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A NEW SYNTHETIC APPROACH TO SOME FUNCTIONALIZED CYCL[3.2.2]AZINE DERIVATIVES[1]

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Abstract – Dehydrogenation of some ethyl 4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylates with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were examined. No simply dehydrogenated products such as 4-oxo-1*H*- and 4-oxo-8*H*-1,4-thiazino[3,4,5-*cd*]indolizines or their full conjugated enol forms could be obtained, but ethyl cycl[3.2.2]azine-1-carboxylates were directly obtained via the cyclization and the subsequent desulfurization of the 4*H*-1,4-thiazine ring in the dehydrogenated intermediates.

INTRODUCTION

Aromaticity is a very important concept in organic chemistry. The fact that planar cyclic polyenes containing (4n+2)π electrons have an aromatic character from Hückel rules[2,3] is widely known and applied to the syntheses of various aromatic compounds. In contrast, the difficulty of generating planar cyclic polyenes having an anti-aromatic 4nπ system and the instability of such compounds are also well known. We have previously reported the smooth generation of bicyclic intermediates such as pyrido[2,1-*c*]-1,4-thiazine intermediates (**A**) (see Figure 1) having an anti-aromatic 12π electron system and their efficient transformation to aromatic indolizine derivatives (**C**) via the intramolecular cyclization followed by the rearrangement or the desulfurization depending upon the nature of the R^1 substituent in the tricyclic thiirane intermediates (**B**).[4-7] In connection with this reaction it is readily imaginable that the 4,6-tethered pyrido[2,1-*c*]-1,4-thiazines should be potential intermediates for cycl[3.2.n]azine derivatives such as (**E**) whose preparative routes are limited.[8,9] We have also described the formation of some functionalized 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinone derivatives (**F**), which are prospective precursors for the 4,6-tethered pyrido[2,1-*c*]-1,4-thiazines (**D**), from the reaction of *(Z)*-3-[mercapto(methylthio)methylene]-2(3*H*)-indolizinones with various alkyl halides in the presence of

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Dedicated to Professor Dr. Albert Eschenmoser on his 85th birthday.

a base.[10-12] Hence, we were interested in the dehydrogenation of compounds such as (**F**), because the subsequent vinylogous keto-enol tautomerization of the resulting 4-oxo-1*H*- (**H**) and/or 4-oxo-8*H*-1,4-thiazino[3,4,5-*cd*]indolizines (**G**) may lead to the full-conjugated 1,4-thiazino[3,4,5-cd]indolizin-4-ols (**D**) which in turn provide the corresponding cycl[3.2.2]azines (**E**). In this paper we report the syntheses of some functionalized cycl[3.2.2]azine derivatives from the dehydrogenation of ethyl 3-alkylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate derivatives.

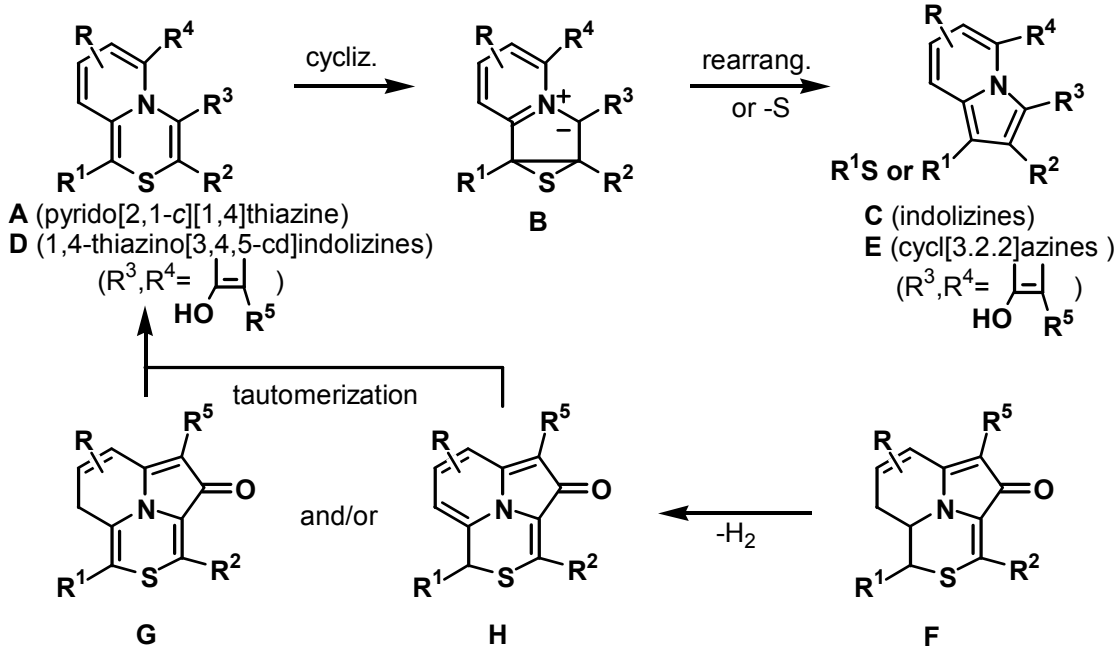


Figure 1

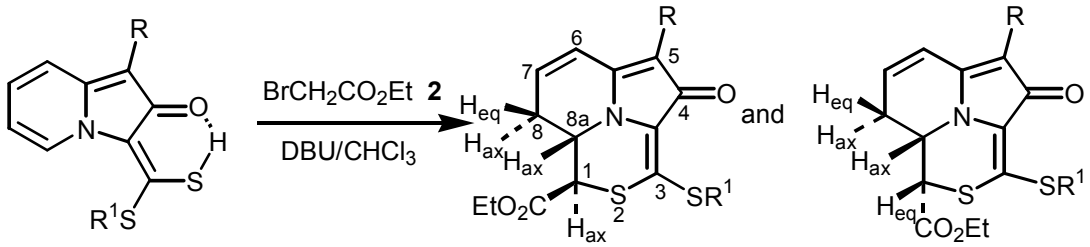
RESULTS AND DISCUSSION

Preparation of 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinone derivatives (3 and 4).

We first selected ethyl 3-alkylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylates (**3** and **4**) as the substrates in the expectation of their high solubility and easy handling in this dehydrogenation because of the low yields and low solubility of the 1-cyano compounds.[12] The required 4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine derivatives were obtained as the *trans*- **3a**–**n** and *cis*-mixtures **4a**–**n** at the 1- and 8a-positions from the reactions of (*Z*)-3-[alkylthio(mercapto)-methylene]-2(3*H*)-indolizinones (**1a**–**n**)[13,14] with ethyl bromoacetate (**2**) in the presence of 2-equivalents of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) at 50 °C for 10 min. In these reactions the trans isomers **3a**–**n** were always formed predominantly (Scheme 1). Our attempts to separate the *trans*-*cis* mixtures to perspective isomers by column chromatography were unsuccessful because of their similar solubility. However, we decided to use the *trans*-*cis* mixtures (**3a**–**n** and **4a**–**n)** in the subsequent reactions, because both dehydrogenation reactions should form the same products such as 4(8*H*)-1,4-thiazino-

[2,3,4-*cd*]indolizinones (**6**) and 1,4-thiazino[3,4,5-*cd*]indolizin-3-ols (**7**) or the enantiomeric pair in 4(1*H*)-1,4-thiazino[3,4,5-*cd*]indolizinones (**5**) (see Scheme 2).

The predominant formation of the *trans* derivatives **3a**–**n** over the *cis* ones **4a**–**n** was unexpected for us since we have previously observed the formation of only the *cis* derivatives **4a**,**e**,**h** in the reaction of **1a**,**e**,**h** with **2** in the presence of small excess DBU at room temperature for 12 h.[12] Considering the stability of these compounds, however, it can be thought that the use of excess base at a higher temperature promoted the transformation from the less stable *cis* derivatives **4a**–**n**, in which the 1-ethoxycarbonyl group occupies the pseudo-axial position, to more stable *trans* ones **3a**–**n**, in which the same group holds the pseudo-equatorial position, during the base-catalyzed isomerization of the active 1-methine proton.



