Preparation of New Nitrogen-Bridged Heterocycles. 56.[1] Syntheses and Reactions of 1-[2,2-Bis(alkylthio)-1-(ethoxycarbonylacetyl)vinyl]pyridinium Salts[1]

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The title compounds, readily available from the *S*-alkylation of pyridinium 1-[alkylthio(thiocarbonyl)]-(ethoxycarbonylacetyl)methylides with alkyl halides or alkyl bromoacetates, were treated with a base and then a dehydrogenating agent to provide some unique products such as 3-[bis(alkylthio)methylene]-2(3*H*)-indolizinones and dialkyl 7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylates. On the other hand, similar reaction of these pyridinium salts in the absence of the dehydrogenating agent afforded alkyl 2-hydroxyindlizine-3-carboxythiolates, whose yields were increased by adding trifluoroacetic acid to the reaction mixture. The structures of some products were confirmed by the X-ray analyses.

Key words pyridinium salt; thiazino[3,4,5-*cd*]indolizine; 3-methylene-2(3*H*)-indolizinone; 2-indolizinol; X-ray analysis

In our previous paper[2] we described that treatment of pyridinium salts, prepared by the *S*-alkylation of pyridinium 1-[alkylthio(thiocarbonyl)](ethoxycarbonylacetyl)methylides with phenacyl halides, with a base and then a dehydrogenating agent gave the corresponding 3-alkylthio-1-(arylcarbonyl)thieno[3,4-*b*]indolizine derivatives in low to moderate yields. At the same time, however, we also noticed that brief screening for the corresponding pyridinium salts derived from other alkylating agents such as ethyl bromoacetate and bromoacetonitrile always afforded tarry materials, while any significant products, including the expected thieno[3,4-*b*]indolizine derivatives, could not be obtained at all. On the other hand, our recent research disclosed a more effective synthesis of thieno[3,4-*b*]indolizine derivatives using the pyridinium salts formed from 5-arylcarbonyl-4-ethoxycarbonylmethyl-3-(1-pyridinio)thiophene-2-thiolates and various alkyl halides.[3—5] Since the former type of pyridinium salts is more functionalized than the latter and several reactions associated with their functionality could also be expected,[2—11] in this paper we examine more closely the reactivity for these pyridinium salts. We describe the formation of two types of products, 1,4-thiazino[3,4,5-*cd*]indolizin-4-one and 3-[bis(alkylthio)methylene]-2(3*H*)-indolizinone derivatives from the treatment of the title pyridinium salts with a base and then a dehydrogenating agent, though their yields are always low. In addition, we also report the unexpected formation of thiols and alkyl 2-hydroxyindolizine-3-carboxythiolate derivatives in these reactions in the absence of the dehydrogenating agent, which can be considered to cause little or no yields of the initially expected products.

Results and Discussion

Treatment of Pyridinium Salts with a Base and then a Dehydrogenating Agent As described above, pyridinium salts prepared by the *S*-alkylation of pyridinium 1-[alkylthio(thiocarbonyl)](ethoxycarbonylacetyl)methylides with alkyl halides have many reactive sites in the molecule and, other than thieno[3,4-*b*]indolizines **6**,[2—5] the formation of products such as 3-[bis(alkylthio)methylene]-2(3*H*)-indolizinones,[6,7] 1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizin-4-ones,[8,9] and/or aromatic indolizines[10,11] in these reactions was also expected. So, we examined first the reactions of 1-[1-ethoxycarbonylacetyl-2-(ethoxycarbonylmethylthio)-2-(methylthio and ethylthio)vinyl]pyridinium bromides (**3a**, **b**), prepared from the *S*-alkylation of pyridinium 1-[(ethoxycarbonylacetyl)[methylthio and ethylthio(thiocarbonyl)]]methylides (**1a**, **b**) with ethyl bromoacetate (**2a**), with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) and then chloranil in chloroform, but no significant product could be obtained. On the other hand, similar treatment of 4-methylpyridinium salts **3c**—**f** formed from 4-methylpyridinium methylides **1c**, **d** with **2a** and methyl bromoacetate (**2b**) provided the *trans* and *cis* mixtures of the corresponding diethyl 7-methyl-3-methylthio- **4c**+**5c** and diethyl 3-ethylthio-7-methyl- **4d**+**5d**, 5-ethyl 1-methyl 7-methyl-3-methylthio- **4e**+**5e**, and 5-ethyl 1-methyl 3-ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylates **4f**+**5f** in 12%, 11%, 7%, and 23% yields, respectively. The *trans* isomers **4c**—**f** in the above reactions were always major products. The reactions using pyridinium salts **3g**, **h** obtained from methylides **1c**, **d** and *tert*-butyl bromoacetate (**2c**) afforded only the corresponding *trans* isomers **4g**, **h** in 23% and 20% yields. In the above reactions thieno[3,4-*b*]indolizine derivatives such as **6** were not obtained at all, but the formation of trace amounts of aromatic indolizines of type **7** was sometimes detected by ^{1}H-NMR spectral inspection of the reaction mixtures. These results are shown in Chart 1.

