Enamines of 3,3-Dimethylazetidine[1]

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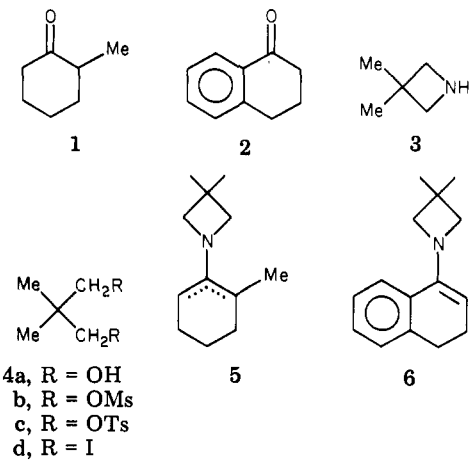
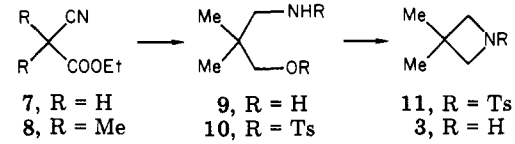
In an improvement over previous procedures, 3,3-dimethylazetidine (3) has been synthesized in 26% yield from ethyl cyanoacetate. Rates of formation for the enamines of 3 and of pyrrolidine with 2-methylcyclohexanone (1) and 1-tetralone (2) have been studied. The 5- to 10-fold rate increase observed for 3 is attributed to diminished steric hindrance relative to pyrrolidine. Compared to the enamines of pyrrolidine with 1 and 2, those of 3 methylate initially on nitrogen to a greater degree and are less selective for monomethylation. The enamine formed between 1 and 3 exists at equilibrium as an 83:17 mixture of tri- and tetrasubstituted isomers, in which the less substituted isomer has its vinyl H ^{1}H NMR peak at δ 4.10. These properties are compared to those of other enamines of 1, in which a predictive relationship had previously been suggested.

An extremely useful facet of the enamine alkylation of ketones is the large selectivity exhibited between the first and subsequent alkylation steps.[2] Frequently this allows complete but clean monoalkylation even with excesses of alkylating agent. However, the factors responsible for this selectivity often render it quite difficult to alkylate at all beyond the monosubstitution stage should it be desired to do so. Moreover, the same structural features and interactions which render polyalkylation difficult make the very formation of enamines from substituted ketones a slow process.[2b,c,3] Among the examples of this behavior cited repeatedly in the enamine literature, 2-methylcyclohexanone (1 Chart I) can be converted to its enamines, but at rates so much slower than those for cyclohexanone that acid catalysis or the toluene azeotrope or both are invariably used. Even so, rates are still extremely slow; typically, with pyrrolidine in benzene, cyclohexanone requires ca. 2 h,[2b] whereas 1 requires ca. 16 h even with toluenesulfonic acid.[4] Enamines of 1 undergo cyanation,[5] acylation,[6] Michael condensation,[2a,7] and other reactions, but under some conditions reaction with alkyl halides has led to no isolable C-alkylated product.[7a,8] Similarly, it has been claimed that formation of enamines of 1-tetralone (2) does not proceed at all without acid catalysis,[2b,9] and several of the attempted reactions of enamines of 2 have proceeded in extremely low yield.[10]

Chart I



Scheme I



A possibility which interested us was that of utilizing enamines of azetidine, since the small ring size should diminish many of the steric interactions which render ketones like 1 and 2 problematic. The questions of concern were whether azetidine enamines would form more easily than the usual ones, whether they would alkylate more easily without undergoing polyalkylation, and whether they would alkylate on carbon. The last point was of particular importance; alkylation of carbon yields a product that is trigonal at nitrogen, whereas N-alkylation gives one whose N-hybridization is tetrahedral. It was easy to imagine that, with a four-membered nitrogen ring, the latter course, leading to a species with less angle strain, would be favored.

On the other hand, a review of the literature revealed that the azetidine enamine of cyclohexanone had been reported and had a ^{1}H NMR signal for its vinyl proton which was as far or farther upfield than that of any other simple cyclohexanone enamine.[11] This large degree of

(1) Taken in part from the M.S. thesis of J.S., Rutgers University, 1980.

(2) (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. (b) Szmuszkovicz, J. *Adv. Org. Chem.* **1963**, *4*, 1. (c) Cook, A. G., Ed. "Enamines: Their Synthesis Structure and Reactions"; Marcel Dekker: New York, 1969. (d) Dyke, S. F. "The Chemistry of Enamines"; Cambridge University Press: London and New York, 1973. (e) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972.

