FIRST RING CONTRACTION-DESULFURIZATION OF 1-(ARYL-CARBONYL)PYRIDO[2,1-*c*]-1,4-THIAZINES TO 1-(ARYLCARBONYL)-INDOLIZINES AND ITS APPLICATION TO 3-ARYLTHIENO[3,2-*a*]-INDOLIZINE SYNTHESIS[1]

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Dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

The ring contraction-desulfurization route from transient 1-(arylcarbonyl)-pyrido[2,1-*c*]-1,4-thiazine intermediates, generated in situ from the treatment of the corresponding pyridinium salts with a base and then a dehydrogenation agent, to 1-(arylcarbonyl)indolizines was first observed.   By using this route three 1-arylcarbonyl-6,8-dimethylindolizines having the protected 2-thiol group were prepared and their transformation to 2-acyl-3-arylthieno[3,2-*a*]indolizine derivatives were performed in good yields.

We previously developed a novel and convenient synthetic method for various functionalized indolizine derivatives.[2—6]   We also disclosed that this method involves transient pyrido[2,1-*c*]-1,4-thiazine intermediates (**I**) with an anti-aromatic 12   system and the intermediates (**Ia**) bearing the 1-arylcarbonyl group select the ring contraction-rearrangement route (Path a) to provide the 1-(arylcarbonylthio)indolizines (**II**), and those (**Ib**) possessing the 1-cyano, 1-alkoxycarbonyl, or 1-aryl group undergo the ring contraction-desulfurization route (Path b) to afford the corresponding products (**III**) (See Figure 1).[2-4]   However, we could not explain the reason why such a difference in the reactivity

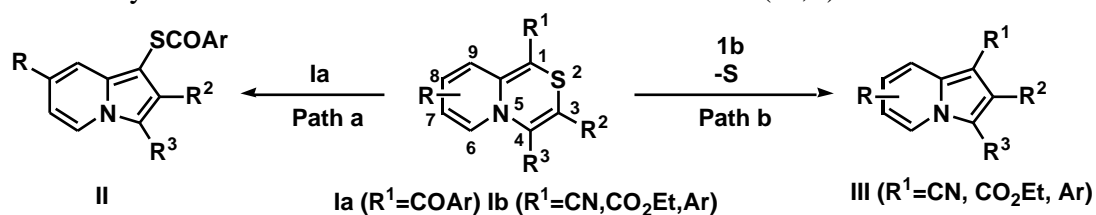was caused by the kind of 1-substituent in these intermediates (**Ia,b**).


Figure 1

In our continuing effort to introduce a ketone group to the 1-position of indolizine ring, we recently examined to apply this type of reaction to the more substituted 7,9-dimethylpyrido[2,1-*c*]-1,4-thiazine system, which can be smoothly generated from the corresponding 3,5-dimethylpyridinium salts, and found that the corresponding 1-arylcarbonyl-6,8-dimethylindolizine derivatives were formed. In this paper we describe the first appearance of a ring contraction-desulfurization route from 1-(arylcarbonyl)pyrido[2,1-*c*]-1,4-thiazine intermediates to 1-(arylcarbonyl)indolizine derivatives, and, as an extension, we also report the synthesis of 1-arylcarbonyl-2-[(2-ethoxycarbonylethyl)thio]indolizines possessing the protected 2-thiol group and their transformation to 2-acyl-3-arylthieno[3,2-*a*]indolizine derivatives.

RESULTS AND DISCUSSION

Ring contraction-desulfurization route of 1-(arylcarbonyl)pyrido[2,1-*c*]-1,4-thiazine intermediates

We already reported that the reactions of parent and 4-methyl substituted 1-[1-ethoxycarbonyl-2-methylthio-2-(phenacylthio)vinyl]pyridinium salts with a base and then a dehydrogenating agent afforded only the ring contraction-rearrangement products, ethyl 1-arylcarbonylthio-2-(methylthio)indolizine-3-carboxylates.[3] However, when the corresponding 3,5-dimethylpyridinium bromides (**3a—c**), prepared by the *S*-alkylation of 3,5-dimethylpyridinium 1-ethoxycarbonyl-2-methylthio-2-thioxoethylide (**1a**) with phenacyl bromide (**2a**), *p*-chlorophenacyl bromide (**2b**), and *p*-bromophenacyl bromide (**2c**), were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and chloranil in chloroform at 0 °C, the corresponding ethyl 1-arylcarbonyl-6,8-dimethyl-2-(methylthio)indolizine-3-carboxylates (**4a—c**) were unexpectedly obtained in 63, 46, and 55% yields. In these reactions we could not detect any alternative products such as 1-(arylcarbonylthio)indolizine derivatives (**5**). Similar treatment of salts (**3d—f**), which were formed from 3,5-dimethylpyridinium 1-ethoxycarbonyl-2-[(2-ethoxycarbonylethyl)thio]-2-thioxoethylide (**1b**) having a protected 2-thiol group and **2a—c**, gave the corresponding 1-arylcarbonyl-2-[(2-

