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PREPARATION OF NEW NITROGEN-BRIDGED HETEROCYCLES. 47.[1] REACTIONS OF 2-INDOLIZINE-THIOLATES WITH ACETYLENIC COMPOUNDS

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Abstract - The reactions of potassium 2-indolizinethiolates having an ester group at the 3-position with some electron deficient acetylenic compounds were investigated. Their Michael additions or Michael addition-cyclizations proceeded with the elimination of an ester group to provide the corresponding 2-vinylthioindolizine and 4*H*-thiino[2,3-*b*]-indolizin-4-one derivatives.

INTRODUCTION

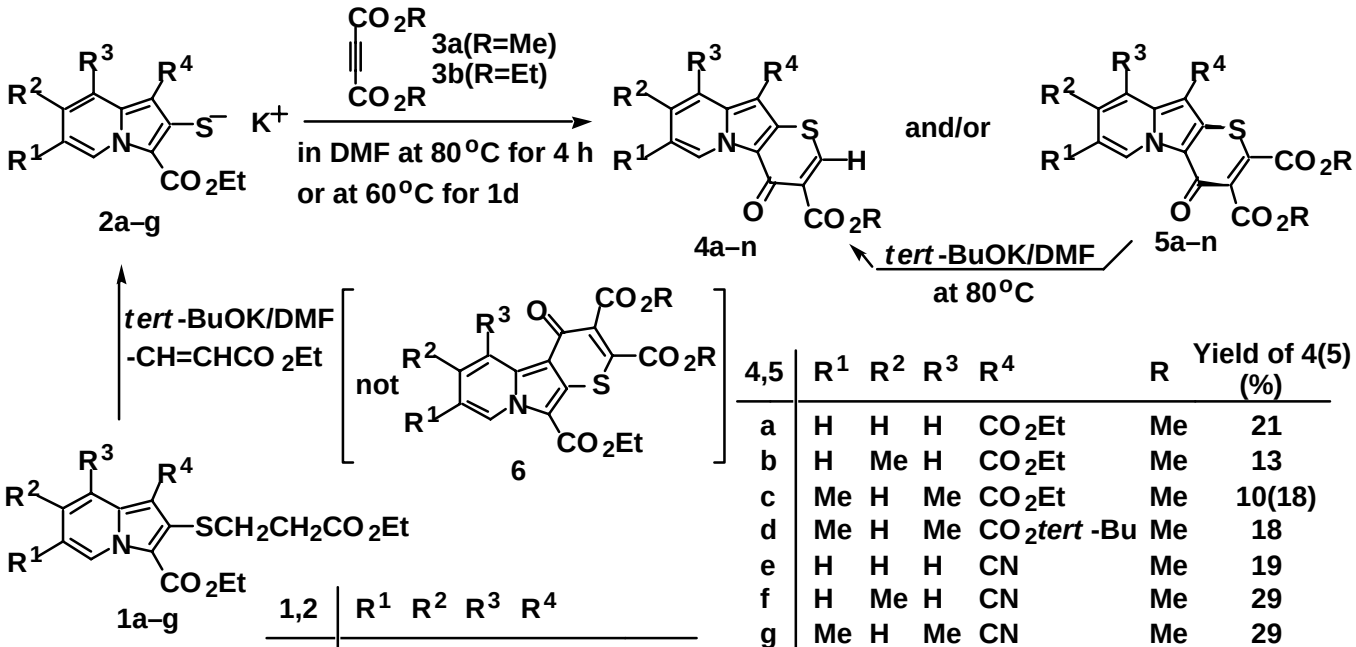
Potassium 2-indolizinethiolates and the related compounds are very useful precursors for the preparations of various functionalized and heterocycle-fused indolizine derivatives.[2] In general, the reactions of 2-indolizinethiolates with alkyl halides smoothly proceed to give the corresponding *S*-alkylated products in good yields,[2a,b,d] but those with unsaturated substrates do not necessarily provide good results because of the presence of its reverse process (β-elimination).[2c] As a part of our synthetic programs of new nitrogen-bridged heterocycles, we recently examined the reactions of these 2-indolizinethiolates with electron-poor alkynes such as dialkyl acetylenedicarboxylates and ethyl propiolate, and found that they afforded some interesting products depending upon the reaction temperature, though their yields were low to moderate. In this paper we report the syntheses of 2-vinylthioindolizine and 4*H*-thiino[2,3-*b*]indolizin-4-one derivatives from the title reactions.

RESULTS AND DISCUSSION

Since we previously observed the formation of 2,3-dihydro-4*H*-1,3-thiazino[6,5-*b*]indolizin-4-one derivatives from the reactions of potassium 3-ethoxycarbonyl-2-indolizinethiolates (**2**) with some isothiocyanates and isocyanates,[1c] we expected that 4*H*-thiino[2,3-*b*]indolizin-4-

† Dedicated to Professor Teruaki Mukaiyama in pre-celebration of his 73th birthday.

one derivatives might be formed from the reactions of **2** with electron-poor alkynes through a similar addition-cyclization path. Actually, the reactions of potassium 3-ethoxycarbonyl-2-indolizinethiolates (**2a**–**g**), readily available from the treatment of ethyl 2-[(2-ethoxycarbonylethyl)thio]indolizine-3-carboxylates (**1a**–**g**) with potassium *tert*-butoxide in DMF,[2] with dimethyl (**3a**) and diethyl acetylenedicarboxylate (**3b**) at 80°C for 4 h afforded the corresponding addition-cyclization products (**4a**–**n**) with strong fluorescence in 10–33% yields, respectively. Interestingly, when their reaction time at 80₀C was shortened or their reaction temperature was lowered to 60°C, the mixtures of the same **4a**–**n** and another type of adducts (**5a**–**n**) were formed, and only three compounds (**5c**,**h**,**j**) were isolated as the sole product from the reactions of **2a**,**c** with **3a**,**b** at 60°C. We also found that the treatment of adducts (**5a-n**) with potassium *tert*-butoxide in DMF at 80°C gave compounds (**4a**–**n**). Other regioisomers such as **6** in these reactions could not be detected at all. These results are shown in Scheme 1.



