The 1,3-Dipolar Cycloaddition Reactions of Heteroaromatic Dicyanomethylides with Phenylsulfinylethene and Bis(trimethylsilyl)ethyne: Synthesis of 1,2-Unsubstituted 3-Cyanoindolizines

Kiyoshi MATSUMOTO,* Takane UCHIDA,† Yukio IKEMI, Toshio TANAKA,† Momoyo ASAHI,††
Tomoe KATO,† and Hideyuki KONISHI†††
Department of Chemistry, College of Liberal Arts and Sciences, Kyoto University, Kyoto 606
†Laboratory of Chemistry, Faculty of Education, Fukui University, Fukui 910
††Fukui Prefectural College, Fukui 910
†††Department of Chemistry, Aichi Kyoiku University, Kariya, Aichi 448
(Received April 1, 1987)

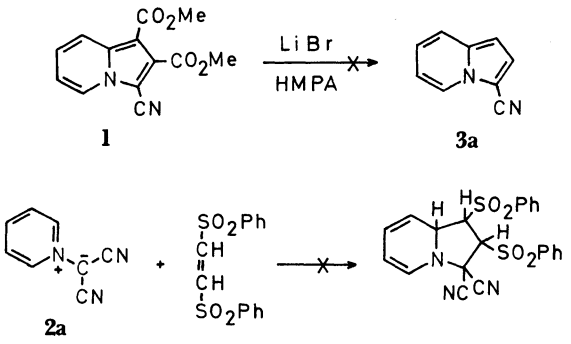
Pyridinium and diazinium dicyanomethylides underwent 1,3-dipolar cycloaddition-extrusion reactions with phenylsulfinylethene, producing the corresponding 3-cyanoindolizines in moderate to good yields. 1,3-Dipolar cycloadditions of these ylides with bis(trimethylsilyl)ethyne gave either the 1,2-bis(trimethylsilyl)-3-cyanoindolizines or the 1-trimethylsilyl-3-cyanoindolizines, or mixtures of these, depending on the substituents and the presence of another nitrogen atom in the pyridine ring. 1,2-Bis(trimethylsilyl)-3-cyanoindolizines underwent regiospecific protodesilylation at the 2-position upon a treatment with silica gel in refluxing chloroform, yielding 1-trimethylsilyl-3-cyanoindolizines. The 1,2-bis(trimethylsilyl)-, and 1-trimethylsilyl-3-cyanoindolizines suffered from quantitative protodesilylation under catalysis by tetrabutylammonium fluoride to afford 1,2-unsubstituted 3-cyanoindolizines.

The preparation of indolizines and their aza analogues[1] has been the subject of considerable interest from physical, chemical, and biological points of view.[2] Controlled reductions of appropriate indolizines would provide a stereospecific and general route to indolizidine alkaloids that comprise a large family of naturally occuring molecules with important medicinal and agricultural properties.[3] In the course of our studies on cycl[3.2.2]azine derivatives, it became necessary to know whether 1,2-unsubstituted 3-cyanoindolizines could serve as key intermediates in cycl[3.2.2]azine synthesis.[4] Unfortunately, however, there are few precedents for 3-substituted indolizines substituted only in the pyridine ring.[5]

In this paper we wish to report in full detail on the simple preparation of 1,2-unsubstituted 3-cyanoindolizines by 1,3-dipolar cycloaddition of heteroaromatic dicyanomethylides with phenylsulfinylethene and bis(trimethylsilyl)ethyne, followed by protodesilylation in the latter case.[6]

Results and Discussion

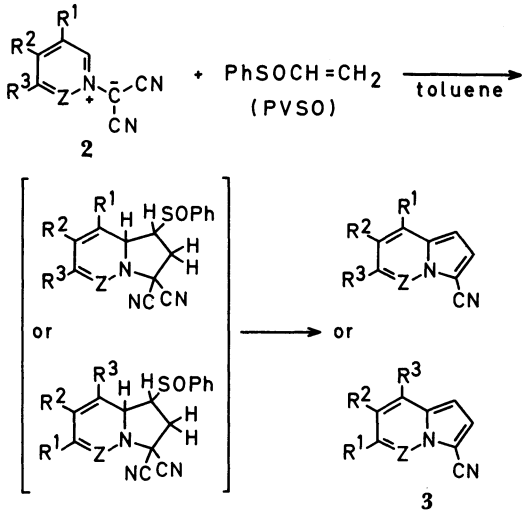
Although a wide variety of acetylene equivalents in cycloaddition reactions have been devised,[7] only few are suitable for the preparation of nitrogen heterocycles since most of the acetylene equivalents require either an oxidative or reductive procedure after cycloaddition in order to remove the functional groups. For example, in the case of 1,2-bis(methoxycarbonyl)-3-cyanoindolizine (**1**) that was prepared in good yield by a reaction of bis(methoxycarbonyl)ethyne with pyridinium dicyanomethylide (**2a**), a procedure employing LiBr/HMPA that is amenable to the demethoxycarbonylation of tetraheterafulvalenes[8] was unsuccessful, resulting in the formation of a complex reaction mixture. On the other hand, the reaction



of (*Z*)- and (*E*)-1,2-bis(phenylsulfonyl)ethenes, excellent acetylene equivalents in cycloadditions of acyclic compounds[7,9] with pyridinium dicyanomethylide was extremely sluggish, producing a complex mixture after 4 days in refluxing toluene.

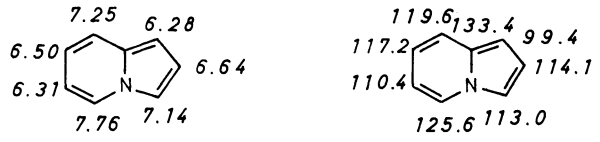
We have found that both phenylsulfinylethene (PVSO) and bis(trimethylsilyl)ethyne (BTMSA) serve as reliable acetylene equivalents in 1,3-dipolar cycloadditions. The reaction of pyridinium dicyanomethylide (**2a**) with PVSO[10] produced 3-cyanoindolizine (**3a**) in 43% yield. The elemental and mass spectral analyses as well as IR, ^{1}H and ^{13}C NMR spectra are in agreement with structure **3a** (Tables 2 and 3). The generality of this cycloaddition-extrusion reaction follows from Table 1; the yields are moderate to good. These 3-cyanoindolizines are highly fluorescent in solution. Those possessing an electron-withdrawing group in the pyridine moiety are pale yellow and stable, whereas indolizines like **3a** and **3b** form colorless crystals which turn dark brown on standing.