ethoxycarbonylethyl)thio]indolizine derivatives (**4d—f**) in 64, 43, and 50% yields. These results are summarized in Scheme 1.
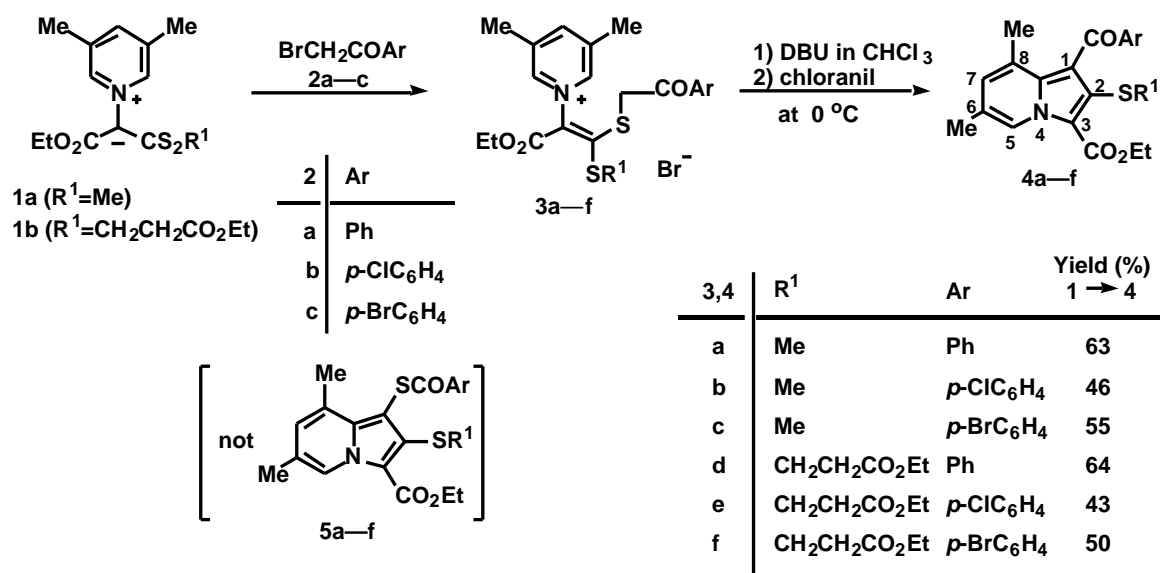
Scheme 1

The elemental analyses for these products (**4a—f**) were in good accord with our proposed structures and not with those for the rearranged 1-(arylcarbonylthio)indolizines (**5**). The IR spectra of **4a—f** showed strong carbonyl absorption bands at 1645—1693 cm^{-1} due to the ,β-unsaturated ketone and ester carbonyl groups.[7] The IR spectra of **4d—f** also exhibited a saturated ester carbonyl band near 1730 cm^{-1}. In the ^{1}H-NMR spectra of **4a—f** the chemical shifts for the 5-, 7-, and 6-methyl protons provided reasonable values in comparison with those for known indolizine derivatives,[2—6] but the 8-methyl proton signal appeared at a considerably high magnetic field (δ 2.13—2.15) in comparison with those of 1-cyano-2-methylthio- (δ 2.70—2.80) and 1-ethoxycarbonyl-2-(methylthio)indolizine derivatives (δ 2.40—2.50).[6] This high field shift must be caused by the proximity between the 1-arylcarbonyl and 8-methyl groups which are at the peri-position because we have already observed the non-coplanarity between the indolizine ring and the 1-ester carbonyl group in diethyl 6,8-dimethylindolizine-1,3-dicarboxylates.[8] To confirm the detailed structures of products (**4a—f**) we performed an X-ray analysis for one compound (**4b**). The ORTEP drawing[9] of compound (**4b**) is shown in Figure 2. As expected, the bond lengths of the methyl carbon (C20) to the carbonyl carbon (C9) or oxygen (O1) are 3.158 and 3.186 Å and the deference between them was little. Furthermore, the dihedral angle (O1-C9-C1-C2) between the indolizine ring and the 1-carbonyl group was very large (111.9 ° (5)) and the coplanarity
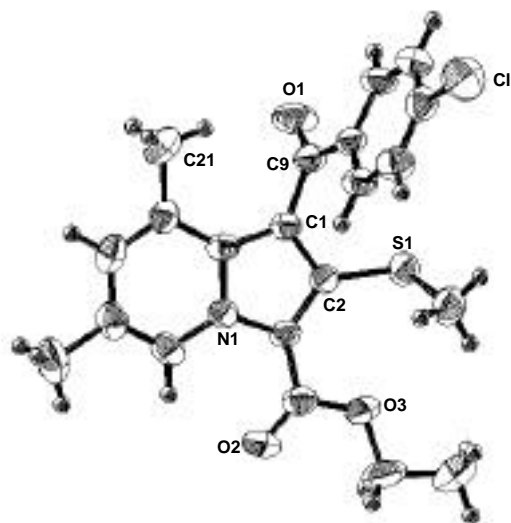
between them was almost lost.

