On the Reaction of Acyl Chlorides and Carboxylic Anhydrides with Phosphazenes

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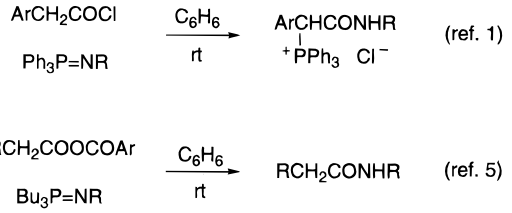
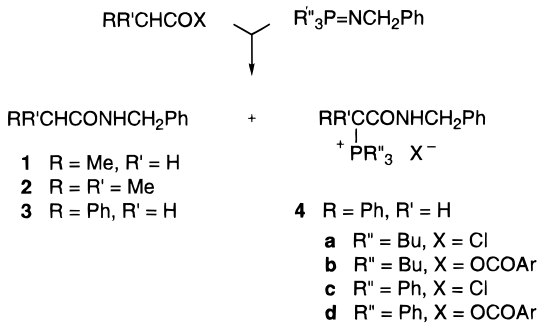
Recently, Molina et al. reported[1] that the reaction between arylacetyl chorides and triphenylphosphazenes[2] gave phosphonium-substituted amides (see Scheme 1) in 25−97% yields. These results are in sharp contrast with other reports in which acyl chlorides are heated with triphenylphosphazenes to afford imidoyl chlorides (chloroimines) and, after aqueous treatment, the expected carboxamides.[3,4] The results of Molina et al.[1] also seem to disagree with the reactivity shown by mixed carboxylic anhydrides when treated with trialkylphosphazenes, which after the workup afford normal amides (Scheme 1); these reactions are the basis of a method developed by us for the formation of macrolactams and peptides under mild conditions.[5]

Why in some cases these unexpected *C*-phosphonium salts are the predominant products whereas in many others standard carboxamides are chiefly isolated is not clear. It is surprising that such small changes in the substrates and reagents could give rise to such a disparate behavior. We present here chemical and spectroscopic evidence that accounts for the differences observed.

Scheme 1



Scheme 2



Results and Discussion

Influence of the Reaction Conditions. Reaction of three simple acyl chlorides and three aliphatic−aromatic carboxylic anhydrides with $Bu_3P{=}NCH_2Ph$ [(*N*-benzyl)-tributylphosphazene] or with $Ph_3P{=}NCH_2Ph$ [(*N*-benzyl)-triphenylphosphazene] has been systematically investigated in order to determine the percentages of amides **1**−**3** and *C*-phosphonium salts (see Scheme 2) that may be achieved in each case. The results obtained in benzene, the solvent most commonly used in previous papers,[1,5] are summarized in Table 1.

Table 1 shows that aliphatic carboxyl derivatives, either acyl chlorides or mixed anhydrides (Table 1, entries 1−8), gave the normal carboxamides after workup; the abnormal amides (*C*-phosphonium salts) were not detected.[6] Thus, there are no practical differences between using simple aliphatic acyl chlorides or the corresponding alkanoyl−aroyl anhydrides.

The yields of *N*-benzylpropanamide (**1**) were higher with $Bu_3P{=}NCH_2Ph$ (Table 1, entries 1 and 2) than with $Ph_3P{=}NCH_2Ph$ (Table 1, entries 3 and 4). Apparently, the former reacted more quickly than the latter; in fact, we noted that the reaction was complete after 5 h in the two first cases but not in the other two. These differences may be accounted for bearing in mind that, in general, trialkylphosphines are more basic and nucleophilic than triarylphosphines[7] and that the basicity and nucleophilicity of the corresponding phosphazenes is not identical either;[4,8] it may then be assumed that some reactive intermediates are formed and converted into the final products more rapidly in the former examples than in the latter. Similarly, the yields of *N*-benzylisobutyramide (**2**) were also higher in entries 5 and 6 than in entries 7 and 8 (Table 1), respectively. What is clear, however, is that $Bu_3P{=}NCH_2Ph$ and $Ph_3P{=}NCH_2Ph$ show a parallel behavior.

On the other hand, entries 9−18 of Table 1 indicate clearly that phenylacetic derivatives are prone to give phosphonium salts (**4a**−**d**), since both **3** and **4** were isolated in all runs. Shortening of the reaction time to 30 min (Table 1, entry 13) gave rise to a poor yield of **3** but to almost the same yield of **4a** (compare entry 13 to entry 9 of Table 1). By lengthening the reaction time to 15 h, the sums of yields of **3** and **4** increased with respect to those after 5 h (compare entries 14 and 15 to entries 9 and 10 of Table 1, respectively),[9] but mainly the yield of **3** improved. The experiments of entries 16−18 (Table 1) were also illuminating, since it was noted that low temperature and, especially, dropwise addition of the phosphazene solution to the carboxyl derivative (in order

(1) Molina, P.; Alajarín, M.; López-Leonardo, C.; Alcántara, J. *Tetrahedron* **1993**, *49*, 5153. Molina, P.; Alajarín, M.; López-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041.

(2) *P,P,P*-Triphenylphospha-λ^5-azenes; phosphazenes are also called iminophosphoranes and phosphimines.

(3) For example, see: Zbiral, E.; Stroh, J. *Liebigs Ann. Chem.* **1969**, 29. Bachi, M. D.; Vaya, J. *J. Org. Chem.* **1979**, *44*, 4393. Bachi, M. D.; Klein, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1925. Barluenga, J.; Ferrero, M.; Palacios, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2193. Katritzky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1994**, *59*, 4556.

