeated replacing the benzoylating agent by a phosphorylating agent, diethyl phosphorochloridate. It was found that besides yielding the imidophosphate **8**, the phase-transfer-catalysed reaction of **2a** with diethylphosphorochloridate also yields triethylphosphate, the phosphoric analogue of **3** (Eq. (3)).



(3)

Since no phosphorus-containing products (other than **1a**) were isolated from the reaction mixtures (Scheme 2), the fate of the metaphosphorimidate product **6**, is unknown. This reactive species could polymerise or react with chloride ion or traces of moisture to yield products that are either insoluble in organic solvents or acidic and thus difficult to isolate by silica gel chromatography. However, we believe that the formation of **6** is related to the appearance of an unidentified *N*-methyl

absorption (δ 2.74, d, J = 13 Hz) in all ^{1}H NMR spectra in which **3** is also apparent. A review of the literature[17] has revealed no previous reports of the possible participation of ElcB elimination in the reactions of phosphoramidate anions in the presence of carbonyl and phosphoryl electrophiles. In particular, Edmundson and Moran[11] do not report the formation of either ethyl or phenyl benzoate in their study of the benzoylation of $(RO)_2P(O)\bar{N}R'$ anions (R = Et, Ph).[18] Similarly, Stec *et al.*[19] do not report the loss of *p*-nitrophenoxide ion in the reaction of 2′-deoxynucleoside-3′-O(*p*-nitrophenyl) phosphoranilidate anions with CX_2 (X = O, S).

2. *Amide and Imide Formation*

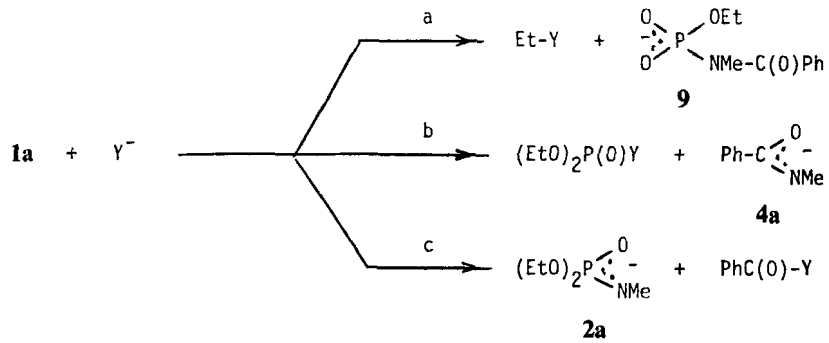
The reaction products **1a**, **4** and **5** all result from an initial *N*-benzoylation reaction. The mixed imide **1a**, although not observed by Edmundson and Moran,[11] is the first of the *N*-benzoylated products formed, with its formation apparently requiring relatively mild conditions. However, even under optimal reaction conditions, the yield of **1a** remains low (< 30%), and any attempt at increasing the yield by increasing the temperature and the strength of the base, leads to the formation of the carboxamide derivatives **4** and **5**, and the subsequent gradual disappearance of **1a**.

Although the formation of **5** can be readily explained by the base-catalysed reaction of **4** with remaining benzoyl chloride, the mechanism of formation of **4**, which arises from an *N*-methyl transfer from the phosphorus to the carboxyl carbon atom of the benzoylating agent, is less obvious. The fact that the mixed imide **1a** is the logical intermediate in this transfer process necessitated the design of experiments aimed at establishing the role (if any) of this species in the formation of **4**. The reaction of **1a** with a nucleophile Y^- can occur in principle via the three pathways indicated in Scheme 3.

Since nucleophilic attack of **1a** at the phosphoryl centre (Scheme 3, pathway b) offers an avenue for the formation of **4**, the reactivity of independently synthesised[4] **1a** towards the various nucleophiles present in the reaction medium was investigated.

