Synthesis of 2-Methylthioindolizine-3-carbonitriles Using Nitro Ketene Dithioacetal

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The reaction of 1-cyanomethylpyridinium chloride or bromide, **1a-i**, with 1,1-bis(methylthio)-2-nitroethylene (**2**) in the presence of triethylamine as a base in ethanol gave the corresponding 2-methylthioindolizine-3-carbonitrile **3** and 2-methyl-thio-1-nitroindolizine-3-carbonitrile **4** in good yields, respectively. Compounds **3a,f** were key intermediates for the synthesis of cycl[3.2.2]azine derivatives.

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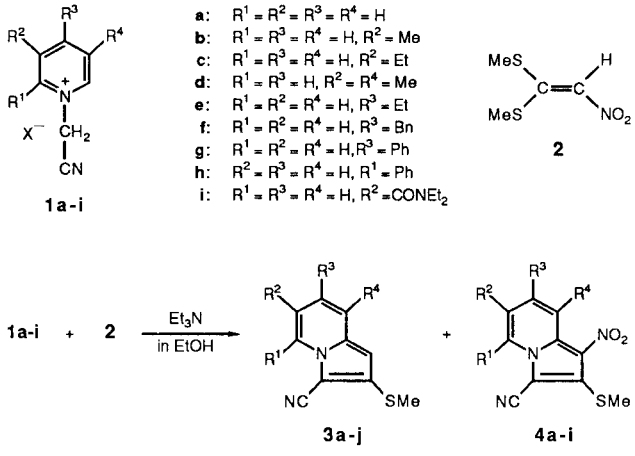
A convenient and general method for preparing cycl[3.2.2]azines is the [2 + 8] cycloaddition reaction of 3-unsubstituted indolizines with suitable acetylenic compounds [1-4]. It has recently been reported that the reaction of some indolizines, containing a leaving group in the 3-position, with dimethyl acetylenedicarboxylate (DMAD) gives the corresponding cycl[3.2.2]azine derivatives in which the dehydrogenation step can be omitted [5,6]. Matsumoto *et al.* have reported that indolizine-3-carbonitrile derivatives are also useful starting materials for the synthesis of cycl[3.2.2]azine derivatives [7]. Namely, indolizine-3-carbonitriles undergo the [2 + 8] cycloaddition reaction with electron-deficient acetylenes and olefins in a manner similar to 3-unsubstituted indolizines to give cyclazine derivatives. Indolizine-3-carbonitriles are prepared by cycloaddition-extrusion reactions of dicyanomethylides with phenyl vinyl sulfoxide [8] or bis(trimethylsilyl)ethene [9]. However, 1,2-unsubstituted indolizine-3-carbonitriles are not so stable and turn dark brown on standing except derivatives bearing an electron-withdrawing group on the pyridine ring.

In this paper, we describe the synthesis of indolizine-3-carbonitrile derivatives by the reaction of *N*-cyanomethylpyridinium salts **1a-i** with nitro ketene dithioacetal, 1,1-bis(methylthio)-2-nitroethylene (**2**) [10]. Previously we reported the synthesis of ethyl indolizine-3-carboxylate, 3-aroylindolizines, and pyrazolo[1,5-*a*]pyridines by the 1,5-dipolar cyclization reaction of the corresponding pyridinium *N*-ylides or pyridinium *N*-imines with the ketene dithioacetals [11-13]. In an extension of the studies, we applied these procedures to the synthesis of 3-cyanoindolizines. The reaction of *N*-cyanomethylpyridinium chloride (**1a**) with **2** in the presence of triethylamine as a base in ethanol gave two 1,5-cyclization products, 2-methylthioindolizine-3-carbonitrile (**3a**) and 2-methylthio-1-nitroindolizine-3-carbonitrile (**4a**), in 43 and 47% yields, respectively. These products are readily separated by alumina column chromatography and more stable than the corresponding 1,2-unsubstituted indolizine-3-carbonitrile. In a similar manner, 3-methyl-1-cyanomethylpyridinium chloride (**1b**) was allowed to react with **2** to give three products, 6-methyl-2-methylthioindolizine-3-carbonitrile (**3b**), 8-methyl-2-methylthioindolizine-3-carbonitrile (**3c**), and 6-methyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4b**) in 4, 82, and 10% yields, respectively. This method is a facile synthesis of 8-alkylated indolizines and an example of the regiospecific 1,5-dipolar cyclization (Scheme 2). In

