H); ^{13}C NMR, see Table II; IR (CCl_4) 3400–2400 (br), 1690, 1635 cm^{-1}; mass spectrum, calcd for $C_7H_{10}O_2$ m/e 126.0681, found m/e 126.0684.

1-Methylcyclopropanecarboxylic Acid (4b). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise 1.3 mL (20 mmol) MeI in 2 mL THF. After the addition was complete, the ice bath was removed and the solution stirred for 1 h. The standard workup afforded 0.874 g of a light yellow oily residue, which was identified (^1H NMR) as 47% 1 and an 89% yield of **4b** based on the 53% of 1 converted. The identity of **4b** was confirmed by comparison of the ^1H NMR spectrum and a GC trace (3% OV1) with those of an authentic commercial sample (Aldrich).

1-(Trimethylsilyl)cyclopropanecarboxylic Acid (4c). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise 2.5 mL (20 mmol) of Me_3SiCl in 2.5 mL of THF. After the exothermic reaction had subsided, the ice bath was removed and the mixture stirred for 3 h. The standard workup afforded 1.165 g of crude product as white crystals. Recrystallization (pentane) gave a 70% yield of **4c**, mp 131–134 °C (lit.[4] mp 106 °C). Despite the large difference between the present and past-reported melting points, the ^1H NMR (CCl_4) [δ 11.3 (s, 1 H), 1.3–0.6 (A_2B_2, 4 H), 0.05 (s, 9 H)] followed closely that reported:[4] for the ^{13}C NMR, see Table II; mass spectrum, calcd for $C_7H_{14}O_2SiCH_3$ m/e 143.0528, found m/e 143.0536.

1-Benzylcyclopropanecarboxylic Acid (4d). To a solution of 10 mmol of **2**, at 0 °C, was added dropwise a solution of 1.5 mL (12 mmol) of benzyl bromide in 1.5 mL of THF. The mixture first turned brown but became light yellow toward the end of the addition. After removal of the ice bath and stirring for 2 more h, the standard workup gave a solid which was recrystallized (hexane) to yield **4d**: 303 mg (17%); mp 102–104 °C; ^1H NMR (CCl_4) δ 12.3 (s, 1 H), 7.2 (s, 5 H), 3.0 (s, 2 H), 1.4–0.8 (A_2B_2, 4 H); ^{13}C NMR, see Table II; IR (CCl_4) 3400–2400, 1700, 1610, 1500 cm^{-1}; mass spectrum, calcd for $C_{11}H_{12}O_2$ m/e 176.0837, found m/e 176.0836.

The intial organic layer, after base extraction, was washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated. Three products (*trans*-stilbene, bibenzyl, 1,2,3-triphenylpropane) were observed and isolated by GC (3% OV1 on Chromosorb W, 12 ft × 8 mm); they were identified by spectral comparison with authentic samples.

Registry No. 1, 1759-53-1; 2, 80375-26-4; **4a**, 80360-57-2; **4b**, 6914-76-7; **4c**, 31469-29-1; **4d**, 27356-91-8; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; MeI, 74-88-4; Me_3SiCl, 75-77-4; *trans*-stilbene, 103-30-0; bibenzyl, 103-29-7; 1,2,3-triphenylpropane, 26898-17-9.

Diels–Alder Reaction of Heterocyclic Azadienes. 2. "Catalytic" Diels–Alder Reaction of in Situ Generated Enamines with 1,2,4-Triazines. General Pyridine Annulation

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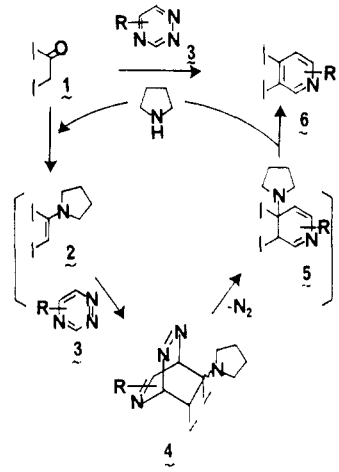
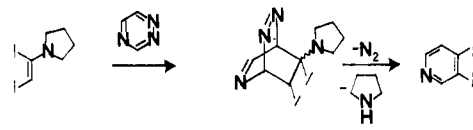
Received October 28, 1981