A comparison of the NMR data of **3** with those of the parent indolizine (**4**)[11,12] deserves to be mentioned. In general, δ(H-2) and δ(H-5) appear in a lower field than those of **4** due to conjugation with the electron-withdrawing 3-CN. Similar to the cyano-substituted



2 and 3:

a: Z=CH, R^1=R^2=R^3=H
b: Z=CH, R^1=R^3=H, R^2=Me
c: Z=CH, R^1=R^3=H, R^2=$PhCH_2$
d: Z=CH, R^1=R^3=H, R^2=Ph
e: Z=CH, R^1=R^3=H, R^2=PhCO
f: Z=CH, R^1=R^3=H, R^2=MeOCO
g: Z=CH, R^1=R^3=H, R^2=CN
h: Z=CH, R^1=R^2=Me, R^3=H
i: Z=CH, R^1=R^3=Me, R^2=H
j: Z=CH, R^1=—(CH=CH)$_2$—=R^2, R^3=H
k: Z=N, R^1=R^2=R^3=H



4(^{13}C NMR)

J (Hz)

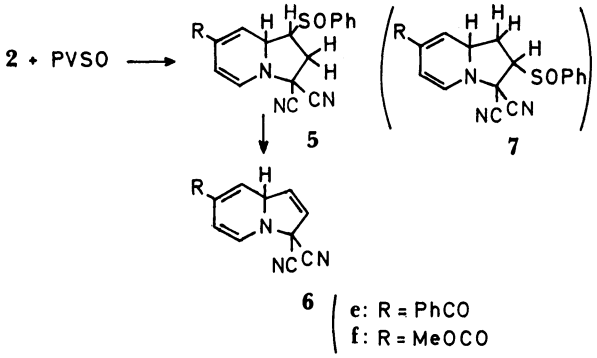
1 - 2 = 3.9	1 - 3 = 1.2
2 - 3 = 2.7	5 - 6 = 6.8
5 - 7 = 1.0	6 - 7 = 6.4
6 - 8 = 1.0	7 - 8 = 8.9

4(^{1}H NMR: δ & J)

benzene series, the cyano causes higher field shifts of δ(C-3) by 14—18 ppm (16 ppm in benzonitrile). The ^{13}C resonances at the 6-, 7-, and 8-positions appear lower than those of **4**.

Although no initial adducts **5** have been isolated, a probable mechanism for the formation of **3** involves a 1,3-dipolar cycloaddition of **2** to PVSO to give a primary adduct **5** followed by the elimination of benzenesulfenic acid and hydrogen cyanide. Indeed, the intermediates **6e**, **f** were isolated in reactions of 4-benzoyl- and 4-methoxycarbonylpyridinium dicyanomethylides (**2e**, **f**) in yields as poor as 4 and 3%, respectively. The regioisomeric structure **7** might be unlikely, both on steric and electronic grounds (see discussion below).

Although silylacetylenes could be employed as an acetylene equivalent,[7] they usually do not exceed the unsilylated acetylenes in reactivity.[13]



The reaction of pyridinium dicyanomethylide (**2a**) with BTMSA in refluxing toluene afforded a mixture of 1,2-bis(trimethylsilyl)-3-cyanoindolizine (**8a**) and 1-trimethylsilyl-3-cyanoindolizine (**9a**) each in 2% yield (^{1}H NMR analysis). They could be separated by medium-pressure liquid chromatography (MPLC), though accompanied by some protodesilylation, **8a**→**9a**. One run (Entry 2, Table 4) gave a 1 : 5 mixture of **8a** and **9a** in 24 % yield (^{1}H NMR analysis). The MPLC separation of crude **8a** afforded a mixture of **8a** and **9a** in the ratio of 1 : 8; the ratio did not change appreciably upon refluxing the mixture in xylene. 4-Methyl- and 4-(*t*-butyl)pyridinium dicyanomethylide, (**2b**) and (**2l**), reacted sluggishly with BTMSA in refluxing toluene, giving **9b** and a mixture of **8l** and **9l** respectively (Table 4). The low yield could be improved when the reaction was performed in refluxing xylene (Entry 9). In contrast, the pyridinium dicyanomethylides (**2e**, **f**, **g**, **m**) having an electron-withdrawing substituent gave better yields of the indolizines (**8e**, **f**, **g**, **m**) and (**9e**). For instance, heating of 4-cyanopyridinium dicyanomethylide (**2g**) with BTMSA in refluxing toluene produced 1,2-bis(trimethylsilyl)-3-cyanoindolizine (**8g**) in 65% isolated yield. Diazinium ylides (**2k**, **n**, **o**) that are more π-deficient than the pyridinium analogues reacted smoothly with BTMSA affording the

Table 1. Preparation of 3-Cyanoindolizines **3a**—**i** and Their Analogues **3j**, **k** from Heteroaromatic Dicyanomethylides **2a**—**k** and Phenylsulfinylethene (PVSO)

Product	Reaction Time/h	Yield/%[a]	Mp θ_m/°C
3a	20	43	49—52
3b	15	37	58—60
3c	15	73	60—62
3d	19	33	114—115
3e	20	22	141—142
3f	11	20	167—168
3g	20	19	187—189
3h[b]	14	33	78—82
3i	20	58	108—109
3j	30	51	102—104
3k	8	42	66—68

a) Isolated yield. b) Mixture of 6,7- and 7,8-dimethyl-3-cyanoindolizine.

Table 2. IR and ^{1}H NMR Spectroscopic Data of 3-Cyanoindolizines **3a—i** and Their Analogues **3j, k**

Compound	ν(KBr)/cm^{-1}		Chemical shift ($CDCl_3$)/δ							Coupling constant; J/Hz					
	CN	CO	H-1	H-2	H-5	H-6	H-7	H-8	Others	1-2	5-6	5-7	6-7	6-8	7-8
3a	2210	—	6.37	7.19	8.15	6.68	6.91	7.41	—	3.9	6.4	1.1	6.0	1.5	7.1
3b	2220	—	6.23	7.14	8.02	6.53	—	7.15	2.29(Me)	4.2	6.8	—	—	1.3	—
3c	2230	—	6.28	—[a]	8.10	6.56	—	—[a]	3.89 (CH_2) 7.0—7.5 (Ph+H-2, 8)	4.5	7.1	—	—	1.5	—
3d	2220	—	6.43	—[a]	8.21	7.00	—	—[a]	7.2—7.8 (Ph+H-2, 8)	3.9	6.4	—	—	1.5	—
3e	2220	1620 1640	6.69	—[a]	8.26	—[a]	—	—[a]	7.2—7.8(Ph+H-2, 5, 8)	4.2	7.2	—	—	—	—
3f	2215	1715	6.74	7.43	8.25	7.36	—	8.30	3.96 (MeO)	4.0	7.8	—	—	1.2	—
3g	2230	—	6.71	7.36	8.26	6.87	—	7.38	—	4.1	6.8	—	—	1.0	—
3h	2220	—	6.27	7.10	7.96	6.54	—	—	2.24, 2.26, 2.29 (Me)	4.5	6.6	—	—	—	—
3h′			6.19	6.86	7.92	—	—	7.19		3.8	—	—	—	—	—
3i	2250	—	6.35	7.19	7.93	—	6.63	—	2.26, 2.40 (Me)	4.1	—	—	—	—	—
3j[b]	2230	—	—[a]	—[a]	8.10	—[a]	—	—	6.9—7.7 (Ar)	—	5.0	—	—	—	—
3k[b]	2260	—	6.50	7.27	—	8.26	6.80	7.83	—	4.5	—	—	2.9	1.5	8.6

a) Overlapped with aromatic protons. b) For convenience, the numberings are formally based upon indolizine system.

