J = 7 Hz), 6.26 (s, 1), 7.72 (s, 4); (Me_2SO-d_6) δ 2.72 (t, 2, J = 7 Hz), 3.24 (quintet, 3, J = 7 Hz), 6.09 (s, 1), 7.08, 7.30 (br, total 1), 7.63, 7.88 (d, 4, J = 7 Hz), 9.20 (br, 1) (H_2O present); UV (same between pH 1 and 12) λ_{max} 268 nm (ϵ 8700), 327 (25 400), at pH 12 a rapid decay with an increase in low λ_{max} values, after 10 min (100 °C) λ_{max} 258 nm, 320–330 (very small); IR (KBr) 1701 (s), 1642 (s). Anal. Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.83; H, 3.76; N, 9.49. Found: C, 48.89; H, 4.05; N, 9.49.

Degradation of the above product by heating 200 mg with 14 mL of 0.1 N NaOH plus 10 mL of EtOH on a steam bath for 30 min produced an oil which solidified on cooling: 60 mg; mp 49.5–50.5 °C; NMR (CCl_4) δ 2.51 (s, 3), 7.55, 7.79 (d, 4, J = 9 Hz); UV (EtOH) λ_{max} 256–257 nm (ϵ 17 600, calcd for mol wt 198). The analysis was confirmatory for ***p*-bromoacetophenone (6)**. Anal. Calcd for C_8H_7BrO: C, 48.51; H, 3.56. Found: C, 48.69; H, 3.87. A mixture of other fragments was obtained, which were not characterized.

ω-(Phenylthio)-*p*-bromoacetophenone (23). Thiophenol (2.75 g, 0.025 mol) was treated with **2a** by the general procedure for pyrimidyl sulfides; there was obtained 7.44 g (97%) of **23**, mp 52–55 °C (EtOH). Anal. Calcd for $C_{14}H_{11}BrOS$: Br, 26.01; S, 10.44. Found: Br, 26.17; S, 10.59.

2-Amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (26a). This compound was prepared from 6-mercaptoisocytosine (**24a**) by the method described for **26b** below on a 0.04-mol scale: weight of crude product 4 g (51%); the compound did not melt below 320 °C (dilute EtOH); NMR (Me_2SO-d_6) δ 2.21 (s, 3, Me), 2.26 (s, 3, Me), 6.34 (br s, 2, NH_2), 10.70 (br s, 1, NH). Anal. Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.62; N, 21.53. Found: C, 48.84; H, 4.53; N, 21.33.

2,4-Diamino-5,6-dimethylthieno[2,3-*d*]pyrimidine (26b). A mixture of 5.66 g (0.04 mol) of **24b**, 2.16 g (0.04 mol) of NaOMe, 6.04 g (0.04 mol) of **25a**, and 50 mL of $(CH_2OH)_2$ was heated on a steam bath for 1 h. When the mixture cooled, crystals separated; these were isolated and washed with water: 6.5 g (84%); mp 127–129 °C (EtOH); NMR (Me_2SO-d_6) δ 2.24 (s, 3, Me), 2.29 (s, 3, Me), 5.84 (br s, 2, NH_2), 6.29 (br s, 2, NH_2). Anal. Calcd for $C_8H_{10}N_4S$: C, 49.49; H, 5.56; N, 28.85. Found: C, 49.46; H, 5.25; N, 28.63.

2,4-Diamino-5-methylthieno[2,3-*d*]pyrimidine (26c). The method used for **26b** was used with **25b** as the halo ketone, except that the mixture was heated for 4 h: crude yield 44%; mp 210–212 °C (absolute EtOH); NMR (Me_2SO-d_6) δ 2.405 (d, 3, Me, J = 1 Hz), 5.94 (br s, 2, NH_2), 6.37 (br s, 2, NH_2), 6.495 (d, H-6, J = 1 Hz, decoupled at 2.405 ppm). Anal. Calcd for $C_7H_8N_4S \cdot 0.2H_2O$: C, 45.84; H, 4.61; N, 30.48; S, 17.44. Found: C, 45.70; H, 4.43; N, 30.52; S, 17.52.

When this reaction was carried out in water at 40 °C for 45 min with 1 equiv of alkali, the sulfide **30** was obtained (see Table I).

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Registry No. **1a**, 591-28-6; **1b**, 15184-02-8; **2a**, 99-73-0; **2b**, 70-11-1; **2c**, 2632-13-5; **3a**, 74195-29-2; **3b**, 74195-30-5; **3c**, 74195-31-6; **3d**, 74203-17-1; **4a**, 74195-32-7; **4b**, 74195-33-8; **4c**, 74195-34-9; **4d**, 74195-35-0; **5**, 74195-36-1; **6**, 99-90-1; **7**, 14001-60-6; **8**, 5798-75-4; **9**, 74195-37-2; **10**, 15231-48-8; **11**, 104-88-1; **12**, 74195-38-3; **13**, 33268-02-9; **14**, 74195-39-4; **15a**, 74195-40-7; **15b**, 74195-41-8; **18**, 74195-42-9; **19**, 74195-43-0; **20**, 74195-44-1; **21a**, 17649-29-5; **21b**, 74195-45-2; **21c**, 17649-28-4; **22a**, 74195-46-3; **22b**, 74195-47-4; **23**, 27047-19-4; **24a**, 6973-81-5; **24b**, 56-08-6; **25a**, 814-75-5; **25b**, 78-95-5; **26a**, 74195-48-5; **26b**, 74195-49-6; **26c**, 74195-50-9; **27**, 74195-51-0; **28**, 74195-52-1; **29**, 74195-53-2; **30**, 21863-73-0; **31**, 74195-54-3; **32**, 74195-55-4; **33**, 74195-56-5; **34**, 74195-57-6; **35**, 74195-58-7; **36**, 74195-59-8; 3-bromo-3-methyl-2-butanone, 2648-71-7; thiophenol, 108-98-5.

Lewis Acid Promoted Reactions of Diazocarbonyl Compounds. 3.[1a] Synthesis of Oxazoles from Nitriles through Intermediate β-Imidatoalkenediazonium Salts

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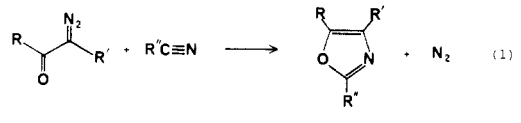
Lewis acid promoted reactions of α-diazocarbonyl compounds with nitriles provide a general method for the production of oxazoles in high isolated yields. The generality of this method is evaluated by the effectiveness of oxazole formation in surveys of Lewis acids, diazocarbonyl compounds, and nitriles. Because of the relative absence of α-halogenation products in reactions performed with $BF_3 \cdot Et_2O$, this Lewis acid is preferred when the nitrile is employed as the reaction solvent. Reactions of diazo ketones in nitrile solvents generally result in higher oxazole yields (70–99%) than do reactions of ethyl diazoacetate (26–31%). When these transformations are performed at or below room temperature, at least 1 equiv of the Lewis acid is required, although catalytic activity is observed in reactions performed at 65 °C. In $BF_3 \cdot Et_2O$ promoted reactions, a minimum tenfold molar excess of nitrile is required for optimum oxazole production, although use of SbF_5 results in high yields of oxazoles even when only a threefold excess of the nitrile is employed. The mechanism for oxazole formation is established as involving initial activation of the nitrile through association with the Lewis acid, followed by attack of the nitrilium complex at the carbonyl oxygen of the diazocarbonyl compound and internal displacement of nitrogen. Although Lewis acid association with the diazocarbonyl compound is the more favorable process in reactions performed with equivalent amounts of nitrile and diazocarbonyl compound, only equilibrium association of the Lewis acid with the nitrile effectively leads to oxazole formation.

