Preparation of New Nitrogen-Bridged Heterocycles. 49.¹⁾ A New Access to Thieno[3,4-*b*]indolizine Derivatives

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The title compounds, together with 3-vinylindolizine-1-carbonitriles (4—56%), were prepared in 1—18% yields from the *S*-alkylation of pyridinium 1-[3-ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]]allylides with alkyl halides, followed by treatment of the resulting pyridinium salts with a base and then a dehydrogenating agent. In several reactions of pyridinium salts obtained from reaction of the allylides with benzylic halides, trace amounts of bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides with an interesting superimposed structure were also isolated. The structures of these compounds were confirmed by X-ray analyses.

Key words thieno[3,4-*b*]indolizine; 3-vinylindolizine; pyridinium allylide; cyclization; stacked structure; X-ray analysis

We recently reported the unexpected formation of ethyl 1-cyano-3-(methylthio)thieno[3,4-*b*]indolizine-9-carboxylates in the reactions of 1-[1-[cyanomethylthio(methylthio)methylene]-3-ethoxycarbonyl-2-propenyl]pyridinium bromides with a base and a dehydrogenating agent, and proposed a possible reaction mechanism.¹⁾ In order to develop a general and effective preparative method for this type of heterocycle, we examined substituent effects and various reaction conditions such as bases, solvents, and reaction temperature. However, similar reactions of the salts obtained from pyridinium 1-[3-ethoxycarbonyl-1-[methylthio(thiocarbonyl)]]allylides and various alkylating agents, except bromoacetonitrile, gave exclusively 3-vinylindolizine derivatives and none of the desired thieno[3,4-*b*]indolizine derivatives. We then examined the use of pyridinium 1-allylides having a cyanomethylthio(thiocarbonyl) group on the ylidic carbanion for the synthesis of this type of compound. In this paper we report the preparation of the title compounds starting from pyridinium 1-[3-ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]]allylides with various alkylating agents, and of by-products, bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides, which have an interesting superimposed structure between the two indolizine rings in the molecule.

Results and Discussion

Reactions of Pyridinium 1-[3-Ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]]allylides When pyridinium 1-[3-ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]]allylides (**1a—c**) were alkylated with various alkyl halides (**2a—e**), and the resulting *S*-alkylated pyridinium salts treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and then chloranil at 0 °C, the expected ethyl 3-alkylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates (**3a—o**) were formed in 1—18% yields as orange crystals with very strong fluorescence, together with ethyl 3-(2-alkylthio-3-cyanoindolizin-3-yl)acrylates (**4a—o**, 4—56%). Interestingly, another type of product, bis(1-cyano-9-ethoxycarbonylthieno[3,4-*b*]indolizin-3-yl) disulfides **5a, b** were also formed in the reactions of pyridinium allylides (**1a, b**) with benzylic halides (**2c—e**), but yields were very low (trace). These results are shown in Chart 1.

The structures of ethyl 3-alkylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates (**3a—o**) were determined by physical

and spectral means and by spectral comparison with those (**3a, k**) prepared earlier by us.¹⁾ The proton and methyl proton signals on the pyridine ring in the ¹H-NMR spectra of new compounds **3b—j, l—o** appeared at δ 6.43–9.19 and 2.14–2.75, respectively, and the chemical shifts were almost parallel to those of the known **3a, k**. Their IR spectra showed a characteristic aromatic cyano (2183–2220 cm^{−1}) and a carbonyl absorption band (1664–1709 cm^{−1}). Since an alternative structural contribution (**3'**) for these thieno[3,4-*b*]indolizine derivatives (**3**) can be considered (see Chart 2), as seen in thieno[3,4-*a*]indolizine,²⁾ we carried out a single crystal X-ray analysis of **3g** in order to confirm this structure and to obtain further structural information. The ORTEP drawing³⁾ for **3g** is shown in Fig. 1. This structural data distinctly showed that thieno[3,4-*b*]indolizine has the structure **3** in preference to the alternative **3'**, because the S(1)–C(1) (1.751 Å) and the S(1)–C(2) bond length (1.727 Å) of **3g** are nearly parallel to or longer than the S–C bond lengths (1.714 Å) in thiophene⁴⁾ and the C(3)–C(10) bond length (1.431 Å) is longer than the C(1)–C(10) (1.389 Å) and the C(2)–C(3) bond length (1.371 Å). Furthermore, the C(3)–C(10) bond length (1.431 Å) of **3g** is clearly longer than those (1.370–1.411 Å) in an indolizine⁵⁾ and some 2,3-fused indolizines⁶⁾ but it is close to that (1.423 Å) in thiophene.⁴⁾

The structures of the main products, ethyl 3-(2-alkylthio-1-cyanoindolizin-3-yl)acrylates (**4a—o**) were also confirmed by physical and spectral means. Compounds **4a, f, k** were in accord with authentic samples in all respects. The *trans* carbon–carbon double bond in products **4a—o** was indicated by an olefinic absorption band (1607–1622 cm^{−1}) in the IR spectra and by the presence of a set of AB type proton signals (near δ 6.7 and 7.8) with a 16.0 Hz coupling constant in the ¹H-NMR spectra. The elemental analyses of **4a—o** were also in accord with the composition of the proposed structures.