(4) For reviews on phosphazene chemistry, see: Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1. Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353. Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209. Johnson, A. W. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993.

(5) Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671. For a related paper, see: Bosch, I.; Urpí, F.; Vilarrasa, J. *J. Chem. Soc., Chem. Commum.* **1995**, 91.

(6) Although not indicated in Table 1, the reactions of entries 1 and 5 were repeated at 60 °C, with phosphazene excess, but *C*-phosphonium salts were not detected either, while the normal carboxamides were isolated in 90−92% yields.

(7) For a review, see: Hudson, H. R. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: New York, 1990; Vol. 1, pp 385 and 473. For early studies: Henderson, W. A.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *20*, 5791. Henderson, W. A.; Buckler, S. A. *J. Am. Chem. Soc.* **1960**, *20*, 5794. For illustrative examples, from ourselves: Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1986**, *27*, 4623. Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 7497.

(8) Genkina, G. K.; Korolev, B. A.; Gilyanov, V. A.; Kabachnik, M. I. *Zh. Obshch. Khim.* **1971**, *41*, 80; *Chem. Abstr.* **1971**, *75*, 129120w.

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Table 1. Reaction of Carboxyl Derivatives with Phosphazenes in Benzene[a]

entry	acid derivative	phosphazene	reactn time (h)	amide	yield (%)	phosp salt	yield (%)
1	CH_3CH_2COCl	$Bu_3P{=}NCH_2Ph$	5	**1**	88	*e*	*e*
2	$CH_3CH_2COOCOAr$[b]	$Bu_3P{=}NCH_2Ph$	5	**1**	91		
3	CH_3CH_2COCl	$Ph_3P{=}NCH_2Ph$	5	**1**	51		
4	$CH_3CH_2COOCOAr$	$Ph_3P{=}NCH_2Ph$	5	**1**	50		
5	$(CH_3)_2CHCOCl$	$Bu_3P{=}NCH_2Ph$	5	**2**	87		
6	$(CH_3)_2CHCOOCOAr$	$Bu_3P{=}NCH_2Ph$	5	**2**	95		
7	$(CH_3)_2CHCOCl$	$Ph_3P{=}NCH_2Ph$	5	**2**	79		
8	$(CH_3)_2CHCOOCOAr$	$Ph_3P{=}NCH_2Ph$	5	**2**	71		
9	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$	5	**3**	30	**4a**	36
10	$PhCH_2COOCOAr$	$Bu_3P{=}NCH_2Ph$	5	**3**	24	**4b**	40
11	$PhCH_2COCl$	$Ph_3P{=}NCH_2Ph$	5	**3**	30	**4c**	33
12	$PhCH_2COOCOAr$	$Ph_3P{=}NCH_2Ph$	5	**3**	21	**4d**	36
13	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$	0.5	**3**	17	**4a**	34
14	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$	15	**3**	46	**4a**	38
15	$PhCH_2COOCOAr$	$Bu_3P{=}NCH_2Ph$	15	**3**	44	**4b**	42
16	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$	15[c]	**3**	40	**4a**	29
17	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$	dropw,[d] 5	**3**	62	**4a**	13
18	$PhCH_2COCl$	$Ph_3P{=}NCH_2Ph$	dropw,[d] 5	**3**	59	**4c**	10

[a] 0.2 M solutions of both reagents. With the exceptions pointed out by footnotes, *the carboxyl derivative solution was added to the phosphazene solution* at 5 °C, and the mixture was then stirred at rt as indicated. [b] Ar = 2,4,6-trichlorophenyl, but the results were practically identical with Ar = 3,5-dinitrophenyl in several experiments. [c] Addition at −20 °C in toluene instead of benzene. [d] *Dropwise addition,* over 45 min, *of the phosphazene solution to the acid chloride solution.* [e] Not detected (no precipitate was formed; after the workup, no species of this kind was present in the crude product or was isolated after column chromatography).

Table 2. Effect of the Temperature and Reagent Excess in the Reaction of Phenylacetyl Chloride with (*N*-Benzyl)tributylphosphazene[a]

entry	acid chloride	phosphazene (equiv)	solvent	*T* (°C)	time (h)	yield of **3** (%)	yield of **4a** (%)
1	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (2.0)	$CHCl_3$	60	15	16	65
2	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	$CHCl_3$	60	15	30	49
3	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	$CHCl_3$	rt	15	41	37
4	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	$CHCl_3$	−20/rt[b]	15	49	30
5	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	$CHCl_3$	−78/rt[b]	15	64	16
6	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (0.9)	$CHCl_3$	−78/rt[b]	dropw,[c] 15	70	9
7	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	CH_3CN	rt	15	47	32
8	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (2.0)	CH_3CN	−35/rt[b]	15	61	14
9	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (1.0)	CH_3CN	−35/rt[b]	15	71	5
10	$PhCH_2COCl$	$Bu_3P{=}NCH_2Ph$ (0.9)	CH_3CN	−35/rt[b]	dropw,[c] 15	78	trace

[a] 0.2 M solutions of both reagents. Addition of the acyl chloride to the phosphazene. [b] Addition at the first temperature, and stirring at the second one for several hours, as indicated. [c] Dropwise addition over 45 min of the phosphazene to the acyl chloride at the first temperature (bath temperature) and stirring for ca. 15 h at rt.

to avoid a relative excess of the phosphazene) decreased the formation of *C*-phosphonium salts **4**.