(a) *Reaction of* **1a** *with* **2a**

The phase-transfer-catalysed reaction of the anion **2a** with **1a** in benzene under reflux was conducted under strictly anhydrous conditions.[20] The major product of this reaction is the ester **3**, which is presumably formed via ethoxide attack at the

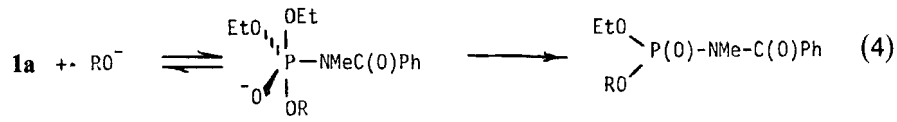


SCHEME 3

carbonyl centre of **1a** according to the mechanisms discussed above (structure **7**, X = N(Me)P(O)$(OEt)_2$). The absence of the distinctive *N*-methyl triplet (δ 2.96, $J_{H,P}$ = 9.5 Hz) of **8**[21] in the ^{1}H NMR spectrum of the product mixture argues against nucleophilic attack by **2a** at the phosphoryl centre of **1a** (Scheme 3, pathway b).

(b) Reaction of **1a** *with Alkoxide Ion*

The reaction of **1a** with sodium ethoxide in benzene in the presence of 8 mol% TBAB is complete within 0.5 h at room temperature. The only observed products of the reaction are **2a** and **3**, which result from ethoxide ion attack at the carbonyl centre of **1a**. This reaction thus offers an additional route to the ester **3** in the original reaction described in Scheme 2. Nucleophilic attack by ethoxide ion at the phosphoryl centre of **1a** would give rise to the oxyphosphorane intermediate **10** (R = Et) which may collapse by P—OEt cleavage to yield the transesterified product **11** (Eq. (4)) prior to the pseudorotation step that necessarily precedes the P—N cleavage of **10**, and expulsion of the conjugate base of **4**.



10 **11** (4)

The possible participation of a transesterification reaction was ruled out by the outcome of the reaction of **1a** with sodium methoxide (Eq. (4), R = Me) under the same reaction conditions. The total lack of methoxyl incorporation at phosphorus (**11**, R = Me), argues against the formation of **10** (and hence, alkoxide ion attack at P=O), in view of the comparable leaving abilities of methoxide and ethoxide ion. The exclusive formation of **2a** and methyl benzoate is thus consistent with exclusive attack of alkoxide ion at the carbonyl centre of **1a**.

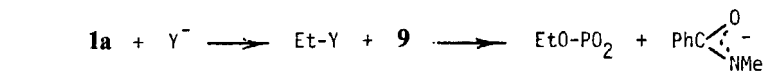
(c) Reaction of **1a** *with Halide Ion*

The TBAB catalysed reaction of **1a** with dry NaCl was carried out in benzene under reflux; slow increase in the concentration of **4**, followed by the formation of **5** and the simultaneous appearance of **2a** and **3** were observed. However, the most noticeable feature of this reaction is the deficiency of the ethyl groups in the final product mixture (*ca.* 70% loss as indicated by ^{1}H NMR after 70 h). The attack of Cl^- at an ester α-carbon atom of **1a** (Scheme 3, pathway a) liberates ethyl chloride (Y = Cl) to yield the mixed imide monoanion **9**. Attack at the carbonyl centre (Scheme 3, pathway c) yields benzoyl chloride (Y = Cl) and **2a**, which are capable of reacting as discussed above (see Scheme 2) to yield the remaining products observed in the reaction mixture. As a result, although the outcome of the reaction of **1a** with Cl^- closely parallels that represented in Scheme 2, these observations do not yield any additional information regarding the mechanism of the *N*-methyl transfer reaction.

The outcome of the reactions shown in Schemes 2 and 3 necessitated an investigation of the role of the 5–10 mol% bromide ion present in the reaction medium in the form of the catalyst, TBAB. Reaction of **1a** with a stoichiometric quantity of TBAB, in the absence of added NaCl does not lead to the formation of **4**, but is accompanied by a degree of de-ethylation. On the basis of the observed reactivity of **1a** towards halide ion, it is apparent that nucleophilic attack occurs predominantly at the ester and carbonyl carbon atoms. It thus seems unlikely that nucleophilic attack by halide ion at the phosphorus atom of **1a** is directly responsible for the *N*-methyl transfer reaction (i.e. formation of **4**). This observation is consistent with the high activation energy that would be required in order to pseudorotate the initially formed P^v intermediate **10**, in which the weakly apicophilic *N*-methylbenzamide ligand is equatorial, in such a way as to locate this group in an apical position from which it can depart.