We have already prepared similar type of 1,4-thiazino[3,4,5-*cd*]indolizin-4-one derivative in the intramolecular nucleophilic addition (Michael type addition) of 3-[(acylmethylthio)methylene]-2(3*H*)-indolizinone intermediates in the presence of a base.[8,9] To confirm the intervention of such intermediates, we studied next the reactions using 1-[2,2-bis(alkylthio)-1-(ethoxycarbonylacetyl)vinyl]pyridinium halides **8a**—**d**, prepared by the *S*-alkylation of pyridinium methylides **1a**—**d** with iodomethane (**2d**) or iodoethane (**2e**), as a substrate. As expected, the corresponding ethyl 3-

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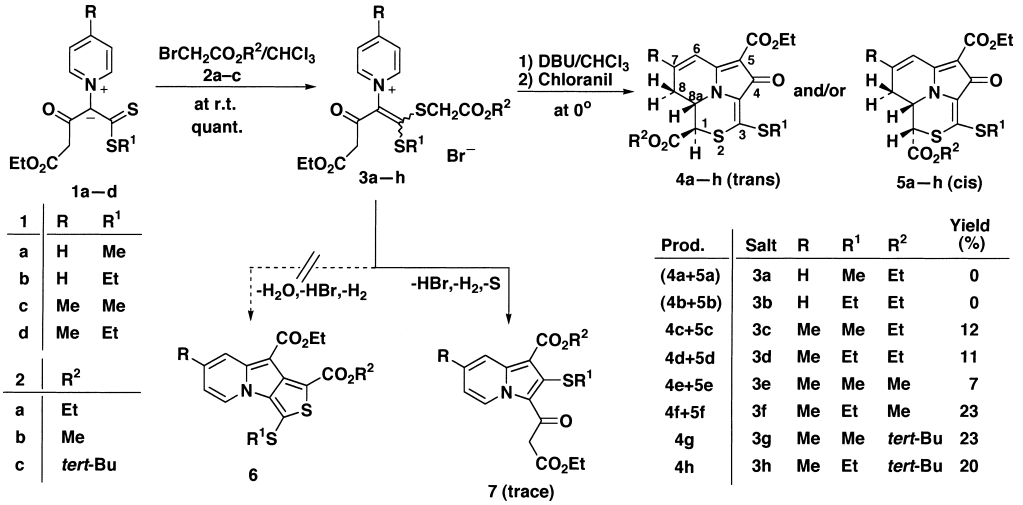
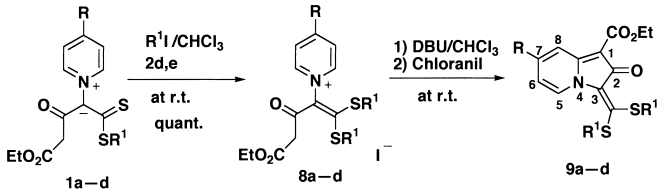


1	R	R^1
a	H	Me
b	H	Et
c	Me	Me
d	Me	Et

2	R^2
a	Et
b	Me
c	*tert*-Bu

Prod.	Salt	R	R^1	R^2	Yield (%)
(4a+5a)	3a	H	Me	Et	0
(4b+5b)	3b	H	Et	Et	0
4c+5c	3c	Me	Me	Et	12
4d+5d	3d	Me	Et	Et	11
4e+5e	3e	Me	Me	Me	7
4f+5f	3f	Me	Et	Me	23
4g	3g	Me	Me	*tert*-Bu	23
4h	3h	Me	Et	*tert*-Bu	20

Chart 1



2	R^1
d	Me
e	Et

Prod.	Salt	R	R^1	Yield (%)
9a	8a	H	Me	27
9b	8b	H	Et	21
9c	8c	Me	Me	26
9d	8d	Me	Et	15

Chart 2

[bis(methylthio)- (**9a**, **c**) and 3-[bis(ethylthio)methylene]-2-oxo-2(3*H*)-indolizine-1-carboxylates (**9c**, **d**) were obtained in 15—27% yields from the reactions of pyridinium salts **8a**—**d** with DBU and then chloranil, as shown in Chart 2.

The structures of 1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizin-4-ones **4** and **5** were mainly determined by NMR spectral inspection and X-ray analysis of two compounds **4h** and **5c**. In ^{1}H-NMR spectra, both the chemical shifts (δ near 7.2) for the olefinic proton at the 6-position in **4c**—**h** and **5c**—**f** and the coupling constants (9.8 Hz) observed for the methine proton at the 1-position in **4g**, **h** were very informative for this structural assignment, because the broad singlet signals for the 6-H in the *trans* isomers **4c**—**h** appeared clearly at slightly higher field than those in *cis* ones **5c**—**f**[12] and the large coupling constants between the 1- and 8a-protons in **4g**, **h** exhibited distinctly the *trans* configuration. This structural assignment for **4c**—**h** and **5c**—**f** based on the ^{1}H-NMR spectral inspection was finally confirmed by the X-ray analyses for **4h** and **5c**. Interestingly, the single crystal for the trans derivative **4h** consisted of its *dl*-mixture and two molecules of chloroform used as a solvent for recrystallization (see Experimental). The single crystals of the minor *cis* compound **5c** were also obtained in the recrystallization of the *cis–trans* mixture **4c** and **5c**, but the single crystals of the major *trans* isomer **4c** were not. The ORTEP drawings[13] of the *trans* isomer **4h** and the *cis* one **5c** are shown in Figs. 1 and 2. The structures of 3-methylene-2(3*H*)-indolizinones **9a**—**d** were determined by the IR and ^{1}H-

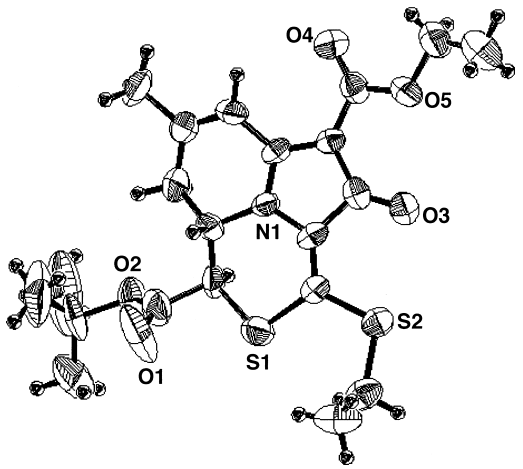


Fig. 1. ORTEP Drawing of One Molecule on the *dl*-Mixture of 1-*tert*-Butyl 5-Ethyl 3-Ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino-[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4h**, *trans* Isomer)

The chloroform molecule involved in the lattice is removed.