1a–n **3a–n** (*trans* form) **4a–n** (*cis* form)

Reactant	Products	Yield (%)	Ratio (**3**/**4**)	R	R^1
1a	**3a+4a**	59	8/1	Ph	Me
1b	**3b+4b**	49	9/1	Ph	Et
1c	**3c**	23	1/0	Ph	Bn
1d	**3d**	34	1/0	Ph	CH_2CO_2Et
1e	**3e+4e**	55	4/1	4-ClC_6H_4	Me
1f	**3f+4f**	36	28/1	4-ClC_6H_4	Et
1g	**3g+4g**	59	94/1	4-ClC_6H_4	Bn
1h	**3h+4h**	63	11/1	Me	Me
1i	**3i+4i**	73	4/1	Me	Et
1j	**3j+4j**	72	4/1	Me	Bn
1k	**3k+4k**	58	6/1	Me	CH_2CO_2Et
1l	**3l**	70	1/0	Et	Me
1m	**3m+4m**	58	7/1	Et	Et
1n	**3n+4n**	30	6/1	Et	Bn

Scheme 1

The structural assignment for compounds **3a**–**n** and **4a**–**n** was accomplished by some physical and spectral means and by the comparison with those of the known substances **4a**,**e**,**h**.[12] Their elemental

analyses were in accord with our proposed compositions, and the IR spectra showed the absorption bands at 1618–1624 and 1720–1737 cm^{-1} due to saturated ester carbonyl group(s) and an enone carbonyl one, respectively. The assignment of the *trans* and *cis* configurations for compounds **3a**–**n** and **4a**–**n** was made by comparing the coupling constants between each 1-methine proton and the 8a-proton in their ^{1}H-NMR spectra (Table 1), since it is already known that the *trans* coupling constant is ca. 10.0 Hz and fairly larger than the *cis* coupling constant (ca. 2.0 Hz).[10-12] In addition, the NOE measurement of compound **3a** confirmed the signal position of the 8-H (axial), because the irradiation to the 1-H (axial, δ 4.21) increased the intensity of a multiplet signal at δ 2.52. Thus, the alternative signal appeared at δ 2.83 was confirmed to be the 8-H (equatorial). The analyses of the proton signals for other compounds

Table 1. ^{1}H-NMR spectral data of 1,4-thiazino[3,4,5-*cd*]indolizin-4-ones **3a**–**n** and **4a**–**n** in $CDCl_3$

No[a]	1-H	8a-H	8-H$_{(ax)}$	8-H$_{(eq)}$	7-H	6-H	R	R^{1}S	CO_2Et
3a	4.21	b)	2.52	2.83	6.28	6.69	7.1–7.6	2.54	1.37 4.33
4a	3.86	b)	2.5–2.7	2.5–2.7	6.30	6.71	7.1–7.6	2.54	1.26 4.25
3b	4.22	b)	2.49	2.81	6.27	6.68	7.1–7.6	1.39 3.07	1.36 4.31
4b	3.82	4.37	2.5–2.7	2.5–2.7	6.31	6.71	7.1–7.6	1.38 3.0–3.2	1.26 4.1–4.3
3c	4.19	c)	2.50	2.83	6.30	6.69	7.1–7.6	4.2–4.4 d)	1.35 c)
4c	3.76	c)	2.61	2.61	6.30	6.70	7.1–7.6	4.29 d)	1.23 4.1–4.3
3d	4.21	4.36	2.50	2.84	6.30	6.69	7.2–7.5	1.29 3.81 4.21	1.35 4.30
4d	3.81	4.38	2.5–2.8	2.5–2.8	6.32	6.69	7.1–7.5	1.26 3.83 4.23	1.27 4.19
3e	4.21	b)	2.51	2.84	6.31	6.64	7.33 7.42	2.54	1.37 4.33
4e	3.87	4.3–4.5	2.6–2.7	2.6–2.7	6.33	6.65	7.3, 7.44	2.57	1.26 4.25
3f	4.21	b)	2.51	2.84	6.31	6.64	7.33 7.42	1.40 3.07	1.37 4.32
4f	3.83	4.3–4.5	2.65	2.65	6.34	6.65	7.33 7.44	1.39 3.0–3.2	1.26 4.24
3g	4.20	b)	2.50	2.84	6.32	6.64	7.32 7.41	4.29 7.2–7.5	1.36 4.31
4g	3.77	b)	2.62	2.62	6.34	6.65	7.32 7.41	4.29 7.2–7.5	1.26 4.31
3h	4.15	4.0–4.3	2.44	2.78	6.19	6.47	1.80	2.51	1.35 4.30
4h	3.80	4.0–4.3	2.4–2.7	2.4–2.7	6.22	6.49	1.81	2.51	1.24 4.21
3i	4.14	4.0–4.3	2.42	2.78	6.20	6.47	1.80	1.37 3.04	1.35 4.30
4i	3.76	b)	2.57	2.57	6.22	6.48	1.81	1.36 3.03	1.24 4.1–4.3
3j	4.11	4.0–4.3	2.41	2.78	6.20	6.47	1.80	4.26 7.2–7.5	1.34 4.28
4j	3.69	b)	2.55	2.55	6.22	6.49	1.82	4.26 7.2–7.5	1.21 4.0–4.3
3k	4.14	b)	2.43	2.81	6.23	6.48	1.79	1.28 3.80 4.20	1.33 4.28
4k	3.74	b)	2.60	2.60	6.25	6.49	1.80	1.27 3.80 4.1–4.3	1.24 4.1–4.3
3l	4.14	4.19	2.43	2.78	6.19	6.48	1.07 2.29	2.51	1.35 4.30
4l	3.80	b)	2.5–2.7	2.5–2.7	6.21	6.49	1.08 2.30	2.50	1.23 4.1–4.3
3m	4.14	4.1–4.3	2.43	2.78	6.19	6.48	1.07 2.28	1.38 3.04	1.34 4.30
4m	3.76	b)	2.58	2.58	6.21	6.49	1.08 2.29	1.36 3.03	1.23 4.0–4.4
3n	4.11	4.16	2.41	2.78	6.20	6.48	1.07 2.28	4.26 7.2–7.5	1.34 4.28
4n	3.70	b)	2.4–2.7	2.4–2.7	6.22	6.49	1.09 2.30	4.25 7.2–7.5	1.21 4.0–4.4

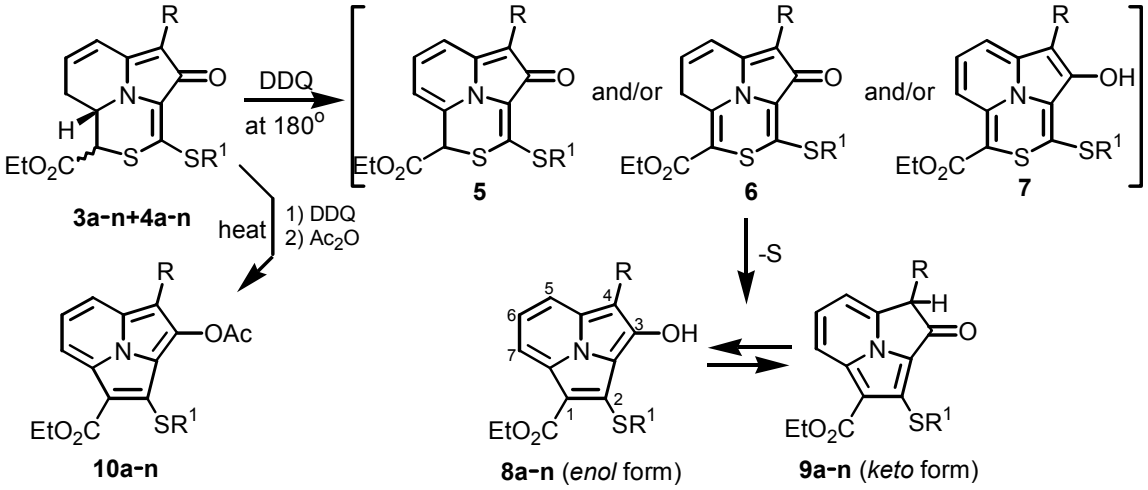
a) The principal coupling constants are as follows: $J_{1,8a}$ = 9.1–9.3 (trans) or 3.2–3.3 Hz (cis), $J_{6,7}$ = 9.9–10.0 Hz, $J_{6,8(ax)}$ = 2.9–3.1 Hz, $J_{7,8(eq)}$ = 6.5–6.7 Hz, $J_{7,8(ax)}$ = 2.4–2.5 Hz, $J_{8(eq),8(ax)}$ = 17.7–17.8 Hz, $J_{8(eq),8a}$ = 5.2–5.4 Hz, $J_{8(ax),8a}$ = 10.9–12.1 Hz, J_{EtO} = 7.0–7.1 Hz, J_{EtS} = 7.4 Hz. b) Overlapped with the ethoxy methylene proton signals. c) Overlapped with the benzyl methylene proton signals. d) Overlapped with the phenyl proton signals.

