is less complicated than that followed for the preparation of "standard" Gilman-type reagents.[2] The implications of this work, we feel, are far reaching, not only with respect to further studies with these and related intermediates in synthesis[22] but also for potential replacement of CuI by CuCN in many situations where cost, reagent and/or product sensitivity, and time are crucial factors. Finally, we are striving to develop a modified protocol which utilizes even more highly mixed systems, $R_TR'Cu(CN)Li_2$, where only a single (potentially valuable) transferable group (R_T) is needed,[23] along with two nontransferable, "dummy" ligands (i.e., R' and CN).

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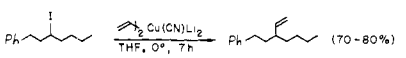
(21) In a typical procedure, CuCN (1 mmol) was placed in a dry two-necked flask and azeotroped with toluene (2 × 1 mL) at room temperature under vacuum. The tan powder was placed under argon and THF (1 mL) was introduced. The slurry was cooled to −78 °C and RLi (2 mmol) was added dropwise. The heterogeneous mixture was allowed to warm to 0 °C (becomes homogeneous) at which temperature it was stirred for a further 1–2 min and then recooled to −78 °C (may get cloudy). The iodide (bromide) was introduced (neat or in THF) and stirred at the appropriate temperature until TLC (or VPC) indicated that the reaction was complete. The mixture was quenched with 10% concentrated NH_4OH/saturated NH_4Cl solution followed by a standard extractive workup (Et_2O). In the case below, chromatography on silica gel with hexanes gave 3-(β-phenethyl)hept-1-ene in 70–80% isolated yield [TLC: R_f = 0.56 (hexanes); IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (5 H, s, br), 5.55 (1 H, m), 5.0 (1 H, d, J = 1 Hz), 4.85 (1 H, dd, J = 2.7 Hz), 2.52 (2 H, m), 1.25 (12 H, m). MS, m/e (relative intensity, %) 202 (M^+, 4.7), 160 (4.0), 145 (4.7), 131 (4.7), 118 (3.4), 117 (8.1), 105 (34.9), 104 (100). High-resolution MS, calcd for $C_{15}H_{22}$ 202.1720; found 202.1728].



(22) For example, we have found that these reagents react very efficiently with mono-, di-, and trisubstituted epoxides, as well as α,β-unsaturated ketones: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J., manuscripts in preparation.

(23) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400. Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *Chem. Commun.* **1973**, 88.

Racemization-Free Photochemical Coupling of Peptide Segments

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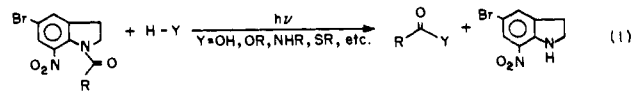
Today, segment condensation is the strategy of choice for the preparation of long peptides. However, in order to form a peptide bond between two segments, the C-terminal amino acid of one of them must be activated; present-day methods for this lead to considerable racemization of the activated amino acid and to optically impure products. Some techniques, though, are better than others, and condensation by the azide method or by use of dicyclohexylcarbodiimide with various additives produce minimal racemization. Yet, even with these methods, optical impurity at bothersome levels occurs sometimes.[1,2]

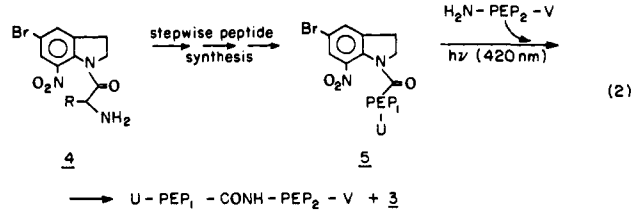
We wish to describe a novel method for peptide segment condensation which is virtually free of racemization. This condensation is based on the unusual photochemical properties of the 5-bromo-7-nitroindolinyl (Bni) group.[3]