Table 3. ^{13}C NMR Spectroscopic Data of 3-Cyanoindolizines **3a—i** and Their Analogues **3j, k**[a]

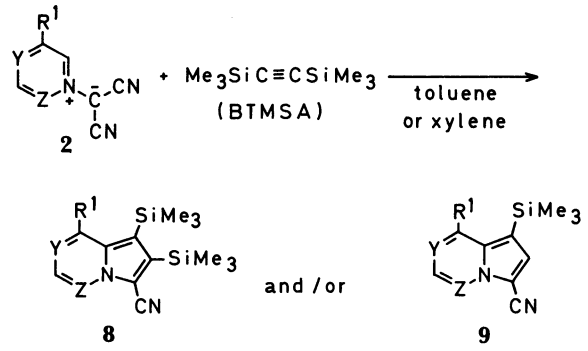
Compound	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	CN	Other substituent
3a	101.2	122.5	95.3	129.3	113.1	119.4	121.7	131.3	113.9	——
3b	99.9	122.8	94.4	124.6	115.8	137.0	117.9	132.6	114.4	21.1 (Me)
3c	100.6	122.9	94.7	125.0	115.9	136.0	118.0	135.8	114.2	41.2 (CH_2); 139.1 (s) 126.7, 128.7, 129.0 (each d)
3d	101.9	123.2	94.9	125.2	113.0	136.8	116.3	134.7	114.1	138.2 (s) 126.5, 128.3, 129.1 (each d)
3e	106.0	123.5	97.3	125.1	112.7	137.0	123.8	134.6	113.1	193.9 (CO); 132.7(s) 128.6, 129.6, 130.4 (each d)
3f	105.3	122.4	97.6	124.1	112.0	122.4	122.3	134.8	112.3	52.5 (MeO); 163.9 (CO)
3g	105.7	123.8	99.0	126.1	112.8	104.9	125.7	134.0	112.3	117.4 (CN)
3i	99.3	123.0	95.1	124.3	120.8	136.1	121.5	136.1	114.4	17.8, 18.2 (each Me)
3j[b]	101.3	122.9	97.6	127.7	113.5	124.9	127.5	134.0	113.7	121.6, 122.4, 127.1, 127.7 (each d)
3k[b]	101.2	120.7	100.2	—	143.5	113.9	127.4	129.9	112.6	——

a) In ppm relative to TMS in $CDCl_3$. b) For convenience, the numberings are formally based upon indolizine system.

azaindolizines (**8k, n, o**) and (**9n**); e.g., pyridazinium dicyanomethylide (**2k**) with BTMSA in refluxing toluene gave 92% of **8k**.

In some cases (Entries 5, 6, 7, and 10), protodesilylation was not observed (Table 4). The higher temperature improved the yield, but also promoted protodesilylation, as exemplified with Entry 11.

The structures of **8** and, partially, **9** were confirmed by elemental (see Experimental) and mass analyses as well as ^{1}H and ^{13}C NMR data (Tables 5 and 6). However, the spectral data did not permit an unambiguous determination of the position of the trimethylsilyl group in **9**. The 1,2-bis(trimethylsilyl)-3-cyanoindolizines (**8**) underwent regiospecific protodesilylation in refluxing chloroform with suspended silica gel yielding **9**; as an exception, **8k** did not undergo protodesilylation under these conditions. The regiochemistry of **9a** was mainly based on the probable regioselectivity in the reaction of **2a** with trimethylsilylethyne (see below). Attempts to convert **8a** to the known 1-methoxycarbonyl-3-cyanoindolizine (**10**)[14] with



2, **8**, and **9**:

a: Z=Y=CH, R^1=H
b: Z=CH, Y=CMe, R^1=H
e: Z=CH, Y=CCOPh, R^1=H
f: Z=CH, Y=CCO_2Me, R^1=H
g: Z=CH, Y=CCN, R^1=H
k: Z=N, Y=CH, R^1=H
l: Z=CH, Y=$CCMe_3$, R^1=H
m: Z=CH, Y=CCOMe, R^1=H
n: Z=N, Y=C-$(CH=CH)_2$-=R^1
o: Z=CH, Y=N, R^1=H

Table 4. Reactions of Heteroaromatic Dicyanomethylide with Bis(trimethylsilyl)ethyne (BTMSA)

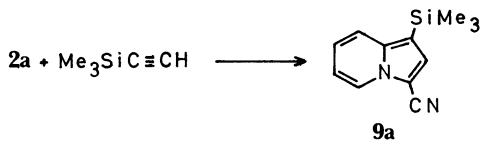
Entry	Ylide	Reaction condition		Product	Yield/%[a]	Mp	IR (KBr)/cm^{-1}	
		Solvent	Reflux time/h			θ_m/°C		
1	**2a**	toluene	62	**8a**	2.4 (30)	106—107	2210	
				9a	2.1 (27)	95—96	2180	
2		xylene	45.5	**8a**	4 (14)			
				9a	20 (61)			
3	**2b**	toluene	72	**9b**	4.9 (44)	59—60	2200	
4	**2e**	toluene	68	**8e**	20 (66)	152—153	2200	1620, 1610 (sh)
				9e	0.7 (2)	130—133	2225	1640, 1620 (sh)
5	**2f**	toluene	72	**8f**	36 (93)	160—161	2250	1715
6	**2g**	toluene	72	**8g**	65 (72)	129—130	2250, 2225	
7	**2k**	toluene	56	**8k**	92 (—)[b]	73—74	2250	
8	**2l**	toluene	72	**8l**	5.7 (33)	105—107	2200	
				9l	3.4 (20)	84—86	2180	
9		xylene	85	**9l**	45 (86)			
10	**2m**	toluene	72	**8m**	22 (69)	189—190	2210	1682
11		xylene	88.5	**8m**	48 (58)			
				9m	16 (19)	124—125	2250	1720
12	**2n**	toluene	56	**8n**	71 (—)[b]	152—153	2220	
				9n	19 (—)[b]	205—206	2195	
13	**2o**	toluene	86	**8o**	96 (98)	136—137	2250	

a) Parentheses indicate yields based on the consumed ylides. b) Not be recovered.