(3) Consequently, several alternative methods have been developed for driving the enamine formation reaction to completion, e.g.: (a) Weingarten, H.; White, W. A. *J. Org. Chem.* **1966**, *31*, 4041. (b) White, W. A.; Weingarten, H. *Ibid.* **1967**, *32*, 213. (c) Nelson, P.; Pelter, A. *J. Chem. Soc.* **1965**, 5142. (d) Comi, R.; Franck, R. W.; Reitano, M.; Weinreb. S. M. *Tetrahedron Lett.* **1973**, 3107. (e) Djerassi, C.; Tursch, B. *J. Org. Chem.* **1962**, *27*, 1041. (f) Brannock, K.; Bell, A.; Burpill, R. D.; Kelly, C. A. *Ibid.* **1964**, *29*, 801. (g) Curphy, T. J.; Hung, J. C.; Chu, C. C. C. *Ibid.* **1975**, *40*, 607. (h) Mannich, C.; Davidson, H. *Ber.* **1936**, *69*, 2106. (i) Johnson, J. L.; Herr, M. E.; Babcock, J. C.; Fonken, A. E.; Safford, J. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1956**, *78*, 430. (j) Blanchard, E. P., Jr. *J. Org. Chem.* **1963**, *28*, 1937. (k) Dulou, R.; Elkik, E.; Veillard, A. *Bull. Soc. Chim. Fr.* **1960**, 967.

(4) This work; see Table I.

(5) Kuehne, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 5400.

(6) (a) Berchtold, G. *J. Org. Chem.* **1961**, *26*, 3043. (b) Schaeffer, H. J.; Jain, V. K. *Ibid.* **1964**, *29*, 2595. (c) Johnson, F.; Starkovsky, N. A.; Paton, A. C.; Carlson, A. A. *J. Am. Chem. Soc.* **1966**, *88*, 149. (d) Colonna, F. P.; Forchissin, M.; Pitacco, G.; Rosaliti, A.; Valentin, E. *Tetrahedron* **1970**, *26*, 5289.

(7) (a) House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34. (b) Fleming, I.; Harley-Mason, J. *J. Chem. Soc.* **1964**, 2165. (c) Kuehne, M. E.; Foley, L. *J. Org. Chem.* **1965**, *30*, 4280. (d) Könst, W. M. B.; Witteveen, J. G.; Boelens, H. *Tetrahedron* **1976**, *32*, 1415. (e) Hickmott, P. W.; Firrell, N. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 340.

(8) (a) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029. (b) Cf.: Stork, G.; Dowd, S. R. *Ibid.* **1963**, *85*, 2178.

(9) Williamson, W. R. N. *Tetrahedron* **1958**, *3*, 314.

(10) (a) Locke, D. M.; Pelletier, S. W. *J. Am. Chem. Soc.* **1959**, *81*, 2246. (b) Parfitt, R. T. *J. Chem. Soc. C* **1967**, 140. Paquette, L. A.; Rosen, M. *J. Org. Chem.* **1968**, *33*, 2130. Halleux, A.; Viehe, H. G. *J. Chem. Soc. C* **1970**, 881.

(11) (a) Chen, T.-Y.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1964. (b) Tourwé, D.; Van Binst, G.; De Graaf, S. A. G.; Pandit, U. K. *Org. Magn. Reson.* **1975**, *7*, 433.

0022-3263/81/1946-4907$01.25/0

Table I. Relative Rates for Enamine Formation

ketone	solvent (catalyst)	reaction time at reflux, h: pyrrolidine 50%	pyrrolidine 100%	pyrrolidine 82%	3 50%	3 100%
1	PhH	1.67		16	0.175	0.38
1	PhH (TsOH)	1.0	16			
2	PhH	120	380		24	49
2	PhH (TsOH)	51		168	0.72	6.2
2	PhMe (TsOH)	24	198			

shielding suggests strong n–π overlap even in the neutral enamine and implies that the angle strain associated with this hybridization may not be as serious as imaginable at first glance. Thus we were encouraged to hope that C-alkylation might not be seriously impeded in such enamines.

The only literature data on relative rates of enamine formation with azetidines vs. other amines appears in a brief report which contrasts the behavior toward deoxybenzoin of 3,3-dimethylazetidine (**3**) with that of 3,3,4,4-tetramethylpyrrolidine.[12] The different conditions used for the two amines prevent direct rate comparison, but it is clear that the reaction rate with **3** was at least 17 times greater, as might be expected since the pyrrolidine is obviously extremely hindered.

