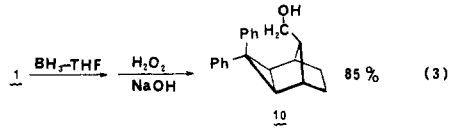
doublet (J = 8 Hz) at δ 6.30 and 6.50, respectively, together with the absence of the cyclopropyl proton singlet (H-2,4) in the δ 1.5–1.8 region characteristic of the unrearranged parent system.[8] Analogous LRAMERO rearrangement was observed in the additions of HBr, CF_3COOD, $HOAc/HClO_4$, and Br_2.

Contrariwise, hydroboration–oxidation of **1** (eq 3) led



to unrearranged syn alcohol **10**, mp 135–137 °C ($C_{21}H_{22}O$: calcd C, 86.84; H, 7.65. Found: C, 86.69; H, 7.61). This alcohol was characterized by the H-2,4 singlet resonance at δ 1.65. The syn epimeric configuration has been presently assigned to **10** because the δ CH_2O resonance is quite upfield (δ 2.2, d, J = 6 Hz), as would be expected from shielding caused by the proximate phenyl group.

Radical additions to **1** thus far have led to complex mixtures and work is continuing on this aspect, as well as others, of the chemistry of **1**. Even at this early stage, however, it is clear that **1** undergoes LRAMERO rearrangement extraordinarily rapidly whenever cationic character develops at C-8, whereas no skeletal change attends nonpolar addition. Moreover, rearrangement or its absence is easily detected by spectral (particularly ^1H NMR) analysis. The remarkably clean and efficient course of the additions recommends the use of **1** as a mechanistic probe.

Registry No. **1**, 96791-93-4; **3**, 694-70-2; **4**, 96791-94-5; **5**, 96791-95-6; **6**, 96791-96-7; **7**, 29302-44-1; **8** (isomer 1), 96791-97-8; **8** (isomer 2), 96791-98-9; **9**, 96791-99-0; **10**, 96792-00-6.

(8) Full spectral characterization of all products will be given later in a complete paper.

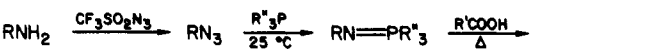
James W. Wilt,* Michael D. Tufano
Department of Chemistry
Loyola University of Chicago
Chicago, Illinois 60626
Received March 19, 1985

A New Synthesis of Peptides from Azides and Unactivated Carboxylic Acids

Summary: The title reaction, in which an azido compound is treated first with a tertiary phosphine, followed by warming in an inert solvent with a carboxylic acid, has been used to synthesize a number of small peptides and appears from mechanistic studies to proceed via a pentacoordinate phosphorus intermediate.

Sir: We describe a new method of amide bond formation involving treatment of an azido compound with a tertiary phosphine followed by heating in the presence of a carboxylic acid and application of this sequence to the synthesis of a series of small peptides. This reaction complements the recently reported synthesis[1] of optically pure azido carboxylic acids, esters, and peptides from their respective amino precursors; together they represent a novel method of peptide synthesis (eq 1) which is based on very different chemistry from that usually employed.

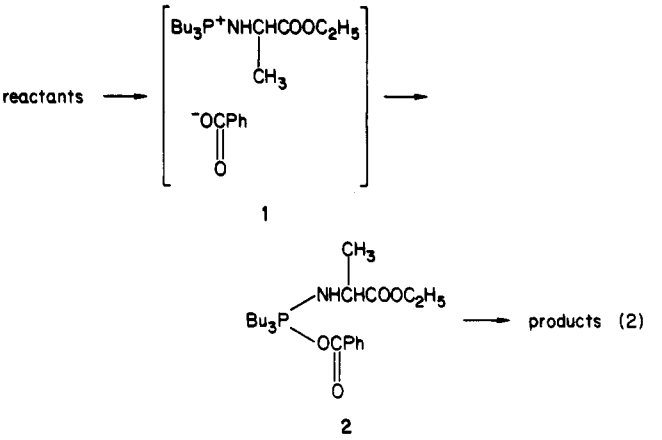
(1) Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173–5176.



