(m, 10, cyclohexyl CH_2), 2.65 (s, 2, CH_2), 3.18 (m, 1, CH); MS, m/e 210 (M^+). Anal. Calcd for $C_{11}H_{22}N_2Si$: C, 62.80; H, 10.54; N, 13.31. Found: C, 62.62; H, 10.55; N, 13.24.

(ii) From Isothiocyanates 9. A solution of iminophosphorane **3a**, which was prepared from azide 1 (1.29 g, 10 mmol) and phosphine **2a** (2.62 g, 10 mmol) in dry benzene (10 mL), was refluxed with ethyl isothiocyanate (**9c**) (0.87 g, 10 mmol) for 1 h. The solvent was evaporated in vacuo, and the residue was extracted with hexane (50 mL). The extract was concentrated in vacuo, and bulb-to-bulb distillation of the residue gave 1.26 g (81%) of *N*-ethyl-*N'*-((trimethylsilyl)methyl)carbodiimide (**10c**), bp 120 °C (bath) (34 mmHg), as a colorless oil: bp 78–81 °C (26 mmHg); IR (neat) 2120 (N=C=N), 1250, 850 cm^{-1} (Me_3Si); ^1H NMR ($CDCl_3$) δ 0.10 (s, 9, $(CH_3)_3Si$), 1.19 (t, 3, CH_2CH_3), 2.64 (s, 2, CH_2), 3.18 (q, 2, CH_2CH_3); MS, m/e 156 (M^+). Anal. Calcd for $C_7H_{16}N_2Si$: C, 53.79; H, 10.32; N, 17.92. Found: C, 53.77; H, 10.28; N, 17.80.

The reaction with **9a** or **9b** under the same conditions gave the carbodiimide **10a** (1.92 g, 94%) or **10b** (1.98 g, 94%), respectively.

***N,N'*-Bis((trimethylsilyl)methyl)carbodiimide (11).** A solution of iminophosphorane **3a**, which was prepared from azide **1** (1.29 g, 10 mmol) and phosphine **2a** (2.62 g, 10 mmol) in dry benzene (10 mL), was refluxed with phenyl isocyanate (**8a**) (0.59 g, 5 mmol) for 2 h. The solvent was evaporated in vacuo, and the residue was extracted with hexane (10 mL × 2). The extract was concentrated in vacuo, and the residue was distilled under reduced pressure to give 1.04 g (97%) of **11**, bp 77–80 °C (23 mmHg), as a colorless oil: IR (neat) 2120 (N=C=N), 1250, 850 cm^{-1} (Me_3Si); ^1H NMR ($CDCl_3$) δ 0.09 (s, 18, $(CH_3)_3Si$), 2.60 (s, 4, CH_2); MS, m/e 214 (M^+). Anal. Calcd for $C_9H_{22}N_2Si_2$: C, 50.41; H, 10.34; N, 13.06. Found: C, 50.65; H, 10.23; N, 13.13.

The reaction of iminophosphorane **3a** with 1 equiv of carbodiimide **10a** in refluxing benzene for 1 h afforded **11** in a quantitative yield.

Diphenylketene *N*-((Trimethylsilyl)methyl)imine (13). A solution of iminophosphorane **3a**, which was prepared from azide **1** (1.29 g, 10 mmol) and phosphine **2a** (2.62 g, 10 mmol) in dry benzene (10 mL), was refluxed witthdiphenylketene (**12**) (1.94 g, 10 mmol) for 1 h. The solvent was evaporated in vacuo, and the residue was extracted with hexane (50 mL). The extract was concentrated in vacuo, and the residue was distilled under reduced pressure to give 2.60 g (93%) of **13**, bp 132–136 °C (1.0 mmHg), as a colorless oil: IR (neat) 2000 (N=C=C), 1250, 850 cm^{-1} (Me_3Si); ^1H NMR ($CDCl_3$) δ 0.06 (s, 9, $(CH_3)_3Si$), 3.16 (s, 2, CH_2e, 7.1–7.4 (m, 10, ArH); ^{13}C NMR ($CDCl_3$) δ −2.70 (q, CH_3), 44.27 (t, CH_2), 73.86 (s, N=C=*C*), 183.29 (s, N=*C*=C); MS, m/e 279 (M^+). Anal. Calcd for $C_{18}H_{21}NSi$: C, 77.36; H, 7.57; N, 5.06. Found: C, 77.21; H, 7.49; N, 4.80.

Registry No. 1, 87576-94-1; **2a**, 603-35-0; **2b**, 121-45-9; **2c**, 122-52-1; **3a**, 90606-07-8; **3b**, 90606-08-9; **3c**, 90606-09-0; **4a**, 100-52-7; **4b**, 104-88-1; **4c**, 123-11-5; **4d**, 98-01-1; **4e**, 1121-60-4; **4f**, 630-19-3; **4g**, 123-72-8; **4h**, 14371-10-9; **4i**, 123-73-9; **4j**, 67-64-1; **4k**, 108-94-1; **5a**, 90606-10-3; (*E*)-**5b**, 90606-11-4; (*Z*)-**5b**, 90606-12-5; (*E*)-**5c**, 90606-13-6; (*Z*)-**5c**, 90606-14-7; (*E*)-**5d**, 90606-15-8; (*Z*)-**5d**, 90606-16-9; **5e**, 90623-29-3; **5f**, 90606-17-0; **5g**, 90606-18-1; (*E*)-**5h**, 90606-19-2; (*Z*)-**5h**, 90606-20-5; (*E*)-**5i**, 90606-21-6; (*Z*)-**5i**, 90606-22-7; **5j**, 90606-23-8; **5k**, 90606-24-9; **6**, 14283-35-3; **7**, 18293-48-6; **8a**, 103-71-9; **8b**, 3173-53-3; **9a**, 103-72-0; **9b**, 1122-82-3; **9c**, 542-85-8; **10a**, 90606-25-0; **10b**, 90606-26-1; **10c**, 90606-27-2; **11**, 90606-28-3; **12**, 525-06-4; **13**, 90606-29-4; CO_2, 124-38-9; CS_2, 75-15-0.

Novel Synthesis of 3,5-Disubstituted Pyridines by 1,4-Cycloaddition of 1-Aza-1,3-butadienes with Enamines

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A new method for the synthesis of 3,5-disubstituted pyridines is described. Reactions of the N-substituted methanimines **1** with the β-substituted enamines **2** give 1-aza-1,3-butadienes **3a–i** and/or symmetrically 3,5-disubstituted pyridines **4a–c,e–h** in moderate to good yields. At reaction temperatures of 150 °C the azadienes **3** are the predominant products, and the reaction provides a good route to 1-azadienes with no substituent at the 4-position. At reaction temperatures of 200 °C, and particularly using *N-tert*-butylmethanimine **1a** and *p*-toluenesulfonic acid catalyst, the principal products are symmetrically 3,5-disubstituted pyridines. The cycloaddition was shown to proceed via the azabutadiene intermediate **3**. Reactions of **3** with the enamines **2** lead to unsymmetrically 3,5-disubstituted pyridines. The mechanisms of these cycloadditions are discussed.

The pyridine ring system is often found in alkaloids and in compounds used in pharmacy and agriculture.[1] In a preliminary report,[2] we described a new preparation of symmetrically 3,5-disubstituted pyridines from *N-tert*-butylmethanimine and enamines by cycloaddition of a 1-aza-1,3-butadiene with an enamine. Although 3,5-disubstituted pyridines have not been extensively investigated,[3] 3(or 5)-alkyl- or 3,5-dialkylpyridine derivatives are useful precursors of pyridine mono- or dicarboxylic acids,[3] which are directly related to nicotinoids or to pyridine-containing macrocycles.[4]

There are several reports on reactions of imines with enamines,[5] but formation of a pyridine ring has not been observed. We have reported on the isolation of 1-azabutadienes,[2] and recently Nomura et al. reported formation of 1,2,4-triaryl-substituted 1-azabutadienes from aryl-substituted imines and enamines.[5b]

We here report on further investigations of the addition of *N*-substituted methanimines to enamines for the syn-

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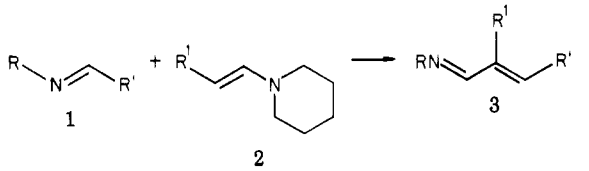
Table I. Formation of 1-Azabutadiene 3b and Pyridine 4b from Imine 1a and Enamine 2b

mole ratio 1a/2b	solvent	catalyst[a]	conditions: temp, °C	conditions: time, h	yield, %: 3b	yield, %: 4b
1.0	PhH		150	6	53	3
1.0	MeCN		150	6	15	16
1.0	$CHCl_3$		150	6	0	50
0.5	$CHCl_3$		150	6	0	58
1.0	PhH		200	6	39	29
0.5	PhH		200	9	0	31
0.5	PhH	PTS[b]	80	9	0	0
0.5	PhH	PTS[b]	150	6	c	32
0.5	PhH	PTS[b]	200	9	0	72
0.5	PhH	$HCl{\cdot}\overline{N(CH_2)_4CH_2}$	150	6	c	19
0.5	PhH	$HCl{\cdot}\overline{HN(CH_2)_4CH_2}$	200	9	0	58
0.5	PhH	PhCOOH	150	6	0	8

[a] 3 mol%. [b] *p*-Toluenesulfonic acid. [c] Not determined.