Diazocarbonyl compounds react with nitriles under diverse reaction conditions to produce oxazoles (eq 1).[2]



(1)

Thermal decomposition of diazocarbonyl compounds in nitrile solvents at temperatures normally exceeding 100

(1) (a) For papers 1 and 2 see ref 8 and 17. (b) Camille and Henry Dreyfus Foundation Undergraduate Student-Scholar at Hope College, 1979–1980. (c) National Science Foundation Undergraduate Research Participant, Summer, 1977.

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°C forms oxazoles but usually in less than 50% yield.[3] In thermal reactions, diazocarbonyl compounds are considered to produce reactive dipolar α-ketocarbenoid intermediates that subsequently undergo 1,3 dipolar cycloaddition to nitriles.[2a] Oxazoles are also formed by unsensitized photodecomposition of diazocarbonyl compounds in nitrile solvents.[4] More recently, a varied selection of transition-metal catalysts has been employed to effect this transformation,[3b,c,5-7] and oxazole formation has been used as evidence for the intermediacy of metallocarbenoid species in these reactions. However, although oxazole yields are often improved in the catalytic processes over those obtained by thermal decomposition, only moderate yields of oxazoles (50–60%) based on the diazocarbonyl reactant are optimally obtained.

We have recently reported that Lewis acids effectively promote 1,3 dipolar addition of diazocarbonyl compounds to nitriles.[8] In that study we described the use of aluminum chloride in a general procedure for oxazole formation, with isolated yields normally greater than 80%. Subsequently, Ibata and Sato reported improved oxazole yields when boron trifluoride etherate was employed as the Lewis acid.[9] The use of trifluoromethanesulfonic acid for the synthesis of oxazoles from diazo ketones has also been reported recently.[10] In these studies of acid-promoted oxazole formation, as in earlier thermal, photolytic, and catalytic reactions, the nitrile component was employed in large excess over the diazocarbonyl compound, usually as the solvent.

In this paper we present results that describe the generality of Lewis acid promoted cycloaddition reactions of diazocarbonyl compounds with nitriles and define the limitations of these reactions. The suitability of the Lewis acid promoted cycloaddition process for the preparation of complex oxazoles is similarly described. The mechanistic implications for this and related Lewis acid promoted reactions of diazocarbonyl compounds are presented and discussed.

Results and Discussion

The Lewis Acid. As we have previously reported,[8] anhydrous aluminum chloride effectively promotes oxazole formation when employed in nitrile solvents in at least molar equivalent amounts relative to the reactant diazocarbonyl compound. When less than an equivalent amout of aluminum chloride is used, α-chlorination dominates and the α-chlorocarbonyl compound is isolated after the addition of aqueous base. Indeed, as described by the results presented in Table I, α-chlorination approaches being the sole process for product formation when only 0.2 equiv of $AlCl_3$ is employed, and the product recovery demonstrates a remarkably efficient utilization of chloride. Even when this reaction is performed at 65 °C, only a slight change in the product distribution is observed.

Ferric chloride is dramatically different from aluminum chloride in its activity toward diazocarbonyl compounds. α-Chlorination is not an important process with this Lewis acid. In addition, ferric chloride exhibits catalytic activity in reactions performed at 65 °C (Table I) and, unlike aluminum chloride, provides optimal oxazole yields when only 1.0 equiv of this acid is used at 25 °C.

The contrasting behavior of $AlCl_3$ and $FeCl_3$ characterizes a broad selection of inorganic halides that can be described as Lewis acids (Table II). Halide transfer is observed in varying degrees with $AlCl_3$, $ZrCl_4$, $MoCl_5$, $SnCl_4$, and even TiF_4.[11] In contrast, $FeCl_3$, $TaCl_5$, WCl_6, BF_3, and SbF_5 do not form products derived from halide transfer when the diazocarbonyl compound is combined with an equivalent amount of the acid in acetonitrile. Under the same reaction conditions, $NiBr_2$, $ZnCl_2$, and CuF_2 are not active in promoting oxazole formation, and the diazocarbonyl compound is recovered intact.

Table I. Effect of Lewis Acid Concentration of Product Formation in Reactions of Diazo Ketones with Nitriles[a]

acid	equiv of acid[b]	relative yield, % ArCO-CHN_2	ArCO-CH_2Cl	oxazole	isolated yield, %
$AlCl_3$	0.2	46	49	5	98
	0.2[c]	35	52	13	97
	0.6	0	63	37	91
	1.0	0	36	64	91
	1.4	0	11	89	85
	2.0	0	8	92	90
	2.4	0	0	100	94
$FeCl_3$	0.2	56	0	44	57
	0.2[c]	14	8	78	92
	0.6	0	3	97	63
	1.0	0	0	100	76
	1.4	0	0	100	83

[a] α-Diazoacetophenone or the *p*-toluyl derivative (5.0 mmol) in 5.0 mL of acetonitrile was added over a 5-min period to the Lewis acid in 30 mL of acetonitrile. Reactions were performed at 25 °C unless noted otherwise. [b] Relative to the diazoketone. [c] Reaction performed at 65 °C.

Table II. Product Yields from Reactions of Diazo Ketones with Acetonitrile in the Presence of Representative Lewis Acids[a]

acid	relative yield, % ArCOC-H_2X	oxazole	isolated yield, %	acid	oxazole, %[b]
$AlCl_3$	36	64	91	$FeCl_3$	76
$ZrCl_4$	31	69	99	WCl_6	86
$MoCl_5$	28	72	95	$TaCl_5$	84
$SnCl_4$[c]	24	76	41	$BF_3 \cdot Et_2O$	99
TiF_4	5	95	99	SbF_5[d]	99

[a] α-Diazoacetophenone or the *p*-toluyl derivative (5.0 mmol) in 5.0 mL of acetonitrile was added over a 5-min period to the Lewis acid (5.0 mmol) in 30 mL of acetonitrile. Reactions were performed at 25 °C. [b] Isolated yield of oxazole. [c] Stannous chloride was produced in reactions employing stannic chloride. [d] Reaction performed at 15 °C.

(2) For reviews of methods for the formation of oxazoles, see (a) I. J. Turchik and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975); (b) R. Lakhan and B. Turnai, *Adv. Heterocycl. Chem.*, **17**, 99 (1974); (c) J. W. Cornforth in "Heterocyclic Compounds", R. C. Elderfield, Ed., Wiley, New York, 1956; (d) R. H. Wiley, *Chem. Rev.*, **37**, 401 (1945).

(3) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963); (b) R. Huisgen, H. J. Sturm, and G. Binsch, *Chem. Ber.*, **97**, 2864 (1964); (c) R. Huisgen, G. Binsch, and L. Ghosez, *ibid.*, **97**, 2628 (1964); (d) R. Huisgen and H. Blaschke, *Justus Liebigs Ann. Chem.*, **686**, 145 (1965).

(4) (a) N. T. Buu and J. T. Edward, *Can. J. Chem.*, **50**, 3730 (1972); (b) H. Dworschak and F. Weygand, *Chem. Ber.*, **101**, 302 (1968).

(5) (a) K. Kitatani, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 1647 (1977); (b) K. Kitatani, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, 1531 (1974).

(6) (a) R. Paulissen, Ph. Moniotte, A. J. Hubert, and Ph. Teyssie, *Tetrahedron Lett.*, 3311 (1974); (b) Ph. G. Moniotte, A. J. Hubert, and Ph. Teyssie, *J. Organomet. Chem.*, **88**, 115 (1975).

(7) R. K. Armstrong, *J. Org. Chem.*, **31**, 618 (1966).

(8) M. P. Doyle, M. Oppenhuizen, R. C. Elliott, and M. R. Boelkins, *Tetrahedron Lett.*, 2247 (1978).

