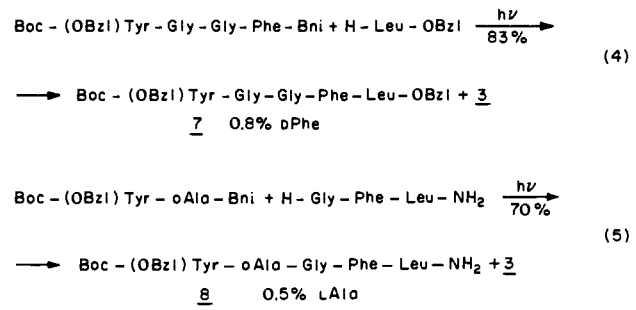
Table I. Degree of Racemization during Peptide Bond Formation[a]

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]



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

Petrus G. Wiering, Jan W. Verhoeven, and Herbert Steinberg*

Laboratory for Organic Chemistry, University of Amsterdam 1018 WS Amsterdam, The Netherlands

Received July 13, 1981

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.

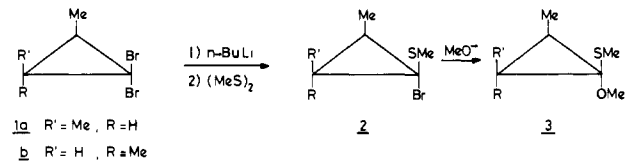
(3) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, West Germany, 1970; pp 65–77.

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

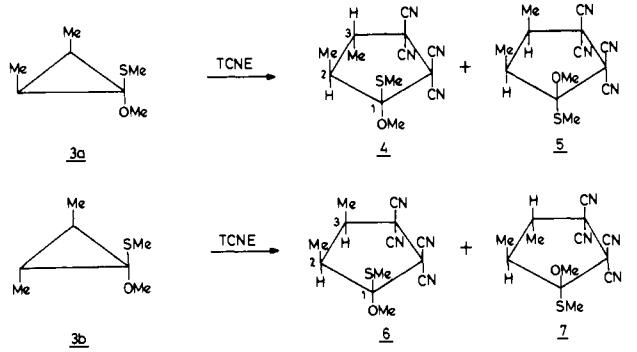
(5) (a) Jorritsma, R.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 184–194. (b) Braun, M.; Seebach, D. *Chem. Ber.* **1976**, *109*, 669–691.

0002-7863/81/1503-7675$01.25/0

Scheme I



Scheme II

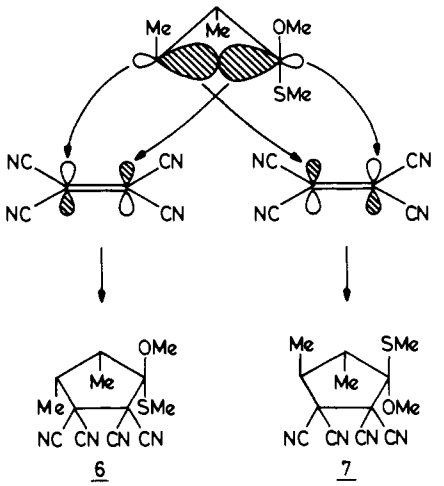


sodium methoxide in methanol at room temperature to give the acetal **3a,b**.[6]

Mixing equimolar amounts of the *cis*-acetal **3a** and TCNE in methylene chloride immediately produced a red coloration (λ_{max} = 483 nm) due to a charge-transfer complex between the reactants (Scheme II).[9] When the mixture was heated for 2 weeks at 80 °C, the reddish color slowly faded, and after workup the cycloadducts **4** and **5** were obtained almost quantitatively in the ratio of 98:2.[10] The stereochemistry of **4** (mp 137–138 °C) and **5** was determined by ^{1}H NMR experiments, and the structure of **4** was unequivocally determined by x-ray crystal analysis.[11] **4**: ^{1}H NMR (250 MHz in $CDCl_3$) δ 1.23 (d, C_2–CH_3, J = 7.3 Hz), 1.48 (d, C_3–CH_3, J = 6.4 Hz), 2.21–2.39 (m, C_2–H, J_{HH} = 11 Hz), 2.55–2.70 (m, C_3–H, J_{HH} = 11 Hz), 2.27 (s, SCH_3) and 3.39 (s, OCH_3). Irradiation of the OCH_3 peak induced a positive NOE on the C_2–H signals.[12]

When a methylene chloride solution of a 1:1 mixture of the *trans*-acetal **3b** and TCNE was heated under similar conditions, a complex mixture of six isomeric cycloadducts was obtained in high yield.[13] Although we have not as yet been able to isolate all isomers, the main products **6** and **7** (ratio **6**/**7** = 1.3) were obtained in about 70% yield.[14] The configurational assignment

Scheme III



of the (separated) cycloadducts **6** and **7** is firmly established from comparison of their ^{1}H NMR data with those of **4** and on the basis of NOE difference experiments while irradiating the OCH_3 signal and the vicinal coupling constant $^3J_{cis}$ = 6.7 Hz (in **6**) and $^3J_{trans}$ = 9.8 Hz (in **7**) and 11.0 Hz (in **4**). Solvent polarity (CH_2Cl_2, CH_3CN) has hardly an effect on the reaction rate and product distribution, thus indicating that no dipolar intermediates are involved.[2]