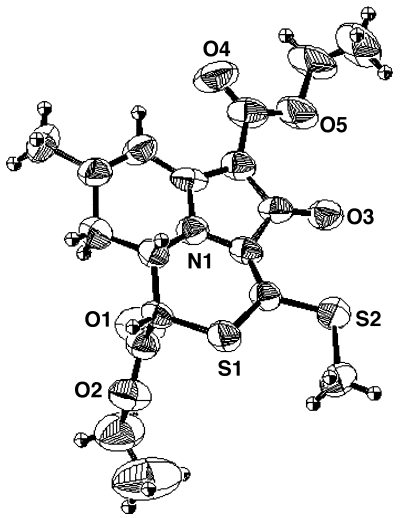
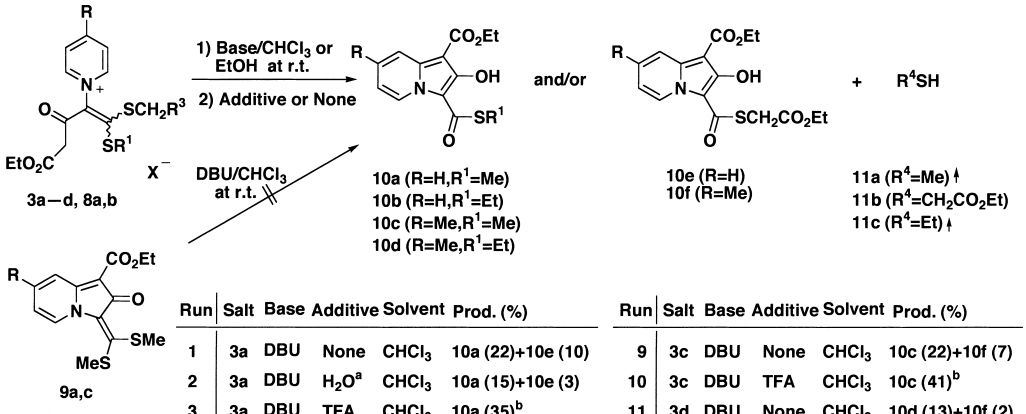


Fig. 2. ORTEP Drawing of Diethyl 7-Methyl-3-methylthio-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**5c**, *cis* Isomer)



Run	Salt	Base	Additive	Solvent	Prod. (%)	Run	Salt	Base	Additive	Solvent	Prod. (%)
1	3a	DBU	None	$CHCl_3$	10a (22)+10e (10)	9	3c	DBU	None	$CHCl_3$	10c (22)+10f (7)
2	3a	DBU	H_2O[a]	$CHCl_3$	10a (15)+10e (3)	10	3c	DBU	TFA	$CHCl_3$	10c (41)[b]
3	3a	DBU	TFA	$CHCl_3$	10a (35)[b]	11	3d	DBU	None	$CHCl_3$	10d (13)+10f (2)
4	3a	DBU	None	EtOH	10a (4)+10e (1)	12	3d	DBU	TFA	$CHCl_3$	10d (25)[b]
5	3a	DBU	H_2O[a]	EtOH	10a (12)+10e (2)	13	8a	DBU	None	$CHCl_3$	10a (24)
6	3a	Et_3N	None	$CHCl_3$	10a (6)+10e (trace)	14	8a	DBU	TFA	$CHCl_3$	10a (20)
7	3b	DBU	None	$CHCl_3$	10b (12)+10e (2)	15	8b	DBU	None	$CHCl_3$	10b (5)
8	3b	DBU	TFA	$CHCl_3$	10b (17)[b]	16	8b	DBU	TFA	$CHCl_3$	10b (18)

a) A drop of water was added to the reaction solution. b) Ethyl thioglycolate (11b) was detected from the NMR spectra of the reaction mixture, but the yields could not be determined.

Chart 3

NMR spectral inspection. For example, the IR spectra of **9a**—**d** showed two absorption bands at 1628—1657 and 1669—1691 cm^{-1} attributable to a ketone carbonyl at the 2-position and an ester carbonyl in the 1-substituent, respectively. Their ^{1}H-NMR spectra exhibited distinctly the four or three olefinic proton signals in the range δ 6.51—9.07 and/or a methyl proton signal (δ 2.35 or 2.38) on the pyridine ring in **9a**—**d**, together with the corresponding signals for two alkylthio and an ethoxycarbonyl groups.

In contrast with 1-unsubstituted, 1-alkyl- and 1-aryl-3-[bis(alkylthio)methylene-2(3*H*)-indolizinones prepared earlier by us,[6,7] compounds **9a**—**d** were very stable and less reactive because, even under more drastic conditions, the reactions of **9a**—**d** with activated acetates such as ethyl cyanoacetate and diethyl malonate in the presence of a base did not give the corresponding pyrano[2,3-*b*]indolizin-2-one derivatives at all.