(9) (a) T. Ibata and R. Sato, *Chem. Lett.*, 1129 (1978); (b) T. Ibata and R. Sato, *Bull. Chem. Soc. Jpn.*, **52**, 3597 (1979).

(10) W. T. Flowers, G. Holt, and P. P. McCleery, *J. Chem. Soc., Perkin Trans. 1*, 1485 (1979).

(11) As is described for $AlCl_3$ in Table I, halide transfer is minimized with the use of excess acid.

Table III. Oxazole Yields from Reactions of α-Diazocarbonyl Compounds with Representative Nitriles in the Presence of Either $AlCl_3$ or $BF_3 \cdot Et_2O$[a]

$RCOCHN_2$	R'CN	oxazole (1)	yield of 1, %, with $AlCl_3$[b]	yield of 1, %, with $BF_3 \cdot Et_2O$[c]
p-$CH_3OC_6H_4COCHN_2$	CH_3CN	a, 2-methyl-5-(*p*-methoxyphenyl)oxazole		93 (95)[d]
	$H_2C=CHCN$	b, 2-vinyl-5-(*p*-methoxyphenyl)oxazole		91
	$H_2C=C(CH_3)CN$	c, 2-(β-propenyl)-5-(*p*-methoxyphenyl)oxazole		96
p-$CH_3C_6H_4COCHN_2$	CH_3CN	d, 2-methyl-5-(*p*-toluyl)oxazole	94	(96)[d]
$C_6H_5COCHN_2$	CH_3CN	e, 2-methyl-5-phenyloxazole	96	99 (94)[d]
	$H_2C=CHCN$	f, 2-vinyl-5-phenyloxazole	63	87
	$H_2C=C(CH_3)CN$	g, 2-(β-propenyl)-5-phenyloxazole		95
	$(CH_3)_3CCN$	h, 2-(*tert*-butyl)-5-phenyloxazole	71	88
	C_6H_5CN	i, 2,5-diphenyloxazole	73	(92)[d]
	$C_6H_5CH_2CN$	j, 2-benzyl-5-phenyloxazole	80	72 (77)[d]
	$NCCH_2CH_2CN$	k, 2-(β-cyanoethyl)-5-phenyloxazole	51	71
$(CH_3)_3CCOCHN_2$	CH_3CN	l, 2-methyl-5-(*tert*-butyl)oxazole		89
	$(CH_3)_3CCN$	m, 2,5-di-*tert*-butyloxazole		46
$CH_3(CH_2)_5COCHN_2$	CH_3CN	n, 2-methyl-5-(*n*-hexyl)oxazole	74	
$N_2CHCO(CH_2)_8COCHN_2$	CH_3CN	o, 5,5'-octamethylene-2,2'-dimethylbisoxazole	89	94 (96)[d]
$CH_3CH_2OCOCHN_2$	CH_3CN	p, 2-methyl-5-ethoxyoxazole	26	30 (62)[d]
	$C_6H_5CH_2CN$	q, 2-benzyl-5-ethoxyoxazole	31	

[a] All reactions were performed at 25 °C. [b] 2.0 equiv of $AlCl_3$, based on diazocarbonyl compound, was used. The yield of the α-chlorocarbonyl byproduct was generally less than 6%. [c] 1.0 equiv of $BF_3 \cdot Et_2O$, based on diazocarbonyl compound, was used. [d] Yield of oxazole reported by Ibata and Sato[9] for reactions performed at 0 °C with approximately 3 equiv of $BF_3 \cdot Et_2O$.

The extent of nitrogen evolution from the reactions of α-diazoacetophenone in acetonitrile with those Lewis acids that function like $FeCl_3$ (Table II) corresponded to the molar equivalent of Lewis acid that was employed. Quantitative loss of nitrogen was observed only when an equivalent amount of Lewis acid, based on α-diazoacetophenone, was used. With those acids whose behavior parallelled $AlCl_3$, the extent of nitrogen evolution was variable and generally reflected the combined yield of 2-methyl-5-phenyloxazole and α-chloroacetophenone; the only exception was $SnCl_4$ which, when treated with diazo compounds, is known to undergo metal–halogen insertion at the dinitrogen-substituted carbon.[12]

Oxazoles are very weak bases.[13] Yet they can be expected to associate with Lewis acids and, through this association, deactivate the Lewis acid to prevent subsequent catalysis of 1,3 dipolar addition. The behavior of each of the acids examined in this study corresponds to this model (eq 2.)[14] However, catalytic activity can be

(2)

found for Lewis acids that are employed for oxazole formation if the Lewis acid can be dissociated from the weakly basic oxazole. For example, whereas the optimum yield of oxazole in $FeCl_3$-promoted reactions at 25 °C requires an equivalent amount of this Lewis acid, the amount of oxazole formed at 65 °C is 3.5 times the amount of the catalyst (Table I). Similar results have been obtained with $BF_3 \cdot Et_2O$. The difference in basicity between the oxazole and the diazocarbonyl compound or nitrile toward the Lewis acid should determine the catalytic potential of that acid.

Of the catalysts that have been examined thus far for oxazole formation from diazocarbonyl compounds, only $Cu(OTf)_2$[6b] (OTf = trifluoromethanesulfonate) and $Pd(OAc)_2$[5a] may actually activate the reactants other than as a Lewis acid. Of the two catalysts, $Cu(OTf)_2$ generates oxazoles in higher yields:[15] for example, 2-methyl-5-*n*-butoxyoxazole is formed from *n*-butyl diazoacetate in 60% isolated yield within 20 h at 25 °C when $Cu(OTf)_2$ is employed in a catalytic amount.[6b] In contrast we have observed that $Cu(OTf)_2$ is relatively inactive toward α-diazoacetophenone in acetonitrile: at 25 °C 2-methyl-5-phenyloxazole is formed in only 42% yield after 72 h, even when as much as 1 equiv of $Cu(OTf)_2$ is employed. The higher reactivity of diazo esters relative to diazo ketones, although of considerable advantage in the $Cu(OTf)_2$-catalyzed process, does not favor oxazole formation in reactions promoted by Lewis acids. Relative to α-diazoacetophenone, which in acetonitrile forms 2-methyl-5-phenyloxazole with $AlCl_3$ and $BF_3 \cdot Et_2O$ in 94 and 99% yield, respectively, ethyl diazoacetate yields 2-methyl-5-ethoxyoxazole in only 26% ($AlCl_3$) and 30% ($BF_3 \cdot Et_2O$) yield. In studies where such comparisons can be made, diazo esters appear to be more suitable in thermal reactions[3] and for processes involving transition-metal catalysts,[6,16] whereas the normally less basic diazo ketones often provide higher product yields in Lewis acid promoted reactions.[17,18]

(12) (a) D. Seyferth and E. G. Rochow, *J. Am. Chem. Soc.*, 77, 907 (1955); (b) R. A. Shaw, *J. Chem. Soc.*, 2831 (1957).
(13) (a) P. Haake and L. P. Bausher, *J. Phys. Chem.*, 72, 2213 (1968); (b) D. J. Brown and P. P. Ghosh, *J. Chem. Soc. B*, 270 (1969).
(14) Oxazole formation using WCl_6, whose activity has been associated with the intermediacy of a metallocarbenoid intermediate,[4] is more appropriately described in terms of Lewis acid promotion of oxazole production.
(15) The copper(I) complex Cu(OTF) is presumably the active catalyst for these transformations.[6b]
(16) A. Nakamura, A. Konishi, Y. Tatsuno, and S. Otsuka, *J. Am. Chem. Soc.*, 100, 3443 (1978).
(17) M. P. Doyle, W. E. Buhro, and J. F. Dellaria, Jr., *Tetrahedron Lett.*, 4429 (1979).