Table II. Formation of 1-Azabutadienes 3 from Imine 1 and Enamine 2



1 2 3

imine	R	R′	enamine	R^1	conditions[a]: temp, °C	conditions[a]: time, h	3	yield, %
1a	*t*-Bu	H	2a	Me	150	6	3a	46[b]
1a	*t*-Bu	H	2b	Et	150	6	3b	53
1a	*t*-Bu	H	2b	Et	200	9	3b	58[c]
1a	*t*-Bu	H	2c	*i*-Pr	150	6	3c	43
1b	*i*-Pr	H	2b	Et	200	9	3d	28
1d	Ph	H	2b	Et	200	9	3e	8[b]
1e	*t*-Bu	Me	2a	Me	200	9	3f	30[b]
1e	*t*-Bu	Me	2b	Et	200	9	3g	24[b]
1f	*t*-Bu	Ph	2b	Et	200	21[d]	3h	42[e]
1a	*t*-Bu	H	2m	PhS	110[f]	12	3i	34[g]

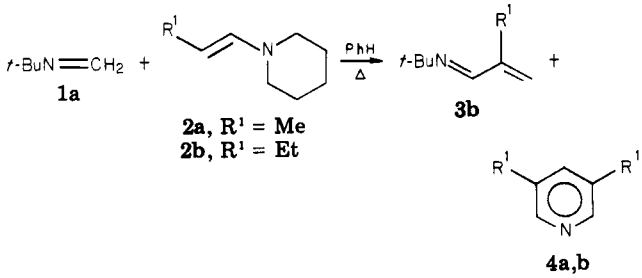
[a] Mole ratio 1/2 = 1.0; solvent, benzene; heated in a sealed tube. [b] Determined by NMR. [c] 3,5-Diethylpyridine (**4b**) was obtained (35%). [d] Mole ratio 1/2 = 0.5; *p*-toluenesulfonic acid (3 mol%) was added. [e] 3,5-Diethyl-4-phenylpyridine (**4i**) was obtained (55%). [f] Refluxed in toluene. [g] 3,5-Bis(phenylthio)pyridine (**4h**) was obtained (20%).

thesis of 3,5-disubstituted pyridines and 4-unsubstituted 1-aza-1,3-butadienes. We also describe the cycloaddition of 1-aza-1,3-butadienes with enamines leading to unsymmetrically 3,5-disubstituted pyridines.

1-Aza-1,3-butadienes should be versatile building blocks for nitrogen-containing heterocyclic compounds and while some of their cycloadditions have been documented,[6,7] their 1,4-cycloaddition reactions are not well-known.[2,6,8] On the contrary, many 1,4-cycloadditions of 2-aza-1,3-dienes have been reported.[6,9,10] Recently the Diels–Alder reactions of an in situ generated *N*-acyl-1-aza-1,3-butadiene[11] and cycloaddition of α,β-unsaturated hydrazones with electron-poor olefins[12] were reported. The new 1,4-cycloaddition reactions reported here involve the use of isolated 1-azabutadienes and their addition to electron-rich dienophiles.

Results and Discussion

Reaction of Imines with Enamines To Form 1-Aza-1,3-butadienes and Symmetrically 3,5-Disubstituted Pyridines. 1-Azabutadienes and symmetrically 3,5-disubstituted pyridines are formed by heating a mixture of *N*-*tert*-butylmethanimine (**1a**) and an enamine. The imine **1a** was employed in the reaction as its triazine



1a 2a, R^1 = Me; 2b, R^1 = Et 3b 4a,b

trimer. For example, **1a** reacted with an equimolar amount

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Table III. Formation of Symmetrically 3,5-Disubstituted Pyridines from Imine 1a and Enamines 2[a]

	enamine				
	R^1	NR^2_2	catalyst[b]	product	yield,[c] %
2a	Me	piperidino	PTS	**4a**	67 (25)
2b	Et	piperidino	PTS	**4b**	72 (31)
2c	*i*-Pr	piperidino	PTS	**4c**	78 (53)
2d	*t*-Bu	piperidino	PTS	(**4d**)[d]	(20)[d] (0)
2e	c-Hex	piperidino	none	**4e**	85
2f	Ph	morpholino	none	**4f**	73
2h	$PhCH_2$	piperidono	PTS	**4g**	80 (24)
2l	PhS	dimethylamino	PTS	**4h**	87

[a] Conditions: 200 °C for 9 h in PhH solution in a sealed tube. [b] 3 mol% was added. [c] The yields in parentheses are those obtained without catalyst. [d] **4d** was detected by NMR in 20% yield but was not isolated.

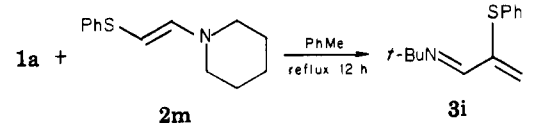
of 1-piperidino-1-propene (**2a**) or 1-piperidino-1-butene (**2b**) in benzene at 200 °C for 9 h to give 3,5-dimethylpyridine (**4a**) and 3,5-diethylpyridine (**4b**) in 25% and 29% yields, respectively. In the latter reaction, 1-*tert*-butyl-3-ethyl-1-aza-1,3-butadiene (**3b**) was also obtained in 39% yield. The structures of the products were determined by spectral and analytical data.

The effects of reaction conditions on the reaction of **1a** with **2b** are shown in Table I. The reaction under milder conditions (150 °C, 6 h) afforded a better yield of the azadiene **3b** (53%). The reaction also proceeded in refluxing toluene, but very slowly. A decrease in the ratio **1a**/**2b** caused an increase in pyridine formation, and the use of an excess of **1a** lowered the yields of both the azadiene and the pyridine. As for the solvent, acetonitrile and chloroform were not suitable for azadiene formation. The former gave rise to a complicated mixture of products and the latter caused exclusive formation of pyridines.

Other 1-azabutadienes were prepared in moderate yields (Table II). Thus the reaction of imines with enamines is a useful synthetic route to 1-azabutadienes, especially to 4-unsubstituted compounds. Normally 1-azabutadienes are prepared by careful condensation of an α,β-unsaturated aldehyde with a primary amine.[13] In some cases, olefin-forming reactions using reagents containing imino groups lead to azadienes.[14] However, synthetic methods for the preparation of 1-azadienes with no substituents on the 4-position are less well-known.[15]

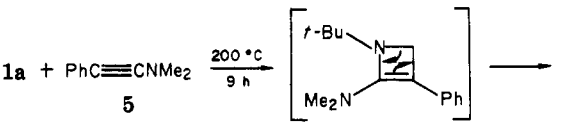
When enamines bearing a cyclohexyl or phenyl group as the substituent R^1 were employed, the yields of azadienes **3** were less than 16% (by NMR). Furthermore, an isopropyl or phenyl group on the nitrogen of the methanimine **1** retarded the reaction, which had to be run at higher temperature, and the yields of **3** were diminished. Similar results were obtained with *C*-substituted methanimines.

We also prepared a heteroatom-substituted 1-azabutadiene. Thus 1-(phenylthio)-2-piperidinoethylene (**2m**) was reacted with **1a** to give 3-(phenylthio)-1-*tert*-butyl-1-aza-1,3-butadiene (**3i**, 34%) along with a considerable amount

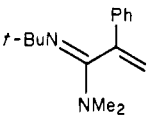


2m **3i**

of 3,5-bis(phenylthio)pyridine. On the other hand, the reaction of 1,2-dipiperidinoethylene (**2j**) with **1a** gave a



5 **6**



3j (63%)

pyrrole derivative instead of a 3(or 2)-amino-1-aza-1,3-diene derivative. A 2-aminoazadiene was obtained by using an ynamine instead of **2j**.

As shown in Table I, use of 2 equiv of the enamine **2b** and a higher temperature (200 °C) favored pyridine formation. Chloroform seemed to be better than benzene as the solvent and, in this case, piperidine hydrochloride was obtained. This suggested catalysis by hydrogen chloride, and the reaction was therefore carried out in benzene in the presence of acidic additives. Among the three additives tested, *p*-toluenesulfonic acid (PTS) was the most effective for pyridine formation. Piperidine hydrochloride showed some catalytic activity, but no positive effect was observed with benzoic acid.

The syntheses of symmetrically 3,5-disubstituted pyridines from a variety of enamines are summarized in Table III. The absence of 2,5-disubstituted pyridines in any of the runs shows high regioselectivity in the cycloaddition.

The pyridine synthesis is particularly effective with enamines that have bulky substituents such as phenyl and cyclohexyl (73% and 85% yields, respectively); in these cases the reactions could be carried out without the acid catalyst. The pyridines with smaller substituents were obtained in poor yields when PTS was not added, and the *tert*-butyl substituent on **2** hindered the reaction.