Alkaline Treatment of Pyridinium Salts Of the initially expected products we could obtain only two types of compounds, 1,4-thiazino[3,4,5-*cd*]indolizin-4-ones **4** and **5** and 3-methylene-2(3*H*)-indolizinones **9**, as described above. However, all of their yields were low at best and, in spite of our many efforts, improvement was unsuccessful. In order to discover the origin of this inefficiency we investigated the reactions of pyridinium salts **3** and **8** under various reaction conditions, and found a clue. For example, when the reactions of salt **3a** with DBU were performed without the addition of chloroanil as a dehyrogenating agent, the evolution of a considerable amount of methanethiol (**11a**) was observed by its characteristic odor and ethyl 3-[(methylthio)carbonyl]-(**10a**) and ethyl 3-[(ethoxycarbonylmethylthio)carbonyl]-2-hydroxyindolizine-3-carboxylate (**10e**) were isolated in 22% and 10% yields, respectively, from the reaction mixture. Similar reactions of salts **3b**—**d** and **8a**, **b** gave the corresponding 2-hydroxyindolizine-3-carboxythioates **10b**—**f** in 2—24% yields with the generation of thiols **11a**—**c**. Since the formation of such products **10** and **11** immediately suggested the participation of water molecules in these reactions (see Mechanisms), the influences of solvents, bases, and additives involving water or trifluoroacetic acid were further investigated. These results are shown in Chart 3. These data exhibited that the yields for products **10a**—**f** are significantly improved by adding trifluoroacetic acid, and chloroform and DBU are a superior solvent and base, respectively. The results also showed that the addition of water does not necessarily lead to the improvement in the yields of products **10a**, **e**, though the intervention of water in these reactions is evident. Furthermore, the treatment of 3-[bis(methylthio)methylene]-2(3*H*)-indolizinones (**9a**, **c**) with DBU in chloroform did not create 2-hydroxyindolizines **10a**, **c** and methanethiol (**11a**) at all.

The structures of compounds **10a**—**f** were deduced from ^{1}H-NMR and IR spectral inspection and X-ray analysis of compound **10a**. For example, the ^{1}H-NMR spectra of **10a** exhibited clearly the signals due to methylthio protons (δ 2.47), four aromatic protons (δ 6.96, 7.40, 7.94, 9.79) on the pyridine ring, and a hydrogen-bonded hydroxy proton (δ 10.41), together with a ethoxycarbonyl proton signals. In particular, the chemical shifts of the methyl (δ 2.47 for **10a** or δ 2.46 for **10c**) or methylene (δ near 3.1 for **10b**, **d** or δ near 3.9 for **10e**, **f**) adjacent to the sulfur atom in the 3-substituent were informative for the structural assignment. The X-ray analysis of compound **10a** confirmed this structure. The ORTEP drawing[13] for **10a** is shown in Fig. 3.

Mechanisms Possible mechanisms for the formation reactions of compounds **4**, **5**, **9**, and **10** are shown in Chart 4. The reactions of pyridinium salts **3a**—**h** and **8a**—**d** with a base such as DBU is initiated by the deprotonation of the active methylene group to afford dipolar species **12**, which then can cyclize to 3-methylene-1,2,3,8a-tetrahydroindolizin-2-ones **13**. The dehydrogenation of the intermediates **13** by chloranil produces 3-methylene-2(3*H*)-indolizinones **9**, whose several derivatives **9a**—**d** were actually isolated (Path a). Of these types of compounds, the derivatives **9** having a

3-[1-(alkoxy)carbonylmethylthio) group undergo further deprotonation under the same reaction conditions to give carbanions **14**, which are finally able to cyclize *via* intramolecular Michael type addition to lead to the *cis* and *trans* mixtures **4** and **5** of 1,4-thiazino[3,4,5-*cd*]indolizin-4-ones (Path a), but the reason for the inaccessibility of 7-unsubstituted derivatives is unclear. On the other hand, 2-hydroxyindolizines **10a**—**f** must be formed *via* the attack of one molecule of water[14] onto intermediates **13**, followed by the elimination of the corresponding thiol(s) and dehydrogenation leading to aromatization (Path b), because an alternative route (Path c) starting from 3-methylene-2(3*H*)-indolizinones **9** did not provide compounds **10** at all. Furthermore, the increased yields of **10a**—**f** by adding trifluoroacetic acid can be easily explained in terms of the acid-catalyzed activation of the enone system in **13**. Though high reactivity at the β-position of β,β-bis(alkylthio)enones toward various nucleophiles is well known,[15—17] that of the system in molecules such as **13** to water, which is a very weak nucleophile, is very interesting. However, this high reactivity of intermediate **13** toward every nucleophiles involved in the reaction system might decrease the yields of our expected products.

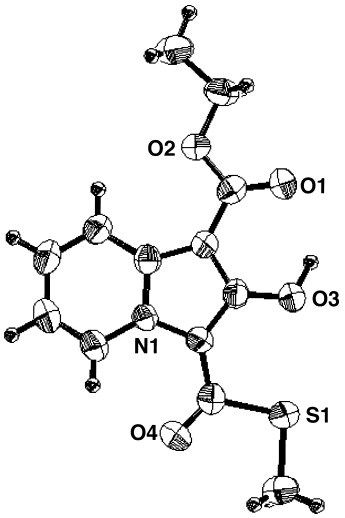


Fig. 3. ORTEP Drawing of Ethyl 3-(Methylthio)carbonyl-2-hydroxyindolizine-1-carboxylate (**10a**)

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Hitachi R-600 (60 MHz) or JEOL JNM-LA400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) spectrometer in deuteriochloroform with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 IR spectrophotometer.

