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NEW SYNTHETIC "TRICKS".
TRIPHENYLPHOSPHINE-MEDIATED AMIDE FORMATION FROM CARBOXYLIC ACIDS AND AZIDES

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Summary.- Equimolar amounts of carboxylic acids, aryl or alkyl azides, and Ph_3P in refluxing benzene (hexane, toluene) afford amides in good yields. Insolubility of zwitterions $Ph_3\overset{+}{P}-NH(CH_2)_nCOO^-$, arising from ω-azido acids and Ph_3P, limits the utilization of the method for lactame formation.

A plethora of phosphorus derivatives have been used to obtain amides from carboxylic acids and amines under mild conditions: Ph_3P plus CCl_4, $Ph_3P(OR)_2$, $R_2P(=O)X$, polystyryldiphenylphosphine plus CCl_4, Ph_3P plus py-S-S-py or other disulphides, Palomo's 2-oxazolidone derivative, Bu_3P plus o-$C_6H_4(NO_2)X$, etc.[1] Some of them have found application in the peptide field[1,2] as well as in macrolactonisation reactions.[3] Apparently, all these reagents activate the carboxyl group against the attack of the amines by generating in situ, by means of different P(V) species, either the corresponding acyl halide/pseudohalide or the acyloxyphosphonium salts ($R-COO-\overset{+}{P}R_3$ or related intermediates); these react with amines, in the presence of a base, to give the expected carboxamides.

An alternative preparation of carboxamides from carboxylic acids could be based on the previous modification/activation of the amino fragment, as indicated below. In fact, we realized that the one-pot reaction of R-COOH, N_3-R', and Ph_3P could afford R-CONH-R', under esentially non-acidic conditions and/or without employing

$$R-COOH + Ph_3P{=}N-R' \longrightarrow R-CONH-R' + Ph_3P{=}O$$

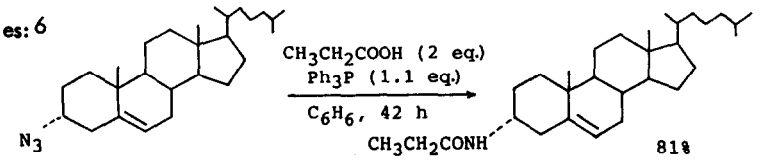
expensive additional reagents, by taking advantage of the Staudinger reaction (formation of phosphazenes from azides and phosphines).[4] To the best of our knowledge, this application of the Staudinger reaction has been never reported. Since the most confident way of introducing an amino group into a carbon backbone, especially in the field of natural products, is through the substitution of azide anion for halogen-like substituents, followed by reduction of the azide group, the method here described can be used to obtain directly amino-protected derivatives, avoiding the azide reduction and carboxyl activation steps.

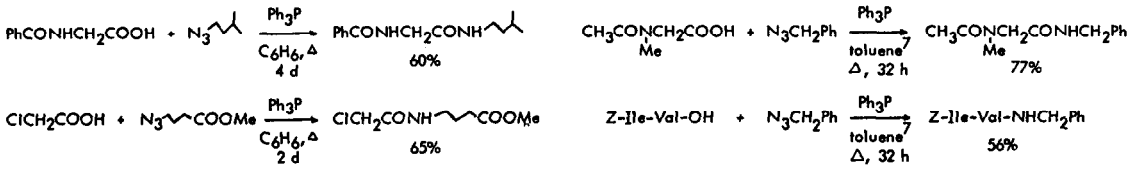
From the practical viewpoint, 1.0-1.2 mmols of carboxylic acid, 1.0 mmols of azide, and 1.0 mmols of Ph_3P were heated in ca. 10 ml of anhydrous benzene[5] for several hours, under nitrogen, the reaction being monitored by TLC. After washing with diluted base, elimination of the solvent yielded generally only the desired amide and Ph_3PO, which were separated by column chromatography on silica gel.

As shown in the examples below, the reaction works well either using aliphatic or aromatic acids and aliphatic (primary, secundary) or aromatic azides.

