those for the trans isomer. VPC using the dimethylsulfolane column distinguishes between them.

Anal. Calcd for C_8H_{16} (85% cis/15% trans sample): C, 85.64; H, 14.36. Found: C, 85.79; H, 14.02.

3,4-Dimethyl-2-hexene (7) was prepared by the sodium in liquid ammonia reduction of *cis,cis*-3,4-dimethyl-2,4-hexadiene (1). The 3,4-dimethyl-2-hexene was separated from the 3,4-dimethyl-3-hexenes by VPC on a Carbowax 1000 column: micro boiling point 113 °C; IR (film) 3000–2850, 1660, 1460, 1380, 1090, 1025, 1010, 960, 825 cm^{-1}; NMR (CCl_4) δ 5.20 (q, 1, J = 7 Hz, $=CHCH_3$), 2.00 (m, 1, allylic CH), 1.58 (d, 3, J = 7 Hz, $=CHCH_3$), 1.50 (s, 3, $C(CH_3)=$), 1.36–0.60 (m, 8).

Anal. Calcd for C_8H_{16}: C, 85.64; H, 14.36. Found: C, 85.37; H, 14.08.

3,4-Dimethyl-2-hexene theoretically exists in cis and trans forms, but we could not separate them or distinguish between them by any method, including VPC. Thus the 3,4-dimethyl-2-hexenes from the reduction of either *cis,trans-* or *trans,trans*-3,4-dimethyl-2,4-hexadiene could not be distinguished from the above.

Registry No. 1, 18265-39-9; 2, 2417-88-1; 3, 21293-01-6; 4, 32388-98-0; 5, 32388-99-1; 6, 16356-05-1; (*E*)-7, 19550-82-4; (*Z*)-7, 19550-81-3; (*E*)-3,4-dimethyl-3-hexene, 19550-88-0; (*Z*)-3,4-dimethyl-3-hexene, 19550-87-9; 2-ethyl-3-methyl-1-pentene, 3404-67-9; *dl*-3,4-dimethyl-3,4-hexanediol, 32388-94-6; *dl*-4,5-dimethyl-4,5-diethyl-1,3-dioxolane-2-thione, 73367-88-1; *meso*-3,4-dimethyl-3,4-hexanediol, 32388-93-5.

Specific Enolates from α-Amino Ketones

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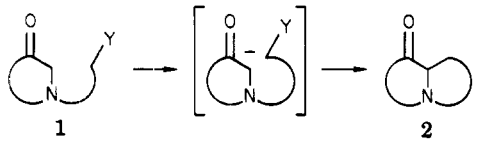
Received September 10, 1979

The enolization of 11 tertiary α-amino ketones was investigated under three different conditions (kinetic base, thermodynamic base, thermodynamic acid) to determine the directionality of such enolates for application to alkaloid synthesis. The ketone structural variables examined were the geometry of the amine nitrogen lone pair–carbonyl array and the electronic nature of the nitrogen substituent. With the exception of 3-pyrrolidinones, increasing the electron-withdrawing nature of the nitrogen increases the amount of enolization toward nitrogen (**3**, **6**, and **9** or **21**, **24**, and **27**). *N*-Alkyl-substituted amino ketones (**3**, **12**, **21**, **33**) under kinetic base conditions yield enolate distributions similar to those of the corresponding all-carbon compounds. *N*-Carbamato-substituted amino ketones (**6**, **24**, **27**, **30**) enolize predominantly toward nitrogen under all conditions. The 3-pyrrolidinones **12**, **15**, and **18** afford enolates away from nitrogen under all conditions.

A common structural feature of many alkaloids, including the pyrrolizidines, lycopodines, and aspidosperimines, is a tertiary bridgehead nitrogen. A key step in one general synthetic approach to these diverse compounds might be an intramolecular ring closure of an N-substituted amino ketone enolate (**1** → **2**). Such specific enolates could also be useful in a variety of other applications in alkaloid synthesis. Little information is available regarding the effect of nitrogen on the directionality of ketone enolization, although numerous enolates have been studied in carbon systems[2-4] and with the α-heteroatoms halogen,[5] sulfur,[6] and oxygen.[7] We report the full details of our work with amino ketones communicated in 1978[8] as well as some additional information about the specificity of these enolate-forming reactions.



1 **2**

Ketone Variables. Of the numerous structural and electronic variables for α-amino ketones, the geometrical arrangement of the nitrogen-carbonyl group and the electronic nature of the nitrogen substituent are critical. Systematic examination of these features should establish general trends for synthetic application. The geometrical relationship of the nitrogen lone pair–carbonyl array was varied from freely rotating acyclic species (**3**, **6**, **9**) to fixed in a cisoid array (**30**, **33**) or in a transoid configuration (**12**, **15**, **18**, **21**, **24**, **27**). The nitrogen substituents were varied from alkyl to the synthetically versatile carbamate functionality. In all cases, the actual choice of ketone was based upon availability and spectroscopic simplicity.

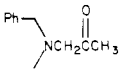
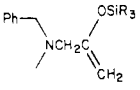
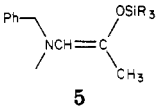
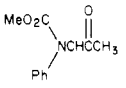
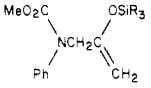
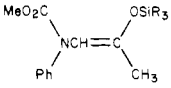
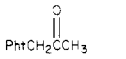
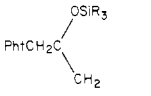
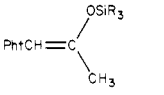
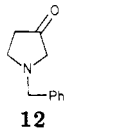
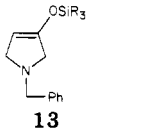
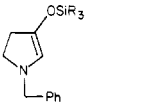
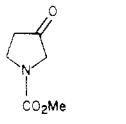
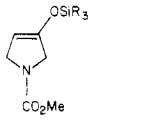
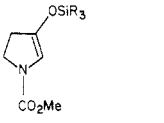
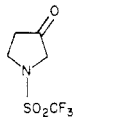
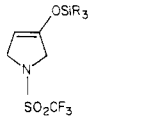
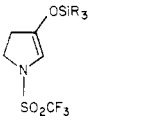
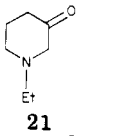
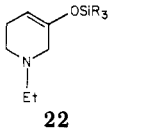
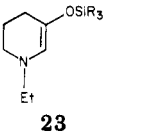
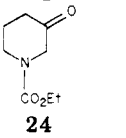
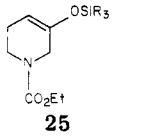
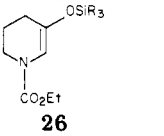
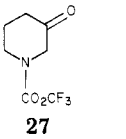
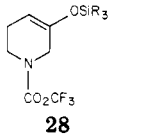
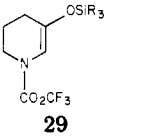
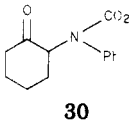
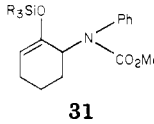
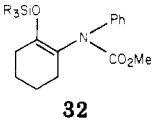
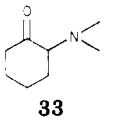
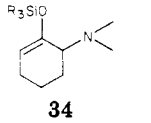
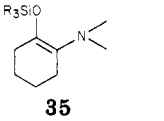
Enolization and Product Identification. The enolization of the ketones was effected by three different methods: method A, excess lithium diisopropylamide in tetrahydrofuran (THF) at −78 °C; method B, 0.8 equiv of lithium hexamethyldisilazide in THF at 0 °C; method C, chlorotrialkylsilane and triethylamine in dimethylformamide (DMF) at 80 °C. The base in method B was chosen to eliminate potential carbonyl reduction (vide infra). All enolates were trapped with trialkylsilyl chlorides; some enolates were also trapped with acetic anhydride and with methyl iodide. These procedures were developed by House,[3] who was shown that methods B and C afford similar results in all-carbon compounds. The results for silyl trapping are summarized in Table I.

Many of the silyl enol ethers were identified by isolation either directly from the reaction mixture or by preparative GLC. All products exhibited the expected spectral properties, including a distinctive NMR shift of the olefinic protons. Silyl enol ethers formed by enolization away from nitrogen demonstrated olefin peaks in the 3.8–4.8-ppm region as observed by House in carbon systems.[3] Enol

(1) (a) Partial fulfillment of M.S. requirements, 1978. (b) Undergraduate research participant, Summer 1977.
(2) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.
(3) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(4) Posner, G. W.; Lenz, G. *J. Am. Chem. Soc.* **1979**, *101*, 934.
(5) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601. House, H. O.; Fischer, W. F.; Gall, M.; McLaughlin, T. E.; Peet, N. P. *Ibid.* **1971**, *36*, 3429.
(6) Seebach, D. *Tetrahedron Lett.* **1973**, 5113. Coates, R. M.; Pigott, H. D.; Ollinger, J. *Ibid.* **1974**, 3955.
(7) Wilson, S. R. *J. Org. Chem.* **1976**, *41*, 378. Dickinson, C. M. *Diss. Abstr. B* **1976**, *36*, 6164.
(8) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *Tetrahedron Lett.* **1978**, 2671.