3b–**n** and **4b**–**n** were performed on the analogy of these findings.

Preparation of cycl[3.2.2]azines.

In contrast to the smooth dehydrogenation of 1,9a-dihydropyrido[2,1-*c*]-1,4-thiazine derivatives such as (**A**) with DDQ or chloranil in an ice bath, the treatment of 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]-indolizinones (**3a**–**n** and **4a**–**n**) with the same dehydrogenating agents in chloroform in the range from 0 ^{o}C to the reflux temperature did not provide any expected dehydrogenated compounds such as 4(1*H*)-(**5**), 4(8*H*)-1,4-thiazino[3,4,5-*cd*]indolizinones (**6**), and/or their full conjugated enol forms (**7**). The formation of a new product was confirmed when the dehydrogenation of **3a**+**4a** with DDQ was examined in dioxane/toluene at 80 ^{o}C, but its conversion was very slow. Hence, the reactions at higher temperatures were examined, and we found that ethyl 3-hydroxy-2-(methylthio)cycl[3.2.2]azine-1-carboxylate (**8a**) involving a small amount of its keto form (**9a**) was directly obtained in 36 or 46% yield from the reaction in *N*,*N*-dimethyformamide or *N*-methyl-2-pyrrolidone at 150–170 ^{o}C, respectively. The yield was slightly improved when 2,4,6-collidine was used as a solvent and the reaction temperature was raised to 180 ^{o}C. The treatment of **3b**–**g**,**l**–**n** + **4b**–**g**,**l**–**n** with DDQ under the optimized reaction conditions gave the corresponding cycl[3.2.2]azine derivatives (**8b**–**g**,**l**–**n** + **9b**–**g**,**l**–**n**) in 16–51% yields. On the other hand, similar reactions of **3h**–**k**+**4h**–**k** bearing the 5-methyl group did not provide the expected products **8h**–**k**+**9h**–**k** because of their thermal instability. To improve these yields and the stability of these products **8a**–**n**+**9a**–**n**, acetic anhydride was added into the reaction solutions of **3a**–**n**+**4a**–**n** and DDQ to afford the corresponding ethyl 3-acetoxycycl[3.2.2]azine-1-carboxylate derivatives (**10a**–**n**) in 10–65% yields respectively. These results are shown in Scheme 2.

The structural assignments for compounds **8a**–**g**,**l**–**n** + **9a**–**g**,**l**–**n** and **10a**–**n** were carried out by their elemental analyses, HRMS, and IR and ^{1}H-NMR spectral analyses. In particular, their HRMS and elemental analyses were completely in accord with the compositions for the dehydrogenated and desulfurized structures in comparison with those of the materials **3a**–**n**+**4a**–**n**. The IR spectra of **8a**–**g**,**l**–**n** + **9a**–**g**,**l**–**n** and **10a**–**n** showed an α,β-unsaturated ester carbonyl band at 1655–1686cm^{-1}. The ^{1}H-NMR spectra (see Table 2) of these products **8a**–**g**,**l**–**n** + **9a**–**g**,**l**–**n** showed the disappearance of the saturated 1-, 8-, and 8a-proton characteristics of 4(1*H*)-8,8a-dihydrothiazinoindolizinones **3a**–**n**+**4a**–**n** and the new appearance of the three aromatic protons with an ABC pattern. Interestingly, the ^{1}H-NMR spectra of these products in DMSO-*d*6 exhibited only the proton signals for the enol forms **8a**–**g**,**l**–**n**, while those in $CDCl_3$ indicated the proton signals both for the keto-enol mixtures **8a**–**g**,**l**–**n**+**9a**–**g**,**l**–**n**. For example, the spectrum in DMSO-*d*6 showed only the signals of **8a** due to the 5-, 6-, and 7-protons on the cycl[3.2.2]azine ring at δ 7.77 (1H, d, J = 7.9 Hz), 7.84 (1H, t, J=7.9 Hz),



8,9	R	R^1	Yield (%)	10	R	R^1	Yield (%)
a	Ph	Me	51	**a**	Ph	Me	65
b	Ph	Et	49	**b**	Ph	Et	53
c	Ph	Bn	36	**c**	Ph	Bn	26
d	Ph	CH_2CO_2Et	24	**d**	Ph	CH_2CO_2Et	23
e	4-ClC_6H_4	Me	32	**e**	4-ClC_6H_4	Me	49
f	4-ClC_6H_4	Et	44	**f**	4-ClC_6H_4	Et	56
g	4-ClC_6H_4	Bn	21	**g**	4-ClC_6H_4	Bn	18
h	Me	Me	a)	**h**	Me	Me	10
i	Me	Et	a)	**i**	Me	Et	11
j	Me	Bn	a)	**j**	Me	Bn	15
k	Me	CH_2CO_2Et	a)	**k**	Me	CH_2CO_2Et	17
l	Et	Me	24	**l**	Et	Me	43
m	Et	Et	16	**m**	Et	Et	38
n	Et	Bn	24	**n**	Et	Bn	23

a) Unstable.

Scheme 2

and 8.01 (1H, d, J = 7.9 Hz) respectively, together with a hydroxy proton (δ 10.77 (1H, br s)), ethoxy protons (δ 1.42 (3H, t, J = 7.1 Hz) and 4.38 (2H, q, J = 7.1 Hz)), methylthio protons (δ 2.96 (3H, s)) and aromatic protons (δ 7.37 (2H) 7.54 (1H), and 7.77 (2H)). On the other hand, that in $CDCl_3$ exhibited the characteristic proton signals of minor **9a** at *inter alia* δ 4.95 (1H, s, 4-H), 6.78 (1H, dd, J = 7.1 Hz, 5-H), 7.46 (1H, q, J = 7.1, 8.9 Hz, 6-H), and 7.86 (1H, d, J = 8.9 H, 7-Hz), together with the proton signals for major **8a**. The ratio of **8a** to **9a** in $CDCl_3$ was 88 : 12. The keto-enol tautomerism between **8l** and **9l** was also observed in the ^{1}H-NMR measurement in $CDCl_3$, but the ratio (5<95) of **8l** to **9l** reversed. As expected, the *O*-acetylated cycl[3.2.2]azines **10a**–**n** are stable crystalline substances and the signal

Table 2. ^{1}H-NMR spectral data for products **8a**–**n** (DMSO-*d*6) and **10a**–**n** ($CDCl_3$)