Furthermore no traces of ene-type isomerization and dimerization products are formed which are indicative of diradical intermediates as found in the [$_\pi$2 + $_\sigma$2] cycloaddition of electronegatively substituted olefins to single bonds of highly strained carbocycles.[16] Judging from the stereochemical results, the thermal cycloaddition reaction of **3a,b** and TCNE occurs very stereoselectively. The most consistent, albeit unprecendented, explanation is that the reactions occur in a symmetry-allowed [$_\pi$2$_s$ + $_\sigma$2$_a$] pathway (Scheme III). The observation of a charge-transfer complex between **3a,b** and TCNE makes it plausible that TCNE approaches the cyclopropane ring at the face where the –SMe group is situated. During the formation of the bonds between **3** and TCNE, one of the cyclopropyl carbon atoms is inverted, thus always leading to a mixture of *cis*- and *trans*-dimethyl cycloadducts. Preliminary data on the sterochemistry of the other cycloadducts from **3b** and TCNE also indicate these geometries.

Irradiation of a methylene chloride solution of **3a** or **3b** and TCNE, by using a visible light source, strongly accelerated the reaction which is terminated after 10 h at 0 °C. We propose that the photochemical process probably involves radical ions as intermediates in which the stereospecificity is largely lost.[17]

Further studies are in progress to clarify the thermal and photochemical cycloaddition mechanisms in detail.

Acknowledgment. We thank Professor H. Schenk, Laboratory for Crystallography, for the X-ray crystal structure determination of **4**, C. Kruk for recording the 250-MHz spectra, and Professor Th. J. de Boer for helpful discussions.

(6) The all cis position of the methylthio and the methyl groups in **2a** and **3a** is based on the ^{1}H NMR spectral data and is consistent with similar findings of others (see ref 7 and 8). **2a**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.0–1.3 (m, 6 H), 1.6–2.0 (m, 2 H) and 2.2 (s, 3 H). **2b**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.05–1.45 (m, 8 H) and 2.25 (s, 3H). **3a**: ^{1}H NMR (60 MHz, CCl_4) δ 0.8–1.2 (m, 8 H), 2.0 (s, SCH_3) and 3.2 (s, OCH_3). **3b**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.6–0.95 (m, 2 H), 1.05–1.32 (m, 6 H), 2.10 (s, SCH_3), and 3.31 (s, OCH_3).

(7) (a) DePuy, C. H.; Breitbeil F. W.; Debruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347–3354. (b) Schöllkopf, U.; Ruban, E.; Tonne, P.; Riedel, K. *Tetrahedron Lett.* **1970**, 5077–5080.

(8) The selective lithium-cis bromine exchange has been reported by: Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 949–951.

(9) Sulfide–TCNE interactions (λ_{max} between 400–600 nm) have already been reported by: Moreau, W. M; Weiss, K. *J. Am. Chem. Soc.* **1966**, *88*, 204–210.

(10) Although we could not yet isolate the isomer **5**, the ^{1}H NMR spectrum pointed to the formation of a trace of **5**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22 (d, CH_3, J = 7.0 Hz), 1.42 (d, CH_3, J = 7.6 Hz), 2.32 (s, SCH_3), and 3.68 (s, OCH_3).

(11) Schenk, H., private communication.

(12) **4**: MS gave M^+ 274.0888; calcd for $C_{13}H_{14}N_4OS$, M^+ 274.0888.

(13) The ^{1}H NMR spectrum (250 MHz, $CDCl_3$) of the mixture revealed 6 different singlet absorptions of OCH_3 and SCH_3 and 12 doublets of CH_3.

(14) **6**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.19 (d, C_2–CH_3, J = 7.6 Hz), 1.44 (d, C_3–CH_3, J = 7.3 Hz), 2.29 (s, SCH_3), 2.59–2.80 (m, C_2–H, J_{HH} = 6.7 Hz), 3.12–3.29 (m, C_3–H, J_{HH} = 6.7 Hz), and 3.44 (s, OCH_3). Irradiation of the OMe absorption induced NOE on the C_2–H peak. MS gave M^+ 274.0891; calcd for $C_{13}H_{14}N_4OS$, M^+ 274.0888. **7**: ^{1} NMR (250 MHz, $CDCl_3$) δ 1.19 (d, C_2–CH_3, J = 7.6 Hz), 1.46 (d, C_3–CH_3, J = 6.7 Hz), 2.35 (s, SCH_3), 2.66–2.81 (m, C_2–H, J_{HH} = 9.8 Hz), 3.15–3.30 (m, C_3–H, J_{HH} = 9.8 Hz), and 3.69 (s, OCH_3). Irradiation of the SMe absorption induced NOE on the C_2–H peak. MS gave M^+ 274.0885; calcd for $C_{13}H_{14}N_4OS$, M^+ 274.0888.

(15) Similar coupling constants were found in 2,3-dimethylcyclopentyl acetates by: van Haver, D.; Tavernier, D.; Anteunis, M.; van der Walle, M. *Tetrahedron* **1974**, *30*, 105–108.

(16) (a) Gassman, P. G. *Acc. Chem. Res.* **1971**, *4*, 128–136. (b) Mazur, M. R.; Berson, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 685–686.

(17) Roth, H. D.; Mannion Schilling, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 7956–7958 and references cited therein.