Figure 2. ORTEP drawing of compound **4b**

The factors which separated the ring contraction-rearrangement (Path a) and the ring contraction-desulfurization (Path b) in the behavior of transient pyrido[2,1-*c*]-1,4-thiazine intermediate (**I**) are still unclear but, at this time, the large contribution of the 9-methyl group on **Ia** in path b could be confirmed.

Transformation from 1-(arylcarbonyl)indolizines having the *S*-protected 2-thiol group to 2-acyl-3-arylthieno[3,2-*a*]indolizines   Although some thieno[3,2-*a*]indolizines with an amino, hydroxy, or alkoxy group at the 3-position have been already prepared by us,[5,8,10,11] those possessing an aryl group at the same position could not be synthesized until now because of the inaccessibility of the corresponding 1-(arylcarbonyl)indolizine derivatives.   The smooth access to 1-arylcarbonyl-6,8-dimethylindolizine derivatives (**4a**—**f**) prompted us to investigate the reactivity of the 1-keto function in the expectation of the formation of the corresponding 3-arylthieno[3,2-*a*]indolizines.   In our previous investigation for the intramolecular cyclization of various indolizines possessing cyano, acetyl, and ethoxycarbonyl groups at the 1- or 3-position and an nucleophilic center at the 2-position, the order of the reactivity, (3-CN>1-CN>3-Ac>3-CO$_2$Et>1-CO$_2$Et), has been already established.[8,10—12]   Furthermore, the reactivity of the 1-ketone carbonyl group in **4a**—**f** was expected to be higher than that of the 3-ester carbonyl one, because it is known that a ketone carbonyl group is generally more susceptible to a nucleophilic attack than a ester carbonyl one and that the reactivity of the 1-carbonyl group on diethyl 6,8-dimethylindolizine-1,3-dicarboxylate derivatives is increased strongly by the steric repulsion of the 8-methyl group.[7]   When the deprotection of the 2-substituent of **4d**—**f**, the removal of the ethyl acrylate generated, and the addition of

phenacyl bromide (**2a**) to the reaction solution under the heating conditions were performed, the expected

ethyl 3-aryl-2-benzoyl-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylates **7a**—**c** were obtained in

excellent yields (86—96%). Similar treatment of **4d**—**f** with alkylating agents such as *p*-chlorophenacyl

bromide (**2b**), *p*-bromophenacyl bromide (**2c**), ethyl bromoacetate (**2d**), and chloroacetone (**2e**) provided

the corresponding products (**7d**—**o**) in 60—90% yields. The intermediacy of 2-acylmethylthio-1-

arylcarbonylindolizines such as **6a**—**o** in these thienoindolizine syntheses was detected sometimes by the

^{1}H NMR spectral analyses for the products under the incomplete reaction time, but the isolations of the *S*-

alkylated products (**6**) were not carried out because of their low yields (<5%). These results are shown

in Scheme 2.
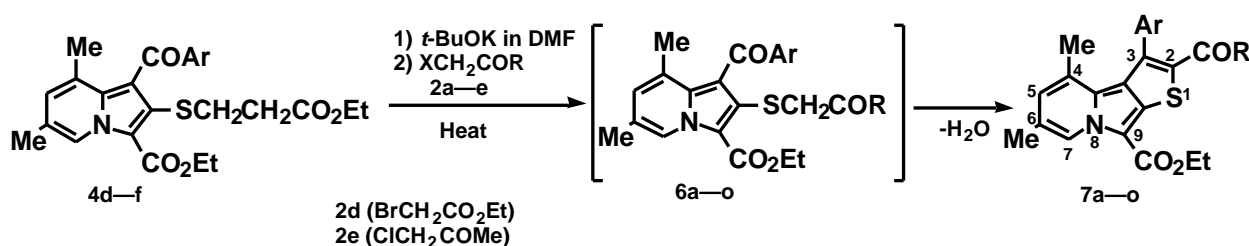
Prod.	React.	R	Ar	Yield(%) 4 → 7	Prod.	React.	R	Ar	Yield(%) 4 → 7
7a	4d+2a	Ph	Ph	96	7i	4f+2c	*p*-BrC$_6$H$_4$	*p*-BrC$_6$H$_4$	78
7b	4e+2a	Ph	*p*-ClC$_6$H$_4$	93	7j	4d+2d	OEt	Ph	60
7c	4f+2a	Ph	*p*-BrC$_6$H$_4$	86	7k	4e+2d	OEt	*p*-ClrC$_6$H$_4$	88
7d	4d+2b	*p*-ClC$_6$H$_4$	Ph	90	7l	4f+2d	OEt	*p*-BrC$_6$H$_4$	68
7e	4e+2b	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	86	7m	4d+2e	Me	Ph	81
7f	4f+2b	*p*-ClC$_6$H$_4$	*p*-BrC$_6$H$_4$	89	7m	4e+2e	Me	*p*-ClC$_6$H$_4$	63
7g	4d+2c	*p*-BrC$_6$H$_4$	Ph	71	7o	4f+2e	Me	*p*-BrC$_6$H$_4$	65
7h	4e+2c	*p*-BrC$_6$H$_4$	*p*-ClC$_6$H$_4$	74					