Scheme 1

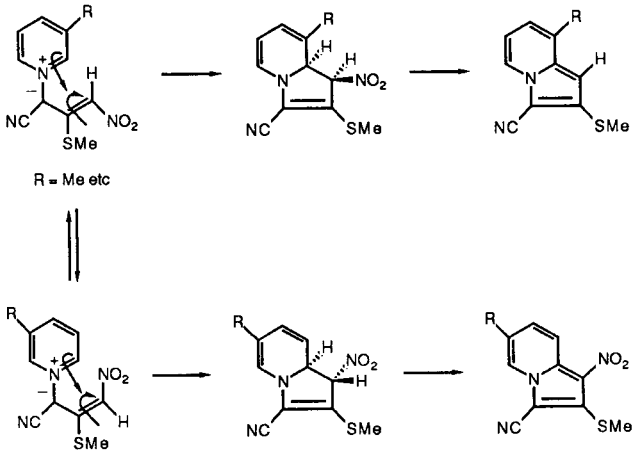


No.	R^1	R^2	R^3	R^4	mp (°C)	Yield (%) [a]
3a	H	H	H	H	41	43
b	H	Me	H	H	---	4 [b]
c	H	H	H	Me	97	82
d	H	Et	H	H	---	3 [b]
e	H	H	H	Et	67	64
f	H	Me	H	Me	105	90
g	H	H	Et	H	36	24
h	H	H	Bn	H	95	45
i	H	H	Ph	H	112	61
j	Ph	H	H	H	135	24
4a	H	H	H	H	223	47
b	H	Me	H	H	231	10
c	H	Et	H	H	205	14
d	H	Me	H	Me	162	4
e	H	H	Et	H	210	3
f	H	H	Bn	H	189	29
g	H	H	Ph	H	213	33
h	Ph	H	H	H	208	41
i	H	NEt	H	H	136	42

Me = methyl, Et = ethyl, Bn = benzyl, Ph = phenyl, NEt = *NN*-diethylcarbamoyl
[a] Isolated yield. [b] Detemined by nmr spectrum.

this reaction, 8-methyl-2-methylthio-1-nitroindolizine-3-carbonitrile was not detected in a reaction mixture. The reaction of **1c** with **2** gave also three products, **3d**, **3e**, and **4c**, in 3, 64, and 14% yields, respectively. 3,6-Dimethyl-1-cyanomethylpyridinium chloride (**1d**) was allowed to react **2** to give 6,8-dimethyl-2-methylthioindolizine-3-carbonitrile (**3f**) in 90% yield. In this reaction, the corresponding 6,8-dimethyl-1-nitroindolizine-3-carbonitrile (**4d**) was only 4% yield. In a similar manner, the reaction of **1e** with **2** gave a mixture of **3g** and **4e**, in 24 and 3% yields, respectively. In the above results, the reaction of pyridinium *N*-ylides bearing alkyl groups like a methyl group on the pyridinium *N*-ylides bearing alkyl groups like a methyl group on the pyridine rilng with **2** increased the formation of 1-unsubstituted indolizine-3-carbonitriles **3a-g**. When 4-benzyl or 4-phenyl pyridinium salts **1f,g** were allowed to react with **2** in the same condition, 1-nitroindolizine-3-carbonitriles **4f,g** were obtained in 29 and 33% yields, respectively, alone with **3h** and **3i** (45 and 61%). In the case of the reaction of 2-phenylpyridinium salt **1h** with **2**, 2-methylthio-1-nitro-5-phenylindolizine-3-carbonitrile (**4h**) was obtained as a major product in 41% yield. The yield of **3j** in this reaction was 24% (Scheme 1).

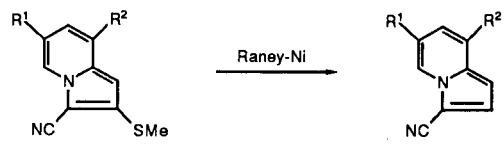
Scheme 2



The reaction of **1i** bearing a *N,N*-diethylcarbamoyl group as the electron-withdrawing group with **2** in a similar procedure gave only 6-*N,N*-diethylaminocarbamoyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4i**) in 42% yield. In this case, the 1,5-dipolar cyclization reaction occurred only at the 5-position on the pyridinium ring. This reaction is useful for the direct preparation of 1-nitroindolizine derivatives without nitration.

