The Acylation of Neutral Phosphoramidates

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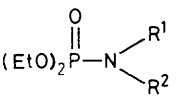
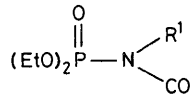
Kinetic studies of the acylation of neutral secondary phosphoramidates by acid halides and anhydrides are reported. The reactions produce both *N*-acylphosphoramidates and carboxamides by cleavage of the P–N bond. The extent of carboxamide formation varies with the strength of the acid co-product and with steric and electronic factors associated with both the acylating agent and the nitrogen substituent of the phosphoramidate. Except for pivaloyl chloride, the presence of a base diminishes the amount of carboxamide formed. With either acid halides or anhydrides tertiary phosphoramidates produce carboxamides directly. The formation of both *N*-acylphosphoramidate and carboxamide follow the equation: rate = k_2[phosphoramidate] [acid halide or anhydride]. Second-order rate constants, k_2, for the formation of *N*-acylphosphoramidates vary with the structure of the acylating agent: AcBr is 18 times more reactive than AcCl; in solvent pyridine the Hammett ρ-value for substituted benzoyl chlorides is 1.8; in solvent CCl_4 Taft ρ* and δ values for substituted acid chlorides are 0.7 and 0.76 respectively. These data are best interpreted in terms of a bimolecular substitution reaction involving nucleophilic attack by the phosphoramidate nitrogen atom at the carbonyl carbon of the acylating agent to form an *N*-acylphosphoramidate cation (**5**). Breakdown of this cation can give either the *N*-acylphosphoramidate *via* deprotonation, or the carboxamide *via* P–N bond cleavage. Carboxamide formation is favoured for reactions where P–N bond cleavage either relieves steric strain or the carboxamide is a good nucleofuge.

Catalysis of the reaction between phosphoramidates and acetic anhydride by electrophiles such as AcX and HX is shown to involve acylation by AcX followed by a rapid re-formation of AcX from Ac_2O and HX.

Neutral phosphoramidates [*e.g.* (**1**)] are potential [1,3]-ambident nucleophiles in which electrophilic attack may occur at either the oxygen or nitrogen atoms. In this respect, they



(**1**) a; R^1 = Ph, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = $PhCH_2O$, R^2 = H
d; R^1 = R^2 = Me

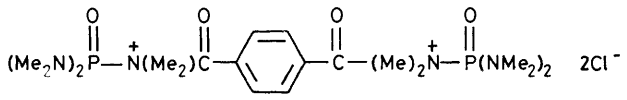


(**2**) a; R^1 = Ph, R^2 = Me
b; R^1 = Ph, R^2 = CF_3
c; R^1 = R^2 = Me
d; R^1 = Me, R^2 = CF_3
e; R^1 = Me, R^2 = CCl_3
f; R^1 = Me, R^2 = Ph
g; R^1 = Me, R^2 = 4-ClC_6H_4
h; R^1 = $PhCH_2O$, R^2 = Me
i; R^1 = $PhCH_2O$, R^2 = CF_3

resemble amides and sulphonamides. For amides, it has been shown that the oxygen atom is more nucleophilic than the nitrogen atom for protonation,[1] alkylation,[2] acylation,[3] and sulphonation.[4] One outcome is the formation of imidates which can rearrange either spontaneously or in the presence of a suitable catalyst to the thermodynamically more stable amide.[5]

Phosphoramidates are not so well studied and the interpretation of their reactions is less clear cut. Although the P–N bond is rapidly cleaved in aqueous acidic solutions, in oleum[6] or trifluoromethanesulphonic acid CF_3SO_3H[7] phosphoramidates are stable enough to record ^1H n.m.r. spectra. In both media protonation of the phosphoryl oxygen atom is preferred. Alkylation[8] and silylation[9] occur at both oxygen and nitrogen atoms but we have recently interpreted these results in terms of kinetically controlled reaction at the oxygen atom followed by a subsequent rearrangement to the thermodynamically favoured nitrogen-substituted product.[10] The reactions of hexamethylphosphoramide, $(Me_2N)_3P{=}O$, (HMPA), with sulphonating reagents[11,12] and with phosphorylating reagents[13,14] also yield products of *O*-attack, although monosubstituted phosphylamidates ‡ are phosphorylated at the nitrogen atom.[15]