Scheme 2

The structures of products (**7a**—**o**) were determined mainly by the elemental and IR and ^{1}H NMR

spectral analyses. The elemental analyses for **7a**—**o** were in good accord with our proposed

compositions and the IR spectra showed characteristic carbonyl absorption band(s) in the range of

1611—1688 cm^{-1}. In particular, the largely shifted carbonyl absorption band (1611—1651 cm^{-1})

appeared in the IR spectra of **7a**—**o** are characteristic of the 2-acyl group in 5-membered heteroaromatic

furans and thiophenes.[3,8,10—12] In the ^{1}H-NMR spectra (Table 1) of **7a**—**o** the signals for 5-H, 6-Me, and

7-H were very similar to those for 7-H, 6-Me, and 5-H in indolizines (**4a**—**f**) respectively, but the 4-Me

signals appeared at a fairly higher magnetic region (1.65—1.77) than those (2.13—2.15) in **4a—f**. This large high field shift to the 4-Me group suggested the presence of the large shielding effect attributable to the 3-aryl group.   The conformations of these molecules were confirmed finally by the X-ray analysis of compound (**7e**).   The ORTEP drawing[9] of **7e** is showed in Figure 2.   As seen from this figure 3, the 3-aryl group was closely surrounded by the 4-methyl and the 2-benzoyl groups, and the dihedral angle between the least-squares planes of the thieno[3,2-*a*]indolizine and the 3-phenyl ring was 114.9 °C.
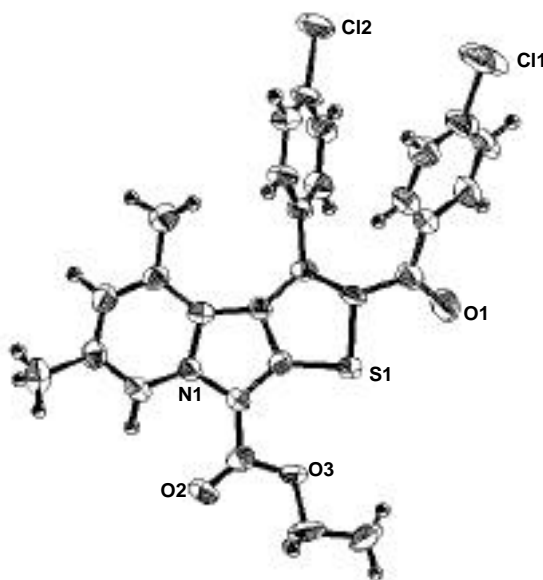

Figure 3.   ORTEP drawing of compound **7e**

In conclusion, we found the ring contraction-desulfurization route for 1-(arylcarbonyl)pyrido[2,1-*c*]-1,4-thiazine intermediates, and succeeded in the preparation of 3-arylthieno[3,2-*a*]indolizine derivatives by using this reaction route.

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) spectrometer in deuteriochloroform with tetramethylsilane used as the internal standard; the chemical shifts are expressed in   values.   The IR spectra were taken with JASCO FT/IR-5300 IR spectrophotometers.

Preparation of 3,5-dimethylpyridinium methylides (1)   These 3,5-dimethylpyridinium ethylides (**1a,b**) were prepared from the reactions of 1-ethoxycarbonylmethyl-3,5-dimethylpyridinium bromide, carbon disulfide and ethyl bromoacetate or ethyl acrylate in the presence of a base according to the

Tominaga's procedure.[13]   Compound (**1b**) was reported in our previous paper[8] and some data of new compound (**1a**) are as follows: 3,5-Dimethylpyridinium 1-Ethoxycarbonyl-2-methylthio-2-thioxoethylide (**1a**); 70%, mp 250—252 °C (CHCl$_3$-Et$_2$O). IR (KBr) cm^{-1}: 1649, 1381. ^{1}H-NMR (CDCl$_3$) : 1.20 (3H, t, *J*=7.0 Hz), 2.50 (6H, s, 3,5-diMe), 2.61 (3H, s, SMe), 4.18 (2H, q, *J*=7.0 Hz), 7.94 (1H, br s), 8.14 (2H, br s), *Anal.* Calcd for C$_{13}$H$_{17}$NO$_2$S$_2$: C, 55.10; H, 6.05; N, 4.94. Found: C, 54.97; H, 6.01; N, 4.87.