The Bni group has been used in the past to block the carboxylic function[3] through formation of an amide derivative, 1-acyl-5-bromo-7-nitroindoline (**1**). Irradiation of **1** at 420 nm or below activates the acyl function toward nucleophilic attack. In the presence of water, this results in photohydrolysis of the amide bond with quantitative formation of a free carboxylic acid **2** (Y = OH, reaction 1) and 5-bromo-7-nitroindoline (**3**).[3,4] When **1** is irradiated in the presence of other nucleophiles (reaction 1), carboxylic acid derivatives **2** are formed by a unique photoacylation reaction.[5]



1 **2** **3**

Clearly, the Bni group can be used to protect the carboxylic function, as well as to activate it, upon irradiation, toward the attack of nucleophiles. Because of this dual function, the Bni group is promising for use in peptide synthesis. It may be initially used to block the C terminus during the stepwise synthesis of peptide segment **5** and finally to couple this segment photochemically to a second segment (reaction 2).



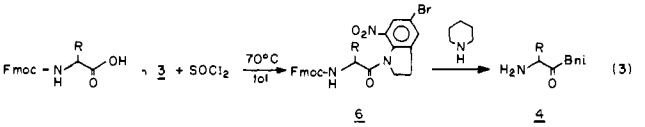
4 **5**

$\longrightarrow$ U-PEP_1-CONH-PEP_2-V + **3**

PEP - o peptide segment

U;V - protecting groups

The attachment of the Bni group to a Boc- or Z-protected amino acid to form **4** fails with standard acylation methods due to the poor nucleophilicity of 5-bromo-7-nitroindoline. Other workers were therefore forced to use an indirect and rather lengthy route for the preparation of Bni derivatives.[4] We have, however, developed a simple, one-step attachment method, which involves heating a mixture of **3** and 9-[(fluorenylmethyl)oxy]carbonyl (Fmoc)-protected amino acids with thionyl chloride in toluene at 40–70 °C for several hours. This yielded the desired derivatives **6** in high optical purity (99.5 ± 0.5%).[6] The Fmoc group is easily and selectively removed from **6** by brief treatment with piperidine[7] to afford **4** in 70–85% overall yield.



6 **4**

Following the scheme presented in reaction 2, we have prepared two opiate peptides: [Leu^5]-enkephalin (**7**) and [D-Ala^2]-[Leu^5]-enkephalinamide (**8**) via [4 + 1] and [2 + 3] photocoupling reactions, respectively[8] (reactions 4 and 5). In the initial attempts

(1) (a) Finn, F. M.; Hofmann, K. *Proteins (3rd Ed.)* **1976**, *2*, 192–193. (b) Erikson, B. W.; Merrifield, R. B. *Ibid.* **1976**, *2*, 412–415.

(2) (a) Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A. "Peptide Synthesis", 2nd ed.; Wiley: New York, 1976; pp 181–182. (b) Kemp, D. S. In "The Peptides: Analysis, Synthesis, Biology"; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. I, pp 315–383.

(3) Amit, B.; Ben-Efraim, D. A.; Patchornik, A. *J. Am. Chem. Soc.* **1976**, *98*, 843–844. In Hebrew, Bni means *my son.*

(4) Goissis, G.; Erikson, B. W.; Merrifield, R. B. *Pept., Proc. Am. Pept. Symp., 5th*, **1977**, 559–561.

(5) For a recently reported example of some similarity, see: Burton, L. P. J.; White, J. D. *Tetrahedron Lett.* **1980**, 3147–3150.

(6) The optical purity of amino acids and peptides was determined according to: Charles, R.; Butler, U.; Feibush, B.; Gil-Av, E. *J. Chromatogr.* **1975**, *112*, 121–133. Amino acid derivatives or peptides were hydrolyzed in 6 N HCl and the resulting set of amino acids transformed to the corresponding set of trifluoroacetyl aminoacyl isopropyl esters. The set was analyzed gas chromatographically on an optically active, stationary phase—docosanoyl-L-valine-*tert*-butyl amide which is able to separate each derivativatized L-amino acid from its D enantiomer.