No[a]	C-5	C-6	C-7	R^1	R^2S	CO_2Et	OH or OAc
8a	a)	7.84	8.01	7.37 7.54 7.77	2.96	1.42 4.38	10.77
8b	a)	7.84	8.01	7.37 7.54 7.77	1.36, 3.57	1.42 4.38	10.85
8c	a)	7.85	8.02	7.38 7.56 7.80	4.86, 7.25, 7.32, 7.46	1.40 4.36	11.10
8d	7.84	7.79	8.13	7.36 7.54 7.90	1.26, 4.10(s), 4.23	1.52 4.51	8.85
8e	7.78	7.86	8.01	7.59 7.79	2.95	1.42 4.38	10.86
8f	7.78	7.85	8.02	7.59 7.80	1.35, 3.56	1.42 4.38	10.94
8g	7.81	7.86	8.02	7.60 7.82	4.85, 7.25, 7.32, 7.45	1.40 4.36	11.17
8l	7.68	7.74	7.90	1.27 2.94	2.92	1.40 4.34	10.52
8m	7.67	7.73	7.90	1.27 2.94	1.35, 3.53	1.40 4.34	10.56
8n	7.76	7.71	7.91	1.29 2.97	4.83, 7.26, 7.32, 7.44	1.38 4.32	10.80
10a	7.93	7.83	8.24	7.40 7.52 7.71	2.84	1.52 4.51	2.35
10b	7.94	7.83	8.25	7.39 7.52 7.71	1.43 3.35	1.52 4.51	2.37
10c	7.96	7.86	8.29	7.40 7.52 7.71	4.55 7.28 7.31 7.42	1.52 4.52	2.30
10d	7.98	7.86	8.31	7.40 7.53 7.71	1.17 4.13 4.15	1.52 4.52	2.42
10e	7.88	7.85	8.24	7.50 7.64	2.83	1.52 4.51	2.35
10f	7.89	7.84	8.26	7.50 7.64	1.43 3.35	1.52 4.51	2.38
10g	7.92	7.87	8.29	7.50 7.65	4.54 7.29 7.32 7.43	1.52 4.51	2.30
10h	7.74	7.77	8.17	2.43	2.81	1.50 4.49	2.46
10i	7.74	7.76	8.18	2.43	1.43 3.32	1.50 4.49	2.47
10j	7.76	7.79	8.21	2.37	4.53 7.29 7.32 7.42	1.49 4.48	2.45
10k	7.78	7.77	8.23	2.51	1.17 4.12 4.15	1.50 4.49	2.44
10l	7.78	7.75	8.17	1.39 2.88	2.79	1.50 4.49	2.46
10m	7.78	7.75	8.19	1.39 2.88	1.41 3.30	1.50 4.49	2.47
10n	7.80	7.77	8.22	1.40 2.89	4.50 7.28 7.31 7.42	1.49 4.49	2.38

a) The principal coupling constants are as follows: $J_{5,6} = J_{6,7} = 7.8–8.0$ Hz, $J_{5,7} = 0–1.8$ Hz, $J_{EtO} = 7.1–7.2$ Hz, $J_{EtS} = 7.4–7.5$ Hz, $J_{Ph} = 7.5–8.6$ H. b) Overlapped with the phenyl proton signal**.**

patterns and the chemical shifts of the skeletal protons in their ^{1}H-NMR spectra in $CDCl_3$ were very similar to those of **8a**–**g**,**l**–**n** in DMSO-*d*6. The X-ray analysis of one compound **10i** finally confirmed this structure. The ORTEP drawing[15] is shown in Figure 2.

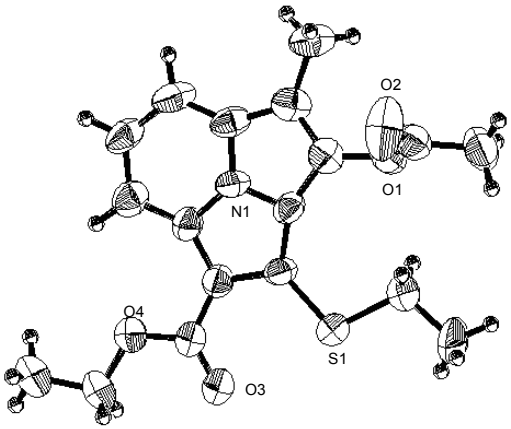


Figure 2. ORTEP drawing of 10i

Mechanistically, there seemed to be no problem in the desulfurization from a 4*H*-1,4-thiazine form having an unstable 8π electron system in the above reactions. However, we could not show the positions of the first dehydrogenation, because we could not obtain any

intermediates such as 4(1*H*)- **5** and/or 4(8*H*)-1,4-thiazino[3,4,5-*cd*]indolizinone **6**.

In summary we have developed a novel approach to functionalized cycl[3.2.2]azine derivatives which are not easily available by other methods, though their yields were low to moderate.

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 Bruker AMX-500 (^1H: 500MHz) spectrometer in deuteriochloroform or DMSO-*d*6 with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR and HRMS spectra were taken with NICOLET AVATAR320 Fourier transform infrared spectrophotometer and Agilent 6520 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS.

Preparation of 3-[(alkylthio)mercaptomethylene]-2(3*H*)-indolizinones (1a–n). General Method. An ethanolic solution (50 mL) of the corresponding 1-(ethoxycarbonylmethyl)pyridium bromide (17.5 mmol) was treated with DBU (36.8 mmol) under stirring at 60 °C for 15 min. After cooling to room temperature, carbon disulfide (18.4 mmol) was added to this reaction solution and the resulting mixture was allowed to react under stirring for 5 min. Alkylating reagent such as dimethyl sulfate, diethyl sulfate, benzyl bromide, and ethyl bromoacetate was then added and allowed to react under stirring at room temperature for 90 min. The separated precipitates were collected by suction, dried, and recrystallized from CH_2Cl_2-Et_2O to give the corresponding 3-[(alkylhio)mercaptomethylene]-2(3*H*)-indolizinones (**1a**–**n**).

The physical and spectral data of known compounds **1a** (46%), **1b** (31%), **1e** (55%), **1h** (43%), and **1l** (65%) were in accord with those reported previously by us, and some data for new compounds **1c**,**d**,**f**,**g**,**i–k**,**m**,**n** are as follows.

(*Z*)-3-[(Benzylthio)mercaptomethylene]-1-phenyl-2(3*H*)-indolizinone (1c): 72% (from 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and benzyl bromide), red prisms, mp 125–126 °C. IR (KBr) cm^{-1}: 1581 (CO), 2510 (SH). ^{1}H-NMR ($CDCl_3$): 4.74 (2H, s, CH_2Ph), 6.81 (1H, dt, *J* = 7.0, 1.4 Hz, 6-H), 7.20–7.52 (10H, m, 7-H, 8-H, and aryl-H), 7.60–7.66 (2H, m, aryl-H), 9.40 (1H, d, *J* = 7.1 Hz, 5-H), 12.85 (1H, br s, SH). *Anal*. Calcd for $C_{22}H_{17}NOS_2$: C, 70.37; H, 4.56; N, 3.73. Found: C, 70.21; H, 4.38; N, 3.59. Positive ion ESI-HRMS Calcd for $C_{22}H_{17}NOS_2$ $[M+H]^+$: 376.0824. Found *m*/*z* 376.0828.

(*Z*)-3-[(Ethoxycarbonylmethylthio)mercaptomethylene]-1-phenyl-2(3*H*)-indolizinone (1d): 76% (from 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and ethyl bromoacetate), red powder, mp 104–105 °C. IR (KBr) cm^{-1}: 1582 (CO), 1742 (CO), 2619 (SH). ^{1}H-NMR ($CDCl_3$): 1.33 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 4.28 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.35 (2H, s, SCH_2), 6.89 (1H, dt, *J* = 7.1, 1.4

Hz, 6-H), 7.24–7.68 (7H, m, 7-H, 8-H, and aryl-H), 9.45 (1H, d, *J* = 7.1 Hz, 5-H), 12.52 (1H, br s, SH). *Anal*. Calcd for $C_{19}H_{17}NO_3S$: C,61.43; H, 4.61; N, 3.77. Found: C, 61.40; H, 4.74; N, 3.61. Positive ion ESI-HRMS Calcd for $C_{19}H_{17}NO_3S_2$ $[M+H]^+$: 372.0723. Found *m*/*z* 372.0726.

1-(*p*-Chlorophenyl)-(*Z*)-3-[(ethylthio)mercaptomethylene]-2(3*H*)-indolizinone (1f): 78% (from 2-(*p*-chlorobenzyl)-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and diethyl sulfate), brown prisms, mp 119–120 °C. IR (KBr) cm^{-1}: 1581 (CO), 2813 (SH). ^{1}H-NMR ($CDCl_3$): 1.49 (3H, t, *J* = 7.5 Hz, SCH_2CH_3), 3.54 (2H, q, *J* = 7.5Hz, SCH_2CH_3), 6.88 (1H, dt, *J* = 7.0, 1.4 Hz, 6-H), 7.25–7.31 (1H, m, 7-H), 7.43 (2H, d, *J* = 8.5 Hz, aryl-H), 7.55–7.61 (3H, m, aryl-H), 9.49 (1H, d, *J* = 7.1 Hz, 5-H), 12.97 (1H, br s, SH). *Anal*. Calcd for $C_{17}H_{14}ClNOS_2$: C, 58.70; H, 4.06; N, 4.03. Found: C, 58.82; H, 4.07; N, 3.87. H Positive ion ESI-HRMS Calcd for $C_{17}H_{14}ClNOS_2$ $[M+H]^+$: 348.0278. Found *m*/*z* 348.0289.