Preparation of ethyl 2-alkylthio-1-arylcarbonyl-6,8-dimethylindolizine-9-carboxylates.   General method   A mixture of 3,5-dimethylpyridinium 2-alkylthio-1-ethoxycarbonyl-2-thioxoethylide (**1**, 2 mmol) and phenacyl bromide (**2**, 2.2 mmol) in chloroform (20 mL) was kept at r t until the disappearance of pyridinium methylide (**1**) is detected by TLC monitoring (2 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 any unaltered alkylating agent.   Without further purification the resulting pyridinium salt (**3**) was dissolved in chloroform (30 mL) and the solution was treated with DBU (0.30 g, 2.0 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—6 h.   The reaction mixture was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using CHCl$_3$ as an eluent. The yellowish layers of product (**4**) were combined and concentrated at reduced pressure. Recrystallization of the crude product from ethanol afforded the corresponding ethyl 1-(arylcarbonyl)indolizine-9-carboxylate.   Some data for products **4a**—**f** are as follows:

Ethyl 1-benzoyl-6,8-dimethyl-2-(methylthio)indolizine-3-carboxylate (**4a**): 63% (from **1a** and phenacyl bromide (**2a**)), pale yellow prisms, mp 124—125 °C.   IR (KBr) cm^{-1}: 1672. ^{1}H-NMR (CDCl$_3$) : 1.46 (3H, t, *J*=7.0 Hz), 2.14 (3H, s, 8-Me), 2.26 (3H, s, SMe), 2.32 (3H, s, 6-Me), 4.48 (2H, q, *J*=7.0 Hz), 6.76 (1H, br s), 7.3—8.0 (5H, m), 9.29 (1H, br s), *Anal.* Calcd for C$_{21}$H$_{21}$NO$_3$S: C, 68.64; H, 5.76; N, 3.81. Found: C, 68.92; H, 5.73; N, 3.56.

Ethyl 1-(*p*-chlorobenzoyl)-6,8-dimethyl-2-(methylthio)indolizine-3-carboxylate (**4b**): 46% (from **1a** and *p*-chlorophenacyl bromide (**2b**)), pale yellow prisms, mp 110—111 °C.   IR (KBr) cm^{-1}: 1674, 1658. ^{1}H-NMR (CDCl$_3$) : 1.46 (3H, t, *J*=7.0 Hz), 2.15 (3H, s), 2.26 (3H, s), 2.32 (3H, s), 4.48 (2H, q, *J*=7.0 Hz), 6.78 (1H, br s), 7.2—8.0 (4H, m), 9.29 (1H, br s), *Anal.* Calcd for C$_{21}$H$_{20}$ClNO$_3$S: C, 62.76; H, 5.02; N, 3.49. Found: C, 62.64; H, 5.25; N, 3.37.

Ethyl 1-(*p*-bromobenzoyl-6,8-dimethyl-2-(methylthio)indolizine-3-carboxylate (**4c**): 55% (from **1a** and *p*-bromophenacyl bromide (**2c**)), pale yellow prisms, mp 118—120 °C.   IR (KBr) cm^{-1}: 1693, 1645. ^{1}H-NMR (CDCl$_3$) : 1.46 (3H, t, *J*=7.0 Hz), 2.14 (3H, s), 2.27 (3H, s), 2.32 (3H, s), 4.48 (2H, q, *J*=7.0 Hz), 6.78 (1H, br s), 7.4—8.1 (4H, m), 9.30 (1H, br s), *Anal.* Calcd for C$_{21}$H$_{20}$BrNO$_3$S: C, 56.51; H, 4.52; N,

3.14. Found: C, 56.77; H, 4.55; N, 2.85.

Ethyl 1-benzoyl-2-[(2-ethoxycarbonylethyl)thio]-6,8-dimethylindolizine-3-carboxylate (**4d**): 64% (from **1b** and **2a**), yellow needles, mp 72—74 $^{\circ}$C.   IR (KBr) cm^{-1}: 1728, 1684, 1665. ^{1}H-NMR (CDCl$_3$) : 1.19 (3H, t, *J*=7.0 Hz), 1.45 (3H, t, *J*=7.0 Hz), 2.13 (3H, s), 2.33 (3H, s), 2.38 (2H, t, *J*=7.0 Hz), 3.01 (2H, t, *J*=7.0 Hz), 4.07 (2H, q, *J*=7.0 Hz), 4.48 (2H, q, *J*=7.0 Hz), 6.79 (1H, br s), 7.3—8.0 (5H, m), 9.33 (1H, br s). *Anal.* Calcd for C$_{25}$H$_{27}$NO$_5$S: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.22; H, 5.98; N, 3.09.