Preparations of Dialkyl 3-Alkylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylates 4 and 5. General Method A chloroform solution (20 ml) of 4-methylpyridinium methylide (**1c**, **d**,[2] 2 mmol) and alkyl bromoacetate (**2**, 2.2 mmol) was allowed to react at room temperature until the disappearance of the starting methylide was confirmed by TLC monitoring (*ca.* 1 d). After *S*-alkylation was completed, the resulting solution was concentrated at reduced pressure and the residue was washed three times with 10 ml portions of ether to remove the unaltered alkylating agent. Without further purification, the 4-methylpyridinium salt (**3**) was dissolved in chloroform (30 ml) and the solution was treated with DBU (0.365 g, 2.4 mmol) under stirring in an ice bath for 10 min and then with chloranil (0.492 g, 2 mmol) under the same conditions for a further 4 h. The reaction mixture was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using chloroform as an eluent. The pale yellow chloroform layers of product (**4** and/or **5**) were combined and concentrated at reduced pressure. Recrystallization of the crude products from chloroform–hexane afforded the corresponding dialkyl 3-alkylthio-7-methyl-4-oxo-1,4,8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylates. However, we were unable to separate the *cis* and *trans* adducts formed from above reactions, because of their similar solubility and low yields.

On the other hand, similar reactions of pyridinium salts **3a**, **b** prepared from 4-unsubstituted pyridinium ylides **1a**, **b**[2] with ethyl bromoacetates (**2a**) afforded only tarry materials, and we could not isolate any significant product from them. Furthermore, similar reactions of the corresponding pyridinium salts prepared from the ylides **1a**—**d** and bromoacetonitrile were also unsuccessful. In the reactions of pyridinium salts **3a**—**h** the formation of ethyl 2-alkylthio-3-(ethoxycarbonylacetyl)indolizine-1-carboxylates such as **7** was sometimes confirmed by NMR spectral inspection of the reaction mixtures, but their further characterization could not be performed because of their low yields (<1%).

Some data for compound **4** and/or **5** are as follows;

Diethyl 7-Methyl-3-methylthio-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino-

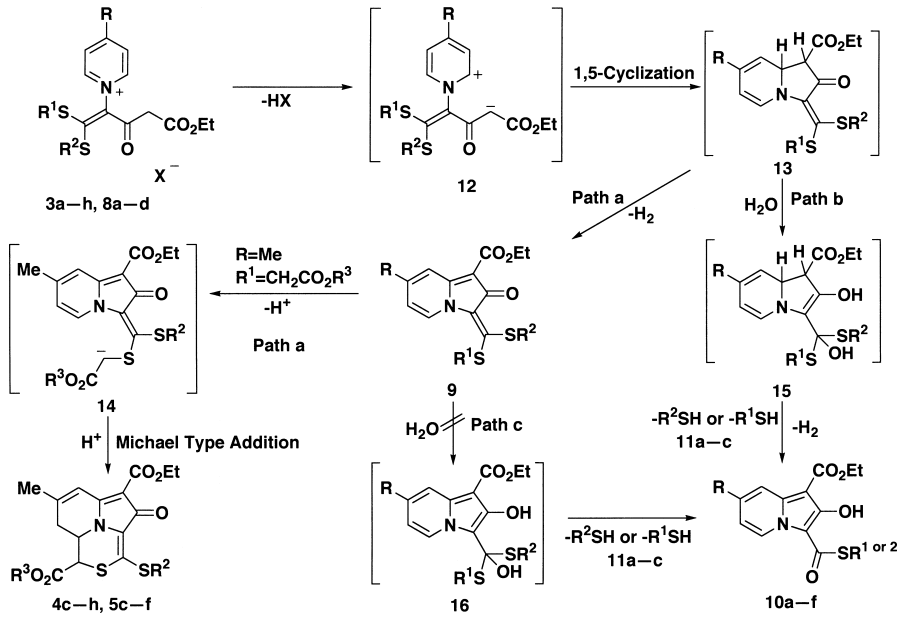


Chart 4

[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4c**+**5c**, the ratio is 2 : 1): From pyridinium methylide **1c** and ethyl bromoacetate (**2a**), yield 12%, pale yellow prisms, IR (KBr) 1738, 1666, 1628 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): **4c**, 1.36 (each 3H, t, J=7.1 Hz, 2×$OCH_2C\underline{H}_3$), 2.02 (3H, s, 7-Me), 2.48 (3H, s, SMe), 2.51—2.71 (2H, m, 8-H), 4.24—4.38 (6H, m, 1-H, 8a-H, 2×$OC\underline{H}_2CH_3$), 7.15 (1H, s, 6-H), and **5c**, 1.22 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.02 (3H, s, 7-Me), 2.49 (3H, s, SMe), 4.19 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 3.86 (1H, d, J=3.4 Hz, 1-H), 4.51 (1H, m, 8a-H), 7.18 (1H, s, 6-H).[18] *Anal.* Calcd for $C_{18}H_{21}NO_5S_2$: C, 54.66; H, 5.35; N, 3.54. Found: C, 54.65; H, 5.36; N, 3.55.

Diethyl 3-Ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino-[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4d**+**5d**, the ratio is 6 : 1): From pyridinium methylide **1d** and ethyl bromoacetate (**2a**), yield 11%, pale yellow prisms, IR (KBr) 1739, 1670, 1630 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): **4d**, 1.35, 1.35, and 1.36 (each 3H, t, J=7.1 Hz), 2.02 (3H, s), 2.52—2.73 (2H, m), 2.94—3.15 (2H, m), 4.24—4.38 (6H, m), 7.15 (1H, s), and **5d**, 1.22 (3H, t, J=7.1 Hz), 2.02 (3H, s), 3.83 (1H, d, J=3.2 Hz), 4.19 (2H, q, J=7.1 Hz), 4.51 (1H, m), 7.19 (1H, s).[18] *Anal.* Calcd for $C_{19}H_{23}NO_5S_2$: C, 55.72; H, 5.66; N, 3.42. Found: C, 55.67; H, 5.69; N, 3.46.