As part of an effort to develop short synthetic routes to naturally occurring alkaloids[2] we have had the occasion to investigate methods for the construction of substituted pyridines. These studies led to the development of a simple pyridine annulation based on the regiospecific inverse electron-demand Diels–Alder reaction of enamines with 1,2,4-triazine (eq 1).[3] Despite the convenience and

Scheme I





(1)

simplicity of this pyridine annulation, two immediate limitations surfaced which have proven to restrict the applicability of the reaction. First there is the requirement for a preformed pyrrolidine enamine, a venture approached with some concern when complex or valuable synthetic intermediates are involved. This problem is further compounded by the instability of some enamines, which often precludes their purification and occasionally isolation. A second and puzzling limitation discovered in our initial studies is the unique behavior of cyclohexanone pyrrolidine enamines. Although pyrrolidine enamines of aliphatic or five- and seven-membered cyclic ketones afforded the annulated pyridines in high yield (64–78%), a series of cyclohexanone pyrrolidine enamines uniformly yielded the pyridine products in modest yields (22–40%).[3] In this latter case, the problems reside in the final aromatization step (loss of pyrrolidine)[3] and persisted despite considerable effort to optimize the reaction conditions for elimination.

Herein, we disclose a convenient solution to the first of these limitations, which fortuitously serves to eliminate the unusual behavior of pyrrolidine enamines derived from six-membered cyclic ketones. The solution, which we refer to as a "catalytic" Diels–Alder reaction, constitutes a novel variant of the conventional Diels–Alder reaction. Experimentally we have demonstrated that the cycloaddition reaction of 1,2,4-triazine with pyrrolidine enamines proceeds under *exceptionally mild conditions*, often being exothermic, indicating that successful efforts to prepare the enamine in the presence of 1,2,4-triazine would result in the concomitant cycloaddition and subsequent pyridine formation. This further suggested that the process might well be capable of being conducted catalytically, under mild conditions. Thus, catalytic and/or in situ generation of a pyrrolidine enamine (1 → 2) in the presence of a 1,2,4-triazine (3) precedes the ensuing inverse electron-

(1) (a) Chicago Community Trust/Searle Scholar Recipient, 1981–1984. (b) National Science Foundation Undergraduate Research participant, 1980 (NSF-URP Grant No. SPI-8026418); Sterling-Winthrop Undergraduate Research Fellow, 1981.

(2) Typified by (+)-sesbanine, purported cytotoxic constituent of *Sesbania drummondii*. See: Powell, R. G.; Smith, C. R., Jr.; Weisleder, D.; Muthard, D. A.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 2784. Powell, R. G.; Smith, C. R., Jr. *J. Nat. Prod.* **1981**, *44*, 86. Also typified by streptonigrin, antitumor antibiotic isolated from cultures of *Streptomyces flocculus*. See: Gould, S. J.; Weinreb, S. M. *Prog. Chem. Org. Nat. Prod.*, in press.

(3) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.

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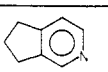
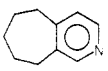
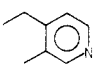
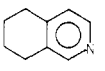
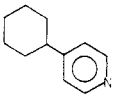
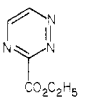
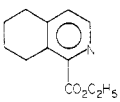
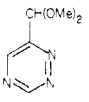
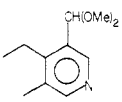
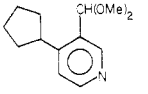
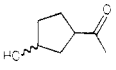
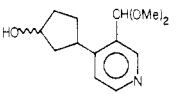
Table I. Catalytic Diels–Alder Reaction of 1,2,4-Triazines with in Situ Generated Pyrrolidine Enamines