Ethyl 1-(*p*-Chlorobenzoyl)-2-[(2-ethoxycarbonylethyl)thio]-6,8-dimethylindolizine-3-carboxylate (**4e**): 43% (from **1b** and **2b**), yellow needles, mp 62—64 $^{\circ}$C.   IR (KBr) cm^{-1}: 1728, 1684, 1665. ^{1}H-NMR (CDCl$_3$) : 1.20 (3H, t, *J*=7.0 Hz), 1.46 (3H, t, *J*=7.0 Hz), 2.14 (3H, s), 2.33 (3H, s), 2.39 (2H, t, *J*=7.0 Hz), 3.00 (2H, t, *J*=7.0 Hz), 4.07 (2H, q, *J*=7.0 Hz), 4.47 (2H, q, *J*=7.0 Hz), 6.79 (1H, br s), 7.2—8.0 (4H, m), 9.33 (1H, br s).   *Anal.* Calcd for C$_{25}$H$_{26}$ClNO$_5$S: C, 61.53; H, 5.37; N, 2.87. Found: C, 61.68; H, 5.45; N, 2.64.

Ethyl 1-(*p*-bromobenzoyl)-2-[(2-ethoxycarbonylethyl)thio]-6,8-dimethylindolizine-3-carboxylate (**4f**): 50% (from **1b** and **2c**), yellow needles, mp 51—53 $^{\circ}$C.   IR (KBr) cm^{-1}: 1730, 1686, 1659. ^{1}H-NMR (CDCl$_3$) : ^{1}H NMR (CDCl$_3$) 1.19 (3H, t, *J*=7.0 Hz), 1.45 (3H, t, *J*=7.0 Hz), 2.14 (3H, s), 2.33 (3H, s), 2.39 (2H, t, *J*=7.0 Hz), 2.99 (2H, t, *J*=7.0 Hz), 4.06 (2H, q, *J*=7.0 Hz), 4.47 (2H, q, *J*=7.0 Hz), 6.79 (1H, br s), 7.4—8.1 (4H, m), 9.32 (1H, br s).   *Anal.* Calcd for C$_{25}$H$_{26}$BrNO$_5$S: C, 56.40; H, 4.92; N, 2.63. Found: C, 56.48; H, 4.98; N, 2.49.

Preparation of ethyl 2-Acyl-3-aryl-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylates.   General method   To a *N,N*-dimethylformamide suspension (3 mL) of 1-arylcarbonyl-2-[2-(ethoxycarbonylethyl)thio]indolizine (**4d—f**, 0.5 mmol)   potassium *tert*-butoxide (0.17g, 1.5 mmol) was added and the resulting mixture was heated in a water bath (80 $^{\circ}$C) for 10 min.   Ethyl acrylate which generated was completely removed at reduced pressure.   An alkylating agent (**2a—e**, 0.75 mmol) was added into the solution of potassium indolizine-2-thiolate and the resulting mixture was allowed to react at 80 $^{\circ}$C for 6 h.   The neutralization of the reaction solution with diluted hydrochloric acid, the filtration and dryness of the precipitate which separated, and the column chromatography of the residue on alumina using CHCl$_3$ as an eluent afforded the corresponding ethyl 2-acyl-3-arylthieno[3,2-*a*]indolizine-9-carboxylate (**7**) with strong fluorescence.   Recrystallization of the crude products from ethanol gave pure samples.   The ^{1}H-NMR data for products (**7a—o**) are listed in Table 1 and some other results are as follows:

Ethyl 2-benzoyl-4,6-dimethyl-3-phenylthieno[3,2-*a*]indolizine-9-carboxylate (**7a**): 96% (from **4d** and **2a**),

yellow prisms, mp 200—202 °C.   IR (KBr) cm^{-1}: 1684, 1651.   *Anal.* Calcd for C$_{28}$H$_{23}$NO$_3$S: C, 74.15; H, 5.11; N, 3.09. Found: C, 74.43; H, 5.05; N, 2.87.

Ethyl 2-benzoyl-3-(*p*-chlorophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7b**): 93% (from **4e** and **2a**), yellow needles, mp 188—190 °C.   IR (KBr) cm^{-1}: 1674, 1613.   *Anal.* Calcd for C$_{28}$H$_{22}$ClNO$_3$S: C, 68.92; H, 4.54; N, 2.87. Found: C, 69.15; H, 4.58; N, 2.60.

Ethyl 2-benzoyl-3-(*p*-bromophenyl)-6,8-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7c**): 86% (from **4f** and **2a**), yellow needles, mp 215—217 °C.   IR (KBr) cm^{-1}: 1669, 1616.   *Anal.* Calcd for C$_{28}$H$_{22}$BrNO$_3$S: C, 63.16; H, 4.16; N, 2.63. Found: C, 63.29; H, 4.19; N, 2.63.