In the light of these last results, we carried out a series of additional experiments in chloroform and in acetonitrile, which are summarized in Table 2. In chloroform, it turned out (see Table 2, entries 2−5) that the isolated yields of normal amide **3** and abnormal amide **4a** were strongly dependent on the temperature: **4a** was the major product at 60 °C while **3** predominated at −78 °C. The highest yield of **4a** was obtained in refluxing chloroform with an excess of $Bu_3P{=}NCH_2Ph$ (Table 2, entry 1). On the other hand, the highest yield of **3** was achieved when the addition was carried out at −78 °C by dropwise addition of a small molar deficiency of this phosphazene (Table 2, entry 6). In acetonitrile, in agreement with these results, amide **3** predominated largely over **4a** at −35 °C (Table 2, entries 8 and 9) but not so much at rt (Table 2, entry 7). Again, the yield of **4a** was at a minimum at the lower temperature and when a dropwise addition of a small molar deficiency of phosphazene was used (Table 2, entry 10).

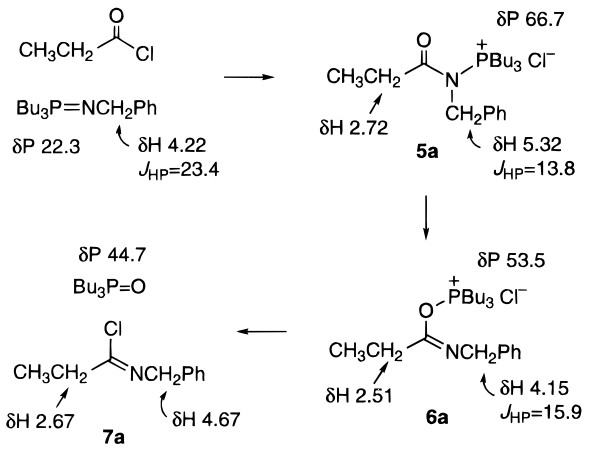
It should be mentioned that **4a**−**d** are stable compounds that could not be hydrolyzed to **3** by heating in water (with a few drops of acetonitrile to increase the solubility) or by refluxing in 2 M HCl for many hours. This means that the abnormal reaction may be very detrimental in practice, when the preparation of peptides and macrolactams[5] is sought.

From Tables 1 and 2, it is clear that the pathways toward **3** and **4** are in competition and that the chance of obtaining phosphorus-containing amides of type **4** is much lower when the reaction is performed in the more polar solvent of the three studied so far, when the reagents are mixed at low temperature, and/or by avoiding an excess of phosphazene during the reaction. In short, the undesired products can be largely avoided under appropriate conditions.

Detection of Reactive Intermediates. To gain insight into the mechanisms involved, a few of the reactions shown in Tables 1 and 2 were monitored by ^{31}P and ^{1}H NMR spectroscopy. First, the reaction of $Bu_3P{=}NCH_2Ph$ (freshly prepared in benzene followed by

(9) After 5 h of reaction (Table 1, entries 9−12), the crudes contained, in the elution order, 5−10% (w/w) of relatively nonpolar products (P-lacking byproducts, according to the NMR spectra), 20−30% of amide **3**, ca. 30% of Bu_3PO, 33−40% of phosphonium salt **4**, small amounts of phosphazenium salt, and very polar products (not eluted with 90:10 CH_2Cl_2−MeOH). At longer reaction times (entries 14 and 15): 5−10% of nonpolar products, ca. 45% of amide **3**, ca. 50% of Bu_3PO, ca. 40% of **4**, small amounts of phosphazenium salt, and no polar products at all.

Scheme 3



removal of the solvent in vacuo) with CH_3CH_2COCl was monitored at −20 °C in $CDCl_3$. In the proton-decoupled ^{31}P NMR spectrum, the singlet at δ 22.3 ($CDCl_3$ solution of the starting phosphazene) disappeared immediately on addition of a $CDCl_3$ solution, previously cooled at −20 °C as well, of the acid chloride (ca. 1 equiv), while an intense peak at δ 66.7 and a small peak at δ 53 was observed. The strong peak began to diminish, and the signal at ca. δ 53 grew slowly (in fact, there were two peaks, at 53.5 and 53.4, in variable ratios);[10] minor amounts of $Bu_3P{=}O$ (δ 44.7) were also noted. On warming the probe temperature to rt this series of consecutive reactions took place more rapidly, as the peak at δ 66.7 eventually disappeared, that at δ 53.5 diminished (but not so that at δ 53.4), and the area due to the $Bu_3P{=}O$ signal became the largest one. Taking also the analysis of the corresponding ^1H NMR spectra and a $^1H-^{31}P$ HETCOR experiment into account, the series of events may be explained as follows (see Scheme 3): the first intermediate detected at low temperature (**5a**) is converted, through a N-to-O migration of the phosphonium group, into **6a** (only one set of proton signals is seen), which in turn slowly gives $Bu_3P{=}O$ and imidoyl chloride **7a**.[11,12]