For our study we decided for several reasons to use 3,3-dimethylazetidine (**3**). First, its boiling point was sufficiently high (92 °C) that, like pyrrolidine (bp 85 °C), the benzene–water azeotrope could be used in forming the enamines without danger of preferentially distilling out the amine, as probably would occur with azetidine itself (bp 63 °C). Second, it seemed possible that the β disubstitution might render N-alkylation less likely.[13] In addition, we were interested in the prospect of a synthesis of **3** from 2,2-dimethylpropanediol (**4a**), a readily available and particularly cheap starting material.[12,14] Attempted reactions of the dimesylate (**4b**),[15a] ditosylate (**4c**),[15b] and diiodide (**4d**)[15c] with a variety of nitrogen species under many different conditions provided no evidence of successful displacement and usually led to high recovered yields of **4**. We therefore undertook the synthesis shown in Scheme I.

Although the previously reported preparations of **3** are characterized by poor overall yields,[12,16–18] the closure of ditosyl derivatives of 1,3-amino-propanols has been reported as successful for a variety of azetidines (but not **3**), with yields of 90% or better for the steps represented by **9** → **10** and **10** → **11**, and ca. 50% yields for the final detosylation.[19] By modification and application of these techniques to **9** we have carried out the sequence in Scheme I with an overall yield of 26%.

Results and Discussion

We have studied rates of formation in benzene of the enamines of 2-methylcyclohexanone (**1**) and of 1-tetralone (**2**) with **3** and with pyrrolidine. These results, presented in Table I, confirm that enamine formation is markedly faster for **3** than for pyrrolidine both with and without acid catalysis. For the uncatalyzed cases, where the data allows more than a single comparison to be made, the rates are consistently greater with **3** by factors of 5–10. Because of the difficulty of measuring asymptotically approached end points, data beyond 50% reaction probably should be used only for order-of-magnitude comparisons. Stork has concluded that "the rate is affected [by] the basicity and steric environment of the secondary amine...".[2a] Since the measured basicities of azetidine and pyrrolidine are negligibly different,[20] this observed rate acceleration for **3** may safely be attributed to steric factors, although "the overall rate is evidently not solely ascribable to any single one of the reversible steps...involved in the formation of the enamine".[2a]

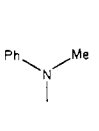
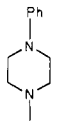
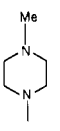
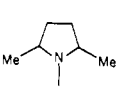
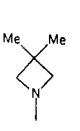
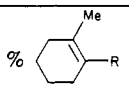
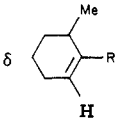
Enamines of unsymmetrical ketones like **1** are of particular interest because they exist at equilibrium as mixtures of tri- and tetrasubstituted isomers.[21,22] The effect of amine structure on the ratio of these isomers has been studied,[11b,21] and it has been suggested that higher percentages of trisubstituted enamine correlate either with strong n–π overlap (as judged by vinyl H shielding) in nonhindered cases or with diminished steric bulk in the amine.[21] The vinyl H signal for **5** is found farther upfield than that of any other reported enamine of **1**, so these correlations, taken together, would predict a very high tri-/tetrasubstituted ratio for **3**. As the observed ratio is only about 5 (cf. pyrrolidine), these correlations appear to work only roughly for **3** at best. From Table II it appears that at least as good a correlation can be made purely on the basis of ring size and steric hindrance. Hindered amines produce 90–100% tetrasubstituted isomer, six-membered rings and dimethylamine, with modest steric demands, are in the 40–60% range (diethylamine falls between these two ranges), and those with low steric hindrance produce 5–20% tetrasubstituted isomer. As in the case of **5**, the tetralone enamine **6** has its vinyl H signal farther upfield (δ 4.62 in CCl_4, 4.73 in $CDCl_3$) than that of the only other reported enamine of **2** (pyrrolidine, δ 5.0–5.19).[10b]

The methylations of **5** and **6** and of the corresponding pyrrolidine enamines (**12** and **13**, Table III) we wished to study were complicated by inhomogeneity, which prevented our obtaining representative aliquots. We therefore ran all alkylations for a fixed period of 120 h at room temperature and worked up each entire mixture for analysis. The workup, involving lengthy heating with an acetate buffer, sufficed to hydrolyze N-alkylated product, since several mixtures yielded high percentages of starting material which could only have arisen from this source.[2] In separate experiments, titration indicated that alkylation of **12** was complete within a few minutes and that of **5** within 1 h. Methylation of both **6** and **13** was extremely slow.

