Silylamines in Organic Synthesis. Reactivity of *N,N*-Bis(silyl) Enamines toward Electrophiles. A Route to Substituted 2-Aza-1,3-butadienes and Pyridines

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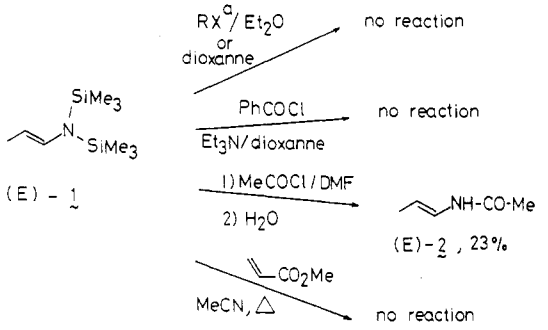
N,N-Bis(silyl) enamines appeared to be weak nucleophilic reagents and exhibited a very low reactivity toward electrophiles. However, in the presence of a nucleophilic catalyst, nucleophilic activation of the silicon–nitrogen bond was observed. Under fluoride ion catalysis (TBAF or CsF), *N,N*-bis(silyl) enamines reacted with carbonyl compounds to give substituted 2-aza-1,3-butadienes. Good yields were obtained in reactions with aromatic aldehydes or ketones. In the case of aliphatic carbonyl compounds, 2-aza 1,3-dienes were only formed in moderate yields. Interestingly, enamidines were easily obtained in high yields upon reactions of dimethylformamide in the presence of MeONa as catalyst. The reaction of aromatic α,β-unsaturated ketones gave 2-aza 1,3,5-trienes, which were not isolated but underwent an intramolecular cycloaddition reaction with regioselective formation of substituted 2,4-diarylpyridines.

Introduction

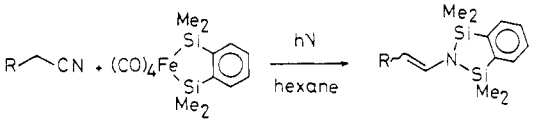
Aminosilanes[1] having one or two silicon–nitrogen bonds represent a class of potential reagents or intermediates for organic synthesis. Interestingly, the silicon–nitrogen bond in these compounds can play two roles. In the case of bis(silyl)amines or monosilylamines with bulky substituents at silicon, the silicon–nitrogen bond can withstand a variety of reaction conditions providing efficient protection of primary and secondary amines.[2-5] On the other hand, the silicon–nitrogen bond can, however, be cleaved by electrophiles in many cases. The formation of nitrogen to carbon bond can be obtained from aminosilanes,[6-14] providing useful new synthetic routes.

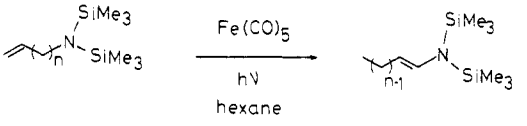
As part of our effort to develop the use of silylamines for the synthesis of organic nitrogen compounds and heterocycles, we examined the possible uses of bis(silyl) enamines. Several synthetic routes to these compounds, which are the nitrogen analogues of enol silyl ethers, have been proposed.[15-20] We, for example, reported easy and general preparations of bis(silyl) enamines by use of a chemioselective silylation of nitriles with a silyl iron carbonyl complex[17] (eq 1) or by iron carbonyl photocatalyzed isomerization of unsaturated amines[18] (eq 2).

Scheme I. Attempted Reactions of Enamine 1



[a] RX = MeI, $PhCH_2Br$, .





Bis(silyl) enamines having two silyl substituents at nitrogen can be expected to present a reactivity different from that of the well-known carbon enamines.[21] We have already reported that they exhibit remarkable stability in the presence of nucleophilic reagents.[17] No cleavage of the silicon–nitrogen bond by $LiAlH_4$, Grignard, or lithium reagents was observed. Hydrolysis to aldehydes only occurred in acidic media. We now give a detailed account

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(17) (a) Corriu, R. J. P.; Moreau, J. J. E.; Pataud-Sat, M. *J. Org. Chem.* **1981**, *46*, 3372. (b) Corriu, R. J. P.; Moreau, J. J. E.; Pataud-Sat, M. *Orgamometallics* **1985**, *4*, 623.
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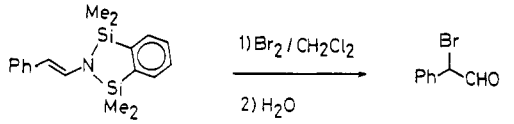
of the reactivity of bis(silyl) enamines toward electrophilic reagents. We show that whereas they are considerably less reactive than their carbon analogues, interesting new reactions can be performed, especially in the presence of nucleophilic catalysts. A portion of this study has been communicated.[11]

Results and Discussion

1. Reactions of Bis(silyl) Enamines with Electrophiles. *N,N*-Bis(silyl) enamines prepared from nitriles[17] or by isomerization of allylic amines[18] were reacted with various electrophilic reagents. Some attempted reactions of (*E*)-propenylamine **1** are presented in Scheme I.

Under the reaction condition used in the case of carbon enamines,[21] we did not observe any alkylation reaction upon treatment with methyl iodide, allyl bromide, or benzyl bromide in ether or dioxane. Similarly, no acylation reaction was observed with benzoyl chloride in the presence of Et_3N/dioxane. Reaction of acetyl chloride occurred in dimethylformamide at 80 °C to give a moderate yield of enamide by cleavage of the silicon–nitrogen bond. No reaction of ethyl acrylate was observed upon heating at 60 °C in acetonitrile. Under these reaction conditions essentially no reaction was observed and contrary to carbon enamines, no carbon–carbon bond formation occurred.

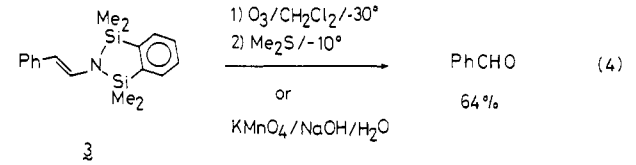
We also examined the reactions of strong electrophilic reagents such as bromine. Addition to enamine **1** probably occurred at low temperature. However, the adduct rapidly decomposed, probably via elimination of bromosilane.[20] The expected α-bromo aldehyde was isolated only in the reaction of enamine **2** prepared from benzyl cyanide[22] (eq 3).



(3)

3 **4**, 49%

We also tried oxidation of the enamine double bond. The reaction of enamines **1** and **3** with MCPBA gave a complex mixture and no hydroxy aldehyde was isolated. The reaction of stronger oxidizing agents resulted in the cleavage of the carbon–carbon bond. Ozonolysis or $KMnO_4$ oxidation[23] gave benzaldehyde (eq 4).