When *N*-benzylmethanimine (**1c**) was employed instead of the *N*-*tert*-butyl derivative **1a**, the yield of pyridine **4b** was less than 14%; the *N*-isopropyl analogue **1b** gave only a 7% yield of **4b**. No pyridine was obtained from *N*-methyl- and *N*-phenylmethanimines. This might be because of the poor leaving ability of these substituents. Furthermore, *N*-*tert*-butylethanimine (**1e**) did not give the corresponding pyridine when treated with enamine **2b** under these conditions. The well-known equilibrium[16] between an imine and an enamine is probably one of the reasons that no pyridine derivatives were formed.

$$t\text{-BuN=CHCH}_3 \rightleftharpoons t\text{-BuNHCH=CH}_2$$

1e

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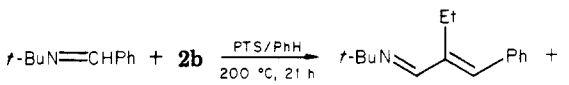
(16) Cook, G. "Enamines: Synthesis, Structure, and Reactions"; Marcel Dekker: New York, 1969.

Table IV. Formation of Unsymmetrically 3,5-Disubstituted Pyridines from Enamines 2 and 1-Azabutadienes 3[a]

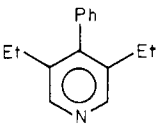
enamine			azadiene			
	R^1	NR^2_2		R	product	yield, %
2a	Me	piperidino	3b	Et	4j	73
2a	Me	piperidino	3c	*i*-Pr	4k	32
2b	Et	piperidino	3b	Et	4b	71
2b	Et	piperidino	3c	*i*-Pr	4l	50
2c	*i*-Pr	piperidino	3b	Et	4l	74
2f	Ph	morpholino	3b	Et	4m	53[b]
2g	Ph	piperidino	3b	Et	4m	23
2i	EtOCO	piperidino	3b	Et	4n	31
2j	piperidino	piperidino	3b	Et	4o	26
2k	PhO	piperidino	3b	Et	4p	21[c]
2l	PhS	dimethylamino	3b	Et	4q	51
2n	$PhSO_2$	dimethylamino	3b	Et	4r	50

[a] Conditions: mole ratio 2/3 = 1.0–1.2, 200 °C, 20–24 h in a sealed tube. [b] Determined by NMR. [c] Hydroquinone (1 mol%) was added.

N-tert-Butylbenzaldimine (**1f**), which cannot participate in such an equilibrium, gave the trisubstituted pyridine **4i** along with the 1-azadiene **3h** when treated with **2b**.



1f 3h (42%)



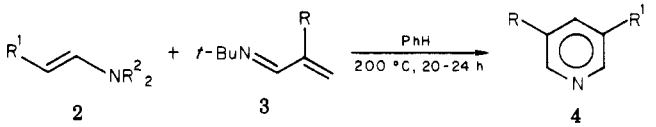
4i (55%)

Another trisubstituted pyridine, 3,5-bis(phenylthio)-4-phenylpyridine, was detected by NMR (singlet at δ 8.08, yield 25%) when the imine **1e** was treated with 1-(phenylthio)-2-piperidinoethylene (**2m**) at 150 °C for 6 h.

Formation of Unsymmetrically 3,5-Disubstituted Pyridines by Cycloaddition of 1-Aza-1,3-butadienes and Enamines. Since formation of 3,5-disubstituted pyridines **4** was assumed to proceed via the 1-aza-1,3-butadienes **3**, the reactions of the enamines **2** with the azadienes **3** were studied. The cycloaddition of **2** and **3** leading to unsymmetrically 3,5-disubstituted pyridines did occur, confirming the assumption and providing a novel route for pyridine synthesis.

An equimolar mixture of 1-piperidino-1-propene (**2a**) and 3-ethyl-1-*tert*-butyl-1-aza-1,3-butadiene (**3b**) in benzene was heated at 200 °C for 24 h in a sealed tube. Workup of the reaction mixture and treatment with picric acid gave the picrate of 3-ethyl-5-methylpyridine (**4j**). The yield was 73% and the structure was determined by spectral data and elemental analysis. 2,5-Disubstituted and 2,6-disubstituted structures were excluded mainly by the coupling constants in the NMR spectra.[17] 5-Ethyl-2-methylpyridine was not detected, showing the high regioselectivity of the cycloaddition reaction.

Similarly, a variety of unsymmetrically 3,5-disubstituted pyridines were prepared from **2** and **3**, with the results

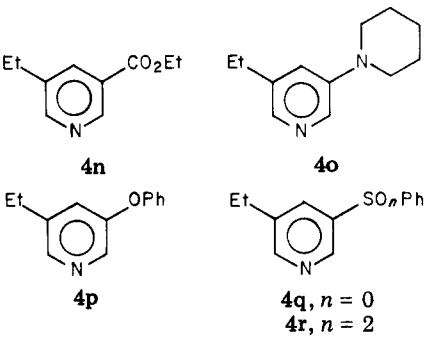


2 3 4

shown in Table IV. Although the reaction time could be shortened by addition of *p*-toluenesulfonic acid, it caused the formation of a small amount of a symmetrically 3,5-disubstituted pyridine as a byproduct.

By this route we were able to introduce such substituents as ethoxycarbonyl, piperidino, phenoxy, phenylthio, and phenylsulfonyl groups onto the 3-position of the pyridine ring. The introduction of the ethoxycarbonyl group could provide a new and direct route to 5-substituted nicotinoids.

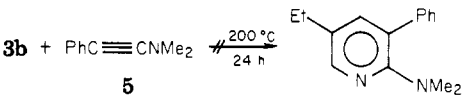
The yields of 3-amino- and 3-(aryloxy)pyridines **4o** and **4p** were low. A byproduct, 1-*tert*-butyl-3-piperidinopyrrole, was obtained in the former case, and polymerization of the phenoxyethylene **2k** occurred in the latter.



4n 4o 4p 4q, n = 0 4r, n = 2

In these reactions elimination of the phenoxy or the piperidino group from the 3-position was also conceivable, and would lead to the formation of 2-piperidino-5-ethylpyridine,[18] but this compound was not detected.

It was expected that 2-aminopyridines could also be synthesized by using an ynamine instead of an enamine. However, formation of a 2-aminopyridine was not detected by NMR when 1-(dimethylamino)-2-phenylacetylene (**5**) was reacted with the azadiene **3b**.



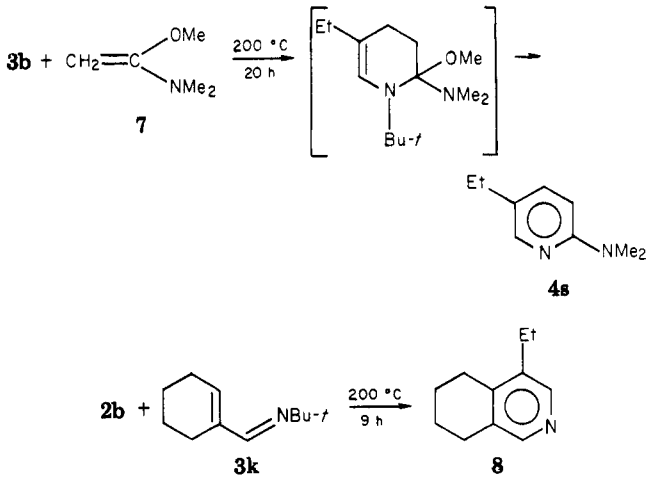
5

The reaction of the ketene *O,N*-acetal, 1-(dimethylamino)-1-methoxyethylene (**7**), with azadiene **3b** gave 2-(dimethylamino)-5-ethylpyridine (**4s**) in 23% yield without formation of an alkoxypyridine. The NMR spectrum of **4s** supports the 2,5-structure and excludes the alternative possibility of a 3,5-product. The result suggested that the methoxy group is a better leaving group than the dimethylamino group. However, ketene diethyl acetal did not react with the azadiene **3b** on heating at 200 °C for 20 h.

Application of this reaction to the synthesis of a bicyclic pyridine was examined. The azadiene **3k**, which has a

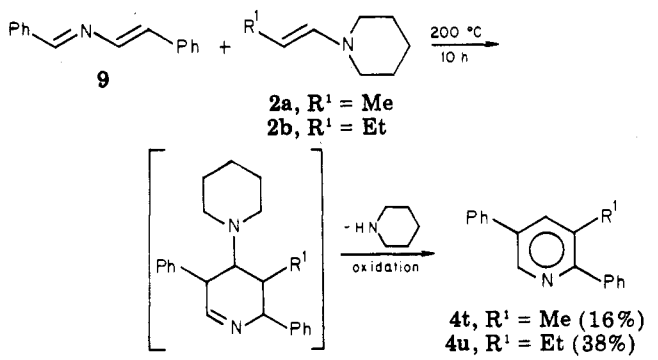
(17) The coupling constants between the ring protons were 2.0–2.2 Hz, which were not consistent with those for vicinal protons but with long-range coupling constants between 4-H and 2-(or 6-)H.