Similarly, the structures for the minor products, bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides (**5a, b**), were deduced by the absence of the alkylthio group and the presence of another thieno[3,4-*b*]indolizine moiety in the ¹H-NMR spectra, and their elemental analyses were in good accord with the structures. However, considerable up-field shifts for the protons on the pyridine ring in the ¹H-NMR spectra of **5a, b** were observed. For example, the

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Chart 1

Chart 2

Fig. 1. ORTEP Drawing of Ethyl 1-Cyano-3-ethylthio-7-methylthieno[3,4-*b*]indolizine-9-carboxylate (**3g**)

¹H-NMR spectrum of **5a** showed only a set of signals at δ 6.46, 7.32, 8.14, and 8.16 attributable to the 6-, 7-, 8-, and 5-protons on the two thieno[3,4-*b*]indolizine rings, respectively. In comparison with those (δ 6.86, 7.47, 8.43, 9.07) of **3a**, the values are at higher magnetic field by 0.40, 0.15, 0.29, and 0.91 ppm, respectively, and a similar tendency was exhibited for disulfide **5b**. The order of the up-field shift in disulfides **5a, b** was 5-H > 6-H > 8-H > 7-H. In view of the

Fig. 2. ORTEP Drawing of Bis(1-cyano-9-ethoxycarbonyl-7-methylthieno[3,4-*b*]indolizine-3-yl) Disulfide (**5b**)

steric effect, disulfide can usually be expected to permit the two substituents to be as remote as possible. However, this obvious up-field shift of the pyridine proton signals prompted us to suspect a superimposed structure between the two thieno[3,4-*b*]indolizine rings in **5a, b**. The structures of disulfides were finally confirmed by X-ray analysis of **5b**. The ORTEP³⁾ and PLUTO drawings⁷⁾ for **5b** are shown in Figs. 2 and 3. As shown in Fig. 3, the two thieno[3,4-*b*]indolizine rings are superimposed, as judged by the least-square plane (15.3°) and a C(2)–S(2)–S(3)–C(17) torsion angle (90.9°). The reason for the acquisition of this interesting stacked structure in disulfides **5a, b** is unclear, but favorable attractions between the cationic pyridine ring in a thieno[3,4-*b*]indolizine moiety and the anionic pyrrole ring in the other and *vice versa* may operate in this molecule. The contribution of such an ionic resonance structure for the indolizine ring is well known.⁸⁾

Reaction Mechanism Since the transformation mechanism from 1-[1-substituted 2-(acylmethylthio)vinyl]pyri-

Fig. 3. PLUTO Drawing of Bis(3-cyano-9-ethoxycarbonyl-7-methylthieno[3,4-*b*]indolizin-3-yl) Disulfide (**5b**)

Chart 3

dinium halides to the corresponding indolizine derivatives is well established,^{1,9)} we describe here a possible formation mechanism (Chart 3) for ethyl 3-alkylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates (**3a–o**) and bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides (**5a, b**). Alkaline treatment of *S*-alkylated pyridinium salts **6**, formed from the reactions of pyridinium 1-allylides (**1a–c**) with halides **2a–e**, would provide the ethyl 3-alkylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates (**3a–o**) via intramolecular Michael addition of anion intermediates **7**, aromatization of the generated 2,3-dihydrothiophene derivatives **8**, followed by cyclization of the resulting 1,5-dipoles **9** and aromatization of the dihydroadducts. On the other hand, disulfides **5a, b** may be formed by homolytic fission of the sulfide linkage in 3-(benzylthio)thieno[3,4-*b*]indolizines (**3c–e, h–j**), and subsequent dimerization of radical component **10**, although no product derived from benzyl radicals could be detected.

