Preparation of New Nitrogen-Bridged Heterocycles. XXXIII.[1] A New Preparative Method for Thieno[3,2-*a*]indolizines

Akikazu KAKEHI,* Suketaka ITO, Tatsuya UEDA, and Satoshi TAKANO

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan. Received April 12, 1993

The treatment of 2-iminothieno[3,2-*a*]indolizine derivatives with potassium *tert*-butoxide generated exclusively potassium 1-(2-cyanovinyl)indolizine-2-thiolates through the ring opening of the initially formed thiin-2-imide ions. These 2-indolizinethiolates reacted with various alkylating agents to give the corresponding *S*-alkylated 1-vinylindolizine derivatives, and 2-acetonylthio- and 2-phenacylthio-1-(2-cyanovinyl)indolizines of these products smoothly underwent intramolecular Michael addition under the conditions employed here to afford the corresponding 2-acetyl- and 2-aroylthieno[3,2-*a*]indolizines in high yields with the elimination of a methylene compound.

Keywords indolizine; thiino[3,2-*a*]indolizine; thieno[3,2-*a*]indolizine; ring transformation; alkylation; intramolecular Michael addition

In previous papers[2] from this laboratory, we reported that some tricyclic indolizine derivatives fused with a sulfur-containing ring can be smoothly prepared *via* intra- and intermolecular reaction sequences from polyfunctionalized indolizines. We also described functionalization at appropiate positions on the indolizine skeleton for further cyclization. In a continuation of our efforts to develop a novel method for the preparation of nitrogen-bridged heterocycles, we found recently that the thiino[3,2-*a*]-indolizine-2-imide ion, generated by treatment of the corresponding 2-iminothiino[3,2-*a*]indolizine derivative with a strong base, is in equilibrium with its tautomer, 1-(2-cyanovinyl)-2-indolizinethiolate ion. We were very interested in this phenomenon because of the synthetic versatility of 2-indolizinethiolate derivatives reported earlier by us.[2g,3] In this paper we wish to describe facile preparations of 2-alkylthio-1-(2-cyanovinyl)indolizines through the reactions of 2-iminothiino[3,2-*a*]indolizines with alkyl halides in the presence of a base such as potassium *tert*-butoxide and the spontaneous transformation of some *S*-alkylated compounds to thieno[3,2-*a*]indolizine derivatives.

Results and Discussion

Reactions of 2-Iminothiino[3,2-*a*]indolizines with Some Alkylating Agents in the Presence of a Strong Base When the alkylation reaction of diethyl 2-iminothiino[3,2-*a*]-indolizine-3,9-dicarboxylate hydrochloride (**1a**)[2a] with ethyl bromoacetate **2a** in the presence of potassium *tert*-butoxide was examined in the expectation of the formation of *N*-functionalized thiino[3,2-*a*]indolizine, the corresponding 2-(ethoxycarbonylmethyl)imino derivative such as **4** could not be obtained at all but, instead, ethyl 1-(2-cyano-2-ethoxycarbonylvinyl)-2-(ethoxycarbonylmethylthio)indolizine-3-carboxylate (**3a**) was obtained in 92% yield. Similar reaction of **1a** with methyl iodide **2b** gave the corresponding 2-methylthio compound **3b** in 89% yield (Chart 1). The structure of **3a** was assigned mainly on the basis of a cyano absorption band at 2213 cm^{-1} in the infrared (IR) spectrum and of a *S*-methylene singlet at δ 3.67 in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, and that of compound **3b**, mp 107 °C (lit.[4] mp 107 °C), was determined by direct comparison with an authentic sample.

Mechanistically, the fact that the products in these reactions were *S*-alkylated 1-(2-cyanovinyl)indolizines **3a**, **b** and not *N*-alkylated 2-iminothiino[3,2-*a*]indolizines **4** strongly suggested the existence of an equilibrium between the thiino[3,2-*a*]indolizine-2-imide ion **5** and the 1-(2-cyanovinyl)-2-indolizinethiolate ion **6**, and the exclusive

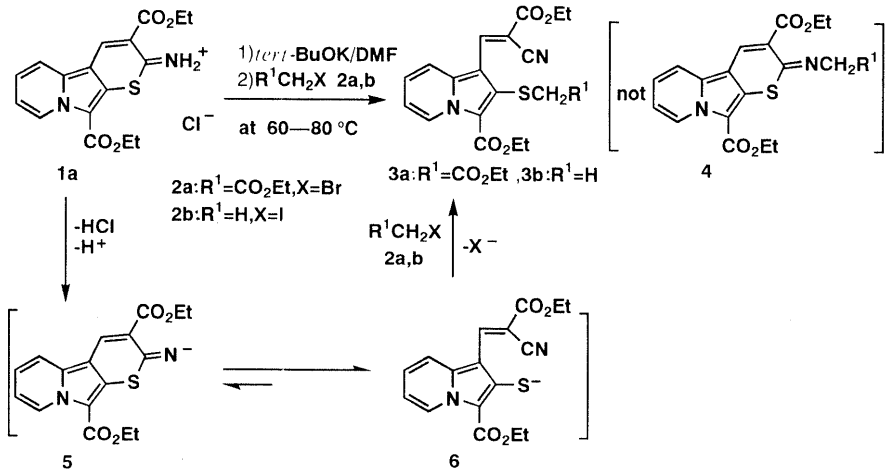
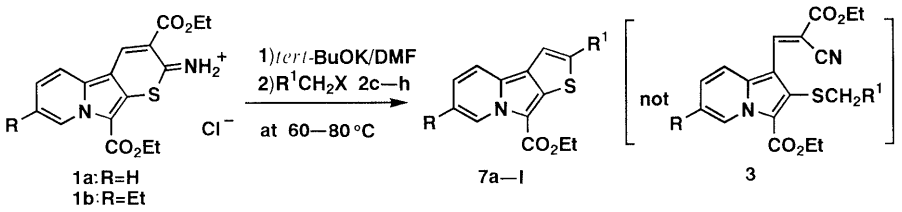