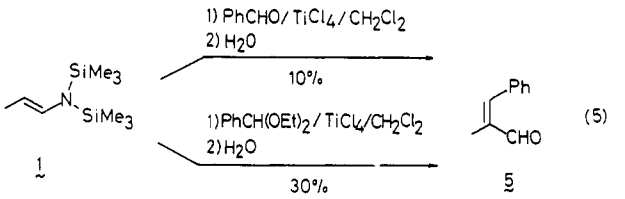


(4)

3

The reactions of bis(silyl) enamines in the presence of Lewis acid were also examined. We did not observed the formation of C-acylation products upon reaction of acetyl or benzoyl chloride in the presence of titanium tetrachloride or aluminum chloride. However, some reaction at the β-carbon atom was observed in the reaction of benzaldehyde or its diethyl acetal, as shown in eq 5. A low yield of α-methylcinnamaldehyde (**5**) was obtained.

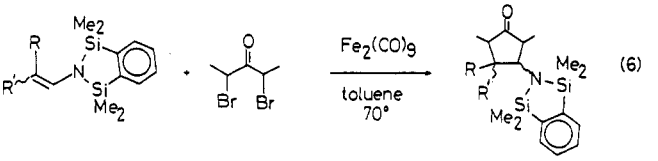
Bis(silyl) enamines thus appeared to be of low reactivity with most electrophiles. We also examined some transition-metal-mediated reactions. Enamines were reacted with α,α'-dibromo ketones according to the procedure of Noyori and co-workers.[24] The reaction of enamines **6–9**



(5)

1 **5**

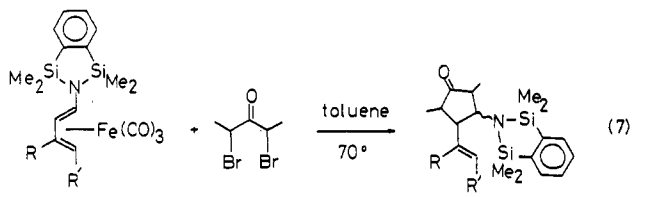
in the presence of $Fe_2(CO)_9$ led to [bis(silyl)amino]cyclopentanone derivatives **10–13** (eq 6). However, pure compounds were isolated in only 15–20% yields.



(6)

R = R' = H, **6**, **10**, 15%.
R = R' = Me, **7**, **11**, 20%.
R = Ph, R' = H, **8**, **12**, 20%.
R = OMe, R' = H, **9**, **13**, 17%.

Interestingly, the iron carbonyl complex of dienamines **14** and **16**[17] reacted without added $Fe_2(CO)_9$ to give a 20% yield of enamino cyclopentanones **15** and **17**, respectively (eq 7). Addition of $Fe_2(CO)_9$ did not improve the yield. In contrast with 1,3-dienic amines[24] only 1,2-addition was observed here.



(7)

R = H, R' = Me2Si, N, Si, Me2 (**14**), **15**, 20%.
RR' = $-(CH_2)_4-$, **16**, **17**, 18%.

From this study, bis(silyl) enamines appeared to be quite stable and much less reactive than the carbon analogues. Owing to the stability of the silicon–nitrogen bond, they represent protected aldehydes. When more drastic reaction conditions were used, mainly decomposition occurred and no evidence for a synthetically useful reaction was obtained.

2. Nucleophilic Activation of the Silicon–Nitrogen Bond. 2.1. Access to Substituted 2-Aza-1,3-butadienes. Nucleophilic activation at silicon has been shown to enhance the reactivity of Si–H, Si–O, and Si–C bonds.[25] We found similarly that bis(silyl) enamines present an enhanced reactivity in the presence of a nucleophilic catalyst. The activation of the silicon–nitrogen bond resulted in the formation of a carbon–nitrogen bond with electrophilic reagents. The reactions of enamine **1** are presented in Scheme II.

Whereas no reaction was observed in the absence of catalyst, the CsF-catalyzed reaction of benzoyl chloride

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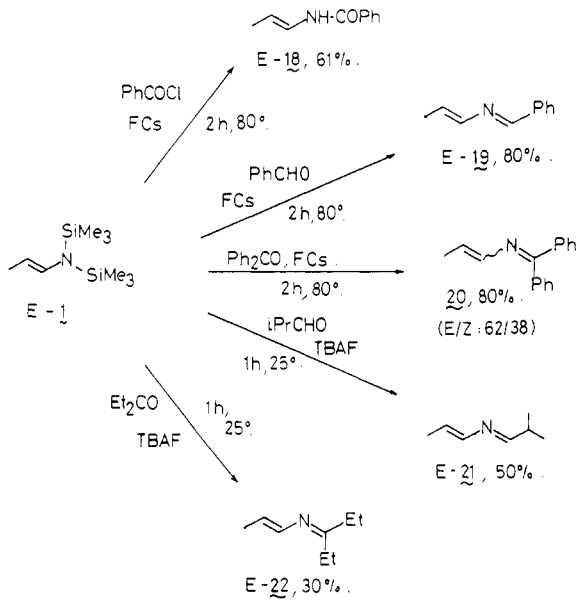
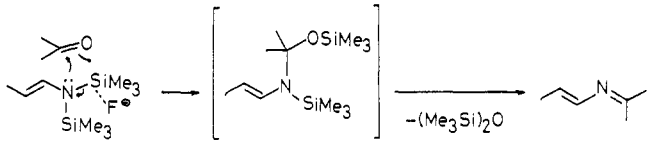
Scheme II. Fluoride Ion Catalyzed Reactions of Propenylamine 1 with Electrophiles



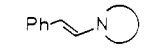
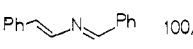
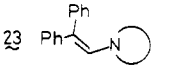
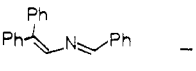
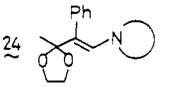
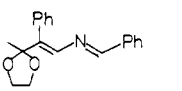
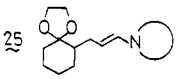
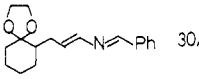
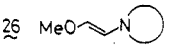
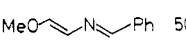
Scheme III



gave the enamide 18 in 61% yield. Interestingly the reaction of carbonyl compounds gave rise to substituted 2-aza-1,3-butadienes **19–22**. The reactions were carried out by using 5% CsF in DMF at 80 °C or 5% TBAF in THF at room temperature. Good yields were obtained with benzaldehyde and benzophenone. However, aliphatic carbonyl compounds gave lower yields owing to a competing enolization and crotonization reaction. In all reactions with the exception of benzophenone, the *E* configuration of the carbon–carbon double bond of the enamine was retained. The assignment of the *E* stereochemistry of the carbon–nitrogen double bond is based on previously recorded spectroscopic properties. The ^1H NMR spectra of all compounds showed a singlet for C*H*=N protons and are in agreement with reported values.[26] The formation of the hetero diene can be explained according to Scheme III.

