d_4, 42% d_5, 19% d_6).
(8) R. Cramer, *J. Am. Chem. Soc.*, **88**, 2272 (1966), and references cited therein.
(9) A. J. Birch and G. S. R. Subba Rao, *Tetrahedron Lett.*, 3797 (1968).
(10) E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3224 (1973).
(11) It is of interest to note that octalone **14** is thermodynamically favored over the starting octalone.
(12) Fellow of the Alfred P. Sloan Foundation, 1974–1976.

Paul A. Grieco,*[12] Mugio Nishizawa, Nebojsa Marinovic
Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

William J. Ehmann
Glidden Organics, Division of SCM Corporation Jacksonville, Florida 32201

Received July 26, 1976

The Reaction of Tertiary Ethynyl Alcohols with Formamide Acetals: Formation of Dienamines and Enamine Orthoformates

Sir:

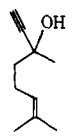
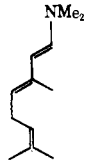
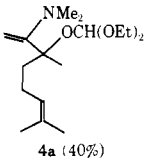
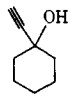
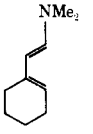
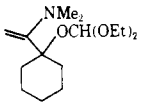
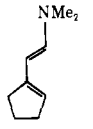
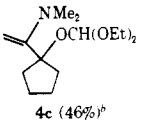
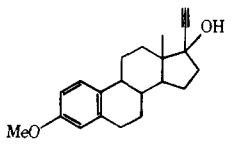
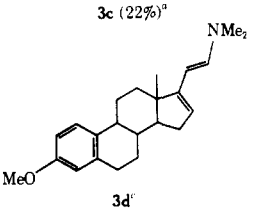
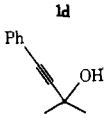
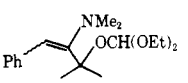
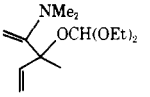
The addition of nucleophiles to unactivated acetylenic bonds has been effected in the presence of strong base and by transition metal/Lewis acid catalysis. Neither of these methods, however, provides an efficient synthesis of enamines.[1] We have previously observed that tertiary ethynyl carbinols may be converted by *N,N*-dimethylacetamide diethyl acetal to enamines with rearranged skeletons.[2,3] We now report that with *N,N*-dimethylformamide acetals (**2**), these carbinols (**1**) afford dienamines **3** and/or enamine orthoformates **4** (see Table I), formally the products of addition of dimethylamine to the acetylene bond.

The conversion involves heating the alcohol, **1**, with excess amide acetal. Maximum total yields were obtained when ethanol and a trace of pivalic acid were added. The enamine product(s) may be isolated directly by distillation or the total reaction mixture may be hydrolyzed and the corresponding carbonyl compounds isolated.

The ratio of enamine orthoformate to dienamine appears to be a function of the structure of the alcohol. Carbinols **1a–c** afford good yields of mixtures of the enamine orthoformate and dienamine products. In the case of 17α-ethynyl 17β-sterols (e.g., **1d**), the dienamine containing no detectable amount of enamine orthoformate is formed; hydrolysis of the steroidal dienamines (by elution through wet silica gel with chloroform) affords the $\Delta^{17(20)}$-en-21-al derivatives, key intermediates in the synthesis of corticosteroids.[4]

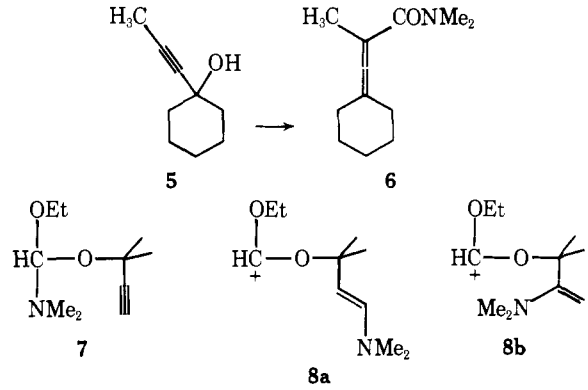
Tertiary propargyl alcohols in which the acetylene is substituted with an alkyl group do not undergo either of these