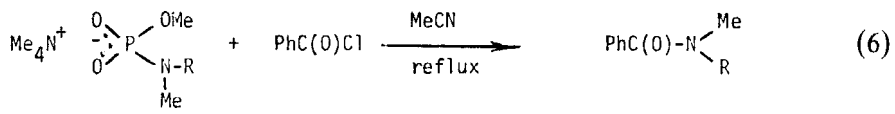
The Role of the Monoanion 9

In view of the significant contribution of the de-ethylation to both the benzoylation reactions of **2a** (Scheme 2) and to the reaction of **1a** with halide ion, the possibility of involvement of this reaction in the *N*-methyl transfer process, according to the reaction indicated in Eq. (5), was investigated.



(5)

Preliminary results of the reactivity of the tetraethylammonium salts of the model monoanions **12a, b** with benzoyl chloride in acetonitrile under reflux have revealed a facile, quantitative conversion of **12a, b** to the corresponding *N*-substituted benzamide derivatives **13a, b** respectively (Eq. (6)).



(6)

12 a, R = C(O)Me
b, R = Me

13 a, R = C(O)Me
b, R = Me

However, we have found that in the absence of benzoyl chloride, no P—N cleavage of the monoanions can be detected, indicating that the collapse of **12** via P—N cleavage requires electrophilic assistance by the benzoylating agent.[22] In this respect, the conversion of **12** → **13** is analogous to the conversion of **2a** → **3** discussed above (Eq. (2), structure **7**). It is worthwhile to point out that the reactions shown in Eq. (6) yield no trace whatsoever of the ester $PhCO_2Me$, that would have arisen via an electrophilically assisted P—OMe cleavage reaction of **12**. This constitutes a major difference in the behaviour of the anions **2a** and **12** in the presence of benzoyl chloride. The observed intramolecular selectivity in the collapse of the monoanion **12** (P—N vs P—O cleavage) is however consistent with the proposed mechanism for this type of reaction. If electrophilic assistance is necessary for the transfer of the

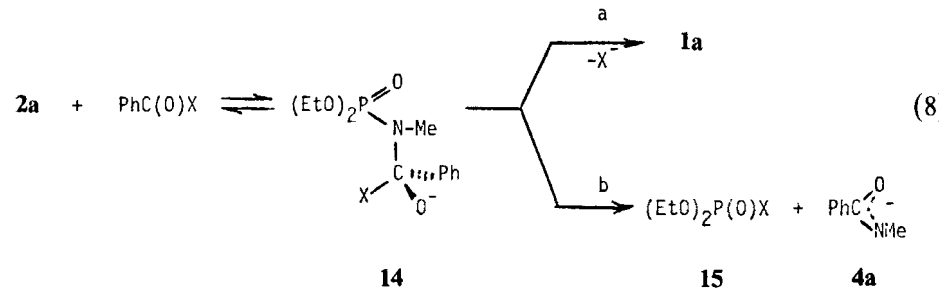
functional group from phosphorus to carbonyl carbon (cf structure **7**), it follows that the energy changes accompanying the P—O/P—N bond-breaking and C—O/C—N bond-making processes, rather than the stability of the leaving group itself, should determine the course of the reaction.[23] In agreement with this conclusion is the observation that dimethylphosphate anion reacts with benzoyl chloride without a P—O bond cleavage (no ethyl benzoate formed) but yields the mixed phosphoric-carboxylic anhydride:

$$(MeO)_2PO_2^- + PhC(O)Cl \longrightarrow (MeO)_2P(O)\text{-}O\text{-}C(O)Ph + Cl^- \qquad (7)$$