(18) The 2-piperidino structure was excluded because the coupling constant between 3-H and 4-H should be as large as 7–8 Hz and the chemical shift in δ of 3-H should be greater than 7.0.



cyclohexenyl moiety in its diene system, was treated with **2b** at 200 °C for 9 h in the presence of *p*-toluenesulfonic acid to give a 13% yield of 4-ethyl-5,6,7,8-tetrahydroisoquinoline (**8**). Although the conditions were not optimized, the reaction shows the possibility of forming bicyclic pyridines by this method.

The addition reaction of the enamine to the 1-azadiene system is also applicable to 2-aza analogues. The reaction of the 2-azabutadiene **9** with the enamines **2a** and **2b** at 200 °C gave the 3-alkyl-2,5-diphenylpyridines **4t** and **4u**, respectively.



In these reactions, a considerable amount of styrylpiperidine (**2g**) was obtained (34% when R^1 = Me and 55% when R^1 = Et), probably formed by disproportionation via a cycloaddition–cycloreversion process that occurs across the C=N bond of **9**.

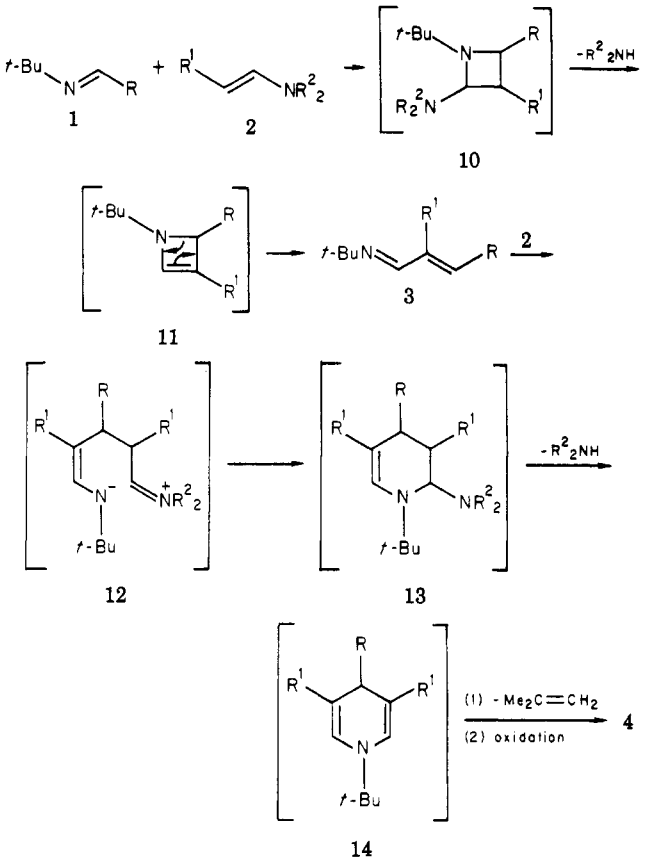
Reaction Path. A plausible elucidation of the formation of pyridines from **1** and **2** is 1,4-cycloaddition of the 1-aza-1,3-butadiene intermediate **3** to **2**, which we confirmed experimentally.

1-Azabutadiene **3** is presumably generated by a thermal cycloreversion of the azacyclobutene intermediate **11**, which is formed by [2 + 2] cycloaddition of **1** and **2** followed by elimination of R^2_2NH (Scheme I). Intermediate **11** is similar to the postulated intermediate cycloadduct **6** in the reaction of **1a** with ynamine **5**.

An alternative path for the generation of **3** is via an acyclic 1:1 adduct formed by Michael-type addition of the enamine **2** to the imine **1**.[2] But the path shown in Scheme I is clearly supported by the fact that the 4-phenyl-substituted 1-azadiene **3h** was obtained together with the 3,4,5-trisubstituted pyridine **4i** when the C-substituted methanimine **1f** was employed in the reaction.

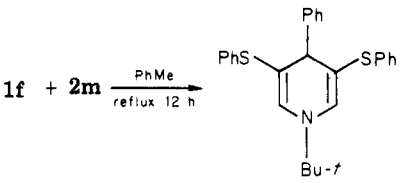
The tetrahydropyridine intermediate **13** is converted to the pyridine **4** with elimination of R^2_2NH followed by loss of isobutylene and oxidation. The generation of isobutylene was ascertained by GLC analysis of the gaseous product, which contained a mixture of isobutylene and

Scheme I



isobutane in a ratio of ca. 9:1.

It was almost impossible to isolate or detect the tetrahydro- and dihydropyridine intermediates **13** and **14** even under mild conditions. However, a small amount (3%) of the dihydropyridine **14a** could be isolated along with the corresponding pyridine (yield 14%) when the imine **1f** and the enamine **2m** were heated in boiling toluene for 12 h. The compound showed satisfactory spectral data and elemental analysis, but was slowly oxidized to the corresponding pyridine during repeated recrystallization. The isolation of the dihydropyridine supports the last step of the path in Scheme I.

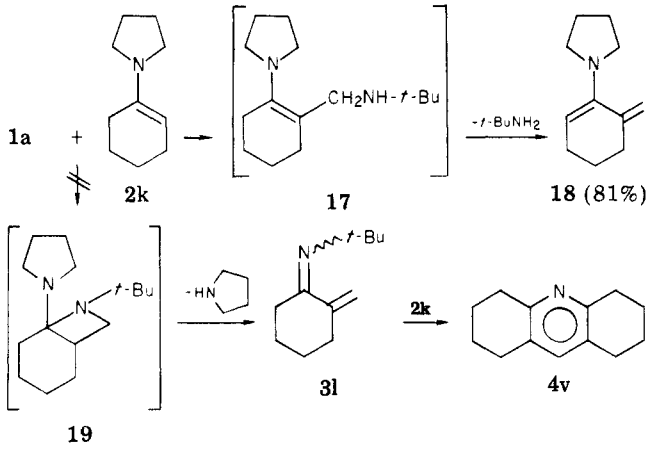


14a

Usually cycloaddition between an electron-deficient dienophile and an electron-rich diene is favored in the Diels–Alder reaction. Since **2** is an electron-rich olefin, the present reaction is apparently an "inverse electron demand" Diels–Alder reaction[19] with a considerable polar nature. The high regioselectivity leading to exclusive formation of 3,5-disubstituted pyridines seems to be caused mainly by the polar nature of the enamines and the azadienes. Hence the cycloaddition of **3** with **2** is assumed to proceed via the polar intermediate **12**, which is formed by Michael addition of **2** to **3** (Scheme I). The higher reactivity observed for the enamines **2e** (R^1 = c-Hex) and **2f** (R^1 = Ph) in the reactions with **1a** is attributed to steric factors; the bulky substituent R^1 of the intermediate **12**

(19) Sauer, J.; Wiest, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 269.

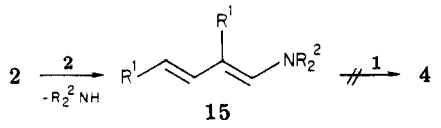
Scheme II



favors the trans configuration between R^1 and t-BuN$^-$, which accelerates the cyclization of **12** to **13**.

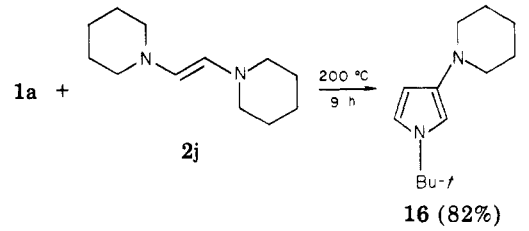
The role of the acidic additives is not clear, but it is reasonable to assume that they promote formation of monomers from the imine trimers and elimination of the amine or the *tert*-butyl group by acidic catalysis. It is also possible that they may accelerate the addition of the electron-rich enamine to the azabutadiene intermediate by protonation of the latter.

Another possible path for the formation of 3,5-disubstituted pyridines is cycloaddition of **1** to the dieneamine **15** formed by self-condensation of **2**, which is known to



occur under acidic conditions.[20] However, formation of the pyridine **4a** was not detected when 1-piperidino-2-methyl-1,3-pentadiene (**15a**, R^1 = Me, NR^2_2 = piperidino) was treated with **1a** under the same conditions used in the other runs. Furthermore, this path cannot explain the formation of the 3,4,5-trisubstituted pyridine **4i**.