1-(*p*-Chlorophenyl)-(*Z*)-3-[(benzylthio)mercaptomethylene]-2(3*H*)-indolizinone (1g): 76% (from 2-(*p*-chlorobenzyl)-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and benzyl bromide), orange prisms, mp 137–138 °C. IR (KBr) cm^{-1}: 1580 (CO), 2508 (SH). ^{1}H-NMR ($CDCl_3$): 4.76 (2H, s, SCH_2Ph), 6.83 (1H, dt, *J* = 7.0Hz, 1.4 Hz, 6-H), 7.23–7.50 (9H, m, 7-H, 8-H, and aryl-H), 7.57 (2H, d, *J* = 8.6 Hz, aryl-H), 9.39 (1H, d, *J* = 7.0 Hz, 5-H), 12.88 (1H, br s, SH). *Anal*. Calcd for $C_{22}H_{16}ClNOS_2$: C, 64.46; H, 3.93; N, 3.42. Found: C, 64.19; H, 3.91; N, 3.42. Positive ion ESI-HRMS Calcd for $C_{22}H_{16}ClNOS_2$ $[M+H]^+$: 410.0434. Found *m*/*z* 410.0437.

(*Z*)-3-[(Ethylthio)mercaptomethylene]-1-methyl-2(3*H*)-indolizinone (1i): 36% (from 2-ethyl-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and diethyl sulfate), orange prisms, mp 156–158 °C. IR (KBr) cm^{-1}: 1592 (CO), 2546 (SH). ^{1}H-NMR ($CDCl_3$): 1.47 (3H, t, *J* = 7.4 Hz, SCH_2CH_3), 2.17 (3H, s, 1-Me), 3.52 (2H, q, *J* = 7.2Hz, SCH_2CH_3), 6.77 (1H, dt, *J* = 7.0, 1.6 Hz, 6-H), 7.19–7.30 (2H, m, 7-H and 8-H), 9.38 (1H, d, *J* = 7.0Hz, 5-H), 12.61 (1H, br s, SH). *Anal*. Calcd for $C_{12}H_{13}NOS_2$: C, 57.34; H, 5.21; N, 5.57. Found: C, 57.64; H, 5.16; N, 5.31. Positive ion ESI-HRMS Calcd for $C_{12}H_{13}NOS_2$ $[M+H]^+$: 252.05113. Found *m*/*z* 252.0519.

(*Z*)-3-[(Benzylthio)mercaptomethylene]-1-methyl-2(3*H*)-indolizinone (1j): 62% (from 2-ethyl-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and benzyl bromide), orange prisms, mp 134–135 °C. IR (KBr) cm^{-1}: 1596 (CO), 2588 (SH). ^{1}H-NMR ($CDCl_3$): 2.17 (3H, s, 1-Me), 4.75 (2H, s, SCH_2Ph), 6.72 (1H, dt, *J* = 7.0, 1.6 Hz, 6-H), 7.15–7.50 (7H, m, 7-H, 8-H and aryl-H), 9.29 (1H, d, *J* = 7.0Hz, 5-H), 12.52 (1H, br s, SH). *Anal*. Calcd for $C_{17}H_{15}NOS_2$: C, 65.15; H, 4.82; N, 4.47. Found: C, 65.40; H, 4.77; N, 4.27. Positive ion ESI-HRMS Calcd for $C_{17}H_{15}NOS_2$ $[M+H]^+$: 314.06678. Found *m*/*z* 314.0675.

(*Z*)-3-[(Ethoxycarbonylmethylthio)mercaptomethylene]-1-methyl-2(3*H*)-indolizinone (1k): 46% (from 2-ethyl-1-(ethoxycarbonylmethyl)pyridinium bromide, CS_2, and ethyl bromoacetate), orange

prisms, mp 125–126 °C. IR (KBr) cm^{-1}: 1596 (CO), 1732 (CO), 2662 (SH). ^{1}H-NMR ($CDCl_3$): 1.32 (3H, t, *J* = 7.1 Hz,), 2.16 (3H, s, 1-Me), 4.26 (2H, q, *J* = 7.1 Hz,), 4.33 (2H, s, SCH_2), 6.77–6.83 (1H, m, 6-H), 7.23–7.31 (2H, m, 7-H and 8-H), 9.34 (1H, d, *J* = 7.0Hz, 5-H), 12.22 (1H, br s, SH). *Anal*. Calcd for $C_{14}H_{15}NO_3S_2$: C, 54.35; H, 4.89; N, 4.53. Found: C, 54.58; H, 4.84; N, 4.34. Positive ion ESI-HRMS Calcd for $C_{14}H_{15}NO_3S_2$ $[M+H]^+$: 310.0566. Found *m*/*z* 310.0574.

1-Ethyl-(*Z*)-3-[(ethylthio)mercaptomethylene]-2(3*H*)-indolizinone (1m): 38% (from 1-ethoxycarbonylmethyl-2-propylpyridinium bromide, CS_2, and diethyl sulfate), red prisms, mp 59–61 °C. IR (KBr) cm^{-1}: 1589 (CO), 2612 (SH). ^{1}H-NMR ($CDCl_3$): 1.21 (3H, t, *J* = 7.5Hz), 1.47 (3H, t, *J* = 7.4Hz), 2.68 (2H, q, *J* = 7.5Hz), 3.52 (2H, q, *J* = 7.4Hz), 6.77 (1H, dt, *J* = 7.0, 1.5Hz, 6-H), 7.18–7.33 (2H, m, 7-H and 8-H), 9.39 (1H, d, *J* = 7.1Hz, 5-H), 12.60 (1H, br s, SH). *Anal*. Calcd for $C_{13}H_{15}NOS_2$: C, 58.84; H, 5.70; N, 5.28. Found: C, 58.87; H, 5.55; N, 4.98. Positive ion ESI-HRMS Calcd for $C_{13}H_{15}NOS_2$ $[M+H]^+$: 266.0667. Found *m*/*z* 266.0676.

1-Ethyl-(*Z*)-3-[(benzylthio)mercaptomethylene]-2(3*H*)-indolizinone (1n): 44% (from 1-ethoxycarbonylmethyl-2-propylpyridinium bromide, CS_2, and benzyl bromide), red prisms, mp 98–99 °C. IR (KBr) cm^{-1}: 1589 (CO), 2640 (SH). ^{1}H-NMR ($CDCl_3$): 1.21 (3H, t, *J* = 7.6Hz, 1-CH_2CH_3), 2.68 (2H, q, *J* = 7.6 Hz, 1-CH_2CH_3), 4.74 (2H, s, SCH_2Ph), 6.71 (1H, dt, *J* = 6.9, 1.4 Hz, 6-H), 7.15–7.49 (7H, m, 7-H, 8-H, and aryl-H), 9.29 (1H, d, *J* = 7.2 Hz, 5-H), 12.51 (1H, br s, SH). *Anal*. Calcd for $C_{18}H_{17}NOS_2$: C, 66.02; H, 5.23; N, 4.28. Found: C, 66.26; H, 5.13; N, 4.14. Positive ion ESI-HRMS Calcd for $C_{18}H_{17}NOS_2$ $[M+H]^+$ 328.0824. Found *m*/*z* 328.0825.

Preparation of 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinone derivatives (3a–n and 4a–n). General method. A chloroform solution (40 mL) of 3-(mercaptomethylene)-2(3*H*)-indolizinone (**1**, 8.4 mmol) and ethyl bromoacetate (**2**, 16.9 mmol) was treated with DBU (16.9 mmol) at 50 °C for 10 min. The mixture was diluted with $CHCl_3$ and washed with 2*N*-HCl twice. The organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using hexane-EtOAc as an eluent. Evaporation of the solvent and recrystallization from Et_2O to provide the corresponding 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinone derivatives(**4a**–**n**) as *cis*/*trans* mixtures.