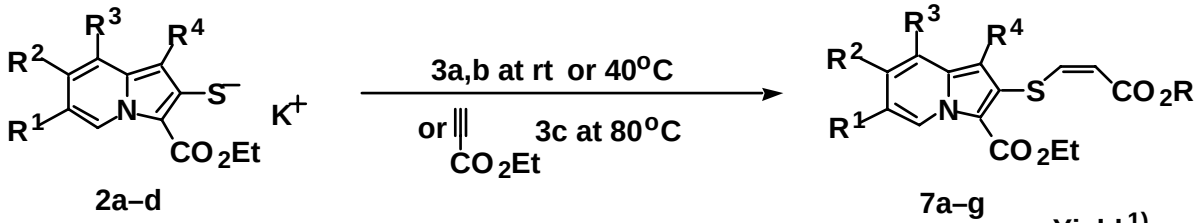
1,2	R^1	R^2	R^3	R^4
a	H	H	H	CO_2Et
b	H	Me	H	CO_2Et
c	Me	H	Me	CO_2Et
d	Me	H	Me	CO_2*tert*-Bu
e	H	H	H	CN
f	H	Me	H	CN
g	Me	H	Me	CN

4,5	R^1	R^2	R^3	R^4	R	Yield of 4(5) (%)
a	H	H	H	CO_2Et	Me	21
b	H	Me	H	CO_2Et	Me	13
c	Me	H	Me	CO_2Et	Me	10(18)
d	Me	H	Me	CO_2*tert*-Bu	Me	18
e	H	H	H	CN	Me	19
f	H	Me	H	CN	Me	29
g	Me	H	Me	CN	Me	29
h	H	H	H	CO_2Et	Et	20(16)
i	H	Me	H	CO_2Et	Et	14
j	Me	H	Me	CO_2Et	Et	19(11)
k	Me	H	Me	CO_2*tert*-Bu	Et	25
l	H	H	H	CN	Et	28
m	H	Me	H	CN	Et	18
n	Me	H	Me	CN	Et	33

Scheme 1

On the other hand, the reactions of potassium 2-indolizinethiolates (**2a**–**g**) and dialkyl acetylenedicarboxylates (**3a**,**b**) at room temperature or at 40°C did not afford tricyclic products such as **4a**–**n** and **5a**–**n** or corresponding primary Michael adducts such as 2-[[(1,2-bis(alkoxycarbonyl)vinyl]thio]indolizines (**9**, see Scheme 3), but, instead of them,2- [(2-

alkoxycarbonylvinyl)thio]indolizine derivatives (**7a**–**h**) were formed in 14–35% yields. The same products (**7e**–**g**) were also obtained in 23–39% yields from the reactions of **2a**–**c** with ethyl propiolate (**3c**) in DMF at 80°C (Scheme 2).



2a–d

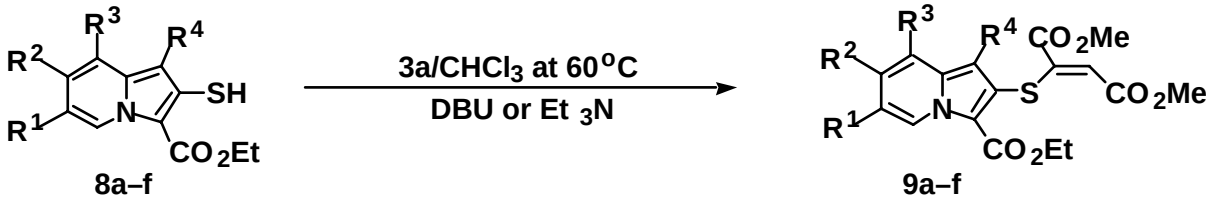
7a–g

7	R^1	R^2	R^3	R^4	R	Yield [1] (%)
a	H	H	H	CO_2Et	Me	18
b	H	Me	H	CO_2Et	Me	17
c	Me	H	Me	CO_2Et	Me	14
d	Me	H	Me	CO_2*tert* -Bu	Me	14
e	H	H	H	CO_2Et	Et	35(39)[2]
f	H	Me	H	CO_2Et	Et	30(37)[2]
g	Me	H	Me	CO_2Et	Et	19(23)[2]

1) From 3a,b. 2) From 3c.

Scheme 2

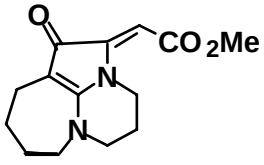
Primary Michael adducts, 2-[[1,2-bis(methoxycarbonyl)vinyl]thio]indolizine derivatives **(9a**–**f**), could be prepared from the reactions of 2-indolizinethiols (**8a**–**f**) with dimethyl acetylenedicarboxylate (**3a**) in the presence of other base, DBU or triethylamine. Although the effect of DBU in these reactions was higher than that of triethylamine, a by-product, methyl 2-oxo-4,8-diazatricyclo[6.4.1.$0^{4,13}$]tridec-$\Delta^{1,13}$-en-3-ylideneacetate (**10**),[3] in the reactions using DBU as a base was always formed in 20–25% yields (See Scheme 3).