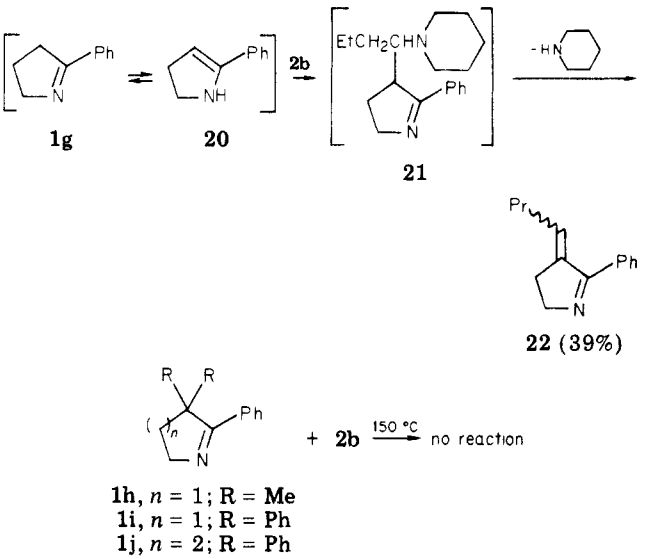
Reactions of Imines with Enamines Leading to Other Products. The reaction of 1,2-dipiperidinoethylene (**2j**) with **1a** unexpectedly gave rise to the aminopyrrole **16**. No 3,5-dipiperidinopyridine was obtained, and the



yield of **16** was 55% (82% by NMR).[21] The pyrrole ring carbons apparently come from **2j**, since **16** was also obtained in 40% yield by heating **2j** with *tert*-butylamine at 200 °C for 9 h.

The reaction of the cyclohexenylamine **2o** with **1a** was studied with the expectation that it would result in the cis-fused 1-azabutadiene **3l** and/or the bicyclopyridine **4v** if the reaction proceeds via the paths shown in Scheme I. The product isolated was, however, 6-methylenecyclo-

Scheme III



1h, n = 1; R = Me
1i, n = 1; R = Ph
1j, n = 2; R = Ph

hexenylamine **18** in 81%. The NMR spectrum of the reaction mixture of 1-pyrrolidinocyclopentene and **1a** also indicated the formation of the corresponding 5-methylene compound but the yield was lower (25%). The results suggest the intermediacy of the acyclic 1:1 adduct **17**; the α-substituent of the enamine seems to suppress the formation of the cyclic intermediate **19** (Scheme II). Similarly, the α-substituted enamine **2p**, 2-piperidino-2-pentene, also did not give the anticipated 1-azabutadiene but rather an unstable compound whose NMR spectrum implied 2-methyl-3-piperidino-1,3-pentadiene.

The reaction of cyclic imines with the enamine **2b** was also studied. It was found that the reaction of **1g** with **2b** proceeds via the isomeric enamine form of **1g** to afford the condensation product **22** (Scheme III). A similar condensation reaction of a cyclic imine with an aldehyde is known.[22] The role of an isomeric enamine as a reactive species is supported by the fact that cyclic imines **1h–j**, which cannot isomerize to enamine forms, did not react with **2b** under the same conditions.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus; melting and boiling points are uncorrected. IR spectra were taken on a JASCO IRA-1 spectrometer. NMR spectra were obtained on JEOL JNM PMX-60 and JNM FT-100 spectrometers in $CDCl_3$ solutions with tetramethylsilane as an internal standard. Mass spectrometry was performed with a Hitachi RMU-6E spectrometer at an ionizing voltage of 70 eV. GLC analysis of gaseous products was done with a Shimadzu Model 3BF by using a column (4m × 3mm) packed with Al_2O_3 (60–80 mesh) treated with DMF. When yields determined by NMR are given in the text, they were obtained as follows. After the workup shown in the general procedures (vide infra) and removal of solvents, a weighed amount of a suitable standard compound (e.g., toluene, 1,1,2,2-tetrachloroethane, dibromomethane, or benzaldehyde) was added to the reaction mixture. Amounts of the products were calculated from the relative areas of signals due to the standard and the products.

Materials. The imines **1** and the enamines **2** were prepared by condensation of the corresponding amines and carbonyl compounds. The C-unsubstituted methanimines such as **1a** were isolated and employed in the reactions as their triazine trimers. 2-Phenyl-1-pyrroline (**1g**),[23] 3,3-dimethyl-2-phenyl-1-pyrroline

(20) Domschke, G. *Chem. Ber.* **1966**, *99*, 934.
(21) The possibility of the 2-piperidino structure was excluded by the coupling constants between the ring protons (2.6–3.2 Hz), since the value for that between 3-H and 4-H of N-substituted pyrroles is normally 3.7–4.1 Hz.
(22) Patrick, T. M., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2984. Nomura, Y.; Bando, T.; Takeuchi, Y.; Tomoda, S. *Tetrahedron Lett.* **1979**, 3453.
(23) Craig, L. C.; Bulbrook, H.; Hixon, R. M. *J. Am. Chem. Soc.* **1931**, *53*, 1831.

(**1h**),[22,24] 2,3,3-triphenyl-1-pyrroline (**1i**),[23,24] 2,3,3-triphenyl-1-piperideine (**1j**),[23,25] ethyl-3-piperidinoacrylate (**2i**),[26] 1,2-dipiperidinoethylene (**2j**),[27] 1-phenoxy-2-piperidinoethylene (**2k**),[28] 1-(dimethylamino)-2-(phenylthio)ethylene (**2l**),[29] 1-(phenylthio)-2-piperidinoethylene (**2m**),[30] 1-(phenylsulfonyl)-2-(dimethylamino)ethylene (**2n**),[29] *N,N*-dimethyl-2-phenylethynylamine (**5**),[31] 1-(dimethylamino)-1-methoxyethylene (**7**),[32] and 1,4-diphenyl-2-aza-1,3-butadiene (**9**)[33] were prepared according to reported methods. *N-tert*-Butylcyclohexenaldimine (**3k**) and 1-piperidino-2-methyl-1,3-pentadiene (**15a**) were prepared by condensations of *tert*-butylamine with cyclohexenal[34] and of piperidine with 2-methylprop-2-en-1-al,[35] respectively.

General Procedure for the Preparation of 1-Aza-1,3-butadienes 3. A solution of the imine **1** (100 mmol) and the enamine **2** (100 mmol) in benzene (50 mL) was sealed in a stainless steel tube (200 mL) and was heated at 150 °C for 6 h. The reaction mixture was concentrated and distilled under reduced pressure to give the azadiene **3** as a colorless liquid. Compounds **3a–c** should be distilled carefully through a Vigreaux column (15-cm length) to separate piperidine. Pure samples were obtained by redistillation after addition of a small amount of phenyl isocyanate. The azadienes must be stored in a dry atmosphere because of their high sensitivity toward hydrolysis, which was the reason for unsatisfactory elemental analyses of them. Boiling points and spectral data are as follows.

3a: bp 28–30 °C (10 mmHg); IR (neat) 1620 and 1640 cm^{-1}; NMR δ 1.22 (s, 9 H, *t*-Bu), 1.93 (s, 3 H, Me), 5.28 (br s, 1 H, =C*H*H), 5.50 (br s, 1 H, =CH*H*), 7.84 (s, 1 H, N=CH); MS, *m/e* 125 (M^+).

3b: bp 55–57 °C (30 mmHg); IR (neat) 1620 and 1640 cm^{-1}; NMR δ 1.10 (t, 3 H, Me), 1.19 (s, 9 H, *t*-Bu), 2.40 (m, 2 H, CH_2), 5.33 (s, 1 H, =C*H*H), 5.51 (m, 1 H, =CH*H*), 7.90 (s, 1 H, N=CH); MS, *m/e* 139 (M^+).

3c: bp 55–58 °C (16 mmHg); IR (neat) 1620 and 1640 cm^{-1}; NMR δ 1.12 (d, 6 H, 2 Me), 1.30 (s, 9 H, *t*-Bu), 3.00 (m, 1 H, CH), 5.33 (br s, 1 H, =C*H*H), 5.50 (br s, 1 H, =CH*H*), 7.90 (s, 1 H, N=CH); MS, *m/e* 143 (M^+).

3d: bp 100–110 °C (45 mmHg); IR (neat) 1620 and 1640 cm^{-1}; NMR δ 1.06 (t, 3 H, Me), 1.15 (d, 6 H, 2 Me), 2.40 (q, 2 H, CH_2), 3.38 (sept, 1 H, CH), 5.33 (br s, 1 H, =C*H*H), 5.50 (br s, 1 H, =CH*H*), 7.89 (s, 1 H, N=CH).

3i: bp 125–145 °C (1 mmHg) by bulb-to-bulb distillation; IR (neat) 1620 cm^{-1}; NMR δ 1.25 (s, 9 H, *t*-Bu), 5.00 (br s, 1 H, =C*H*H), 5.53 (br s, 1 H, =CH*H*), 7.93 (s, 1 H, N=CH); MS, *m/e* 219 (M^+).

Azabutadienes **3e–g** were not isolated, but their formation was detected by the imino proton at δ 7.7 and the olefinic protons at δ 5.5–5.7 in the NMR spectra.

Reaction of the Imine 1a with the Ynamine 5. A solution of **1a** (1.4 g, 16 mmol) and **5** (2.2 g, 15 mmol) in benzene (50 mL) was heated at 200 °C for 9 h in a sealed tube. The reaction mixture was distilled to give 2.2 g (63%) of N^2-*tert*-butyl-N^1,N^1-dimethyl-2-phenylacrylamidine (**3j**) as a colorless liquid: bp 82–90 °C (1 mmHg); IR (neat) 1610 cm^{-1}; NMR δ 1.10 (s, 9 H, *t*-Bu), 2.83 (s, 6 H, NMe_2), 5.18 (s, 1 H, =C*H*H), 5.87 (s, 1 H, =CH*H*), 7.2–7.5 (m, 5 H, Ph); MS, *m/e* 230 (M^+).