The ^{1}H-NMR spectra for compounds **3a**–**n** and **4a**–**n** are shown in Table 1 and the other data are as follows.

Ethyl 3-methylthio-4-oxo-5-phenyl-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3a+4a): 59% (from **1a** and **2**), red powder. IR (KBr) cm^{-1}: 1618 (CO), 1736 (CO). *Anal*. Calcd for $C_{20}H_{19}NO_3S_2$: C, 62.31; H, 4.97; N, 3.63. Found: C, 62.11; H, 5.03; N, 3.57.

Ethyl 3-ethylthio-4-oxo-5-phenyl-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate

(3b+4b): 49% (from **1b** and **2**), red powder. IR (KBr) cm^{-1}: 1623 (CO), 1724 (CO). *Anal*. Calcd for $C_{21}H_{21}NO_3S_2$: C, 63.13; H, 5.30; N, 3.51. Found: C, 63.09; H, 5.23; N, 3.25.

Ethyl 3-benzylthio-4-oxo-5-phenyl-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3c+4c(trace)): 23% (from **1c** and **2**), red powder, mp 164–166 °C (**3c**). IR (KBr) cm^{-1}: 1618 (CO), 1732 (CO). *Anal*. Calcd for $C_{26}H_{23}NO_3S_2$: C, 67.65; H, 5.02; N, 3.03. Found: C, 67.81; H, 5.00; N, 2.90.

Ethyl 3-ethoxycarbonylmethylthio-4-oxo-5-phenyl-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]-indolizine-1-carboxylate (3d+4d(trace)): 34% (from **1d** and **2**), red powder, mp 105–109 °C (**3d**). IR (KBr) cm^{-1}: 1624 (CO), 1735 (CO). *Anal*. Calcd for $C_{23}H_{23}NO_5S_2$: C, 60.38; H, 5.07; N, 3.06. Found: C, 60.21; H, 5.29; N, 3.00.

Ethyl 5-(*p*-chlorophenyl)-3-methylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3e+4e): 55% (from **1e** and **2**), red powder. IR (KBr) cm^{-1}: 1621 (CO), 1732 (CO). *Anal*. Calcd for $C_{20}H_{18}ClNO_3S_2$: C, 57.20; H, 4.32; N, 3.34. Found: C, 57.29; H, 4.41; N, 3.10.

Ethyl 5-(*p*-chlorophenyl)-3-ethylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3f+4f): 36% (from **1f** and **2**), red powder. IR (KBr) cm^{-1}: 1623 (CO), 1721 (CO). *Anal*. Calcd for $C_{21}H_{20}ClNO_3S_2$: C, 58.12; H, 4.65; N, 3.23. Found: C, 58.29; H, 4.65; N, 2.95.

Ethyl 3-benzylthio-5-(*p*-chlorophenyl)-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3g+4g): 59% (from **1g** and **2**), red powder. IR (KBr) cm^{-1}: 1615 (CO), 1729 (CO). *Anal*. Calcd for $C_{26}H_{22}ClNO_3S_2$: C, 62.96; H, 4.47; N, 2.82. Found: C, 63.11; H, 4.73; N, 2.52.

Ethyl 5-methyl-3-methylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3h+4h): 63% (from **1h** and 2), red powder. IR (KBr) cm^{-1}: 1616 (CO), 1720 (CO). *Anal*. Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.71; H, 5.30; N, 4.33. Found: C, 55.77; H, 5.29; N, 4.21.

Ethyl 5-methyl-3-ethylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3i+4i): 73% (from **1i** and **2**), orange powder. IR (KBr) cm^{-1}: 1621 (CO), 1729 (CO). *Anal*. Calcd for $C_{16}H_{19}NO_3S_2$: C, 56.95; H, 5.68; N, 4.15. Found: C, 56.89; H, 5.66; N, 4.04.

Ethyl 3-benzylthio-5-methyl-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3j+4j): 72% (from **1j** and **2**), red powder. IR (KBr) cm^{-1}: 1618 (CO), 1737 (CO). *Anal*. Calcd for $C_{21}H_{21}NO_3S_2$: C, 63.13; H, 5.30; N, 3.51. Found: C, 63.04; H, 5.41; N, 3.22.

Ethyl 3-ethoxycarbonylmethylthio-5-methyl-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]-indolizine-1-carboxylate (3k+4k): 58% (from **1k** and **2**), red powder. IR (KBr) cm^{-1}: 1616 (CO), 1736 (CO). *Anal*. Calcd for $C_{18}H_{21}NO_5S_2$: C, 54.67; H, 5.35; N, 3.54. Found: C, 54.53; H, 5.31; N, 3.59.

Ethyl 5-ethyl-3-methylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3l+4l(trace)): 70% (from **1l** and **2**), red prisms, mp 105–108 °C (**3l**). IR (KBr) cm^{-1}: 1618 (CO),

1736 (CO). *Anal*. Calcd for $C_{16}H_{19}NO_3S_2$: C, 56.95; H, 5.68; N, 4.15. Found: C, 57.01; H, 5.70; N, 4.07.

Ethyl 5-ethyl-3-ethylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3m+4m): 58% (from **1m** and **2**), red prisms. IR (KBr) cm^{-1}: 1619 (CO), 1731 (CO). *Anal*. Calcd for $C_{17}H_{21}NO_3S_2$: C, 58.09; H, 6.02; N, 3.99. Found: C, 58.11; H, 6.05; N, 3.88.

Ethyl 5-ethyl-3-methylthio-4-oxo-1*H*-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizine-1-carboxylate (3n+4n): 30% (from **1n** and **2**), red prisms. IR (KBr) cm^{-1}: 1618 (CO), 1725 (CO). *Anal*. Calcd for $C_{22}H_{23}NO_3S_2$: C, 63.90; H, 5.61; N, 3.39. Found: C, 63.99; H, 5.71; N, 3.15.

Preparation of 2-(alkylthio)cycl[3.2.2]azin-3-ol derivatives (8a–n) and 3-Acetoxy-2-(alkylthio)cycl-[3.2.2]azine derivatives. (10a–n). General method A. A suspension of 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]indolizinone (**3+4**, 1 mmol), DDQ (0.341g, 1.5 mmol), and 2,4,6-collidine (5 mL) was heated at 180 °C for 15 min. After cooling, the reaction mixture was diluted with AcOEt (30 mL) and 1*N*-HCl (30 mL). The separated precipitates were removed by suction. The organic layer which was collected using a separatory funnel was washed was then washed with 1*N*-HCl (30 mL). The organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using hexane-AcOEt as an eluent. Evaporation of the solvent and recrystallization from CH_2Cl_2-Et_2O provided the corresponding 2-(alkylthio)cycl[3.2.2]azin-3-ol derivatives (**8a**–**n**).

General method B. In these reactions, mixtures of 4(1*H*)-8,8a-dihydro-1,4-thiazino[3,4,5-*cd*]-indolizinone (**3+4**, 1 mmol), DDQ (0.341g, 1.5 mmol), acetic anhydride (0.49 mL), and 2,4,6-collidine (5 mL) were heated at 180 °C for 15 min. The same work-ups described above for the resulting reaction mixtures afforded the corresponding 3-Acetoxy-2-(alkylthio)cycl[3.2.2]azine derivatives (**10a**–**n**).

The elemental analyses of some cycl[3.2.2]azin-3-ol derivatives (**8h**–**k**) having the 4-methyl group were unsuccessful because of their thermal instability. Interestingly, the ^{1}H-NMR measurements of these cycl[3.2.2]azin-3-ols (**8a**–**n**) in $CDCl_3$ indicated the presence of the keto type tautomers, 3(4*H*)-cycl[3.2.2]azin-3-ones (**9a**–**n**), while those in DMSO-*d*6 exhibited only the enol forms **8a**–**n**.

The ^{1}H-NMR spectral data for cycl[3.2.2]azine derivatives **8a**–**n** and **10a**–**n** are listed in Table 2 and the other results are as follows.