Acylation studies of neutral phosphoramidates are few. Diethyl phosphoramidate (**1**; R^1 = R^2 = H) reacts with acetyl chloride in the presence of a tertiary amine to give diethyl *N*-acetylphosphoramidate (**2**; R^1 = H, R^2 = Me).[16] HMPA



(**3**)

reacts with terephthaloyl dichloride to give salt (**3**),[17] but is cleaved by other acyl halides according to equation (1).[18]

$$(Me_2N)_3P{=}O + RCOCl \longrightarrow (Me_2N)_2ClP{=}O + RCONMe_2 \quad (1)$$

Although these results are indicative of nitrogen substitution, reaction of HMPA with either $COCl_2$ or the Vilsmeier reagent, $Me_2\overset{+}{N}{=}CHCl\ Cl^-$, gives compounds, $(Me_2N)_3\overset{+}{P}Cl\ Cl^-$, which are the products of oxygen substitution.[14]

In contrast, phosphoramidate anions acylate exclusively at

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‡ Phosphylamidate is the generic term for phosphon-, phosphin-, and phosphor-amidates.

nitrogen.[19–22] However, P–N bond fission is observed as an important competing process in these reactions,[21,22] which makes difficult the synthesis of *N*-acylphosphoramidates by the acylation of phosphoramidate anions.

Given the current interest in mixed phosphyl-carbonyl imides, *i.e.* *N*-acylphosphoramides (see ref. 22 and references therein), and the possible role of *O*-acylphosphoramidates as acyl-transfer and peptide-linking reagents, we herein report the results of our investigation into the acylation of phosphoramides under neutral conditions.

Experimental

Substrates and Products.—Diethyl *N*-phenyl- (**1a**), diethyl *N*-methyl- (**1b**), diethyl *N*-benzyloxy- (**1c**), and diethyl *N*,*N*-dimethyl- (**1d**) phosphoramidates were synthesised from the appropriate amine by the method of Atherton *et al.*[23] HMPA (Aldrich) was used as supplied. *N*-Acetyl derivatives (**2a**, **c**, and **h**) were prepared by treating the phosphoramidates with sodium hydride under nitrogen, followed by addition of acetyl chloride to the phosphoramidate anion. Only (**2c**) could be purified by distillation (b.p. 56—58 °C/3.5 × 10^{-3} mmHg); both (**2a**) and (**2h**) decomposed on distillation or chromatography. Diethyl *N*-methyl-*N*-trichloroacetyl- (**2e**), diethyl *N*-benzoyl-*N*-methyl- (**2f**),[24] and diethyl *N*-methyl-*N*-(4-chlorobenzoyl)- (**2g**) phosphoramidates were prepared similarly. Trifluoroacetyl derivatives (**2b**, **d**, and **i**) were prepared by treating the phosphoramidate (**1**) with an excess of trifluoroacetic anhydride in pyridine. Evaporation of solvent and excess of reagent under reduced pressure followed by washing the residue with ether and evaporation of the ether extract gave pure *N*-trifluoroacetylphosphoramidate in *ca.* 95% yield. ^{1}H N.m.r. and i.r. data for the compounds (**1**) and (**2**) are summarised in Table 1.

Solvents and Reagents.—AnalaR CCl_4 was dried over $CaCl_2$ and redistilled. AnalaR benzene (sodium dried) and AnalaR cyclohexane were used without further purification. AnalaR pyridine was refluxed over BaO, distilled, and stored over 4A molecular sieves. [$^2H_1$]Chloroform, [$^2H_3$]acetonitrile, and [$^2H_5$]pyridine were stored over 4A molecular sieves.

The acyl halides and anhydrides were either obtained commercially or made by standard procedures and were redistilled just prior to use. *O*-Acetyl-*N*,*N*-dimethylformamidium bromide was prepared by a literature method.[25] Anhydrous HBr in acetonitrile was prepared as described previously.[10] Imidazole was recrystallised from benzene. Triethylamine was distilled from CaH_2 and stored over KOH.

Kinetics.—Conversion of the phosphoramides (**1**) into their acylated products (**2**) was best monitored by recording the ^{1}H n.m.r. spectrum of the reaction mixture at various time intervals. I.r. and u.v. spectrophotometry were also used, but u.v. was relatively insensitive. Reactions were initiated by addition of the acylating reagent to a solution of the phosphoramidate in the appropriate solvent. For (**1a**) the *N-Ph* signal, for (**1b**) with *N-Me* signal, and for (**1c**) the *O*-CH_2Ph signal proved the most convenient for monitoring the reactions and measuring the substrate concentration. These concentrations were calculated from equation (2), where x = the signal integration for the

$$[\text{Substrate}]_t = [\text{Substrate}]_0\,[x/(x + a)] \qquad (2)$$

substrate and a = the signal integration for the product. Depending on the reaction conditions, rate constants were calculated using either pseudo-first-order or second-order integrated rate equations. Reactions were followed to 80—95% completion after which the n.m.r. technique introduced significant errors in the measurement of small signals.