The desulfurization of **3a** with Raney-nickel in ethanol occurred smoothly to give a desired indolizine-3-carbonitrile (**5a**) in 72% yield [9]. 6,8-Dimethylindolizine-3-carbonitrile (**5b**) was also prepared from **3f** in good yield in a manner similar to that described for **5a** [9] (Scheme 3).

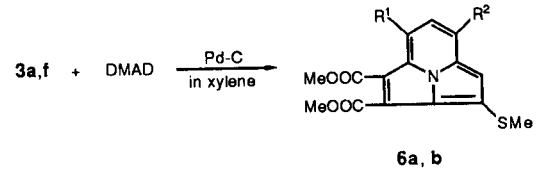
Scheme 3



No.	R^1	R^2	mp (°C)	Yield (%)
5a	H	H	48	72
b	Me	Me	104	88

It has been reported that the [2 + 8] cycloaddition reaction of 1,2-unsubstituted indolizine-3-carbonitriles with DMAD occurred smoothly on heating in toluene to give the corresponding dimethyl cycl[3.2.2]azine-1,2-dicarboxylates in moderate yields [9]. 2-Methylthioindolizine-3-carbonitrile (**3a**) are also expected as a key intermediate for the synthesis of cycl[3.2.2]azine derivatives. The reaction of 2-methylthioindolizine-3-carbonitrile (**3a**) with DMAD in xylene gave a cyclized product, dimethyl 3-methylthiocycl[3.2.2]azine-1,2-dicarboxylate (**11a**) in 22% yield. In a similar manner, dimethyl 5,7-dimethyl-3-methylthiocycl-[3.2.2]azine-1,2-dicarboxylate (**11b**) was obtained in 12% yield (Scheme 4).

Scheme 4



No.	R^1	R^2	mp (°C)	Yield (%)
6a	H	H	113	22
b	Me	Me	138	12

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on JASCO IRA-2 spectrometer and Shimadsu IR-460 and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-100(100 MHz), JNM-FX-90Q(90 MHz), JNM-GX-270(270 MHz), spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-01SG and JMS-303D mass spectrometers.

2-Methylthioindolizine-3-carbonitrile (**3a**) and 2-Methylthio-1-nitroindolizine-3-carbonitrile (**4a**).

A mixture of 0.755 g (5 mmoles) of chloroacetonitrile and 0.791 g (5 mmoles) of pyridine was heated at 40-50° for 30 minutes and then continued at 100° for 1 hour. This crystallized 1-cyanomethylpyridinium chloride (**1a**) was dissolved in 50 ml of ethanol and 0.826 g (5 mmoles) of

1,1-bis(methylthio)-2-nitroethylene (**2**) and 3 ml of triethylamine was added to this solution. The mixture was refluxed for 10 hours. After removal of the solvent and excess of triethylamine, 50 ml of water was added to the residue and extracted with benzene (50 ml x 2). The combined extract was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on neutral alumina column using a mixture of hexane-benzene (3:1) as an eluent to give 0.405 g (2.15 mmoles, 43%) of **3a** as colorless needles, mp 42°: ir (potassium bromide): ν max cm^{-1} 2180 (CN); uv (ethanol): λ max nm (log ϵ) 224 (3.86), 232 (3.85), 272 (4.21), 328 (3.48); ^1H nmr (deuteriochloroform): δ 2.58 (3H, s, SCH_3), 6.37 (1H, d, J = 0.9 Hz, 1-H), 6.75 (1H, m, 6-H), 7.00 (1H, m, 7-H), 7.36 (1H, m, 8-H), 8.13 (1H, m, 5-H).

Anal. Calcd. for $C_{10}H_8N_2$: C, 63.80; H, 4.28; N, 14.88; S, 17.03. Found: C, 63.67; H, 4.43; N, 14.89; S, 17.04.