0022-3263/80/1945-2307$01.00/0

Table I. Enol Ethers

ketone	ethers		products	product ratios: method A[a]	method B[b]	method C[c]
 3	 4	 5	4:5 (*E*)-5:(*Z*)-5	1:0.33 (*E*)-5 > 98	1:2.3 9:1	1:19 1:1
 6	 7	 8	7:8 (*E*)-8:(*Z*)-8	1:4.5 1:4	>1:49[d] (*Z*)-8 > 98	1:9 3:1
 9	 10	 11	10:11	2:98[d] 11 (1 isomer)	NE[e]	NE[e]
 12	 13	 14	13:14	1:0.43	1:0.05	dec[f]
 15	 16	 17	16:17	1:1	1:0.60	1:0.25
 18	 19	 20	19:20	1:0.33	dec[f]	NE[e]
 21	 22	 23	22:23	1:0.20	1:0.02[d]	1:6
 24	 25	 26	25:26	1:3.5	1:3	1:19[d]
 27	 28	 29	28:29	1:4	1:49[d]	NE[e]
 30	 31	 32	31:32	1:2	1:49[d]	NE[e]
 33	 34	 35	34:35	1:0.02[d]	1:0.02[d,g]	1:0.02[d,g]

[a] Method A: The ketone was added to 1.1–1.5 equiv of LDA in THF at −78 °C. [b] Method B: The ketone was added to 0.8 equiv of lithium hexamethyldisilazide at −78 °C and equilibrated at 0 °C. [c] Method C: The ketone, 1.2 equiv of trialkylchlorosilane, 2.4 equiv of triethylamine, and DMF were heated at 80 °C for 48 h. [d] The ratio given represents the limits of our detection. [e] Not examined. [f] Decomposition. [g] This reaction provides 40–50% starting material. [h] Substantial decomposition is noted (only ca. 40% material recovery after evaporative distillation). [i] Pht = phthalimido.

ethers conjugated with the nitrogen showed olefinic protons in the 5.3–6.3-ppm region as predicted from Pascal's rules.[9] The *E* and *Z* isomers of **5** and **8** could not be preparatively separated, and structures were assigned by the following four arguments: (1) the correlation of NMR spectral data with similar systems;[3] (2) the determination that *E* isomers have more intense, higher energy IR absorptions in analogous carbon systems,[3] in *cis*- and *trans*-1,2-dimethoxyethanes,[10] and in **5** ((*E*)-**5**, 1670 cm;$^{-1}$ (*Z*)-**5**, 1684 cm^{-1}); (3) the application of Pascal's rules to

(9) Jackman, L. M.; Sternhall, S. "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Elmsford, NY, 1969; pp 184–6.

(10) Waldron, J. T.; Snyder, W. H. *J. Org. Chem.* **1973**, *38*, 3059.

determine relative olefinic shifts (predicted, (*E*)-**5**, 4.62 ppm; (*Z*)-**5**, 4.45 ppm; observed, (*E*)-**5**, 5.0 ppm; (*Z*)-**5**, 4.85 ppm); (4) the observation that the addition of hexamethylphosphoramide has no effect upon the (*E*)-**5**:(*Z*)-**5** ratio (vide infra).[11,12] Unfortunately, products from one ketone (**18**) could only be characterized as mixtures, the analysis of which relies heavily upon the NMR olefin shift information. Furthermore, in many instances the minor isomers could not be isolated.

Related Studies. Methods for the selective formation of enolate anions have developed rapidly in the last few years. Particularly, the ketone substitution pattern controls the regio- and stereochemistries of these carbanions. House and co-workers have established both trends in carbon-substituted ketones and the techniques for preparing and evaluating the enolates.[3,13] Even subtle structural changes can produce dramatic alterations in enolate composition. For example, Posner and Lenz have shown pendant aryl groups coordinate with the enolate cation to stabilize one enolate selectively.[4]

The addition of one heteroatom adjacent to a ketone presents additional interactions. The α-heteroatom halogen[5] or sulfur[6] stabilizes the adjacent enolate anions. Oxygen groups may stabilize or destabilize carbanions, depending on both the method of anion formation and the oxygen substituent.[7] Inductive arguments have been used to rationalize all of these observations.

Nitrogen in the enolate array adds the potential for cation–nitrogen lone pair coordination. A number of imine-like species with interacting groups attached to the nitrogen (rather than the carbon) yield anions (or dianions) which may have geometries and electronic arrays similar to amino ketone enolates. These species, including oxime ethers,[14a] oxime dianions,[14b] tosylhydrazone dianions,[14c] aldimines,[14d] ketimines,[14e] and certain hydrazones,[14f] have been reported to give exclusive deprotonation on the same side as the interacting group (syn). In contrast with the above examples *N,N*-dimethylhydrazones afford anti deprotonation followed by facile isomerization to the more stable syn species,[15] at least suggesting a related path for some of the imine-type anions. Internal chelation,[14] extended Hückel calculations,[16a,17] and CNDO/2 calculations[16b,17] have been used to explain syn selectivity.

The nitrogen-containing functionalities *N,N*-dialkyl-*N*-nitrosamines[18] and *N,N*-dialkylarylamides[19] have been shown to yield anions syn to the nitroso and carbonyl group, respectively. These anions are called "dipole stabilized", a term describing all nonclassical π–π or d–π delocalization.[19]

The combination of nitrogen–carbonyl-substituted carbanions has been examined in two contexts. First, scattered reports of aldol reactions with 3-piperidinones suggest enolization away from nitrogen, although product analyses were limited to crystallized products (40–60%) obtained from in situ dehydration.[20] The aldol products may not reflect enolate regiochemistry. The racemization of peptides is less directly related to amino ketones in that peptide enolization must occur adjacent to nitrogen. Recent preliminary CNDO/2 calculations explain relative racemization rates of various peptides but conflict with experimental results for simple amides.[21]

In addition to ketone structural changes both solvent and cation[13] can alter enolate distribution. In most of the work mentioned and in this study, the cation is lithium. Solvent effects are observed in the aryl–cation coordination observed by Posner,[4] the syn–cis selectivity of the anions mentioned,[12,14] and the enolate geometry of simple ketone or ester enolate anions.[22,23] Formation of these anions in THF favors the cisoid enolate while the use of THF–HMPA mixtures provides the transoid enolates. The solvent additive HMPA often promotes enolate equilibration, decreasing the amount of internally "stabilized" enolate.[4,11] Enolate cation solvation by HMPA, altering the aggregation of the enolates, has been a frequently used argument for this change.

Results and Discussion

Amino ketones certainly offer the possibility for cation coordination and inductive increase of kinetic acidity. When we began this study we naively assumed the formation of enolates toward nitrogen as in **1** would be favored. The experimental observations have, in part, supported this assumption.

Two striking general trends immediately emerge from the data in Table I. With the exception of the 3-pyrrolidinones (**12**, **15**, **18**; vide infra) all other amino ketones within a single geometrical type exhibit an increasing tendency to enolize toward nitrogen under basic conditions as the electronegativity of the nitrogen moiety increases. For instance, the series **21**, **24**, and **27** gives progressively greater enolization toward nitrogen as the substituent is changed from ethyl (**21**) to carbethoxy (**24**) to trifluoroacetyl (**27**),[24] as does the series **3**, **6**, and **9**. Secondly, the reactions of carbamates (**6**, **15**, and **24**) by methods B and C yield qualitatively similar product ratios while amino ketones sometimes give different product ratios. Method C with sterically unhindered amino ketones affords mainly enol ethers conjugated with nitrogen, provided that the enol ether is stable to the reaction conditions.

Although the trends within the *N*-alkyl-substituted species (**3**, **12**, **21**, **33**) are less developed in part owing to ketone and product instability, some general conclusions are apparent. Enolization of these ketones under kinetic

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(12) Hoobler, M. A.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1978**, *100*, 8182. ACS/CSJ Chemical Congress, April 1979, Organic Division, Abstract 33.
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(20) McElvain, S. M.; Vozza, J. F. *J. Am. Chem. Soc.* **1949**, *71*, 896. Bly, R. K.; Zoll, E. C.; Moore, J. A. *J. Org. Chem.* **1964**, *29*, 2128. Nielson, A. T. *Ibid.* **1966**, *31*, 1053.
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(22) (a) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(23) Certain species have geminal α protons with different acidities. See: Perrin, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 5628, 5631. Perrin, C. L.; Johnston, E. R. *Ibid.* **1979**, *101*, 4753.
(24) Hansch, C.; Leo, A.; Unger, S. H.; Kina, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. Other α-meta values are as follows: NMe_2, –0.15; $NHCO_2Et$, 0.07; $NHCOCF_3$, 0.30; $C(CH_3)_2$, –0.07; $NHSO_2CH_3$, 0.21.