The reaction of $Bu_3P{=}NCH_2Ph$ with propanoyl 2,4,6-trichlorobenzoyl anhydride, $CH_3CH_2COOCOAr$ (Ar = 2,4,6-trichlorophenyl), was also investigated at −20 °C. The proton-decoupled ^{31}P NMR spectra looked like those of the above-mentioned reaction of $Bu_3P{=}NCH_2Ph$ with CH_3CH_2COCl, but differences were noted: (i) the signal that can be attributed to the *N*-phosphonium species of type **5** (**5b**) was much less intense; (ii) the *O*-phosphonium species of type **6** predominated; (iii) afterwards, the signal at δ 53 decreased and the signal at δ 44.7 due to $Bu_3P{=}O$ grew more rapidly than in the former experiment. This last fact indicates that intermediate $CH_3CH_2C(=NCH_2Ph)OPBu_3^+$ $ArCOO^-$ (**6b**) is converted into acyl imidate $CH_3CH_2C(=NCH_2Ph)OCOAr$ (**7b**) more readily than intermediate **6a** is converted into imidoyl chloride **7a**. Apparently, the aza-Wittig-like product **7b** is not formed directly either.

It can be seen that only phosphorus-containing intermediates of type **5** and **6** appear to have a half-life long enough to be detected under the above-mentioned conditions. The differences between using an acid chloride or an active mixed anhydride are few: at low temperature **5a** predominates for a long time in the former case while it is **6b** the most abundant species detected in the latter. However, the series of events are similar. This agrees with the fact that, in practice, provided that the reaction time is over 5 h (compare, e.g., entries 1 and 2 of Table 1), the desired amide (**1**) is obtained in similar yields.[13]

Reaction of $Bu_3P{=}NCH_2Ph$ with isobutyryl chloride, $(CH_3)_2CHCOCl$, was also monitored at −20 °C in $CDCl_3$. In the proton-decoupled ^{31}P NMR spectrum, it was observed that the singlet at δ 22.3 due to the starting phosphazene disappeared immediately on addition of ca. 1 equiv of the acid chloride, while a new signal at δ 66.7 appeared. Then, this signal diminished quite rapidly and new peaks grew at δ 53 and, more slowly, at δ 45 (see the supporting information). Essentially, the reaction sequence was identical to that shown in Scheme 3.

Also, the reaction of $Bu_3P{=}NCH_2Ph$ with isobutyryl 2,4,6-trichlorobenzoyl anhydride, $(CH_3)_2CHCOOCOAr$, was parallel to that of phosphazene and $CH_3CH_2COOCOAr$.

On the other hand, when the reaction of $Bu_3P{=}NCH_2Ph$ *with* $PhCH_2COCl$ was monitored by ^{31}P NMR in $CDCl_3$ at −20 °C as in the preceding cases, *significant differences were noted*. Besides two small signals at δ 69.5 and 67.5, a broad peak at δ 53.4 and another peak at δ 29.8 (which was confirmed independently to correspond to *C*-phosphonium salt **4a**, by addition of a sample of pure compound) appeared immediately upon mixing; the last signal did not increase upon time.[14] The reaction was repeated starting at −40 °C, but again a peak at ca. δ 30 (much smaller than in the previous experiment) was instantaneously observed; this signal did not increase at the expense of the large signal at δ 53.4 (nor probably of the smaller signals, although this turned out to be difficult to see by integration) when the sample was warmed. At −65 °C, **4a** was hardly noted; apart from the already mentioned signals at δ 69, 67, and 53, no other peaks (i.e., no other P-containing intermediates) were detected. On the other hand, when the reaction was carried out at 50 °C, the peak due to

(10) The ratio between these two peaks depended on propanoyl chloride purity (whether freshly distilled or not), on the time elapsed before registering the first spectrum, and on the addition order of the reagents and their relative excess.

(11) By adding a drop of water into the NMR tube and shaking, all the signals attributed to **5a**, **6a**, and **7a** disappeared, while the formation of the desired amide was clearly seen by ^1H NMR at the same time that the ^{31}P signal of Bu_3PO increased. Only a set of signals (δP at 53.4; double doublet at δH 4.15 and NH proton at δH 8.07) remained, which we confirmed to belong to small amounts of phosphazenium salt (much more stable to hydrolysis than *O*-phosphonium salts) by addition of an authentic sample of $PhCH_2NHPBu_3^+$ Cl^-, prepared independently. The percentage of this phosphazenium salt in the reaction mixture was estimated to be around 10% (by ^1H NMR).

(12) When trimethylphosphine derivative $Me_3P{=}NCH_2Ph$ (δCH_2-Ph 4.22, J_{HP} = 26.2 Hz; δMe 1.41, J_{HP} = 12.6 Hz), instead of $Bu_3P{=}NCH_2Ph$, was treated with CH_3CH_2COCl in $CDCl_3$, parallel results were noted by ^1H NMR: (i) instantaneous formation of $CH_3CH_2CON(PMe_3^+$ $Cl^-)CH_2Ph$ (δCH_2Ph 5.20, J_{HP} = 15.0 Hz; δMe 2.50, J_{HP} = 14.5 Hz); (ii) slow appearance of $CH_3CH_2C(=NCH_2Ph)OPMe_3^+$ Cl^- (δCH_2Ph 4.15, J_{HP} = 16.5 Hz; δMe 1.92, J_{HP} = 14.0 Hz); (iii) even slower appearance of $CH_3CH_2C(=NCH_2Ph)Cl$ (δCH_2Ph 4.68) and Me_3PO (δMe 1.49, J_{HP} = 12.6 Hz).