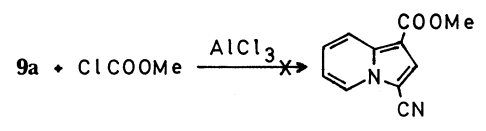
Table 5. ^{1}H NMR Spectroscopic Data of 3-Cyanoindolizines and Their Analogues **8** and **9**[a]

Compound	H-2	H-5	H-6	H-7	H-8	$J_{5\text{-}6}$[b]	$J_{6\text{-}8}$[b]	$J_{7\text{-}8}$[b]	TMS		Other substituent
8a	—	8.36	6.85	7.02	7.77	6.2	—	7.7	0.43	0.50	—
8e	—	8.35	7.34	—	8.16	7.2	1.2	—	0.37	0.50	7.4—7.7 (3H), 7.7—7.9 (2H)
8f	—	8.32	7.36	—	8.52	7.3	1.2	—	0.46	0.50	3.90 (Me)
8g	—	8.28	6.82	—	8.04	7.2	1.2	—	0.47	0.51	—
8k[d]	—	—	8.26	6.77	8.06	4.2[c]	1.5	9.2	0.43	0.50	—
8l	—	8.32	6.94	—	7.71	7.4	1.9	—	0.43	0.49	1.33 (Me)
8m	—	8.31	7.35	—	8.39	6.8	1.7	—	0.50	0.51	2.62 (Me)
8n[d]	—	8.61	—	—	—	—	—	—	0.51	0.56	7.62—8.03 (3H), 8.13—8.38 (1H)
8o[d]	—	7.89	7.93	—	9.26	4.2	1.3	—	0.51	0.52	—
9a	6.52	8.28	6.86	6.98	7.49	6.2	—	7.8	0.39		—
9b	6.31	8.09	6.55	—	7.17	7.0	1.7	—	0.36		2.31 (Me)
9e	6.75	8.29	7.35	—	7.90	7.2	2.7	—	0.40		7.5—7.8 (Ar)
9f	6.76	8.26	7.34	—	8.24	7.2	1.8	—	0.38		3.93 (Me)
9g	6.75	8.26	6.84	—	7.84	8.0	1.8	—	0.41		—
9l	6.50	8.28	6.91	—	7.45	7.4	1.6	—	0.39		1.34 (Me)
9m	6.82	8.25	7.35	—	8.10	7.6	2.0	—	0.42		2.63 (Me)
9n[d]	6.94	8.54	—	—	—	—	—	—	0.39		7.54—8.19 (Ar)

a) δ in $CDCl_3$. b) Coupling constants; Hz. c) $J_{6\text{-}7}$. d) For convenience, the numberings are formally based upon indolizine system.



9a



10

methyl chloroformate catalyzed either by aluminium (III) chloride[15] or by potassium fluoride/18-crown-6[16] were unsuccessful, resulting in the formation of 3-cyanoindolizine (**3a**) in low yields. 7-(*t*-Butyl)-1,2-bis(trimethylsilyl)-3-cyanoindolizine (**8l**) readily lost the trimethylsilyl moiety at 2-position in deuteriochloroform even at room temperature. The reaction is presumably acid-catalyzed.

Tetrabutylammonium fluoride catalyzed the protodesilylation of the trimethylsilylindolizines **8** and/or **9** to give the 3-cyanoindolizines **3** in excellent yields (see Experimental).

The ^{29}Si NMR chemical shifts of **8** reveal a mutual deshielding of the ortho trimethylsilyl groups, as established in the benzene analogues.[17a] the magnitude (0.2—0.3 ppm) is here slightly smaller than in the benzene analogues (ca. 0.6 ppm).[17]

It is now well-documented that, to a more or less extent, most 1,3-dipolar cycloadditions[18] receive

Table 6. ^{13}C NMR Spectroscopic Data of 3-Cyanoindolizines and Their Analogues **8** and **9**[a]

Compound	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	CN	TMS	Other substituent
8a	139.7	115.4	103.3	125.2	112.9	120.5	122.0	142.4	115.6	1.9 2.7	—
8e	140.4	121.5	105.4	128.4	112.2	137.0	125.0	141.1	114.8	1.8 2.6	130.0 (s), 128.4, 129.5, 132.5 (each d), 193.9 (s)
8f	140.9	114.9	105.2	124.8	111.8	120.9	123.4	140.9	114.5	1.8 2.7	52.4 (q), 165.6 (s)
8g	140.5	118.6	105.5	127.7	113.1	107.2	126.5	142.7	115.0[b]	2.3 2.4	115.0[b]
8k[c]	138.1	116.3	100.5	—	143.2	113.9	128.3	135.6	114.4	1.7 2.7	—
8m	140.6	121.5	105.4	124.8	110.4	130.3	122.6	141.2	114.7	1.7 2.7	26.0 (q), 195.2 (s)
8n[c]	137.6	117.5	110.3	—	145.5	122.0	127.7	133.1	114.6	2.1 2.8	126.1, 128.0, 128.1, 131.8 (each d)
8o[c]	136.6	120.7	105.1	129.6	117.8	—	146.2	140.2	113.8	1.7 2.7	—
9a	134.7	122.9	99.2	124.9	107.0	113.0	119.2	137.6	115.1	−1.0	—
9b	134.9	117.5	98.4	124.3	105.6	132.3	115.7	137.4	115.5	−0.9	21.1 (q)
9e	136.2	123.5	101.7	124.7	111.9	135.1	112.5	127.1	114.2	−1.0	130.1 (s), 128.5, 129.6, 132.6 (each d), 193.9 (s)
9f	135.5	122.3	101.6	124.4	111.2	123.2	112.0	136.0	114.2	−1.0	52.6 (q), 165.4 (s)
9g	134.4	125.4	102.7	125.8	111.5	104.4	112.6	136.8	113.6	−1.1	117.7 (s)
9l	134.6	124.1	98.0	113.4	106.2	145.2	112.3	137.0	115.1	−1.1	30.1 (q), 34.3(s)
9m	135.3	121.4	101.8	124.6	110.6	130.1	112.0	136.1	114.1	−1.1	26.0 (q), 195.2 (s)
9n[c]	131.4	122.1	105.1	—	145.3	120.6	126.8	127.6	114.1	−0.9	105.5, 128.0, 128.1, 133.0 (each d)

a) In ppm relative to tetramethylsilane in $CDCl_3$. b) Overlapped with another cyano group. c) For convenience, the numberings are formally based upon indolizine system.