8a–f

9a–f

8	R^1	R^2	R^3	R^4
a	H	H	H	CO_2Et
b	H	Me	H	CO_2Et
c	Me	H	Me	CO_2Et
d	H	H	H	CN
e	H	Me	H	CN
f	Me	H	Me	CN



10(20–25%)

9	R^1	R^2	R^3	R^4	Base	Yield (%)
a	H	H	H	CO_2Et	DBU	32
b	H	Me	H	CO_2Et	DBU	52
c	Me	H	Me	CO_2Et	Et_3N	20
d	H	H	H	CN	DBU	21
e	H	Me	H	CN	Et_3N	13
f	Me	H	Me	CN	DBU	25

Scheme 3

The structural assignments for tricyclic adducts (**4a**–**n**) and (**5c**,**h**,**j**) and 2-vinylthioindolizines (**7a**–**h**) and (**9a**–**f**) were mainly accomplished by their elemental and spectral analyses. For example, their elemental analyses coincided with the compositions for our proposed structures and IR spectra revealed the presences of the cyano (2212–2222 cm^{-1}) and/or carbonyl groups (1658–1743 cm^{-1}). The remarkable characteristics in ^{1}H-NMR spectra of **4a-n** are that they have a singlet signal at near δ 8.7 due to a proton on the thiine ring and only one methoxy or ethoxy signals derived from acetylenic compounds (**3a**,**b**), while that of **5c**,**h**,**j** is the conservation of the two ester signals. In addition, the loss of the ethoxy signals of the 3-ester substituent and the inertness of the 1-cyano group or the 1-(*tert*-butoxycarbonyl) group in 2-indolizinethiolates (**2d**–**g**) during these reactions were distinctly indicated by the IR and ^{1}H-NMR spectra, indicating clearly the orientation of the cyclization. We have already reported the theoretical and practical results that the electrophilic reactivity of the 3-ester carbonyl group in dialkyl 1,3-indolizinedicarboxylate derivatives is higher than the 1-ester carbonyl one.[2b,d] From these data, we concluded that compounds (**4a**–**n**) and (**5a**-**n**) have 4*H*-thiino[2,3-*b*]indolizin-4-one structures. However, we could not decided whether the structures of **4a**-**n** are alkyl 4-oxo-4*H*-thiino[2,3-*b*]indolizine-2-carboxylates or -3-carboxylates. To determine the decarbalkoxylation point in **4a**–**n** the X-Ray analysis of one compound (**4b**) was carried out, and the structure, alkyl 4-oxo-4*H*-thiino[2,3-*b*]indolizine-3-carboxylate, was finally confirmed. The ORTEP drawing of **4b** is shown in Figure 1.[4]

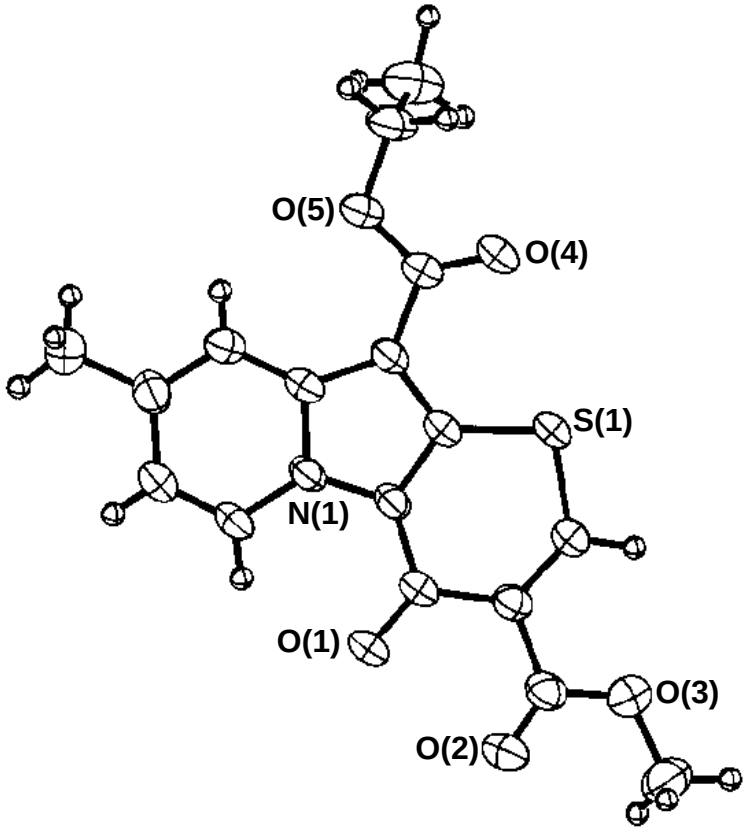


Figure 1. ORTEP drawing of **4b**

The structures of **7a**–**h** were decided to be *Z*-2-[(2-alkoxycarbonylvinyl)thio]indolizine derivative because their ^{1}H-NMR spectra showed characteristic AB-type vinyl proton signals coupled with 10.0 Hz (*cis*-configuration) at near δ 5.9 and 7.2 together with other proton signals characteristic of indolizine skeleton. Similarly, the structures of **9a**–**f** were assigned to be *Z*-2-[[1,2-bis(methoxycarbonyl)vinyl]thio]indolizine derivatives because of the indication of a singlet signal (δ 6.46–6.91) due to the vinyl proton in their ^{1}H-NMR spectra and its large down-field shift (0.6–1.0 ppm) compared with that (near δ 5.9) in **7a**–**h**. Such large down-field shift must be caused by an ester carbonyl group which presents at the *cis* position. This assumption was proved by X-Ray analysis of compounds (**9b**). The ORTEP drawing of **9b** is shown in Figure 2.[4]