(13) On the other hand, if reactions between $Bu_3P{=}NCH_2Ph$ and CH_3CH_2COX are quenched with water at much shorter reaction times, when intermediates of type **5** may predominate, the amide yields are much lower (more polar products were mainly obtained).

(14) By adding of drop of water to this sample and shaking, the signal at δ 29.8 did not change either, those at δ 69.5 and 67.5 disappeared, and that at δ 53.4 diminished significantly (but not completely), while the signal due to Bu_3PO became the largest peak, as expected. The peak remaining at δ 53.4 can be attributed to a phosphazenium salt, as in the preceding case (see ref 11). In parallel experiments, the phosphazenium salt $PhCH_2NHPBu_3^+$ Cl^- was isolated in 12% yield by column chromatography. We believe that part of the phosphazenium salt arises from the presence of acid impurities in the (water-sensitive) acid chloride.

4a, was more intense than in previous experiments (see the supporting information).

By mixing $Bu_3P{=}NCH_2Ph$ and $PhCH_2COCl$ solutions, again in a 1:1 molar ratio, in a bath at −78 °C and allowing then the sample to warm to rt in the ^1H NMR probe, *N*-phosphonium species **8a**, *O*-phosphonium species **9a**, and imidoyl chloride **10a** (but not **4a**) were clearly seen. In a subsequent experiment, to an identical reaction mixture, at −78 °C as well, 0.5 molar equiv of phosphazene was further added before registering the spectra, in order to check if an excess of phosphazene when the reaction had already started showed any effect, but no significant changes could be noted in relation to the preceding experiment (**8a** and **9a** did not disappear much more rapidly; only small signals attributable to **4a** could be seen).[15] These experiments corroborate the fact that the abnormal *C*-phosphonium salts have less chance by carrying out the reactions at low temperature. They also point out that a relative excess of phosphazene, although it is essential at the beginning for the formation of **4**, is not important afterwards and that most **4a** does not come from the reaction of **8a** or **9a** with phosphazene.

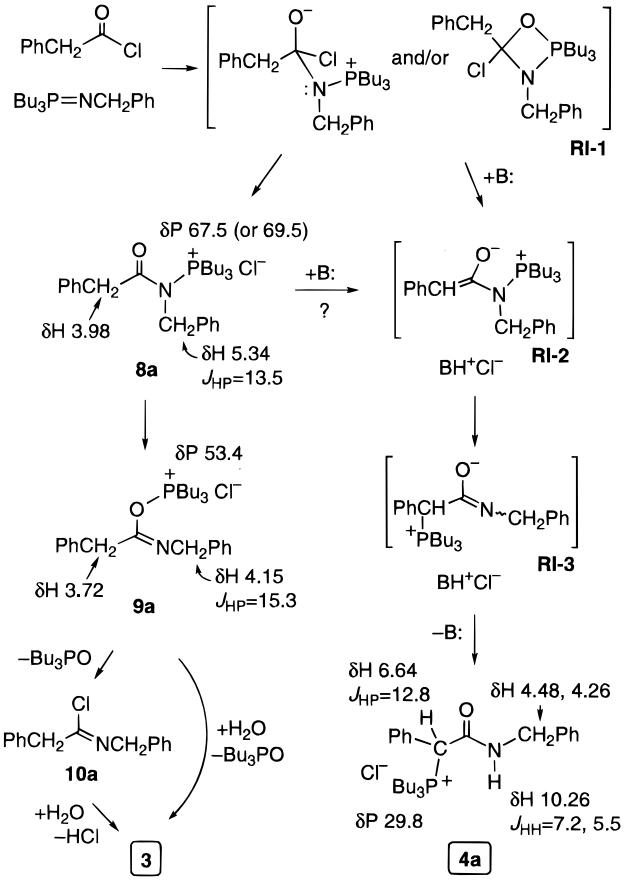
In short, it seems that most of the anomalous product **4a** does not arise from the other P-containing species that are seen by NMR, but it is mainly formed at the very beginning, from a previous, short-lived reactive intermediate. (This agrees with the fact that the isolated yields of **4a** are quite similar at very different reaction times, as shown in entries 9, 13, and 14 of Table 1.) Accordingly, a plausible mechanism for this reaction is suggested in Scheme 4, which shows that the precursor of **4a** could be one of the first reactive intermediates that can be reasonably written (see, e.g., **RI-1** in Scheme 4). In the presence of small amounts of a base such as a phosphazene, **RI-1** would lose HCl to afford **RI-2**, which would undergo an N-to-C phosphonium-group rearrangement to give **RI-3**.

Similar results were noted by treating $Bu_3P{=}NCH_2Ph$ with $PhCH_2COOCOAr$, even though as in the former experiments with mixed anhydrides the relative areas of the peaks along the reaction time were not the same as with acyl chlorides.