On the basis of the results given in Eq. (6), we conclude that the monoanion that is formed by de-ethylation of **1a**, is capable of reactivity with benzoyl chloride to yield the imide **5**, thus offering an additional route (i.e. besides base-catalysed benzoylation of **4**) to this product. However, the de-ethylation of **1a** does not account for the formation of the carboxamide product **4**. This conclusion is consistent with the observation that under certain reaction conditions, the appearance of significant quantities of **4** in the product mixture is not accompanied by any detectable concomitant de-ethylation.[25] In addition, the conclusion that de-alkylation does not play a role in the nitrogen group transfer reaction is in accordance with the observation that the benzoylation of phosphinamide anions $R_2P(O)\bar{N}R'$ (R = alkyl, aryl) similarly results in the formation of nitrogen group transfer products (PhC(O)NHR', $(PhCO)_2NR'$).[11,26]

Proposed Mechanism of Nitrogen Group Transfer

Nucleophilic attack by **2a** at the C=O centre of a benzoylating agent PhC(O)X gives rise to a tetrahedral intermediate **14**. Collapse of **14** via loss of X^- yields the mixed **1a** (Eq. (8), pathway a). However, **14** may also collapse via intramolecular transfer of X from the tetrahedral carbon atom to the P=O centre, resulting in P—N cleavage and expulsion of the conjugate base **4a** (Eq. (8), pathway b).



14 **15** **4a** (8)

Reaction via pathway b (Eq. (8)) provides a means of accounting for the *N*-methyl transfer process. The fact that this reaction involves an interaction between X and the phosphoryl centre of **14**, implies that its contribution is dependent upon the nature of X. In order to examine the effect of the group X in a benzoylating agent on its reaction with sodium salt of *N*-methyl diethylphosphoramidate (**2a**) we determined products of the uncatalysed reaction of **2a** with benzoyl fluoride,

chloride and bromide. For the series of PhC(O)X, X = F, Cl, Br, the relative yields of ethyl benzoate (**3**) are 21, 38 and 53% respectively, while the relative yields of *N*-methylbenzamide anion (**4a**) are 79, 62, and 47%, respectively. The observed increase in ester formation and the relative decrease in the NMe group transfer (formation of **4a**) is in excellent agreement with the proposed mechanisms of these reactions. Formation of benzoic ester is virtually a nucleophilic substitution of an acyl halide, and the usual order of reactivity in such a reaction is RC(O)F < RC(O)Cl < RC(O)Br.[27] If the collapse of **14** involves the intramolecular transfer of halogen, the relative yield of **4a** should reflect the affinity of a halide for a phosphoryl center. It is known[28] that this affinity decreases in the order F > Cl > Br. Wadsworth and Emmons[29] have found that phosphoramidate anions react with a variety of carbonyl and thiocarbonyl compounds (e.g. CX_2[19] RR'C = X; X = O, S) to form an adduct which collapses with P—N cleavage via a mechanism which is analogous to that operating in the Wittig-Horner reaction.[30] The collapse of **14** via pathway b (Eq. (8)) is thus a similar type of reaction with the lability of the C—X bond and the favourable incipient carboxamide formation directing the intramolecular nucleophilic attack at phosphorus by X rather than by the oxyanion.