The N → C isomerization which occurs when N-alkylated enamine salts are heated for 18–24 h at 100 °C (either with or without excess enamine) should not occur at room temperature.[23] Hence the extents of C-alkylation we have

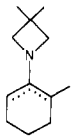
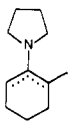
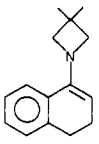
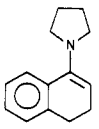
(12) (a) Hendrickson, J. B.; Sufrin, J. R. *Tetrahedron Lett.* **1973**, 1513. (b) Sufrin, J. R., Ph.D. Thesis, Brandeis University, Waltham, MA, 1972.
(13) However, see ref 12.
(14) See also: Anderson, A. G., Jr.; Wills, M. T. *J. Org. Chem.* **1968**, *33*, 2123.
(15) (a) Newman, M. S.; LeBlanc, J. R.; Karnes, H. A.; Axelrad, G. *J. Am. Chem. Soc.* **1964**, *86*, 868. (b) Nelson, E. R.; Maienthal, M.; Lane, L. A.; Benderly, A. A. *Ibid.* **1957**, *79*, 3467. (c) Campbell, A.; Rydon, H. N. *J. Chem. Soc.* **1953**, 3002.
(16) (a) Testa, E.; Fontanella, L.; Fava, F. *Farmaco, Ed. Sci.* **1958**, *13*, 152; *Chem. Abstr.* **1959**, *53*, 324c. (b) Testa, E.; Fontanella, L. *Justus Liebigs Ann. Chem.* **1959**, *625*, 95. (c) Testa, E.; Fontanella, L.; Christiani, G. F. *Ibid.* **1959**, *626*, 114. Testa, E.; Bonati, A.; Pazani, G.; Gatti, E. *Ibid.* **1961**, *647*, 92.
(17) Komppa, G.; Sevón, J. *Ann. Acad. Sci. Fenn., Ser. A.* **1933**, *37*; *Chem. Abstr.* **1933**, *27*, 3914.[9]
(18) Higgins, R. H.; Cromwell, N. H.; Paudler, W. W. *J. Heterocycl. Chem.* **1971**, *8*, 961.
(19) Vaughan, W. R.; Klonowski, R. S.; McElhinney, R. S.; Millward, B. B. *J. Org. Chem.* **1961**, *26*, 138.
(20) Perrin, D. D. *Aust. J. Chem.* **1964**, *17*, 484.
(21) Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* **1967**, *32*, 3289.
(22) (a) Mazarguil, H.; Lattes, E. *Bull. Soc. Chim. Fr.* **1969**, 319. (b) Mazarguil, H.; Lattes, E. *Tetrahedron Lett.* **1971**, 975.
(23) Kuehne, M. E.; Garbacik, T. *J. Org. Chem.* **1970**, *35*, 1555.

Table II. Isomer Distribution and Vinyl H ^{1}H NMR Position for Enamines of 2-Methylcyclohexanone (1)[a]

	R = 									
% 	97–100[b]	44[c] 49[d]	53[d] 54[b] 60[h]	55[d]	44[d] 48[b] 53[h]	75[e]	≥90[b]	40[e]	4[f] 9[h] 10[b,i] 15[j]	17[g]
δ 	5.32[b]	4.71[d]	4.62[b] 4.63[d]	4.62[d]	4.60[b] 4.65[d]	4.55[b]	4.53[b]	4.45[b]	4.14[i] 4.18[b] 4.21[j]	4.10[g,k]

[a] Unless otherwise noted, enamines were prepared with acid catalysis (therefore presumably equilibrated) and used neat for ^{1}H NMR analysis. [b] Reference 21. [c] Reference 22b; intentionally equilibrated with CF_3COOH. [d] Reference 22a; prepared without acid catalysis; $CDCl_3$ used for ^{1}H NMR. [e] Reference 21; prepared without acid catalysis but subsequently treated with MeOH to equilibrate; see references cited. [f] Reference 11b; conditions of formation not given; value determined by ^{13}C NMR on a neat sample. [g] This work. [h] Reference 6d; conditions of formation not given; $CDCl_3$ used for ^{1}H NMR. [i] Reference 7d; CCl_4 used for ^{1}H NMR. [j] Reference 7a. [k] $CDCl_3$ used for ^{1}H NMR.