Table II. Attempted Equilibrations

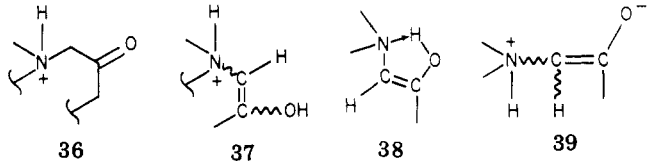
starting materials (ratio)[a]	reacn conditions[b]	products[a,c] (ratio)
3:4:(*E*)-5 (1.5:2.5:5)	Et_3N, Et_3SiCl, DMF, 80 °C, 48 h	3:4:(*E*)-5:(*Z*)-5 (4.5:1.5:4:5)
3:4:(*E*)-5[a] (1.5:2.5:5)	Et_3N·HCl/DMF, 80 °C, 48 h	3:(*E*)-5 (11.5:7)
21:22 (1:9)[e]	Et_3N, Et_3SiCl, DMF, 80 °C, 48 h	21:22:23 (3.5:40:30)

[a] Determined by NMR. [b] Longer reaction times lead to substantial decomposition. [c] Recovery greater than 90% in each case. [d] Contains trace amounts of (*Z*)-5, detected by NMR but not accurately determined. [e] Contains trace amounts of 23, detected by NMR but not accurately determined.

conditions (method A) affords qualitatively similar product ratios to their all-carbon analogues.[3,4,13] That is, the alkyl-substituted nitrogen has little effect on the kinetic acidity. Although the Pauling electronegativity value is greater for nitrogen than for carbon, enolization toward nitrogen may create a severe lone pair–lone pair repulsion akin to that of hydrazine or hydroxylamine.[25] The Hammett σ-meta values for dimethylamino and for isopropyl substituents are –0.15 and –0.07, respectively,[24] suggesting qualitatively similar inductive effects.

Under equilibrating basic conditions the enolization occurs toward nitrogen in ketone **3** but away from nitrogen in **12**, **21**, and **33**. We presume that the product **35** has some severe steric interaction avoided in **5** which offsets the difference in thermodynamic stability of a trisubstituted (**5**, **35**) vs. a disubstituted (**4**, **34**) olefin. The large amount of **33** (30% vs. 43% of **35**) recovered from method B complicates any explanation. Nonetheless, the formation of **13**, **22**, and **34** clearly shows amino ketone enolates often prefer to be nonconjugated. The large amount of **13** formed suggests that the nitrogen–anion destabilization in the enolate is greater than the aryl–lithium interaction observed in cyclopentanones.[4] The ratio of the products (**4**, (*E*)-**5**, (*Z*)-**5**) was independent of added hexamethylphosphoramide, an additional argument for the stability of the anion leading to (*E*)-**5**. We cannot predict the relative thermodynamic stability of (*Z*)-**5** and (*E*)-**5**. *cis*-1,2-Dimethoxyethene is ca. 1.2 kcal/mol more stable than the trans isomer while *trans*-1,2-bis(dimethylamino)ethene is presumed to be more stable than the unknown cis isomer.[17,26]

Two (**3**, **21**) of the four amino ketones in the same series provide mainly enol ethers conjugated with nitrogen when subjected to method C conditions. This process is complicated by the instability of enol ethers **5**, **14**, and **23** and the presumed lability of **35**. The difference in product ratios between methods B and C might arise from the trapping of an ammonium salt enol under method C (**36** → **37**), from a hydrogen-bonded enol **38**, or from an ammonium enolate **39**. Attempts to favor **36**/**38** by using limited amounts of triethylamine (0–1.0 equiv) or **21**·HCl with no triethylamine afforded little change in enol ether ratio but substantially lowered the overall yields. Attempted acid-catalyzed enol acetylation of **21** gave only decomposition. As recorded in Table II, treatment of silyl ethers from **3** and **21** obtained by method B under method C reaction conditions afforded product ratios approaching those of method C. Longer reaction times led to substantial decomposition. We have been unable to achieve complete equilibration. Treatment of **12** by method C conditions gives only complete decomposition without detection of **13** or **14** (>3% by GLC). Attempted isomerization of **13** and **14** as for **4** and **5** or **22** and **23** also affords only decomposition. Compound **14** disappears more rapidly than any of these other silyl enol ethers are formed or isomerized, without **12** being detected or **13** increasing. Isomer **13** disappears at a rate comparable to the isomerization of **4** → **5**. We believe these observations and the well-known instability of $\Delta^{2,3}$ pyrrolines[28] to be consistent with the formation of **14** from **12** by trimethylsilyl chloride/triethylamine treatment followed by the rapid acid-catalyzed decomposition of **14**. We cannot distinguish among **36**, **38**, **39**, or a related enol–enolate as the intermediate, although electrostatic arguments suggest **38** or **39** might give only (*Z*)-**5**. The lack of **35** from **33** under these conditions is puzzling. Although the recovery is low, at least 40% of **33** is converted into **34**, an unexpectedly high percentage based on any argument. We assume that **35** must be sterically disfavored for some reason. Since (*Z*)-**5** is formed in reasonable amounts, any electronic arguments seem illogical.[27]



36 **37** **38** **39**

From a synthetic standpoint, these experiments for acyclic and 3-piperidinone amino ketones (**3**, **21**) show that base-catalyzed enolization gives unconjugated enolates and that acid-catalyzed enolization affords conjugated enol ethers, both in preparative specificity and yield. The examination of other more highly substituted acylic amino ketones and 3-piperidinones is necessary to determine the magnitude of the nitrogen interaction. Unfortunately, the β-silyloxy substituent does not stabilize the enamine as recently noted for the β-phenylthio group.[28]

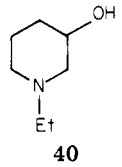
The reactions of the carbamates and amides show clearer trends. In all cases examined, except 3-pyrrolidinones, enolization is predominantly toward nitrogen. This directionality is enhanced by making the nitrogen a better electron-withdrawing group and by using equilibrating conditions. With similar nitrogen substituents, these equilibrating procedures demonstrate a geometrical effect. That is, compounds permitting a cisoid array of enolate and carbamate (**6**, **30**) provide more effective anion stabilization than those requiring a transoid array (**24**). This geometrical effect has been observed in other dipolar-stabilized carbanions,[18,19] numerous dianions, and certain imines[14] but is contrary to predictions from calculations for peptide racemization.[21] Previously we reported **30** yielded only **31** under kinetic deprotonation conditions. We subsequently noticed a precipitate forming at –78 °C upon addition of **30** to base. At twofold dilution, the reaction remains homogeneous and the ratio in Table I is obtained. A strain in carbamate **30** may cause substantial amounts of the axial isomer,[29] providing an equatorial

(25) Pauling, L. "The Nature of the Chemical Bond"; Cornell University Press: Ithaca, NY, 1960; p 93.
(26) Attempts to "equilibrate" (*Z*)-**5**/(*E*)-**5** thermally or by regeneration of the enolate and trapping have led to decomposition.
(27) Enamines have been shown to be thermodynamically more stable than allylamines: Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027. Fowler, F. W., personal communication.
(28) Stevens, R. V.; Loh, T. *Tetrahedron Lett.* **1976**, 3799.
(29) 2-Isopropylcyclohexanone contains about 30% of the axial isomer at room temperature, owing to $A^{1,3}$ strain: Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 777. Amino substituents have free energy differences comparable to isopropyl groups in cyclohexanes (Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199) in addition to a dipolar interaction favoring the axial conformation.

proton with poor geometrical overlap for kinetic removal. The formation of only **34** under thermodynamic conditions attests to the powerful effect of a cisoid dipolar stabilizing group in overcoming the steric problems of **33**. Finally, the general similarity between methods B and C with these compounds is reminiscent of House's work[3] and supports our suggestion of the involvement of ammonium enols in the method C reactions of **3** etc.

The pyrrolidine series **12**, **15**, and **18** always gives predominant enolization away from nitrogen. Under thermodynamic conditions, the eclipsing interaction of the two methylenes caused by the three adjacent sp^2 atoms must be greater than the inductive stabilization of the $\Delta^{2,3}$ olefin by the carbamate or the $n-\pi$ destabilization of the olefin in $\Delta^{3,4}$ pyrrolines as detected by photoelectron spectroscopy.[30] The predominance of **19** from **18** under kinetic conditions is puzzling.