Table 7. ^{29}Si NMR Chemical Shifts of **8** and **9**[a]

Compound	1-TMS[b]	2-TMS[b]	Compound	1-TMS
8a	−7.40	−9.54	**9a**	−7.62
8b	—[c]		**9b**	−7.68
8e	−6.98	−8.99	**9e**	−7.21
8f	−7.07	−8.94	**9f**	−7.29
8g	−6.64	−8.67	**9g**	−6.88
8k	−6.90	−9.09		
8l	—[c]		**9l**	−7.86
8m	−6.94	−8.89	**9m**	−7.24
8n	−6.80	−8.60	**9n**	−7.13
8o	−6.69	−8.72		

a) In ppm relative to tetramethylsilane. b) Tentatively assigned. c) Could not be taken for the instability in solution.

Table 8. Energy Levels of HOMO and LUMO of the Ylides **2**[a]

Ylide	HOMO/eV	LUMO/eV
2a	−8.677	1.016
2b	−8.473	1.030
2l	−8.381	1.177
2g	−8.830	0.349
2m	−8.815	0.168

a) Calculated by the CNDO/2 method.

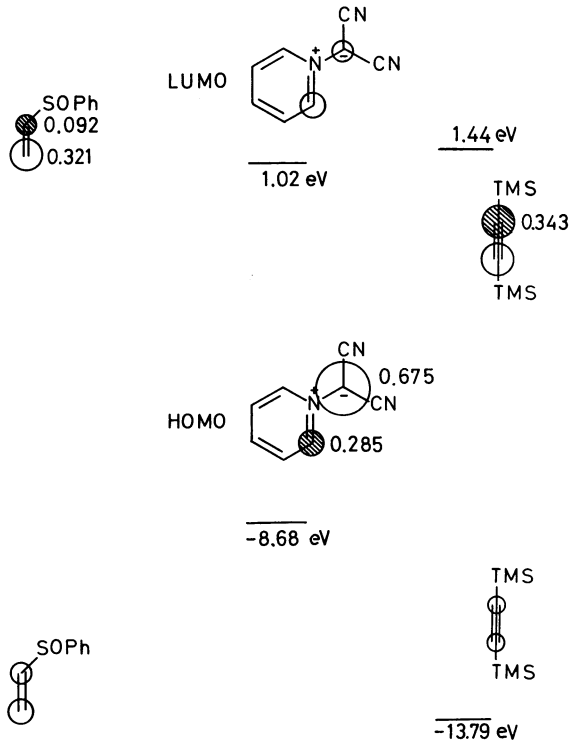


Fig. 1. Frontier molecular orbital interactions in 1,3-dipolar cycloadditions of **2a** with PVSO and BTMSA.

contributions from HOMO-LUMO interactions.[19] Clearly, cycloadditions of highly electron-deficient PVSO with **2** are predominantly HOMO (1,3-dipole)-LUMO(dipolarophile) controlled [type I in Sustmann's classification],[20] whereas those of BTMSA with **2** tend to be under major HOMO(1,3-dipole) control and partial LUMO(1,3-dipole) control when an electron-withdrawing group is introduced in the pyridine ring of **2** (Fig. 1);[21] CNDO/2 calculations of some ylides **2** show that LUMO energy levels are highly affected by a 4-substituent of **2**, while HOMO energy levels vary much less (Table 8).

A consideration of the LUMO-HOMO coefficient would lead to the regioselective formation of **9a** in a reaction of **2a** with trimethylsilylethyne when this reaction is HOMO(1,3-dipole)-LUMO(dipolarophile) controlled, as depicted in Fig. 2.[21]

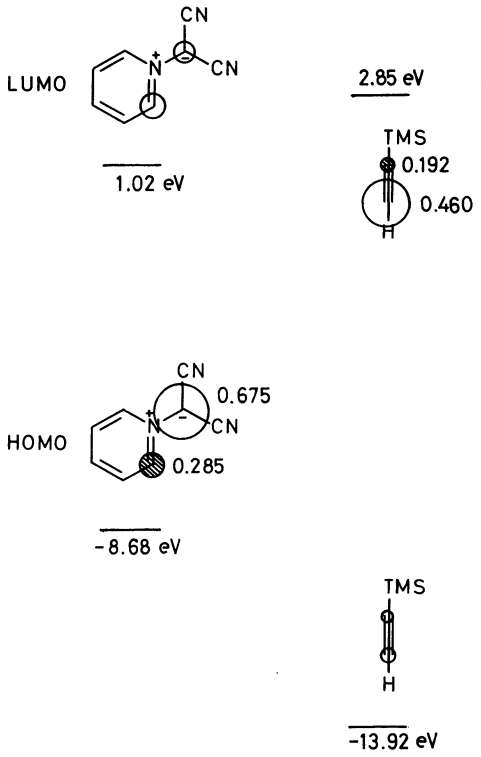


Fig. 2. Frontier molecular orbital interactions in 1,3-dipolar cycloaddition of **2a** with trimethylsilylethyne.

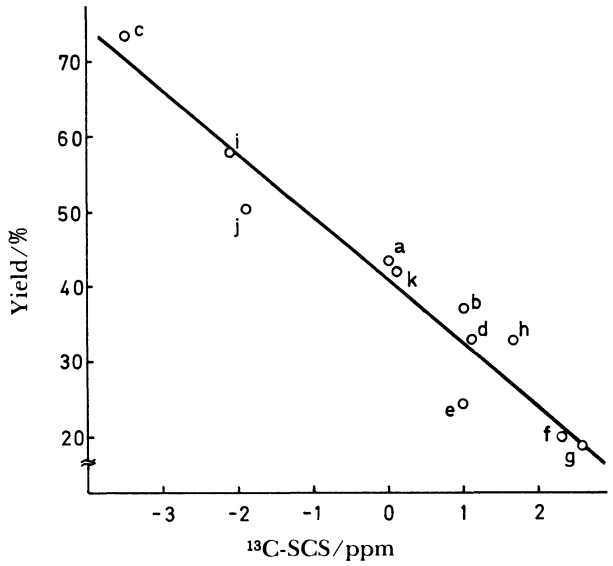


Fig. 3. Plot of the isolated yields of **3** vs ^{13}C-SCS of C-2 of **2**. Yields=−8.26(^{13}C-SCS)+40.91 (r=0.959).

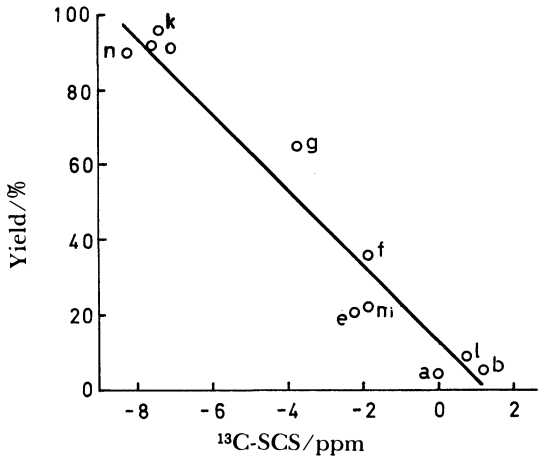


Fig. 4. Plot of the total yields of **8** and **9** (in refluxing toluene) vs. ^{13}C-SCS of the ylidic carbons of **2**. Yields=−10.42(^{13}C-SCS)+11.63 (r=0.971).