Experimental

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

Preparation of Pyridinium 1-[3-Ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]allylides These pyridinium 1-[3-ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]allylides (**1a–c**) were prepared from the alkaline treatment of 1-(3-ethoxycarbonyl-2-propenyl)pyridinium bromides, carbon disulfide, and chloroacetonitrile in ethanol according to the procedure described earlier.^{1,9)} Some data of compounds **1a–c** are as follows:

Pyridinium 1-[3-Ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]allylides (**1a**): 56%, yellow needles (CHCl₃–ether), mp 162–164 °C. IR (KBr) cm^{−1}: 2185, 1672, 1626. ¹H-NMR (CDCl₃) δ : 1.28 (3H, t, *J*=7.0 Hz), 4.24 (2H, q, *J*=7.0 Hz), 4.41 (2H, s), 4.49 (1H, d, *J*=15.0 Hz), 7.9–8.8 (5H, m), 8.38 (1H, d, *J*=15.0 Hz). Anal. Calcd for C₁₄H₁₄N₂O₂S₂: C, 54.88; H, 4.61; N, 9.14. Found: C, 54.91; H, 4.62; N, 9.10.

4-Methylpyridinium 1-[3-Ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]allylides (**1b**): 46%, yellow needles (CHCl₃–ether), mp 145–147 °C. IR (KBr) cm^{−1}: 2243, 1687, 1635. ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, *J*=7.0 Hz), 2.78 (3H, s), 4.22 (2H, q, *J*=7.0 Hz), 4.40 (2H, s), 4.45 (1H, d, *J*=15.0 Hz), 7.8–8.6 (4H, m), 8.36 (1H, d, *J*=15.0 Hz). Anal. Calcd for C₁₅H₁₆N₂O₂S₂: C, 56.23; H, 5.03; N, 8.74. Found: C, 56.08; H, 5.06; N, 8.54.

3,5-Dimethylpyridinium 1-[3-Ethoxycarbonyl-1-[cyanomethylthio(thiocarbonyl)]allylides (**1c**): 65%, orange needles (CHCl₃–ether), mp 143–145 °C. IR (KBr) cm^{−1}: 2241, 1689, 1620. ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, *J*=7.0 Hz), 2.59 (6H, s), 4.22 (2H, q, *J*=7.0 Hz), 4.39 (2H, s), 4.40 (1H, d, *J*=15.0 Hz), 8.0–8.5 (3H, m), 8.32 (1H, d, *J*=15.0 Hz). Anal. Calcd for C₁₆H₁₈N₂O₂S₂+H₂O: C, 57.46; H, 5.42; N, 8.38. Found: C, 57.60; H, 5.47; N, 8.18.

Preparation of Thieno[3,4-*b*]indolizine and 3-Vinylindolizine Derivatives. General Method A chloroform solution (20 ml) of pyridinium 1-[(cyanomethylthio)thiocarbonyl]methylide (**1**, 2 mmol) was treated with alkyl halide (**2**, 2.4 mmol) at room temperature for 1 d. Evaporation of the

solvent from the reaction mixture, followed by the removal of the excess alkylating agent by washing three times with ether (each 20 ml) gave the corresponding pyridinium salt. The salt was again dissolved in chloroform (30 ml), and the solution was treated with DBU and then chloranil with stirring at 0 °C. The reaction mixture was allowed to react for a further 4 h under the same reaction conditions. The mixture was concentrated under reduced pressure and the residue was separated by column chromatography on alumina using ether and then chloroform. The separated portions were concentrated under reduced pressure. Recrystallization of crude products from chloroform–hexane gave the corresponding ethyl 3-alkylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates (**3a–o**) as orange crystals and ethyl 3-(2-alkylthio-1-cyanoindolizin-3-yl)acrylates (**4a–o**) as yellow crystals, respectively.

In the reactions of **1a**, **b** with benzyl halides (**2c–e**) trace amounts of bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides (**5a**, **b**) were also isolated, and recrystallization from chloroform afforded brown prisms.

Selected data for compounds **3a–o**, **4a–o** and **5a**, **b** are as follows:

Ethyl 1-Cyano-3-(methylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3a**): 3% (from **1a** and methyl iodide (**2a**)), mp 204–205 °C (Lit.¹) 203–205 °C).

Ethyl 1-Cyano-3-(ethylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3b**): 8% (from **1a** and ethyl iodide (**2b**)), mp 123–125 °C. IR (KBr) cm^{-1} : 2197, 1678. ¹H-NMR (CDCl_3) δ : 1.37, 1.50 (each 3H, t, $J=7.0$ Hz), 3.04, 4.54 (each 2H, q, $J=7.0$ Hz), 6.82 (1H, br t, $J=7.0$ Hz), 7.47 (1H, br dd, $J=7.0$, 9.0 Hz), 8.42 (1H, br d, $J=9.0$ Hz), 9.19 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.13; H, 4.27; N, 8.44.

Ethyl 3-Benzylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylate (**3c**): 10% (from **1a** and benzyl bromide (**2c**)), mp 168–171 °C. IR (KBr) cm^{-1} : 2197, 1678. ¹H-NMR (CDCl_3) δ : 1.49 (3H, t, $J=7.0$ Hz), 4.11 (2H, s), 4.52 (2H, q, $J=7.0$ Hz), 6.61 (1H, br t, $J=7.0$ Hz), 6.9–7.6 (6H, m), 8.32 (1H, br d, $J=9.0$ Hz), 8.82 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$: C, 64.26; H, 4.11; N, 7.14. Found: C, 64.16; H, 4.36; N, 6.99.