The study of Posner and Lenz regarding remote π-aryl–lithium coordination, complete with dramatic solvent effects,[3] prompted us to attempt enolization of amino ketones in hexane. If the early premise that nitrogen–cation coordination could direct enolization was correct, the effect of solvent would be dramatic. After considerable experimentation, we found that LDA and **21** were both soluble in hexane solution at −78 °C. From this reaction we only observed *N*-ethyl-3-piperidinol (**40**). This single reaction is the only instance in which ketone reduction was observed at −78 °C with LDA.[5,31]

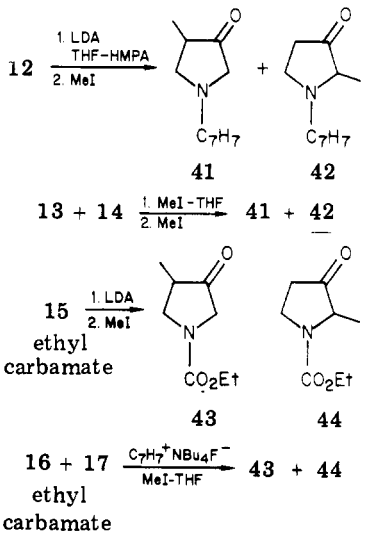


40

Our initial goal was to use the reaction **1** → **2** to prepare pyrrolizidine alkaloids. Since **12**, **15**, or **18** did not permit enolate control, we briefly examined both alternative methods of achieving functionalization at C-2 and the alkylation of enolates from **12** and **15** to determine if nitrogen presented any unusual features in this process. Both attempts to prepare *N*-acyl or *N*-silyl salts from **12** followed by in situ [1,2] migration[32] and attempts to trap allyl anions from **13**/**14** or **16**/**17** failed.[33,34] A final approach to the C-2 anion of **12** and **15** using dianions of β-keto esters[35] is now being investigated.[36]

The alkylation of enolates derived from **12** and **15** with methyl iodide proved to be comparable to many other ketone enolate alkylations (Scheme I).[37] Preparation of the enolates as in method A followed by HMPA-mediated methyl iodide quenching yielded **41** and **42** or **43** and **44** in approximately the same ratio as **13** and **14** or **16** and **17**, respectively. Alternatively, the enolates from **13**/**14**

Scheme I



could be generated with methyllithium[38] or from **16**/**17** with tetra-*n*-butylammonium fluoride;[39] quenching of each with methyl iodide yielded the products described above. The ethyl carbamates were used in these reactions. Their silyl enol ethers were formed in the same ratios as the methyl carbamates. Both of the converse procedures failed. N-Methylation competes with fluoride cleavage when **13**/**14** is treated with fluoride and methyl iodide to provide substantial amounts of material lacking the *N*-benzyl group. Methyllithium appears to attack both the methyl carbamate and silicon in **16**/**17**. All monoalkylations occurred in modest, albeit unoptimized yield (20–40%) and were accompanied by unreacted ketone and polyalkylated materials. All four of the monoalkylated compounds were prepared by unequivocal, independent synthesis[40] for positive identification. Thus, the enolates generated directly or from silyl ether cleavage behave normally in alkylation reactions.

Ketone Synthesis

The preparation of the ketone starting materials is unexceptional. Ketones **3** and **9**[41] were prepared by α-chloroacetone alkylation. Carbamates **15**,[42] **24**,[43] and **41**–**44**[40] were constructed by slight modifications of known routes by using Dieckmann cyclization procedures or by acylation of the commercial hydroxyamines followed by oxidation (**18**, **24**, **27**). Carbamates **6** and **30** were made by nucleophilic-amine epoxide opening, acylation, and oxidation. The oxidation was troublesome in *all* cases. The two most successful procedures employed a large excess of Jones' reagent[44] at 0 °C for a short time (**24**, **29**) or unbuffered pyridinium chlorochromate[45] for 12–24 h (**6**, **15**, **18**). The yields and rates of these oxidations varied randomly. When **45** was oxidized with Jones' reagent both

(30) Morishima, I.; Yoshikawa, K.; Hashimoto, M.; Bekki, K. *J. Am. Chem. Soc.* **1975**, *97*, 4283.
(31) Scott, L. T.; Carlin, K. J.; Schultz, T. H. *Tetrahedron Lett.* **1978**, 4637.
(32) For analogous [1,2] acyl migrations see: Ganem, B. *Tetrahedron Lett.* **1976**, 1951. Beak, P.; Brubaker, G. R.; Farney, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 3621. Hayashi, T.; Baba, H. *Ibid.* **1975**, *97*, 1608.
(33) For (allylsilyl)oxy anions prepared from metalation of allylsilyl ethers (not β-substituted vinyl silyl ethers as **13** and **14**) see: Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. Still, W. C.; MacDonald, T. L. *Ibid.* **1974**, *96*, 5561.
(34) For allylamine metalation see: Martin, S. F.; DuPriest, M. T. *Tetrahedron Lett.* **1977**, 3925.
(35) Weiler, L.; Huchin, S. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(36) Garst, M. E.; Johnson, A. T., unpublished observations.
(37) For a discussion of and solution to polyalkylation see: Rathke, M. W.; Lindert, A. *Synth. Commun.* **1978**, *8*, 9.
(38) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464. House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.
(39) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346.
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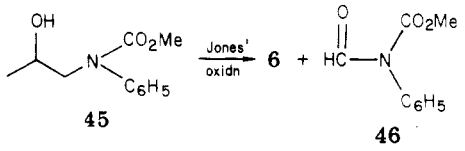
(41) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1905.
(42) Viscontini, M.; Bühler, H. *Helv. Chim. Acta* **1967**, *50*, 1289.
(43) Plieninger, H.; Leonhäuser, S. *Chem. Ber.* **1959**, *92*, 1579.
(44) Prepared according to: Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(45) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

the desired **6** and *N*-phenyl-*N*-formylurethane (**46**) were obtained in equal amounts. Products analogous to **46** were not detected from other oxidations in this series.[46]



45 46

Unfortunately, despite numerous attempts to prepare 1-type compounds for pyrrolizidine synthesis, the motivation for this study, our efforts have met with failure.

Conclusions

We have demonstrated that ketones with α-amino groups can be used to generate specific enolates which may be useful in alkaloid synthesis. To a first approximation, these amino ketone systems behave kinetically like their carbon analogues. Thermodynamic enolizations with triethylamine–triethylsilyl chloride yield preparatively useful amounts of silyl ethers with enolization toward nitrogen in many cases. The corresponding carbamates can be enticed to provide enolization toward nitrogen in all instances except 3-pyrrolidinones. Although detailed examination of additional compounds might refine these observations, our interests have turned completely toward other synthetic applications.

Experimental Section

General Procedures. Infrared spectra were recorded as thin films on a Beckman IR 18-AX spectrophotometer Bands yielding structural information are reported in reciprocal centimeters (cm^{-1}); polystyrene calibration was used. Nuclear magnetic resonance spectra were recorded on a Varian EM390 at 35 °C in deuteriochloroform, and peak positions are reported in parts per million from tetramethylsilane internal standard. The following abbreviations are used: m, multiplet; q, quartet; t, triplet; d, doublet; s, singlet. Low-resolution mass spectra were obtained from an LKB 9000 at 70-eV and 16–20-eV ionizing voltages. High-resolution spectra were performed at the California Institute of Technology Analytical Laboratory.

GLC analysis was performed on a Varian 3700 gas chromatograph with an FID and preparative GLC was performed with a Hewlett-Packard 5700 gas chromatograph with a TC detector. Both instruments were outfitted with a 6 ft × $^1/_4$ in. glass column containing 3% H1-EFF 8 BP on 100/120 Gas-Chrom Q (Applied Science). Column chromatography was executed at medium pressure (50–100 psi) on E. Merck silica gel 60, particle size 0.040–0.063 mm; an LDC refractometer was used to monitor effluent.

The term "standard workup" means that the organic layer was washed with brine, dried over Na_2SO_4, and filtered, and the solvent removed on a rotary evaporator at aspirator pressure. The term "base wash" means the organic layer was washed with saturated aqueous Na_2CO_3.

Reagents and Solvents. Tetrahydrofuran was distilled from sodium–benzophenone immediately prior to use. All secondary amines were distilled from barium oxide and stored over molecular sieves under nitrogen. Chlorotrimethylsilane and chlorotriethylsilane were purified by the method of Bloomfield, Owsley, and Nelke.[47] Ketones **12** and **21** were purchased from Aldrich Chemical Co; **30**, from K & K Labs. *n*-Butyllithium was purchased from Alfa-Ventron and used as received (2.0–2.5 M solution in hexane). All other reagents and solvents were purchased from Aldrich Chemical Co. and Mallinckrodt Chemical Co., respectively, and were used as received after determining purity by usual spectroscopic methods.

All reactions were magnetically stirred under a nitrogen atmosphere.

Ketone Synthesis. Ketone **9** was prepared according to Gabriel[41] and **15** was prepared via the method of Viscontini and Bühler[42] without any modifications.

(Benzylmethylamino)acetone (3). A stirred solution of 11.45 g (0.095 mol) of benzylmethylamine and 8.50 g (0.080 mol) of sodium carbonate in 64 mL of water was treated with 6.4 mL (0.080 mol) of chloroacetone over 2 h, with care taken to keep the reaction in the dark. The solution was allowed to stand for 20 h and then ether-extracted. The standard workup followed by distillation yielded 8.8 g (53%) of **3**: bp 70–75 °C (aspirator); IR 1715 cm^{-1}; NMR δ 2.0 (5, 3 H), 2.2 (s, 3 H), 2.97 (s, 2 H), 3.5 (s, 2 H), 7.2 (s, 4.7 H); MS (70 eV) *m/e* 177 (M^+), 91 (base).

Anal. Calcd for $C_5H_{15}NO$: 177.115. Found: 177.115.

