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SPECIFIC ENOLATES FROM α-AMINOKETONES

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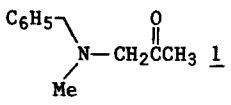
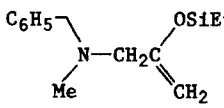
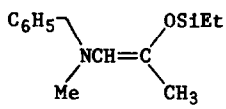
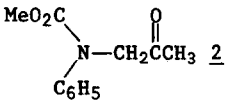
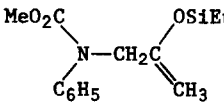
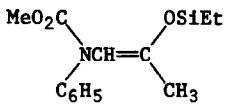
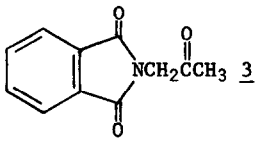
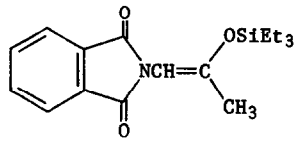
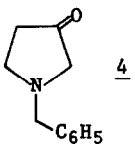
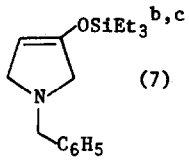
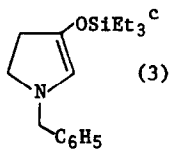
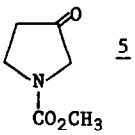
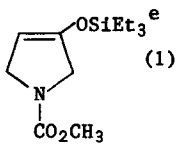
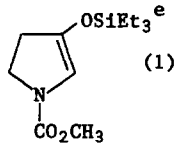
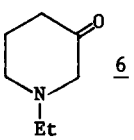
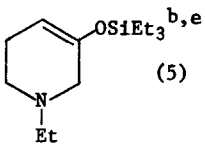
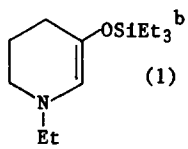
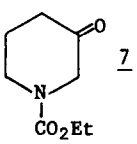
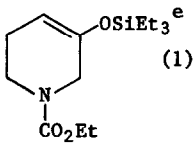
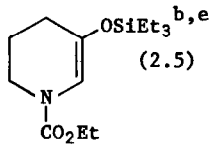
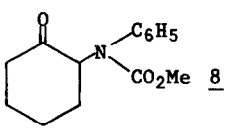
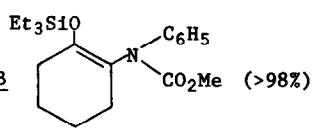
Although the effects of the α-heteroatoms halogen[1], sulfur[2], and oxygen[3] on ketone enolate formation have been documented, the effect of an α-nitrogen substituent on enolization does not appear to have been examined. We anticipate the use of enolates from α-aminoketones in alkaloid synthesis and wish to report results addressing the directionality of these enolates.

A series of α-aminoketones has been prepared and converted into the silyl enol ethers (see Table I). Two structural variables in the aminoketone were of interest to us. First, the geometry of the nitrogen/carbonyl has been changed from freely rotating acyclic species to fixed transoid (4-7) and cisoid (8) structures. Secondly, the substituents on the nitrogen are of two electronic types, alkyl groups and carbamates. Enolization of these ketones was effected by standard procedures developed by House, et al.[4] Kinetic enol ethers were formed from the ketone and strong base at low temperature and thermodynamic enol ethers by silyl chloride/triethyl amine in dimethylformamide at 80°.

Ketone 1 was prepared by simple amine alkylation of the commercial α-chloroketone. Ketones 3[5], 5[6] and 7[7] were made by classical routes. Carbamates 2 and 8 came from treatment of the appropriate oxirane with aniline followed by acylation with methylchloroformate and then Jones oxidation[8]. The silyl enol ethers were either characterized after purification by preparative vpc (1A, 1B, 2A, 2B, 6A and 6B), prepared specifically (vida infra), or characterized as a mixture. In all cases, the isomer A (enolization away from nitrogen) exhibited an olefin signal in the pmr at δ3.8 to 4.8 ppm which corresponded well with the analogous carbon systems reported by House.[4] The isomer B (enolization toward nitrogen) showed a signal in the δ5.3 to 6.3 ppm range. This downfield shift is expected on the basis of Pascal's rules.[9]

Several conclusions can be drawn from examination of the isomer distribution represented in Table I. From ketones 1,4, and 6 we have noted no geometrical effects on enolization from nitrogen. These aminoketones behave similarly to their respective carbon analogues.[4] However, the addition of electron-withdrawing groups to nitrogen encourages enolization toward nitrogen. This observation is predicted on the basis of the dipolar stabilization of anions reported by Seebach[10] and Beak.[11] A single carbamate group does not appear to be sufficient to provide complete selectivity in acetone derivative 2 or cyclic structures 5 and 7. The phthalimido