Ethyl 1-Cyano-3-(*p*-methylbenzylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3d**): 15% (from **1a** and *p*-methylbenzyl chloride (**2d**)), mp 170–172 °C. IR (KBr) cm^{-1} : 2200, 1668. ¹H-NMR (CDCl_3) δ : 1.50 (3H, t, $J=7.0$ Hz), 2.22 (3H, s), 4.09 (2H, s), 4.54 (2H, q, $J=7.0$ Hz), 6.99 (4H, s), 7.40 (1H, br dd, $J=7.0$, 9.0 Hz), 8.35 (1H, br d, $J=9.0$ Hz), 8.81 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 65.06; H, 4.44; N, 6.85.

Ethyl 3-(*p*-Bromobenzylthio)-1-cyanothieno[3,4-*b*]indolizine-9-carboxylate (**3e**): 7% (from **1a** and *p*-bromobenzyl bromide (**2e**)), mp 169–171 °C. IR (KBr) cm^{-1} : 2204, 1664. ¹H-NMR (CDCl_3) δ : 1.51 (3H, t, $J=7.0$ Hz), 4.04 (2H, s), 4.54 (2H, q, $J=7.0$ Hz), 6.60 (1H, br t, $J=7.0$ Hz), 6.7–7.6 (5H, m), 8.36 (1H, br d, $J=9.0$ Hz), 8.75 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{BrN}_2\text{O}_2\text{S}_2$: C, 53.51; H, 3.21; N, 5.94. Found: C, 53.71; H, 3.16; N, 5.95.

Ethyl 1-Cyano-7-methyl-3-(methylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3f**): 1% (from **1b** and methyl iodide (**2a**)), mp 172–174 °C. IR (KBr) cm^{-1} : 2193, 1680. ¹H-NMR (CDCl_3) δ : 1.50 (3H, t, $J=7.0$ Hz), 2.44, 2.67 (each 3H, s), 4.54 (2H, q, $J=7.0$ Hz), 6.69 (1H, dd, $J=7.0$, 2.0 Hz), 8.21 (1H, br s), 8.95 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2$: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.11; H, 4.43; N, 8.37.

Ethyl 1-Cyano-3-ethylthio-7-methylthieno[3,4-*b*]indolizine-9-carboxylate (**3g**): 4% (from **1b** and ethyl iodide (**2b**)), mp 121–124 °C. IR (KBr) cm^{-1} : 2195, 1680. ¹H-NMR (CDCl_3) δ : 1.37, 1.49 (each 3H, t, $J=7.0$ Hz), 2.46 (3H, s), 3.03, 4.53 (each 2H, q, $J=7.0$ Hz), 6.67 (1H, dd, $J=7.0$, 2.0 Hz), 8.22 (1H, br s), 9.09 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.13; H, 4.62; N, 8.09.

Ethyl 3-Benzylthio-1-cyano-7-methylthieno[3,4-*b*]indolizine-9-carboxylate (**3h**): 8% (from **1b** and benzyl bromide (**2c**)), mp 192–194 °C. IR (KBr) cm^{-1} : 2199, 1680. ¹H-NMR (CDCl_3) δ : 1.49 (3H, t, $J=7.0$ Hz), 2.40 (3H, s), 4.11 (2H, s), 4.50 (2H, q, $J=7.0$ Hz), 6.43 (1H, dd, $J=7.0$, 2.0 Hz), 6.9–7.4 (5H, m), 8.10 (1H, br s), 8.71 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.75; H, 4.36; N, 7.14.

Ethyl 1-Cyano-7-methyl-3-(*p*-methylbenzylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3i**): 2% (from **1b** and *p*-methylbenzyl chloride (**2d**)), mp 182–185 °C. IR (KBr) cm^{-1} : 2195, 1672. ¹H-NMR (CDCl_3) δ : 1.49 (3H, t, $J=7.0$ Hz), 2.23, 2.40 (each 3H, s), 4.06 (2H, s), 4.52 (2H, q, $J=7.0$ Hz), 6.44 (1H, dd, $J=7.0$, 2.0 Hz), 6.99 (4H, s), 8.15 (1H, br s), 8.68 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2$: C, 65.69; H, 4.79; N, 6.66. Found: C, 65.98; H, 4.61; N, 6.45.