[(Carbomethoxy)phenylamino]acetone (6). The procedure of Rohrmann and Shonle was modified.[48]

A solution of 53 mL (0.5 mol) of benzylamine, 29 mL (0.5 mol) of propylene oxide, and 250 mL of methanol was heated at 40–50 °C for 21 h. Solvent evaporation followed by distillation yielded 39.2 g (47%) of 1-(benzylamino)-2-propanol: bp 110–130 °C (0.25 mm).[49]

A solution of 29.9 g (0.20 mol) of the amino alcohol, 21.2 g (0.21 mol) of sodium carbonate, and 50 mL of water at 0 °C was treated with 23 mL (0.3 mol) of methyl chloroformate over 1 h and then allowed to stir 24 h. The standard workup provided 15.1 g (36%) of 1-[(carbomethoxy)phenylamino]-2-propanol: bp 132–134 °C (0.25 mm).

A suspension of 5.0 g (2.4×10^{-2} mol) of the alcohol and 6.70 g (3.1×10^{-2} mol) of pyridinium chlorochromate[45] in 50 mL of methylene chloride was prepared at 0 °C and stirred for 5 h at 0 °C and 12 h at room temperature. Dilution with ether, filtration through Florisil, and evaporation followed by distillation in a Kugelrohröffen yielded 3.0 g (60%) of **6**: IR 1745, 1700 cm^{-1}; NMR δ 2.10 (s, 3), 3.05 (s, 3), 4.32 (s, 2), 7.2 (m, 5); MS (70 eV) *m/e* 207 (M^+), 129 (base).

Anal. Calcd for $C_{11}H_{13}NO_3$: 207.0895. Found: 207.092.

Use of Jones' reagent[44] provided 40% of **6** accompanied by varying amounts (10–20%) of **33**: NMR δ 3.8 (s, 3), 7.0–7.5 (m, 5), 9.4 (s, 1); MS (70 eV) *m/e* 179 (M^+), 151 (base).

***N*-[(Trifluoromethyl)sulfonyl]-3-pyrrolidinone (18).** A solution of 1.010 g (1.10×10^{-2} mol) of 3-pyrrolidinol and 1.15 g (1.15×10^{-2} mol) of triethylamine in 60 mL of methylene chloride was cooled to 0 °C and treated with 4.00 g (1.40×10^{-2} mol) of trifluoromethanesulfonic anhydride over 20 min. The solution was stirred for 3 h and then washed with 10 mL of 4% HCl. Completion of the standard workup gave 1.13 g (45%) of light brown oil: NMR δ 2.15 (m, 2), 3.60–3.95 (m, 5), 4.6 (m, 1).

A solution of 3.7 g (1.7×10^{-2} mol) of pyridinium chlorochromate in 20 mL of methylene chloride was treated with 1.9 g (8.7×10^{-3} mol) of the alcohol.[45] The reaction was stirred for 24 h and filtered through Florisil with ether followed by evaporative distillation to yield 1.1 g of pale yellow oil. Chromatography on neutral alumina gave 0.41 g of a colorless oil: IR 1760, 1390, 1230 cm^{-1}; NMR δ 2.71 (t, J = 7.8 Hz, 2), 3.85 (s, 2), 3.91 (t, J = 7.8 Hz, 2).

Anal. Calcd for $C_5H_6F_3NO_3S$: 217.172. Found: 217.002.

***N*-Carbethoxy-3-piperidinone (24). Method A.** A modified version of the method of Plieninger and Leonhäuser[43] was used. A suspension of 4.78 g (0.2 mol, 50% mineral oil) of sodium hydride in 150 mL of THF was cautiously treated with 17.07 g (0.2 mol) of 2-pyrrolidinone. In a separate flask, a suspension of 4.78 g of sodium hydride in 150 mL of THF was cautiously treated with 27.79 g (0.2 mol) of bromoacetic acid. After 1.5 h, the carboxylate salt was added to the amide anion and the resulting suspension stirred for 12 h. The solution was acidified with 10% HCl and extracted with ether. Standard workup of the ether followed by trituration of the oil yielded 14 g (48%) of 2-pyrrolidinone-*N*-acetic acid: IR 2100–2300 (bd), 1700, 1620 cm^{-1}; NMR (D_2O) ca. δ 2.0 (q, $J \sim 7$ Hz, 2), 2.5 (t, $J \sim 7$ Hz, 2), 3.2 (t, $J \sim 7$ Hz, 2), 4.0 (s, 2).

(46) One attempt to oxidize *N*-(carbomethoxy)ethanolamine with Jones' reagent gave only trace amounts of *N*-formylurethane. [(Carbomethoxy)amino]acetone has been prepared by oxidation: Keana, J. F. W.; Keana, S. B.; Bertham, D. *J. Org. Chem.* **1967**, *32*, 3057.

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A solution of 7 g of the above acid in 56 mL of 27% HCl was refluxed for 48 h and then concentrated at aspirator pressure. The residue was diluted with 30 mL of absolute ethanol and 10 mL of dry benzene. This solution was distilled until the boiling point of ethanol was reached, cooled, saturated with gaseous HCl, and refluxed for 8 h. The solvent was removed to leave *N*-[3-(ethoxycarbonyl)propyl]glycine ethyl ester hydrochloride.

A solution of this diester and a huge excess of potassium carbonate in water at 0 °C was treated with 1.5 equiv of ethyl chloroformate and stirred for 12 h. The solution was extracted several times with methylene chloride. The standard workup of the pooled methylene chloride layers yielded 3 g (36%) of the carbamate: IR 1740, 1700 cm^{-1}; NMR δ 1.2 (m, 9), 1.8–2.4 (m, 4), 3.2–3.4 (m, 2), 3.8–4.4 (m, 8).

A solution of *tert*-butyl alcohol free potassium *tert*-butoxide (0.1 mol) in 15 mL of toluene was prepared; this solution was cooled to 0 °C and treated with 3 g (0.1 mol) of the carbamate over 20 min. After 1.5 h at 0 °C, the reaction was diluted with 60 mL of ice water and 30 mL of 10% HCl. Chloroform extraction and completion of the standard workup yielded a 1:1 ratio of 4,*N*-dicarbethoxy-3-piperidinone and 2,*N*-dicarbethoxy-3-piperidinone in 70% yield: IR 1740–1650 (bd); NMR δ 1.2 (m, 6), 1.7–2.4 (m, 4), 3.1 (m, 1), 3.2–3.6 (m, 2), 3.9–4.2 (m, 5).

The mixture of β-keto esters was refluxed in 1% aqueous HCl for 20 h and extracted with methylene chloride; after completion of the standard workup **24** was obtained in 20% yield from 2-pyrrolidinone-*N*-acetic acid: NMR δ 1.2 (t, $J \sim 7$ Hz, 3), 2.0 (m, 2), 2.45 (t, $J \sim 7$ Hz, 2), 3.6 (t, $J \sim 7$ Hz, 2), 4.0 (s, 2), 4.15 (q, $J \sim 7$ Hz, 2).[49]

Method B. *N*-Carbethoxy-3-piperidinol was prepared according to Wu et al.[50] in 57% yield.

A solution of 2.0 g (1.15×10^{-2} mol) of this carbamate in 50 mL of reagent acetone was treated with 4 mL of Jones' reagent over 10 min.[44] The reaction was stirred for 15 min, quenched with 2-propanol, neutralized with aqueous bicarbonate, and thoroughly washed with methylene chloride. Completion of the standard workup left 1.96 g of product.[51,52]

***N*-(Trifluoroacetyl)-3-piperidinone (27).** A solution of 10.0 g (0.07 mol) of 3-piperidinol hydrochloride and 9.0 g (0.11 mol) of pyridine in 150 mL of CH_2Cl_2 was cooled to 0 °C and treated wth 21.0 g (0.10 mol) of trifluoroacetic anhydride in 20 mL of anhydrous ether over 2 h. After the addition was complete, the reaction was stirred for 0.5 h, washed with 10% aqueous hydrochloric acid, and subjected to the standard workup to give an oil. This oil was stirred in 70 mL of 20% aqueous sodium carbonate for 15 h. Ether extraction (3 × 50 mL) followed by the standard workup provided 12.0 g (87%) of *N*-(trifluoroacetyl)-3-piperidinol: IR 3450, 1690, 1200 cm^{-1}; NMR δ 1.6–2.1 (m, 4), 3.1–4.1 (m, 5 H).

A solution of 7.0 g (0.04 mol) of the above piperidinol in 100 mL of acetone was cooled to 0 °C and treated with Jones' reagent[44] dropwise until the orange color persisted. The reaction was stirred for 4 h, quenched with 2-propanol, diluted with methylene chloride (50 mL), and filtered through solid sodium carbonate; filtration through Florisil with methylene chloride and completion of the standard workup yielded 4.1 g (53%) of **27**: bp 160 °C (0.25 mm); IR 1730, 1690, 1200 cm^{-1}; NMR δ 2.15 (m, 2), 2.60 (t, $J = 2.8$ Hz, 2), 3.85 (t, $J = 2.8$ Hz, 2), 4.20 (bd s, 2 H); MS (70 eV) *m/e* 195 (M^+), 43 (base).