Product Analysis.—Products were generally identified from their ^{1}H n.m.r. spectra by comparison with authentic compounds. In many cases, the products were isolated and identified by their i.r., ^{1}H n.m.r. and e.i. mass spectra, and, where appropriate, by their m.p.s.

Results and Discussion

Acylation by Acid Halides in the Absence of Bases.—Phosphoramidates (**1b** and **c**) reacted with acetyl chloride in apolar, aprotic solvents such as CCl_4 and C_6H_6 to give the corresponding *N*-acetyl products (**2c** and **h**) [equation (3)].

$$(Et_2O)_2PONHR^1 + R^2COX \longrightarrow (EtO)_2PON(R^1)COR^2 + HX \qquad (3)$$

Solvents of low polarity were used to slow down the rearrangement of phosphorimidates to phosphoramidates.[10] On addition of acetyl chloride to compound (**1b**), the ^{1}H n.m.r. spectrum of the reaction solution showed that the *N*-Me double doublet of (**1b**) had collapsed to a doublet. No *N*-acetyl product (**2c**) was detected at this stage. Several observations indicated that the change in multiplicity related to an exchange process and not to the formation of an *O*-acetylphosphorimidate intermediate. Thus, (i) there was no change in the chemical shift of the *N*-Me signal and the *P*–N–C–*H* coupling was unaltered; (ii) the only signal observed in the ^{31}P n.m.r. spectrum was that of (**1b**); (iii) the i.r. spectrum of the reaction solution showed only the presence of starting materials; and (iv) the u.v. spectrum of the reaction solution was that expected from the superimposition of the individual spectra of the starting materials. Similar spectroscopic changes were observed using other acyl halides, such as acetyl bromide and substituted acetyl and benzoyl chlorides.

The initial reaction rates for the *N*-acylation of compounds (**1b** and **c**) were proportional to the concentration of (**1**), and the reactions obeyed the second-order integrated rate equation (4)

$$k_2t = \{\ln[(\mathbf{1})]_0/[\text{acyl halide}]_0 - \ln[(\mathbf{1})]_t/[\text{acyl halide}]_t\}/\{[\text{acyl halide}]_0 - [(\mathbf{1})]_0\} \qquad (4)$$

which implied a first-order dependence on [acyl halide] also. Moreover, under pseudo-first-order conditions where [acyl halide] remained constant (*vide infra*), linear plots of $\ln[(\mathbf{1})]_t/[(\mathbf{1})]_0$ *versus* time (*t*) confirmed that the reaction was first-order in phosphoramidate. Second-order rate constants, k_2, calculated by either method agreed to within ±10%. Thus the reaction is bimolecular and the rate equation for the acylation of (**1**) is given by equation (**5**).

$$\text{Rate} = k_2[(\mathbf{1})][\text{RCOX}] \qquad (5)$$

Values of k_2 for the acylation of (**1a**—**c**) by various acyl halides are listed in Table 2. These data make evident that the rate of acylation depends, as anticipated, on (i) the steric bulk of the acyl group (Me > CMe_3) and (ii) the electronic effect of the acyl group (CH_nCl_{3-n} > Me > 4-ClC_6H_4) and AcBr > AcCl. Indeed, the rate constants for the reaction of (**1b**) with AcCl, $CH_2ClCOCl$, $CHCl_2COCl$, and 4-ClC_6H_4COCl followed the Taft relationship with values of 0.7 and 0.76 for ρ^* and δ respectively (r = 0.996), indicating that both steric and electronic effects have almost an equal influence on reactivity. We are unable to account for the unreactivity of pivaloyl chloride under these conditions.

The reactivity of the phosphoramidate substrates towards acetyl chloride decreased in the order (**1b**) > (**1c**) ⩾ (**1a**), in accordance with the expected electronic and steric contributions of the substituent to the nucleophilicity of the nitrogen atom.