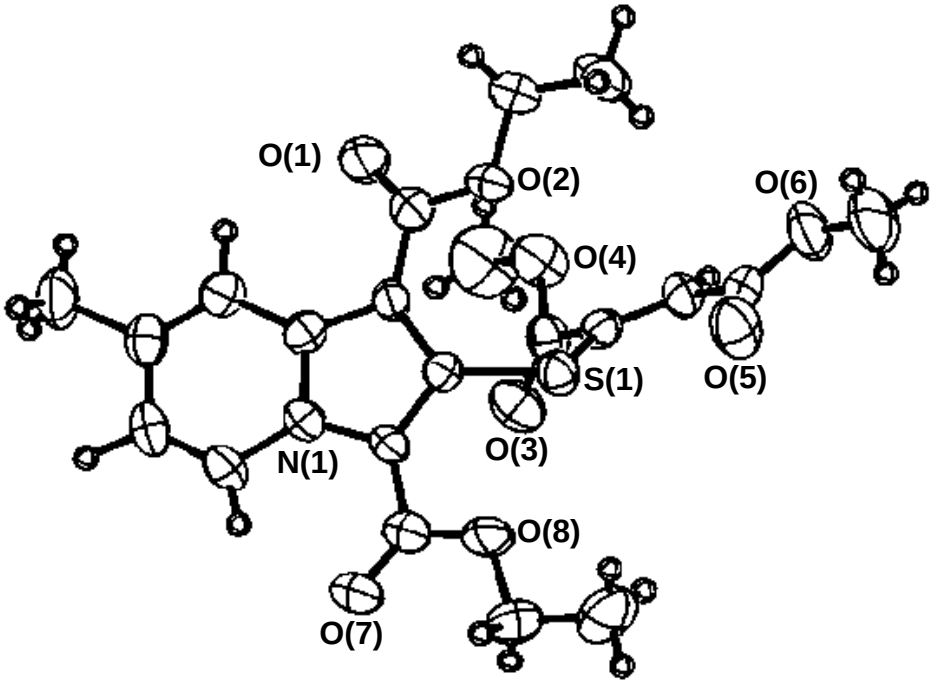
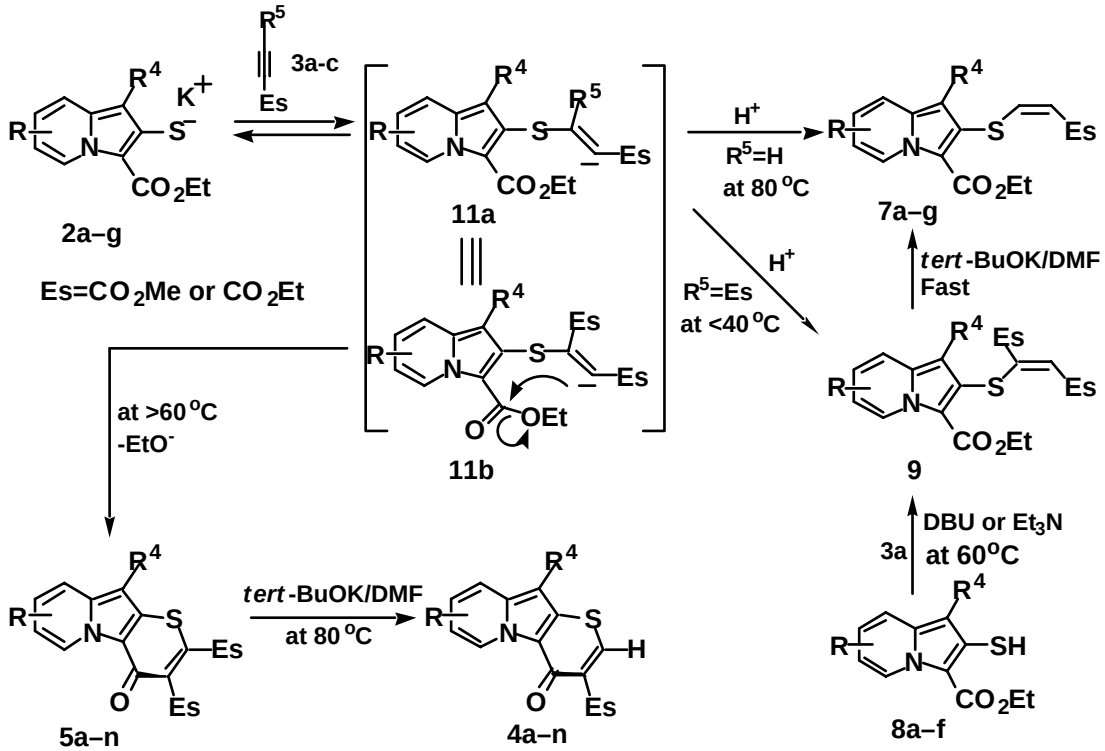


Figure 2. ORTEP drawing of **9b**

Mechanistically, the transformation from 2-indolizinethiolates (**2a**–**g**) to alkyl4-oxo-4*H*-thiino[2,3-*b*]indolizine-3-carboxylates (**4a**–**n**) and to *Z*-2-[(2-alkoxycarbonylvinyl)thio]-indolizines (**8a**–**f**) seems to proceed *via* a Michael addition–cyclization–decarbalkoxylation and Michael addition–decarbalkoxylation sequences, respectively (Scheme 4). The corresponding intermediates such as **5a**–**n** and **9a**–**f** were actually isolated or detected under modified reaction conditions. The temperature dependency of the products indicates that the irreversible cyclization process with the elimination of an ethoxide ion from the Michael addition intermediates (**11b**) to 4*H*-thiino[2,3-*b*]indolizin-4-one (**5a**–**n**) needs considerably high energy, and the low yields of products (**4**, **5**, **8**, and **9**) may reflect the equilibrium (Michael addition–β-elimination) between the intermediates (**11a**) and reactants (**2a**–**g**) and (**3a-c**) under the strong alkaline conditions employed here. On the other hand, direct

decarbalkoxylations of some organic esters are known,[5] but the attainment of such conversion without any changes toward other groups and at a specific position is rare.[5e] Though its mechanistic detail and the origin of the regiospecificity are still unclear, direct decarbalkoxylation like this is very interesting and useful in organic synthesis because of the simple procedure and the comparatively mild conditions.



Scheme 4

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 spectrometer (60 MHz) in deuteriochloroform with tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 IR spectrophotometer.