Anal. Calcd for $C_7H_8F_3NO_2$: 195.051. Found: 195.053.

2-[(Carbomethoxy)phenylamino]cyclohexanone (30). A solution of 9.8 g (10^{-1} mol) of cyclohexene oxide and 9.3 g (10^{-1} mol) of aniline was heated at 100 °C for 12 h.[53] This solution was dissolved in 50 mL of 95% ethanol and treated sequentially with 14 g of potassium carbonate in 20 mL of water and 7.8 mL of methyl chloroformate over 30 min. It was kept at 0 °C for 16 h and partitioned between ether and brine (100 mL each). The brine was washed with ether (2 × 100 mL). The pooled ether layers were washed with 10% HCl and base, and the standard workup was completed to yield after crystallization from methanol 7.5 g (30%) of the hydroxy carbamate: mp 82–84 °C; NMR δ 1.0–2.5 (m), 2.5 (s), 3.1–3.5 (m), 3.5 (s), 3.8–4.2 (m), 7.1–7.4 (m).

A solution of 2.0 g of the above carbamate was dissolved in 50 mL of reagent acetone and cooled to 0 °C. Jones' reagent[44] (10 mL) was added, and the mixture was stirred for 3 min and quenched with 2-propanol. The mixture was filtered through potassium carbonate and then Celite with 100 mL of USP ether. The standard workup yielded 1.40 g (71%) of **30** after recrystalization from hot ether: mp 135–137 °C; NMR δ 1.5–2.3 (m, 6), 2.3–2.5 (m, 2), 3.5 (s, 3), 4.5–4.8 (m, 1), 7.3 (s, 5).

Anal. Calcd for $C_{14}H_{17}NO_3$: 247.121. Found: 247.123.

Silyl Enol Ether (Enol Acetate). Method A. A solution of *n*-butyllithium in hexane (1.4×10^{-3} mol) was concentrated under an N_2 stream. This concentrate was cooled to 0 °C and charged with 7 mL of THF and 0.19 mL (1.4×10^{-3} mol) of diisopropylamine. The resulting clear yellow solution was stirred at 0 °C for 10 min and cooled to −78 °C. A solution of ketone ($(1.0–1.2) \times 10^{-3}$ mol) in 3 mL of THF was added dropwise over 5 min. The reaction was stirred for 30 min followed by quenching with 1.7×10^{-3} mol of chlorotrialkylsilane or acetic anhydride. The resulting mixture was stirred at −78 °C for 10 min, warmed rapidly to room temperature, and concentrated on a rotary evaporator. The residue was partitioned between 10% aqueous Na_2CO_3 and hexane. The aqueous layer was separated and washed with equal volumes of hexane (2×). Completion of the standard workup yielded the crude product which was analyzed spectrally and by VPC and then evaporatively distilled to yield products for analysis or further purification by VPC etc.[3]

Method B. A solution of 1.4×10^{-3} mol of lithium hexamethyldisilazide in 7 mL of THF was prepared and cooled to −78 °C as per method A. To this solution was added a solution of 1.6×10^{-3} mol of ketone in 3 mL of THF over 5 min. The resulting solution was stirred at −78 °C for 30 min and at 0 °C for 30 min and then quenched. Workup was completed as for method A.

Method C. The procedure of House[3] was modified. A solution of 3.0×10^{-3} mol of triethylamine, 2.8×10^{-3} mol of chlorotrialkylsilane, and 10 mL of DMF was treated with 2.5×10^{-3} mol of ketone and heated at 80 °C for 48 h. After cooling to room temperature, the reaction mixture was diluted with an equal volume of hexane and washed with cold saturated $NaHCO_3$ several times. The hexane solution was subjected to the standard workup and processed as in method A.

All three of these methods have been scaled up or down as needed.

Spectral Data on Silyl Enol Ethers and Enol Acetates

Silyl enol ethers **4/5** and **22/23** were separated by preparative GC. Isomers **7/8**, **16/17**, and **19/20** were characterized only as mixtures by NMR. Acetates corresponding to **7/8** and **16/17** were also identified.

Silyl Ether 4 (R = Et) (method A, purified by GLC): IR 1670, 1635, 1130 cm^{-1}; NMR δ 0.40–1.00 (m, 15, CH_3CH_2Si), 2.30 (s, 3, NCH_3), 3.00 (s, 2, NCH_2), 3.7 (s, 2, NCH_2), 4.30 (s, 1, olefin), 4.40 (s, 1, olefin), 7.3 (m, 5); MS (70 eV) *m/e* 291 (M^+), 133 (base).

Silyl ether 5 (R = Et) (method A, purified by GLC): IR 1665, 1445, 1230, 1200, 1000 cm^{-1}; NMR δ 0.40–1.00 (m, 15, CH_3CH_2Si), 1.85 (s, 3, vinyl CH_3), 2.30 (s, 3, NCH_3), 3.55 (s, 2, NCH_2), 5.00 (s, 1, vinyl), 7.20 (s, 5, aryl); MS *m/e* 291 (M^+), 91 (base).

Silyl ethers 4 and 5 (R = Et) (method B): NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 1.70 (s, 0.44, *Z* $C{=}CCH_3$), 1.85 (s, 2.06, *E* $C{=}CCH_3$), 2.10 (s, 1.18, $COCH_3$), 2.30 (s, 4.12, NCH_3), 2.45 (s, 0.44, NCH_3 of *Z* isomer), 2.98 (s, 0.58, $=CCH_2N$), 3.15 (s, 0.78), 3.55 (s, 3.1, $NCH_2C_6H_5$), 3.90 (s, 0.14, $NCH_2C_6H_5$, *Z* isomer), 4.30 (s, 0.29, $=CH_2$), 4.40 (s, 0.21, $=CH_2$), 4.85 (s, 0.07, *Z* olefin), 5.00 (s, 0.68, *E* olefin), 7.0–7.3 (m, 6.96, C_6H_5).

Silyl ethers 4 and 5 (R = Et) (method C): IR 1685, 1670, 1665 cm^{-1}; NMR δ 0.40–1.00 (m, 15), 1.70 (s, 1.40, *Z* $C{=}CCH_3$), 1.85 (s, 1.40, *E* $C{=}CCH_3$), 2.10 (s, 0.6, $COCH_3$), 2.30 (s, 2.15, NCH_3), 2.45 (s, 1.40, NCH_3, *Z* isomer), 2.98 (s, 0.10, $=CCH_2N$), 3.15 (s, 0.4, NCH_2COCH_3), 3.55 (s, 1.43, $CH_2C_6H_5$), 3.90 (s, 0.93, $CH_2C_6H_5$, *Z* isomer), 4.30 (s, 0.05, $=CH_2$), 4.40 (s, 0.05, $=CH_2$), 4.85 (s, 0.46, *Z* olefin), 5.0 (s, 0.46, *E* olefin), 7.0–7.3 (m, 6.1, C_6H_5).

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(52) We acknowledge the assistance of D. Dillon in some experiments related to **24**.

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Table III. Isolated Yields for Ketones and Silyl Ethers

	method		
	A	B	C
3:4/5	5:82	20:35	16:80
6:7/8	2:78	10:72	9:78
9:10/11	*a*:90	NE[b]	NE[b]
12:13/14	2:86	16:45	dec
15:16/17	2:63	30:55	5:75
18:19/20	4:64	dec	NE[b]
21:22/23	5:78	11:40	14:81
24:25/26	10:75	7:73	*a*:70
27:28/29	10:75	15:80	NE[b]
30:31/32	5:85	10:77	NE[b]
33:34	5:82	30:43	40:28

[a] Not detected (<1%). [b] Not examined.

Silyl ethers 7 and 8 (R = Et) (method A): IR 1700 (very broad), 1210, 1000 cm^{-1}; NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 1.60 (s, 0.42, $=CCH_3$, *E* isomer), 1.68 (s, 1.7, $=CCH_3$, *Z* isomer), 3.10 (s, 3, OCH_3), 4.12 (m, 1.1, $NCH_2C=CH_2$), 5.55 (m, 0.57, *Z* olefin), 5.58 (m, 0.14, *E* olefin), 7.00–7.40 (m, 5, C_6H_5).

Anal. Calcd for $C_{17}H_{27}NO_3Si$: 321.176. Found: 321.178.

Silyl ether 7 (R = Et) (method B): IR 1700 (very broad), 1245, 1015 cm^{-1}; NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 1.68 (s, 3, *Z* $=CCH_3$), 2.10 (s, 0.5, $COCH_3$), 3.70 (s, 3.3, OCH_3), 4.35 (s, 0.3, NCH_2CO), 5.55 (m, 1, *Z* olefin), 7.00–7.40 (m, 5.7, C_6H_5). Less than 2% of **8** is observed.

Anal. Calcd for $C_{17}H_{27}NO_3Si$: 321.176. Found: 321.177.