Subsequent elution using benzene as an eluent gave 0.55 g (47%) of yellow needles, **4a**, mp 223°; ir (potassium bromide): ν max cm^{-1} 2195 (CN); uv (ethanol): λ max nm (log ϵ) 261 (4.47), 297 (4.00), 374 (4.20); ^1H nmr (deuteriochloroform): δ 2.87 (3H, s, SCH_3), 7.20 (1H, m, 6 or 7-H), 7.62 (1H, m, 6 or 7-H), 8.37 (1H, m, 8-H), 8.51 (1H, m, 5-H).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 51.49; H, 3.03; N, 18.02; S, 13.75. Found: C, 51.67; H, 3.22; N, 18.05; S, 13.88.

6-Methyl-2-methylthioindolizine-3-carbonitrile (**3b**), 8-Methyl-2-methylthioindolizine (**3c**), and 6-Methyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4b**).

These compounds were prepared from 3-picoline (0.93 g, 10 mmoles), chloroacetonitrile (0.755 g, 10 mmoles), and **2** (0.826 g, 5 mmoles) in a manner similar to that described for synthesis of **3a** and **4a**. The reaction mixture was separated on neutral alumina column chromatography. The first elution using a mixture of hexane:benzene (3:1) gave 0.869 g (4.3 mmoles, 86%) of a mixture **3b** and **3c**. The mixture was recrystallized from methanol to give 0.530 g (2.6 mmoles, 82%) of **3c**, colorless needles, mp 97°; ir (potassium bromide): ν max cm^{-1} 2180 (CN); uv (ethanol): λ max nm (log ϵ) 226 (4.17), 237 (4.16), 269 (4.53), 330 (3.88); ^1H nmr (deuteriochloroform): δ 2.41 (3H, s, 8-CH_3), 2.60 (3H, s, SCH_3), 6.35 (1H, d, J = 0.9 Hz, 1-H), 6.61-6.84 (2H, m, 6, 7-H), 8.02 (1H, m, 5-H).

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85; S, 15.85. Found: C, 65.32; H, 5.08; N, 13.86; S, 15.87.

Compound **3b** was not purified by alumina column chromatography and recrystallization. The yield was determined by nmr spectrum (*ca.* 4%).

Subsequent elution using benzene as an eluent gave 0.124 g (0.5 mmole, 10%) of **4b**, colorless needles, mp 231°; ir (potassium bromide): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 262 (4.52), 302 (3.99), 310 (shoulder, 3.96), 379 (4.26); ^1H nmr (deuteriochloroform): δ 2.46 (3H, d, J = 1.1 Hz, 6-CH_3), 2.86 (3H, s, SCH_3, 7.46 (1H, dd, J = 1.4, 9.1 Hz, 7-H), 8.17 (1H, m, 5-H), 8.39 (1H, d, J = 9.1 Hz, 8-H).

Anal. Calcd. for $C_{11}H_9N_3O_2S$: C, 53.43; H, 3.67; N, 16.99; S, 12.97. Found: C, 53.42; H, 3.67; N, 16.97; S, 12.88.

6-Ethyl-2-methylthioindolizine-3-carbonitrile (**3d**), 8-Ethyl-2-methylthioindolizine-3-carbonitrile (**3e**), and 6-Ethyl-2-methylthio-1-nitroindolizine (**4c**).

These compounds were prepared from 3-ethylpyridine (2.14 g, 20 mmoles), chloroacetonitrile (1.51 g, 20 mmoles), and **2** (1.65 g, 10 mmoles) in a manner similar to that described for the synthesis of **3b**, **3c**, and **4b**. The hexane:benzene (3:1) elution gave 1.65 g (7.76 mmoles, 76%) of a mixture of **3d** and **3e**. The reaction mixture was recrystallized from methanol to give 0.95 g (4.3 mmoles, 64%) of colorless prisms, **3e**, mp 67°; ir (potassium bromide): ν max cm^{-1} 2200 (CN); uv (ethanol): λ max nm (log ϵ) 226 (4.21), 238 (4.20), 270 (4.54), 330 (3.93); ^1H nmr (deuteriochloroform): δ 1.32 (3H, t, J = 7.3 Hz, 8-CH_2-CH_3), 2.60 (3H, s, SCH_3), 2.78 (2H, q, J = 7.3 Hz, 8-CH_2-CH_3), 6.38 (1H, d, J = 0.9 Hz, 1-H), 6.72 (1H, m, 6-H), 6.84 (1H, m, 7-H), 8.03 (1H, m, 5-H).