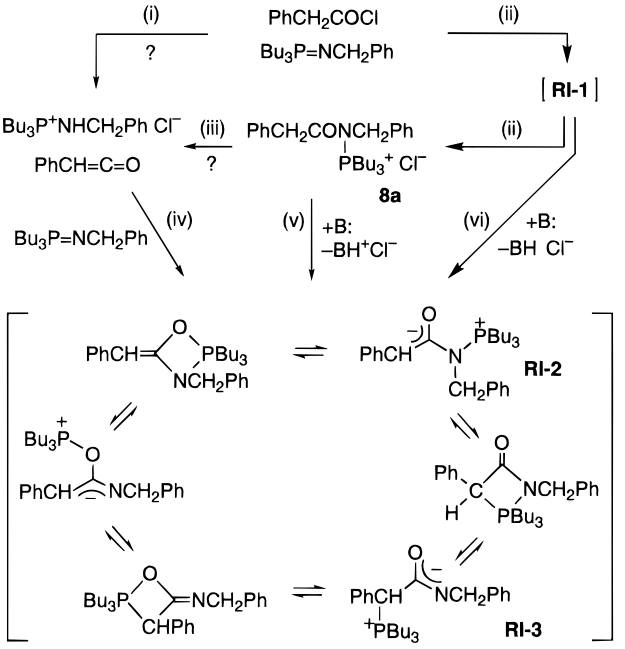
Comparison of Schemes 3 and 4 suggests that the main basis for the differences is the tendency of reactive intermediates arising from $PhCH_2COCl$ to lose HCl, which may be temporarily trapped by unreacted phosphazene present in the reaction flask. There is an obvious connection between this fact and the higher acidity of the $PhCH_2$ methylene protons as compared to the RCH_2 ones. That the pathway leading to **4a** becomes predominant above rt may be accounted for if the rate of the HCl elimination step is accelerated by rising the temperature much more than the formation of the *N*-phosphonium intermediate **8a**.

Finally, we would like to discuss another possible route to the abnormal products (**4a**−**d**). Since the tendency of arylacetic acid derivatives to give arylketenes in the presence of tertiary amines is higher than that of standard aliphatic acid derivatives,[16] the possibility that

Scheme 4



Scheme 5



the generation of phenylketene is the first step of an alternative pathway leading to **4a**−**d** should not be ruled out. This is shown in Scheme 5 (route i, or indirectly steps ii + iii), which summarizes only the possible pathways toward the abnormal product **4a**. Phenylketene would then react with another molecule of phosphazene (route iv) to give several species such as those suggested in the roundabout of Scheme 5 (stereoisomers not shown), outstanding among them is **RI-3**. This reactive inter-

(15) When these experiments were repeated with triphenylphosphazene $Ph_3P{=}NCH_2Ph$, instead of the tributylphosphazene, the spectra were analogous although the *O*-phosphonium species (that related with **9a**) was much less abundant.

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mediate, through a proton exchange with the protonated phosphazene, could obviously afford *C*-phosphonium salt **4a**.

However, there are some results that argue against a significant participation of phenylketene as a precursor of **4** when phosphazenes and acid derivatives are mixed in equimolar amounts. In several reactions of $PhCH_2COCl$ summarized in Tables 1 and 2, we isolated small amounts of a mixture of relatively nonpolar byproducts,[9] whose NMR spectra suggested that the well-known phenylketene dimers and trimers[16] had been formed. A similar mixture was rapidly and quantitatively formed when $PhCH_2COCl$ was treated with DMAP (but not so with the less basic and nucleophilic 2,6-lutidine) in $CDCl_3$ at −20 °C; addition of 1.1 equiv of $Bu_3P{=}NCH_2Ph$ within 5 min did not give **3** and/or **4a** at all, even after 5 h at rt, but a complex mixture of relatively nonpolar products (apparently, phenylketene dimers as well as their reaction products with phosphazene; dimerization is so rapid that phosphazene is unable to trap substantial amounts of monomer under these conditions). When $PhCH_2COCl$ was added to a well-stirred mixture of DMAP (1 equiv) and $Bu_3P{=}NCH_2Ph$ (1 equiv), as in entry 14 of Table 1 but in the presence of DMAP, we obtained ca. 30% (w/w) of relatively nonpolar byproducts, 28% of **3**, and 29% of **4a**. Thus, under conditions that may favor the formation of phenylketene the yield of both **3** and **4a** decreased. It seems that those substrate molecules that react first with DMAP—those that thereafter may be converted into phenylketene through this route—do not enter into the pathway leading to **3** and/or **4a**. On the other hand, when $PhCH_2COCl$ was added to a well-stirred mixture of 2,6-lutidine (1 equiv) and $Bu_3P{=}NCH_2Ph$ (1 equiv), we isolated ca. 5% of nonpolar byproducts, 31% of **3**, and 49% of **4a**. Thus, the presence of a sterically hindered pyridine such as 2,6-lutidine did not increase the percentages of phenylketene-derived byproducts but increased the yield of **4a** at the expense of **3**, in the same way that an excess of $Bu_3P{=}NCH_2Ph$ did (i.e., acting as the base, B:, shown in Schemes 4 and 5). We interpret that, in the reaction of $PhCH_2COCl$ with phosphazenes in a 1:1 molar ratio, phenylketene is usually a minor product, as routes i and iii (Scheme 5) are not important in relation to others; it is expected that phenylketene reacts instantaneously and unselectively with any nucleophile present in the medium (phenylketene precursor, remaining phosphazene, etc.) to afford dimers, P-containing intermediates, etc., but, as it is generated in relatively small amounts, most **3** and **4a** do not arise from it.

Conclusions

Phosphazenes react similarly with acid chlorides and mixed anhydrides to give almost identical yields of standard carboxamides after the workup. Closely related intermediates are detected by ^{31}P and ^{1}H NMR at low temperature, although some differences have been noted in the relative areas of the NMR signals that indicate that the counterions (Cl^-, $ArCOO^-$) may also play a role in the reaction course.