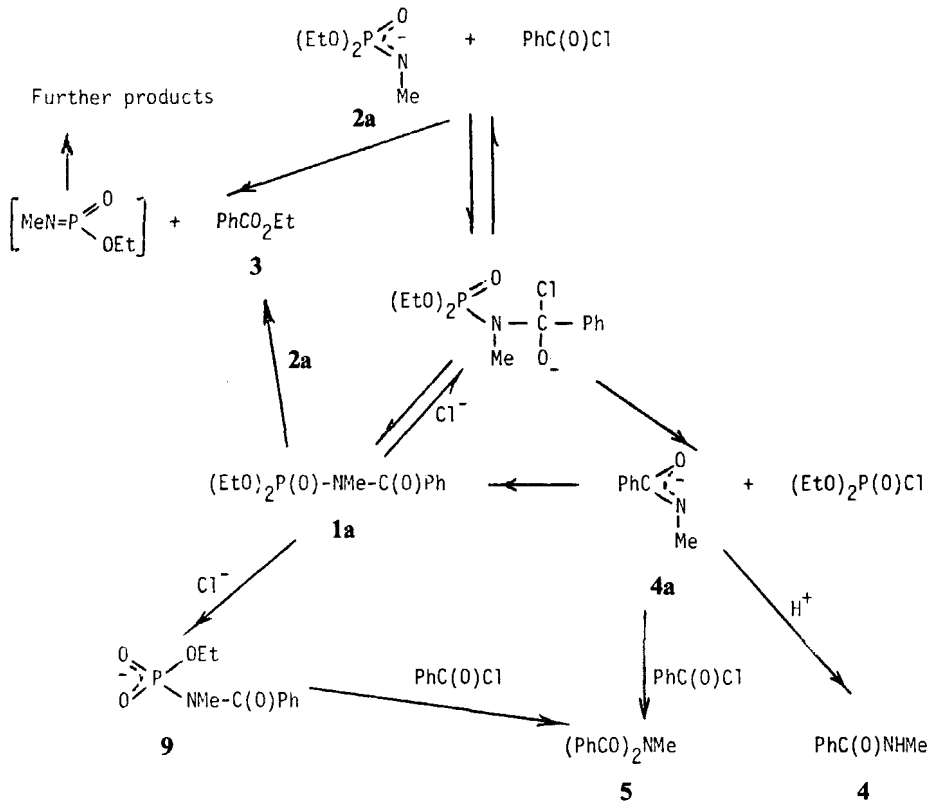
However, while this reaction may offer an explanation of the *N*-methyl transfer process, it also introduces the new, reactive electrophile **15** into the reaction medium. Independent experiments have shown that under the same reaction conditions, **15** (X = Cl) reacts with **2a** according to Eq. (3) and with **4a** according to Scheme 1. The absence of the readily identifiable **8** in the product mixtures of the various base-catalysed benzoylation reactions of **2a** that were studied, is thus particularly conspicuous, and appears to argue against the formation of **15** and hence, against the proposed mechanism of the *N*-methyl transfer reaction (Eq. (8), pathway b). On the other hand, the absence of **8** in the product mixture may be due to the participation of alternative reactions that preclude the interaction between **2a** and **15** that is necessary to form **8**.

Since reaction with benzoyl chloride is a major alternative available to **2a**, we conducted a competitive experiment aimed at establishing the relative reactivities of **2a** towards benzoyl chloride and phosphorochloridate **15** (X = Cl). The major product of this reaction (Eq. (9)) that is obtained after 17h in benzene under reflux is **3** indicating that the presence of the competitive electrophile, benzoyl chloride, precludes the reaction between **2a** and **15** (X = Cl). The outcome of the reaction completely parallels that of the uncatalysed benzoylation of **2a** conducted in benzene (see above).

$$\mathbf{2a} + \mathrm{PhC(O)Cl} + \mathbf{15}\ (\mathrm{X = Cl}) \xrightarrow[\text{reflux}]{\text{benzene}} \mathbf{3} \qquad (9)$$

This result indicates that under competitive reaction conditions, a phosphoramidate anion displays greater reactivity towards a carbonyl than towards a phosphoryl centre.

The diverse range of reactions that are associated with the base-catalysed benzoylation of **2**, are summarised in Scheme 4. As a result of this strong driving force away from phosphoric amidoester substrate towards carboxylic amide and ester products, complex product mixtures are found to prevail under a variety of reaction condi-



SCHEME 4

tions. We thus conclude that the benzoylation of **2a** is an unsatisfactory synthetic route to the corresponding tertiary *N*-benzoyl mixed imide system. However, in attempting to establish the role of **1a** in the formation of the major reaction products, additional insight into its reactivity towards nucleophilic species has been gained: whilst hydroxylic nucleophiles exclusively attack the phosphoryl centre under neutral and acidic conditions,[2] anionic nucleophiles are selective towards the carbonyl and ester carbon centres.