Table 1. ^{1}H N.m.r. chemical shifts in $CDCl_3$ and i.r. stretching frequencies for the phosphoramidates (**1**) and their *N*-acylated products (**2**)

			δ/p.p.m.							
Phosphoramidate	$\nu_{C=O}$/cm^{-1}	$\nu_{P=O}$/cm^{-1}	*Me*CH_2– (6 H, t, *J* 7.5 Hz)	Me*C*H_2 (4 H, dq, *J* 7.5 and 7.5 Hz)	–N*Me* (3H)	–N*Ph* (5H)	–O*C*H_2Ph (2 H, s)	–OCH$_2$*Ph* (5 H, s)	*Me*CO– (3 H, s)	Other
(**1a**)		1 225	1.35	4.10		7.05 (m)				8.10 (N*H*)
(**1b**)		1 232	1.33	4.08	2.60 (dd)					3.20 (N*H*)
(**1c**)		1 250	1.35	4.17			4.80	7.35		6.50 (N*H*)
(**1d**)		1 245	1.32	4.03	2.68 (d)					
(**2a**)	1 700	1 275	1.21	4.10		7.33 (s)			2.07	
(**2c**)	1 690	1 300—1 260	1.43	4.19	3.00 (d)				2.35	
(**2h**)	1 705	1 275	1.43	4.29			5.01	7.43	2.29	
(**2b**)	1 730	1 180—1 150	1.13	4.13		7.31 (s)				
(**2d**)	1 720	1 200—1 150	1.25	4.11	3.15 (d)					
(**2i**)	1 737	1 210—1 160	1.40	4.40			5.13	7.39		
(**2e**)	1 705	1 295	1.23	4.29	3.57 (d)					
(**2g**)	1 670	1 290	1.30	4.05	3.12 (d)					7.53—8.13 (4 H, AA′BB′)

Table 2. Second-order rate coefficients, k_2 for the acylation of phosphoramidates (**1a**—**c**) in CCl_4; initial [(**1**)] = 0.5—2M, [acid halide] = 0.15—1.5M

Substrate	Acid halide	*T*/°C	10^6k_2/l mol^{-1} s^{-1}
(**1a**)	AcCl	35	0
		100	*a*
(**1b**)	AcCl	25	24.1
		30	33.3
		35	43.1
		40	55.6
	AcCl[b]	25	13.2
	AcCl[c]	35	102.0
	AcCl[d]	35	36.7
	AcBr	35	772.0
	$CH_2ClCOCl$	35	106.6
	$CHCl_2COCl$	35	72.5
	CCl_3COCl	35	2.9[e]
	Me_3CCOCl	35	0
	4-ClC_6H_4COCl	35	1.52
	4-ClC_6H_4COCl[f]	35	20.4
(**1c**)	AcCl	35	6.75
(**1d**)	AcCl	35	5.69[g]

[a] Extensive decomposition occurs yielding AcNHPh, EtCl, and polyphosphate gum. No evidence of formation of (**2**). [b] In C_6H_6 solvent. [c] In $CDCl_3$ solvent. [d] In CD_3CN solvent. [e] Refers to formation of $CCl_3CONHMe$, see text. [f] In pyridine solvent. [g] Refers to formation of $AcNMe_2$, see text.

The solvent dependence for the reaction of (**1b**) with acetyl chloride ($CDCl_3 > CCl_4 \approx CD_3CN > C_6H_6$) showed that factors other than solvent polarity were influential.

The effect of temperature on the reaction of (**1b**) with acetyl chloride in CCl_4 solution was examined and the data in Table 2 give values of E_a 45 kJ mol^{-1} and $\Delta S^{\ddagger}$ −208 J K^{-1} mol^{-1}.

In the absence of added base to remove the HX co-product, cleavage of the P–N bond of (**2c**) subsequent to its formation was observed in CCl_4. Thus, with AcCl the product (**2c**) gradually decomposed to form *N*-methylacetamide over a period of weeks, whereas with AcBr rapid decomposition was observed [equation (6)].

$$(EtO)_2PON(Me)COMe + HX \longrightarrow (EtO)_2POX + AcNHMe \quad (6)$$

The reactivity of halide ions towards a phosphoryl centre in water decreases in the order F > Cl > Br,[26] which indicates that it is the acidity of HX which controls this decomposition. The extent of carboxamide formation *via* P–N bond cleavage is also dependent on the structure of the acyl group in the acyl halide. Thus, (**1b**) forms (**2c**) with AcCl without concomitant P–N bond cleavage, whereas with 4-ClC_6H_4COCl P–N bond cleavage occurred almost as rapidly as *N*-acylphosphoramidate formation and with CCl_3COCl only the formation of $CCl_3CONHMe$ could be observed. Undoubtedly, electron withdrawal by the acyl moiety facilitates P–N bond cleavage.