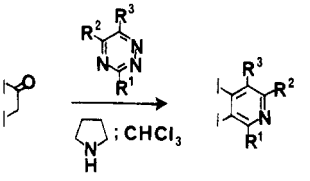
			reaction conditions[a]				
entry	ketone	1,2,4-triazine	temp, °C	time, h	equiv of pyrrolidine	product	yield,[b] %
1		 3a[c]	45	22	0.20[d]		52
			45	20	0.40		45
			45	20	0.60		52
			45	22	0.80		50
2		3a	45	58	0.20[d]		86
3		3a	45	96	2.0[e]		93
4		3a	45	32	1.0[e]		66
5		3a	45	48	1.0[e]		trace
			45 (benzene)	144	1.0[e]		22
			50 (toluene)	84	4.0[e]		36
6		 3b[c]	45	36	1.0[e]		19[f]
7		 3c[c]	45	72	1.0[e]		43
8		3c	45	28	4.0[e]		34
9		3c	45	48	2.0[e]		50[g]

[a] Typical reaction conditions are detailed in ref 5. [b] The yield recorded is based on pure, homogeneous product isolated by column chromatography (SiO_2). All compounds exhibited the reported or expected ^1H NMR, IR, and mass spectral characteristics. New compounds exhibited satisfactory C, H, and N analysis (±0.40%). [c] For preparation see ref 5. [d] Reaction run without the aid of 4-Å molecular sieves. [e] Reaction run in the presence of 4-Å molecular sieves. [f] The major product isolated (38%) was an unaromatized dihydropyridine. [g] Mixture (1:1) of cis and trans isomers.

demand cycloaddition (**2** → **4**) which is followed by the immediate loss of nitrogen (**4** → **5**) and finally aromatization (**5** → **6**) with loss (regeneration) of pyrrolidine, completing a mild, one-flask pyridine annulation (Scheme I).

Table I details the results of our investigation of this "catalytic" Diels–Alder reaction. Although simply mixing the starting components together in chloroform (**1**, **3**, and 0.2–1.0 equiv of pyrrolidine) is sufficient to allow the entire annulation sequence to be carried out in one flask (entries 1 and 2, Table I), in some instances the effectiveness of this process requires the inclusion of activated 4-Å molecular sieves in the reaction mixture (entries 3–9, Table I). While the principal role of the 4-Å molecular sieves is to catalyze and complete the enamine formation, often a slow step under the mild reaction conditions (for instance entries 5, 8, and 9; Table I), they fortuitously serve as an excellent catalyst for the final aromatization step involving the loss (regeneration) of pyrrolidine. This is especially evident in the case of cyclohexanone (entry 4, Table I) where the uncatalyzed reaction of 1,2,4-triazine with preformed 1-pyrroldinylcyclohex-1-ene produced the annulated pyridine in lower yield (40%), and the addition of conventional catalysts failed to improve the overall conversion.[3]

The results of this investigation indicate that the "catalytic" inverse electron-demand Diels–Alder reaction of in situ generated pyrrolidine enamines with 1,2,4-triazines constitutes an efficient and general one-flask pyridine annulation (eq 2). The simplicity of the sequence,



(2)

the availability of substituted 1,2,4-triazines[4] (**3**), and the central role of carbonyl groups in organic synthesis indicate that this process is capable of broad and timely application.[2,5]

Experimental Section

General Procedure for the Catalytic Diels–Alder Reaction of 1,2,4-Triazines with in Situ Generated Pyrrolidine Enamines. 5,6,7,8-Tetrahydroisoquinoline. A solution of 1,2,4-triazine[5] (**3a**; 41.0 mg, 0.5 mmol) in chloroform (1.0 mL) under

(4) Neunhoeffer, H.; Wiley, P. F. *Chem. Heterocycl. Compd.* **1978**, *33*, 189.