5-Ethyl 1-Methyl 7-Methyl-3-methylthio-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4e**+**5e** (trace)): From pyridinium methylide **1c** and methyl bromoacetate (**2b**), yield 7%, pale yellow prisms, mp 206—208 °C, IR (KBr) 1739, 1674, 1631 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): **4e**, 1.36 (3H, t, J=7.1 Hz), 2.03 (3H, s), 2.49 (3H, s), 2.50—2.71 (2H, m), 3.88 (3H, s), 4.23—4.34 (3H, m), 4.42 (1H, m), 7.17 (1H, s), and **5e**, 3.75 (3H, s), 7.19 (1H, s).[18] *Anal.* Calcd for $C_{17}H_{19}NO_5S_2$: C, 53.53; H, 5.02; N, 3.67. Found: C, 53.72; H, 4.94; N, 3.55.

5-Ethyl 1-Methyl 3-Ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4f**+**5f** (trace)): From pyridinium methylide **1d** and methyl bromoacetate (**2b**), yield 23%, pale yellow prisms, mp 190—192 °C, IR (KBr) 1749, 1674, 1635 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): **4f**, 1.34 and 1.35 (6H, t, J=7.1 Hz), 2.02 (3H, s), 2.58—2.71 (2H, m), 2.94—3.08 (2H, m), 3.87 (3H, s), 4.19—4.35 (2H, m), 4.34—4.49 (2H, m, 1-H), 7.15 (1H, s), and **5f**, 3.74 (3H, s), 7.18 (1H, s).[18] *Anal.* Calcd for $C_{18}H_{21}NO_5S_2$: C, 54.66; H, 5.35; N, 3.54. Found: C, 54.84; H, 5.30; N, 3.42.

tert-Butyl 1-Ethyl 7-Methyl-3-methylthio-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4g**): From pyridinium methylide **1c** and *tert*-butyl bromoacetate (**2c**), yield 23%, pale yellow prisms, mp 166—168 °C, IR (KBr) 1728, 1676, 1637 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.36 (3H, t, J=7.1 Hz), 1.54 (9H, s, *tert*-butyl), 2.03 (3H, s), 2.50 (3H, s), 2.50—2.71 (2H, m), 4.13 (1H, d, J=9.8 Hz), 4.25—4.42 (3H, m), 7.16 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 14.5, 24.3, 28.0, 33.4, 50.8, 52.9, 59.6, 84.7, 101.2, 115.0, 125.9, 133.8, 147.4, 155.0, 164.3, 165.6, 176.7. *Anal.* Calcd for $C_{20}H_{25}NO_5S_2$: C, 56.72; H, 5.95; N, 3.31. Found: C, 56.71; H, 5.96; N, 3.31.

tert-Butyl 1-Ethyl 3-Ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (**4h**): From pyridinium methylide **1d** and *tert*-butyl bromoacetate (**2c**), yield 20%, pale yellow prisms, mp 163—165 °C, IR (KBr) 1726, 1672, 1641 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.35 (6H, t, J=7.1 Hz), 1.54 (9H, s), 2.03 (3H, s), 2.50 (3H, s), 2.51—2.71 (2H, m), 2.98—3.11 (2H, m), 4.17 (1H, d, J=9.8 Hz), 4.20—4.41 (3H, m), 7.16 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.3, 14.5, 24.3, 25.3, 28.0, 33.4, 50.6, 53.0, 59.6, 84.6, 101.2, 115.0, 126.1, 133.0, 147.5, 155.2, 164.3, 165.7, 176.6. *Anal.* Calcd for $C_{21}H_{27}NO_5S_2$: C, 57.64; H, 6.22; N, 3.20. Found: C, 57.75; H, 6.21; N, 3.10.

Syntheses of Ethyl 3-[Bis(alkylthio)methylene]-2-oxo-2,3-dihydroindolizine-1-carboxylates 9a—d. General Method A chloroform solution (20 ml) of pyridinium methylide (**1**, 2 mmol) and iodomethane (**2d**, 1 g) or iodoethane (**2e**, 1 g) was allowed to react at room temperature until the disappearance of the starting methylide was confirmed by TLC monitoring (*ca.* 1 d). After *S*-alkylation was completed, the resulting solution was concentrated at reduced pressure and the residue was washed three times with 10 ml portions of ether to remove the unaltered alkylating agent. The residual oil was again dissolved in chloroform (30 ml) and the solution was treated with DBU (0.365 g, 2.4 mmol) under stirring in an ice bath for 10 min and then with chloranil (0.492 g, 2 mmol) under the same conditions for an additional 4 h. The reaction mixture was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using chloroform as an eluent. The red chloroform layers of product (**9**) were combined and concentrated at reduced pressure. Recrystallization of the crude products from ether–hexane afforded the corresponding ethyl 3-bis(alkylthio)methylene-2-oxo-2,3-dihydroindolizine-1-carboxylates. Some data for the compounds **9a**—**d** are as follows.

Ethyl 3-Bis(methylthio)methylene-2-oxo-2,3-dihydroindolizine-1-carboxylate (**9a**): Yield 27%, red prisms, mp 166—168 °C, IR (KBr) 1689, 1657 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.39 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.23 and 2.69 (each 3H, s, SMe), 4.36 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.69 (1H, dt, J=6.8, 6.8, 1.6 Hz, 6-H), 7.27 (1H, br q, J=9.3, 6.8 Hz, 7-H), 8.15 (1H, br d, J=9.3 Hz, 8-H), 8.89 (1H, br d, J=6.8 Hz, 5-H). *Anal.* Calcd for $C_{14}H_{15}NO_3S_2$: C, 54.35; H, 4.89; N, 4.53. Found: C, 54.61; H, 4.80; N, 4.36.