Nucleophilic attack of the nitrogen atom in 1 on the carbonyl group was followed by a β-elimination of hexamethyldisiloxane, which was identified in the reaction mixture. As previously reported for nucleophilic substitution activated by nucleophiles,[25] the role of the fluoride catalyst is to weaken the silicon–nitrogen bond through coordination at the silicon center. It is at first surprising to observe exclusively nucleophilic attack by an anionic nitrogen. We assume that this reaction at the carbonyl is controlled by the subsequent elimination of disiloxane. This behavior contrasts sharply with that of silyl enol ethers[27] or *N,N*-dialkyl enamines[21] for which nucleophilic attack occurs at the β-carbon atom. It is also noteworthy

Table I. Reactions of Cyclic Bis(silyl) Enamines with Benzaldehyde According to Eq 8

	starting enamine[a]	*E/Z*		reaction product[b]	*E/Z*	yield (%)
3		100/0	27		100/0	65
23		–	28		–	67
24		c	29			65
25		56/44	30		30/70	50
26		40/60	31		50/50	42

a) —N stands for

[b] ^1H NMR spectra of all compounds showed a singlet for C*H*=N protons. [c] Only one isomer was used; the configuration of the double bond was not determined.

that monosilyl enamines have been reported to give C-acylation products under fluoride ion catalysis and aldol condensation reactions.[28] Bis(silyl) enamines therefore display a peculiar chemical behavior.

From a synthetic viewpoint, the reaction of carbonyl compounds provides a simple route to 2-aza 1,3-dienes, for which few general syntheses are available.[29–31] Hetero dienes have been extensively used in the synthesis of six-membered heterocycles.[32] Extension of the reaction to nitrogen-containing dienes, particularly 2-aza 1,3-dienes, has received much recent attention.[33,34] Bis(silyl) enamines are useful precursors of hetero dienes. The reaction has been extended to the case of bis(silyl) enamines derived from nitriles (eq 8). The enamines **3** and **23–26** present a similar reactivity. 2-Aza 1,3-dienes were obtained in

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(31) (a) Schoeni, J. P.; Fleury, J. P. *Tetrahedron* **1975**, *31*, 671. (b) Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, *40*, 1349. (c) Dehnel, A.; Finet, J. P.; Lavielle, G. *Synthesis* **1977**, 474. (d) Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866. (e) Chen, S. F.; Mariano, P. S. *Tetrahedron Lett.* **1985**, *26*, 47. (f) Barluenga, J.; Joglar, J.; Fustero, S.; Gotor, V.; Kruger, C.; Romao, M. J. *Chem. Ber.* **1985**, *118*, 3652. (g) Lasarte, J.; Palomo, C.; Picard, J. P.; Dunogues, J.; Aizpurua, J. M. *J. Chem. Soc., Chem. Commun.* **1989**, 72.

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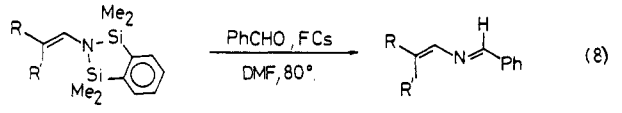


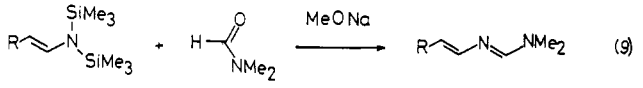
(8)

3,23-26 27-31.

yields ranging from 42 to 67%

The results are presented in Table I. It is noteworthy that aza dienes derived from functional enamines were obtained. Whereas the reaction is somewhat limited to nonenolizable carbonyl compounds, a variety of hetero dienes are accessible.

Interestingly, we observed a related reaction with the carbonyl group in *N,N*-dimethylformamide. In this case, no reaction occurred in the presence of fluoride ion but sodium methoxide or potassium *tert*-butoxide proved to be efficient catalysts. The reaction of enamines **1** and **32** gave high yields of enamidines **33** and **34**, respectively (eq 9).



(9)

1, R = Me
32, R = Me_3SiCH_2

33, R = Me
34, R = Me_3SiCH_2

It provided an easy access to enamidines,[33,35] which have been shown to be worthwhile precursors of pyridines.[33]

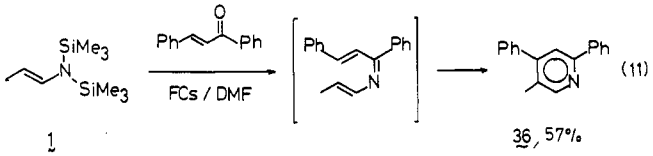
2.2. Access to Substituted Pyridines. In order to examine some possible heterocyclization reactions, we studied the reaction of α,β-unsaturated carbonyl compounds. According to the previous reactions, the formation of an aza triene should be observed upon reaction on the carbonyl group in an enone. The formation of a six-membered nitrogen heterocycle should then be possible upon an intramolecular cycloaddition reaction.

The reaction of enamine **1** with cinnamaldehyde in the presence of 5% TBAF in THF was found to give the expected aza triene, arising from the Peterson-type reaction of the silyl enamine. It was, however, isolated in only 29% yield owing to the moderate stability of the compound (eq 10). Attempted intramolecular cyclization of triene **35** failed; polymers were mainly formed.

(10)

1 35, 29%

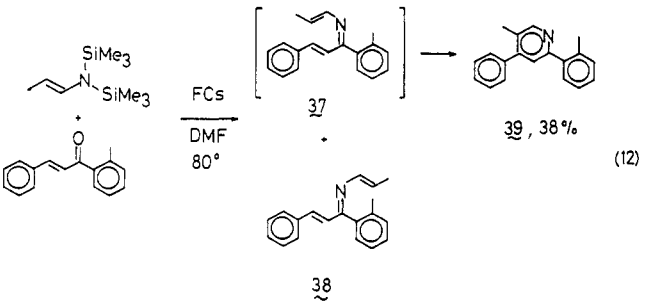
This was not so in the case of chalcone, for which the reaction with enamine **1** in the presence of CsF allowed isolation of 3-methyl-2,4-diphenylpyridine (**36**) in good yield (eq 11).



(11)

1 36, 57%

The pyridine **36** probably arose from the initial formation of a 2-aza 1,3,5-triene intermediate by a mechanism analogous to that presented in Scheme III. This intermediate could then undergo intramolecular cyclization reaction probably to a dihydropyridine, which oxidized to the aromatic pyridine under the reaction conditions. According to this mechanism the formation of the pyridine involves a selective 1,2-addition process of the enamine to the chalcone. The regioselectivity of the heterocyclization reaction was established by a reaction involving an unsymmetrical chalcone, as shown in eq 12.