TABLE I

Ketone	Enol Products (Relative Amounts)			Yield[a]
 1	1A  (3)	1B  (1)		82%
 2	2A  (1)	2B  (4.5)		78%
 3	3B  (>98%)			90%
 4	4A  (7)	4B  (3)		86%
 5	5A  (1)	5B  (1)		63%
 6	6A  (5)	6B  (1)		78%
 7	7A  (1)	7B  (2.5)		85%
 8	8B  (>98%)			86%

(a) Isolated yield. (b) Isomers purified by prep. vpc and characterized by nmr, ir, ms, and high resolution ms. (c) Characterized as a mixture by above methods. The corresponding enol acetates were also characterized as a mixture and determined to be present in ca. the same ratio. (d) Cis and trans isomers. (e) Characterized as a mixture as above.

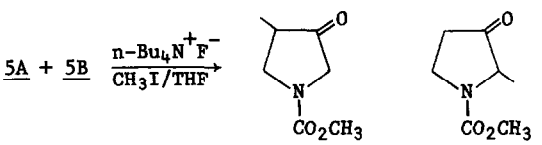
group in structure 3 gives greater dipolar stabilization and hence only formation of 3B. Carbamate 8 yields only isomer 8B probably due to the constrained cisoid geometry.[10-12] Finally, the enol ether ratios of 2, 7, and 8 suggest that 2 resembles the transoid structure of 7 more than the cisoid geometry of 8. The acidifying effect of the carbamate on adjacent protons is evident, yet not always synthetically useful.

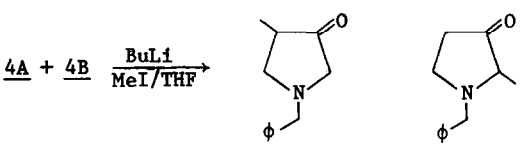
Formation of silyl enol ethers from 1, 2, 6, and 7 under "thermodynamic conditions" has yielded mainly isomer B (~90% regioselective, see Table II) in each case.[13] Carbamate pyrrolidinone 5 provided an A:B ratio of 4:1;[14] pyrrolidinone 4 afforded only decomposition products, possibly derived from 4B.[15]

TABLE II

Ketone	Ratio A:B	Yield
1	>1:19	82%
2	1:9	78%
4	Decomposition	
5	4:1	75%
6	1:6	81%
7	>1:19	70%

Finally we have preliminarily examined the reactivity of the enolates from 4 and 5 as well as the silyl enol ethers. Both 4 and 5 are alkylated by treatment with lithio diisopropyl amide followed by methyl iodide-hexamethylphosphoramide to afford mixtures of monomethylpyrrolidinones accompanied by presumed dialkylation products.[16] Treatment of 5A and 5B with tetrabutylammonium fluoride and methyl iodide by the method of Kuwajima[17,18] yielded the two alkylated ketones accompanied by 5. This procedure does not work with 4A and 4B probably due to competing N-alkylation of 4A and 4B prior to enol ether cleavage, although the enolate from 4A and 4B can be regenerated with methyl lithium and then alkylated with methyl iodide. The product ratios of monoalkylated pyrrolidinones from these reactions were similar to the kinetic enol ether ratios.





In summary, judicious choice of reaction conditions permits formation of silyl enol ethers from most α-aminoketones with excellent specificity. Methods have been outlined which in all cases except 3-pyrrolidinones yield enolization toward nitrogen.

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12. For similar geometrical arrangements see reference 1 in M. E. Jung and T. J. Shaw, Tetrahedron Lett., 3305 (1977).
13. Thermodynamic enolization of aminoketones may proceed via an ammonium ketone. Attempts to use this latter species with functionalized migrating groups (Stevens rearrangement) on 3-pyrrolidinones have not yet been successful in our hands.
14. The distribution of this enol ether is not completely unexpected based upon the stability of cyclopentenone isomers.
15. The well-known instability of $\Delta^{2,3}$ pyrroline has been overcome by R. V. Stevens, et al., Tetrahedron Lett., 3799 (1976).
16. All possible monomethyl pyrrolidinones have been prepared independently by appropriate condensation reactions (see reference 6).
17. I. Kuwajima, et al., J. Am. Chem. Soc., 98, 2346 (1976).
18. The trimethylsilyl enol ethers were used for all cleavage reactions. The trimethylsilyl ethers were prepared in the manner described and in identical A:B ratios as determined for the triethylsilyl enol ethers. Attempted cleavage of the more stable triethylsilyl ethers has led to several side products in our hands.