The nucleophilicity of the nitrogen atom of the phosphoramidate also influences P–N bond cleavage *vis à vis* the temperature required for the initial acylation. Thus, the less reactive phosphoramidate (**1a**) requires elevated temperatures to react with AcCl which produces *N*-phenylacetamide rather than (**2a**) (Table 2). Compound (**1b**), however, reacts with AcCl at 35 °C to form (**2c**) which then slowly decomposes to AcNHMe.

Of interest to the P–N bond cleavage reaction is the observation that, in contrast to the secondary phosphoramidates (**1a**—**c**), the tertiary *N*,*N*-disubstituted compound (**1d**) forms *N*,*N*-dimethylacetamide and the corresponding phosphoryl chloride on reaction with acetyl chloride [equation (7)]. A similar reaction is observed with HMPA.

$$X_2PONMe_2 + AcCl \longrightarrow AcNMe_2 + X_2POCl \quad (7)$$
$$(X = EtO, NMe_2)$$

Acylation by Acid Halides in the Presence of Bases.—Cleavage of the P–N bond as described above was inhibited by the presence of bases. Thus in pyridine solvent at 35 °C compound (**1b**) reacted with either CCl_3COCl or 4-XC_6H_4COCl to give the corresponding acylated phosphoramidate (**2**) without any observation of the carboxamide cleavage product. These reactions obeyed second-order kinetics [equation (5)] and the second-order rate constants, k_2^{pyr}, are given in Table 3. Unfortunately, several acid chlorides, *i.e.* AcCl, $CH_2ClCOCl$,

Table 3. Second-order rate coefficients, k_2^{pyr}, for the acylation of (**1b**) by acid chlorides in pyridine solvent; initial [(**1a**)] = 0.665M, [acid chloride] = 0.5—0.7M

Acid chloride	T/°C	$10^6 k_2^{pyr}$/ l mol^{-1} s^{-1}
PhCOCl	35	10.8
4-ClC_6H_4COCl	35	20.4
	45	32.0
	61	64.3[a]
4-MeC_6H_4COCl	35	4.6
CCl_3COCl	35	628.0
Me_3CCOCl	35	*b*
	60	*c*

[a] Formation of 4-$ClC_6H_4CONHMe$ was observed to occur following *ca.* 50% formation of (**2g**). [b] No observation of (**2**) but very slow formation (25% in 35 d) of $Me_3CONHMe$. [c] As for *b* except that 50% reaction occurred in 7 d.

and $CHCl_2COCl$, formed insoluble *N*-acylpyridinium salts which acylated the phosphoramidate (**1b**) to give *N*-acylphosphoramidates but did not give sensible kinetics due to the heterogeneity of the reaction. Values of k_2^{pyr} agree with the k_2 values in CCl_4, and the faster rate anticipated for CCl_3COCl over 4-ClC_6H_4COCl (but not observed in CCl_4 due to competitive P–N bond cleavage) is apparent. The Hammett ρ value calculated from the very limited data set of three 4-substituted benzoyl chlorides is 1.8, consistent with bimolecular nucleophilic attack at the carbonyl carbon atom. The data in Table 3 lead to values of E_a 37 kJ mol^{-1} and $\Delta S^{\ddagger}$ −222 J K^{-1} mol^{-1} for the acylation of (**1b**) by 4-ClC_6H_4COCl and these are consistent with the values for the reaction of (**1b**) with AcCl in CCl_4. The behaviour of pivaloyl chloride remained anomalous (Table 3) in that, in pyridine solution, only the P–N bond-cleavage product *N*-methylpivalamide was observed, even at ambient temperatures.