R'CONHR + R"$_3$P=O (1)

It has been known for some time[2] that organic azides react under very mild conditions with trivalent phosphines to give iminophosphoranes. The latter compounds undergo Wittig-type reactions with aldehydes,[3] ketones,[4] ketenes,[5] and other compounds containing polarizable oxygen or sulfur.[6] By analogy with these reactions, a free carboxylic acid would be expected to react with an iminophosphorane to provide an amide as product. The reaction was first reported by Horner and Gross[7] in 1955; since the original version of this article was submitted, Garcia et al.[8] have reported the synthesis of a variety of simple amides using this reaction. The reported conditions employed high temperatures and long reaction times; we felt that it might be possible to devise a more practical version of this reaction suitable for the synthesis of peptides.

Initial studies in our laboratory verified that when a carboxylic acid is allowed to react with an iminophosphorane derived from an α-amino ester, an acylated amino acid (ester) is obtained. Benzoyl-DL-alanine ethyl ester was obtained in this way in 73% yield from ethyl DL-2-azidopropanoate and benzoic acid; the reaction employed tributylphosphine and the coupling step was carried out in refluxing toluene. Phosphorus NMR studies of this reaction reveal that an initial proton transfer to form salt **1** (eq 2) takes place upon mixing solutions of the reactants.



Upon heating, formation of products occurs concomitantly with loss of **1**, with no additional intermediates observed. The reaction appears to be much more sluggish in polar solvents such as dioxane or ethyl acetate; this is consistent with the formation of an uncharged intermediate (such as **2**) in the rate-determining step.

The intermediacy of **2** would be highly desirable for two reasons: first, this intermediate is not an especially "activated" carboxyl derivative; the driving force for amide bond formation would lie in the intramolecularity of the acyl transfer and the expulsion of the phosphine oxide rather than in the intrinsic reactivity of the acylating agent. The latter serves as the basis for most other peptide coupling methods but is often responsible for oxazolone-me-

(2) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 619–635.
(3) Schmidbaur, H.; Jonas, G. *Chem. Ber.* **1967**, *100*, 1120–1128.
(4) Wiberg, N.; Schwenk, G.; Schmid, K. H. *Chem. Ber.* **1972**, *105*, 1209–1215.
(5) Shaw, R. A.; Fitzsimmons, B. W.; Smith, B. D. *Chem. Rev.* **1962**, *62*, 247–281.
(6) Wabel, E.; Mucklejohn, S. A. *Phosphorus Sulfur* **1981**, *9*, 235–264.
(7) Horner, L.; Gross, A. *Liebigs Ann. Chem.* **1955**, *591*, 117–134.
(8) Garcia, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841–4844.

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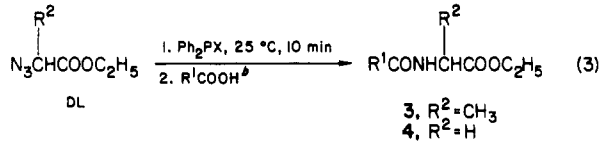
Table I. Peptides Prepared by New Coupling Method (Eq 3)[a]



(3)

compd	X	R^1CO_2H	yield,[c] %	mp, °C	recryst solvent	ref
3a	Ph	Boc-Gly-OH	50	87–89	EtOAc/hexane	
3b	Ph	Bz-Gly-OH	65	121–123	EtOAc	11
3c	Ph	Z-Gly-OH	42	51–53	EtOAc/cyclohexane	12
3d[d]	Ph	L-$N_3CH(i\text{-}Bu)CO_2H$	55	oil		
3e[d]	Ph	Z-DL-Ala-OH	69	74–76	EtOAc	13
3f	Ph	Z-Gly-Gly-OH	38	168–171 dec	MeOH[e]	14
3g[d]	OEt	Z-L-Val-OH	70	79–81	EtOAc/petroleum ether	
4a[f]	OEt	Z-Gly-L-Phe-OH	70	112–114	EtOAc	15
4b	OEt	Z-Gly-OH	72.5	80–81	EtOAc/petroleum ether	16