EXPERIMENTAL

Benzene and toluene used as reaction media were distilled from over metallic sodium and stored over sodium wire. Other solvents were purified in conventional manner. Silica gel (Merck, 60 F_{254}) was used for TLC and silica gel (Merck, 40, 70–230 mesh) was used for column chromatography; in both cases ethyl acetate–chloroform (1 : 4) mixture was used as a solvent, unless otherwise stated. The ^{1}H NMR spectra were recorded on a 60 MHz Varian EM 360 and a 100 MHz Varian XL 100 spectrometer with TMS as internal standard. IR spectra were recorded on a Model 180 Perkin Elmer spectrometer. Mass spectra were recorded on a VG Micromass 16F Spectrometer operating at 70 eV and on ion source temperature of 200°C.

All reactions involving sodium salts of amides were carried out under dry nitrogen with rigorous exclusion of moisture.

Substrates. (**1a**) and *N*-methyl diethylphosphoramidate (**2**) were prepared as described before.[4] Benzoyl chloride was distilled before use. Benzoyl fluoride was prepared from benzoyl chloride and KF in benzene in the presence of 18-crown-6, according to the literature procedure.[31] Bp 156–158°C; lit. bp 154–155°C. Benzoyl bromide was prepared from benzoic acid and PBr_3.[32] Bp 48–50°C/0.05 mm; lit. bp 218–219°C. *N*-methylbenzamide (Aldrich) was used as supplied. Diethylphosphorochloridate was prepared according to the literature procedure.[33] Bp 86–87°C/7 mm; lit. bp 69–71°C/3 mm. Tetramethylammonium salts of *N*-substituted methylphosphoramidate, $Me_4N^+(R'RN)(MeO)PO_2^-$ were prepared by demethylation of the corresponding dimethyl ester: A solution of $(MeO)_2P(O)NRR'$ (1 mmol) and trimethylamine (*ca.* 1.5 mmol) in 5 ml of dry acetonitrile was heated in a sealed tube at 70–80°C for a period of *ca.* 12 h. White solid was filtered and identified by ^1H NMR (D_2O) due to the characteristic signal of Me_4N^+ (δ 3.19, s, 12 H) and of the remaining ester group (δ 3.54, d, $J_{H,P}$ = 11.5 Hz, 3 H). These salts were used directly for further reactions. Sodium dimethylphosphate was prepared according to the literature procedure.[34] Sodium salts of *N*-methyl diethylphosphoramidate and *N*-methylbenzamide were prepared in the following way. $(EtO)_2PONNaMe$ was prepared by allowing (**2**) to react with stoichiometric amount of NaH in benzene under anhydrous conditions at room temp. When hydrogen was no longer evolved, the mixture was heated to ensure that conversion to the salt was complete. For PhCONNaMe a benzene or toluene solution of (**4**) was heated under reflux in the presence of finely divided sodium metal for at least 4 h. The salt appeared as a yellow suspension.

Reaction of (**2**) *with benzoyl chloride in the presence of* $PhNEt_2$.[12] The reaction was carried out independently at 20, 50 and 75°C. A mixture of (**2**) (1.68 g), PhCOCl (1.41 g) and $PhNEt_2$ (1.49 g) was stirred at a fixed temperature for a total period of 20 h. Fractions of the reaction mixture were withdrawn periodically, added to dry ether, filtered and after evaporation of ether the products were examined by TLC and ^1H NMR.

Reaction of sodium salt of (**2**) *with benzoyl chloride.* A solution of freshly distilled PhCOCl (0.06 mol in 30 ml benzene) was added dropwise over 15 min to a stirred suspension of $(EtO)_2P(O)NNaMe$ (0.06 mol) and TBAB (8 mol%) in 150 ml of benzene at 6°C. After 0.5 h at this temp., a sample of the reaction mixture was withdrawn, filtered, evaporated and examined by TLC and ^1H NMR. The same was repeated after 0.5 h at room temp., and then at regular intervals over a 46 h period of heating the reaction under reflux. After filtration, the reaction mixture was separated by column chromatography, yielding the following products: Fraction 1, ethyl benzoate (26%). ^1H NMR ($CDCl_3$): δ 1.33 (3 H, t, $J_{H,H}$ = 7 Hz, β-Me); δ 4.33 (2 H, q, $J_{H,H}$ = 7 Hz, α-CH_2); δ 7.25–8.03 (5 H, m, Ph). MS, m/e 150 (M^+). R_f = 0.71.