37 39, 38%

(12)

38

The reaction led to the isolation of pyridine **39**, the structure of which was established unambiguously. The ^1H NMR spectrum is consistent with the proposed structure and addition of $Eu(fod)_3$ to the NMR sample caused an approximately 0.3 ppm downfield shift of the three signals attributed to the pyridine proton α to the nitrogen atom and to the ortho and methyl protons of the tolyl substituent. Pyridine **39** therefore arose from the intramolecular cyclization of aza triene **37**. Analysis of the crude reaction mixture by NMR revealed the presence of signals (in addition to those of pyridine **39**) at δ values (ppm) 1.6 (3 H, dd), 2.4 (3 H, s), 5.2 (1 H, dq), 6.2 (1 H, d). They may correspond to the propenyl ($CH_3CH{=}CH$) and tolyl (CH_3Ph) substituents in the triene isomer **38**. It is possible that the triene **38** with *E* stereochemistry of the C=N bond cannot be cyclized. However, pure triene **38** could not be obtained and decomposed on attempted isolation.

From a synthetic point of view, the reaction offers a regioselective access to substituted pyridine rings. It appears, however, to be limited to chalcone-type enones. The reaction could only be extended to a variety of aromatic enones (eq 13).

(13)

1 39-44

A regioselective one-pot synthesis of 2,4-diarylpyridines was obtained. The formation in the initial step of two triene isomers, only one of which can cyclize, may account for the moderate yields of pyridines. The results are summarized in Table II. Aromatic substituted and heteroaromatic pyridines were obtained accordingly.

Conclusion

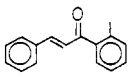
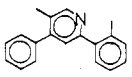
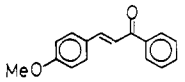
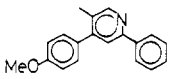
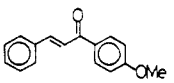
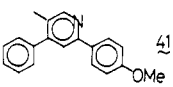
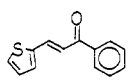
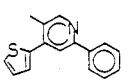
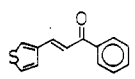
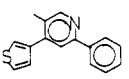
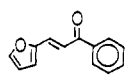
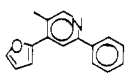
N,N-Bis(silyl) enamines exhibit very weak nucleophilic character when compared to carbon enamines or enol silyl ethers. They are stable to many electrophilic reagents under usual reaction conditions. In the presence of a nucleophilic catalyst, however, enamines appear quite reactive toward carbonyl compounds. Upon activation of the Si–N bond, aza dienes, enamidines, and pyridines are selectively obtained.

Experimental Section

General Remarks. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer in the form indicated. The

(35) (a) Cook, L. S.; Wakefield, B. J. *Tetrahedron Lett.* **1976**, 147. (b) Cook, L. S.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. I* **1980**, 2392.

Table II. Reactions of Enamine 1 with Aromatic Enones According to Eq 13

enone	reaction conditions[a]	pyridine		isolated yield (%)
	4h,80°C		39	38
	2h,80°C		40	50
	2h,80°C		41	34
	5h,80°C		42	35
	5h,80°C		43	25
	3h,80°C		44	42

[a] All reactions were performed by using 5% CsF as catalyst in *N,N*-dimethylformamide.

^{1}H NMR spectra were measured on Varian EM 360 or EM 390 spectrometer and ^{13}C NMR spectra on a Brucker WP 200 apparatus. Chemical shifts (δ ppm) are relative to Me_4Si. The mass spectra were obtained on a JEOL JMS D100 apparatus. Elemental analyses were carried out by the Service Central de Microanalyse du CNRS. Satisfactory C, H, N analyses (±0.3%) were obtained for the new compounds. Solvents were dried and distilled before use. The preparation of *N,N*-bis(silyl) enamines has been previously described either by isomerization of allylic amines[18] or silylation of nitriles.[17,22] Cesium fluoride was dried by heating at 100 °C in vacuo for 2 h. A commercial 1 M solution of tetrabutylammonium fluoride (TBAF) in THF was used.

Reactions with Electrophiles. Reaction of Enamine 1 with Acetyl Chloride. Enamine 1, 2.01 g (0.01 mol), and 0.78 g (0.01 mol) of acetyl chloride in 20 mL of *N,N*-dimethylformamide were stirred at 80 °C for 2 h. After cooling, the reaction mixture was hydrolyzed with water, extracted with ether, and dried over $MgSO_4$. After removal of the solvent, distillation of the residue afforded 0.23 g (23%) of enamide **2** (lit.[18] bp 125 °C) having identical characteristics with those reported.[36]

Bromination of Enamine 3. To a solution containing 3.0 g (0.01 mol) of enamine **3** in 20 mL of CH_2Cl_2 at −78 °C was added 0.6 mL (0.01 mol) of bromine in 10 mL of CH_2Cl_2. The mixture was warmed to +10 °C and Et_3N (1.08 g, 0.01 mol) was added. The mixture was filtered, concentrated, and hydrolyzed with an acidic aqueous solution (pH ~1). Extraction with ether, drying over Na_2SO_4, and evaporation of the solvent gave a brown oil, which was distilled. The bromophenylacetaldehyde (**4**), 0.98 g (49%), was collected: bp$^{0.1}$ 78 °C (lit.[37] bp$^{0.8}$ 78–80 °C); IR (CCl_4, cm^{-1}) ν(C=O) 1745; ^{1}H NMR (CCl_4, δ) 3.6 (1 H, s), 7.5 (5 H, m), 9.2 (1 H, s); mass spectrum *m/e* 198 (M^+, ^{79}Br).

Ozonolysis of Enamine 3. Ozone was passed through a solution containing 4.0 g (0.013 mol) of enamine **3** in 100 mL of CH_2Cl_2 at −30 °C. The mixture was then warmed to −10 °C, an excess Me_2S (5 mL) was added, and the solution was stirred for 1 h at room temperature. Evaporation of the solvent and distillation of the residue gave 0.88 g (64%) of benzaldehyde.

Potassium Permanganate Oxidation of Enamine 3. The reaction was performed as described.[23] A solution containing 6.18 g (0.02 mol) of enamine **3**, 0.8 g (0.02 mol) of NaOH, and 0.33 g (0.9×10^{-3} M) of $CH_3(CH_2)_{13}N(CH_2Ph)(CH_3)_2Cl$ in 40 mL of CH_2Cl_2 and 40 mL of H_2O was cooled to 5 °C. $KMnO_4$ (3.14 g, 0.02 mol) was then added in small portions over 2 h and the mixture stirred for 16 h at 5 °C. Extraction with ether and elimination of the solvents followed by distillation allowed isolation of 0.64 g (30%) of benzaldehyde.