[a] All products given in the table were prepared also via the carbodiimide method;[10] the products resulting from the two methods were in all cases shown to be identical by their TLC behavior, melting points and mixed melting points, and IR and NMR spectra. [b] Coupling was carried out overnight in toluene at 70–80 °C, except in the case of products **3g** and **4**, in which a temperature of 50–60 °C was employed. [c] Yields are isolated and based on starting azido ester; intermediate iminophosphoranes were not isolated. [d] Product was obtained as a mixture of diastereomers. [e] After removal of toluene from the crude reaction mixture, the residual oil was stirred in chloroform upon which the crude tripeptide precipitated from solution. [f] This reaction was also carried out by using 2,2,4,4-tetramethyl-1-phenylphosphetane as the phosphine component, affording an identical yield of product.

diated racemization from which many such methods suffer. An additional point of interest concerning the intermediacy of **2** is the fact that it would lead to an intramolecular amide bond forming reaction: consequently the coupling would be expected to exhibit little sensitivity to steric effects, which are often pronounced in "active ester" couplings[9] and would possibly prove highly efficient in the coupling of large peptides where molecular weight and solubility problems often limit the effective concentration of reactants.

We therefore report the application of this reaction to the synthesis of a series of peptide derivatives (Table I) and the results of additional studies on the scope and mechanism of this reaction.

In a typical coupling reaction, 7 mmol of triphenylphosphine or ethyl diphenylphosphinite was dissolved in 10 mL of dry toluene. To the stirred solution was added 7 mmol of the azido compound; gas evolution was observed to cease after 15 min, and the solution was stirred for an additional 30 min. Thereupon, 1.2 equiv (8.4 mmol) of the desired carboxylic acid component was added and the mixture was heated to 60–70 °C for 8 h. At the end of this time the solution was cooled, placed in a separatory funnel, and washed with 10 mL of 2 N HCl, 10 mL of saturated aqueous $NaHCO_3$, and finally with water until washings were neutral to litmus. The workup procedure depended upon the nature of the phosphine component employed. In the case of triphenylphosphine, the oxide was removed by evaporating the organic phase after the wash steps and stirring the residue in 15 mL of anhydrous ether; after removing the bulk of the phosphine oxide by filtration, the solution was passed through a short silica gel column and evaporated to dryness. The use of ethyl diphenylphosphinite as the phosphine component proved advantageous, as the HCl treatment hydrolyzes its oxide to diphenylphosphinic acid, which is subsequently extracted out of the mixture; the pure product was isolated simply by removal of solvent in vacuo. In most cases, the product was further purified by recrystallization from an appropriate solvent.

It should be pointed out that the azido function can serve as a protected amino group provided that strongly acidic or basic workup conditions are avoided, as illustrated by product **3d**. This suggests that the process could serve as the basis for a repetitive method of peptide synthesis.

A number of additional observations bear directly upon the mechanistic questions raised above. These are summarized in the paragraphs that follow. The studies of Garcia et al.[8] provide additional evidence consistent with the proposed mechanism.

It is well established that both electronegative substituents and incorporation into a small ring facilitate valence shell expansion in phosphorus; it was therefore expected, and in fact found, that iminophosphoranes derived from both ethyl diphenylphosphinite and 2,2,4,4-tetramethyl-1-phenylphosphetane would couple appreciably with carboxylic acids at room temperature, in contrast to the case with triphenyl- or tributylphosphine. Although byproducts apparently resulting from ring cleavage were formed in the phosphetane case, ethyl diphenylphosphinite gave a smooth and clean coupling, which, taken along with ease of workup described above, made it the reagent of choice for the couplings.

Further support for the proposed mechanism derives from our observation that when a model coupling reaction (Ph_2POEt, ethyl 2-azidopropionate, benzoic acid) was carried out (2 trials) in the presence of benzylamine, a product mixture was obtained (crude yield approximately 80%) which contained only 4.5–8.3% of *N*-benzylbenzamide relative to benzoylalanine ethyl ester, as determined by quantitative HPLC calibrated by using authentic samples of the two products. This essentially rules out mechanisms invoking a highly activated acyl derivative such as an (acyloxy)phosphonium ion and strongly supports our contention that amide bond formation is intramolecular.