Ethyl 3-hydroxy-2-methylthio-4-phenylcycl[3.2.2]azine-1-carboxylate (8a): 51% (from **3a+4a**), pale yellow powder, mp 86–88 ^{o}C. IR (KBr) cm^{-1}: 1665 (CO). ^{1}H-NMR ($CDCl_3$): **8a**; 1.51 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.98 (3H, s, SMe), 4.49 (2H, q, J = 7.1 Hz, OCH_2CH_3), 6.27 (1H, br s, OH), 7.41, 7.58, and 7.69 (5H, aryl-H), 7.49 (1H, d, J = 7.9 Hz, 5-H), 7.74 (1H, t, J = 7.9 Hz, 6-H), 8.07 (1H, d, J = 7.9 Hz, 7-H). **9a**; 1.46 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.90 (3H, s, SMe), 4.44 (2H, q, J = 7.1 Hz,

OC*H*$_2$CH$_3$), 4.95 (1H, s, 4-H), 7. 1–7.4 (5H, aryl-H), 6.78 (1H, d, *J* = 7.1 Hz, 5-H), 7.46 (1H, q, *J* = 7.1, 8.9 Hz, 6-H), 7.86 (1H, d, *J* = 8.9 Hz, 7-H). Positive ion ESI-HRMS Calcd for $C_{20}H_{18}NO_3S$ $[M+H]^+$: 352.1002. Found *m*/*z* 352.1013. *Anal*. Calcd for $C_{20}H_{17}NO_3S+H_2O$: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.18; H, 5.11; N, 3.69.

Ethyl 2-ethylthio-3-hydroxy-4-phenylcycl[3.2.2]azine-1-carboxylate (8b): 49% (from **3b+4b**), pale yellow prisms, mp 53–54 °C. IR (KBr) cm^{-1}: 1664 (CO), 1686 (CO). Positive ion ESI-HRMS Calcd for $C_{21}H_{20}NO_3S$ $[M+H]^+$: 366.1158. Found *m*/*z* 366.1158. *Anal*. Calcd for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; N, 3.83. Found: C, 69.15; H, 5.22; N, 3.73.

Ethyl 2-benzylthio-3-hydroxy-4-phenylcycl[3.2.2]azine-1-carboxylate (8c): 36% (from **3c+4c**), pale yellow powder, mp 65–67 °C. IR (KBr) cm^{-1}: 1686 (CO). Positive ion ESI-HRMS Calcd for $C_{26}H_{22}NO_3S$ $[M+H]^+$: 366.1158. Found *m*/*z* 366.1158. *Anal*. Calcd for $C_{26}H_{21}NO_3S$: C, 73.05; H, 4.95; N, 3.28. Found: C, 73.31; H, 4.97; N, 3.17.

Ethyl 2-ethoxycarbonylmethylthio-3-hydroxy-4-phenylcycl[3.2.2]azine-1-carboxylate (8d): 24% (from **3d+4d**), pale brown powder, mp 119–121 °C. IR (KBr) cm^{-1}: 1686 (CO), 1697 (CO). Positive ion ESI-HRMS Calcd for $C_{23}H_{22}NO_5S$ $[M+H]^+$: 424.1213. Found *m*/*z* 424.1217.

Ethyl 4-(*p*-chlorophenyl)-2-methylthio-3-hydroxycycl[3.2.2]azine-1-carboxylate (8e): 32% (from **3e+4e**), yellow powder, mp 178–180 °C. IR (KBr) cm^{-1}: 1664 (CO). Positive ion ESI-HRMS Calcd for $C_{20}H_{17}ClNO_3S$ $[M+H]^+$: 386.0612. Found *m*/*z* 386.0624. *Anal*. Calcd for $C_{20}H_{16}ClNO_3S$: C, 62.25; H, 4.18; N, 4.21. Found: C, 62.55; H, 4.21; N, 3.53.

Ethyl 4-(*p*-chlorophenyl)-2-ethylthio-3-hydroxycycl[3.2.2]azine-1-carboxylate (8f): 44% (from **3f+4f**), pale yellow powder, mp 156–158 °C. IR (KBr) cm^{-1}: 1656 (CO). Positive ion ESI-HRMS Calcd for $C_{21}H_{19}ClNO_3S$ $[M+H]^+$: 400.1036. Found *m*/*z* 400.1031. *Anal*. Calcd for $C_{21}H_{18}ClNO_3S$: C, 63.07; H, 4.54; N, 3.50. Found: C, 63.27; H, 4.62; N, 3.22.

Ethyl 4-(*p*-chlorophenyl)-2-benzylthio-3-hydroxycycl[3.2.2]azine-1-carboxylate (8g): 21% (from **3g+4g**), red powder, mp 173–174 °C. IR (KBr) cm^{-1}: 1655 (CO). Positive ion ESI-HRMS Calcd for $C_{26}H_{21}ClNO_3S$ $[M+H]^+$: 462.1192. Found *m*/*z* 462.1188. *Anal*. Calcd for $C_{26}H_{20}ClNO_3S$: C, 67.60; H, 4.36; N, 3.03. Found: C, 67.61; H, 4.35; N, 2.78.

Ethyl 4-ethyl-2-methylthio-3-hydroxycycl[3.2.2]azine-1-carboxylate (8l): 24% (from **3l+4l**), pale brown powder, mp 110–111 °C. IR (KBr) cm^{-1}: 1685 (CO). ^{1}H-NMR ($CDCl_3$). **8l**; 0.90 (3H, t, *J* = 7.4 Hz, 4-CH$_2$C*H*$_3$), 1.45 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.9–2.3 (2H, m, 4-C*H*$_2$CH$_3$), 2.92 (3H, s, SMe), 4.45 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 7.63 (1H, d, *J* = 7.8 Hz, 5-H), 7.79 (1H, q, *J* = 7.8, 8.3 Hz, 6-H), 8.09 (1H, d, *J* = 8.3 Hz, 7-H), 9.93 (1H, br s, OH). **9l**; 0.98 (3H, t, *J* = 7.5 Hz, 4-CH$_2$C*H*$_3$), 1.49 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.9–2.3 (2H, m, 4-C*H*$_2$CH$_3$), 2.95 (3H, s, SMe), 3.80 (1H, m, 4-H), 4.43 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 6.85 (1H, d, *J*=7.1 Hz, 5-H), 7.45 (1H, q, *J* = 7.1, 8.9 Hz, 6-H), 7.82 (1H, d, *J* = 8.9

Hz, 7-H). Positive ion ESI-HRMS Calcd for $C_{16}H_{18}NO_3S$ $[M+H]^+$: 366.1158. Found *m*/*z* 366.1158. *Anal*. Calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.35; H, 5.66; N, 4.53.

Ethyl 4-ethyl-2-ethylthio-3-hydroxycycl[3.2.2]azine-1-carboxylate (8m): 16% (from **3m+4m**), pale yellow powder, mp 96–97 °C. IR (KBr) cm^{-1}: 1655 (CO). Positive ion ESI-HRMS Calcd for $C_{17}H_{19}NO_3SNa$ $[M+Na]^+$: 340.0979. Found *m*/*z* 340.0978.

Ethyl 2-benzylthio-4-ethyl-3-hydroxycycl[3.2.2]azine-1-carboxylate (8n): 24% (from **3n+4n**), pale brown powder, mp 108–110 °C. IR (KBr) cm^{-1}: 1676 (CO). Positive ion ESI-HRMS Calcd for $C_{21}H_{20}NO_3S$ $[M+H]^+$: 380.1315. Found *m*/*z* 380.1324.

Ethyl 3-acetoxy-2-methylthio-4-phenylcycl[3.2.2]azine-1-carboxylate (10a): 65% (from **3a+4a**), yellow prisms, mp 196–198 °C. IR (KBr) cm^{-1}: 1690 (CO), 1769 (CO). Positive ion ESI-HRMS Calcd for $C_{22}H_{20}NO_4S$ $[M+H]^+$: 394.1108. Found *m*/*z* 394.1110. *Anal*. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56. Found: C, 67.15; H, 4.83; N, 3.61.

