and 2.0×10^{-4} min^{-1} (CD_3CN). The Gly/Ala rate ratios are 2.8 ($CDCl_3$) and 3.3 (PhH), and the Gly/Val rate ratios are 8 (CD_3CN) and 22 ($CDCl_3$); they are thus comparable with the intermolecular cases.[7]

A successful intramolecular amide synthesis must exhibit (1) a rapid intramolecular *O,N*-acyl transfer in nonhindered cases and (2) a small sensitivity to steric effects. Our model has successfully rationalized and predicted steric sensitivity. We lack a satisfactory means of predicting nonhindered acyl transfer rates.[10] In this study, nearly a 10^6-fold range of rate constants have been observed for acyl transfer via cyclic five- or six-atom linkages, the noteworthy cases being the sluggish 5-ring acyl transfers observed for *o*-aminophenyl derivatives (low nucleophilicity of N and strain in the intermediate are important contributors)[11] and the very rapid 6- and 7-ring acyl transfers to carbinolamines.[1]

Although *O,O*-acyl transfers are well documented and almost invariably rapid,[10] the more interesting *O,N*-acyl shifts are rarer, and rapid cases are unusual. Despite the advanced state of knowledge concerning the principles of acyl transfer in biological systems, there remains a remarkable disparity between the facility of enzymatic acyl transfer and the ease with which it can be achieved in model systems.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453) is gratefully acknowledged.

References and Notes

(1) D. S. Kemp and F. Vellaccio, Jr., *J. Org. Chem.*, **40**, 3003 (1975).
(2) D. S. Kemp, J. A. Grattan, and J. Reczek, *J. Org. Chem.*, following paper.
(3) D. E. Worrall, *J. Am. Chem. Soc.*, **49**, 1598 (1927). **1**, mp 73–74°, is prepared by acetylation of 2-hydroxynitrostyrene [G. Hahn and K. Stiehl, *Chem. Ber.*, **71**, 2154 (1938)].
(4) Acyl transfer was demonstrated by NMR, ir, and uv; rate constants were measured by NMR. Satisfactory elemental analyses were observed for nitrostyrenes and for products **3**.
(5) D. S. Kemp, S. Choong, and J. Pekaar, *J. Org. Chem.*, **39**, 3841 (1974).
(6) *N*-(2-Hydroxyphenyl)amino acid esters were prepared from *o*-aminophenol as follows: Gly by alkylation with ethyl chloroacetate, mp 91–93°; Ala by Pd/C hydrogenation with ethyl pyruvate, hydrochloride salt, mp 152–153°; Val by hydrogenation with ethyl α-ketoisovalerate, mp 88–89°. *O*-Acetylation was achieved by reaction with acetic anhydride–perchloric acid at −70°, followed by dilution with ether and liberation with $NaHCO_3$. Rates of transfer were followed by NMR.
(7) Contrary to the implication of an authoritative review,[8] rapid intramolecular acyl transfer of this type has not been previously demonstrated.[9]
(8) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", W. A. Benjamin, New York, N.Y., 1966, Vol. 1, p 188.
(9) A. L. LeRosen and E. D. Smith, *J. Am. Chem. Soc.*, **71**, 2815 (1949).
(10) See ref 8, Chapter 1.
(11) It can also be argued that an antiperiplanar arrangement of N lone pair and leaving group is difficult to achieve: P. Deslongchamps, P. Atlani, D. Frebel, and A. Malaval, *Can. J. Chem.*, **50**, 3405 (1972).