Anal. Calcd. for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.96; S, 14.82. Found: C, 66.75; H, 5.70; N, 12.96; S, 15.04.

Compound **3d** was not purified by chromatography and recrystallization. The yield was determined by nmr (*ca.* 3%). The elution of benzene:hexane (3:1) gave 0.27 g (1.05 mmoles, 11%) of tan needles, **4c**, mp 205°; ir (potassium bromide): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 229 (4.20), 262 (4.49), 302 (3.95); ^1H nmr (deuteriochloroform): δ 1.34 (3H, t, J = 7.6 Hz, 6-CH_2-CH_3) 2.77 (2H, q, J = 7.6 Hz, 6-CH_2-CH_3), 2.86 (3H, s, SCH_3), 7.49 (1H, dd, J = 1.4, 9.2 Hz, 7-H), 8.15 (1H, m, 5-H), 8.42 (1H, dd, J = 0.9, 9.2 Hz, 8-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.75; H, 5.70; N, 12.96, S, 15.04.

6,8-Dimethyl-2-methylthioindolizine-3-carbonitrile (**3f**) and 6,8-Dimethyl-2-methylthio-1-nitroindolizine (**4d**).

These compounds were prepared from 3,5-lutidine (1.07 g, 10 mmoles), chloroacetonitrile (0.775 g, 10 mmoles), and **2** (0.826 g, 5 mmoles) in a manner similar to that described for the synthesis of **3a** and **4a**. The reaction mixture was separated on neutral alumina column chromatography. The first elusion using a mixture of hexane:benzene (1:2) gave 0.972 g (4.5 mmoles, 90%) of colorless needles, **3f**, mp 105°; ir (potassium bromide): ν max cm^{-1} 2175 (CN), uv (ethanol): λ max nm (log ϵ) 227 (4.04), 240 (4.02), 270 (4.39), 330 (3.72); ^1H nmr (deuteriochloroform): δ 2.27 (3H, d, J = 1.1 Hz, 6-CH_3), 2.38 (3H, s, 8-CH_3), 2.57 (3H, s, SCH_3), 6.29 (1H, d, J = 0.9 Hz, 1-H), 6.66 (1H, bs, 7-H), 7.83 (1H, bs, 5-H).

Anal. Cacld. for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.80; H, 5.64; N, 13.02; S, 14.90.

Subsequent elusion using hexane:benzene (1:3) as an eluent gave 0.05 g (0.2 mmoles, 4%) of yellow needles, **4d**, mp 162°; ir (potassium bromide): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 264 (4.53), 313 (4.00), 384 (4.06); ^1H nmr (deuteriochloroform): δ 2.38 (3H, d, J = 0.7, 6-CH_3 or 8-CH_3), 2.62 (3H, s, 6-CH_3 or 8-CH_3), 2.79 (3H, s, SCH_3), 7.14 (1H, S, 6-H), 8.04 (1H, s, 5-H).

Anal. Calcd. for $C_{12}N_{11}O_2S$: C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.37; H, 4.32; N, 16.08; S, 12.17.

7-Ethyl-2-methylthioindolizine-3-carbonitrile (**3g**) and 7-Ethyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4e**).

These compounds were prepared from 4-ethylpyridine (1.07 g, 10 mmoles), chloroacetonitrile (0.75 g, 10 mmoles) and **2** (0.83 g, 5 mmoles) in a manner similar to that described for the synthesis of **3a** and **4a**. The reaction products were chromatographed on alumina column using benzene:hexane (1:3) as an eluent to give 0.26 g (1.20 mmoles, 24%) of colorless needles , **3g**, mp 36°; ir (potassium bromide): ν max cm^{-1} 2195 (CN); uv (ethanol): λ max nm (log ϵ) 227 (4.20), 238 (4.18), 272 (4.54), 330 (3.94); ^1H nmr (deuteriochloroform): δ 1.26 (3H, t, J = 7.5 Hz, 7-CH_2-CH_3), 2.57 (3H, s, SCH_3), 2.59 (2H, J = 7.5 Hz, 7-CH_2-); 6.26 (1H, d, J = 0.9 Hz, 1-H), 6.64 (1H, dd, J = 1.8, 7.0 Hz, 6-H), 7.14 (1H, dd, J = 0.9 Hz, 1.8 Hz, 8-H), 8.05 (1H, d, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.75; H, 5.68; N, 13.08; S, 14.98.