The method was subjected to the Anderson racemization test[15] utilizing optically pure Z-Gly-L-Phe-OH along with the iminophosphorane derived from ethyl azidoacetate and Ph_2POEt. This provided a product from which no Z-

(9) Kemp, D. S.; Choong, S.-L. H.; Pekaar, J. *J. Org. Chem.* **1974**, *39*, 3841–3846.

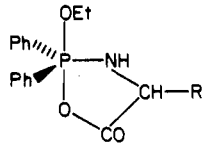
(10) Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798.
(11) Curtius, T.; Lambotte, E. *J. Prakt. Chem.* **1904**, *70*, 116–128.
(12) Gante, J. *Chem. Ber.* **1966**, *99*, 1576–1579.
(13) Losse, G.; Weddige, H. *Liebigs Ann. Chem.* **1960**, *636*, 144–149.
(14) Nikolenko, L. N.; Badalova, R. *Chem. Nat. Compd.* **1968**, *4*, 27–31.
(15) Anderson, G.; Callahan, F. *J. Am. Chem. Soc.* **1958**, *80*, 2902–2903.
(16) Anderson, G.; Young, R. *J. Am. Chem. Soc.* **1952**, *74*, 5307–5309.

Gly-DL-Phe-Gly-OEt was isolated under specified conditions; instead, the pure L tripeptide was isolated in 70% yield. A carbodiimide coupling carried out in parallel provided an 8% yield of racemate. The test is said to be sensitive to as little as 1% racemization. This further suggests the proposed mechanism and is very encouraging as regards future applicability of our new method.

On the surface, our new coupling method is reminiscent of another amide-bond-forming process—the "phosphazo method"[17]—which employs trivalent P–N compounds (formed from the amine component and PCl_3) and unactivated carboxylic acids; however, this reaction suffers considerable racemization due to the apparent intermediacy of mixed anhydrides.[18] The phosphazo compounds therefore appear to function simply as dehydrating agents, in marked contrast to our method. Another unusual amide-forming reaction, possibly of greater relevance to the present work, is one reported by Mukaiyama, employing a sulfenamide, a phosphine, and a carboxylic acid.[19]

The sensitivity of the coupling to steric effects was tested as follows: a competition experiment was carried out by using the iminophosphorane derived from Ph_2POEt and ethyl azidoacetate, carrying out the coupling as usual but using 1 equiv each of Z-Gly and Z-L-Val. The resulting product mixture was found by NMR to contain 20.5% valine dipeptide and 79.5% glycine dipeptide. This gives a rate ratio of about 1:4 for valine vs. glycine. In comparable couplings using the *p*-nitrophenyl ester method the rate ratio is about 1:20 for these residues.[9] Thus, the present method exhibits about one-fifth the steric sensitivity of a traditional ester aminolysis, supporting the proposed intramolecular acyl transfer as the rate-determining step. It should be noted as well that the isolated yield obtained in a Z-Val coupling using this method was comparable (70%) to those obtained in other couplings (Table I).

Further strong support for our proposed mechanism was obtained by the successful synthesis and characterization of a stable amino(acyloxy)phosphorane in which the acyl transfer step is inhibited by incorporation of the reactive groups into a five-membered ring. Upon mixing equimolar amounts of ethyl diphenylphosphinite and DL-2-azido-3-methylbutanoic acid in ether solution, nitrogen was evolved and crystals of the adduct separated and were removed by filtration. The product **5a** (mp 100–120 °C dec) exhibited a ^{31}P chemical shift of −35.2 ppm (upfield from H_3PO_4); this is typical of pentacoordinate phosphorus compounds which generally exhibit large negative ^{31}P chemical shifts, and the value agrees well with that reported by Chaus and co-workers[20] for a similar amino(acyloxy)phosphorane.