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

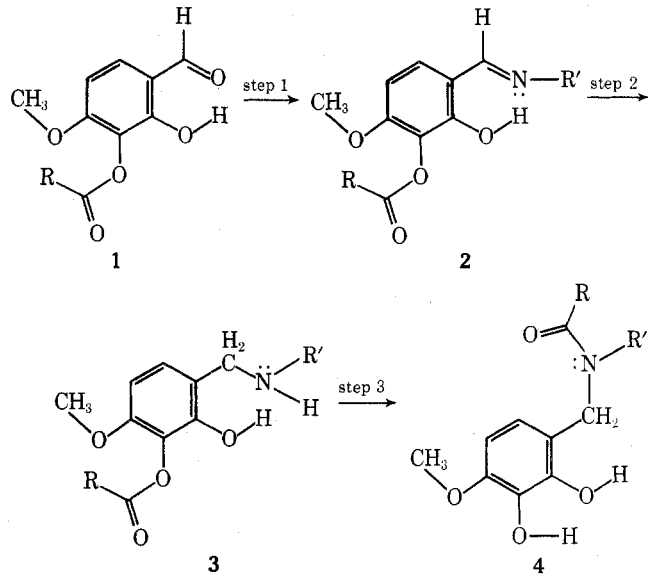
D. S. Kemp*
Frank Vellaccio, Jr.

Received August 15, 1975

Peptide Bond Formation by the Prior Amine Capture Principle

Summary: Amino acid esters react with 4-methoxy-3-acyloxy-2-hydroxybenzaldehydes to form imines, which upon reduction undergo intramolecular acyl transfer to form *N*-4-methoxy-2,3-dihydroxybenzyl amides, useful in peptide synthesis.

Scheme I



Sir: As outlined in Scheme I, we wish to report the feasibility of peptide bond formation through a new principle of intramolecular acylation which is preceded by amine capture.[1]

Step 1—Amine Capture. Imine formation from salicylaldehydes occurs with unusually large rate and equilibrium constants.[2] Thus, **1**[3] (R = ZGly) reacts with methyl esters of Ala, Leu, or Phe (CH_3CN, 25°, 0.2–0.3 *M*) with half-times of 4–5 min. Only small rate changes result from variation of R ($t_{1/2}$ = 5–6 min for R = ZAla, R′ = HAlaOMe; R = HPhe, R′ = HValOMe). From two cases, rates appear to be ~10 times as fast as in DMSO.

Step 2—Reduction. As a reducing agent for **2**, pyridine borane in acetic acid[4] is mild, rapid, and quantitative. With a 1:1 molar stoichiometry, reaction is complete in <3 min; somewhat slower, complete reaction is also observed with 0.5 equiv of borane. In practice, solvent is removed from **2**, which is dissolved without purification in acetic acid, followed by pyridine borane. Disappearance of the yellow color of **2** indicates complete reaction, whereupon solvent is removed, and **3** is isolated by partitioning between an organic solvent and aqueous bicarbonate.

Step 3—Acyl Transfer. Although the unimolecular[5] isomerization, **3** → **4**, is somewhat retarded by polar solvents (slow in DMSO),[6] it occurs with half-times in the range of 0.2–4 hr in other media, including neat **3**. Thus for **3** (R = ZGly) transfer to captured Ala, Leu, and Phe occurs with half-times of 15, 40, and 70 min, respectively ($CDCl_3$, 25°). For **1** (R = ZPhe or ZAla) transfer to Ala gives $t_{1/2}$ values of 120 and 70 min. Steric effects at the amine substitution site are normal[7] (the Val/Gly rate ratio appears to be ~10). Preparatively, reaction times of 12 hr were convenient.

The yield for the conversion of **1** (R = ZGly) and 1 equiv of DL-HPheOEt to **4** was 85%.[8] Reaction of **1** (R = ZGly) with HLeuGlyOH tetramethylguanidine salt (DMSO, 25°, 5 min), followed by precipitation with ether, reduction, and isomerization, resulted in an isolated yield of 92% **4**.