Reaction of Enamine 1 with Benzaldehyde. To a solution of benzaldehyde (2.64 g, 0.025 mol) and 2.75 mL (0.025 mol) of $TiCl_4$ in 20 mL of CH_2Cl_2 at −78 °C was added slowly 5.0 g (0.025 mol) of enamine **1**. The mixture was stirred for 5 h, warmed to 0 °C, and hydrolyzed by addition of water. Extraction with ether, drying over $MgSO_4$ and distillation gave 0.37 g (10%) of α-methylcinnamaldehyde (**5**): bp^{20} 13 °C (lit.[14] bp 125 °C); IR (CCl_4, cm^{-1}) ν(C=O) 1690; ^{1}H NMR (CCl_4, δ) 1.9 (3 H, d), 7.0 (1 H, d, J = 2 Hz), 7.3 (5 H, m); mass spectrum *m/e* 146 (M^+).

Reaction of Enamine 1 with Benzaldehyde Diethyl Acetal. The reaction was performed as above, using 5.0 g (0.025 mol) of enamine 1, 4.48 g (0.025 mol) of benzaldehyde diethyl acetal, and 2.75 mL (0.025 mol) of $TiCl_4$ in 20 mL of CH_2Cl_2. The mixture was stirred for 16 h at −78 °C and hydrolyzed at 0 °C. α-Methylcinnamaldehyde (1.1 g, 30% yield) was isolated.

Reactions of Enamines 6–9 with α,α'-Dibromopentanone. Enamine 6. A solution containing 1.35 g (0.006 mol) of enamine **6**, 1.41 g (0.006 mol) of α,α'-dibromopentanone, and 2.20 g (0.006 mol) of iron nonacarbonyl in 20 mL of toluene was stirred at 70 °C for 20 h. The solution was then diluted with 50 mL of ethyl acetate and washed first with an aqueous saturated $NaHCO_3$ solution and then with KNO_3 solution. The solvent was then evaporated of the residue extracted with pentane and filtered quickly through Celite. Crystallization at −20 °C afforded 0.28 g (15%) of colorless crystals of amino ketone **10**: bp 98–99 °C; IR (CCl_4, cm^{-1}) ν(C=O) 1745; ^{1}H NMR (CCl_4, δ) 0.2 (12 H, s), 0.9 (3 H, d), 1.0 (3 H, d), 1.8 (4 H, m), 3.0 (1 H, dt), 7.3 (4 H, m); mass spectrum *m/e* 317 (M^+).

Enamine 7. The above procedure with 2.3 g (0.009M) of enamine **7** allowed isolation of 0.61 g (20%) of colorless crystals of amino ketone **11**: mp 115.5–116.5 °C; IR (CCl_4, cm^{-1}) ν(C=O) 1745; ^{1}H NMR (CCl_4, δ) 0.2 (12 H, s) 0.7 (3 H, s) 0.8 (3 H, d), 0.9 (3 H, d), 1.0 (3 H, s), 1.7 (1 H, q), 2.1 (1 H, m), 3.0 (1 H, d) 7.3 (4 H, m); mass spectrum *m/e* 345 (M^+).

Enamine 8. From 1.22 g (0.005 mol) of enamine **8**, according to the above procedure, 0.44 g (20%) of amino ketone **12** were collected as colorless crystals. mp 145–146 °C; IR (CCl_4, cm^{-1}) ν(C=O) 1745; ^{1}H NMR (CCl_4, δ) 0.1–0.4 (12 H, m), 1.2 (3 H, d), 2.3–3.9 (4 H, m), 7.4 (9 H, m); mass spectrum *m/e* 393 (M^+).

Enamine 9. As above, from 2.33 g (0.009 mol) of methoxy enamine **9**, 0.53 g (17%) of amino ketone **13** were obtained: IR (CCl_4, cm^{-1}) ν(C=O) 1750; ^{1}H NMR (CCl_4, δ) 0.4 (12 H, s), 1.0 (3 H, d), 1.1 (3 H, d), 1.7–2.8 (3 H, m), 3.3 (3 H, s), 3.7 (1 H, m), 7.4 (4 H, m); mass spectrum *m/e* 347 (M^+).

Reactions of Dienamines 14 and 16 with α,α'-Dibromopentanone. Dienamine 14. The procedure was as described previously for enamines **6–9**. Starting with 2.46 g (0.004 mol) of dienamine **14**, crystallization from hexane gave 0.45 g (20%) of compound **15**: mp 159–160 °C; IR (CCl_4, cm^{-1}) ν(C=O) 1745, ν(C=C) 1650; ^{1}H NMR (CCl_4, δ) 0.1 (24 H, m), 0.9 (3 H, d), 1.0 (3 H, d), 1.4–2.6 (3 H, m), 2.8 (1 H, m), 4.5 (1 H, q), 6.0 (1 H, d, J = 14 Hz), 7.3 (8 H, m); mass spectrum *m/e* 548 (M^+).

Dienamine 16. As above, from 7.4 g (0.015 mol) of dienamine **16**, 1.07 g (18%) of ketone **17** were isolated: mp 126–127 °C; IR (CCl_4, cm^{-1}) ν(C=O) 1745; ^{1}H NMR (CCl_4, δ) 0.1 (6 H, s), 0.2 (6 H, s), 0.85 (3 H, d), 0.9 (3 H, d), 1.45 (4 H, m), 1.85 (4 H, m), 1.9–2.3 (3 H, m), 3.0 (1 H, q), 5.5 (1 H, t), 7.3 (4 H, m); mass spectrum *m/e* 397 (M^+).

Nucleophilic Activation of *N,N*-Bis(silyl) Enamines. Reactions of Enamine 1. With Benzoyl Chloride. Enamine 1 (2.01 g, 0.01 mol) and benzoyl chloride (1.40 g, 0.01 mol) were dissolved in 10 mL of DMF and stirred with 0.076 g (5 mol % of CsF) for 2 h at 80 °C. The mixture was then cooled, hydrolyzed by addition of 10 mL of H_2O, and extracted with ether. After drying and evaporation of the solvents, the residue was distilled. Enamide **18** (0.98 g, 61%) was collected, bp$^{0.1}$ 120–130 °C. The compound crystallized upon cooling: mp 91–92 °C; IR (CCl_4, cm^{-1}) ν(N—H) 3310, ν(C=C) 1640; ^{1}H NMR (CCl_4, δ) 1.7 (3 H, d), 5.4 (1 H, dq, J = 13 Hz), 6.8 (0.5 H, d, J = 13 Hz), 7.0 (0.5 H, d, J = 13 Hz), 7.2–8.0 (5 H, m), 9.5 (0.5 H, s), 9.7 (0.5 H, s); mass spectrum *m/e* 161 (M^+).