Ethyl 2-(*p*-chlorobenzoyl)-4,6-dimethyl-3-phenylthieno[3,2-*a*]indolizine-9-carboxylate (**7d**): 90% (from **4d** and **2b**), yellow prisms, mp 164—166 °C.   IR (KBr) cm^{-1}: 1680, 1609.   *Anal.* Calcd for C$_{28}$H$_{22}$ClNO$_3$S: C, 68.92; H, 4.54; N, 2.87. Found: C, 69.17; H, 4.43; N, 2.62.

Ethyl 2-(*p*-chlorobenzoyl)-3-(*p*-chlorophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7e**): 86% (from **4e** and **2b**), yellow prisms, mp 185—187 °C.   IR (KBr) cm^{-1}: 1672, 1611.   *Anal.* Calcd for C$_{28}$H$_{21}$Cl$_2$NO$_3$S: C, 64.37; H, 4.05; N, 2.68. Found: C, 64.64; H, 3.97; N, 2.50.

Ethyl 3-(*p*-bromophenyl)-2-(*p*-chlorobenzoyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7f**): 89% (from **4f** and **2b**), yellow prisms, mp 275—277 °C.   IR (KBr) cm^{-1}: 1671, 1613.   *Anal.* Calcd for C$_{28}$H$_{21}$BrClNO$_3$S: C, 59.32; H, 3.73; N, 2.47. Found: C, 59.61; H, 3.67; N, 2.22.

Ethyl 2-(*p*-bromobenzoyl)-4,6-dimethyl-3-phenylthieno[3,2-*a*]indolizine-9-carboxylate (**7g**): 71% (from **4d** and **2c**), yellow prisms, mp 143—145 °C.   IR (KBr) cm^{-1}: 1682, 1627.   *Anal.* Calcd for C$_{28}$H$_{22}$BrNO$_3$S: C, 63.16; H, 4.16; N, 2.83. Found: C, 63.44; H, 4.16; N, 2.36.

Ethyl 2-(*p*-bromobenzoyl)-3-(*p*-chlorophenyl)-6,8-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7h**): 74% (from **4e** and **2c**), yellow prisms, mp 231—233 °C.   IR (KBr): 1676, 1611 cm^{-1}.   *Anal.* Calcd for C$_{28}$H$_{21}$BrClNO$_3$S: C, 59.32; H, 3.73; N, 2.47. Found: C, 59.47; H, 3.70; N, 2.32.

Ethyl 2-(*p*-bromobenzoyl)-3-(*p*-bromophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7i**): 78% (from **4f** and **2c**), yellow prisms, mp 261—263 °C.   IR (KBr): 1672, 1611 cm^{-1}.   *Anal.* Calcd for C$_{28}$H$_{21}$Br$_2$NO$_3$S: C, 55.01; H, 3.46; N, 2.29. Found: C, 55.09; H, 3.51; N, 2.16.

Diethyl 4,6-dimethyl-3-phenylthieno[3,2-*a*]indolizine-2,9-dicarboxylate (**7j**): 60% (from **4d** and ethyl bromoacetate (**2d**)), yellow prisms, mp 159—161 °C.   IR (KBr): 1688 cm^{-1}.   *Anal.* Calcd for C$_{24}$H$_{23}$NO$_4$S: C, 68.39; H, 5.50; N, 3.32. Found: C, 68.66; H, 5.43; N, 3.12.

Diethyl 3-(*p*-chlorophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-2,9-dicarboxylate (**7k**): 88% (from **4e** and **2d**), yellow prisms, mp 208—209 °C.   IR (KBr) cm^{-1}: 1682.   *Anal.* Calcd for C$_{24}$H$_{22}$ClNO$_4$S: C, 63.22; H, 4.86; N, 3.07. Found: C, 63.41; H, 4.86; N, 2.89.

Diethyl 3-(*p*-bromophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-2,9-dicarboxylate (**7l**): 68% (from **4f** and **2d**), yellow prisms, mp 202—204 °C.   IR (KBr) cm^{-1}: 1674.   *Anal.* Calcd for C$_{24}$H$_{22}$BrNO$_4$S: C, 57.61; H, 4.43; N, 2.80. Found: C, 57.39; H, 4.30; N, 2.55.

Ethyl 2-acetyl-4,6-dimethyl-3-phenylthieno[3,2-*a*]indolizine-9-carboxylate (**7m**): 81% (from **4d** and chloroacetone (**2e**), yellow needles, mp 222—224 °C.   IR (KBr) cm^{-1}: 1659, 1630.   *Anal.* Calcd for C$_{23}$H$_{21}$NO$_3$S: C, 70.57; H, 5.41; N, 3.58. Found: C, 70.57; H, 5.50; N, 3.48.