Step 4—Cleavage. Cleavage of this **4** with HBr/HOAc yielded 84% HGly-L-LeuGlyOH, after neutralization. With trifluoroacetic acid in the presence of the trapping agent resorcinol, the 4-methoxy-2,3-dihydroxybenzyl moiety (DHMB) could be selectively cleaved.[9] Treatment of PhthGly(N-DHMB)PheOEt with Tfa (1 hr, 25°, 5 equiv of resorcinol) generated 100% PhthGlyPheOEt. A similar

treatment of ZGly(N-DHMB)PheOEt gave 83.3% ZGlyPheOEt and 11% HGlyPheOEt; the half-time for DHMB cleavage is 12 min in Tfa and in 3:1 Tfa–CH_2Cl_2.[10] The N-DHMB group is resistant to hydrogenation (Pd, 1 atm, 3 hr).[9]

Other Issues. 1. Racemization. Scheme I is expected to minimize normal racemization processes or other side reactions which occur at the acyl site,[11] but it is potentially vulnerable to epimerization at the amino site of **2**. To test the extent of this problem, we applied our isotopic dilution assay.[11] Reaction of **1** (R = Z-2-^{14}C-Gly) with H-L-PheGlyOEt was followed by conversion to **4** and treatment with Tfa, without purification of intermediates. Reaction times for **1** → **2** of 1.5 and 14 hr (0.2 *M*, CH_3CN) gave 0.1 and 0.3% DL tripeptide, respectively.[12] **2. Diketopiperazines.** The sequence HGlyProX readily forms diketopiperazines.[13] A similar problem is observed for HGly(N-DHMB)XY. When ZGly(N-DHMB)PheOEt was hydrogenolyzed (3 hr, Pd, HOAc), 62% diketopiperazine was isolated. The tripeptide HGly(N-DHMB)-L-LeuGlyOH formed diketopiperazine and HGlyOH slowly in DMSO solution. **3. Solubility.** As noted by Weygand,[9] substitution of *N*-benzyl groups on the amide backbone markedly increases peptide solubility. Unlike their counterparts which lack the N-DHMB group, ZGly(N-DHMB)-L-LeuGlyOH is soluble in chloroform and HGly(N-DHMB)-L-LeuGlyOH is soluble in DMSO. The solubilizing effect in these two cases appears to be at least an order of magnitude. **4. Protection of 1.** In order to be useful as a "safety catch" activated group, **1** must be convertible to an unreactive derivative. Reaction of **1** (R = ZGly) with NaH/DMF and benzyl bromide, followed by acidic ethyl orthoformate, generates 4-methoxy-3-ZGlyO-2-benzyloxybenzaldehyde diethyl acetal, which aminolyzes very slowly with peptide nucleophiles (with HGlyOEt in CH_3CN, $k_2 = 5 \times 10^{-6}$ sec^{-1}, 25°) and which is reconverted to **1** by treatment with Tfa for 1 hr.

Summary. The potential virtues of amide formation by prior amine capture and intramolecular acylation have been summarized previously.[1] Several of these (diminished steric effects on rate, first-order acylation rate, solubilization) have been demonstrated in this system; others are likely but remain to be proved. Although its feasibility awaits testing, the following scheme can be envisaged from the results here obtained. The amino acid ester of **1**, blocked by benzylation and acetal formation, could be introduced at the C terminus of a medium-sized peptide acid by conventional amide-forming reagents. Liberation of **1** at some later stage by Tfa treatment would permit a fragment condensation to yield a peptide bearing the solubilizing N-DHMB group at an N site of its amide backbone. A critical question concerns the minimum ratio of DHMB amide to secondary amide which is required for useful solubility effects. Until these questions are resolved, the importance of Scheme I is the demonstration of the feasibility of a new approach to amide synthesis.

Acknowledgment. Financial support from the National Institutes of Health (GM 13453) is gratefully acknowledged.