With Benzaldehyde. As above, a mixture of enamine 1 (2.01 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in 10 mL of DMF

(36) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.
(37) Riehl, J. J. *C. R. Acad. Sci. Paris* **1957**, *245*, 1321.

was stirred for 2 h at 80 °C. After hydrolysis, the previous workup allowed distillation of 1.16 g (80%) of aza diene **19**: $bp^{0.1}$ 67 °C (lit.[38] bp^{9} 98–100 °C); ^1H NMR (CCl_4, δ) 1.9 (3 H, d), 6.1 (1 H, dq, J = 13 Hz), 7.2 (1 H, d, J = 13 Hz), 7.6 (5 H, m), 8.1 (1 H, s); mass spectrum m/e 145 (M^+).

With Benzophenone. The reaction of 2.01 g (0.01 mol) of enamine **1** and 1.82 g (0.01 M) of benzophenone in the presence of 0.076 g (5 mol %) of CsF in 10 mL of DMF allowed isolation of 1.77 g aza dienes **20** (80%): $bp^{0.1}$ 101–104 °C; E/Z = 62:38; ^1H NMR (CCl_4, δ) 1.7 (0.62 × 3 H, d), 2.1 (0.38 × 3 H, d), 5.3 (0.38 H, qd, J = 7 Hz), 6.1 (0.62 H, qd, J = 13 Hz), 6.6 (0.38 H, d), 6.7 (0.62 H, d), 7.0–7.8 (10 H, m); mass spectrum m/e 221 (M^+).

With Isobutyraldehyde. A mixture of enamine **1** (2.01 g, 0.01 mol) and isobutyraldehyde (0.72 g, 0.01 mol) in 30 mL of THF, containing 0.5 mL of a 1 M solution of TBAF in THF, was stirred at room temperature for 1 h. The mixture was then hydrolyzed and extracted with ether. Distillation gave 0.56 g (50%) of aza diene **21**: bp^{18} 40 °C; IR (CCl_4, cm^{-1}) ν(C=C) 1630; ^1H NMR (CCl_4, δ) 1.3 (6 H, d), 1.9 (3 H, d), 2.6 (1 H, m), 5.9 (1 H, qd, J = 13 Hz), 6.5 (1 H, d, J = 13 Hz), 7.5 (1 H, d); mass spectrum m/e 111 (M^+).

With Diethyl Ketone. The same procedure using 0.86 g (0.01 mol) of diethyl ketone led to the isolation of 0.38 g (30%) of aza diene **22**: bp^{18} 60–70 °C; ^1H NMR (CCl_4, δ) 1.0 (6 H, t), 1.5 (3 H, d), 2.2 (4 H, q), 5.6 (1 H, qd, J = 13 Hz), 6.7 (1 H, d, J = 13 Hz); mass spectrum m/e 125 (M^+).

Reactions of Enamines 3 and 23–26 with Benzaldehyde. Enamine 3. The reaction was performed as for enamine **1**, using 3.1 g (0.01 mol) of enamine **3**. Aza diene **27**, 1.35 g (65%), was collected, bp^{3} 160 °C, and was recrystallized from hexane: mp 51–53 °C; ^1H NMR (CCl_4, δ) 6.0 (1 H, d, J = 13 Hz), 6.9 (1 H, d, J = 13 Hz), 7.0–8.1 (10 H, m), 8.2 (1 H, s); mass spectrum m/e 207 (M^+).

Enamine 23. As above, 3.85 g (0.01 mol) of enamine **23** led to 1.90 g (67%) of aza diene **28**, which was crystallized from heptane: mp 124–126 °C; IR (CCl_4, cm^{-1}) ν(C=C) 1627; ^1H NMR (CCl_4, δ) 7.0–7.3 (16 H, m), 8.2 (1 H, s); mass spectrum m/e 283 (M^+).

Enamine 24. From 3.95 g (0.01 mol) of enamine **24**, 1.91 g (65%) of aza diene **29** were obtained: mp 76–78 °C; IR (CCl_4, cm^{-1}) ν(C=C) 1625; ^1H NMR (CCl_4, δ) 1.4 (3 H, s), 3.9 (4 H, s), 7.2–7.7 (11 H, m), 8.2 (1 H, s); mass spectrum m/e 293 (M^+).

Enamine 25. Similarly, 3.87 g (0.01 mol) of enamine **25** (E/Z = 56:44) upon reaction with benzaldehyde gave 1.43 g (50%) of aza diene **30**: $bp^{0.01}$ 138 °C (E/Z = 30:70); IR (CCl_4, cm^{-1}) ν(C=C) 1647; ^1H NMR (CCl_4, δ) 1.0–2.2 (8 H, m), 2.6 (2 H, t), 3.9 (4 H, s), 5.4 (0.7 H, qd, J = 8 Hz), 6.0 (0.3 H, td, J = 13 Hz), 6.7 (0.7 H, d), 7.2–7.8 (5.3 H, m), 8.0 (0.3 H, s), 8.1 (0.7 H, s); mass spectrum m/e 285 (M^+).

Enamine 26. Similarly, 2.63 g (0.01 mol) of enamine **26** (E/Z = 40:60) and benzaldehyde gave 0.68 g (42%) of methoxy aza diene **31**: bp^{22} 153–156 °C; E/Z = 50:50; IR (CCl_4, cm^{-1}) ν(C=C) 1655; ^1H NMR (CCl_4, δ) 3.5 (0.5 × 3 H, s), 3.7 (0.5 × 3 H, s) 5.5 (0.5 H, d, J = 5 Hz), 5.6 (0.5 H, d, J = 5 Hz), 6.3 (0.5 H, d, J = 12 Hz), 6.8 (0.5 H, d, J = 12 Hz), 7.0–7.6 (5 H, m), 7.70 (0.5 H, s), 7.72 (0.5 H, s); mass spectrum m/e 161 (M^+).

Reaction of Enamine 1 with DMF. Enamine **1** (4.02 g, 0.02 mol) in 10 mL of *N,N*-dimethylformamide was stirred in the presence of 0.22 g (20 mol %) of MeONa at 80 °C for 2 h. After cooling, the reaction mixture was poured onto a mixture of 30 mL of H_2O and 30 mL of ether, extracted with ether, dried over $MgSO_4$, and distilled. Enamidine **33**, 1.83 g (82%), was collected: bp^{20} 88 °C; IR (CCl_4, cm^{-1}) ν(C=C) 1630; ^1H NMR (CCl_4, δ) 1.6 (3 H, d, J = 7 Hz), 2.9 (6 H, s), 5.25 (1 H, dq, J = 13 Hz), 6.4 (1 H, d, J = 13 Hz), 7.3 (1 H, s); mass spectrum m/e 112 (M^+).