Trialkylphosphazenes and triphenylphosphazenes react similarly with carboxyl-activated derivatives, although amide yields are systematically better with the former.

Phenylacetic acid derivatives tend to give anomalous products **4a**−**d** (involving a N-to-C transfer of the PR_3^+ group), especially when there is a relative excess of phosphazene. However, we have shown that **4a** is formed only in small amounts when the reaction is carried out in the reverse mode (by dropwise addition of the phosphazene to the $PhCH_2COCl$ solution), by mixing the substrate and reagent at low temperature, and in acetonitrile.

In general, $Bu_3P{=}NCH_2Ph$ reacts firstly and chiefly as a nucleophile, with attack at the COX carbon atom of RR′CHCOX to give $RR'CHCON(PBu_3^+\ X^-)CH_2Ph$, rather than as a base. However, for substrates $PhCH_2COX$ (with a relatively acid α-CH proton, which can give intermediates with a double bond conjugated with the aromatic ring), the presence of a relative excess of phosphazene in the medium catalyzes the anomalous reaction, which begins with an elimination reaction. Elimination of HX may occur from $PhCH_2COX$ (Scheme 5, route i), from a short-lived reactive intermediate such as **RI-1** (route vi) and/or from *N*-phosphonium species such as **8a** (route v). We suggest that most HX is lost from **RI-1**. The difference is subtle—it concerns only the timing of the HX elimination—but agrees better with the available experimental results.

Experimental Section

Melting points are uncorrected. Crude products were purified by column cromatography on silica gel of 230−400 mesh (flash chromatography). ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were obtained in $CDCl_3$ at 200 and 50.3 MHz, respectively; chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. Variable-temperature ^{31}P and ^{1}H NMR spectra were recorded in $CDCl_3$ at 121.4 MHz (with respect to an external standard of 85% H_3PO_4) and 300 MHz, respectively. Infrared spectra were obtained in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). All the solvents were distilled from an appropriate drying agent and stored under nitrogen atmosphere. All the reactions were carried out under an atmosphere of nitrogen or argon, using dry glassware.

Phosphazene Preparation. To a stirred solution of benzyl azide (133 mg, 1.0 mmol) in benzene (5 mL) was added tributylphosphine (250 μL, 202 mg, 1.0 mmol) via syringe. The mixture was stirred for 2 h at rt, and the product was used without purification.

Reaction of Phosphazenes with Acyl Chlorides. Typical Procedure. To a stirred solution of (*N*-benzyl)tributylphosphazene [*N*-(tributylphosphoranylidene)benzylamine] (307 mg, 1.0 mmol), in benzene (5 mL) cooled at 5 °C, under nitrogen, was added phenylacetyl chloride (130 μL, 155 mg, 1.0 mmol) in benzene (1 mL). The reaction mixture was allowed to warm to rt and stirred for 5 h. The solvent was removed in vacuo (procedure A), and the residue was separated by chromatography on silica gel (95:5 CH_2Cl_2−MeOH) to afford *N*-benzylphenylacetamide (**3**) (68 mg, 30%) and then [α-(*N*-benzylcarbamoyl)]-benzyltributylphosphonium chloride (**4a**) (168 mg, 36%).[9] Alternatively (procedure B), the reaction mixture was poured into a separatory funnel containing an excess of CH_2Cl_2 and was washed with water; drying of the organic layer, evaporation of the solvent, and separation of the residue by chromatography as above afforded practically identical results.

Reaction of Phosphazenes with Mixed Anhydrides. Typical Procedure. To a stirred solution of (*N*-benzyl)-tributylphosphazene (307 mg, 1.0 mmol), in benzene (5 mL) cooled at 5 °C, under nitrogen, was added a solution of phenylacetic 2,4,6-trichorobenzoic anhydride (343 mg, 1.0 mmol), prepared according to the method of Yamaguchi et al.,[17] in benzene (1 mL). The reaction mixture was allowed to warm to rt and stirred for 5 h. Separation of the crude product following any of the two above-mentioned procedures afforded **3** (55 mg,

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24%) and [α-(*N*-benzylcarbamoyl)]benzyltributylphosphonium 2,4,6-trichlorobenzoate (**4b**) (258 mg, 40%).

Yields of the amides and *C*-phosphonium salts obtained in every case are summarized in Table 1. Physical and spectroscopical data are as follows:

***N*-Benzylpropionamide [*N*-(phenylmethyl)propanamide, 1]:** mp 50.4−52.1 °C (lit.[18] mp 52−53 °C); ^{1}H NMR δ 7.31−7.26 (5 H, m), 5.78 (1 H, br s), 4.44 (2 H, d, J = 5.8), 2.25 (2 H, q, J = 7.7), 1.18 (3 H, t, J = 7.7); ^{13}C NMR δ 174.4, 138.4, 128.7, 127.8, 127.5, 43.6, 29.7, 9.9; IR 3300, 1650.

***N*-Benzylisobutyramide [2-methyl-*N*-(phenylmethyl)-propanamide, 2]:** mp 84.1−86.3 °C (lit.[19] mp 86.7−87.5 °C); ^{1}H NMR δ 7.32−7.27 (5 H, m), 5.81 (1 H, br s), 4.42 (2 H, d, J = 5.7), 2.39 (1 H, hept, J = 6.9), 1.17 (6 H, d, J = 6.9); ^{13}C NMR δ 176.8, 138.5, 128.6, 127.7, 127.4, 43.4, 35.6, 19.7; IR 3300, 1650.