Acylation by Acid Anhydrides in the Absence of Catalysts.—In the absence of electrophilic or basic catalysts, none of the phosphoramides (**1a—c**) reacted with acetic, benzoic, 4-chlorobenzoic, or 4-nitrobenzoic anhydrides at either room temperature or 100 °C in C_6D_6, CCl_4, pyridine, or CD_3CN solvents. Reaction of the compounds (**1a—c**) with $(CF_3CO)_2O$ in CCl_4, however, proceeded rapidly at 25 °C and kinetic information was obtained from initial rate measurements (Table 4). These indicated that the reaction was bimolecular and obeyed equation (8).

$$\text{Rate} = k_2[(1)][(CF_3CO)_2O] \quad (8)$$

The products of these reactions were the *N*-acylated phosphoramidates (**2b**, **d**, and **i**), confirmed for (**2d**) by its mass and i.r. spectra and $^3J_{PHCH}$ coupling constant of 9 Hz ($^3J_{PNCH}$ for phosphorimidates is typically 25 Hz[27]). As with acid chlorides, the tertiary phosphylamidates (**1d**) and HMPA underwent P–N cleavage with $(CF_3CO)_2O$ to form *N*,*N*-dimethyltrifluoroacetamide [equation (9)]. For HMPA, the

$$X_2PONMe_2 + (CF_3CO)_2O \longrightarrow X_2PO_2COCF_3 + CF_3CONMe_2 \quad (9)$$

phosphorus containing co-product, $(Me_2N)_2POCOCF_3$, was identified by its mass spectrum [*m*/*z* 248 ($M^{+\bullet}$), 179 ($M - CF_3$), and 135 ($M - CF_3CO_2$)]. These products resulted from *N*-acylation and differed from the *O*-substituted products

Table 4. Initial rate measurements for the reaction of (**1a—c**) with $(CF_3CO)_2O$ in CCl_4 at 25 °C

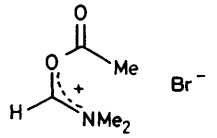
Substrate	$[(CF_3CO)_2O]$/ M	[(1)]/M	10^4 Initial rate[a]/mol l^{-1} s^{-1}	$10^3 k_2$/l mol^{-1} s^{-1}
(**1a**)	1.277	0.795	17.4	1.71
	1.221	0.407	8.2	1.65
(**1b**)	0.557	1.109	37.5	7.07
	1.170	0.583	35.4	5.19
	0.665	0.665	22.9	5.18
	0.665	0.665	23.6	5.34
(**1c**)	0.442	0.442	3.1	1.60

[a] d[(1)]/d*t*.

produced in the reaction of HMPA with sulphonic anhydrides,[11,12] $POCl_3$,[14] and $COCl_2$.[14]

Compound (**1b**) also reacted in CCl_4 solutions with other reactive acid anhydrides *e.g.* $(CCl_3CO)_2O$ and $(CHCl_2CO)_2O$. However, rates of formation of the *N*-acylated phosphoramidates could not be determined due to concomitant cleavage of the P–N bond to form the corresponding carboxamides. ^{1}H N.m.r. of reaction mixtures containing *equimolar* amounts of the phosphoramidate (**1b**) and the acid anhydride showed a new *N*-Me doublet characteristic of the product (**2**). The amount of this product formed before P–N cleavage became apparent was *ca.* 15% for $(CCl_3CO)_2O$ and *ca.* 40% for $(CHCl_2CO)_2O$.

O-Acetyl *N*,*N*-dimethylformamidium bromide (**4**),[25] the acetyl derivative of a tertiary amide, acetylated compound (**1b**) to give compound (**2c**). The second-order rate constant for the reaction between (**1b**) and (**4**) in CCl_4 at 35 °C is 15.6 × 10^{-4} l mol^{-1} s^{-1}. This is twice as fast as that with acetyl bromide itself (Table 2) and implies that formation of such *O*-acetylated amide derivatives increases the acylating potential of the original acid halide.



(**4**)

Acylation by Acid Anhydrides in the Presence of Basic or Electrophilic Catalysts.—In order to increase the reactivity of acetic anhydride and to avoid P–N bond-cleavage reactions the acylation of the phosphoramidates (**1**) by acid anhydrides was examined in the presence of bases. Triethylamine, *N*-methylimidazole, and pyridine did not catalyse the acetylation of (**1a—c**) by acetic anhydride. However, 4-dimethylaminopyridine (DMAP) proved to be an effective catalyst for the acetylation of compounds (**1a**) and (**1c**), which were quantitatively acetylated using equimolar amounts of the phosphoramidate, acetic anhydride, and pyridine in the presence of DMAP (*ca.* 0.1 equiv.). This method proved the most useful for the synthesis of compound (**2a**) which could only be synthesised with difficulty from the phosphoramide anion and acetyl chloride.[21] The reaction was first-order in catalyst with $t_{0.5}$ values 8 h and 13.5 h for [DMAP] = 0.148M and 0.075M respectively, at 35 °C. Given the order of reactivity of the phosphoramidates (**1a—c**) towards acid halides (*vide supra*), surprisingly compound (**1b**) was not acetylated by acetic anhydride in the presence of DMAP.