Table IV. Effect of Variations in Acetonitrile and $BF_3 \cdot Et_2O$ Concentration on the Yield of 2-Methyl-5-phenyloxazole (1e)[a]

$[CH_3CN]$ / $[C_6H_5COCHN_2]$	$[BF_3 \cdot Et_2O]$ / $[C_6H_5COCHN_2]$	1e, % yield	$[CH_3CN]$ / $[C_6H_5COCHN_2]$	$[BF_3 \cdot Et_2O]$ / $[C_6H_5COCHN_2]$	1e, % yield
1.0	1.0	18	2.0	1.0	42
2.0	1.0	42	2.0	2.0	59
5.0	1.0	69	2.0	5.0	71
10.0	1.0	91	2.0	10.0	65
100[b]	1.0	99			

[a] α-Diazoacetophenone (2.0 mmol) in 5.0 mL of methylene chloride was added over a 15-min period to the nitrile–acid combination in 5.0 mL of methylene chloride. Reactions were performed at 25 °C. [b] Acetonitrile employed as the reaction solvent.

Products from the Wolff rearrangement[19] were not formed in reactions of diazocarbonyl compounds with nitriles that are promoted by Lewis acids. Indeed, even when treated with anhydrous $AgBF_4$ in acetonitrile, α-diazoacetophenone did not exhibit any observable reaction as evidenced by the evolution of nitrogen; the diazo ketone was recovered after 11 h at 25 °C together with an insignificant amount of phenylacetic acid (<5% after quenching with aqueous acid). The use of nitrile solvents apparently inhibits operation of this rearrangement process.

Diazocarbonyl Compound and Nitrile. The effect of variation of the yield of oxazole formed by Lewis acid promoted dipolar addition is identified by the results presented in Table III. In anhydrous $AlCl_3$-promoted reactions, in which 2.0 equiv of the Lewis acid was employed in order to minimize the yield of α-chloro ketone or α-chloro ester byproducts, α-chlorination generally accounted for less than 6% of the products derived from the diazocarbonyl compound. In $BF_3 \cdot Et_2O$-promoted reactions, α-fluorinated products were not normally observed when these reactions were performed with 1.0 equiv of this acid. However, oxazole products were generally formed in higher yields with the use of $BF_3 \cdot Et_2O$ than with $AlCl_3$, and, as has been reported by Ibato and Sato,[9] boron trifluoride etherate is the acid of choice for these transformations.

A broad spectrum of oxazoles can be prepared in exceptionally high yields from diazocarbonyl compounds through the action of Lewis acids in nitrile solvents. Conjugated nitriles such as acrylonitrile undergo dipolar addition exclusively at the nitrile functional group; pyrazoline formation from dipolar addition across the carbon–carbon double bond[6a] is not observed. Dinitriles such as succinonitrile are capable of forming both the corresponding monooxazole and bisoxazole and, depending on the conditions employed for these reactions, both products are observed, although the bisoxazole is formed in less than 10% yield even when only a twofold molar excess of succinonitrile is employed. However, the use of the dinitrile in a 15-fold excess over the diazo compound results in exclusive formation of the monooxazole. From reactions performed with succinonitrile, approximately 75% of the unreacted nitrile could be recovered.

Relative Concentrations of Diazocarbonyl Compound, Lewis Acid, and Nitrile. Although Lewis acid promoted reactions of diazocarbonyl compounds with nitriles afford oxazoles in exceptionally high yields, these reactions are usually performed in the presence of minimum 15-fold molar excess of nitrile. The limitation inherent in this process for the synthesis of oxazoles possessing complex functionalities at the 2-position is obvious. In order to further elaborate this limitation, we have investigated the effect of variations in the relative amounts of diazocarbonyl compounds, Lewis acids, and nitriles on the yields of oxazoles formed in these reactions. Results from the study employing α-diazoacetophenone, $BF_3 \cdot Et_2O$, and acetonitrile in the solvent methylene chloride are presented in Table IV. As expected, increasing the concentration of acetonitrile relative to α-diazoacetophenone results in a marked increase in the yield of 2-methyl-5-phenyloxazole (**1e**). Suprisingly, in this case, increasing the relative concentration of $BF_3 \cdot Et_2O$ at constant nitrile concentration also leads to an increase in the yield of oxazole; however, when the amount of the Lewis acid surpasses the combined amount of nitrile and diazocarbonyl compound, no further increase in oxazole yield is observed. Similar results are observed for reactions of α-diazoacetophenone with trimethylacetonitrile in the presence of $BF_3 \cdot Et_2O$.

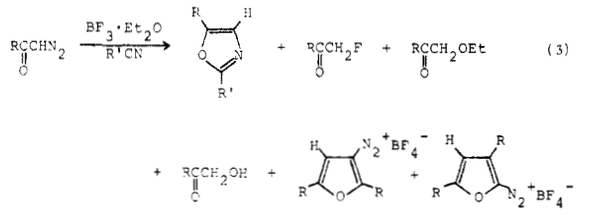
The use of SbF_5 provides an interesting contrast to the results obtained with $BF_3 \cdot Et_2O$. Employing an α-diazoacetophenone–acetonitrile–SbF_5 molar ratio of 1.0:1.5:1.0 gave 2-methyl-5-phenyloxazole in 66% yield, or more than double that expected from the results in Table IV. Oxazole **1a** was produced from α-diazo-*p*-methoxyacetophenone in 45% yield, using the same molar ratio of reactants; the associative influence of the polar *p*-methoxy substituent is evident in this result. With only a threefold molar excess of succinonitrile, the reaction of α-diazoacetophenone with an equivalent amount of SbF_5 afforded the corresponding monooxazole (88%) and bisoxazole (12%) in nearly quantitative yield (98%). Thus SbF_5, a stronger Lewis acid than $BF_3 \cdot Et_2O$, promotes oxazole formation more effectively than does $BF_3 \cdot Et_2O$ and, despite relative handling difficulties, may be more advantageous than even $BF_3 \cdot Et_2O$ for the synthesis of oxazoles in select cases.

With decreasing amounts of the nitrile, the production of α-fluoroacetophenone becomes a detectable process, although this product never amounts to more than 10% of the oxazole yield when only 1.0 equiv of $BF_3 \cdot Et_2O$ is employed. Similarly α-ethoxyacetophenone and α-hydroxyacetophenone are formed in reactions of α-diazoacetophenone with $BF_3 \cdot Et_2O$ at low nitrile concentrations, but normally in less than 6% and 3% yield, respectively, even when only equivalent amounts of the nitrile and diazocarbonyl compound are used. The principal process that occurs in the relative absence of nitrile is self-condensation of the α-diazocarbonyl compound, resulting in the formation of 1,4- and/or 2,5-disubstituted furandiazonium tetrafluoroborates[20] (eq 3). Highly colored in-

(18) However, results obtained by Ibata and Sato[9] indicate only a moderate decrease in the yield of oxazole **1p** with the use of ethyl diazoacetate and an approximate threefold excess of $BF_3 \cdot Et_2O$, rather than the stoichiometric amount of this acid employed in the present study.

(19) (a) J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Am. Chem. Soc.*, **95**, 124 (1973); (b) L. L. Rodina and I. K. Korobitzyna, *Russ. Chem. Rev.*, **36**, 260 (1967); (c) W. Kirmse, "Carbene Chemistry", Academic Press, New York, 1964.

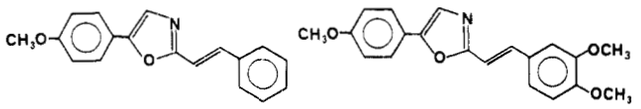
(20) W. Ried and W. Bodenstedt, *Justus Liebigs Ann. Chem.*, **667**, 96 (1963); **679**, 77 (1964). The formation of **7** and **9** is strikingly sensitive to substituents: para substituents on α-diazoacetophenone direct condensation to **9** whereas meta substituents selectively direct condensation to **7**.