General procedure for the syntheses of 4*H*-thiino[2,3-*b*]indolizin-4-one derivatives

Method A: Potassium *tert*-butoxide (0.168g, 1.5 mmol) was added to a solution (3 mL) of ethyl 2-[(2-ethoxycarbonylethyl)thio]indolizine-3-carboxylate (**1**, 1 mmol) in DMF (2 mL) . After the mixture was heated at 80 °C in an water bath for 15 min and ethyl acrylate generated was then completely removed at reduced pressure, dialkyl acetylenedicarboxylate (**3a**,**b**, 2 mmol) was added to the resulting potassium 2-indolizinethiolate. The reaction mixture was heated

at 80 ^{o}C in a water bath for 4 h. The mixture was acidified with diluted hydrochloric acid (2M, 10mL). The precipitate separated was collected by suction and washed with two portions of water (10 mL). The precipitate was dissolved in chloroform and filtered through a phase separating filter. The filtrate was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using chloroform as an eluent. The yellow chloroform fractions were combined and concentrated at reduced pressure. Recrystallization of the crude product from chloroform or chloroform–hexane provided the corresponding alkyl 4-oxo-4*H*-thiino[2,3-*b*]indolizin-3-carboxylate derivatives (**4a**–**n**) as orange needles with strong fluorescence.

4a: yield 21% (from **1a** and **3a**), mp 174—176^{o}C ($CHCl_3$-hexane); IR (KBr) 1697, 1732 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.54 (3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 4.06 (3H, s, OCH_3), 4.54 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.24 (1H, br t, *J*=7.0 Hz, 7-H), 7.70 (1H, br q, *J*=7.0, 9.0 Hz, 8-H), 8.55 (1H, br d, *J*=9.0 Hz, 9-H), 8.79 (1H, s, 2-H), 10.51 (1H, br d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.95; N, 4.23. Found: C, 58.03; H, 4.09; N, 4.06.

4b: yield 13% (from **1b** and **3a**), mp 193—195^{o}C ($CHCl_3$-hexane); IR (KBr) 1697, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.53 (3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.59 (3H, s, 8-CH_3), 4.02 (3H, s, OCH_3), 4.55 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.04 (1H, dd, *J*=7.0, 2.0 Hz, 7-H), 8.27 (1H, br s, 9-H), 8.74 (1H, s, 2-H), 10.37 (1H, d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06 Found: C, 59.26; H, 4.39; N, 3.91.

4c: yield 10% (from **1c** and **3a**), mp 141—143^{o}C ($CHCl_3$-hexane); IR (KBr) 1658, 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.50 (3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.41 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 4.02 (3H, s, OCH_3), 4.50 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.27 (1H, br s, 8-H), 8.69 (1H, s, 2-H), 10.41 (1H, br s, 6-H). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.39; H, 4.77; N, 3.68.

4d: yield 18% (from **1d** and **3a**), mp 199—201^{o}C ($CHCl_3$-hexane); IR (KBr) 1703, 1743 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.71 (9H, s, $OC(CH_3)_3$, 2.40 (3H, s, 7-CH_3), 2.83 (3H, s, 9-CH_3), 4.01 (3H, s, OCH_3), 7.28 (1H, br s, 8-H), 8.68 (1H, s, 2-H), 10.41 (1H, br s, 6-H). *Anal.* Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62. Found: C, 62.12; H, 5.41; N, 3.81.

4e: yield 19% (from **1e** and **3a**), mp 247—249^{o}C ($CHCl_3$); IR (KBr) 1687, 2214 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 4.02 (3H, s, OCH_3), 7.22 (1H, br t, *J*=7.0 Hz, 7-H), 7.69 (1H, br q, *J*=7.0, 9.0 Hz, 8-H), 7.96 (1H, br d, *J*=9.0 Hz, 9-H), 8.71 (1H, s, 2-H), 10.34 (1H, br s, 6-H). *Anal.* Calcd for $C_{14}H_8N_2O_3S$: C, 59.15; H, 2.84; N, 9.85. Found: C, 59.17; H, 2.80; N, 9.86.

4f: yield 29% (from **1f** and **3a**), mp 248—250^{o}C ($CHCl_3$); IR (KBr) 1703, 2214 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 4.05 (3H, s, OCH_3), 2.60 (3H, s, 8-CH_3), 7.09 (1H, dd, *J*=7.0, 2.0 Hz, 7-H), 7.70 (1H, br s, 9-H), 8.71 (1H, s, 2-H), 10.24 (1H, d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{15}H_{10}N_2O_3S$: C, 60.39; H, 3.38; N, 9.39. Found: C, 60.36; H, 3.40; N, 9.40.

4g: yield 29% (from **1g** and **3a**), mp 145—147^{o}C ($CHCl_3$); IR (KBr) 1734, 2214 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 4.01 (3H, s, OCH_3), 2.41 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 7.28 (1H, br s, 8-H), 8.69

(1H, s, 2-H), 10.11 (1H, br s, 6-H). *Anal.* Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.82; H, 3.84; N, 8.71.

4h: yield 20% (from **1a** and **3b**), mp 149—151°C ($CHCl_3$-hexane); IR (KBr) 1674, 1728 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.45, 1.54 (each 3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 4.51, 4.57 (each 2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.19 (1H, br t, *J*=7.0 Hz, 7-H), 7.68 (1H, br q, *J*=7.0, 9.0 Hz, 8-H), 8.50 (1H, br d, *J*=9.0 Hz, 9-H), 8.70 (1H, s, 2-H), 10.49 (1H, br d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{17}H_{15}NO_5S$: C, C, 59.12; H, 4.38; N, 4.06. Found: C, 59.09; H, 4.47; N, 4.00.

4i: yield 14% (from **1b** and **3b**), mp 165—167°C ($CHCl_3$-hexane); IR (KBr) 1670, 1732 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.45, 1.52 (each 3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.56 (3H, s, 8-CH_3), 4.45, 4.49 (each 2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.02 (1H, dd, *J*=7.0, 2.0 Hz, 7-H), 8.23 (1H, br s, 9-H), 8.64 (1H, s, 2-H), 10.31 (1H, d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.05; H, 4.74; N, 3.89.