Ethyl 3-Bis(ethylthio)methylene-2-oxo-2,3-dihydroindolizine-1-carboxylate (**9b**): Yield 21%, red prisms, mp 123—125 °C, IR (KBr) 1691, 1626 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.29 (6H, t, J=7.1 Hz), 1.40 (3H, t, J=7.1 Hz), 2.78 and 3.12 (each 2H, q, J=7.1 Hz), 4.38 (2H, q, J=7.1 Hz), 6.59 (1H, dt, J=6.8, 6.8, 1.6 Hz), 7.37 (1H, br q, J=9.3, 6.8 Hz), 8.18 (1H, br d, J=9.3 Hz), 9.07 (1H, br d, J=6.8 Hz). *Anal.* Calcd for $C_{16}H_{19}NO_3S_2$: C, 56.95; H, 5.68; N, 4.15. Found: C, 57.14; H, 5.62; N, 4.09.

Ethyl 7-Methyl-3-bis(methylthio)methylene-2-oxo-2,3-dihydroindolizine-1-carboxylate (**9c**): Yield 26%, red prisms, mp 181—183 °C, IR (KBr) 1686, 1628 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.41 (3H, t, J=7.1 Hz), 2.38 (3H, s), 2.38 and 2.68 (each 3H, s), 4.39 (2H, q, J=7.1 Hz), 6.51 (1H, dd, J=6.8, 1.6 Hz), 8.00 (1H, br s), 8.86 (1H, d, J=6.8 Hz). *Anal.* Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.30; N, 4.33. Found: C, 55.66; H, 5.30; N, 4.35.

Ethyl 3-Bis(ethylthio)methylene-7-methyl-2-oxo-2,3-dihydroindolizine-1-carboxylate (**9d**): Yield 15%, viscous red oil, IR (neat) 1680, 1633 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.27 (6H, t, J=7.1 Hz), 1.39 (3H, t, J=7.1 Hz), 2.35 (3H, s), 2.84 and 3.22 (each 2H, q, J=7.1 Hz), 4.36 (2H, q, J=7.1 Hz), 6.47 (1H, dd, J=6.8, 1.6 Hz), 8.00 (1H, br s), 9.00 (1H, d, J=6.8 Hz). The elemental analysis for this compound was not performed because crystallization was not possible.

Syntheses of Ethyl 3-[(Alkylthio)carbonyl]-2-hydroxyindolizine-1-carboxylates 10a—f. Method A A chloroform solution (20 ml) of pyridinium salt **3** or **8** prepared from pyridinium methylide **1** (1 mmol) with an alkylating agent **2** (1.2 mmol) was treated with DBU (1 mmol) under stirring at room temperature for 4 h in the absence of chloranil. The concentration of the reaction mixture, column separation of the residue, and recrystallization of the crude product from ether–hexane gave the corresponding ethyl 3-[(alkylthio)carbonyl]-2-hydroxyindolizine-1-carboxylate (**10**).

Method B A drop of water was added to the chloroform solution (20 ml) of pyridinium salt **3a** (1 mmol) described in method A, and then the resulting solution was treated with DBU under stirring at room temperature for 4 h.

Method C A chloroform solution (20 ml) of pyridinium salt **3** or **8** (1 mmol) was treated with DBU under stirring at room temperature for 4 h and then with trifluoroacetic acid (0.114 g, 1 mmol) for an additional 2 h.

Method D An ethanolic solution (20 ml) of pyridinium salt **3a** (1 mmol) was treated with DBU under stirring at room temperature for 4 h.

Method E A drop of water was added to an ethanolic solution (20 ml) of pyridinium salt **3a** (1 mmol), and then the resulting solution was treated with DBU at room temperature under stirring for 4 h.

Method F A chloroform solution (30 ml) of pyridinium salt **3a** (1 mmol) was treated with triethylamine (0.121 g, 1.2 mmol) under stirring at room temperature for 12 h.

These results are shown in Chart 3 and some data for products **10a**—**f** are as follows.

Ethyl 2-Hydroxy-3-[(methylthio)carbonyl]indolizine-1-carboxylate (**10a**), 22% (from **3a**, Method A), 24% (from **8a**, Method A),15% (from **3a**, Method B), 35% (from **3a**, Method C), 20% (from **8a**, Method C), 4% (from **3a**, Method D), 12% (from **3a**, Method E), and 6% (from **3a**, Method F), pale yellow needles, mp 119—121 °C, IR (KBr) 3422, 1665, 1599 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.46 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.47 (3H, s, SMe), 4.48 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.96 (1H, br t, J=7.0, 7.0 Hz, 6-H), 7.40 (1H, br q, J=8.5, 7.0 Hz, 7-H), 7.94 (1H, d, J=8.5 Hz, 8-H), 9.79 (1H, d, J=7.0 Hz, 5-H), 10.41 (1H, s, 2-OH). *Anal.* Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 55.90; H, 4.71; N, 4.95.

Ethyl 3-[(Ethylthio)carbonyl]-2-hydroxyindolizine-1-carboxylate (**10b**), 12% (from **3b**, Method A), 5% (from **8b**, Method A), 17% (from **3b**, Method C), 18% (from **8b**, Method C), pale yellow needles, mp 125—127 °C, IR (KBr) 3429, 1658, 1608 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.35 (3H, t, J=7.1 Hz), 1.48 (3H, t, J=7.1 Hz), 3.11 (2H, q, J=7.1 Hz), 4.49 (2H, q, J=7.1 Hz), 6.97 (1H, br t, J=7.0, 7.0 Hz), 7.42 (1H, br q, J=8.8, 7.0 Hz), 7.95 (1H, d, J=8.8 Hz), 9.76 (1H, d, J=7.0 Hz), 10.46 (1H, s). *Anal.* Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.61; H, 5.12; N, 4.48.