Preparation of Symmetrically 3,5-Disubstituted Pyridines. A General Procedure. A solution of the imine **1** (1.0 to 100 mmol), the enamine **2** (2.0 to 200 mmol) (mole ratio of **1** to **2** is 0.5), and *p*-toluenesulfonic acid (PTS, 2–3 mol%) in benzene (2.5–150 mL) was sealed in a glass or stainless steel tube (10–300 mL) and was heated at 200 °C for 9 h. The reaction mixture was then treated in one of three ways. (a) The mixture was washed with dilute NaOH solution to remove acidic components. The organic layer was dried (Na_2CO_3) and concentrated under reduced pressure to give the pyridine **4** as crystalline material. The filtrate was chromatographed on a silica gel column to give the same pyridine (in the cases of **4f–h**). (b) When oily material was obtained after basic treatment as above, microdistillation or chromatography on a silica gel column was used for separation (in the cases of **4a–c**). (c) The reaction mixture was concentrated and hydrolyzed in refluxing EtOH after addition of 2 N HCl. The reaction mixture was concentrated and extracted (Et_2O/2 N HCl). The water layer was made alkaline, extracted (Et_2O), dried (Na_2CO_3), and concentrated under reduced pressure to remove low-boiling amines. The pyridine **4** thus obtained was isolated as the picrate (in the case of **4e**).

3,5-Lutidine (**4a**) was obtained as a colorless oil and was identified by comparison with an authentic sample. Spectral and analytical data of the other pyridines are as follows.

4b: bp 52–56 °C (2 mmHg); mp 166–167 °C (picrate, yellow needles from MeOH); NMR (picrate) δ 1.40 (t, J = 7.5 Hz, 6 H, 2 Me), 2.95 (q, J = 7.5 Hz, 4 H, 2 CH_2), 8.10 (t, J = 2.0 Hz, 1 H, 4-H), 8.59 (d, J = 2.0 Hz, 2 H, 2-H and 6-H); MS, *m/e* 135 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4O_7$ (picrate): C, 49.45; H, 4.43; N, 15.38. Found: C, 49.45; H, 4.26; N, 15.41.

4c: bp 72–74 °C (23 mmHg) (a colorless oil); mp 36–39 °C (colorless needles); NMR δ 1.27 (d, J = 7.2 Hz, 12 H, 4 Me), 2.95 (sept, J = 7.2 Hz, 2 H, 2 CH), 7.38 (t, J = 2.0 Hz, 1 H, 4-H), 8.35 (d, J = 2.0 Hz, 2 H, 2-H and 6-H); MS, *m/e* 163 (M^+).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.51; H, 10.54; N, 8.66.

4e: mp 230 °C (picrate, yellow needles from MeOH); NMR (picrate) δ 1.2–2.3 (m, 20 H, 10 CH_2), 2.5–3.1 (m, 2 H, 2 CH), 8.15 (t, J = 2.2 Hz, 1 H, 4-H), 8.60 (d, J = 2.2 Hz, 2 H, 2-H and 6-H); MS, *m/e* 243 (M^+).

Anal. Calcd for $C_{23}H_{28}N_4O_7$ (picrate): C, 58.46; H, 5.97; N, 11.86. Found: C, 58.23; H, 6.07; N, 11.67.

4f: mp 138–139 °C (colorless needles from Et_2O); NMR δ 7.3–7.6 (m, 10 H, 2 Ph), 7.95 (t, J = 2.2 Hz, 4-H), 8.76 (d, J = 2.2 Hz, 2 H, 2-H and 6-H); MS, *m/e* 231 (M^+).

Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.50; H, 5.45; N, 5.97.

4g: mp 95–96 °C (colorless needles from EtOH); mp 126–127 °C (picrate, yellow needles from MeOH); NMR δ 3.93 (s, 4 H, 2 CH_2), 7.0–7.4 (m, 11 H, 2 Ph and 4-H), 8.33 (d, J = 2.0 Hz, 2 H, 2-H and 6-H); MS, *m/e* 259 (M^+).

Anal. Calcd for $C_{25}H_{20}N_4O_7$ (picrate): C, 61.47; H, 4.13; N, 11.47. Found: C, 61.29; H, 3.97; N, 11.33.

4h: mp 56 °C (colorless needles from Et_2O); NMR δ 7.1–7.5 (m, 11 H, 2 Ph and 4-H), 8.26 (d, J = 2.0 Hz, 2 H, 2-H and 6-H); MS, *m/e* 295 (M^+).

Anal. Calcd for $C_{15}H_{13}NS_2$: C, 69.12; H, 4.44; N, 4.74; S, 21.70. Found: C, 69.12; H, 4.31; N, 4.54; S, 21.58.

Reaction of *N-tert*-Butylbenzaldimine (1f) with the Enamine 2b. A solution of the imine **1f** (4.3 g, 27 mmol), the enamine **2b** (8.1 g, 58 mmol), and PTS (134 mg, 0.78 mmol) in benzene (10 mL) was sealed in a 50-mL stainless steel tube and was heated at 200 °C for 21 h. After the workup shown in the general procedure as a, the mixture was distilled to give 2.4 g (42%) of 1-*tert*-butyl-3-ethyl-4-phenyl-1-aza-1,3-butadiene (**3h**) and 3.1 g (55%) of 3,5-diethyl-4-phenylpyridine (**4i**) as a colorless liquid.

3h: bp 93 °C (2 mmHg); IR (neat) 1620 cm^{-1} (C=O); NMR δ 1.15 (t, 3 H, Me), 1.25 (s, 9 H, *t*-Bu), 2.66 (q, 2 H, CH_2), 6.65 (s, 1 H, CH=), 7.15–7.35 (m, 5 H, Ph), 7.80 (s, 1 H, CH=N); MS, *m/e* 215 (M^+). The IR and NMR spectra of the compound were identical with those of an authentic sample prepared from *N-tert*-butylamine and α-ethylcinnamaldehyde, which was obtained by condensation of benzaldehyde and butyraldehyde.

4i: bp 150 °C (2 mmHg); mp 130 °C (picrate, yellow needles from MeOH); NMR δ 1.00 (t, 6 H, 2 Me), 2.35 (q, 4 H, 2 CH_2), 6.95–7.55 (m, 5 H, Ph), 8.35 (s, 2 H, 2-H and 6-H); MS, *m/e* 211 (M^+).

Anal. Calcd for $C_{21}H_{20}N_4O_7$ (picrate): C, 57.27; H, 4.58; N, 12.72. Found: C, 57.14; H, 4.47; N, 12.68.

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General Procedure for the Preparation of Unsymmetrically 3,5-Disubstituted Pyridines 4. An equimolar mixture of the enamine **2** (1.0–100 mmol) and the 1-azabutadiene **3** (1.0–100 mmol) in benzene (2.5–100 mL) was sealed in a stainless steel tube and was heated at 200 °C for 20–24 h unless otherwise noted. To avoid polymerization, 1 mol% of hydroquinone was added when 1-phenoxy-2-piperidinoethylene (**2k**) was employed. The procedures for the isolation of the pyridines **4** were the same as those shown for the symmetrical ones.

4j: bp 98 °C (15 mmHg) (a colorless liquid); mp 178–180 °C (picrate, yellow needles from MeOH); NMR δ 1.36 (t, 3 H, J = 7.5 Hz, Me), 2.30 (s, 3 H, Me), 2.62 (q, 2 H, J = 7.5 Hz, CH_2), 7.30 (br s, 1 H, 4-H), 8.23 (br s, 2 H, 2-H and 6-H); MS, m/e 121 (M^+).

Anal. Calcd for $C_{14}H_{14}N_4O_7$ (picrate): C, 48.00; H, 4.03; N, 16.00. Found: C, 48.22; H, 3.81; N, 15.98.

4k: bp 80 °C (2 mmHg) (a colorless liquid); NMR δ 1.25 (d, 6 H, 2 Me), 2.26 (s, 3 H, Me), 7.30 (br s, 1 H, 4-H), 8.20 (br s, 2 H, 2-H and 6-H); MS, m/e 135 (M^+).

4l was isolated by column chromatography (SiO_2): mp 121 °C (picrate, yellow needles from MeOH); NMR δ 1.22 (t, 3 H, J = 7.5 Hz, Me), 1.25 (d, 6 H, J = 6.8 Hz, 2 Me), 2.63 (q, 2 H, J = 7.5 Hz, CH_2), 2.90 (sept, 1 H, J = 6.8 Hz, CH), 7.33 (t, 1 H, J = 2.0 Hz, 4-H), 8.20 (d, J = 2.0 Hz, 2-H and 6-H); MS, m/e 149 (M^+).

Anal. Calcd for $C_{16}H_{18}N_4O_7$ (picrate): C, 50.79; H, 4.80; N, 14.81. Found: C, 50.35; H, 4.73; N, 14.52.