(7) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409.

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Table I. Degree of Racemization during Peptide Bond Formation[a]

racemization test	peptide product	% racemization: conventional coupling	% racemization: photocoupling
Anderson test[12]	Z-Gly-Phe-Gly-OEt (9)[17]	0.5[b] (azide, 0 °C, 24 h)[18]	0.9[c] (−15 °C) 0.2[c] (−25 °C)
modified Bodanszky test[15]	Tfa-Ile-Gly-OEt (10)[17]	10.1[c,d] (DCC + 1-HOBt, 0 °C, 24 h)[15]	1.9[c,d] (−15 °C) 0[c,d] (−25 °C)
Izumiya test[13]	Z-Gly-Ala-Leu-OBzl (11)[17]	0[e] (azide, 0 °C, 72 h)[13]	0[e] (−25 °C)
Weygand test[14]	Tfa-Val-Val-OMe (12)[17]	<1[f] (azide, −10 °C, 43 h)[19]	0.6[f] (−15 °C)

[a] Abbreviations used: Z, benzyloxycarbonyl; Tfa, trifluoroacetyl; DCC, dicycloxylcarbodiimide; 1-HOBt, 1-hydroxybenzotriazole. [b] Determined by isotope dilution method.[18] [c] Determined by gas-chromatographic method.[6] [d] Determined by amino acid analyzer.[15] [e] Determined by amino acid analyzer.[13] [f] Determined by gas-chromatographic analysis.[19]

to prepare **7** at room temperature, we obtained 18% of Phe in the D configuration, obviously due to racemization of phenylalanine during photoactivation.[9] By lowering the temperature to −15 °C and changing the solvent mixture,[8] we were able to limit racemization to about 0.5% (reaction 4).[10]

$$\text{Boc-(OBzl)Tyr-Gly-Gly-Phe-Bni} + \text{H-Leu-OBzl} \xrightarrow[83\%]{h\nu} \text{Boc-(OBzl)Tyr-Gly-Gly-Phe-Leu-OBzl} + \underline{3} \quad (4)$$

$\underline{7}$ 0.8% DPhe

$$\text{Boc-(OBzl)Tyr-DAla-Bni} + \text{H-Gly-Phe-Leu-NH}_2 \xrightarrow[70\%]{h\nu} \text{Boc-(OBzl)Tyr-DAla-Gly-Phe-Leu-NH}_2 + \underline{3} \quad (5)$$

$\underline{8}$ 0.5% LAla

In order to confirm our findings, we used the photochemical condensation method[8] to prepare four peptides which are widely accepted as "racemization tests".[11] The Anderson,[12] the Izumiya,[13] and the Weygand[14] tests were performed by using their model peptides. The Bodanszky test[15] was modified, however, by preparing trifluoroacetylisoleucylglycine ethyl ester instead of the original model acetylisoleucylglycine ethyl ester. Since activated trifluoroacetylisoleucine is more susceptible to racemization,[16] this modified test is more demanding.

The optical purity of the products obtained by photochemical condensation at low temperatures are compared in Table I with those obtained by the best conventional coupling methods. From these results one can conclude that this photochemical segment condensation, when conducted at −25 °C, furnishes peptides with a very high optical purity. We also found that working at low temperatures did not appreciably lengthen reaction times.[8]

The Bni function is, therefore, a unique example of a group which can be used both for masking and for activation of the terminal carboxylic function of peptide segments. Moreover, the switch from the "masking" mode to the "activating" mode requires no chemical manipulations.

Acknowledgment. We thank the United States–Israel Binational Science Foundation (BSF), Jerusalem, Israel, for partial support of this research. Sh. Pass gratefully acknowledges a Levi Eshkol fellowship by the National Council for Research and Development, Jerusalem, Israel.

Supplementary Material Available: Experimental details and scheme of the irradiation vessel (2 pages). Ordering information is given on any current masthead page.