(3)

tractable materials are also produced but were not further defined.

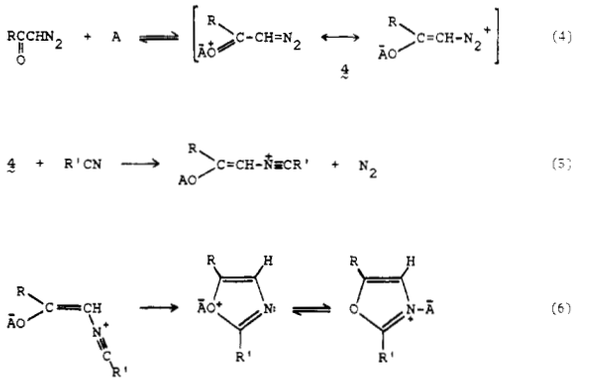
The versatility of the Lewis acid promoted oxazole synthesis is exemplified by the results obtained for the synthesis of 5-(*p*-methoxyphenyl)-2-styryloxazole (**2**) and 2-(3,4-dimethoxystyryl)-5-(4-methoxyphenyl)oxazole (**3**, annuloline). Annuoline, whose brilliant fluorescence



characterizes the annual rye grass *Lolium multiflorum*,[21] is the first known naturally occurring oxazole alkaloid. Since the use of 10 molar equivalents of nitrile represents near optimum conditions for oxazole formation (Table IV), we limited the amount of nitrile to a maximum of 5 molar equivalents based on the diazocarbonyl compound in order to determine the optimum yield of oxazole under conditions that employed less than an optimum amount of nitrile. Thus, employment of α-diazo-*p*-methoxyacetophenone, cinnamonitrile, and BF_3·Et_2O in a molar ratio of 1:5:2 afforded **2** in 62% isolated yield. When the molar ratio of reactants was 1:2:2, **2** was isolated in 42% yield, and increasing the relative concentration of BF_3·Et_2O to a reactant ratio of 1:2:5 acutally resulted in a decrease in the yield of **2** to 38%. The synthesis of annuloline (**3**) was performed with the conveniently prepared α-diazo-*p*-methoxyacetophenone and commercially available 3,4-dimethoxycinnamonitrile.[22] By use of a reactant ratio of 1:5:2, **3** was isolated as its picrate salt in 48% yield.[23] With a reactant ratio of 1.0:1.5:1.0, **3** was formed in 29% yield.

Mechanism for Oxazole Formation. The formation of oxazoles in Lewis acid promoted reactions of α-diazocarbonyl compounds is popularly regarded as occurring through initial formation of an alkenediazonium salt (**4**) derived from association of the Lewis acid at the carbonyl oxygen of the α-diazocarbonyl compound (Scheme I).[8,9] Subsequent substitution of the nitrile at the α-carbon position with resulting loss of nitrogen produces the acid-associated oxazole. That association of Lewis acids with diazocarbonyl compounds occurs in the manner described by eq 4 is currently well-established.[24] However, alkenediazonium salts are known to undergo nucleophilic attack at the β-carbon of the ethylenediazonium group[25] rather than at the α-carbon atom as is described by eq 5. Alternatively, alkenediazonium salts such as **4** can be

Scheme I

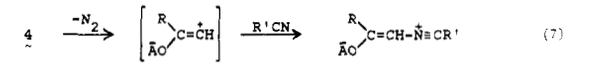


(4)

(5)

(6)

considered to undergo unimolecular loss of nitrogen to form a reactive vinyl cation that is immediately trapped by the nucleophilic nitrile (eq 7). The likelihood of this

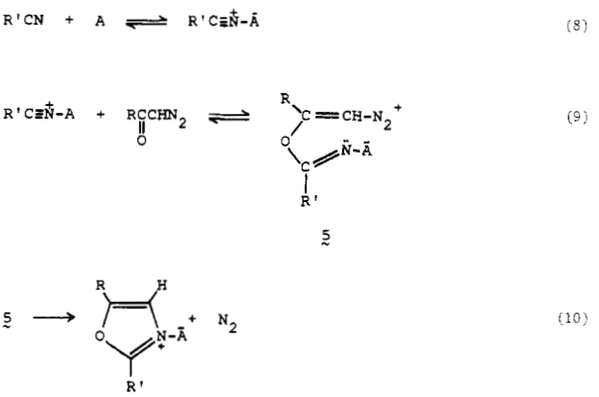


(7)

latter process is somewhat obscured by the reported stability of ethylenediazonium salts derived from alkylation of the carbonyl oxygen of ethyl diazoacetate with triethyloxonium hexachloroantimonate (decomposition at 115 °C).[26]

Recently, Ibata and Sato have reported that the intermediate nitrilium ion proposed in eq 5 could be trapped by conducting the BF_3·Et_2O-promoted reaction between α-diazoacetophenone and acetonitrile in the presence of a trace amount of water.[9b] However, despite our numerous attempts to trap the product from the reaction of **4** with nitriles (eq 5) through the addition of aqueous base or methanolic sodium methoxide, amide products corresponding to this intermediate were not detected. The observation of amide products in reactions performed in the presence of water does not demonstrate the intermediacy of vinyl nitrilium ions and, indeed, such products are suggestive of an alternative mechanistic process: association of water with boron trifluoride to produce the strong protonic acid BF_3·OH_2 can be expected to be determinant. Proton addition by this acid at the α-carbon of the diazo compound followed by displacement of nitrogen by the nitrile will yield the phenacyl nitrilium ion precursor to amide and, through intramolecular ring closure of this nitrilium ion and subsequent proton elimination, to oxazole products.[10,27] The occurrence of α-fluo-

Scheme II



(8)

(9)

(10)

(21) B. Axelrod and J. R. Belzile, *J. Org. Chem.*, **23**, 919 (1958).

(22) The commercially available 3,4-dimethoxycinnamonitrile consisted of 33% of the cis isomer and 67% of the trans isomer. However, only the trans isomer reacted with diazocarbonyl compound to yield oxazole product; the cis isomer was quantitatively recovered after Lewis acid promoted reaction. Molecular models of the cis isomer of **3** show that severe steric constraints exist within this compound and suggest that isomer specificity in oxazole formation could be expected.

(23) Even under these less than optimum conditions, the isolated yield of annuloline is higher than that achieved in a previously employed more conventional procedure: R. S. Karimoto, B. Azelrod, J. Wolinsky, and E. D. Schall, *Phytochemistry*, **3**, 349 (1964).

(24) K. Bott, *Angew. Chem., Int. Ed. Engl.*, **18**, 259 (1979).

(25) K. Bott, *Chem. Ber.*, **108**, 402 (1975).

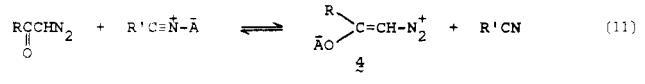
(26) (a) K. Bott, *Angew. Chem., Int. Ed. Engl.*, **3**, 804 (1964); (b) K. Bott, *Tetrahedron*, **22**, 1251 (1966).