Silyl ethers 7 and 8 (method C): IR 1700, 1230, 1020 cm^{-1}; NMR δ 0.40–1.00 (m, 15), 1.60 (s, 2.2, *E* vinyl CH_3), 1.68 (s, 0.7, *Z* vinyl CH_3), 2.10 (s, 0.3, $COCH_3$), 3.70 (3 s, 3, OCH_3), 4.12 (m, 0.2, NCH_2OCH_2), 4.35 (s, 0.1, NCH_2COCH_3), 5.55 (m, 0.35, *Z* olefin), 5.75 (m, 0.60, *E* olefin), 7.0–7.4 (m, 5.6, aromatic); MS *m/e* 321 (M^+), 80 (base).

Enol acetates corresponding to 7 and 8 (method A): IR 1760, 1720 (bd) cm^{-1}; NMR δ 1.35 (s, 1.7, vinyl CH_3), 1.8 (s, 2, $OCOCH_3$), 2.0 (s, 0.7, CH_2COCH_3), 2.1 (bd s, 0.4, vinyl CH_3), 3.7 (s, 3, OMe), 4.3 (bd s, 0.6, NCH_2COCH_3 and $COAc=CHH$), 4.8 (m, 0.5, $NCH_2COAc=CHH$), 6.3 (bd s, 0.8, *Z* vinyl H), 7.0–7.5 (m, 5.5); MS (70 eV) *m/e* 249 (M^+), 149 (base).

Anal. Calcd for $C_{13}H_{15}NO_4$: 249.100. Found: 249.102.

Silyl ether 11 (R = Et): NMR δ 0.40–1.05 (m, 15), 2.00 (s, 3), 5.35 (bd s, 1), 7.6–7.9 (m, 4); MS *m/e* 317 (M^+), 160 (base).

Anal. Calcd for $C_{17}H_{23}NOSi$: 317.145. Found: 317.146.

Silyl ethers 13 and 14 (method A): IR 1656 (bd), 1230, 1015 cm^{-1}; NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 2.60 (m, 0.6), 2.90 (m, 0.6), 3.35 (m, 1.4), 3.40 (m, 1.4), 4.55 (m, 0.7, olefin **13**), 5.32 (m, 0.3, olefin **14**), 7.00–7.25 (m, 5, C_6H_5); MS (70 eV) *m/e* 289 (M^+), 91 (base).

Silyl ether 13 (method B): IR 1656, 1230, 1015 cm^{-1}; NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 3.35 (m, 2), 3.40 (m, 2), 3.71 (s, 2, $CH_2C_6H_5$), 4.55 (m, 1, olefin), 7.00–7.25 (m, 5, C_6H_5); MS (70 eV) *m/e* 289 (M^+), 91 (base).

Anal. Calcd for $C_{17}H_{27}NOSi$: 289.186. Found: 289.186.

Silyl ethers 16 and 17 (R = Et): IR 1710 (bd), 1425, 1105 cm^{-1}; NMR δ 0.40–1.00 (m, 15, $SiCH_2CH_3$), 1.25 (t, 3), 2.60 (t, 1), 3.70 (m, 1), 3.89–4.29 (m, 4, OCH_2, NCH_2), 4.68 (s, 0.5, **16** olefin), 5.96 (s, 0.5, **17** olefin); MS (70 eV) *m/e* 271 (M^+), 129 (base).

Anal. Calcd for $C_{13}H_{25}NO_3Si$: 271.161. Found: 271.161.

Enol acetates corresponding to 16 and 17: NMR δ 1.25 (m, 3), 2.10 (s, 3), 2.83 (m, 2), 4.05–4.25 (m, 4), 5.55 (m, 0.5, **16** olefin), 6.68 (m, 0.5, **17** olefin).

Enol acetate corresponding to 16: isolated by preparative GC; NMR δ 1.25 (t, J = 8 Hz, 3), 2.10 (s, 3, $COCH_3$), 4.05–4.25 (m, 6), 5.55 (m, 1, olefin).

Silyl ethers 19 and 20 (R = Et): NMR δ 0.40–1.00 (m, 15.0, $SiCH_2CH_3$), 2.70–2.80 (m, 0.92), 4.10 (m, 1.54), 4.65 (m, 0.77, **19** olefin), 5.65 (m, 0.23, **20** olefin); MS (70 eV) *m/e* 231 (M^+).

Silyl ether 19 (R = Et): evaporative distillation provided only **19**: NMR δ 0.40–1.00 (m, 15), 4.10 (m, 2), 4.21 (m, 2), 4.65 (m, 1); MS (70 eV) *m/e* 231 (M^+).

Silyl ether 22 (R = Et): IR 1680, 1230 cm^{-1}; NMR δ 0.4–1.1 (m, 15), 2.0–2.2 (m, 2), 2.3–2.5 (m, 4), 2.7–2.9 (m, 2), 4.7–4.9 (m, 1); MS *m/e* 241 (M^+), 155 (base).

Anal. Calcd for $C_{13}H_{27}NOSi$: 241.186. Found: 241.185.

Silyl ether 23 (R = Et): IR 1675 (intense), 1230, 1010 cm^{-1}; NMR δ 0.41–1.51 (m), 1.9–3.0 (m), 3.4 (t, J = 6 Hz), 5.6 (s).

Anal. Calcd for $C_{13}H_{27}NOSi$: 241.186. Found: 241.183.

Silyl ethers 25 and 26 (R = Et) (method A): IR 2990, 1710 (bd), 1430 cm^{-1}; NMR δ 0.40–1.10 (m, 15), 1.25 (t, J = 2.5 Hz, 3), 1.80 (m, 2), 2.15 (m, 2), 3.50 (m, 1.6), 3.85 (m, 0.5), 4.21 (q, J = 2.5 Hz, 2), 4.98 (m, 0.24), 6.56 (m, 0.78).

Anal. Calcd for $C_{14}H_{27}NO_3Si$: 285.176. Found: 285.172.

Silyl ether 26 (R = Et): NMR δ 0.4–1.0 (m, 15, $SiCH_2CH_3$), 1.1–2.3 (m, 4), 3.2–3.6 (m, 2), 4.2 (q, $J \sim 7$ Hz, 2), 6.3, 6.4 (bd s, 1, olefin); MS (70 eV) *m/e* 285 (M^+), 217 (base).

Anal. Calcd for $C_{14}H_{27}NO_3Si$: 285.176. Found: 285.177.

Silyl ethers 28 and 29 (R = Et) (method A): IR 2980, 1700, 1200 cm^{-1}; NMR δ 0.40–1.10 (m, 15), 1.83 (m, 3.6), 2.25 (m, 2), 3.65 (m, 5.4), 4.96 (m, 0.2), 6.35 (bd s, 0.4), 6.65 (bd s, 0.3); MS (70 eV) *m/e* 309 (M^+), 309 (base).

Anal. Calcd for $C_{13}H_{22}F_3NO_2Si$: 309.139. Found: 309.139.

Silyl ether 29 (R = Et) (method B): IR 2980, 1700, 1200 cm^{-1}; NMR δ 0.40–1.10 (m, 15), 1.83 (m, 2), 2.25 (m, 2), 3.65 (m, 2), 6.35 (bd s, 0.6), 6.65 (s, 0.04); MS (70 eV) *m/e* 309 (M^+), 309 (base).

Anal. Calcd for $C_{13}H_{22}F_3NO_3Si$: 309.139. Found: 309.139.

Silyl ethers 31 and 32 (R = Et) (method A): IR 2965, 1710, 1600, 1300 cm^{-1}; NMR δ 0.90–1.10 (m, 15), 1.6–2.2 (m, 7.3), 3.65 (m, 3.3), 7.2 (m, 5).

Silyl ether 31 (R = Et): IR 1720, 1600, 1080, 1020 cm^{-1}; NMR δ 0.4–1.0 (m, 15), 1.5–1.8 (m, 4), 1.9–2.3 (m, 4), 3.8 (s, 3), 7.2 (s, 5); MS (75 eV) *m/e* 361 (M^+), 87 (base).

Anal. Calcd for $C_{20}H_{31}NO_3Si$: 361.208. Found: 361.208.

Silyl ether 34 (R = Me): IR 1660, 1250, 1200, 1140 cm^{-1}; NMR δ 0.2 (s, 6), 1.4–2.0 (m, 8), 2.4 (s, 6), 4.8 (t, J = 3 Hz, 1).

Anal. Calcd for $C_{11}H_{23}NOSi$: 213.155. Found: 213.158.

Pyrrolidinones 41–44. These were prepared according to Mauger et al.[40] and NMR data are included here.

***N*-Benzyl-4-methyl-3-pyrrolidinone 41**: NMR δ 1.10 (d, $J \sim 12$, 3, CCH_3), 2.55 (m, 1), 2.60–2.89 (m, 4), 3.65 (s, 2, $CH_2C_6H_5$), 7.10–7.30 (m, 5, aromatic).