Surprisingly, linear correlations have been observed between the yields of **3** and (**8**+**9**) with the ^{13}C-SCS of the C-2 and ylidic carbons, respectively (Figs. 3 and 4). Yields are just determined by the rate ratio of the desired and undesired reactions. Only if the rate of all the side reactions remains constant upon substituent variation, yields may reflect the rate constants. The linear correlations (Figs. 3 and 4) give examples that are amusing, although we do not ascribe much value to them.

In view of the ready availability of cycloiminium ylides, PVSO, and BTMSA, the present two methods for the preparation of 1,2-unsubstituted 3-cyanoindolizines that are otherwise difficult to obtain directly, seem to be practical even in those cases in which only moderate yields are realized. Thus, both PVSO and BTMSA constitute reliable and complementary acetylene equivalents in 1,3-dipolar cycloadditions.

Experimental

General. Melting points were taken on a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were obtained on a Jasco IR-G or a Hitachi EPI-G spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-C-60HL (60 MHz) or Hitachi R40 (90 MHz) instrument. ^{13}C and ^{29}Si NMR spectra were recorded on a JEOL FX-90Q pulsed Fourier-transform spectrometer operating at 22.49 and 17.75 MHz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Partial proton decoupling was used to distinguish between individual carbon atoms. Mass spectra were obtained on a JEOL 01SG-2 spectrometer at 75 eV of ionization energy. Thin-layer chromatography (TLC) was performed on Kiessel-gel PF-254 (0.25 mm; Merck). Preparative medium-pressure liquid chromatography (MPLC) was carried out using a column (25×310 mm) pre-packed with silica gel (Lobar; LiChroprep Si 60; Merck).

Toluene and xylene were dried over sodium or Drierite. The dicyanomethylides **2** were prepared according to the method of Linn et al.[22]

Action of Lithium Bromide on 1. A magnetically stirred mixture of **1** (0.10 g; 0.4 mmol), lithium bromide (0.53 g; 6 mmol), and HMPA (12 ml) was heated to about 100 °C for 1.5 h. The resultant mixture was poured into cold water (15 ml) and extracted with two portions of cyclohexane containing five percent benzene (total 50 ml). The combined organic layer was dried over anhydrous magnesium sulfate and evaporated, leaving an oil which was fractionated by MPLC (elution with hexane-ethyl acetate (1 : 1)). With the

recovered **1** (20 %), many other fractions were obtained, the amounts of which were too small to determine their structures.

Reaction of 2a with (*Z*)- and (*E*)-1,2-Bis(phenylsulfonyl)-ethenes. A solution of **2a** (118 mg; 0.83 mmol) and the ethenes (254 mg; 0.83 mmol) in dry toluene (20 ml) was heated at reflux for 95 h. The solvent was evaporated and the residue was fractionated by MPLC (elution with hexane-ethyl acetate (2 : 1)) to give very complex fractions. A 20 % of **2a** was recovered.

General Procedure for the Reactions of 2 with PVSO. A solution of **2** (6 mmol) and PVSO (9—12 mmol) in dry toluene (35—50 ml) was refluxed under nitrogen with stirring for the time periods given in Table 1. The resulting mixture was concentrated and chromatographed on silica gel (Wako-gel C-100). Elution with hexane and hexane-benzene (1 : 1) gave diphenyl disulfide in the first fraction. Further elution of the column with benzene or hexane-ethyl acetate (2 : 1) gave the 3-cyanoindolizines **3**, which was purified by recrystallization from hexane containing a small portion of ethanol. Yields of the reactions and the physical properties of **3** are shown in Tables 1—3. The analytical data are tabulated in Table 9. In the cases of the reactions of **2e** and **2f** with PVSO, the third elution of the column with benzene-ethyl acetate (1 : 1) gave **6e** and **6f**, respectively. **6e** (4%): Dark red needles (ethanol-ethyl acetate); mp 182—183 °C; IR (KBr) 2200, 1647, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.22 (d, J=7 Hz, H-8a), 7.1—7.9 (m, 9H, Ph-H+H-1, -2, -5, -6), 9.32 (d, J=7 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ=93.6 (s, C-3), 101.7 (d, C-8a), 114.2 (d, C-1), 117.8 (s, CN), 127.9 (d, C-2), 128.9 (d, C-ortho), 129.8 (d, C-meta), 133.9 (d, C-para), 135.4 (s, C-ipso), 139.5 (d, C-6), 140.2 (s, C-7), 144.4 (d, C-8), 154.6 (d, C-5), 192.7 (CO); MS m/z (rel intensity, %) 273 (M^+, 100), 237 (32, M^+—HCN). Found: C, 75.04; H, 4.20; N, 15.43%. Calcd for $C_{17}H_{11}N_3O$: C, 74.73; H, 4.03; N, 15.38%. **6f** (3%): Dark brown crystals (hexane-benzene); mp 184—186 °C; IR (KBr) 2205, 2150, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.01 (s, 3H, OCH_3), 6.31 (br d, J=8 Hz, 1H, H-8a), 7.41 (dd, J=7.5 and 1.5 Hz, 1H, H-1), 7.53 (d, J=7.5 Hz, 1H, H-2), 8.04 (d, J=8 Hz, 1H, H-6), 8.45 (d, J=8 Hz, 1H, H-5), 9.34 (d, J=8 Hz, 1H, H-8); MS m/z (rel intensity, %), 227 (M^+, 100), 200 (58, M^+—HCN), 169 (40, M^+—HCN—OMe) (MW=227.2; Calcd for $C_{12}H_9N_3O_2$).

General Procedure for the Reactions of 2 with BTMSA. A solution of **2** (5 mmol) and BTMSA (50 mmol) in dry toluene or xylene (40 ml) was refluxed with stirring for the time periods stated in Table 4. The solvent and the excess BTMSA were removed in vacuo giving a dark-brown residue, which was subjected to chromatography on Florisil (Wako; 100—200 mesh). Elution with hexane, benzene, and then benzene-ethyl acetate (10 : 1) gave **8** or a mixture of **8** and **9** as pale-yellow crystals. In the cases of Entries 1, 2, 8, and 11, **8** and **9** were isolated by MPLC (elution with hexane-ethyl acetate (9 : 1)) and purified by recrystallization from hexane. The results of the reactions and physical properties are given in Tables 4—6. The analytical data are tabulated in Table 9. In the cases of the reactions of **2a** and **2m** with BTMSA in xylene, the addition of paradium/carbon