4j: yield 19% (from **1c** and **3b**), mp 156—158°C ($CHCl_3$-hexane); IR (KBr) 1699, 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.44, 1.49 (each 3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.40 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 4.51, 4.51 (each 2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.27 (1H, br s, 8-H), 8.61 (1H, s, 2-H), 10.38 (1H, br s, 6-H). *Anal.* Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C, 61.20; H, 5.22; N, 3.64.

4k: yield 25% (from **1d** and **3b**), mp 152—154°C ($CHCl_3$-hexane); IR (KBr) 1658, 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.41(3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 1.71 (9H, s, $OC(CH_3)_3$, 2.39 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 4.01 (3H, s, OCH_3), 4.49 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.27 (1H, br s, 8-H), 8.63 (1H, s, 2-H), 10.43 (1H, br s, 6-H). *Anal.* Calcd for $C_{21}H_{23}NO_5S$: C, 62.88; H, 5.77; N, 3.49. Found: C, 63.01; H, 5.88; N, 3.20.

4l: yield 28% (from **1e** and **3b**), mp 196—198°C ($CHCl_3$); IR (KBr) 1691, 2214 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.45 (3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 4.50 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.24 (1H, br t, *J*=7.0 Hz, 7-H), 7.80 (1H, br q, *J*=7.0, 9.0 Hz, 8-H), 7.97 (1H, br d, *J*=9.0 Hz, 9-H), 8.67 (1H, s, 2-H), 10.34 (1H, br s, 6-H). *Anal.* Calcd for $C_{15}H_{10}N_2O_3S$: C, 60.39; H, 3.38; N, 9.39. Found: C, 60.56; H, 3.38; N, 9.22.

4m: yield 18% (from **1f** and **3b**), mp 217—219°C ($CHCl_3$); IR (KBr) 1693, 2214 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.45(3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.58 (3H, s, 8-CH_3), 4.48 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.06 (1H, dd, *J*=7.0, 2.0 Hz, 7-H), 7.69 (1H, br s, 9-H), 8.61 (1H, s, 2-H), 10.19 (1H, d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.58; H, 4.03; N,8.77.

4n: yield 33% (from **1g** and **3b**), mp 145—147°C ($CHCl_3$); IR (KBr) 1695, 2212 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.43 (3H, t, *J*=7.0 Hz, $OCH_2C\mathit{H_3}$), 2.42 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 4.50 (2H, q, *J*=7.0 Hz, $OC\mathit{H_2}CH_3$), 7.27 (1H, br s, 8-H), 8.63 (1H, s, 2-H), 10.08 (1H, br s, 6-H). *Anal.* Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.72; H, 4.32; N, 8.42.

Method B: The mixtures of potassium 2-indolizinethiolates, obtained from indolizines (**1a**,**c**) in Method A, and acetylenic compound (**3a**,**b**, 2 mmol) were heated at 60 °C in a water bath for 1 d. Usual work-ups of the resulting reaction mixtures gave dialkyl4-oxo-4*H*-thiino[2,3-

b]indolizine-2,3-dicarboxylate derivatives (**5c**,**h**,**j**) as orange needles.
On the other hand, the reactions other than compounds (**5c**,**h**,**j**) always gave complex mixtures of **4**, **5**, and 2-indolizinethiols (**8**) and their separations were unsuccessful.[6]

5c: yield 18% (from **1c** and **3a**), mp 145—147°C ($CHCl_3$-hexane); IR (KBr) 1664, 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.51 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.40 (3H, s, 7-CH_3), 2.83 (3H, s, 9-CH_3), 4.03, 4.06 (each 3H, s, OCH_3), 4.53 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.32 (1H, br s, 8-H), 10.22 (1H, br s, 6-H). *Anal.* Calcd for $C_{20}H_{19}NO_7S$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.81; H, 4.62; N, 3.12.
5h: yield 16% (from **1a** and **3b**), mp 141—143°C ($CHCl_3$-hexane); IR (KBr) 1684, 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.46, 1.52 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 4.50, 4.57 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.18 (1H, br t, *J*=7.0 Hz, 7-H), 7.69 (1H, br q, *J*=7.0, 9.0 Hz, 8-H), 8.48 (1H, br d, *J*=9.0 Hz, 9-H), 10.29 (1H, br d, *J*=7.0 Hz, 6-H). *Anal.* Calcd for $C_{20}H_{19}NO_7S$: C, 57.55; H, 4.59; N, 3.36. Found: C, 57.50; H, 4.53; N, 3.30.
5j: yield 11% (from **1c** and **3b**), mp 140—142°C ($CHCl_3$-hexane); IR (KBr) 1705, 1728 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.46, 1.51 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.39 (3H, s, 7-CH_3), 2.82 (3H, s, 9-CH_3), 4.49, 4.53 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 7.30 (1H, br s, 7-H), 10.22 (1H, br s, 6-H). *Anal.* Calcd for $C_{22}H_{23}NO_7S$: C, 59.31; H, 5.20; N, 3.14. Found: C, 59.34; H, 5.15; N, 3.05.

General procedure for the syntheses of 2-vinylthioindolizine derivatives
Method A: The mixture of potassium 2-indolizinethiolate (**2**), obtained from indolizines (**1**, 1mmol) in above reactions, and acetylenic compound (**3a**,**b**, 2 mmol) was treated at rt or at below 40 °C for 1 d, or the mixture of **2** and ethyl propiolate (**3c**, 2 mmol) was heated at 80 °C in a water bath for 4 h. Usual work-ups of the resulting reaction mixtures afforded 2-[(2-(alkoxycarbonylvinyl)thiol] indolizine derivatives (**7a**–**h**) as pale yellow needles.