(8) In a typical photochemical reaction, 1 mmol of **1** and 1–1.5 mmol of the amino component were dissolved in a mixture of 120 mL of tetramethylurea and 50 mL of toluene and introduced into a special vessel designed for work at low temperatures. The solution is conveniently irradiated (under nitrogen and with stirring) in a Rayonet photochemical reactor ($\lambda \sim 360$ nm). Progress of reaction was followed by UV and TLC; **1** is consumed within 1–3 h. Yields correspond to chromatographically purified products and are in the range of 70–95%.

(9) Patchornik, A.; Amit, B.; Pass, Sh. In "Peptides 1978"; Siemion, I. Z., Kupryszewski, G., Eds; Wroclaw University Press: Wroclaw, Poland, 1979; pp 135–137.

(10) On the basis of further studies of racemization (Table I), we believe that even this minor fraction of racemization could be further reduced by lowering the temperature from −15 to −25 °C.

(11) Reference 1a, pp 179–182.

(12) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1958**, *80*, 2902–2903.

(13) Izumiya, N.; Muraoka, M.; Aoyagi, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3391–3395.

(14) Weygand, F.; Prox, A.; Schmidhammer, L.; Konig, W. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 183–188.

(15) Bodanszky, M.; Conklin, L. E. *J. Chem. Soc., Chem. Commun.* **1967**, 773–774.

(16) Coupling of acetylisoleucine with ethyl glycinate by the action of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole leads to 8.8% racemization (Itoh, N. *Pept., Proc. Am. Pept. Symp., 3rd*, **1972**, 365–367). By coupling (trifluoroacetyl)isoleucine with ethyl glycinate under the same conditions, we obtained 10.1% of D-alloisoleucine.

(17) Model peptides were prepared photochemically according to the procedure outlined in ref 8. Z-Gly-Phe-Bni, Tfa-Ile-Bni, Z-Gly-Ala-Bni, and Tfa-Val-Bni were used to produce **9**, **10**, **11**, **12**, respectively.

(18) Kemp, D. S.; Wang, S. W.; Bushby, G., III; Hugel, G. *J. Am. Chem. Soc.* **1970**, *92*, 1043–1055.

(19) Weygand, F.; Prox, A.; Schmidhammer, L.; Konig, W. In "Peptides", Young, G. T.; Ed.; Pergamon Press: London, 1963, pp 97–107.

A Unique Stereospecific $[_\pi 2_s + {}_\sigma 2_a]$ Cycloaddition of Tetracyanoethylene to Substituted Cyclopropanone Acetals

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In previous papers we reported that tetracyanoethylene (TCNE) and cyclopropanone acetals gave five-membered cycloadducts.[1] This cycloaddition appeared to be an interesting reaction. Two possible mechanisms can account for this cyclization: a two-step process similar to the cycloaddition of enol ethers to TCNE[2] or a symmetry-allowed $[2_s + 2_a]$ reaction.[3] In order to decide between these mechanisms, the cyclization of the stereochemically labeled isomeric 2,3-dimethylcyclopropanone *O,S*-acetals (**3a,b**) to TCNE was investigated. The synthesis of **3a,b** was straightforward (Scheme I). 1,1-Dibromo-2,3-dimethylcyclopropane **1a,b**[4] was converted into 1-bromo-1-(methylthio)-2,3-dimethylcyclopropane (**2a,b**)[5,6] followed by treatment with a solution of

(1) (a) Noordstrand, A. A. P.; Steinberg, H.; de Boer, Th. J. *Tetrahedron Lett.* **1977**, 2611–2612. (b) Wiering, P. G.; Steinberg, H. *J. Org. Chem.* **1981**, *46*, 1663–1666.

(2) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117–124.

(3) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, West Germany, 1970; pp 65–77.

(4) Makosza, M.; Fedorynski, M. *Synth. Commun.* **1973**, *3*, 305–309.

(5) (a) Jorritsma, R.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 184–194. (b) Braun, M.; Seebach, D. *Chem. Ber.* **1976**, *109*, 669–691.

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