Ethyl 3-acetoxy-2-ethylthio-4-phenylcycl[3.2.2]azine-1-carboxylate (10b): 53% (from **3b+4b**), yellow needles, mp 171–172 °C. IR (KBr) cm^{-1}: 1692 (CO), 1769 (CO). Positive ion ESI-HRMS Calcd for $C_{23}H_{22}NO_4S$ $[M+H]^+$: 408.1264. Found *m*/*z* 408.1267. *Anal*. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.91; H, 5.05; N, 3.46.

Ethyl 3-acetoxy-2-benzylthio-4-phenylcycl[3.2.2]azine-1-carboxylate (10c): 26% (from **3c+4c**), orange prisms, mp 152–153 °C. IR (KBr) cm^{-1}: 1679 (CO), 1770 (CO). Positive ion ESI-HRMS Calcd for $C_{28}H_{24}NO_4S$ $[M+H]^+$: 470.1421. Found *m*/*z* 470.1421. *Anal*. Calcd for $C_{28}H_{23}NO_4S$: C, 71.62; H, 4.94; N, 2.98. Found: C, 71.36; H, 4.78; N, 2.81.

Ethyl 3-acetoxy-2-ethoxycarbonylmethylthio-4-phenylcycl[3.2.2]azine-1-carboxylate (10d): 23% (from **3d+4d**), pale yellow powder, mp 124–125 °C. IR (KBr) cm^{-1}: 1688 (CO), 1747 (CO), 1785 (CO). Positive ion ESI-HRMS Calcd for $C_{25}H_{24}NO_6S$ $[M+H]^+$: 466.1319. Found *m*/*z* 466.1325. *Anal*. Calcd for $C_{25}H_{23}NO_6S$: C, 64.50; H, 4.98; N, 3.01. Found: C, 64.69; H, 4.89; N, 2.84.

Ethyl 3-acetoxy-4-(*p*-chlorophenyl)-2-(methylthio)cycl[3.2.2]azine-1-carboxylate (10e): 49% (from **3a+4a**), pale yellow needles, mp 192–194 °C. IR (KBr) cm^{-1}: 1686 (CO), 1773 (CO). Positive ion ESI-HRMS Calcd for $C_{22}H_{19}ClNO_4S$ $[M+H]^+$: 428.0718. Found *m*/*z* 428.0725. *Anal*. Calcd for $C_{22}H_{18}ClNO_4S$: C, 61.75; H, 4.24; N, 3.27. Found: C, 61.71; H, 4.29; N, 3.17.

Ethyl 3-acetoxy-4-(*p*-chlorophenyl)-2-(ethylthio)cycl[3.2.2]azine-1-carboxylate (10f): 56% (from **3f+4f**), pale yellow needles, mp 145–146 °C. IR (KBr) cm^{-1}: 1697 (CO), 1773 (CO). Positive ion ESI-HRMS Calcd for $C_{23}H_{21}ClNO_4S$ $[M+H]^+$: 442.0874. Found *m*/*z* 442.0874. *Anal*. Calcd for $C_{23}H_{20}ClNO_4S$: C, 62.51; H, 4.56; N, 3.17. Found: C, 62.69; H, 4.70; N, 3.08.

Ethyl 3-acetoxy-4-(*p*-chlorophenyl)-2-(benzylthio)cycl[3.2.2]azine-1-carboxylate (10g): 18% (from **3a+4a**), pale yellow needles, mp 197–198 °C. IR (KBr) cm^{-1}: 1686 (CO), 1773 (CO). Positive ion

ESI-HRMS Calcd for $C_{28}H_{23}ClNO_4S$ $[M+H]^+$: 504.1031. Found *m*/*z* 504.1034. *Anal*. Calcd for $C_{28}H_{22}ClNO_4S$: C, 66.73; H, 4.40; N, 2.78. Found: C, 66.78; H, 4.49; N, 2.72.

Ethyl 3-acetoxy-4-methyl-2-(methylthio)cycl[3.2.2]azine-1-carboxylate (10h): 10% (from **3h+4h**), pale yellow needles, mp 145–146 °C. IR (KBr) cm^{-1}: 1682 (CO), 1764 (CO). Positive ion ESI-HRMS Calcd for $C_{17}H_{18}NO_4S$ $[M+H]^+$: 332.0958. Found *m*/*z* 332.0951. *Anal*. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.61; H, 5.18; N, 4.22.

Ethyl 3-acetoxy-2-ethylthio-4-methylcycl[3.2.2]azine-1-carboxylate (10i): 11% (from **3i+4i**), pale yellow needles, mp 129–130 °C. IR (KBr) cm^{-1}: 1673 (CO), 1774 (CO). Positive ion ESI-HRMS Calcd for $C_{18}H_{20}NO_4S$ $[M+H]^+$: 346.1108. Found *m*/*z* 346.1117. *Anal*. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.66; H, 5.55; N, 3.98.

Ethyl 3-acetoxy-2-benzylthio-4-methylcycl[3.2.2]azine-1-carboxylate (10j): 15% (from **3j+4j**), pale yellow needles, mp 133–135 °C. IR (KBr) cm^{-1}: 1678 (CO), 1764 (CO). Positive ion ESI-HRMS Calcd for $C_{23}H_{22}NO_4S$ $[M+H]^+$: 408.1264. Found *m*/*z* 408.1271. *Anal*. Calcd for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.76; H, 5.17; N, 3.32.

Ethyl 3-acetoxy-2-ethoxycarbonylmethylthio-4-methylcycl[3.2.2]azine-1-carboxylate (10k): 17% (from **3k+4k**), yellow needles, mp 115–116 °C. IR (KBr) cm^{-1}: 1680 (CO), 1739 (CO), 1773 (CO). Positive ion ESI-HRMS Calcd for $C_{20}H_{22}NO_6S$ $[M+H]^+$: 404.1162, Found *m*/*z* 404.1167. *Anal*. Calcd for $C_{20}H_{21}NO_6S$: C, 59.54; H, 5.25; N, 3.47. Found: C, 59.62; H, 5.21; N, 3.43.

Ethyl 3-acetoxy-4-ethyl-2-(methylthio)cycl[3.2.2]azine-1-carboxylate (10l): 43% (from **3l+4l**), yellow needles, mp 111–112 °C. IR (KBr) cm^{-1}: 1679 (CO), 1762 (CO). Positive ion ESI-HRMS Calcd for $C_{18}H_{20}NO_4S$ $[M+H]^+$: 346.1108. Found *m*/*z* 346.1112. *Anal*. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.88; H, 5.42; N, 3.90.

Ethyl 3-acetoxy-4-ethyl-2-(ethylthio)cycl[3.2.2]azine-1-carboxylate (10m): 38% (from **3m+4m**), yellow prisms, mp 97–98 °C. IR (KBr) cm^{-1}: 1697 (CO), 1759 (CO). Positive ion ESI-HRMS Calcd for $C_{19}H_{22}NO_4S$ $[M+H]^+$: 360.1264. Found *m*/*z* 360.1266. *Anal*. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.80; H, 5.76; N, 3.71.

Ethyl 3-acetoxy-2-benzylthio-4-ethylcycl[3.2.2]azine-1-carboxylate (10n): 23% (from **3n+4n**), orange prisms, mp 125–126 °C. IR (KBr) cm^{-1}: 1678 (CO), 1769 (CO). Positive ion ESI-HRMS Calcd for $C_{24}H_{24}NO_4S$ $[M+H]^+$: 422.1421. Found *m*/*z* 422.1428. *Anal*. Calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32. Found: C, 68.69; H, 5.34; N, 3.18.

Crystallography of ethyl 3-acetoxy-2-ethylthio-4-methylcycl[3.2.2]azine-1-carboxylates (10i). A single crystal (0.18×0.32×0.68 mm) grown from CH_2Cl_2–Et_2O was used for the unit-cell determinations and the data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated

MoK_a radiation (l = 0.71069 Å). Crystal data of **10i**: $C_{18}H_{19}NO_4S$; M = 345.41; monoclinic, space group $P2_1/c$ (#14), Z = 4 with a = 9.63 (2) Å, b = 19.14 (3) Å, c = 9.99 (2) Å, β = 109.91° (15); V = 1731 (7) Å^3, and $D_{calc.}$ = 1.326 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a direct method (SIR).[17] 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 0.064 and 0.047 for 1288 (I>2.00(I)) observed reflections, respectively.

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