Ethyl 3-(*p*-Bromobenzylthio)-1-cyano-7-methylthieno[3,4-*b*]indolizine-9-

carboxylate (**3j**): 4% (from **1b** and *p*-bromobenzyl bromide (**2e**)), mp 182–185 °C. IR (KBr) cm^{-1} : 2199, 1668. ¹H-NMR (CDCl_3) δ : 1.50 (3H, t, $J=7.0$ Hz), 2.44 (3H, s), 4.04 (2H, s), 4.54 (2H, q, $J=7.0$ Hz), 6.44 (1H, dd, $J=7.0$, 2.0 Hz), 6.7–7.5 (4H, m), 8.14 (1H, br s), 8.58 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}_2$: C, 54.44; H, 3.53; N, 5.77. Found: C, 54.24; H, 3.62; N, 5.70.

Ethyl 1-Cyano-6,8-dimethyl-3-(methylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3k**): 3% (from **1c** and methyl iodide (**2a**)), mp 235–237 °C (Lit.¹) mp 235–237 °C).

Ethyl 3-Benzylthio-1-cyano-6,8-dimethylthieno[3,4-*b*]indolizine-9-carboxylate (**3l**): 8% (from **1c** and methyl iodide (**2a**)), mp 149–151 °C. IR (KBr) cm^{-1} : 2197, 1697. ¹H-NMR (CDCl_3) δ : 1.36, 1.48 (each 3H, t, $J=7.0$ Hz), 2.32, 2.74 (each 3H, s), 3.05, 4.54 (each 2H, q, $J=7.0$ Hz), 7.08 (1H, br s), 8.98 (1H, br s). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{S}_2$: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.03; H, 4.90; N, 7.72.

Ethyl 3-Benzylthio-1-cyano-6,8-dimethylthieno[3,4-*b*]indolizine-9-carboxylate (**3m**): 8% (from **1c** and benzyl iodide (**2c**)), mp 184–186 °C. IR (KBr) cm^{-1} : 2220, 1705. ¹H-NMR (CDCl_3) δ : 1.46 (3H, t, $J=7.0$ Hz), 2.14, 2.70 (each 3H, s), 4.05 (2H, s), 4.50 (2H, q, $J=7.0$ Hz), 6.94 (1H, br s), 7.0–7.3 (5H, m), 8.50 (1H, br s). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2$: C, 65.69; H, 4.79; N, 6.66. Found: C, 65.58; H, 4.79; N, 6.64.

Ethyl 1-Cyano-6,8-dimethyl-3-(*p*-methylbenzylthio)thieno[3,4-*b*]indolizine-9-carboxylate (**3n**): 18% (from **1c** and *p*-methylbenzyl chloride (**2d**)), mp 161–165 °C. IR (KBr) cm^{-1} : 2214, 1701. ¹H-NMR (CDCl_3) δ : 1.47 (3H, t, $J=7.0$ Hz), 2.15, 2.22, 2.71 (each 3H, s), 4.03 (2H, s), 4.52 (2H, q, $J=7.0$ Hz), 6.97 (5H, br s), 8.52 (1H, br s). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2\text{S}_2$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.09; H, 4.98; N, 6.32.

Ethyl 3-(*p*-Bromobenzylthio)-1-cyano-6,8-dimethylthieno[3,4-*b*]indolizine-9-carboxylate (**3o**): 4% (from **1c** and *p*-bromobenzyl bromide (**2e**)), mp 126–130 °C. IR (KBr) cm^{-1} : 2212, 1709. ¹H-NMR (CDCl_3) δ : 1.50 (3H, t, $J=7.0$ Hz), 2.18, 2.75 (each 3H, s), 4.02 (2H, s), 4.54 (2H, q, $J=7.0$ Hz), 7.01 (1H, br s), 6.7–7.5 (4H, m), 8.43 (1H, br s). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{BrN}_2\text{O}_2\text{S}_2$: C, 55.31; H, 3.83; N, 5.61. Found: C, 55.09; H, 3.92; N, 5.69.

Ethyl 3-[1-Cyano-2-(methylthio)indolizin-3-yl]acrylate (**4a**): 17% (from **1a** and methyl iodide (**2a**)), mp 145–146 °C (Lit.¹⁰) mp 145 °C and Lit.¹) mp 142–143 °C).

Ethyl 3-[1-Cyano-2-(ethylthio)indolizin-3-yl]acrylate (**4b**): 29% (from **1a** and ethyl iodide (**2b**)), mp 112–114 °C. IR (KBr) cm^{-1} : 2205, 1696, 1607. ¹H-NMR (CDCl_3) δ : 1.30, 1.36 (each 3H, t, $J=7.0$ Hz), 3.12, 4.32 (each 2H, q, $J=7.0$ Hz), 6.78 (1H, d, $J=16.0$ Hz), 6.86 (1H, br t, $J=7.0$ Hz), 7.28 (1H, br dd, $J=7.0$, 9.0 Hz), 7.68 (1H, d, $J=9.0$ Hz), 8.00 (1H, d, $J=16.0$ Hz), 8.36 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.90; H, 5.35; N, 9.43.