In contrast to its effect with acetic anhydride, pyridine did catalyse the acylation of compounds (**1a—c**) by $(CF_3CO)_2O$ and $(CCl_3CO)_2O$. The reactions were complete within 2 min

Table 5. Second-order rate constants for the catalysed acetylation of (**1b**) by Ac_2O in CCl_4 at 35 °C, [(**1b**)] = 1—2M, [Ac_2O] = 1—1.2M

Catalyst	$10^5 k_2^{Ac_2O/AcX}$/ l mol^{-1} s^{-1}	$10^5 k_2^{AcX}$/ l mol^{-1} s^{-1}
AcCl	3.70	4.31
AcBr	68.3	77.2
HBr	60.0	
$C_{16}H_{13}\overset{+}{N}Et_3Br^-$	No reaction	
$AlCl_3$	see text	

and therefore too fast for rate measurements by ^{1}H n.m.r., but in both cases the product was the *N*-acylated phosphoramidate (**2**). In the case of $(CCl_3CO)_2O$, the pyridinium trichloroacetate co-product decomposed further to pyridine, $CHCl_3$, and CO_2.

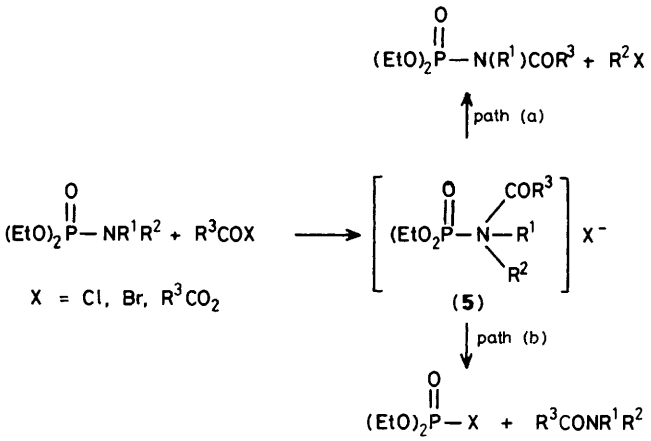
(i) $(EtO)_2PONHMe + AcX \rightleftharpoons (EtO)_2PON(Ac)Me + HX$

(ii) $HX + Ac_2O \rightleftharpoons AcX + AcOH$

Scheme 1. Acetylation of (**1b**) by Ac_2O brought about by AcX and HX catalysts

Electrophilic catalysis of Ac_2O acetylation by acid halides, mineral acids, and ammonium salts is well known.[25] The effect of AcCl, AcBr, HBr, $Cet\overset{+}{N}Et_3Br^-$, and $AlCl_3$ on the acetylation of (**1b**) by Ac_2O was therefore examined in CCl_4 at 35 °C. Whereas the acid halides and HBr catalysed the formation of the *N*-acetylphosphoramidate (**2c**), the tetra-alkylammonium bromide had no catalytic effect and the Lewis acid brought about complete dealkylation of the starting phosporamidate as well as P–N bond cleavage. Catalytic acetylation of (**1b**) by Ac_2O in the presence of AcCl, or AcBr gave complete formation of (**2c**) and was first-order in [(**1b**)]. Mechanistically useful information was obtained by calculating k_2 [equation (5)] assuming that the acid halide was the sole acylating agent and that [AcX] remained constant throughout the reaction. Reasonable agreement between these coefficients and those for the direct acylation by acetyl halides (Table 5) verified this assumption. The catalysis is therefore best explained by the reactions outlined in Scheme 1. Acetylation of (**1b**) by AcX generates compound (**2c**) and HX. The HX co-product then reacts with Ac_2O to give AcOH and more AcX which can go on to react with the substrate. Scheme 1 encompasses the acetylation brought about by HBr in the presence of Ac_2O but requires that equilibrium (ii) lies almost completely in favour of the products and is established faster than the acylation reaction (i).