5a, R = *i*-Pr
b, R = Me

The compound rearranged over a period of several weeks to a compound with a ^{31}P NMR singlet at +26.2 ppm. A similar adduct (**5b**) prepared by using DL-2-azidopropanoic acid (^{31}P NMR −39.6 ppm) rearranged with a half-life of approximately 4 h (product ^{31}P NMR +23.0 ppm). The reaction is probably ethylation of the carboxylate anion such as has been observed for adducts of trialkyl phosphites by Gusar' and co-workers.[21]

The above observations demonstrate that this new coupling reaction is a significant departure from previous methods in terms of the chemistry involved and consequently may represent a strategically useful alternative method of peptide coupling. The demonstration of such usefulness would in particular require the successful application to the coupling of large and/or sterically hindered peptide segments. A significant problem which remains is that nonpolar solvents such as toluene, which work well for the reaction, are generally not suitable for peptide work. The potential value of the new method justifies further investigations of this interesting reaction.

Acknowledgment. We are grateful to Dr. Dorothy Z. Denney for providing ^{31}P NMR spectra and for helpful discussions. Financial support from the Rutgers Research Council and the Rutgers Biomedical Research Support Grant (funded by NIH) is gratefully acknowledged.

* Address correspondence to Mail Stop W-758, The MITRE Corporation, 1820 Dolley Madison Blvd., McLean, VA 22102-3481.

(17) Grimmel, H.; Guenther, A.; Morgan, J. *J. Am. Chem. Soc.* **1946**, *68*, 539–542. Goldschmidt, S.; Lautenschlager, H. *Liebigs Ann. Chem.* **1953**, *580*, 68–82.

(18) Jakubke, H. D.; Jeschkeit, H. "Amino Acids, Peptides, and Proteins", Halsted Press/Wiley: New York, 1977; p 127.

(19) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 94.

(20) Chaus, M. P.; Gusar', N. I.; Gololobov, Yu. G. *J. Gen. Chem. USSR* **1982**, *52*, 21–26. Adducts obtained similarly from phosphines and *o*-azidobenzoic acid appeared to have open-chain iminophosphorane or zwitterionic structures; see this reference for a discussion of this type of tautomerism.

(21) Gusar', N. I.; Chaus, M. P.; Gololobov, Yu. G. *J. Gen. Chem. USSR* **1978**, *48*, 2155; **1979**, *49*, 16–20.

Jeffrey Zaloom, Michael Calandra
David C. Roberts*
Department of Chemistry
Rutgers University
New Brunswick, New Jersey 08903
Received August 7, 1984

(Phenylthio)nitromethane: A Convenient Reagent for the Construction of Bicyclic β-Lactams

Summary: 2-[(Phenylthio)carbonyl]-1-azabicyclo[4.2.0]-octan-8-one (**10**), 2-[(phenylthio)carbonyl]-1-azabicyclo-[3.2.0]heptan-7-one (**12**), and 3,3-dimethyl-2-[(phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one were prepared in high overall yields from monocyclic β-lactams **7**, **11a**, and **13** by using (phenylthio)nitromethane (**1**) as the key reagent for cyclization.

Sir: Recently we described that (phenylthio)nitromethane (**1**)[1] is a versatile reagent for the conversion of aldehydes into α-substituted *S*-phenyl thio esters.[2] For example, sequential reaction of acetaldehyde with **1** and KOH and MsCl–Et_3N according to the Miyashita procedure[3] gave **2**[4] (60%). This nitroalkene **2** reacted smoothly with potassium phthalimide in DMF followed by direct ozonolysis of the intermediate **3** in situ to produce **4** (68%). In ad-

(1) Bordwell, F. G.; Bartmess, J. E. *J. Org. Chem.* **1978**, *43*, 3101.

(2) Banks, B. J.; Barrett, A. G. M.; Russell, M. A. *J. Chem. Soc., Chem. Commun.* **1984**, 670.

(3) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362.

(4) Since our original publication, we have optimized the preparation of **2**. The reaction of MeCHO with **1** in the presence of KO-*t*-Bu (0.1 equiv) in THF: *t*-BuOH (1:1) at 0 °C followed by MsCl (3 equiv) and Et_3N (3 equiv) in CH_2Cl_2 at −78 °C gave **2** (≥89%).

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