Ethyl 3-[2-Benzylthio-1-cyanoindolizin-3-yl]acrylate (**4c**): 12% (from **1a** and benzyl bromide (**2c**)), mp 151–153 °C. IR (KBr) cm^{-1} : 2211, 1694, 1620. ¹H-NMR (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 4.23 (2H, s), 4.31 (2H, q, $J=7.0$ Hz), 6.68 (1H, d, $J=16.0$ Hz), 6.82 (1H, br t, $J=7.0$ Hz), 7.0–7.5 (6H, m), 7.70 (1H, d, $J=9.0$ Hz), 7.85 (1H, d, $J=16.0$ Hz), 8.32 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.83; H, 5.23; N, 7.48.

Ethyl 3-[1-Cyano-2-(*p*-methylbenzylthio)indolizin-3-yl]acrylate (**4d**): 25% (from **1a** and *p*-methylbenzyl chloride (**2d**)), mp 147–149 °C. IR (KBr) cm^{-1} : 2214, 1690, 1609. ¹H-NMR (CDCl_3) δ : 1.37 (3H, t, $J=7.0$ Hz), 2.28 (3H, s), 4.20 (2H, s), 4.32 (2H, q, $J=7.0$ Hz), 6.63 (1H, d, $J=16.0$ Hz), 6.77 (1H, br t, $J=7.0$ Hz), 6.9–7.5 (5H, m), 7.69 (1H, d, $J=9.0$ Hz), 7.83 (1H, d, $J=16.0$ Hz), 8.32 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 70.19; H, 5.35; N, 7.44. Found: C, 70.18; H, 5.33; N, 7.47.

Ethyl 3-[2-(*p*-Bromobenzylthio)-1-cyanoindolizin-3-yl]acrylate (**4e**): 30% (from **1a** and *p*-bromobenzyl bromide (**2e**)), mp 147–149 °C. IR (KBr) cm^{-1} : 2211, 1696, 1609. ¹H-NMR (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 4.19 (2H, s), 4.32 (2H, q, $J=7.0$ Hz), 6.65 (1H, d, $J=16.0$ Hz), 6.7–7.5 (6H, m), 7.72 (1H, d, $J=9.0$ Hz), 7.80 (1H, d, $J=16.0$ Hz), 8.34 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}$: C, 57.15; H, 3.88; N, 6.35. Found: C, 57.14; H, 3.84; N, 6.41.

Ethyl 3-[1-Cyano-7-methyl-2-(methylthio)indolizin-3-yl]acrylate (**4f**): 38% (from **1b** and methyl iodide (**2a**)), mp 148–150 °C (Lit.¹) mp 147–149 °C).

Ethyl 3-[1-Cyano-7-methyl-2-(ethylthio)indolizin-3-yl]acrylate (**4g**): 18% (from **1b** and ethyl iodide (**2b**)), mp 126–128 °C. IR (KBr) cm^{-1} : 2211, 1707, 1622. ¹H-NMR (CDCl_3) δ : 1.28, 1.35 (each 3H, t, $J=7.0$ Hz), 2.45 (3H, s), 3.16, 4.34 (each 2H, q, $J=7.0$ Hz), 6.76 (1H, d, $J=16.0$ Hz), 6.84 (1H, dd, $J=7.0$, 2.0 Hz), 7.49 (1H, br s), 8.04 (1H, d, $J=16.0$ Hz), 8.32 (1H, d, $J=7.0$ Hz). Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 64.94; H, 5.77; N, 8.91.

Found: C, 64.97; H, 5.75; N, 8.73.

Ethyl 3-[2-Benzylthio-1-cyano-7-methylindolizin-3-yl]acrylate (**4h**): 56%, (from **1b** and benzyl bromide (**2c**)), mp 133–136 °C. IR (KBr) cm^{-1} : 2216, 1699, 1616. $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 2.44 (3H, s), 4.23 (2H, s), 4.31 (2H, q, $J=7.0$ Hz), 6.64 (1H, d, $J=16.0$ Hz), 6.84 (1H, dd, $J=7.0, 2.0$ Hz), 7.27 (5H, s), 7.48 (1H, br s), 7.85 (1H, d, $J=16.0$ Hz), 8.23 (1H, d, $J=7.0$ Hz). *Anal.* Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 70.19; H, 5.35; N, 7.44. Found: C, 70.24; H, 5.37; N, 7.37.