Fraction 2, *N*-methyl dibenzamide (22%), mp 96–97°C. ^1H NMR ($CDCl_3$): δ 3.50 (3 H, s, *N*-Me); δ 7.10–7.30 (6 H, m, Ph); δ 7.50 (4 H, d of d, J_{ortho} = 8 Hz, J_{meta} = 2 Hz, ortho Ph). IR (10% CCl_4): 1659 cm^{-1} (str., $\nu_{C=O}$). MS, m/e 239 (M^+). Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.50; N, 5.85%. Found: C, 75.30; H, 5.40; N, 5.80%.

Fraction 3, *N*-methylbenzamide (13%) and Fraction 4, benzoic acid (*ca.* 15%) were identified by comparison with authentic samples.

Reaction of sodium salt of (**2**) *with diethylphosphorochloridate.* To a stirred suspension of $(EtO)_2P(O)N$-NaMe (12 mmol) and TBAB (5 mol%) in 20 ml of toluene, a solution of $(EtO)_2P(O)Cl$ (12 mmole) in 5 ml of toluene was added dropwise over 30 min. The mixture was refluxed with stirring for 12 h, cooled, filtered and solvent evaporated under reduced pressure. The reaction mixture was separated by column chromotography eluting with chloroform–acetone (1 : 1), yielding the following products: Fraction 1, triethylphosphate (8%). ^1H NMR ($CDCl_3$): δ 1.35 (9 H, t, $J_{H,H}$ = 7 Hz, β-Me); δ 4.12 (6 H, quintet, $J_{H,H} = J_{H,P}$ = 7 Hz, α-CH_2). MS, m/e 182 (M^+); 155 (M-C_2H_3.); 99 $[P(OH)_4]^+$.

Fraction 2, *N*-methyl tetraethylimidophosphate (55%). ^1H NMR ($CDCL_3$); δ 1.38 (12 H, t, $J_{H,H}$ = 7 Hz, β-Me); δ 2.96 (3 H, t, $J_{H,P}$ = 9.5 Hz, *N*-Me); δ 4.20 (8 H, m, α-CH_2). Anal. Calcd. for $C_9H_{23}NO_6P_2$: C, 35.65; H, 7.65, N, 4.62%. Found: C, 35.55; H, 7.60; N, 4.55%.

Fraction 3, unreacted *N*-methyl diethylphosphoramidate (35%).

Reaction of (**1a**) *with nucleophiles* Y^- ($Y^- = (EtO)_2P(O)NMe^-$ *PhC(O)NMe*$^-$, EtO^-, MeO^-, Cl^-, Br^-. Sodium alkoxides were prepared by dissolving the required amount of sodium in alcohol and evaporating the excess of alcohol under reduced pressure. Sodium salts of amides were prepared as described before. Chloride was used as NaCl, or $NaCl/Bu_4N^+HSO_4^-$ mixture. Bromide was used as $Bu_4N^+Br^-$. 0.01 mole of the salt Na^+Y^- was introduced into a stirred solution of 2.71 g (0.01 mole) of (**1a**) and 8 mol% of TBAB in 40 ml of benzene at 6°C. After 0.5 h at this temp., a sample of reaction mixture was withdrawn, filtered, evaporated and examined by TLC and ^1H NMR. The reaction mixture was then examined after 0.5 h at room temp. and periodically while being heated under reflux. The overall time of heating varied with the nature of Y^- as the reactions proceed at different rates. In each case the products were identified by comparison with the ^1H NMR spectra and R_f values of authentic samples of possible products of reactions.

Reaction of $(EtO)_2P(O)NNaMe$ with $PhC(O)X$ (X = Br, Cl, F) in the absence of TBAB. A solution of PhC(O)X in benzene (0.016 mol in 5 ml) was added dropwise to a stirred solution of 0.016 mol of the sodium salt of *N*-methyl diethylphosphoramidate in 30 ml of benzene at room temp. After 0.5 h the sample of reaction mixture was withdrawn, filtered, evaporated and examined by TLC and ^{1}H NMR. The remaining mixture was refluxed for 17 h, filtered, benzene evaporated and reaction product were determined in the same way. In all cases no **1a** was observed in reaction product.