Table I

Alcohol 1	Dienamine 3 (yield)	Enamine orthoformate 4 (yield)	2, $MeCCO_2H$, EtOH (mmol, mg, ml/mmol of 1)	T, t (°C, h)
 **1a**	 **3a** (24%)[a]	 **4a** (40%)	3.5, 3.8, 0.20	125, 38
 **1b**	 **3b** (42%)[a]	 **4b** (47%)[b]	3.7, 2.5, 0.13	120, 40
 **1c**	 **3c** (22%)[a]	 **4c** (46%)[b]	3.5, 2.2, 0.12	120, 40
 **1d**	 **3d**[c]		18, 0.6, 0.31	120, 4
 **1e**		 **4e** (55%)[d]	3.6, 1.6, 0.16	145, 90
 **1f**		 **4f** (50%)	1.8, 0.8, 0.16	125, 36

[a] Hydrolysis on wet silica afforded the corresponding aldehydes. [b] Hydrolysis on wet silica afforded the corresponding keto orthoformate. [c] Crude dienamine **3d** could be isolated by removing all volatile materials from the reaction mixture under reduced pressure. Preparation of the corresponding aldehyde was most efficiently accomplished, however, by hydrolyzing the entire reaction mixture on wet silica. This procedure afforded consistently high yields (>90% based on alcohol **1d**) of *trans*-3-methoxyestra-1,3,5,17 (20)-tetraen-21-al, mp 164–168 °C.[6] [d] Some starting alcohol, contaminated with **4e** and possibly traces of dienamine product, was recovered.

reactions; under typical reaction conditions (7.0 mmol in 2 ml of DMF diethyl acetal and 3 ml of ethanol containing 26 mg of pivalic acid) 1-(1-propynyl)cyclohexanol (**5**) is slowly converted to the allenic amide **6** (approximately 60% conversion after 38 h at reflux). When heated with the formamide acetal in toluene (10 mmol of **5**, 3 ml of DMF diethyl acetal, 10 ml of toluene, reflux) the conversion of **5** to **6** was more efficient; a 72% yield of **6** was obtained after 4 h (along with a 12% recovery of **5**). This transformation is analogous to the reaction of allylic alcohols with DMF acetals to form β,γ-unsaturated amides.[5]



The reaction of 4-phenyl-2-methyl-3-butyn-2-ol (**1e**), although slower than those of alcohols in which the acetylene is terminal, affords reasonable yields of the enamine orthoformate **4e**. Alcohol **1f**, which is both propargylic and allylic, afforded no detectable products resulting from rearrangement involving the olefinic bond.

We assume that this reaction proceeds by way of the mixed amide acetal **7**, which undergoes an intramolecular migration of the dimethylamino group, leaving a carbonium ion **8a** or **8b** (or the corresponding carbene) which subsequently eliminates (**8a** → **3**) or adds ethanol (**8b** → **4**). The mechanism and scope of this reaction as well as possible uses of the enamine products in synthesis are being investigated.

Acknowledgment. This work has been supported by the National Cancer Institute, Department of Health, Education and Welfare (Grant No. CA16524), to whom grateful acknowledgment is made. We would also like to thank Professor George Büchi for informing us of his results in this area prior to publication.

References and Notes

(1) See P. F. Hudrlik and A. M. Hudrlik, *J. Org. Chem.*, **38**, 4254 (1973), and references therein.
(2) K. A. Parker and R. W. Kosley, Jr., *Tetrahedron Lett.*, 341 (1976).
(3) K. A. Parker and R. W. Kosley, Jr., *Tetrahedron Lett.*, 3039 (1975).
(4) See G. L. Olson, K. D. Morgan, and G. Saucy, *Synthesis*, 25 (1975), and references therein.
(5) G. Büchi, M. Cushman, and H. Wüest, *J. Am. Chem. Soc.*, **96**, 5563 (1974).
(6) W. Benn, *J. Org. Chem.*, **33**, 3113 (1968).