Subsequent elution using benzene:hexane (3:2) as an eluent gave 0.03 g (0.12 mmole, 3%) of tan needles, **4e**, mp 210°; ir (potassium bromide): ν max cm^{-1} 2208 (CN); uv (insolubility in ethanol): λ max nm 263, 298, 376: λ min nm 233, 290, 325; ^1H nmr (deuteriochloroform): δ 1.53 (3H, t, J = 7.5 Hz, 7-CH_2-CH_3), 2.83 (2H, q, J = 7.5 Hz, 7-CH_2-), 2.86 (3H, s, SCH_3), 7.07 (1H, dd, J = 1.8, 7.1 Hz, 6-H), 8.26 (1H, dd, J = 0.9, 7.1 Hz, 5-H), 8.32 (1H, m, 8-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.18; H, 4.28; N, 16.05; S, 12.24.

7-Benzyl-2-methylthioindolizine-3-carbonitrile (**3h**) and 7-Benzyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4f**).

These compounds were prepared from 4-benzylpyridine (1.69 g, 10 mmoles), chloroacetonitrile (0.75 g, 10 mmoles), and **2** (0.82 g, 5 mmoles) in a manner similar to that described for the synthesis of **3a** and **4a**. The products were separated by chromatograph on a neutral alumina column. The elution of a mixture of hexane:benzene (3:1) as an eluent gave 0.63 g (2.27 mmoles), of **3h** in 45% yield. An analytical sample was re-

crystallized from methanol to give colorless needles, mp 95°; ir (potassium bromide): ν max cm^{-1} 2200 (CN); uv (ethanol): λ max nm (log ϵ) 227 (4.27), 240 (shoulder, 4.19), 273 (4.61), 330 (3.99); ^1H nmr (deuteriochloroform): δ 2.57 (3H, s, SCH_3), 3.94 (2H, s, 7-CH_2-), 6.26 (1H, d, J = 0.9 Hz, 1-H), 6.60 (1H, dd, J = 1.8, 7.0 Hz, 6-H), 7.11 (1H, m, 8-H), 7.31-7.37 (5H, m, phenyl-H), 8.03 (1H, d, J = 7.0 Hz, 5-H).

Anal. Calcd. for $C_{17}H_{14}N_2S$: C, 73.35; H, 5.07; N, 10.06; S, 11.52. Found: C, 73.02; H, 5.17; N, 10.04; S, 11.34.

Subsequent elution using a mixture of hexane:benzene (1:3) gave 0.49 g (1.52 mmoles) of **4f**. An analytical sample was recrystallized from methanol to give **4f** as tan needles, mp 189°; ir (potassium bromide): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 218 (4.24), 265 (4.57), 298 (4.09), 305 (shoulder, 404); ^1H nmr (deuteriochloroform): δ 2.84 (3H, s, SCH_3), 4.11 (2H, s, 7-CH_2-), 6.98 (1H, dd, J = 1.8, 7.0 Hz, 6-H), 7.15-7.37 (5H, m, phenyl-H), 8.23 (1H, dd, J = 0.9, 7.0 Hz, 5-H), 8.36 (1H, dd, J = 0.9, 1.8 Hz, 8-H).

Anal. Calcd. for $C_{10}H_{13}N_3O_2S$: C, 63.14; H, 4.05; N, 12.97; S, 9.92. Found: C, 63.27; H, 4.18; N, 13.12; S, 10.04.

2-Methylthio-7-phenylindolizine-3-carbonitrile (**3i**) and 2-Methylthio-1-nitro-7-phenylindolizine-3-carbonitrile (**4h**).