(27) M. P. Doyle, G. D. Spoelhof, and M. A. Zaleta, *J. Heterocycl. Chem.*, **12**, 263 (1975).

roacetophenone, α-ethoxyacetophenone, and α-hydroxyacetophenone (eq 4) can be also ascribed to proton-induced reactions of the diazocarbonyl compound[10] rather than to the trapping of 4 or the nitrilium ion derived from 4. The production of furandiazonium salts represents one viable source of protonic acid and the hydroxyl group.[20]

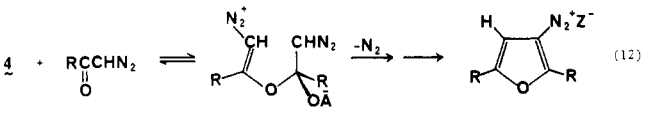
An alternate mechanism for oxazole formation that involves initial activation of the nitrile through association with the Lewis acid must also be considered (Scheme II). In this scheme, reaction of the nitrilium ion at the carbonyl oxygen of the diazocarbonyl compound produces the dipolar β-imidate ester of an alkenediazonium salt (5). To distinguish between these two mechanistic proposals, the order of addition of the reactants at −78 °C was varied. Addition of α-diazoacetophenone to the combination of 1.0 equiv of SbF_5 and 3.0 equiv of acetonitrile in methylene chloride resulted in the formation of 2-methyl-5-phenyloxazole in 12% yield with 47% of the initial diazocarbonyl reactant recovered after quenching of the reaction solution with pyridine at −78 °C after a reaction time of 2 h. In contrast, only a trace amount of oxazole resulted from the alternate addition of 3.0 equiv of acetonitrile to equivalent amounts of SbF_5 and α-diazoacetophenone, and the diazocarbonyl reactant was recovered in 63% yield after quenching of the reaction solution with pyridine at −78 °C after the same reaction time of 2 h. In the absence of nitrile, α-diazoacetophenone was isolated in 77% yield after addition to an equivalent amount of SbF_5 in a reaction performed under identical conditions. When the same comparison was made at −10 °C, using a fivefold molar excess of acetonitrile, addition of α-diazoacetophenone to the nitrile–SbF_5 combination in methylene chloride resulted in the formation of the corresponding oxazole (1e) in 27% yield, with 36% of the diazocarbonyl compound recovered after quenching with base (42% oxazole based on reacted α-diazoacetophenone). In the alternate addition sequence, 2-methyl-5-phenyloxazole was produced in only 15% yield, and only 8% of the diazo compound was recovered (16% oxazole based on reacted α-diazoacetophenone). In addition, an induction period of 2 min for nitrogen evolution was observed for the reaction at −10 °C in which the nitrile was added to the α-diazoacetophenone–SbF_5 combination; no induction period was observed for the reaction in which the diazocarbonyl compound was added to the combined acetonitrile–SbF_5.

These results not only differentiate between the two mechanistic schemes proposed for oxazole formation but also indicate that the Lewis acid exists in equilibrium between the nitrile and α-diazocarbonyl compound (eq 11).



(11)

When the alkenediazonium salt 4 is produced in the presence of the unassociated diazocarbonyl compound, nucleophilic attack by the diazocarbonyl compound at the β-carbon of the alkenediazonium salt produces a reaction intermediate 6 that eventually results in the formation of the observed 2,5-disubstituted furan-4-diazonium salt 7[20] (eq 12). Such processes acount for the instability of 4, as



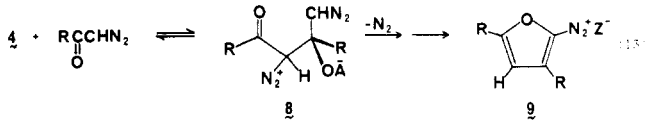
(12)

indicated by the evolution of nitrogen, in the presence of nitrile. In the absence of nitrile, gas evolution is not detected even at −10 °C when either α-diazoacetophenone or 1-diazo-3,3-dimethyl-2-butanone is added to an equivalent amount of SbF_5 in methylene chloride. However, gas evolution ensues immediately after the addition of diazocarbonyl compound and, in separate experiments, after a brief induction period following addition of the nitrile. The addition of nitrile causes the formation of unassociated diazocarbonyl compound, which is capable of reacting with 4 (eq 12) or with the nitrilium complex (Scheme II).

The relative effectiveness of SbF_5 for oxazole formation as compared to $BF_3{\cdot}Et_2O$ is also consistent with the mechanism proposed in Scheme II. Increasing acid strength favors nucleophilic attack by the diazocarbonyl compound on the nitrilium complex (eq 9) relative to acid exchange (eq 11). Similarly, according to Scheme II, the use of acid in excess of nitrile should not result in increased oxazole production but, as a result of acid exchange (eq 11) or formation of 4 (eq 4), may actually lead to a decreased yield of oxazole. Although results with $BF_3{\cdot}Et_2O$ are complicated by the presence of ethyl ether in the reaction medium, the predicted decrease in oxazole yield with increasing $BF_3{\cdot}Et_2O$ concentration is actually observed in the formation of 1e (Table IV) and of 2. With SbF_5 in excess of nitrile, either no reaction (SbF_5 in excess of both nitrile and diazocarbonyl compound) or severely decreased yields of oxazole (SbF_5 in excess of nitrile but not of both nitrile and diazocarbonyl compound) is observed.

Results that describe the effect of increasing nitrile concentration on the yield of oxazole (Table IV) indicate that the acid-exchange process (eq 11) actually favors 4. When the molar amount of nitrile approaches that of the diazocarbonyl compound, the yield of oxazole, which is assumed to be indicative of the equilibrium concentration of the nitrilium complex and unassociated diazocarbonyl compound, plummets. However, as expected from the operation of eq 11, increasing the nitrile concentration relative to that of the diazocarbonyl compound leads to increased yields of oxazole products. An increase in the basicity of the diazocarbonyl compound will also shift the acid-exchange equilibrium to 4 and, as is observed for reactions of ethyl diazoacetate, lead to a decreased yield of oxazole.

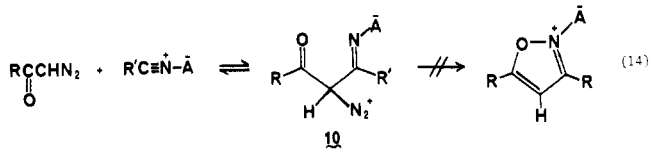
In view of the prior utilization of diazocarbonyl compounds for such processes as aldehyde and ketone homologation reactions[28] and the cyclopropanation of α,β-unsaturated carbonyl compounds,[17] the absence of isoxazoles from Lewis acid promoted reactions of diazocarbonyl compounds with nitriles is surprising. In fact, diazocarbonyl compounds are capable of variable reactions with similar nucleophilic reagents. For example, in addition to the 2,5-disubstituted furan-4-diazonium salts formed in $BF_3{\cdot}Et_2O$-promoted reactions of α-diazoacetophenones (eq 12), the isomeric 2,4-disubstituted furan-5-diazonium salts (9) have also been observed.[20] In a manner similar to homologation and cyclopropanation reactions, the formation of 9 can be understood to occur by electrophilic attack at the α-position of the unassociated diazocarbonyl compound (eq 13). The hypothetical production of isoxazoles



(13)

would be expected to occur similarly (eq 14). However, since only oxazoles are produced in the Lewis acid pro-

(28) W. L. Mock and M. E. Hartman, J. Org. Chem., 42, 459, 466 (1977).



10

moted reactions, we can assume that, although intermediates **5** and **10** may exist in equilibrium, only **5** is sufficiently reactive to be involved in product formation. In contrast, intermediates analogous to **10** are responsible for product formation in homologation and cyclopropanation reactions.[17,28] That unproductive intermediates analogous to **5** in these latter reactions are actually more stable than their productive counterparts (analogous to **10**) is suggested in this analysis.

We are continuing our efforts to define and understand Lewis acid promoted reactions of diazocarbonyl compounds.

Experimental Section

General. Instrumentation has been previously described.[29] For GC analyses, use was made of 5-ft columns of 20% SE-30 on Chromosorb W and of 20% OV-17 on Chromosorb P. Diazo ketones were prepared from the corresponding acid chlorides and diazomethane according to standard procedures.[30] Finely powdered solid Lewis acids were stored in a desiccator over phosphorus pentoxide. Boron trifluoride ertherate was distilled from calcium hydride. Copper(II) trifluoromethanesulfonate was prepared by the standard procedure.[31] Reagent-grade acetonitrile and methylene chloride were distilled from calcium hydride and stored over molecular sieves (type IVA) prior to their use as reaction solvents. All glassware was oven dried and assembled in a dry atmosphere.