Table III. Product Data for Alkylation of Enamines with MeI at 25 °C for 120 h

enamine	solvent	total recov, %	starting matl, %	% monoalkylation	% dialkylation	% trialkylation
 5	PhH	91	45	44	1.5	0.5
	THF	100	93	5	2	trace
	DMF	27	6	11	6	3
 12	PhH	100	29	71	0	0
	THF	76	41	35	trace	trace
	DMF	68	6	62	0	0
 6	PhH	56	52	4	0	
	DMF	42	41	trace	0	
 13	PhH	100	98	trace	0	
	THF	90	82	8	0	
	DMF	86	27	59	0	
	DMF-d_7[a]		98	trace	0	

[a] This reaction was run with Me_2SO_4 in a ^{1}H NMR tube; hence the amount did not permit quantitative isolation, and the yields (measured by GC) in this instance are relative, not absolute. ^{1}H NMR showed persistence of the vinyl H; therefore it is believed almost no alkylation took place.

observed at 25 °C and any C/N ratios inferrable therefrom should represent initial, unisomerized alkylations. As may be seen from Table III, when the enamines of 1 were alkylated with excess methyl iodide in solvents of low, intermediate, and high polarity, 12 was superior in every way to 5. Both absolute yields of C-alkylated material and apparent C/N ratios are worse with 5, and it is clear from the polyalkylation observed with 5 even at 25 °C that any attempts to improve C/N ratios by isomerization could only worsen the contamination by polymethylated products.

Although dialkylation was not observed with either enamine in the case of 2, both the absolute yields of C-methylated material and the C/N ratios are generally inferior with 6. Since yields of recoverable material from these 25 °C alkylations are worse than those with 6 by a factor of about 2, it is unlikely that even successful N → C isomerization could make 6 the preferable enamine here. Incidentally, Table III shows that, of the methylation procedures we have tried, the best procedure for both 1 and 2 is treatment of the pyrrolidine enamine with methyl iodide in DMF. We have not tested extension of these conditions to other substituted ketones nor whether our results could be improved by N → C isomerization.

We conclude that reducing the steric demands of the secondary amine by using an azetidine indeed produces enamines that can be formed at greater rates than ordinary, rates convenient even for hindered ketones. However, once the enamine is formed, this loss of steric bulk in the amine portion also diminishes the discrimination

for monoalkylation which makes most enamines useful. Indeed, in view of our results, it may be questioned whether it is possible to separate the factors which govern rates of formation and of polyalkylation; they may simply be identical.

^{1}H NMR data from the enamines of **3** suggested strong n–π interaction and the corresponding possibility of diminished N-alkylation; the opposite result was found. Despite β disubstitution in the azetidine, N-alkylation is a more serious problem than with the pyrrolidine enamines. The relation between the vinyl H ^{1}H NMR position in **5** and the trisubstituted–tetrasubstituted equilibrium conforms only roughly to previously suggested patterns for enamines of **1**.[21]

Experimental Section[24]

Ethyl 2-Cyano-2-methylpropionate (8). Ethyl cyanoacetate (28.2 g, 0.25 mol) was dissolved in 250 mL of THF, and 0.50 mol of NaH (24.0 g of 50% oil dispersion, washed four times with hexane) was added in four portions with stirring and cooling at intervals of ca. 45 min. Methyl iodide (106.9 g, 0.75 mol) was added in four equal portions, one after each portion of NaH. The mixture was stirred at 25 °C overnight, and precipitated NaI was removed by filtration. Partial evaporation of the solvent and dilution with Et_2O precipitated further NaI, whose complete removal was necessary before distillation. Distillation afforded 22.56 g (64.1%) of **8** as a colorless oil: bp 34 °C (0.1 mm) [lit.[25] bp 77 °C at (9 mm)]; IR (neat) 2250, 1730 cm^{-1}; ^{1}H NMR δ 1.30 (3 H, t, J = 8), 1.60 (6 H, s), 4.27 (2 H, q, J = 8).

3-Amino-2,2-dimethyl-1-propanol (9). A solution of 112.0 g (0.79 mol) of **8** in 100 mL of THF was added dropwise with cooling to a suspension of 47.7 g (1.26 mol) of $LiAlH_4$ in 800 mL of THF. The suspension was stirred at reflux for 48 h under N_2 and cooled before excess hydride was destroyed by careful addition of 150 mL of 15% NaOH, followed by 40 mL of water. The resulting suspension was stirred until all solids turned white, and then 300 mL of Et_2O was added. The granular solids removed by filtration were washed twice with 300 mL of Et_2O. The solvent was removed under reduced pressure from the combined organic portions, and distillation of the residue gave 64.05 g (78.2%) of **9** as a colorless oil, bp 184–187 °C (lit.[26] bp 185–188 °C). This material solidified but was used without further purification:[27] IR (Nujol) broad NH/OH, no C≡N or C=O; ^{1}H NMR δ 0.87 (6 H, s), 2.63 (2 H, s), 2.86 (3 H, s, disappears with D_2O), 3.40 (2 H, s).