Ethyl 3-[1-Cyano-7-methyl-2-(*p*-methylbenzylthio)indolizin-3-yl]acrylate (**4i**): 31%, (from **1b** and *p*-methylbenzyl chloride (**2d**)), mp 138–140 °C. IR (KBr) cm^{-1} : 2214, 1701, 1616. $^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (3H, t, $J=7.0$ Hz), 2.29, 2.44 (each 3H, s), 4.21 (2H, s), 4.32 (2H, q, $J=7.0$ Hz), 6.60 (1H, d, $J=16.0$ Hz), 6.81 (1H, dd, $J=7.0, 2.0$ Hz), 7.12 (4H, s), 7.48 (1H, br s), 7.84 (1H, d, $J=16.0$ Hz), 8.23 (1H, d, $J=7.0$ Hz). *Anal.* Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 70.74; H, 5.68; N, 7.17. Found: C, 71.01; H, 5.76; N, 7.15.

Ethyl 3-[2-(*p*-Bromobenzylthio)-1-cyano-7-methylindolizin-3-yl]acrylate (**4j**): 33%, (from **1b** and *p*-bromobenzyl bromide (**2e**)), mp 131–133 °C. IR (KBr) cm^{-1} : 2209, 1698, 1613. $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 2.45 (3H, s), 4.17 (2H, s), 4.34 (2H, q, $J=7.0$ Hz), 6.62 (1H, d, $J=16.0$ Hz), 6.85 (1H, dd, $J=7.0, 2.0$ Hz), 7.0–7.5 (5H, m), 7.82 (1H, d, $J=16.0$ Hz), 8.25 (1H, d, $J=7.0$ Hz). *Anal.* Calcd for $\text{C}_{22}\text{H}_{19}\text{BrN}_2\text{O}_2\text{S}$: C, 58.03; H, 4.21; N, 6.15. Found: C, 58.09; H, 4.23; N, 6.01.

Ethyl 3-[1-Cyano-6,8-dimethyl-2-(methylthio)indolizin-3-yl]acrylate (**4k**): 45%, (from **1c** and methyl iodide (**2a**)), mp 117–119 °C (Lit.¹⁾ 116–119 °C.

Ethyl 3-[1-Cyano-2-ethylthio-6,8-dimethylindolizin-3-yl]acrylate (**4l**): 4%, (from **1c** and ethyl iodide (**2b**)), mp 113–115 °C. IR (KBr) cm^{-1} : 2213, 1715, 1613. $^1\text{H-NMR}$ (CDCl_3) δ : 1.27, 1.39 (each 3H, t, $J=7.0$ Hz), 2.36, 2.74 (each 3H, s), 3.06, 4.36 (each 2H, q, $J=7.0$ Hz), 6.90 (1H, d, $J=16.0$ Hz), 6.91 (1H, br s), 8.04 (1H, d, $J=16.0$ Hz), 8.09 (1H, br s). *Anal.* Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.78; H, 6.16; N, 8.57.

Ethyl 3-[2-Benzylthio-1-cyano-6,8-dimethylindolizin-3-yl]acrylate (**4m**): 36%, (from **1c** and benzyl bromide (**2c**)), mp 132–134 °C. IR (KBr) cm^{-1} : 2220, 1705, 1618. $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 2.33, 2.72 (each 3H, s), 4.19 (2H, s), 4.34 (2H, q, $J=7.0$ Hz), 6.74 (1H, d, $J=16.0$ Hz), 6.90 (1H, br s), 7.28 (5H, s), 7.84 (1H, d, $J=16.0$ Hz), 8.00 (1H, br s). *Anal.* Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 70.74; H, 5.68; N, 7.17. Found: C, 70.56; H, 5.63; N, 7.22.

Ethyl 3-[1-Cyano-6,8-dimethyl-2-(*p*-methylbenzylthio)indolizin-3-yl]acrylate (**4n**): 8%, (from **1c** and *p*-methylbenzyl chloride (**2d**)), mp 121–125 °C. IR (KBr) cm^{-1} : 2214, 1701, 1622. $^1\text{H-NMR}$ (CDCl_3) δ : 1.34 (3H, t, $J=7.0$ Hz), 2.29 (6H, s), 2.71 (3H, s), 4.12 (2H, s), 4.34 (2H, q, $J=7.0$ Hz), 6.72 (1H, d, $J=16.0$ Hz), 6.88 (1H, br s), 7.15 (4H, s), 7.85 (1H, d, $J=16.0$ Hz), 8.03 (1H, br s). *Anal.* Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$: C, 71.26; H, 5.98; N, 6.93. Found: C, 71.44; H, 6.00; N, 6.73.