Table 9. Analytical Data of Indolizines **3**, **8**, and **9**

Compound	Found/%			Calcd/%			Formula
	C	H	N	C	H	N	
3a	75.83	4.17	19.49	76.04	4.25	19.71	$C_9H_6N_2$
3b	76.82	5.10	17.73	76.90	5.16	17.94	$C_{10}H_8N_2$
3c	82.70	5.18	11.97	82.73	5.21	12.06	$C_{16}H_{12}N_2$
3d	82.28	4.57	12.87	82.54	4.62	12.84	$C_{15}H_{10}N_2$
3e	78.23	4.28	11.50	78.03	4.09	11.38	$C_{16}H_{10}N_2O$
3f	66.23	3.77	13.89	65.99	4.03	13.99	$C_{11}H_8N_2O_2$
3g	72.03	2.85	25.00	71.85	3.01	25.14	$C_{10}H_5N_3$
3h[a]	77.84	6.11	16.31	77.62	5.92	16.46	$C_{11}H_{10}N_2$
3i	77.38	5.65	16.70	77.62	5.92	16.46	$C_{11}H_{10}N_2$
3j	80.96	4.15	14.64	81.23	4.19	14.58	$C_{13}H_8N_2$
3k	67.20	3.53	29.47	67.12	3.52	29.36	$C_8H_5N_3$
3m	71.60	4.35	15.00	71.73	4.38	15.21	$C_{11}H_8N_2O$
3n	74.54	3.69	21.38	74.60	3.65	21.75	$C_{12}H_7N_3$
8a	62.51	7.69	9.99	62.88	7.74	9.78	$C_{15}H_{22}N_2Si_2$
8e	67.69	6.75	7.20	67.65	6.71	7.17	$C_{22}H_{26}N_2OSi_2$
8f	59.58	7.18	7.92	59.26	7.02	8.13	$C_{17}H_{24}N_2O_2Si_2$
8g	62.02	7.01	13.66	61.69	6.79	13.49	$C_{16}H_{21}N_3Si_2$
8k	58.36	7.31	14.63	58.48	7.36	14.62	$C_{14}H_{21}N_3Si_2$
8m	62.16	7.23	8.29	62.14	7.36	8.53	$C_{17}H_{24}N_2OSi_2$
8n	64.20	6.66	12.60	64.04	6.87	12.45	$C_{18}H_{23}N_3Si_2$
8o	58.74	7.37	14.63	58.48	7.36	14.62	$C_{14}H_{21}N_3Si_2$
9a	67.49	6.62	13.10	67.24	7.06	13.07	$C_{12}H_{14}N_2Si$
9b	68.41	7.15	12.02	68.37	7.06	12.27	$C_{13}H_{16}N_2Si$
9e	71.38	5.58	8.63	71.66	5.70	8.80	$C_{19}H_{18}N_2OSi$
9f	61.81	5.88	10.17	61.73	5.92	10.29	$C_{14}H_{16}N_2O_2Si$
9g	65.35	5.31	17.78	65.23	5.48	17.56	$C_{13}H_{13}N_3Si$
9l	71.18	8.18	10.34	71.06	8.20	10.39	$C_{16}H_{22}N_2Si$
9m	65.41	6.38	10.72	65.59	6.29	10.93	$C_{14}H_{16}N_2OSi$
9n	67.80	5.58	15.94	67.89	5.70	15.83	$C_{15}H_{15}N_3Si$

a) A mixture of 6,7- and 7,8-dimethyl-3-cyanoindolizine.

(10%; the same weight to the ylide) raised the yields as follows: **8a** (15%) and **9a** (34%); **8m** (58%) and **9m** (27%).

Reaction of 2a with Trimethylsilylethyne. A mixture of **2a** (0.36 g; 2.5 mmol) and trimethylsilylethyne (1.3 g; 14 mmol) in dry toluene (40 ml) was refluxed with stirring for 50 h. The reaction mixture was allowed to stand at room temperature and filtered to recover **2a** (75%). The solids were rinsed with a small portion of toluene and the combined filtrate was concentrated and chromatographed on silica gel (Wakogel C-100; elution with hexane-ethyl acetate (1 : 9)) to give the crude product, which was purified by MPLC (elution with hexane-ethyl acetate (1 : 9)) to afford **9a** (53 mg; 42% based upon the consumed ylide).

Attempts to Transform 9a to 10. 1. To an ice-cold mixture of anhydrous aluminium chloride (53 mg; 0.4 mmol) in dry tetrachloromethane (10 ml) were added methyl chloroformate (38 mg; 0.4 mmol) and **9a** (43 mg; 0.2 mmol). After 20 min, the reaction mixture was heated at the reflux temperature for 4 d and poured into cold water (20 ml). The aqueous phase was extracted with dichloromethane (total 40 ml). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to leave a dark brown oil that was fractionated by MPLC (elution with hexane-ethyl acetate (4 : 1)). There was isolated a small amount of crude **3a** (ca. 6 mg).

2. A mixture of **9a** (22 mg; 0.1 mmol), methyl chloroformate (19 mg; 0.2 mmol), potassium fluoride (5.8 mg; 0.1 mmol), 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) (26 mg; 0.1 mmol) in dry tetrahydrofuran (4 ml) was stirred at room temperature for 51 h and then refluxed for 6 h under a nitrogen atmosphere. There was no detectable product by TLC of the reaction mixture.

3. A mixture of **9a** (22 mg; 0.1 mmol), methyl chloroformate (19 mg; 0.2 mmol), anhydrous zinc chloride (27 mg; 0.2 mmol) in dry dichloromethane (5 ml) was reacted with stirring at room temperature for 22 h and heated to the reflux temperature under a nitrogen atmosphere. The expected product was not detected by TLC of the solution.

Regioselective Protodesilylations of 8. A magnetically stirred mixture of **8** (1.5 mmol) and silica gel (Wakogel C-100; 0.5 g) in trichloromethane (5 ml) was heated at the reflux temperature for 14 h, filtered, and rinsed with dichloromethane. The combined organic solutions were purified by recrystallizations from hexane. The yields of each reaction and various physical properties are given as follows: **9a** (100%), **9f** (93%): mp 124—125 °C; IR (KBr) 2250, 1720 cm^{-1}, **9g** (89%): mp 133—134 °C; IR (KBr) 2225 cm^{-1}, **9m** (95%), **9n** (83%). The other spectral data and analytical data are shown in Tables 5, 6, and 9.