2,2-Dimethyl-3-(*p*-toluenesulfonamido)-1-propanol *p*-Toluenesulfonate (10). *p*-Toluenesulfonyl chloride (324.1 g, 1.70 mol) in 500 mL of pyridine was added slowly with stirring to a solution of 85.3 g (0.837 mol) of **9** in 2.5 L of pyridine at 5 °C. After the resulting solution was stirred for 1 h and then heated to 80 °C, the precipitate formed upon recooling to 30 °C was removed by filtration and washed twice with 200 mL of pyridine. The combined pyridine solutions were concentrated to ca. 900 mL and diluted with 2.5 L of water, resulting in two layers. The solids obtained by crystallization of the separated organic layer were washed with water and dried to yield 270 g (79.4%) of **10** as white needles: mp 110–112 °C (unchanged by recrystallization from EtOH); IR (Nujol) 3230, 1600, 1325, 1175, 1155 cm^{-1}; ^{1}H NMR δ 0.88 (6 H, s), 2.45 (6 H, s), 2.75 (2 H, d, J = 7), 3.70 (2 H, s), 4.97 (1 H, t, J = 7), 7.27 (2 H, d, J = 8), 7.30 (2 H, d, J = 8), 7.70 (2 H, d, J = 8), 7.73 (2 H, d, J = 8).

Anal. Calcd for $C_{19}H_{25}NO_5S_2$: C, 55.45; H, 6.12; N, 3.40; S, 15,58. Found: C, 55.44; H, 6.22; N, 3.57; S, 15.57.

1-(*p*-Toluenesulfonyl)-3,3-dimethylazetidine (11). To a solution prepared by dissolving 2.0 g (0.05 mol) of K in 1.5 L of *tert*-butyl alcohol was added 20.5 g (0.05 mol) of **10**, and the solution was refluxed for 20 min. After the mixture cooled, a second identical portion of K was added, the mixture was stirred until H_2 evolution ceased, a second 20.5 -g portion of **10** was added, and the mixture was refluxed for 12 h. Removal of the solids precipitated by cooling to 40 °C and removal of the solvent yielded an amber oil which solidified on standing. This was dissolved in 200 mL of MeOH and reprecipitated with 200 mL of water, yielding 20.9 g (87.7%) of **11** as a pale yellow waxy solid, mp 60–62.5 °C. Recrystallization from MeOH–water raised the melting point to 62–64 °C: IR (Nujol) 1595, 1335, 1160 (b) cm^{-1}; ^{1}H NMR δ 1.03 (6 H, s), 2.43 (3 H, s), 3.42 (4 H, s), 7.30 (2 H, d, J = 8), 7.67 (2 H, d, J = 8).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.44; H, 7.20; N, 5.98; S, 13.67.

3,3-Dimethylazetidine (3). To a solution of 41.9 g (0.175 mol) of **11** in 1 L of *n*-amyl alcohol was added 75.0 g (3.62 mol) of Na in ca. 1-g pieces over a period of 3 h. After being stirred at reflux for 96 h, the solution was cooled, and 500 mL of water was added. The mixture was allowed to stand for 24 h in a separatory funnel, during which time the layers separated.

The reaction was repeated with 81.1 g (0.34 mmol) of **11** in 2 L of *n*-amyl alcohol with 150 g (6.52 mol) of Na. After reflux and dilution the solution was distilled, and the fraction boiling up to 100 °C was collected. This was combined with the alcohol layer from the first reaction and extracted with 2 N H_2SO_4 until the aqueous layer remained acidic. The combined aqueous extracts were washed twice with 75 mL of Et_2O and then saturated with KOH. The upper of the resulting two layers was distilled, and the fraction boiling up to 100 °C was collected, resaturated with KOH, and allowed to stand for 48 h. The upper layer was again separated and distilled over KOH, yielding 32.5 g (74.2%) of **3** as colorless oil, bp 88–92 °C (lit. bp 88–91 °C,[12] 90–92 °C[16]). The ^{1}H NMR spectrum indicated absence of *n*-amyl alcohol: δ 1.22 (6 H, s), 3.08 (1 H, s), 3.32 (4 H, s). Material from a similar preparation was characterized as the picrate, mp 186–189 °C (lit.[16c] mp 189–190 °C).

Preparation of Enamines. The ketone (34.0 mmol) was refluxed with a 1.65-fold excess of amine (56.0 mmol) in 100 mL of benzene or toluene, with a Dean–Stark water trap. Catalyzed reactions employed 67 mg (0.34 mmol) of *p*-toluenesulfonic acid monohydrate. Progress of formation was followed by adding 420 mg of triphenylmethane to the above reactants and withdrawing a series of aliquots, whose ^{1}H NMR area ratios were compared after removal of all volatiles under high vacuum. Progress was also followed by measuring the volume of water collected in the calibrated trap; results for these two methods were comparable in all cases.