***N*-Benzylphenylacetamide [*N*-(phenylmethyl)benzeneacetamide, 3]:** mp 102.8−103.1 °C (lit.[20] mp 104 °C); ^{1}H NMR δ 7.31−7.19 (10 H, m), 5.82 (1 H, br s), 4.40 (2 H, d, J = 5.8), 3.61 (2 H, s); ^{13}C NMR δ 170.9, 138.0, 134.7, 129.4, 129.0, 128.6, 127.4, 127.2, 126.8, 43.7, 43.5; IR 3300, 1640.

[α-(*N*-Benzylcarbamoyl)]benzyltributylphosphonium chloride (4a): mp 138.4−140.1 °C; ^{1}H NMR δ 10.26 (1 H, dd, J = 5.5, 7.2), 7.8−7.7 (2 H, m), 7.3−7.2 (8 H, m), 6.64 (1 H, d, J_{HP} = 12.8), 4.48 (1 H, dd, J = 7.2, 14.6), 4.26 (1 H, dd, J = 5.5, 14.6), 2.33−2.02 (6 H, m), 1.44−1.34 (12 H, m), 0.86 (9 H, t, J = 7.3); ^{13}C NMR δ 166.2 (J_{CP} = 1.8), 138.2, 131.2 (J_{CP} = 5.8), 129.4 (J_{CP} = 3.4), 128.9 (J_{CP} = 2.5), 128.6 (J_{CP} = 6.5), 127.9, 127.5, 127.2, 44.7 (J_{CP} = 48.2), 43.7, 27.5 (J_{CP} = 64.8), 23.4 (J_{CP} = 25.9), 18.4 (J_{CP} = 45.4), 13.3; ^{31}P NMR δ 29.8; IR 3190, 1665. Anal. Calcd for $C_{27}H_{41}ClNOP$: C, 70.18; H, 8.94; N, 3.03. Found: C, 69.79; H, 8.63; N, 2.78.

[α-(*N*-Benzylcarbamoyl)]benzyltributylphosphonium 2,4,6-trichlorobenzoate (4b): mp 62.3−65.6 °C; ^{1}H NMR δ 10.34 (1 H, dd, J = 5.3, 7.1), 7.8−7.7 (2 H, m), 7.3−7.2 (8 H, m), 7.23 (2 H, s), 6.65 (1 H, d, J_{HP} = 12.6), 4.49 (1 H, dd, J = 7.1, 14.8), 4.27 (1 H, dd, J = 5.3, 14.8), 2.30−2.05 (6 H, m), 1.45−1.33 (12 H, m), 0.87 (9 H, t, J = 7.1); ^{13}C NMR δ 169.1, 166.3 (J_{CP} = 1.9), 138.3, 138.2, 135.0, 134.2, 131.3 (J_{CP} = 6.0), 129.4 (J_{CP} = 3.2), 129.0 (J_{CP} = 2.7), 128.7 (J_{CP} = 6.6), 127.8, 127.6, 127.3, 127.1, 44.5 (J_{CP} = 48.9), 43.6, 27.4 (J_{CP} = 64.8), 23.6 (J_{CP} = 25.7), 18.4 (J_{CP} = 45.4), 13.4; ^{31}P NMR δ 29.8; IR 3195, 1670, 1620. Anal. Calcd for $C_{34}H_{43}Cl_3NO_3P$: C, 62.72; H, 6.66; N, 2.15. Found: C, 62.36; H, 6.42; N, 2.27.

[α-(*N*-Benzylcarbamoyl)]benzyltriphenylphosphonium chloride (4c): mp 206.8−208.2 °C (lit.[1] mp 207−208 °C). Spectroscopical data (^{1}H, ^{13}C, and ^{31}P NMR) agree with those reported by Molina et al. (compound **5i**).[1]

[α-(*N*-Benzylcarbamoyl)]benzyltriphenylphosphonium 2,4,6-trichlorobenzoate (4d): mp 117.5−119.1 °C; ^{1}H NMR δ 10.48 (1 H, dd, J = 5.2, 7.2), 8.10 (1 H, d, J_{HP} = 12.5), 7.8−7.2 (25 H, m), 7.36 (2 H, s), 4.44 (1 H, dd, J = 7.2, 15.0), 4.17 (1 H, dd, J = 5.2, 15.0); ^{13}C NMR δ 168.4, 166.1 (J_{CP} = 1.7), 138.4, 137.9, 135.0, 134.7 (J_{CP} = 9.5), 134.4 (J_{CP} = 2.3), 134.1, 131.1 (J_{CP} = 5.9), 129.6 (J_{CP} = 12.6), 129.0 (J_{CP} = 3.1), 128.6 (J_{CP}= 2.5), 128.5 (J_{CP} = 6.3), 128.2, 127.7, 127.2, 126.7, 117.9 (J_{CP} = 84.9), 47.7 (J_{CP} = 51.1), 43.5; ^{31}P NMR δ 20.6; IR 3200, 1675, 1620. Anal. Calcd for $C_{40}H_{31}Cl_3NO_3P$: C, 67.57; H, 4.39; N, 1.97. Found: C, 67.29; H, 4.56; N, 2.08.

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Supporting Information Available: Representative proton-decoupled ^{31}P NMR spectra of the reactions of $Bu_3P{=}NCH_2$-Ph with isobutyryl chloride and with phenylacetyl chloride (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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