References and Notes

(1) D. S. Kemp and F. Vellaccio, Jr., *J. Org. Chem.*, **40**, 3003 (1975).
(2) R. Green and P. Alexander, *Aust. J. Chem.*, **18**, 329 (1965); R. Green and E. Le Mesurier, *ibid.*, **19**, 229 (1966); R. Green and R. Sleet, *ibid.*, **19**, 2101 (1966), **22**, 917 (1969).
(3) Prepared by DCCI coupling of ZGlyOH with 4-methoxy-2,3-dihydroxybenzaldehyde: H. Gross, A. Reiche, and G. Mattley, *Chem. Ber.*, **96**, 308 (1963); K. Campbell, P. Hooper, and B. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).
(4) J. Billman and J. McDowell, *J. Org. Chem.*, **26**, 4137 (1961).
(5) Although **3** is a catechol monoester, it is hindered. No aminolysis of the more activated **2** was observed over 24 hr in the presence of excess amine, nor were concentration effects on aminolysis seen. Rate constants were obtained from NMR measurements.
(6) Strikingly, this result is the opposite of that seen for intermolecular phenyl ester aminolysis.
(7) D. S. Kemp and F. Vellaccio, Jr., *J. Org. Chem.*, preceding paper.
(8) Unless otherwise noted, yields were obtained by isotopic dilution.
(9) F. Weygand, W. Steglich, J. Bjarnason, R. Akhtar, and N. Khan, *Tetrahedron Lett.*, **No. 29**, 3483 (1966); F. Wegand, W. Steglich, J. Bjarnason, R. Akhtar, and N. Chytil, *Chem. Ber.*, **101**, 3623 (1968).
(10) E. Schnabel, H. Klostermeyer, and H. Berndt, Proc. *Eur. Pept. Symp., 11th, 1973*, 69 (1973).
(11) D. Kemp, S. Wang, S. Busby, and G. Hugel, *J. Am. Chem. Soc.*, **92**, 1043 (1970).
(12) Since the optical purity of the amine is unknown, the racemization in 1.5 hr must be taken to lie in the range of 0.02 to 0.1%.
(13) E. Schroder and K. Lubke, "The Peptides", Academic Press, New York, N.Y., 1965, p 148.

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

D. S. Kemp*
James A. Grattan
James Reczek

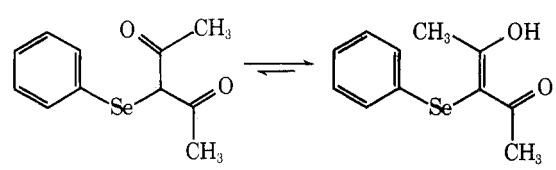
Received August 15, 1975

Heteroatom Directed Photoarylation. Photochemistry of an Organoselenide

Summary: Aryl selenide **1** undergoes photocyclization–rearrangement to give benzoselenophene **4**.

Sir: While the existence of carbonyl and thiocarbonyl ylides has been established,[1] the generation of selenocarbonyl ylides has not been reported.[2] In this paper, we communicate preliminary results concerning possible generation and rearrangement of a selenocarbonyl ylide and describe the first preparative organoselenium photoreaction.[3]

Recent success with photogeneration of carbonyl[4] and thiocarbonyl ylides[5] from 2-aryloxyenones and 2-thioaryloxyenones, with subsequent rearrangement to dihydrofurans and dihydrothiophenes, suggested that selenocarbonyl ylides might be generated from similarly structured 2-selenoaryloxyenones. Because of the known propensity of selenides to eject elemental selenium on exposure to light,[6] we initiated the investigation with aryl selenide **1**, which via enolic form **1b** was expected to give a relatively stable photoproduct, i.e., **4**.



1a **1b**

The elegant method for α-arylselenenylation of ketone enolates developed principally by Sharpless[7] and Reich[8] was used to prepare **1**. Reaction of a suspension of the sodium enolate of acetylacetone in tetrahydrofuran with benzene selenyl bromide gave the required phenyl selenide (**1**), which exists predominately in enolic form **1b** (NMR analysis, 4 *M* **1** in $CDCl_3$, ratio of **1a**:**1b** = 1:9).

Preparative-scale Pyrex-filtered irradiation of **1** in benzene solution (0.05 *M*) saturated with *p*-toluenesulfonic acid at ~15° while purged with argon gave 2-acetyl-3-methylbenzo[*b*]selenophene (**4**) in 60% isolated yield (mp 93–95°, lit.[9] mp 94°). The mechanism[10] for the transformation **1** → **4** presumably involves photocyclization of **1b** to selenocarbonyl ylide (**2**), which undergoes rearrangement