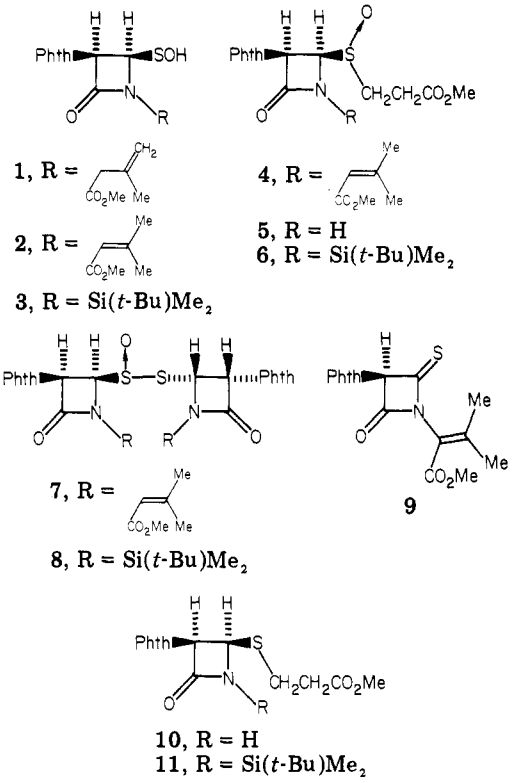
(5) For the preparation of (a) 1,2,4-triazine (**3a**), see: Paudler, W. W.; Chen, T.-K. *J. Heterocycl. Chem.* **1970**, *7*, 767. Krass, D.; Paudler, W. W. *Synthesis* **1974**, 351. Neunhoeffer, H.; Hennig, H. *Chem. Ber.* **1968**, *101*, 3952. (b) For 3-(carboethoxy)-1,2,4-triazine (**3b**), see: Paudler, W. W.; Barton, J. M. *J. Org. Chem.* **1966**, *31*, 1720. Paudler, W. W.; Krass, D. *Synthesis* **1974**, *351*. (c) For 6-(dimethoxymethyl)-1,2,4-triazine (**3c**), see: Boger, D. L.; Panek, J. S. manuscript in preparation.

N_2 was treated sequentially with cyclohexanone (49.0 mg, 0.5 mmol, 1.0 equiv) in chloroform (0.5 mL) and pyrrolidine (36.0 mg, 0.5 mmol, 1.0 equiv). Active 4-Å molecular sieves (ca. 0.2 g) were added, and the reaction mixture was warmed at 45 °C (32 h). Chromatography (SiO_2, 50% ether–pentane eluant) afforded 44.0 mg (66.5 mg theoretical, 66%) of pure 5,6,7,8-tetrahydroisoquinoline as a light yellow oil identical in all respects with authentic material.[3]

Acknowledgment. This work was assisted financially by a grant from the Anna Fuller Fund, a Biomedical Research Grant (RR 5606), the University of Kansas General Research Allocation No. 3783-XO-0038, and the Chicago Community Trust Co./Searle Scholars Program. We are grateful to the Research Corp. and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for funds used in the purchase of equipment.

Registry No. 3a, 290-38-0; **3b,** 6498-02-8; **3c,** 80375-59-3; cyclopentanone, 120-92-3; cycloheptanone, 502-42-1; 3-pentanone, 96-22-0; cyclohexanone, 108-94-1; 1-cyclohexylethanone, 823-76-7; 1-cyclopentylethanone, 6004-60-0; 1-(3-hydroxycyclopentyl)ethanone, 80375-60-6; 6,7-dihydro-5*H*-2-pyridine, 533-35-7; 6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine, 71579-81-2; 4-ethyl-3-methylpyridine, 20815-29-6; 5,6,7,8-tetrahydroisoquinoline, 36556-06-6; 4-cyclohexylpyridine, 13669-35-7; ethyl 4-ethyl-3-methyl-2-pyridinecarboxylate, 80375-61-7; 3-(dimethoxymethyl)-4-ethyl-5-methylpyridine, 80375-62-8; 4-cyclopentyl-3-(dimethoxymethyl)pyridine, 80375-63-9; *cis*-3-(dimethoxymethyl)-4-(3-hydroxycyclopentyl)-pyridine, 80375-64-0; *trans*-3-(dimethoxymethyl)-4-(3-hydroxycyclopentyl)pyridine, 80375-65-1.