The enamines of **3** were found to decompose when distillation was attempted. Therefore excess starting material and solvent were removed under high vacuum at as low a temperature as possible, and **5** and **6** were used in crude form. Enamines **12** and **13** were distilled at 0.1–0.5 mm and gave physical and spectral data consistent with those in the literature.

Alkylation of the Enamines. A weight of enamine corresponding theoretically to 20.0 mmol was dissolved in 20 mL of solvent, and a 1-mL aliquot was removed and titrated with 0.10 N HCl to determine the exact amount of enamine present. Methyl iodide (5.68 g, 40.0 mmol) was then added. After standing for 120 h at ambient temperature, the solvent was removed under aspirator vacuum, and the product was hydrolyzed with 100 mL of a buffer prepared from 50 g of NaOAc, 100 mL of HOAc, and 500 mL of water. This mixture was refluxed for 2 h, sealed, and held at 80 °C for 24 h. After cooling, the mixture was extracted three times with 25 mL of Et_2O, and the organic portions were combined and extracted three times with 25 mL of 2% HCl and

(24) Melting points were determined with a Laboratory Devices Mel-Temp or a Hoover-Thomas Uni-Melt apparatus and are uncorrected, as are boiling points. Infrared (IR) spectra were taken by using a Perkin-Elmer 137 NaCl spectrometer. NMR spectra were taken with Hitachi Perkin-Elmer R-24A and Varian T-60A spectrometers by using $CDCl_3$ solutions and Me_4Si and/or CH_2Cl_2 internal standards; coupling constants are given in hertz. Gas chromatographic (GC) analyses were carried out by using a 6 ft × $^1/_8$ in. column packed with 10% UC W-98 silicone on 80–100-mesh support and a Hewlett-Packard 5750 instrument with flame-ionization detectors. All reactions were run under N_2 with glassware oven dried at 150 °C for several hours before use. All solvents were from newly opened containers supplied by Aldrich, Baker, or Fisher, who also supplied reagents. Solvents used for alkylations were dried with 4A molecular sieves for 1 week before use. Microanalyses were kindly performed by F. Scheidl, through the courtesy of Hoffmann-La Roche, Inc.

(25) Hessler, J. C. *J. Am. Chem. Soc.* **1913**, *35*, 990.

(26) Brannock, K. C.; Lappin, G. R. *J. Am. Chem. Soc.* **1955**, *77*, 6052.

(27) Caldwell, J. R., U.S. Patent 2618658, 1952; *Chem. Abstr.* **1953**, *47*, 9997*h*.

finally with 25 mL of saturated NaCl. The dried solution was evaporated to constant weight at 35 °C (8 mm). From this weight and GC data the percent total recovery and product distribution were calculated.

Attempts to follow the rate of alkylation by titrating aliquots with acid and to determine C- vs. N-alkylation by back-titrating with base were frustrated by precipitation of salts, which prevented uniform sampling. However, the results obtained indicated that **12** was completely alkylated within 5 min, almost exclusively at nitrogen. Enamine **5** required 1 h for complete methylation and showed a small amount of C-alkylation, which could not be accurately determined. Both **6** and **13** were extremely slow in alkylating.

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Registry No. 1, 583-60-8; 2, 529-34-0; 3, 19816-92-3; 3 picrate, 79201-13-1; 5 (1-ene-2-methyl), 79201-14-2; 5 (1-ene-6-methyl), 79201-15-3; 6, 79201-16-4; 7, 105-56-6; 8, 1572-98-1; 9, 26734-09-8; 10, 79201-17-5; 11, 79201-18-6; 12 (1-ene-2-methyl), 5049-40-1; 12 (1-ene-6-methyl), 5049-51-4; 13, 7007-34-3; pyrrolidine, 123-75-1.

Reactions of Dimedone with Sulfur Chlorides

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A comparative study of the reactions of dimedone (1), as a representative β-diketone, with various simple sulfur chlorides has revealed that the product distribution observed can best be accounted for in terms of competing mechanisms of oxygen attack or carbon attack (at C-2) in the enol form. Oxygen attack is particularly important with SCl_2 and S_2Cl_2 and appears to involve a subsequent intramolecular transfer of Cl (or ClS) to C-2, via an intermediate such as **12**. The relative electrophilicity of the reagents and the facility with which **12** can be expected to rearrange to a C-2 substituted product appear to be among the factors influencing the course of these reactions. Some of the reactions show promise as synthetic routes to potentially useful dimedone derivatives.