Complete Protodesilylations of 8 with Tetrabutylammonium Fluoride. A cold (0 °C) solution of **8** (1.0 mmol) in dry tetrahydrofuran (7 ml) was treated with tetrabutylammonium fluoride (0.5 ml of 1.0 mol dm^{-3} in tetrahydrofuran). The mixture was stirred at room temperature for 1 d and treated with cold water (20 ml). The aqueous layer was extracted with benzene (total 80 ml), and the combined organic layers were dried over anhydrous sodium sulfate and evaporated to give the crude products **3**, which were identified as **3** by the ^1H NMR and IR spectroscopic data except **3m** and **3n**. The yields of each reactions and some physical properties are given as follows: **3f** (100%), **3k** (86%), **3m** (93%): mp 149—150 °C; IR (KBr) 2240, 1655, 1620 cm^{-1}; ^1H NMR (δ; $CDCl_3$) 2.62 (s, 3H, Me), 6.75 (d, J=4.5 Hz, 1H, H-2), 7.33 (d, J=4.5 Hz, 1H, H-1), 7.35 (dd, J=7.2, 2.7 Hz, 1H, H-6), 8.09 (d, J=2.7 Hz, 1H, H-8), 8.22 (d, J=7.2 Hz 1H, H-5); ^{13}C NMR (ppm from TMS; $CDCl_3$) 26.0 (q, Me), 97.9 (s, C-3), 106.1 (d, C-1), 110.8 (d, C-2), 113.0 (s, CN), 121.7 (d, C-6), 123.4 (d, C-8), 124.9 (d, C-5), 130.3 (s, C-7), 134.8 (s, C-8a), 195.1 (s, CO). **3n** (100 %): mp 158—159 °C; IR (KBr) 2250 cm^{-1}; ^1H NMR (δ; $CDCl_3$) 6.87 (d, J=4.8 Hz, 1H, H-2), 7.25 (d, J=4.8 Hz, 1H, H-1), 7.5—8.1 (m, 4H, Ar-H), 8.54 (bs, 1H, H-6); ^{13}C NMR (ppm from TMS; $CDCl_3$) 99.8 (d, C-1), 101.2 (s, C-3), 112.9 (s, CN), 119.8 (d, C-2), 120.6 (s, C-7), 127.0 (s, C-8), 130.9 (s, C-8a), 145.5 (d, C-6), 122.2, 128.1, 128.3, 133.2 (each d, Ar-C).

Molecular Orbital Calculations. Molecular orbitals were calculated by the CNDO/2 method.[23] The geometry of **2a** was approximated using data for the crystalline state[24] with a slight modification involving a reforming of the molecule planar. Regarding the substituted compounds, the geometries were assumed by means of standard geometrical models,[25] except for the ylide structure which was kept unchanged. The HMO calculations were performed according to the established method.[26]

The authors wish to thank Professor Rolf Huisgen (University of Munich, West Germany) for his kind and helpful comments. They also extend their gratitude to the Institute for Molecular Science for allotment of CPU time on the HITAC M-680H Computer. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Nos. 61840017 and 62540377).

References

1) Some reviews on indolizines and aza-analogues: K. Matsumoto and T. Uchida, *Yuki Gosei Kagaku Kyokai Shi* **32**, 731 (1974); T. Uchida and K. Matsumoto, *Synthesis*, 209 (1976); F. J. Swinbourne, J. H. Hunt, and G. Klinkert, *Adv. Heterocycl. Chem.*, **23**, 103 (1978); Y. Tamura and M. Ikeda, *Adv. Heterocycl. Chem.*, **29**, 71 (1981).

2) Recent examples on these aspects: H. Duerr, C. Schommer, and T. Muenzmay, *Angew. Chem., Int. Ed. Engl.*, **25**, 572 (1986); Japan Kokai Tokkyo Koho JP 6071296, *Chem. Abstr.*, **103**, 132469q (1985); I. Antonini, F. Claudi, U. Gulini, L. Miscossi, and F. Venturi, *J. Pharm. Sci.*, **68**, 321 (1979).

3) Review: "The Alkaloids, Chemistry and Physiology," ed by R. H. F. Manske, Academic Press, New York, Vol. I—XV.

4) T. Uchida and K. Matsumoto, *Chem. Lett.*, **1980**, 149.

5) To our knowledge, only 3-dialkylaminoindolizines have been reported: A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Lett.*, **1979**, 241.

6) Presented in part at the 9th International Congress of Heterocyclic Chemistry; Aug. 1983; Tokyo; Abstract P-161.

7) O. De Lucchi and G. Modena, *Tetrahedron*, **40**, 2585 (1984).

8) C. U. Pittman, M. Narita, and Y. F. Liang, *J. Org. Chem.*, **41**, 2855 (1976); M. V. Lakshmikanthan and M. P. Cava, *J. Org. Chem.*, **41**, 882 (1976).

9) O. De Lucchi, V. Lucchini, L. Pasquato, and G. Modena, *J. Org. Chem.*, **49**, 596 (1984).

10) L. A. Paquette, R. E. Moerck, H. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978); A novel

1,3-diploar cycloaddition of tetrasulfur tetranitrite with PVSO has been recently described: R. Jones, J. L. Morris, C. W. Rees, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, **1985**, 1654.

11) P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Aust. J. Chem.*, **17**, 1128 (1964).

12) R. J. Pugmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Am. Chem. Soc.*, **93**, 1887 (1971).

13) W. P. Weber, "Silicon Reagents for Organic Synthesis" Springer Verlag, New York (1983), p. 148.

14) R. M. Acheson, M. G. Bite, and M. W. Cooper, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1908.

15) F. Effenberger and A. Krebs, *J. Org. Chem.*, **49**, 4687 (1984).

16) A. Ricci, A. Del'innocenti, M. Florenza, M. Taddei, M. Spartera, and D. R. W. Walton, *Tetrahedron Lett.*, **23**, 577 (1982).

17) a) J. Schraml, V. Chvalovsky, M. Magi, E. Lippmaa, B. Calas, J. Dungues, and P. Bourgeois, *J. Organomet. Chem.*, **120**, 41, (1976); b) K. Mach, H. Antropiusova, L. Petrusova, F. Turecek, V. Hanus, P. Sedmera, and J. Schraml, *J. Organomet. Chem.*, **289**, 331 (1985).

18) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976); "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, Wiley-Interscience, New York (1984).

19) W. Bihlmaier, R. Huisgen, H.-U. Reissig, and S. Voss, *Tetrahedron Lett.*, **1979**, 2621 and references cited.

20) R. Sustmann, *Tetrahedron Lett.*, **1971**, 2717.

21) Sofar, the CNDO/2 calculation of PVSO has been unsuccessful in our hands. The coefficients described in Fig. 1 were obtained by HMO method.[26] The energy levels shown are only qualitative.

22) W. J. Linn, O. W. Webster, and R. E. Benson, *J. Am. Chem. Soc.*, **87**, 3651 (1965).

23) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

24) C. Bugg and R. L. Sass, *Acta Cryst.*, **18**, 591 (1965).

25) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York (1970), p. 110

26) T. Yonezawa, C. Nagata, H. Kato, A. Imamura, and K. Morokuma, "Ryoushi Kakagu Nyuumon," 3rd ed, Kagaku Doujin, Kyoto (1983), pp. 55—73.