7a: yield 18% (from **2a** and **3a**), mp 121—123°C ($CHCl_3$-hexane); IR (KBr) 1688, 1699 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.41, 1.41 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 4.43, 4.46 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.92 (1H, d, *J*=10.0 Hz, vinyl-H), 7.07 (1H, br t, *J*=7.0 Hz, 6-H), 7.20 (1H, d, *J*=10.0 Hz, vinyl-H), 7.41 (1H, br q, *J*=7.0, 9.0 Hz, 7-H), 8.45 (1H, br d, *J*=9.0 Hz, Hz, 8-H), 9.64 (1H, br d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71. Found: C, 57.13; H, 5.05; N, 3.56.
7b: yield 17% (from **2b** and **3a**), mp 141—143°C ($CHCl_3$-hexane); IR (KBr) 1670, 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.42, 1.42 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.50 (3H, s, 7-CH_3), 3.88 (3H, s, OCH_3), 4.46, 4.48 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.98 (1H, d, *J*=10.0 Hz, vinyl-H), 6.97 (1H, dd, *J*=7.0, 2.0 Hz, 6-H), 7.26 (1H, d, *J*=10.0 Hz, vinyl-H), 8.32 (1H, br s, 8-H), 9.62 (1H, d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.17; H, 5.39; N, 3.43.
7c: yield 14% (from **2c** and **3a**), mp 130—132°C ($CHCl_3$-hexane); IR (KBr) 1662, 1739 cm^{-1};

^{1}H-NMR ($CDCl_3$) 1.39, 1.39 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.33 (3H, s, 6-CH_3), 2.49 (3H, s, 8-CH_3), 3.83 (3H, s, OCH_3), 4.42, 4.42 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.90 (1H, d, *J*=10.0 Hz, vinyl-H), 6.92 (1H, br s, 7-H), 7.22 (1H, d, *J*=10.0 Hz, vinyl-H), 9.38 (1H, br s, 5-H). *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.29; H, 5.65; N, 3.21.

7d: yield 14% (from **2d** and **3a**), mp 130—132°C ($CHCl_3$-hexane); IR (KBr) 1662, 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.62 (9H, s, $OC(CH_3)_3$, 2.34 (3H, s, 6-CH_3), 2.52 (3H, s, 8-CH_3), 3.84 (3H, s, OCH_3), 5.91 (1H, d, *J*=10.0 Hz, vinyl-H), 6.92 (1H, br s, 7-H), 7.24 (1H, d, *J*=10.0 Hz, vinyl-H), 9.38 (1H, br s, 5-H). *Anal.* Calcd for $C_{22}H_{27}NO_6S$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.72; H, 6.20; N, 2.99.

7e: yield 35% (from **2a** and **3b**), 39% (from **1a** and **3c**), mp 95—97°C ($CHCl_3$-hexane); IR (KBr) 1668, 1703 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.35, 1.41, 1.41 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3),4.32, 4.46, 4.48 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.92 (1H, d, *J*=10.0 Hz, vinyl-H), 7.07 (1H, br t, *J*=7.0 Hz, 6-H), 7.17 (1H, d, *J*=10.0 Hz, vinyl-H), 7.42 (1H, br q, *J*=7.0, 9.0 Hz, 7-H), 8.40 (1H, br d, *J*=9.0 Hz, 8-H), 9.64 (1H, br d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.05; H, 5.37; N, 3.51.

7f: yield 30% (from **2b** and **3b**), 37% (from **1b** and **3c**), mp 111—113°C ($CHCl_3$-hexane); IR (KBr) 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.33, 1.40, 1.40 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 2.44 (3H, s, 7-CH_3), 4.32, 4.44, 4.44 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.94 (1H, d, *J*=10.0 Hz, vinyl-H), 6.92 (1H, dd, *J*=7.0, 2.0 Hz, 6-H), 7.20 (1H, d, *J*=10.0 Hz, vinyl-H), 8.27 (1H, br s, 8-H), 9.53 (1H, d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.38; H, 5.68; N, 3.35.

7g: yield 19% (from **2c** and **3b**), 23% (from **1c** and **3c**), mp 120—122°C ($CHCl_3$-hexane); IR (KBr) 1689, 1711 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.36, 1.39, 1.39 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3),2.34 (3H, s, 6-CH_3), 2.50 (3H, s, 8-CH_3), 4.31, 4.44, 4.44 (each 2H, q, *J*=7.0 Hz, OCH_2CH_3), 5.91(1H, d, *J*=10.0 Hz, vinyl-H), 6.94 (1H, br s, 7-H), 7.23 (1H, d, *J*=10.0 Hz, vinyl-H), 9.40 (1H, br s, 5-H). *Anal.* Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.00; H, 6.20; N, 3.24.

Method B: The chloroform solution (30 mL) of 2-indolizinethiol (**8a**–**f**, 1mmol),[2a] **3a** (2 mmol), and base (DBU or triethylamine, 0.1 g) was heated at the reflux temperature in a water bath for 1 d. The reaction mixture was concentrated at reduced pressure and the residual oil was separated by column chromatography on alumina using ether and then chloroform. The pale yellow or yellow chloroform fractions were combined and the solvent was removed. Recrystallization from chloroform-hexane provided 2-[(1,2-bis(alkoxycarbonylvinyl)thio]-indolizine derivatives (**9a**–**f**) as pale yellow needles. When DBU was used as a base in these reactions, methyl 2-oxo-4,8-diazatricyclo[6.4.1.0^{4,13}]tridec-$\Delta^{1,13}$-en-3-ylideneacetate (**10**) (mp 147–149 °C)[4] was also obtained in 21–25% yield as red needles.

9a: yield 32% (from **8a**, **3a**, and DBU), mp 94—95°C; IR (KBr) 1693, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.41, 1.41 (each 3H, t, *J*=7.0 Hz, OCH_2CH_3), 3.41, 3,87 (each 3H, s, OCH_3), 4.44, 4.46

(each 2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.51 (1H, s, vinyl-H), 7.05 (1H, br t, *J*=7.0 Hz, 6-H), 7.40 (1H, br q, *J*=7.0, 9.0 Hz, 7-H), 8.47 (1H, br d, *J*=9.0 Hz, 8-H), 9.69 (1H, br d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{20}H_{21}NO_8S$: C, 55.17; H, 4.86; N, 3.22. Found: C, 55.10; H, 4.93; N, 3.22.