4m was isolated by column chromatography (SiO_2): mp 158–159 °C (picrate, yellow needles from MeOH); NMR (picrate) δ 1.46 (t, 3 H, Me), 3.00 (q, 2 H, CH_2), 7.4–7.7 (m, 6 H, Ph and 4-H), 8.40 (m, 1 H, 2-H), 8.67 (m, 1 H, 6-H); MS, m/e 183 (M^+).

Anal. Calcd for $C_{19}H_{16}N_4O_7$ (picrate): C, 55.34; H, 3.91; N, 13.59. Found: C, 55.15; H, 3.78; N, 13.50.

4n: bp 143 °C (5 mmHg) (a pale yellow liquid); mp 122–123 °C (picrate, yellow needles from benzene); IR (neat) 1720 cm^{-1} (C=O); NMR δ 1.26 (t, 3 H, J = 7.5 Hz, Me), 1.40 (t, 3 H, J = 7.0 Hz, Me), 2.73 (q, 2 H, J = 7.5 Hz, CH_2), 4.40 (q, 2 H, J = 7.0 Hz, OCH_2), 8.12 (t, 1 H, J = 2.0 Hz, 4-H), 8.60 (d, 1 H, J = 2.0 Hz, 6-H), 9.03 (d, 1 H, J = 2.0 Hz, 2-H); MS, m/e 179 (M^+).

Anal. Calcd for $C_{16}H_{16}N_4O_9$ (picrate): C, 47.06; H, 3.95; N, 13.76. Found: C, 46.95; H, 3.77; N, 13.72.

4o: bp 175–185 °C (2 mmHg) by bulb-to-bulb method; mp 173–175 °C (picrate, yellow needles from MeOH); NMR δ 1.23 (q, 3 H, Me), 1.4–1.8 (m, 6 H, 3 CH_2), 2.60 (t, 2 H, CH_2), 3.0–3.3 (m, 4 H, 2 NCH_2), 7.03 (dd, J = 2.0 and 2.4 Hz, 4-H), 7.96 (d, 1 H, J = 2.0 Hz, 6-H), 8.13 (d, 1 H, J = 2.4 Hz, 2-H); MS, m/e 190 (M^+).

Anal. Calcd for $C_{18}H_{21}N_5O_7$ (picrate): C, 51.55; H, 5.05; N, 16.70. Found: C, 51.24; H, 4.97; N, 16.60.

4p was isolated by column chromatography (SiO_2–$CHCl_3$/benzene) as a colorless liquid: NMR δ 1.28 (t, 3 H, Me), 2.70 (q, 2 H, CH_2), 6.9–7.5 (m, 6 H, Ph and 4-H), 8.2–8.3 (broad, 2 H, 2-H and 6-H); MS, m/e 199 (M^+).

4q was isolated by column chromatography (SiO_2): mp 141.5–142.5 °C (picrate, yellow needles from MeOH); NMR δ 1.17 (t, 3 H, J = 7.6 Hz, Me), 2.54 (q, 2 H, J = 7.6 Hz, CH_2), 7.0–7.4 (m, 5 H, Ph), 7.43 (t, 1 H, J = 2.0 Hz, 4-H), 8.27 (d, 1 H, J = 2.0 Hz, 6-H), 8.35 (d, 1 H, J = 2.0 Hz, 2-H); MS, m/e 215 (M^+).

Anal. Calcd for $C_{19}H_{16}N_4O_7S$ (picrate): C, 51.35; H, 3.63; N, 12.61; S, 7.20. Found: C, 50.71; H, 3.37; N, 12.64; S, 7.11.

4r was isolated by column chromatography (SiO_2): mp 98–99 °C (colorless needles from benzene/hexane); NMR δ 1.27 (t, 3 H, J = 8.0 Hz, Me), 2.72 (q, 2 H, J = 8.0 Hz, CH_2), 7.4–7.6 (m, 3 H, 3 H of Ph), 7.8–8.1 (m, 3 H, 2 H of Ph and 4-H), 8.55 (d, 1 H, J = 2.0 Hz, 6-H), 8.90 (d, 1 H, J = 2.2 Hz, 2-H); MS, m/e 247 (M^+).

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66; S, 12.96. Found: C, 63.19; H, 5.31; N, 5.61; S, 12.88.

The Reaction of the 1-Azabutadiene 3b with the Ketene *O,N*-Acetal 7. A mixture of the diene **3b** (2.09 g, 15 mmol) and the acetal **7** (2.7 g, 27 mmol) in benzene (9 mL) was heated at 200 °C for 20 h in a sealed tube. Concentration and distillation of the reaction mixture gave a low-boiling liquid containing 4.7 mmol of the unreacted azadiene **3b** and 1.50 g of a high-boiling liquid (bp 81–89 °C (3 mmHg)) which was proved to contain 2.4 mmol (23% based on the reacted **3b**) of 2-(dimethylamino)-5-ethylpyridine (**4s**). An analytical sample was obtained from the distilled liquid by column chromatography (SiO_2–benzene): mp 176–178 °C (picrate); NMR δ 1.17 (t, 3 H, Me), 2.50 (q, 2 H, CH_2), 3.07 (s, 6 H, NMe_2), 6.47 (d, 1 H, J = 10.2 Hz, 3-H), 7.27 (dd, 1 H, J = 10.2 and 2.0 Hz, 4-H), 7.97 (d, 1 H, J = 2.0 Hz, 6-H); MS, m/e 150 (M^+).

Anal. Calcd for $C_{15}H_{17}N_5O_7$: C, 47.49; H, 4.52; N, 18.46. Found: C, .47.45; H, 4.72; N, 18.29.

The Reaction of the Cyclohexenaldimine 3k with the Enamine 2b. A mixture of **3k** (891 mg, 5.4 mmol) and **2b** (782 mg, 5.6 mmol) in benzene (10 mL) was reacted at 200 °C for 9 h in the presence of PTS (3 mol%). A basic extract from the mixture was chromatographed (Al_2O_3–benzene) to give 111 mg (13%) of 4-ethyl-5,6,7,8-tetrahydroisoquinoline (**8**): mp 175 °C (picrate); MS, m/e 161 (M^+).

Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.18; H, 4.61; N, 14.05.

The Reaction of the 2-Azadiene 9 with the Enamines 2. A mixture of **9** (1.035 g, 5.0 mmol) and **2a** (938 mg, 7.5 mmol) in benzene (10 mL) was heated at 200 °C for 10 h in a sealed tube. The reaction mixture was concentrated and chromatographed (SiO_2–benzene) to give 196 mg (16%) of 2,5-diphenyl-3-methylpyridine (**4t**): mp 132 °C (colorless needles from benzene/hexane); NMR δ 7.75 (d, 1 H, J = 2.2 Hz, 4-H), 8.75 (d, 1 H, J = 2.2 Hz, 6-H); MS, m/e 245 (M^+).

Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.12; H, 6.13; N, 5.50.

Similarly 416 mg (32%) of 2,5-diphenyl-3-ethylpyridine (**4u**, eluted with a 5:1 mixture of benzene/hexane) and 37 mg (3%) of 2,3,5-triphenylpyridine (eluted with benzene) were obtained from 1.035 g of **9** and 1.034 g (7.5 mmol) of the enamine **2b**.

4u: mp 100 °C (colorless needles from benzene/hexane); NMR δ 7.77 (d, 1 H, J = 2.2 Hz, 4-H), 8.73 (d, 1 H, J = 2.2 Hz, 6-H); MS, m/e 259 (M^+).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 87.97; H, 6.56; N, 5.41.

2,3,4-Triphenylpyridine: mp 130–130.5 °C (colorless needles from benzene/hexane); NMR δ 7.95 (d, 1 H, J = 2.0 Hz, 4-H), 8.93 (d, 1 H, J = 2.0 Hz, 6-H); MS, m/e 307 (M^+).

Anal. Calcd for $C_{23}H_{17}N$: C, 89.86; H, 5.58; N, 4.56. Found: C, 89.69; H, 5.57; N, 4.49.

Isolation of 1-*tert*-Butyl-3,5-bis(phenylthio)-4-phenyl-1,4-dihydropyridine (14a). A solution of the imine **1f** (810 mg, 5.0 mmol) and the enamine **2m** (1.16 g, 5.3 mmol) in toluene (5 mL) was heated at reflux for 12 h. The reaction mixture was concentrated and distilled to remove low-boiling products. The residue (0.8 g) was chromatographed on a basic Al_2O_3 column to give 72 mg (3.4 %) of the dihydropyridine **14a** (eluted with hexane). From the benzene–chloroform fraction was obtained 265 mg (14%) of 3,5-bis(phenylthio)-4-phenylpyridine, which was identified only by NMR [δ 6.8–7.7 (m, 15 H, 3 Ph), 8.08 (s, 2 H, 2-H and 6-H)].

14a: mp 125–125.5 °C (colorless needles from MeOH); IR 1640 cm^{-1} (C=N); NMR δ 1.33 (s, 9 H, *t*-Bu), 3.90 (s, 1 H, PhCH), 6.67 (s, 2 H, 2 CH=), 6.8–7.5 (m, 15 H, 3 Ph); MS, m/e 429 (M^+).