In an independent experiment $(EtO)_2P(O)NNaMe$ and PhC(O)Cl were refluxed in benzene in the apparatus in which the reflux condenser was connected by a teflon tube with the trap containing CD_2Cl_2 cooled in the dry ice–actone bath. The ^{1}H NMR spectra of the CD_2Cl_2 solution were recorded at $-50°C$ after 1 h and 4 h of refluxing the reaction mixture. For both solutions a considerable quantity of ethyl chloride was observed (δ 1.50, 3 H, t, $J_{H,H}$ = 8 Hz; δ 3.64, 2 H, q, $J_{H,H}$ = 8 Hz).

Reaction of $Me_4N^+(RR'N)(MeO)_2PO_2^-$ (R = Me; R' = Me, MeCO) with $PhC(O)Cl$. A solution of 1 mmol of PhC(O)Cl in 10 ml of acetonitrile was added to the freshly prepared salt and the mixture was heated under reflux for 3–5 h. After filtration and evaporation of the solvent under reduced pressure, the product was separated by column chromatography, yielding the following compounds.

For $R = R'$ = Me: *N,N*-dimethylbenzamide, 65%, mp 39–40°C (lit.[35] mp 41–42°C). MS, m/e 149 (M^+); 105 ($PhCO^+$); 77 (Ph^+); 51 ($C_4H_3^+$); 44 ($C_2H_4NH_2^+$). Anal. Calcd. for $C_8H_{11}NO$: C, 72.45; H, 7.43; N, 9.39%. Found: C, 71.55; H, 7.30; N, 9.04%.

For R = Me; R' = MeCO: *N*-acetyl-*N*-methylbenzamide (78%). Oil. Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91%. Found: C, 67.20; H, 6.30; N, 7.75%.

Reaction of sodium dimethylphosphate and benzoyl chloride. A mixture of anhydrous $(MeO)_2PO_2Na$ (2 mmol), PhC(O)Cl (2 mmol) and TBAB (5 mol%) in benzene (10 ml) was refluxed for 2 h. After filtration and evaporation of solvent the reaction mixture was separated by column chromatography using chloroform as eluting solvent, yielding benzoyldimethylphosphate (40%). ^{1}H NMR ($CDCl_3$): δ 4.07 (6 H, d, $J_{H,P}$ = 13 Hz, POMe); δ 7.60–8.20 (5 H, m, Ph). MS, m/e 230 (M^+); 105 ($PhCO^+$); 77 (Ph^+); 51 ($C_4H_3^+$).

Competitive reaction of diethylphosphorochloridate with sodium salts of N-methyl diethylphosphoramidate and N-methyl benzamide. $(EtO)_2P(O)Cl$ (0.004 mol) was added to a stirred suspension of $(EtO)_2P(O)NNaMe$ (0.004 mole) and PhC(O)NNaMe (0.004 mole) in benzene (60 ml) at room temp. The mixture was refluxed for 1.5 h, filtered, evaporated, and products identified by ^{1}H NMR spectroscopy. NMR spectrum showed high concentration of PhC(O)NHMe, low concentration of $(EtO)_2P(O)NHMe$ and moderate concentration of $[(EtO)_2P(O)]_2NMe$ (δ 2.94, 3 H, t, $J_{H,P}$ = 10 Hz, *N*-Me). (**1a**) was absent in the reaction product.

Competitive reaction of sodium salt of N-methyl diethylphosphoramidate with benzoyl chloride and diethylphosphorochloridate. Equimolar (0.003 mol) amounts of PhC(O)Cl and $(EtO)_2P(O)Cl$ dissolved in benzene (5 ml) were added to a suspension of $(EtO)_2P(O)NNaMe$ in benzene (3 mmol in 30 ml) at room temp. After 1.5 h of refluxing and the usual work-up, the reaction product was examined by ^{1}H NMR spectroscopy. NMR showed ethyl benzoate to be the major product together with small quantities of *N*-methylbenzamide. $[(EtO)_2P(O)]_2NMe$ and (**1a**) were absent in the reaction product.

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