Reaction of Enamine 32 with DMF. The reaction of 5.5 g (0.02 mol) of enamine **32** (E/Z = 30:70) was performed as above for enamine **1**. Enamidine **34** (E/Z = 30:70), 2.2 g (60%), was collected: bp^{20} 95–100 °C; ^1H NMR (CCl_4, δ) 0.0 (9 H, s), 1.6 (2 H, d), 2.9 (6 H, s), 4.6 (0.7 H, td, J = 8 Hz), 5.3 (0.3 H, td, J = 13 Hz), 5.8 (0.7 H, td), 6.3 (0.3 H, td, 7.2 (0.3 H, s), 7.3 (0.7 H, s); mass spectrum m/e 170 (M^+).

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Reactions of Enamine 1 with Unsaturated Carbonyl Compounds. Cinnamaldehyde. A mixture of enamine **1** to give (2.01 g, 0.01 mol) and cinnamaldehyde (1.32 g, 0.01 mol) in 30 mL of THF was stirred for 1 h in the presence of 0.5 mL of a 1 M solution of TBAF in THF. After hydrolysis and the usual workup, 0.5 g (29%) of aza triene **35** were obtained: $bp^{0.01}$ 96–98 °C; IR (CCl_4, cm^{-1}) ν(C=C) 1660; ^1H NMR (CCl_4, δ) 1.7 (3 H, d, J = 7 Hz), 6.0 (1 H, dq, J = 13 Hz), 6.6 (1 H, d, J = 13 Hz), 6.8–7.5 (7 H, m), 7.7 (1 H, d, J = 7 Hz); mass spectrum m/e 171 (M^+).

Chalcone. A mixture containing 4.02 g (0.02 mol) of enamine **1** and 4.15 g (0.02 mol) of chalcone in 10 mL of DMF was stirred for 2 h at 80 °C in the presence of 0.3 g (5 mol %) of CsF. The dark brown-black reaction mixture was hydrolyzed by addition of 10 mL of water to give a pale yellow mixture, which was extracted with ether, dried over Na_2SO_4, and pumped to dryness. The residual oil was distilled to give 2.8 g (57%) of 5-methyl-2,4-diphenylpyridine (**36**): ^1H NMR (CCl_4, δ) 2.25 (3 H, s), 6.9–8.1 (11 H, m), 8.3 (1 H, s); mass spectrum m/e 245 (M^+).

2'-Methylchalcone. The reaction was carried out as above, using 4.44 g (0.02 mol) of 2'-methylchalcone and an excess of enamine **1** (6.0 g, 0.03 mol). The reaction product was purified by TLC, using silica gel plates and a 9:1 CH_2Cl_2/Et_2O mixture as eluant. Pyridine **39**, 1.97 g (38%), was obtained as an oil: ^1H NMR (CCl_4, δ) 2.2 (3 H, s), 2.4 (3 H, s), 7.0–7.4 (10 H, m), 8.4 (1 H, s); ^1H NMR (after addition of 30 mg of Eu(FOD)$_3$ to the sample) 2.2 (3 H, s), 2.7 (3 H, s), 7.0–7.4 (9 H, m), 7.5 (1 H, s), 8.7 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 16.97, 20.39, 124.52, 125.98, 128.12, 128.26, 128.63, 128.80, 129.85, 130.91, 136.02, 139.58, 140.49, 149.57, 150.94, 158.06; mass spectrum /e 259 (M^+).

4-Methoxychalcone. The reaction of 4.0 g (0.02 mol) of enamine **1** and 4.7 g (0.02 mol) of 4-methoxychalcone allowed isolation of 2.7 g (50%) of pyridine **40**: ^1H NMR (C_6D_6, δ) 2.2 (3 H, s), 3.7 (3 H, s), 6.9 (1 H, s), 7.1 (1 H, s), 7.2–7.4 (3 H, m), 7.55 (1 H, s), 7.8–8.1 (2 H, m), 8.45 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 17.06, 55.25, 114.07, 121.00, 126.84, 128.12, 128.76, 129.08, 129.95, 131.82, 139.58, 147.71, 151.39, 155.41, 159.70; mass spectrum m/e 275 (M^+).

4'-Methoxychalcone. The reaction of 2.0 g (0.01 mol) of enamine **1** and 2.4 g (0.01 mol) of 4'-methoxychalcone gave 0.95 g (34%) of pyridine **41**: ^1H NMR (CCl_4, δ) 2.1 (3 H, s), 2.6 (3 H, s), 6.65 (2 H, d, J = 9 Hz), 7.0–7.4 (6 H, m), 7.85 (2 H, d, J = 9 Hz), 8.35 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 16.84, 55.26, 114.20, 120.23, 126.94, 127.49, 128.08, 128.62, 129.72, 132.05, 139.71, 150.03, 151.12, 155.09, 160.48; mass spectrum m/e 275 (M^+).

2-Thenylideneacetophenone. The reaction of 2.0 g (0.01 mol) of enamine **1** and 2.1 g (0.01 mol) of 2-thenylideneacetophenone gave 0.87 g (35%) of pyridine **42**: ^1H NMR (CCl_4, δ) 2.2 (3 H, s), 6.9–7.6 (9 H, m), 8.3 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 18.06, 120.78, 126.98, 127.80, 128.22, 128.90, 128.99, 139.26, 140.67, 142.50, 151.90, 155.73; mass spectrum m/e 251 (M^+).

3-Thenylideneacetophenone. The reaction of 2.0 g (0.01 mol) of enamine **1** and 2.1 g (0.01 mol) of 3-thenylideneacetophenone gave 0.63 g (25%) of pyridine **43**: ^1H NMR (CCl_4, δ) 2.2 (3 H, s), 7.0–7.6 (9 H, m), 8.3 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 17.43, 120.78, 124.25, 126.07, 126.94, 128.26, 128.85, 129.31, 144.78, 151.58, 155.64; mass spectrum m/e 251 (M^+).

2-Furfurylideneacetophenone. From 5.0 g (0.025 mol) of enamine **1** and 4.0 g (0.02 mol) of 2-furfurylideneacetophenone, 1.97 g (42%) of pyridine **44** were isolated: ^1H NMR (C_6D_6, δ) 2.3 (3 H, s), 6.2 (1 H, q), 6.4 (1 H, d), 7.0–7.3 (4 H, m), 7.8 (3 H, m), 8.2 (1 H, s); ^{13}C NMR ($CDCl_3$, δ) 18.66, 111.84, 112.12, 116.72, 127.03, 128.86, 137.52, 139.58, 143.36, 151.59, 152.17, 155.87; mass spectrum m/e 235 (M^+).