Anal. Calcd for $C_{27}H_{27}NS_2$: C, 75.52; H, 6.29; N, 3.26; S, 14.92. Found: C, 75.43; H, 6.28; N, 3.14; S, 14.83.

The Reaction of the Imine 1a with the Dienamine 15a. A solution of **1a** (400 mg, 4.7 mmol) and **15a** (800 mg, 4.8 mmol) in benzene (5 mL) was heated at 200 °C for 9 h in a sealed tube, but neither significant change nor formation of the pyridine **4a** were observed by NMR.

The Reaction of the Imine 1a with the Diaminoethylene 2j. A solution of **1a** (255 mg, 3.0 mmol) and **2j** (582 mg, 3.0 mmol) in benzene (3.5 mL) was heated at 200 °C for 9 h in a sealed tube. Distillation of the reaction mixture gave 170 mg (55%) of 1-*tert*-butyl-3-piperidinopyrrole (**16**). The yield was 82% by NMR before the distillation.

16: bp 80–85 °C (1 mmHg); IR (neat) 1670 cm^{-1}; NMR δ 1.43 (s, 9 H, *t*-Bu), 1.4–1.9 (m, 6 H, 3 CH_2), 2.8–3.0 (m, 4 H, 2 NCH_2), 5.87 (dd, 1 H, J = 3.2 and 2.0 Hz, 4-H), 6.30 (dd, 1 H, J = 2.4 and 2.0 Hz, 2-H), 6.66 (dd, 1 H, J = 3.2 and 2.4 Hz, 2-H); MS, m/e 206 (M^+).

When the reaction was carried out at 150 °C for 6 h, 51% of **16** was detected by NMR with 22% of the unreacted ethylene **2j**. The yield of **16** was decreased when the mole ratio of **2j** to

1a was 2. On the other hand, formation of the pyrrole **16** in 40% yield was detected by NMR when 2.33 g (12 mmol) of **2j** and 415 mg (5.7 mmol) of *N-tert*-butylamine was reacted at 200 °C for 9 h.

The Reaction of the Imine 1a with 1-Pyrrolidinocyclohexene (2o). A solution of **1a** (5.0 g, 59 mmol) and **2o** (7.1 g, 47 mmol) in benzene (50 mL) was heated at 150 °C for 15 h in a sealed tube. Distillation of the reaction mixture gave 6.2 g (81%) of 6-methylene-1-pyrrolidino-1-cyclohexene (**18**) as a colorless liquid: bp 70–72 °C (3 mmHg); IR (neat) 1635 and 1600 cm^{-1}; NMR δ 1.6–2.0 (m, 6 H, 2 CH_2CH_2N and $CH_2CH_2CH_2$), 2.1–2.5 (m, 4 H, 2 $=CCH_2$), 2.7–3.2 (t, 4 H, 2 NCH_2), 4.6–5.0 (m, 1 H, NC=CH), 4.84 (br s, 1 H, =CHH), 5.10 (s, 1 H, =CHH); MS, *m/e* 163 (M^+).

The Reaction of 2-Phenyl-1-pyrroline (1g) with the Enamine 2b. A solution of **1g** (4.24 g, 29 mmol), **2b** (8.23 g, 59 mmol), and PTS (0.53 g, 3.1 mmol) in benzene (30 mL) was heated at 150 °C for 7 h in a sealed tube. Worked as above yielded 2.3 g (39%) of a colorless liquid, which was proved to be 3-butylidene-2-phenyl-1-pyrroline (**22**): bp 95–100 °C (2 mmHg); IR (neat) 1650 and 1580 cm^{-1}; NMR δ 0.93 (t, 3 H, Me), 1.16–1.83 (m, 2 H, $MeCH_2$), 1.83–2.50 (m, 2 H, $=CCH_2$), 2.50–2.90 (m, 2 H, $=CCH_2$), 3.81–4.26 (m, 2 H, NCH_2), 5.70–6.10 (m, 1 H, CH=), 7.26–7.76 (m, 5 H, Ph); MS, *m/e* 199 (M^+).

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Registry No. **1a**, 13987-61-6; **1b**, 77037-04-8; **1c**, 4393-14-0; **1d**, 100-62-9; **1e**, 7020-80-6; **1f**, 6852-58-0; **1g**, 700-91-4; **1h**, 2045-74-1; **1i**, 90554-27-1; **1j**, 90554-28-2; **2a**, 7182-09-4; **2b**, 7182-10-7; **2c**, 51840-50-7; **2d**, 90554-29-3; **2e**, 81816-90-2; **2f**, 36838-59-2; **2g**, 332-15-0; **2h**, 77084-89-0; **2i**, 19524-67-5; **2j**, 882-34-8; **2k**, 90554-30-6; **2l**, 81816-91-3; **2m**, 90554-31-7; **2n**, 67948-52-1; **3a**, 90554-32-8; **3b**, 80716-46-7; **3c**, 90554-33-9; **3d**, 90554-34-0; **3e**, 90554-35-1; **3f**, 62134-70-7; **3g**, 62134-72-9; **3h**, 90331-06-9; **3i**, 90554-36-2; **3j**, 90554-42-0; **3k**, 62135-03-9; **4a**, 591-22-0; **4b**, 699-25-2; **4b**·picrate, 15367-34-7; **4c**, 79169-70-3; **4d**, 90554-37-3; **4e**, 81816-89-9; **4e**·picrate, 90554-43-1; **4f**, 92-07-9; **4g**, 85665-54-9; **4g**·picrate, 90554-44-2; **4h**, 2973-87-7; **4i**, 73669-44-0; **4i**·picrate, 73669-48-4; **4j**, 3999-78-8; **4j**·picrate, 90554-45-3; **4k**, 90554-38-4; **4l**, 79116-22-6; **4l**·picrate, 90554-46-4; **4m**, 81816-92-4; **4m**·picrate, 90554-47-5; **4n**, 68686-59-9; **4n**·picrate, 90554-48-6; **4o**, 90554-39-5; **4o**·picrate, 90554-49-7; **4p**, 90554-40-8; **4q**, 82437-95-4; **4q**·picrate, 82437-96-5; **4r**, 90554-41-9; **4s**, 90554-50-0; **4s**·picrate, 90554-51-1; **4t**, 90554-53-3; **4u**, 90554-54-4; **5**, 4604-65-3; **7**, 867-89-0; **8**, 90554-52-2; **9**, 64244-33-3; **14a**, 90554-55-5; **15a**, 10321-86-5; **16**, 90554-56-6; **18**, 90554-58-8; **22**, 90554-57-7; *N-tert*-butylamine, 75-64-9; α-ethylcinnamaldehyde, 28467-92-7; benzaldehyde, 100-52-7; butyraldehyde, 123-72-8.

Pictet–Spengler Reactions in Aprotic Media

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The reaction of tryptophan methyl ester (**1**) with aldehydes such as benzaldehyde (**2a**) and cyclohexanecarboxaldehyde (**2b**) in refluxing benzene provides the corresponding tetrahydro-β-carbolines **5a** and **5b**, respectively, as earlier reported,[1] in contrast to the report of Grigg.[4]

In 1976 we reported that reaction of tryptophan methyl ester (**1**) with aldehydes such as benzaldehyde (**2a**), cyclohexanecarboxaldehyde (**2b**), or α-keto acids in refluxing benzene (Dean–Stark trap to remove water)[1] provided much improved yields of the Pictet–Spengler reaction with respect to the traditional method performed in aqueous acidic media. The reasons for this were simple for acid-labile substrates were much less prone to decomposition in a nonacidic, nonaqueous medium. Since our original reports,[1,2] a number of 3-methoxycarbonyl tetrahydro-β-carbolines have been successfully prepared by this procedure.[3,5–7,11] In view of these reports it was surprising to find that Grigg et al. reported that "A repeat of Cook's original work (tryptophan methyl ester, benzaldehyde, benzene, 80 °C, 48 h), i.e., generating the Schiffs base in situ gave only Schiffs base (**1a**) and no β-carboline (**2a,b**)."[4] To examine the conflicting experiences regarding this reaction, we have carried out several further experiments.

An important feature of the procedure that was successful in our hands is use of a Dean–Stark trap below the reflux condenser to remove water formed in the reaction.[1,2] In the Grigg report, most of the experiments were carried out in sealed NMR tubes, and no mention is made of the use of a water separator.[4] We have compared the course of the reactions of **1** and benzaldehyde (**2a**, purified by K_2CO_3 wash, drying, and distillation) in benzene with an open system and a water separator and in refluxing benzene in a closed system. Under the former conditions, after 12 h TLC indicated the presence of about 50% imine **4a**, the remainder of the material was a mixture of cis and trans carbolines **5a**. After 48 h the reaction had proceeded almost completely to **5a**. In a closed system without removal of water, the formation of **5a** was negligible, and the Schiff base **4a** was recovered quantitatively (Scheme I). To definitely determine the significance of the use of a Dean–Stark trap in the sequence, identical reactions between **1** and **2a** were performed both open to the air; however, in one case a Dean–Stark trap was used, while in the second experiment none was employed. Afte 24 h at reflux, aliquots of each reaction were analyzed by ^{13}C

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