Kathlyn A. Parker,* Raymond W. Kosley, Jr.
Stephen L. Buchwald, Joseph J. Petraitis
Department of Chemistry, Brown University
Providence, Rhode Island 02912
Received June 21, 1976

A New Method for the Preparation of Sequential Polypeptides Using Matrix-Controlled Thermal Polymerization

Sir:

We wish to report a new method for the preparation of sequential polypeptides which is based on our synthesis of sequential polydepsipeptides.[1] We employ a thermal polymerization of trifluoroacetate salts of tripeptide pentachlorophenyl esters[2] deposited on a celite matrix. The polymerization is rapid compared to solution techniques. High yields of optically pure, high molecular weight polymers are obtained. In this communication, we also report a general approach to assess racemization in the preparation of sequential polypeptides.

We synthesized a sequential polypeptide by this technique from the trifluoroacetate salt of L-valyl-L-valyl-L-alanine pentachlorophenyl ester (F_3CCOOH·Val-Val-Ala-OPcp). A second polymer was synthesized by the same technique from the polymerization of the trifluoroacetate salts of L-valyl-L-alanyl-glycine pentachlorophenyl ester (F_3CCOOH·Val-Ala-Gly-OPcp) and glycyl-L-valyl-L-alanine pentachlorophenyl ester (F_3CCOOH·Gly-Val-Ala-OPcp), both of which yield the same sequence polymer. However, the former contains a C-terminal glycine residue which cannot racemize during polymerization while the latter contains an optically active L-alanine residue which may racemize.[3] By comparison of the optical purity of the L-alanyl residue from the hydrolysis products of both polymers, it is possible to deduce the extent of racemization during polymerization.

Two independent routes were employed to prepare F_3CCOOH·L-Val-L-Val-L-Ala-OPcp (I). In the first synthesis, L-alanine was allowed to react with L-valine *N*-carboxyanhydride to yield the free dipeptide L-valyl-L-alanine[4] which was coupled in situ with *tert*-butoxycarbonyl-L-valine *N*-hydroxysuccinimide ester.[5] The resulting *N*-*tert*-butoxycarbonyl-protected tripeptide free acid was esterified with pentachlorophenol at −20 °C in dimethylformamide by treatment with dicyclohexylcarbodiimide in the presence of *N*-hydroxysuccinimide.[6] The *tert*-butoxycarbonyl group was removed in trifluoroacetic acid to yield the desired tripeptide derivative I. The esterification of the tripeptide free acid can conceivably involve some racemization of the C-terminal L-alanyl residue. To avoid this side reaction, we employed a so-called "backup route".[1,7] In this approach, *tert*-butoxycarbonyl-L-alanine was esterified with pentachlorophenol and the *tert*-butoxycarbonyl protecting group removed by trifluoroacetic acid. This amino acid pentachlorophenyl ester was coupled by the repetitive excess mixed carbonic–carboxylic acid anhydride method[8,9] to *tert*-butoxycarbonyl-L-valine and, after deprotection with trifluoroacetic acid, with *tert*-butoxycarbonyl-L-valine again. Deprotection yielded the optically pure tripeptide derivative Ia.

The polymerizable tripeptide derivative, F_3CCOOH·Gly-Val-Ala-OPcp (II) was synthesized by the same step-by-step backup technique using appropriate repetitive excess mixed anhydride couplings and deprotections. The remaining tripeptide, F_3CCOOH·Val-Ala-Gly-OPcp (III), was prepared by allowing glycine to react with *tert*-butoxycarbonyl-L-alanine *N*-hydroxysuccinimide ester. After deprotection with trifluoroacetic acid, the free dipeptide was treated with *tert*-butoxycarbonyl-L-valine *N*-hydroxysuccinimide ester. Esterification with pentachlorophenol and deprotection with trifluoroacetic acid yielded the desired polymerizable tripeptide derivative III. All the tripeptide active esters were pure by TLC and gave satisfactory elemental and amino acid analysis as well as NMR and ir spectra.

Preliminary attempts at bulk polymerization of pentachlorophenyl ester were unsuccessful, even at high temperature, because of trapping of the liberated pentachlorophenol in the reaction mass.[1] Deposition of the monomers on an inert matrix accelerates the sublimation of liberated pentachlorophenol and allows the polymerization to proceed rapidly at temperatures well below the melting point of the monomer.

The polymerization was accomplished by dissolving the tripeptide active ester in a dimethylformamide/dioxane mixture (1:3 v/v), adding 66% by weight of micron-size celite