***N*-Benzyl-2-methyl-3-pyrrolidinone 42**: NMR δ 1.20 (d, $J \sim 6.3$, 3, CCH_3), 2.40–2.70 (m, 5), 3.35 (d, J = 13.5, 1, $CH_2C_6H_5$), 4.10 (d, J = 13.5, 1, $CH_2C_6H_5$), 7.20–7.23 (m, 5, aromatic).

***N*-Carbethoxy-4-methyl-3-pyrrolidinone 43**: NMR δ 1.15 (m, 6, OCH_2CH_3, CH_3), 2.55 (m, 1, $CHCH_3$), 3.15–3.85 (m, 4), 4.20 (q, J = 12 Hz, 2, OCH_2).

***N*-Carbethoxy-2-methyl-3-pyrrolidinone 44**: NMR δ 1.15 (m, 6, OCH_2CH_3, RCH_3), 2.55 (t, J = 7.5 Hz, 2), 3.50–3.90 (m, 5), 4.20 (q, J = 12 Hz, 2, O-CH_2CH_3).

Acknowledgment. Support for portions of this work has been generously provided by UCSD (Academic Senate and Biomedical Support Funds), the American Cancer Society (Special Grant 873), and the National Cancer Institute (IR01 CA 22238 01). Mass spectra and NMR spectra were recorded on instruments at UCSD supported in part by NIH Grant RR00708 from the Division of Research Resources. Numerous chemists have provided helpful comments. R. Olofson (Penn State), F. T. Bond (UCSD), F. W. Fowler (SUNY, Stony Brook), and C. L. Perrin (UCSD) have often made timely suggestions.

Registry No. 3, 23982-57-2; **4** (R = Et), 69079-21-6; (*E*)-**5** (R = Et), 73193-38-1; (*Z*)-**5** (R = Et), 73193-39-2; **6**, 16938-99-1; **7** (R = Et), 69101-92-4; **7** enol acetate, 73193-40-5; (*E*)-**8** (R = Et), 69079-11-4; (*Z*)-**8** (R = Et), 69079-10-3; (*E*)-**8** enol acetate, 73193-41-6; (*Z*)-**8** enol acetate, 73193-42-7; **9**, 3416-57-7; **11** (R = Et), 69079-12-5; **12**, 775-16-6; **13b** (R = Et), 69079-13-6; **14** (R = Et), 69079-14-7; **15**, 14891-10-2; **16** (R = Et), 73193-43-8; **16** enol acetate, 73193-44-9; **17** (R = Et), 73193-45-0; **17** enol acetate, 73193-46-1; **18**, 73193-47-2; **19** (R = Et), 73193-48-3; **20** (R = Et), 73193-49-4; **21**, 43152-93-8; **22** (R = Et), 69079-17-0; **23** (R = Et), 69079-18-1; **24**, 61995-19-5; **25** (R = Et), 69101-93-5; **26** (R = Et), 69079-19-2; **27**, 73193-50-7; **28** (R = Et), 73193-51-8; **29** (R = Et), 73193-52-9; **30**, 69079-08-9; **31** (R = Et), 73193-53-0; **33**, 6970-60-1; **41**, 69079-25-0; **42**, 69079-26-1; **43**, 73193-54-1; **44**, 73193-55-2; benzylmethylamine, 103-67-3; chloroacetone, 78-95-5; benzylamine, 100-46-9; propylene oxide, 75-56-9; 1-(benzylamino)-2-propanol, 27159-32-6; 1-[(carbomethoxy)phenylamino]-2-propanol, 73193-56-3; 3-pyrrolidinol, 40499-83-0; 2-pyrrolidinone,

616-45-5; 2-pyrrolidinone-*N*-acetic acid, 53934-76-2; *N*-[3-(ethoxycarbonyl)propyl]glycine ethyl ester hydrochloride, 73193-57-4; *N*-(ethoxycarbonyl)-*N*-[3-(ethoxycarbonyl)propyl]glycine ethyl ester, 73193-58-5; 4,*N*-dicarbethoxy-3-piperidinone, 73193-59-6; 2,*N*-dicarbethoxy-3-piperidinone, 73193-60-9; *N*-carbethoxy-3-piperidinol, 73193-61-0; 3-piperidinol hydrochloride, 64051-79-2; *N*-(trifluoroacetyl)-3-piperidinol, 73193-62-1; cyclohexene oxide, 286-20-4; aniline, 62-53-3.

Simplex Optimization of Yields in the Bucherer–Bergs Reaction

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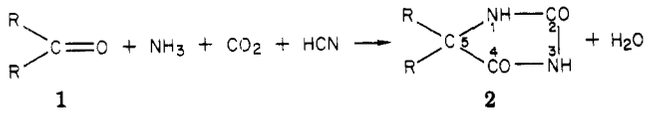
Received July 31, 1979

Yields of the spiro-4-thiohydantoins **5** (RR = $(CH_2)_5$) from cyclohexanone and **4** (X = S, Y = O) from adamantanone have been optimized by systematic variation of concentrations of reactants, temperature, time, and solvent composition, as guided by the simplex evolutionary operation. A modification of the original simplex procedure, in which variables for several experiments, rather than for one only, are specified at each step of the procedure, allows optimization to proceed more rapidly.

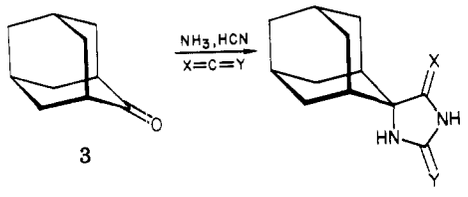
Aldehydes and ketones (**1**) react with ammonia and



1 **2**

hydrogen cyanide to give α-amino nitriles (the Strecker reaction), which may be hydrolyzed to α-amino acids.[1] However, yields with many ketones are poor, and the amino acids are often more conveniently obtained by hydrolysis of hydantoins (**2**), synthesized from ketones by reaction with hydrogen cyanide, ammonia, and carbon dioxide (the latter two in the form of ammonium carbonate). This is the Bucherer–Bergs reaction.[2] Carrington and his colleagues have introduced two variants of this reaction: one employing carbon disulfide in place of carbon dioxide and giving 2,4-dithiohydantoins;[3] the other employing carbonyl sulfide and giving 4-thiohydantoins.[4]

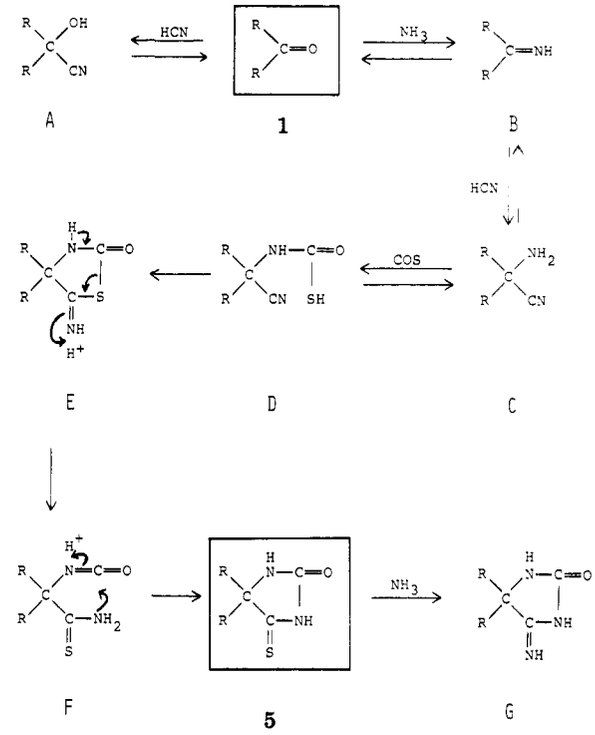
For sterically hindered ketones, even the Bucherer–Bergs reaction sometimes fails unless drastic conditions are used. Thus Nagasawa and co-workers[5] obtained the hydantoin **4** (X = Y = O) from adamantanone (**3**) by the



3 **4**

original (CO_2) procedure only by carrying out the reaction at 120 °C for 3 h in a pressure vessel. Our preliminary studies showed that under less drastic conditions (55 °C at atmospheric pressure) the reaction still took place, but slowly (12% yield of **4**, X = Y = O, after 5 days). Under these conditions Carrington's modified reactions were much faster: with carbon disulfide a 25% yield of **4** (X = Y = S) was obtained after 20 h; and with carbonyl sulfide a 22% yield of **4** (X = S, Y = O) was obtained after 3 h. Since some of the amino acids derived via hydantoins from

Scheme I



hindered ketones have interesting physiological properties,[5,6] we decided to attempt to optimize yields from the modified reaction using carbonyl sulfide.

A possible mechanism for the formation of a 4-thiohydantoin **5** from a ketone **1** is shown in Scheme I.[7,8] The equilibria **1** ⇄ A and **1** ⇄ C have been studied by Commeyras et al.[1] who have shown them to be, as expected, sensitive to pH. The subsequent steps E → F and F → **5** would also be expected to be sensitive to pH. The reaction **5** → G is discussed later.

In carrying out a conventional batchwise preparation of a 4-thiohydantoin, one may expect the yield (based on

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