Registry No. **1**, 63163-76-8; **2**, 5202-80-2; **3**, 78108-67-5; **4**, 16927-13-2; **5**, 66051-14-7; **6**, 78108-63-1; **7**, 78108-66-4; **8**, 125877-27-2; **9**, 83576-00-5; **10**, 125877-28-3; **11**, 125877-29-4; **12**, 125877-30-7; **13**, 125877-31-8; **14**, 95192-89-5; **15**, 125877-32-9; **16**, 95192-88-4; **17**, 125877-33-0; (*E*)-**18**, 5202-76-6; (*E*)-**19**, 68003-58-7; (*E*)-**20**, 83575-90-0; (*Z*)-**20**, 83575-91-1; (*E*)-**21**, 125877-34-1; (*E*)-**22**, 83575-95-5; **23**, 78108-69-7; **24**, 125877-35-2; (*E*)-**25**, 78108-77-7; (*Z*)-**25**, 78108-78-8; (*E*)-**26**, 78108-72-2; (*Z*)-**26**, 78108-73-3; **27**, 125877-36-3; **28**, 125877-37-4; **29**, 125877-38-5; (*E*)-**30**, 125877-39-6; (*Z*)-**30**, 125877-40-9; (*E*)-**31**, 125901-75-9; (*Z*)-**31**, 125877-41-0; (*E*)-**32**, 89333-80-2; (*Z*)-**32**, 89333-79-9; **33**, 125877-42-1; (*E*)-**34**, 125877-43-2; (*Z*)-**34**, 125877-44-3; **35**, 125877-45-4; **36**, 83575-92-2;

39, 125877-46-5; 40, 125877-47-6; 41, 125877-48-7; 42, 125877-49-8; 43, 125877-50-1; 44, 125877-51-2; TBAF, 429-41-4; CsF, 13400-13-0; $TiCl_4$, 7550-45-0; $PhCH(OEt)_2$, 774-48-1; Ph_2CO, 119-61-9; *i*-PrCHO, 78-84-2; PhCHO, 100-52-7; PhCH=CHCHO, 104-55-2; PhCH=CHCOPh, 94-41-7; α,α'-dibromopentanone, 815-60-1; iron nonacarbonyl, 15321-51-4; diethyl ketone, 96-22-0; *N,N*-dimethylformamide, 68-12-2; 2'-methylchalcone, 13565-43-0; 4-methoxychalcone, 959-33-1; 4'-methoxychalcone, 959-23-9; 2-thenylideneacetophenone, 39511-11-0; 3-thenylideneacetophenone, 123293-65-2; 2-furfurylideneacetophenone, 39511-12-1.

Intramolecular 1,4-Dipolar Cycloaddition: A New Approach to the Assembly of Ring-Fused Heterocycles

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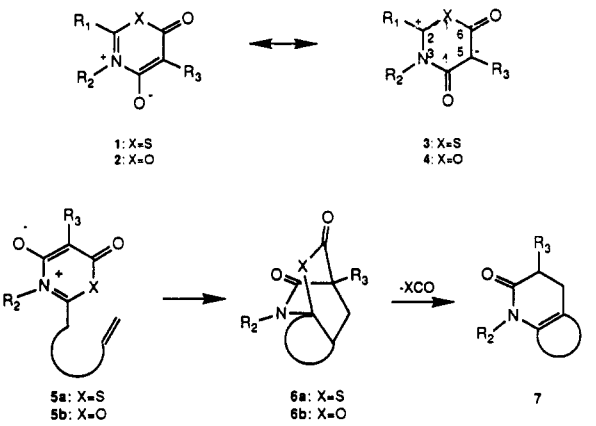
A new approach to ring-fused heterocycle construction involves facile intramolecular 1,4-dipolar cycloadditions with *anhydro*-4-hydroxy-6-oxo-1,3-thiazinium and -oxazinium hydroxides containing the dipolarophilic side chain (alkynes and alkenes) at the 2-position of the thiazinium and oxazinium nucleus and leads to benzo[*h*]-pyrano[4,3-*b*]pyridin-2(1*H*)-ones. The *anhydro*-4-hydroxy-6-oxo-1,3-oxazinium hydroxides were not isolated, being generated in situ from the appropriately substituted benzamides and substituted malonyl dichlorides. The oxazinium cycloadditions were characterized by their "one-pot" nature, the extreme ease with which they occurred, the high yields of pure products obtained, and their versatility. In both series alkenic side chains led to endo cycloadducts; methyl substitution on the alkene resulted in exo cycloadducts. Heating the thiazinium cycloadducts at 200 °C resulted in the loss of COS and rearrangement of the intermediate ylidic species to 3,4-dihydro-benzo[*h*]pyrano[4,3-*b*]pyridin-2(1*H*)-ones via a 1,5-H shift. Similarly, the oxazinium cycloadducts lost CO_2 at 80-200 °C, giving the pyridin-2(1*H*)-ones in excellent yields. With alkynic side chains the cycloadducts were not isolated. Cycloreversion occurred under these reaction conditions, giving benzo[*h*]pyrano[4,3-*b*]pyridin-2-(1*H*)-ones.

Intramolecular dipolar cycloadditions have found[2] widespread application in synthetic organic chemistry, and while intramolecular 1,3-dipolar cycloadditions are becoming well-established methods for the synthesis of ring-fused heterocyclic systems, there have been only a few reports[3] of intramolecular 1,4-dipolar cycloadditions in this important area of chemistry.

In this publication we describe the intramolecular 1,4-dipolar cycloaddition of *anhydro*-1,3-thiazinium hydroxides **1** and *anhydro*-1,3-oxazinium hydroxides **2**, both being cross-conjugated mesomeric betaines containing the elements of a 1,4-dipole as in **3** and **4**. Attachment of a suitable dipolarophilic side chain in the 2-position of **1** and **2** results in a system **5** which underwent intramolecular cycloaddition to a cycloadduct **6**, which, on heating, lost XCO, forming the ring-fused 2(1*H*)-pyridinone **7**.



I. Intramolecular Cycloadditions with *anhydro*-1,3-Thiazinium Hydroxides

Alkenic- and alkynic-substituted *anhydro*-4-hydroxy-6-oxo-2,3,5-trisubstituted-1,3-thiazinium hydroxides have been prepared and are described in Table I. Betaines **8**, **10**, **11**, **16**, **17**, and **25** were readily available by cyclocondensation of the appropriate thioamide[5] with (chlorocarbonyl)phenylketene, while the 5-unsubstituted betaines **29** and **30** were prepared from the appropriate thioamide and carbon suboxide.[6] These last two betaines were unstable and satisfactory analytical data could not be

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