These compounds were prepared from 4-phenylpyridine (0.78 g, 5 mmoles), chloroacetonitrile (0.38 g, 5 mmoles), and **2** (0.42 g, 2.5 mmoles) in a manner similar to that described for **3a** and **4a**. An elution using a mixture of hexane:benzene (3:1) gave 0.40 g (1.5 mmoles) of **3i** in 61% yield. An analytical sample was recrystallized from methanol to give colorless needles of mp 121°; ir (potassium bromide): ν max cm^{-1} 2203 (CN); uv (ethanol): λ max nm (log ϵ) 276 (4.65), 345 (4.19); ^1H nmr (deuteriochloroform): δ 2.60 (3H, s, SCH_3), 6.42 (1H, d, J = 0.7 Hz, 1-H), 7.06 (1H, J = 1.9, 7.2 Hz, 6-H), 7.35-7.68 (5H, m, phenyl-H), 8.19 (1H, d, J = 7.2 Hz, 5-H).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 73.04; H, 4.75; N, 10.65; S, 12.18.

Subsequent elution using a mixture of benzene:hexane (3:1) as an eluent gave 0.24 g (0.7 mmole) of **4h** in 29% yield. An analytical sample was recrystallized from methanol to give yellow needles, mp 213°; ir (potassium carbonate): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 270 (4.41), 308 (4.09), 394 (4.11); ^1H nmr (deuteriochloroform): δ 2.88 (3H, s, SCH_3), 7.41-7.79 (6H, m, 6-H, phenyl-H), 8.39 (1H, dd, J = 0.9, 7.0 Hz, 5-H), 8.70 (1H, m, 8-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 62.12; H, 3.58; N, 13.58; S, 10.37. Found: C, 62.35; H, 3.76; N, 13.58; S, 10.42.

2-Methylthio-5-phenylindolizine-3-carbonitrile (**3j**) and 2-Methylthio-1-nitro-5-phenylindolizine-3-carbonitrile (**4i**).

These compounds were prepared from 2-phenylpyridine (0.776 g, 5 mmoles), bromoacetonitrile (0.59 g, 5 mmoles), **2** (0.412 g, 2.5 mmoles) in a manner similar to that described for **3a** and **4a**. The first elution using a mixture of hexane-benzene (3:1) as an eluent gave 0.16 g (0.61 mmoles) of **3j** in 24% yield. An analytical sample was recrystallized from methanol to give colorless prisms, mp 135°; ir (potassium bromide): ν max cm^{-1} 2195 (CN); uv (ethanol): λ max nm (log ϵ) 232 (4.34), 270 (4.52), 335 (3.90); ^1H nmr (deuteriochloroform): δ 2.53 (3H, s, SCH_3), 6.49 (1H, s, 1-H), 6.58 (1H, dd, J = 1.3, 6.8 Hz, 6 or 8-H), 7.05 (1H, dd, J = 8.8, 6.8 Hz, 7-H), 7.40 (1H, dd, J = 1.4, 8.8 Hz, 6 or 8-H).

Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.82; H, 4.74; N, 10.50; S, 12.15.

Subsequent elution using a mixture of benzene-hexane (2:1) gave 0.30 g (1.02 mmoles) of **4i** in 41% yield. An analytical sample was recrystallized from methanol to give yellow needles, mp 208°; ir (potassium bromide): ν max cm^{-1} 2205 (CN); uv (ethanol): λ max nm (log ϵ) 265 (4.38), 310 (3.89), 383 (4.25); ^1H nmr (deuteriochloroform): δ 2.70 (3H, s, SCH_3), 7.00 (1H, dd, J = 1.4, 7.1 Hz, 6-H), 7.45-7.73 (6H, m, 7-H, phenyl-H), 8.59 (1H, dd, J = 1.4, 8.9 Hz, 8-H).

6-*N*,*N*-Diethylcarbamoyl-2-methylthio-1-nitroindolizine-3-carbonitrile (**4j**).

This compound was prepared from *N*,*N*-diethylnicotinamide (0.89 g, 5 mmoles), bromoacetonitrile (0.60 g, 5 mmoles), and **2** (0.42 g, 2.5 mmoles) in a manner similar to that described for the synthesis of **3a** and **4a**. After the reaction, the products was collected by filtration and recrystallized from methanol to give 0.15 g (0.4 mmoles) of pale yellow needles, **4j**, mp 136°. After evaporation of the solvent of the filtrate, the residue was chromatographed on an alumina column using a mixture of benzene:hexane (3:1) as an eluent to give 0.15 g (0.4 mmoles, 42%) of **4j**. An analytical sample was recrystallized from methanol to give pale yellow needless, mp 136°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1640 (CO); uv (ethanol): λ max nm (log ϵ) 273 (4.59), 376 (4.25); ^1H nmr (deuteriochloroform): δ 1.26 (3H, t, J = 7.1 Hz, O-CH_2-CH_3), 2.88 (3H, s, SCH_3), 3.45 (2H, q, J = 7.1 Hz, O-CH_2-), 7.58 (1H, dd, J = 1.7, 8.8 Hz, 8-H), 8.46 (1H, s, 5-H), 8.50 (1H, dd, J = 1.0, 8.4 Hz, 5-H).