General Procedure for Lewis Acid Promoted Reactions of Diazocarbonyl Compounds with Nitriles. The diazocarbonyl compound (2.0 mmol), dissolved in a minimal volume of the nitrile solvent (ordinarily 5.0 mL), was added dropwise to a continuously stirred solution of the Lewis acid in 15 mL of anhydrous nitrile. Reactions were usually performed at 25 °C since those between α-diazoacetophenone and acetonitrile at 0 °C with either $AlCl_3$, $FeCl_3$, or BF_3·Et_2O gave no evidence of improved oxazole yield. Gas evolution was monitored on the closed system with the use of a gas buret and commenced immediately upon addition of the diazocarbonyl compound. Reactions were usually complete within 5 min after the addition of the final portion of the diazocarbonyl compound. After complete gas evolution, the normally light colored solution was poured into 50 mL of 20% aqueous sodium hydroxide and extracted with two 50-mL portions of ether. The combined ether layer was dried over anhydrous magnesium sulfate, and the ether was distilled under reduced pressure. The weight of the resulting residue was determined, and the yields of individual reaction products were calculated through ^1H NMR analysis of the product mixture using an internal standard, either dibenzyl ether or diphenylmethane. Both ^1H NMR and GC analyses were performed on product mixtures from reactions between α-diazoacetophenone and either acetonitrile or trimethylacetonitrile.

The selective extraction of oxazoles required initial separation of the nitrile from the reaction solution. When the nitrile was water soluble, initial base extraction, as described earlier, was normally sufficient for this separation. The resulting ether layer was then washed twice with 50-mL portions of 3 M aqueous hydrochloric acid. The aqueous layer was separated, sufficient solid sodium hydroxide or sodium bicarbonate was added to make the original acidic solution basic, and the resulting mixture was extracted with 50 mL of ether. The ether solution was then dried over anhydrous magnesium sulfate, and the ether solvent was distilled under reduced pressure. Physical and spectral data for oxazoles **1a–1o** are included as supplementary material (see paragraph at the end of this paper).

Preparation of 2-Benzyl-5-phenyloxazole (1j). The procedure employed for reactions of diazocarbonyl compounds with high-boiling liquid nitriles is exemplified here. α-Diazoacetophenone (0.851 g, 5.0 mmol) dissolved in 8.0 mL of benzyl cyanide was slowly added over a 5-min period to a rapidly stirred solution containing 1.3 g of anhydrous aluminum chloride (10 mmol) in 17.0 mL of benzyl cyanide. After complete gas evolution, the reaction solution was poured into 100 mL of 20% aqueous sodium hydroxide and extracted with 100 mL of ether. The ether layer was then dried over anhydrous magnesium sulfate, and the ether was distilled under reduced pressure. The resulting solution of **1j** in benzyl cyanide was distilled at 1 torr in order to recover the vast majority of unreacted nitrile (bp 78 °C). When approximately 75% of the nitrile had been collected, the residue from the distillation was transferred to a separatory funnel with 25 mL of ether. Slow addition of concentrated hydrochloric acid to this solution without mixing resulted in the selective transfer of the oxazole into the aqueous layer, as is visually evidenced by the fluorescent color of the aqueous solution. (When the two layers are mixed, the majority of the oxazole usually returns to the organic layer.) After the aqueous layer was drawn off and sodium hydroxide was added, the oxazole was isolated after extraction to give 0.94 g of a white crystalline solid (4.0 mmol, 80% yield).

Reactions of α-Diazoacetophenone with Dinitriles. The procedure employed for reactions of diazocarbonyl compounds with solid nitriles is exemplified here. To 16.0 g of succinonitrile (200 mmol) dissolved in 50 mL of methylene chloride and 7.10 g of BF_3·Et_2O (50 mmol) was slowly added 2.92 g of α-diazoacetophenone (20 mmol) dissolved in 30 mL of methylene chloride over a 30-min period. After complete gas evolution, the reaction solution was poured into 100 mL of 20% aqueous sodium hydroxide and extracted with 100 mL of ether. The ether solution was then washed with 40 mL of 20% aqueous sodium hydroxide, and the combined basic aqueous solution was extracted twice with 50-mL portions of ether. The combined ether solution was dried over anhydrous magnesium sulfate, and the ether was removed by distillation under reduced pressure to leave a residual red oil which, after being washed with hot water to dissolve the unreacted succinonitrile, produced a solid. Recrystallization from ether–pentane yielded colorless needles of **1k** (2.81 g, 14.2 mmol, 71% yield).

With a fivefold molar excess of succinonitrile and an equivalent amount of BF_3·Et_2O relative to α-diazoacetophenone, the bisoxazole 2,2′-dimethylene-5,5′-diphenylbisoxazole was formed in 3% yield, but the total yield of oxazole products was less than 50%: ^1H NMR ($CDCl_3$) δ 7.75–7.25 (m, 10 H), 7.31 (s, 2 H), 3.40 (s, 4 H). By use of 2.0 equiv of aluminum chloride and a 15-fold molar excess of succinonitrile, the bisoxazole was formed in 4% yield when the total recovery of **1k** amounted to a 51% yield.

Reactions with malononitrile were only performed for the $AlCl_3$-promoted processes using α-diazoacetophenone. With a 15-fold molar excess of malononitrile and 2.0 equiv of $AlCl_3$, 2-(cyanomethyl)-5-phenyloxazole was produced in 37% yield: ^1H NMR ($CDCl_3$) δ 7.75–7.25 (m, 5 H), 7.33 (s, C_4-H), 4.01 (s, 2 H); IR (film) 2230 cm^{-1} (C≡N). The corresponding bisoxazole was not observed as a product in these reactions.

Preparation of 5-(*p*-Methoxyphenyl)-2-styryloxazole (2). α-Diazo-*p*-methoxyacetophenone (1.79 g, 10.1 mmol) dissolved in 6.0 mL of methylene chloride was slowly added over a 5-min period to a rapidly stirred solution of 2.84 g of BF_3·Et_2O (20.1 mmol) and 6.48 g of cinnamonitrile (50.0 mmol) in 94 mL of methylene chloride. After the rapid evolution of gas, the reaction solution was poured into 150 mL of 20% aqueous sodium hydroxide, 60 mL of chloroform was added, and the resulting mixture was separated after thorough mixing. The organic phase was then washed twice with 50-mL portions of 20% aqueous sodium hydroxide, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to a minimal volume. Addition of hexane precipitated a light yellow solid weighing 1.74 g (6.3 mmol, 62% yield): mp 137.5–138.5 °C; ^1H NMR ($CDCl_3$) δ 7.63 (d, J_o = 9.0 Hz), 7.55 (d, J_{trans} = 16.5 Hz), 7.70–7.25 (m), 7.28 (s, C_4-H), 6.96 (d, J_o = 9.0 Hz), 6.95 (d, J_{trans} = 16.5 Hz), 3.85 (s, OCH_3); mass

(29) M. P. Doyle, M. A. Van Lente, R. Mowat, and W. F. Fobare, *J. Org. Chem.*, **45**, 2570 (1980).

(30) B. Eistert, M. Regitz, G. Heck, and H. Schwall, "Methoden der Organischen Chemie" (Houben-Weyl-Muller), 4th ed, Vol. X, Part 4, Georg Thieme Verlag, Stuttgart, 1968.

(31) R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 3300 (1973).

spectrum, m/e (relative intensity)[31] 279 (1.0, M + 2), 278 (9, M + 1), 277 (58, M), 276 (100, M - 1), 138 (20), 135 (28), 116 (39), 92 (21), 89 (19), 77 (71).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.89; H, 5.54; N, 5.05.