Chart I[a]



[a] Phth = phthalimido.

Thermally Stable Sulfenic Acid: (3*R*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-phthalimido-2-oxoazetidine-4-sulfenic Acid

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Received August 4, 1981

Except for a few sulfenic acids deriving from anthraquinone[1] and from uracyl,[2] which are stabilized by intramolecular hydrogen bonding, sulfenic acids have been considered as highly reactive and elusive compounds. Evidence for the formation of *tert*-butylsulfenic acid in the thermolysis of di-*tert*-butyl sulfoxide was provided by NMR and IR spectral data and by its chemical derivatization in situ.[3] Some aliphatic and aromatic sulfenic acids were produced by flash vacuum pyrolysis of sufoxides and isolated at −196 °C but underwent a spontaneous self-condensation to the corresponding thiolsulfinate on warming to ambient temperature.[4] Various sulfenic acids have been reported as reactive transient species in a wide variety of chemical reactions[5] and biological transformations.[6] Their isolation, except in the very special instances and conditions described above, was unsuccessful until 1974, when the Lilly group reported the isolation of the 2-oxoazetidine-4-sulfenic acids 1 and 2 in crystalline forms at room temperature.[7]

These compounds are not stable in solution: the sulfenic acid 1 (Chart I) underwent a spontaneous annelation to a penicillin sulfoxide, thus reverting the electrocyclic process by which it was originally obtained, while the sulfenic acid 2 underwent a self-condensation to the corresponding thiosulfinate 7.[8] In a previous paper from this laboratory the conversion of the β-lactam sulfoxide 4 into the 4-thioxo-2-azetidinone 9 was described.[9] This transformation which occurred at 100 °C in nonpolar organic solvents involved the generation of the sulfenic acid 2, followed by its spontaneous condensation to the thiosulfinate 7 which afforded the thioxo compound 9. We now describe the synthesis of the sulfenic acid 3 which was found to exhibit an unusually high thermal stability.

Attempts to prepare the silyl derivative 6 by treatment of the β-lactam sulfoxide 5[10] with *tert*-butyldimethylsilyl chloride and triethylamine in DMF resulted in decomposition of the β-lactam. The sulfoxide 5 was therefore reduced quantitatively (trifluoroacetic anhydride and sodium iodide)[11] to the sulfide 10 which was converted to the *N*-silyl derivative 11 (90%).

Oxidation of the sulfide 11 (*m*-chloroperbenzoic acid, methylene dichloride −40 °C) afforded the β-lactam sulf-

(1) Fries, K. *Chem. Ber.* **1912**, *45*, 2965. Bruice, T. C.; Markiw, P. T. *J. Am. Chem. Soc.* **1957**, *79*, 3150. Jenny, W. *Helv. Chem. Acta* **1958**, *41*, 317, 326.
(2) Pall, B. C.; Uziel, D. G.; Doherty, W. E.; Cohn, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 3634.
(3) Shelton, J. R.; Davis, K. E. *J. Am. Chem. Soc.* **1967**, *89*, 718.
(4) Davis, F. A.; Yocklovich, S. G.; Baker, G. S. *Tetrahedron Lett.* **1978**, 97.
(5) Shelton, J. R.; Davis, K. E. *Int. J. Sulfur Chem.* **1973**, *8*, 205. Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32.
(6) Allison, W. S. *Acc. Chem. Res.* **1976**, *9*, 293.
(7) Chou, T. S.; Burgtorf, J. R.; Ellis, A. L.; Lammert, S. R.; Kukolja, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 1609.
(8) Chou, T. S.; Koppel, G. A.; Dorman, D. E.; Paschal, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 7864.
(9) Bachi, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.* **1980**, *45*, 1477. Bachi, M. D.; Vaya, J. *J. Am. Chem. Soc.* **1976**, *98*, 7825.
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(11) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404.

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