9b: yield 52% (from **8b**, **3a**, and DBU), mp 120—122°C; IR (KBr) 1674, 1714, 1732 cm^{-1};^{1}H-NMR ($CDCl_3$) 1.39, 1.39 (each 3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.44 (3H, s, 7-CH$_3$), 3.40, 3.84 (each 3H, s, OCH$_3$), 4.43, 4.45 (each 2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.46 (1H, s, vinyl-H), 6.87 (1H, dd, *J*=7.0, 2.0 Hz, 6-H), 8.25 (1H, br s, 8-H), 9.52 (1H, d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{21}H_{23}NO_8S$: C, 56.12; H, 5.16; N, 3.12. Found: C, 56.34; H, 5.22; N, 2.82.

9c: yield 20% (from **8c**, **3a**, and triethylamine), mp 91—93°C; IR (KBr) 1676, 1714, 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.37, 1.44 (each 3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.35 (3H, s, 6-CH$_3$), 2.50 (3H, s, 8-CH$_3$), 3.43, 3.90 (each 3H, s, OCH$_3$), 4.47, 4.50 (each 2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.52 (1H, s, vinyl-H), 6.98 (1H, br s, 7-H), 9.48 (1H, br s, 5-H). *Anal.* Calcd for $C_{22}H_{25}NO_8S$: C, 57.01; H, 5.44; N, 3.02. Found: C, 56.97; H, 5.43; N, 2.85.

9d: yield 24% (from **8e**,**3a**, and DBU), mp 104—107°C; IR (KBr) 1689, 1732, 2222 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.41 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 3.61, 3.90 (each 3H, s, OCH$_3$), 4.49 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.91 (1H, s, vinyl-H), 7.13 (1H, br t, *J*=7.0 Hz, 6-H), 7.50 (1H, br q, *J*=7.0, 9.0 Hz, 7-H), 7.87 (1H, br d, *J*=9.0 Hz, 8-H), 9.74 (1H, br d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{18}H_{16}N_2O_6S$: C, 55.66; H, 4.15; N, 7.21. Found: C, 55.36; H, 4.16; N, 7.17.

9e: yield 13% (from **2b**, **3b**, and triethylamine), mp 130—132°C; IR (KBr) 1687, 1732, 2218 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.39 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.48 (3H, s, 7-CH$_3$), 3.58, 3.87 (each 3H, s, OCH$_3$), 4.45 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.84 (1H, s, vinyl-H), 6.95 (1H, dd, *J*=7.0, 2.0 Hz, 6-H), 7.55 (1H, br s, 8-H), 9.56 (1H, d, *J*=7.0 Hz, 5-H). *Anal.* Calcd for $C_{19}H_{18}N_2O_6S$: C, 56.71; H, 4.51; N, 7.02. Found: C, 56.96; H, 4.61; N, 7.02.

9f: yield 25% (from **2c**, **3b**, and DBU), mp 134—136°C; IR (KBr) 1689, 1730, 2218 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.38 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 2.37 (3H, s, 6-CH$_3$), 2.77 (3H, s, 8-CH$_3$), 3.54, 3.88 (each 3H, s, OCH$_3$), 4.44 (2H, q, *J*=7.0 Hz, OC*H*$_2$CH$_3$), 6.70 (1H, s, 7.02 (1H, br s, 7-H), 9.38 (1H, br s, 5-H). *Anal.* Calcd for $C_{20}H_{20}N_2O_6S$: C, 57.68; H, 4.84; N, 6.73. Found: C, 57.39; H, 4.98; N, 6.47.

Crystallography of 10-ethyl 3-methyl 8-methyl-4-oxo-4*H*-thiino[2,3-*b*]indolizine-3,10-dicarboxylate (4b)

A single crystal (0.24x0.68x0.92 mm) grown from $CHCl_3$–hexane was used for the unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo*K*α radiation (λ=0.71069 Å). Crystal data of **5d**: $C_{17}H_{15}NO_5S$; *M*=345.37; monoclinic, space group $P2_1/a$ (#14), *Z*=4 with *a*=8.812 (2) Å, *b*=18.792 (2) Å, *c*=10.146 (2) Å; β=111.45 (1)°; *V*=1563.7 (5) Å^3, and D_{calc}=1.467 g/cm^3. All calculations were performed using the TEXSAN program.[7] The structure was solved by a direct method (SIR).[8] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotopically. The final *R*- and R_w-factors after full-matrix least-squares refinements were 0.047

and 0.056, respectively, for 2721 (I>2.00σ(I)) observed reflections.

Crystallography of diethyl 7-methyl-2-[(1,2-bis(methoxycarbonyl)vinyl]thio-indolizine-1,3-dicarboxylate (9b)

A single crystal (0.06x0.34x0.66 mm) grown from $CHCl_3$–hexane was used for the unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo*K*α radiation (λ=0.71069 Å). Crystal data of **9b**: $C_{21}H_{23}NO_8S$; *M*=449.47; triclinic, space group *P*-1 (#2), *Z*=2 with *a*=11.12 (1) Å, *b*=12.69 (1) Å, *c*=9.017 (8) Å; α=95.96° (9), β=112.20 (8)°, γ=69.77 (8)°; *V*=1104 (2) Å^3, and D_{calc}=1.352 g/cm^3. All calculations were performed using the TEXSAN program.[7] The structure was solved by a direct method (SIR).[8] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotopically. The final *R*- and R_w-factors after full-matrix least-squares refinements were 0.062 and 0.059, respectively, for 2206 (I>2.00s(I)) observed reflections.

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