Product analyses for reactions involving variable amounts of cinnamonitrile and BF_3·Et_2O were perfomed by analytical LC on a Waters Associates Model ALC/GPC instrument using a 30-cm Porasil column and 5% methylene chloride in hexane buffered with 0.3% triethylamine.

Preparation of Annuloline (3). α-Diazo-*p*-methoxyacetophenone (0.366 g, 2.03 mmol) dissolved in 5.0 mL of methylene chloride was slowly added over a 5-min period to a rapidly stirred solution of 0.56 g of BF_3·Et_2O (3.94 mmol) and 1.89 g of 3,4-dimethoxycinnamonitrile (10.0 mmol of a 67:33 trans–cis mixture) in 15 mL of methylene chloride. The previously described procedure was followed and, after evaporation of the organic solvent, the resulting orange-red oil was dissolved in 50 mL of anhydrous ethanol. The ethanolic solution was then treated with a saturated picric acid solution until no more precipitate deposited from the solution. After the mixture cooled, the yellow precipitate was filtered and recrystallized from ethanol to yield the picrate derivative of **3** in 48% yield, mp 219–221 °C (lit.[21] mp 216–218 °C). The hydrochloride derivative of **3** was produced in alternate experiments but proved to be more difficult to form and resulted in lower yields of the isolated product: mp 176–178 °C (lit.[21] mp 174–177 °C). Annuloline was liberated from its hydrochloride salt with dilute ammonium hydroxide. Alternatively, annuloline was isolated from the crude reaction mixture by column chromatography on a 10-cm silica gel column using hexane–ether mixtures: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J_o = 9.0 Hz, 2 H), 7.48 (d, J_{trans} = 16.5 Hz, 1 H), 7.24 (s, C_4-H), 7.03 (d, J_m = 2 Hz, 1 H), 6.96 (d, J_o = 9.5 Hz, 1 H), 6.91 (d, J_o = 9.0 Hz, 2 H), 6.82 (d of d, J_o = 9.5 Hz, J_m = 2 Hz, 1 H), 6.78 (d, J_{trans} = 16.5 Hz, 1 H), 3.91 (s, OCH_3), 3.87 (s, OCH_3), 3.82 (s, OCH_3); mass spectrum, m/e (relative intensity)[31] 339 (1, M + 2), 338 (11, M + 1), 337 (58, M), 336 (80, M - 1), 175 (12), 169 (12), 149 (20), 136 (10), 137 (100), 132 (12), 107 (13), 92 (28), 89 (26), 77 (68).

Reactions of α-Diazoacetophenone with Nitriles in the Presence of Antimony Pentafluoride. The handling of SbF_5 and reactions that employed this acid were performed in a glovebag in a dry atmosphere. In a typical procedure, SbF_5 (0.43 g, 2.0 mmol) was combined with 0.123 g of acetonitrile (3.0 mmol) in 5 mL of methylene chloride and the reaction flask was cooled to either −15 or −35 °C. α-Diazoacetophenone (0.299 g, 2.0 mmol) in 5 mL of methylene chloride was added dropwise to the cooled reaction solution over a 30-min period. The color of the reaction solution changed to orange and gas evolution was slow. After gas evolution was complete, 20 mL of 20% aqueous sodium hydroxide was added to the reaction solution, and the reaction mixture was allowed to warm to room temperature. The resulting mixture was extracted with 100 mL of ether, the ether layer was washed with 100 mL of water, and the aqueous extracts were washed with 50 mL of ether. The combined ether solution was dried over anhydrous magnesium sulfate, and ether and methylene chloride were distilled under reduced pressure. Reactions performed at −78 °C involved the sequential addition of acetonitrile and α-diazoacetophenone to SbF_5 in methylene chloride.

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Registry No. 1a, 69163-82-2; **1b**, 74185-52-7; **1c**, 74185-53-8; **1d**, 68395-78-8; **1e**, 3969-09-3; **1f**, 68395-79-9; **1g**, 74195-08-7; **1h**, 68395-80-2; **1i**, 92-71-7; **1j**, 68395-81-3; **1k**, 74185-54-9; **1l**, 74185-55-0; **1m**, 74185-56-1; **1n**, 68395-82-4; **1o**, 68395-83-5; **1p**, 32595-70-3; **1q**, 74185-57-2; **2**, 74185-58-3; **3**, 3988-51-0; **3** picrate, 74185-59-4; **3** hydrochloride, 74185-60-7; bisoxazole 2,2′-dimethylene-5,5′-diphenylbisoxazole, 31995-37-6; p-$CH_3OC_6H_4COCHN_2$, 6832-17-3; $C_6H_5COCHN_2$, 3282-32-4; $(CH_3)_3CCOCHN_2$, 6832-15-1; $CH_3(CH_2)_5COCHN_2$, 58237-58-4; $N_2CHCO(CH_2)_8COCHN_2$, 55349-59-2; $CH_3CH_2OCOCHN_2$, 623-73-4; malononitrile, 109-77-3; *trans*-cinnamonitrile, 1885-38-7; *trans*-3,4-dimethoxycinnamonitrile, 37629-85-9; *cis*-3,4-dimethoxycinnamonitrile, 37627-42-2; CH_3CN, 75-05-8; $H_2C{=}CHCN$, 107-13-1; $H_2C{=}C(CH_3)CN$, 126-98-7; $(CH_3)_3CCN$, 630-18-2; C_6H_5CN, 100-47-0; $C_6H_5CH_2CN$, 140-29-4; $NCCH_2CH_2CN$, 110-61-2; $C_6H_5COCH_2Cl$, 532-27-4; p-$CH_3OC_6H_4COCH_2Cl$, 2196-99-8; $C_6H_5COCH_2F$, 450-95-3; p-$CH_3OC_6H_4COCH_2F$, 73744-44-2.

Supplementary Material Available: Physical and spectral (^{1}H NMR, mass spectra, and elemental analyses) data for oxazoles **1a–1o**; full ^{13}C NMR data for compounds **1a**, **1e**, **1h**, **1j**, and **1k** (5 pages). Ordering information is given on any current masthead page.

Extension of a Nuphar Piperidine Synthesis to Quinolizidines and an Indolizidine

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Nuphar quinolizidines (±)-nupharolutine and (±)-7-epinupharolutine and a (±) Nuphar indolizidine were synthesized from cyclopentanones that were appropriately substituted at the C-2 and C-3 positions. Four cyclopentanones were prepared. Each possessed a terminal double bond incorporated in a C-2 side chain of variable length. These side chains were 2-propenyl, 3-butenyl, 3-methyl-3-butenyl, and 4-pentenyl. The carbocyclic ring of the four C-2-substituted cyclopentanones was expanded, with simultaneous incorporation of nitrogen, by the Beckmann rearrangement. Thereby, 6-substituted 2-piperidones were obtained. Epoxidation of the terminal double bond and subsequent treatment of the resulting epoxypiperidone with sodium hydride gave useful bicyclic products when the piperidone side chains were 3,4-epoxybutyl and 3-methyl-3,4-epoxybutyl. The presence of the 3,4-epoxybutyl group resulted in the formation of a (hydroxymethylene)indolizidone while the presence of the 3-methyl-3,4-epoxybutyl group resulted in the formation of a tertiary hydroxyquinolizidone. These bicyclic lactams were elaborated upon to complete the alkaloid syntheses. Thus the control of the ring size in the ring-formation step rested on the epoxy side chain length and substitution pattern. The measure of steric control rested in part on thermodynamics at the cyclopentanone stage.

Anhydronupharamine (1) and the nupharolutines, **2a** and **2b**, are typical of the stereochemical group of Nuphar piperidines and quinolizidines having only equatorial substituents attached to the furan-bearing ring. In a

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