Mechanism of Phosphoramidate Acylation.—The results described above, *viz.* first-order dependence on both [acid halide or anhydride] and [phosphoramidate], Hammett ρ and Taft ρ*/δ values for acid chlorides, the reactivity of AcBr *vs.* AcCl, phosphoramidate *N*-substituent effects, and the $\Delta S^{\ddagger}$ values all point to a bimolecular reaction involving nucleophilic attack by the phosphoramidate on the acylating agent. Although mechanisms involving either *O*- or *N*-attack by the phosphoramidate are both consistent with these findings, the *N*-attack is the simplest (Scheme 2). For secondary phosphoramidates (R^2 = H), deprotonation of (**5**) leads to formation of the *N*-acylphosphoramidate [path (a)], whereas for tertiary phosphoramidates (R^1, $R^2 \neq$ H) attack by X^- at the phosphorus atom leads to the observed carboxamide product [path (b)].



Scheme 2. Mechanism for the acylation of neutral phosphoramidates

Scheme 2 is also consistent with the observed P–N bond cleavage during the acylation of secondary phosphoramidates. This reaction probably relies on four factors: (i) the relative strengths of the acids HX; (ii) the nucleophilicity of X^-; (iii) the steric and electronic factors affecting the basicity of the N-atom and the P–N bond strength of the intermediate (**5**); and (iv) similar factors affecting the stability of the carboxamide in (**5**) and hence its nucleofugacity. Thus, for acetyl chloride, electronic and steric effects in (**5**) are small and deprotonation [path (a)] is preferred. Protonation of the product regenerates (**5**), however, which eventually forms the carboxamide irreversibly *via* path (b). For acetyl bromide, the stronger acid HBr means that the equilibrium concentration of (**5**) is higher than with HCl, and carboxamide formation is therefore more extensive. As already mentioned, this must be due to the relative acidities of HBr and HCl since nucleophilicity towards phosphorus is greater for Cl^- than for Br^-.

Significantly, when acetyl chloride reacts in the presence of acetic anhydride *no* P–N bond cleavage is observed, because the acetic acid co-product is too weak to reverse significantly path (a). The effect of added bases can be ascribed similarly to removal of the acid co-product, which lowers the concentration of the intermediate (**5**) and therefore inhibits P–N bond cleavage. For aromatic acyl halides, *e.g.* 4-ClC_6H_4COCl, where formation of *N*-acylphosphoramidate and carboxamide is concurrent in the absence of bases, delocalisation of electrons throughout the carboxamide moiety weakens the P–N bond in (**5**) and competition between paths (a) and (b) is therefore greater. In the presence of base, the concentration of (**5**) is reduced and the yield of *N*-acylphosphoramidate is correspondingly greater. For CCl_3COCl in the absence of base, preferential formation of carboxamide can be explained by electron withdrawal weakening of the P–N bond and relief of steric crowding due to the bulky CCl_3 group. In the presence of base, the formation of the *N*-trichloroacetylphosphoramidate again reflects a lowered concentration of the intermediate (**5**). The observation that pivaloyl chloride gives only the carboxamide product, even in the presence of base, is best rationalised by relief of unfavourable steric interactions in (**5**) on breaking the P–N bond. Analogous observations using acid anhydrides can be explained similarly.

The mechanism outlined in Scheme 2 is the simplest one that accounts for the observed products and kinetics. Unfortunately, a mechanism involving *O*-acylation is not entirely precluded, since rapid *O*-to-*N* rearrangement of the *O*-acylphosphorimidate would still give rise to the *N*-acylphosphoramidate, which itself would give rise to the carboxamide products. Further, most *O*-acylimidates are known to undergo a fast *O*-to-*N* rearrangement [3,28] and Drieding models show that the distance

between the nitrogen lone-pair electrons and the carbonyl carbon of the acyl group is equidistant for both *O*-acylimidates and *O*-acylphosphorimidates. *O*-Acylimidates can be isolated, however, when the conformation of the nitrogen lone-pair is *E*- to the *O*-acyl group,[3] since the barrier to rotation about the C=N bond is 95 kJ mol^{-1}.[29] An upper limit to rotation about the P=N bond has been set at 29 kJ mol^{-1} by Goldwhite and co-workers.[27,30] The activation energy measured for the acylation reaction is *ca.* 40 kJ mol^{-1}, from which it follows that rearrangement of an *O*-acylphosphorimidate, if it does exist in these reactions, will be fast compared with the initial acylation. We therefore conclude that *O*-acylphosphorimidates will only be isolated at ambient temperatures for structures whose conformation precludes interaction between the nitrogen lone-pair electrons and the carbonyl carbon.

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