Ethyl 2-Hydroxy-7-methyl-3-[(methylthio)carbonyl]indolizine-1-carboxylate (**10c**), 22% (from **3c**, Method A), 41% (from **3c**, Method C), pale

yellow needles, mp 140—142 °C, IR (KBr) 3422, 1664, 1601 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.47 (3H, t, J=7.1 Hz), 2.46 (6H, s), 4.49 (2H, q, J=7.1 Hz), 6.81 (1H, dd, J=7.1, 1.6 Hz), 7.69 (1H, br s), 9.65 (1H, d, J=7.0 Hz), 10.46 (1H, br s). *Anal.* Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.42; H, 5.13; N, 4.68.

Ethyl 3-[(Ethylthio)carbonyl]-2-hydroxy-7-methylindolizine-1-carboxylate (**10d**), 13% (from **3d**, Method A), 25% (from **3d**, Method C), pale yellow needles, mp 152—156 °C, IR (KBr) 3433, 1666, 1597 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.38 (3H, t, J=7.1 Hz), 1.47 (3H, t, J=7.1 Hz), 2.44 (3H, s), 3.09 (2H, s), 4.48 (2H, q, J=7.1 Hz), 6.79 (1H, br t, J=7.0, 7.0 Hz), 7.67 (1H, br s), 9.64 (1H, d, J=7.0 Hz), 10.46 (1H, s). *Anal.* Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.58; H, 5.60; N, 4.56.

Ethyl 3-[(Ethoxycarbonylmethylthio)carbonyl]-2-hydroxylindolizine-1-carboxylate (**10e**), 10% (from **3a**, Method A), 2% (from **3b**, Method A), 3% (Method B), 0% (Method C), 1% (Method D), 2% (Method E), and trace (Method F), pale yellow needles, mp 141—143 °C, IR (KBr) 3470, 1658, 1601 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.32 (3H, s, J=7.1 Hz), 1.48 (3H, t, J=7.1 Hz), 3.87 (2H, s), 4.26 and 4.48 (each 2H, q, J=7.1 Hz), 6.97 (1H, br t, J=7.0, 7.0 Hz), 7.42 (1H, br q, J=8.8, 7.0 Hz), 7.95 (1H, d, J=8.8 Hz), 9.73 (1H, d, J=7.0 Hz), 10.46 (1H, s). *Anal.* Calcd for $C_6H_7NO_6S$: C, 54.69; H, 4.88; N, 3.99. Found: C, 54.68; H, 4.92; N, 3.97.

Ethyl 3-[(Ethoxycrbonylmethylthio)carbonyl]-2-hydroxy-7-methyindolizine-1-carboxylate (**10f**), 7% (from **3c**, Method A), 0% (from **3c**, Method B), 2% (from **3d**, Method C), 0% (from **3d**, Method C), pale yellow needles, mp 124—126 °C, IR (KBr) 3433, 1655, 1610 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.30 and 1.46 (each 3H, t, J=7.1 Hz), 2.44 (3H, s), 3.85 (2H, s), 4.24 and 4.48 (each 2H, q, J=7.1 Hz), 6.65 (1H, br t, J=7.0, 7.0 Hz), 7.69 (1H, br s), 9.59 (1H, d, J=7.0 Hz), 10.44 (1H, br s). *Anal.* Calcd for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 56.05; H, 5.18; N, 3.74.

Crystallography of 1-*tert*-Butyl 5-Ethyl 3-Ethylthio-7-methyl-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (4h): Chloroform A single crystal (0.04×0.42×0.84 mm) grown from chloroform was used for unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **4h**: $C_{21}H_{27}NO_5S_2$: $CHCl_3$; M=556.95; triclinic, space group $P\bar{1}$ (#2), Z=4 with a=15.433(5) Å, b=19.709(5) Å, c=9.227(4) Å; α=92.96(3)°, β=103.60(3)°, γ=88.65(2)°; V=2724(2) Å^3, and D_{calc}=1.358 g/cm^3. All calculations were performed using the TEXSAN package.[19] The structure was solved by a direct method (SIR92).[20] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.071 and 0.064, respectively, for 2723 (I>2.00σ(I)) observed reflections.

Crystallography of Diethyl 7-Methyl-3-methylthio-4-oxo-1,4,8,8a-tetrahydro-1,4-thiazino[3,4,5-*cd*]indolizine-1,5-dicarboxylate (5c) A single crystal (0.68×0.20×0.20 mm) grown from chloroform was used for unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **5c**: $C_{18}H_{21}NO_4S_2$; M=379.49; triclinic, space group $P2_1/n$ (#14), Z=4 with a=8.742(8) Å, b=24.134(6) Å, c=9.401(7) Å; β=103.51(6)°; V=1928(2) Å^3, and D_{calc}=1.358 g/cm^3. All calculations were performed using the TEXSAN package.[19] The structure was solved by a direct method (SIR92).[20] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.082 and 0.074, respectively, for 1248 (I>2.00σ(I)) observed reflections.

Crystallography of Ethyl 2-Hydroxy-3-[(methylthio)carbonyl]indolizine-1-carboxylate (10a) A single crystal (0.12×0.24×0.68 mm) grown from chloroform was used for unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **10a**: $C_{13}H_{13}NO_4S$; M=279.31; triclinic, space group $P\bar{1}$ (#2), Z=2 with a=9.044(4) Å, b=10.063(2) Å, c=7.689(3) Å; α=95.21(2)°, β=111.80(3)°, γ=81.75(2)°; V=642.5(4) Å^3, and D_{calc}=1.444 g/cm^3. All calculations were performed using the TEXSAN package.[19] The structure was solved by a direct method (SIR92).[20] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.058 and 0.059, respectively, for 1124 (I>2.00σ(I)) observed reflections.

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