	N_3	N_3CH_2Ph	N_3Ph	N_3
CH_3CH_2COOH	CH_3CH_2CONH 88%, 24 h	$CH_3CH_2CONHCH_2Ph$ 95%, 24 h	$CH_3CH_2CONHPh$ 96%, 60 h	CH_3CH_2CONH 95%, 12 h
PhCOOH	PhCONH 75%, 48 h	$PhCONHCH_2Ph$ 78%, 48 h	PhCONHPh 96%, 5 d	PhCONH 85%, 12 h

Additional examples:[6]





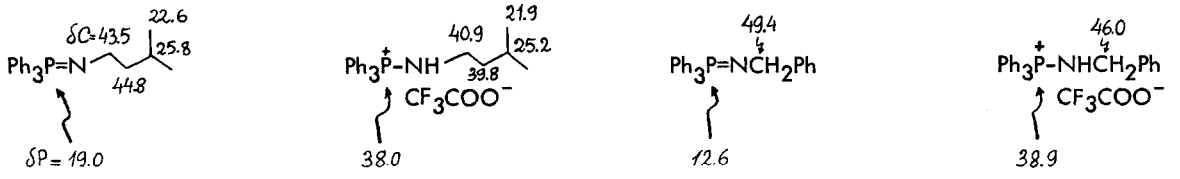
Some other data and trial experiments are worthy of mention:

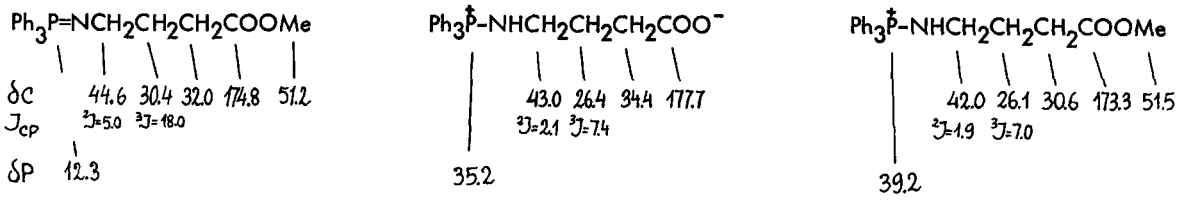
a) Esters such as butyl acetate and ethyl acetate did not react with azides and Ph_3P under identical conditions to those employed with acids, i.e. phosphazenes were recovered at the end.

b) TFA protonates the phosphazenes as expected (see NMR data, in $CDCl_3$ with $\delta^{31}P$ in ppm downfield to ext. 85% H_3PO_4 and $\delta^{13}C$ to int. TMS, summarized below), but trifluoroacetylamines were not obtained.

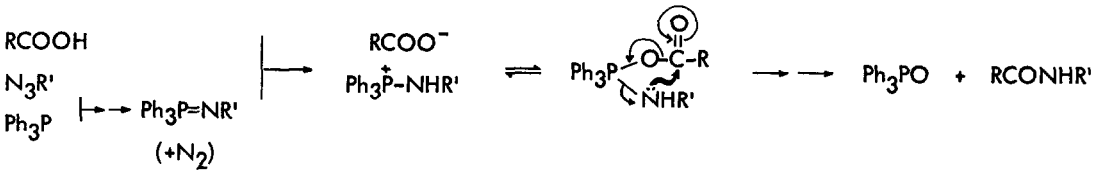
c) Even normal carboxylic acids protonate N-alkylphosphimines. By the way, $Ph_3P{=}NBu$ is a stronger base than NH_2Bu as shown by NMR: when increasing amounts of KOH/CD_3OH were added to an equimolar mixture of $Ph_3\overset{+}{P}NHBu\ Br^-$ and $BuNH_3^+\ Br^-$ in CD_3OH, the latter was completely deprotonated first.[8]

d) When ω-azido acids were treated with 1 eq. of Ph_3P in benzene (even at r. t.), white crystalline precipitates were formed. IR spectra of the solids and NMR spectra of those soluble in $CDCl_3$ indicated that they possessed zwitterionic structures $Ph_3\overset{+}{P}\text{-}NH(CH_2)_nCOO^-$. Under the usual conditions here reported, lactames could not be obtained: the samples were entirely insoluble in refluxing benzene, hexane, etc., and are recovered unchanged. Nevertheless, in refluxing pyridine for 25 h, $Ph_3\overset{+}{P}\text{-}NH(CH_2)_3COO^-$ (but not long-chain zwitterions) afforded in 95% yield the expected lactame (2-pyrrolidone).