Ethyl 3-[2-(*p*-Bromobenzylthio)-1-cyano-6,8-dimethylindolizin-3-yl]acrylate (**4o**): 44%, (from **1c** and *p*-bromobenzyl bromide (**2e**)), mp 139–141 °C. IR (KBr) cm^{-1} : 2213, 1709, 1615. $^1\text{H-NMR}$ (CDCl_3) δ : 1.38 (3H, t, $J=7.0$ Hz), 2.32, 2.72 (each 3H, s), 4.11 (2H, s), 4.34 (2H, q, $J=7.0$ Hz), 6.68 (1H, d, $J=16.0$ Hz), 6.90 (1H, br s), 7.0–7.5 (4H, m), 7.78 (1H, d, $J=16.0$ Hz), 8.00 (1H, br s). *Anal.* Calcd for $\text{C}_{23}\text{H}_{21}\text{BrN}_2\text{O}_2\text{S}$: C, 58.85; H, 4.51; N, 5.97. Found: C, 58.94; H, 4.42; N, 5.97.

Bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] Disulfide (**5a**): Trace, (from **1a** with **2c–e**), mp 266–268 °C. IR (KBr) cm^{-1} : 2206, 1680. $^1\text{H-NMR}$ (CDCl_3) δ : 1.51 (6H, t, $J=7.0$ Hz), 4.52 (4H, q, $J=7.0$ Hz), 6.46 (2H, br t, $J=7.0$ Hz), 7.32 (2H, br dd, $J=7.0, 9.0$ Hz), 8.14 (2H, br d, $J=9.0$ Hz), 8.16 (2H, d, $J=7.0$ Hz). *Anal.* Calcd for $\text{C}_{28}\text{H}_{18}\text{N}_4\text{O}_4\text{S}_4$: C, 55.80; H, 3.01; N, 9.30. Found: C, 56.00; H, 3.08; N, 9.02.

Bis[1-cyano-9-ethoxycarbonyl-7-methylthieno[3,4-*b*]indolizin-3-yl] Disulfide (**5b**): Trace, (from **1b** with **2c–e**), mp 268–273 °C. IR (KBr) cm^{-1} : 2204, 1682. $^1\text{H-NMR}$ (CDCl_3) δ : 1.51 (6H, t, $J=7.0$ Hz), 2.34 (6H,

s), 4.52 (4H, q, $J=7.0$ Hz), 6.16 (2H, dd, $J=7.0, 2.0$ Hz), 7.89 (2H, br s), 7.94 (2H, d, $J=7.0$ Hz). *Anal.* Calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_4\text{S}_4$: C, 57.12; H, 3.52; N, 8.88. Found: C, 56.92; H, 3.41; N, 8.59.

Crystallography of Ethyl 1-Cyano-3-ethylthio-7-methylthieno[3,4-*b*]indolizin-9-carboxylate (3g**)** A single crystal (0.24×0.30×0.66 mm) grown from CHCl_3 –hexane was used for the unit-cell determinations and the data collections of a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated MoK_α radiation ($\lambda=0.71069$ Å). Crystal data of **3g**: $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}_2$; $M=344.46$; triclinic, space group $\text{P}\bar{1}$ (#2), $Z=4$ with $a=11.773$ (2) Å, $b=18.871$ (2) Å, $c=7.610$ (2) Å, $\alpha=100.52^\circ$ (1), $\beta=96.47^\circ$ (1), $\gamma=88.77^\circ$ (1); $V=1651.8$ (5) Å³, and $D_{\text{calc}}=1.385$ g/cm³. All calculations were performed using the TEXSAN program.¹¹⁾ The structure was solved by a direct method (MITHRIL).¹²⁾ 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 0.059 and 0.061 for 4049 ($I>2.00\sigma(I)$) observed reflections, respectively.

Crystallography of Bis(1-cyano-9-ethoxycarbonyl-7-methylthieno[3,4-*b*]indolizin-3-yl) Disulfide (5b**)** A single crystal (0.14×0.26×0.48 mm) grown from CHCl_3 –hexane was used for the unit-cell determinations and the data collections of a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated MoK_α radiation ($\lambda=0.71069$ Å). Crystal data of **5b**: $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_4\text{S}_4$; $M=630.77$; triclinic, space group $\text{P}\bar{1}$ (#2), $Z=2$ with $a=10.930$ (4) Å, $b=14.033$ (4) Å, $c=10.340$ (4) Å, $\alpha=92.42^\circ$ (3), $\beta=108.11^\circ$ (3), $\gamma=72.18^\circ$ (3); $V=1432.6$ (9) Å³, and $D_{\text{calc}}=1.462$ g/cm³. All calculations were performed using the TEXSAN program.¹¹⁾ The structure was solved by a direct method (MITHRIL).¹²⁾ The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R - and R_w -factors after full-matrix least-squares refinements were 0.065 and 0.065 for 3008 ($I>2.00\sigma(I)$) observed reflections, respectively.

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