Ethyl 2-acetyl-3-(*p*-chlorophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7n**): 63% (from **4e** and **2e**), yellow prisms, mp 205—207 °C.   IR (KBr) cm^{-1}: 1676, 1628.   *Anal.* Calcd for C$_{23}$H$_{20}$ClNO$_3$S: C, 64.86; H, 4.73; N, 3.29. Found: C, 65.09; H, 4.69; N, 3.29.

Ethyl 2-acetyl-3-(*p*-bromophenyl)-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**7o**): 65% (from **4f** and **2e**), yellow prisms, mp 259—260 °C.   IR (KBr) cm^{-1}: 1676, 1626.   *Anal.* Calcd for C$_{23}$H$_{20}$BrNO$_3$S: C, 58.73; H, 4.29; N, 2.98. Found: C, 58.83; H, 4.34; N, 2.82.

Table 1. ^{1}H-NMR spectral data for thieno[3,2-*a*]indolizine derivatives **7a—o**

No	C-4	C-5	C-6	C-7	CO$_2$Et[a]	R	Ar
7a	1.67	6.81	2.37	9.57	1.49 4.49	6.8-7.8	6.8-7.8
7b	1.74	6.83	2.38	9.55	1.47 4.49	6.9-7.8	6.9-7.8
7c	1.76	6.85	2.38	9.56	1.48 4.49	7.0-78	7.0-7.8
7d	1.67	6.79	2.36	9.54	1.49 4.49	7.0-7.8	7.0-7.8
7e	1.75	6.83	2.38	9.55	1.47 4.48	7.0-7.8	7.0-7.8
7f	1.76	6.84	2.38	9.55	1.49 4.49	7.0-8.1	7.0-8.1
7g	1.68	6.81	2.38	9.56	1.50 4.50	7.1-7.8	7.1-7.8
7h	1.74	6.84	2.38	9.56	1.49 4.49	7.1-7.8	7.1-7.8
7i	1.77	6.86	2.39	9.59	1.50 4.50	7.0-8.0	7.0-8.0
7j	1.67	6.79	2.35	9.55	1.52 4.51	1.12 4.15[a]	7.3-7.8
7k	1.75	6.82	2.36	9.55	1.52 4.51	1.16 4.18[a]	7.2-8.2
7l	1.74	6.82	2.36	9.54	1.52 4.52	1.18 4.12[a]	7.1-8.2
7m	1.65	6.79	2.35	9.54	1.52 4.49	1.85	7.3-8.0
7n	1.71	6.81	2.36	9.55	1.51 4.49	1.92	7.3-7.8
7o	1.71	6.83	2.36	9.55	1.52 4.50	1.92	7.2-8.0

a) J_{Et}=7.0 Hz.

Crystallography of ethyl 1-(*p*-chlorobenzoyl)-6,8-dimethyl-2-(methylthio)indolizine-9-carboxylate (4b) A pale yellow prismatic single crystal (0.32x0.80x1.00 mm) grown from ethanol was used for the unit-cell determinations and data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo*K* radiation (=0.71069 Å). The crystal data of this compound are as follows: **4c**: $C_{21}H_{20}ClNO_3S$; *M*=401.91; triclinic, space group $P\bar{1}$(#2), *Z*=2 with *a*=10.662 (3) Å, *b*=11.136 (4) Å, *c*=9.363 (3) Å, =111.55 (2)°, =101.42 (3)°; =79.69 (3)°,*V*=1006.6 (6) $Å^3$ and $D_{calc.}$=1.326 g/cm^3. All calculations were performed using the teXsan package.[14] The structure was solved by a direct method (SIR).[15] 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 0.057 and 0.059 respectively for 2514 (*I*>2.00（I）) observed reflections.

Crystallography of ethyl 2-(*p*-chlorobenzoyl)-3-(*p*-chlorophenyl)-4,6-dimethylthieno[3,2-*a*]-indolizine-9-carboxylate (7e) A yellow prismatic single crystal (0.18x0.42x0.82 mm) grown from $CHCl_3$–ethanol was used for the unit-cell determinations and data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo*K* radiation (=0.71069 Å). Crystal data of this compound is as follows: **7e**: $C_{28}H_{21}Cl_2NO_3S$; *M*=522.44; monoclinic, space group $P2_1$/n (#14), *Z*=4 with *a*=18.02 (1) Å, *b*=7.87 (1) Å, *c*=18.80 (1) Å, =111.24 (6)°, *V*=2486 (4) $Å^3$ and $D_{calc.}$=1.396g/cm^3. All calculations were performed using the teXsan package.[14] The structure was solved by a direct method (SIR).[15] 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 0.061 and 0.044 respectively for 2640 (*I*>2.00（I）) observed reflections.

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