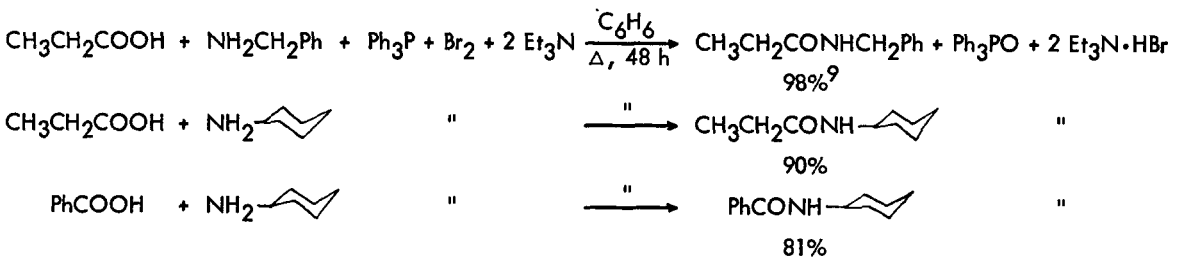




All these facts point out that a plausible mechanism for the reaction could be summarized as follows:



It may be thought that the methods of amide formation based on the acyloxyphosphonium intermediates go also through species like $Ph_3P(OCOR)(NHR)$. It would mean that, to obtain carboxamides, the order of addition of the acid and the amine to the P(V) species would not matter; indeed, the following experiments show that, from a practical viewpoint—being either the phosphazene or the phosphonium salt formed first—, the couplings of acids and amines can be managed in one-pot reactions (mixing all together) with simple reagents:



How to circumvent the problems posed by ω-azido acids to obtain lactames under mild conditions (as a matter of fact, such problems do not differ from those posed by ω-amino acids to the common coupling agents) and whether other phosphines could work better than Ph_3P is going to be studied in our lab.

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REFERENCES AND NOTES

1.- As general references, see: "Compendium of Organic Synthetic Methods", Vols. 1-5, Wiley, New York, 1971-1984; "Polymer-supported Reactions in Organic Synthesis", P. Hodge and D. C. Sherrington, Eds., Wiley, Chichester, 1980. See also C. R. Harrison et al., J. Org. Chem., 48, 3721 (1983), and references therein.

2.- T. Mukaiyama, Angew. Chem. Int. Ed., 15, 94 (1976).

3.- General references: K. C. Nicolaou, Tetrahedron, 33, 683 (1977); T. G. Back, Tetrahedron, 33, 3041 (1977); S. Masamune, G. S. Bates, and J. W. Corcoran, Angew. Chem. Int. Ed., 16, 585 (1977). More recent papers: E. J. Corey et al., J. Am. Chem. Soc., 104, 6818 (1982); T. Kaiho, S. Masamune, and T. Toyoda, J. Org. Chem., 47, 1612 (1982).

4.- Review: Yu. G. Gololobov, I. N. Zhmurova, and L. F. Kasukhin, Tetrahedron, 37, 437 (1981).

5.- In benzene, diethyl ether, dichloromethane, etc. at room temperature, phosphazenes were rapidly formed in most cases, but the coupling between acids and phosphazenes was not observed. The reaction of propionic acid and benzyl azide (quantitative conversion after 24 h in refluxing benzene) was also carried out in refluxing hexane for 24 h (78%), refluxing diethyl ether (only 20% under the same conditions), refluxing dichloromethane (no reaction at all), and refluxing acetonitrile (61% of transformation); thus, heating above 60 °C and solvents of low dipolar moment seem advisable.

6.- α-Cholesteryl azide (mp, $[\alpha]_D$, and ^{1}H NMR spectrum in agreement with those reported by L. A. Freiberg, J. Org. Chem., 30, 2476 (1965)). All over the paper the yields have not been optimized. In all cases, the amides have been characterized by their mp's and IR and NMR spectra.

7.- After 2 days in refluxing benzene, the phosphazene could be recovered almost quantitatively. Although it was not our purpose to evaluate the possible utility of the method in peptide synthesis, since it is unreasonable to use α-azido acids instead of the natural α-amino acids, we brought about two set of experiments with N-acetylsarcosine and Z-Ile-Ile-OH as the acids and N_3CH_2COOEt as the azide in both cases. In refluxing benzene the yields of the coupling products ($CH_3CONMeCH_2CONHCH_2COOEt$, 36%; Z-Ile-Ile-Gly-OEt, 20%) after 2-3 days were too low to deserve more attention. In refluxing toluene, decomposition of phosphazene—already observed in benzene and in independent experiments—was too much rapid, so that those carboxylic acids had no "opportunity" to react with it.

8.- N-Arylphosphimines ($Ph_3P{=}NAr$) are also more basic than the corresponding anilines.[4]

9.- To improve the yield, 1.2-1.3 eq. of propionic acid and 2.2-2.3 eq. of Et_3N were used indeed.

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