The reactions of various classes of active methylene compounds with the simple chlorides of sulfur have frequently been reported, and, in particular, much recent work has focussed on the reactivity of thionyl chloride toward such substrates.[1,2] Less frequently, other recent reports have described the reactivity of the simple sulfur chlorides (SCl_2 and S_2Cl_2)[3] and of sulfenyl chlorides (RSCl)[4] with similar organic substrates. Curiously, given the potential mechanistic similarities, we are not aware of any systematic investigation of the comparative behavior of the above reagents with a common substrate. We have now carried out such an investigation, as an extension of our recent studies[5] on the behavior of malondiamides with disulfur dichloride. We decided to use the easily accessible, relatively simple β-diketone 5,5-dimethyl-1,3-cyclohexanedione (dimedone, **1**) as our standard substrate for reaction with disulfur dichloride (S_2Cl_2), sulfur dichloride (SCl_2), thionyl chloride, sulfuryl chloride,[6] and methanesulfenyl chloride, the results of which we now present.

Results and Discussion

Our initial experiments were carried out by using the reaction of disulfur dichloride with **1**, as Naik[7] had earlier reported the isolation of the thiosulfine (dithio ketone) **2** (Chart I) from the reaction of dimedone with disulfur dichloride under comparable conditions. We have recently shown[5] that other earlier claims by Naik et al. to have prepared thiosulfines from the reaction of substituted

Chart I

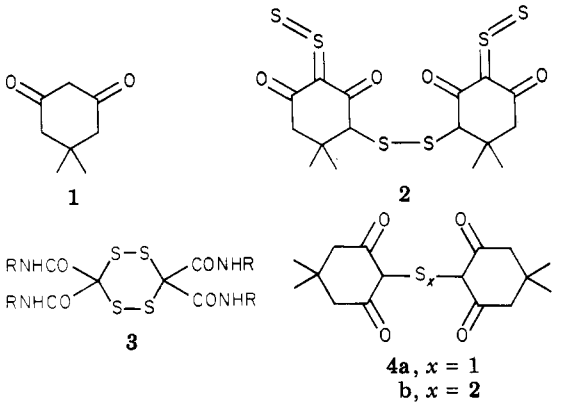

Table I.[a] Product Yields[b] from Reactions of 1 with Sulfur Chlorides

sulfur chloride	yield, % 4a	2-Cl-1 (5)	2,2-Cl_2-1 (6)	other
S_2Cl_2	84			
SCl_2	5	48		
$SOCl_2$[c]	5[d]			5[d] (7)
				2[d] (8)
SO_2Cl_2		26	66	

[a] All reactions were carried out in benzene at 25 °C for 18 h with 2 mol of the sulfur chloride, unless noted otherwise. [b] Isolated yields of chromatographically pure material. [c] A short reaction time (1 h) gave **15a** as the major product (58%) along with recovered **1** (62%). [d] Reaction allowed to proceed for 2 weeks at 25 °C.

(1) (a) Oka, K.; Hara, S. *Tetrahedon Lett.* **1977**, 695. (b) Oka, K.; Hara, S. *Ibid.* **1977**, 3059. (c) Oka, K.; Hara, S. *J. Org. Chem.* **1978**, *43*, 4533.

(2) (a) Senning, A. *Bull. Soc. Chim. Belg.* **1977**, *86*, 675. (b) Tsolomitis, A.; Sandris, C. *J. Heterocycl. Chem.* **1980**, *17*, 1645. (c) Sehgal, R. K.; Krubsack, A. J. *Synth. Commun.* **1980**, *10*, 245. (d) Adiwidjaja, G.; Günther, H.; Voss, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 563. (e) Ireland, C. J.; Pizey, J. S. *J. Chem. Soc., Chem. Commun.* **1972**, 4.

(3) (a) Gompper, R.; Euchner, H.; Kast, H. *Justus Liebigs Ann. Chem.* **1964**, *675*, 151. (b) Gupta, S. K. *J. Org. Chem.* **1974**, *39*, 1944. (c) Senning, A. *Bull. Soc. Chim. Belg.* **1980**, *89*, 323. (d) Ito, S.; Mori, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3403.

(4) (a) Gustaffson, R.; Rappe, C.; Levin, J.-O. *Acta Chem. Scand.* **1969**, *23*, 1843. (b) Kay, I. T.; Lovejoy, D. J.; Glue, S. *J. Chem. Soc. C* **1970**, 445.

(5) Kutney, G. W.; Still, I. W. J. *Can. J. Chem.* **1980**, *58*, 1233.

(6) Sulfuryl chloride was included in the study essentially for completeness, as its well-documented behavior as an oxidizing agent makes it a rather unique sulfur chloride derivative.

(7) Naik, K. G. *J. Chem. Soc.* **1921**, 1231.

0022-3263/81/1946-4911$01.25/0