Anal. Calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86; S, 9.65. Found: C, 54.16; H, 4.91; N, 16.71; S, 9.74.

Indolizine-3-carbonitrile (**5a**).

A mixture of 0.19 g (1 mmole) of **3a**, 0.4 g of Raney-nickel, and 2 ml (x2) of ethanol was refluxed for 20 hours. After removal of the Raney-nickel and the solvent, the residue was chromatographed on a silica gel column using hexane as an eluent to give 0.11 g (0.77 mmole, 77%) of **5a** as colorless needles, mp 48°, (lit [9], mp 48°).

6,8-Dimethylindolizine-3-carbonitrile (**5b**).

This compound was prepared from 0.216 g (1 mmole) of **3f**, 0.4 g of Raney-nickel, and 4 ml of ethanol in a manner similar to that described for the synthesis of **5a**. The residue was chromatographed on a silica gel column using hexane as an eluent to give 0.15 g (0.88 mole, 88%) of **5b** as colorless needles, mp 104° (lit [9], mp 104°).

Dimethyl 3-Methylthiocycl[3.2.2]azine-1,2-dicarboxylate (**6a**).

A solution of 0.188 g (1 mmole) of **9a**, 0.248 g (2 mmoles) of DMAD, 0.3 g of 5% of palladium-on-charcoal (Pd-C), and 15 ml of xylene was refluxed for 30 hours. After removal of the solvent and Pd-C, the residue was chromatographed on alumina column using benzene as an eluent to give yellow crystals. This compound was recrystallized from methanol to give 0.067 g (0.22 mmole, 22%) of **11a** as yellow needles, mp 113°; ir (potassium bromide): ν max cm^{-1} 1735, 1700 (C=O); uv (ethanol): λ max nm (log ϵ) 217 (4.45), 230 (4.34, shoulder), 263 (4.50), 290 (3.74), 370 (4.03), 405 (4.09); ms: m/z 304 (M^+ + 1, 18), 303 (M^+, 95), 271 (69), 239 (37), 136 (25), 81 (51), 69 (100); ^1H nmr (deuteriochloroform): δ 2.69 (3H, s, SCH_3), 4.01 (3H, s, O-CH_3), 7.01 (1H, s, 4-H), 7.67-7.90 (2H, m, 5, 6-H), 8.26 (1H, dd, J = 1.9, 6.9 Hz, 7-H).

Anal. Calcd. for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found; C, 59.65; H, 4.31; N, 4.41; S, 10.28.

Dimethyl 5,7-Dimethyl-2-methylthiocycl[3.2.2]azine-1,2-dicarboxylate (**6b**).

This compound was prepard from 0.126 g (1 mmole) of **3f**, 0.284 g (2 mmoles) of DMAD, of 0.3 g of Pd-C, and 15 ml of xylene in a manner similar to that described for the synthesis of **6a**. The residue was chromatographed on alumina column using hexane as an eluent to give 0.039 g (0.12 mmole, 12%) of **6b** as yellow prisms, mp 138°; ir (potassium bromide): ν max cm^{-1} 1710, 1700 (C=O); uv (ethanol): λ max nm (log ϵ) 220 (4.43), 266 (4.50), 380 (4.11, shoulder), 394 (4.14); ms: m/z 332 (M^+ + 1, 15), 331 (M^+, 73), 299 (100), 284 (18), 81 (48), 69 (84); ^1H nmr (deuteriochloroform): δ 2.66 (3H, s, SCH_3), 2.72 (3H, s, 5 or 7-CH_3), 2.83 (3H, s, 5 or 7-CH_3), 3.99 (3H, s, O-CH_3), 4.03 (3H, s, O-CH_3), 6.93 (1H, s, 1-H), 7.29 (1H, s, 6-H).

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.53; H, 5.23; N, 4.19; S, 9.55.

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