Chart 1



1a: R=H
1b: R=Et

7a—l

3

2	R^1	X
c	COMe	Cl
d	COPh	Br
e	COC_6H_4Cl-*p*	Br
f	COC_6H_4Br-*p*	Br
g	COC_6H_4Me-*p*	Br
h	COC_6H_4Ph-*p*	Cl

7	R	R^1
a	H	COMe
b	H	COPh
c	H	COC_6H_4Cl-*p*
d	H	COC_6H_4Br-*p*
e	H	COC_6H_4Me-*p*
f	H	COC_6H_4Ph-*p*

7	R	R^1
g	Et	COMe
h	Et	COPh
i	Et	COC_6H_4Cl-*p*
j	Et	COC_6H_4Br-*p*
k	Et	COC_6H_4Me-*p*
l	Et	COC_6H_4Ph-*p*

Chart 2

TABLE I. ^{1}H-NMR Spectral Data for Thieno[3,2-*a*]indolizines (7)

Compd. 7[a)]	δ ($CDCl_3$) C-3	C-4	C-5	C-6	C-7	R^1	CO_2Et
7a	8.06 s	7.92 br d	7.39 br t	7.16 dt	9.71 br d	2.64 s	1.46 t, 4.46 q
7b	7.99 s	b)	b)	7.21 dt	9.82 br d	7.3—8.2 m	1.49 t, 4.49 q
7c	8.02 s	b)	b)	7.12 dt	9.90 br d	7.3—8.3 m	1.48 t, 4.43 q
7d	7.91 s	b)	b)	7.27 dt	9.72 br d	7.3—8.1 m	1.50 t, 4.49 q
7e	7.95	b)	b)	7.10 dt	9.79 br d	7.2—8.0 m, 2.40 s	1.45 t, 4.40 q
7f	b)	b)	b)	7.20 dt	9.86 br d	7.1—8.3 m	1.50 t, 4.49 q
7g	7.98 s	7.72 d	7.23 dd	1.35 t, 2.77 q	9.52 br s	2.62 s	1.50 t, 4.47 q
7h	7.93 s	b)	7.22 dd	1.34 t, 2.79 q	9.60 br s	7.5—8.1 m	1.50 t, 4.49 q
7i	7.92 s	b)	7.24 dd	1.33 t, 2.79 q	9.61 br s	7.4—8.2 m	1.48 t, 4.47 q
7j	7.89 s	b)	7.25 dd	1.36 t, 2.80 q	9.59 br s	7.4—8.0 m	1.52 t, 4.48 q
7k	8.03 s	b)	7.27 dd	1.33 t, 2.79 q	9.77 br s	7.3—8.2 m, 2.45 s	1.48 t, 4.44 q
7l	7.98 s	b)	b)	1.33 t, 2.77 q	9.59 br s	7.0—8.3 m	1.49 t, 4.47 q

a) The coupling constants are as follows: $J_{4,5}=9.0$ Hz, $J_{5,6}=J_{6,7}=7.0$ Hz, $J_{5,7}=2.0$ Hz, $J_{Et}=7.0$ Hz. *b*) Overlapped with the phenyl proton signals.

formation of **3a**, **b** by the soft–soft interaction[5)] of alkylating agents **2a**, **b** with the latter ion **6**.

Since it was anticipated that the alkylation of 2-iminothiino[3,2-*a*]indolizine in the presence of a base would lead to various *S*-functionalized 1-(2-cyanovinyl)indolizine derivatives, which are potential precursors for further condensed heterocycles, we next examined the reactions of 2-iminothiino[3,2-*a*]indolizine derivatives with other alkyl halides. However, the treatment of diethyl 2-iminothiino-[3,2-*a*]indolizine-3,9-dicarboxylate hydrochlorides **1a**, **b**[2a)] with potassium *tert*-butoxide followed by the addition of chloroacetone **2c** did not afford the initially expected 2-acetonylthio-1-vinylindolizine derivatives such as **3** or 2-(acetonylimino)thiino[3,2-*a*]indolizine such as **4**, but gave ethyl 2-acetylthieno[3,2-*a*]indolizine-8-carboxylate (**7a**) and its 6-ethyl derivative **7g** in 54 and 80% yields, respectively. Similarly, the reactions of hydrochlorides **1a**, **b** with phenacyl bromide (**2d**), *p*-chlorophenacyl bromide (**2e**), *p*-bromophenacyl bromide (**2f**), *p*-methylphenacyl bromide (**2g**), and *p*-phenylphenacyl chloride (**2h**) yielded the same types of products **7b**—**f**, **h**—**l** in 73—96% yields (Chart 2). Furthermore, the gas chromtographic monitoring of some reaction solutions clearly showed the generation of a methylene compound, ethyl cyanoacetate (**10**) in them. In contrast with the smooth transformation of 2-acetonylthio- and 2-phenacylthio-1-vinylindolizine intermediates to the corresponding thieno[3,2-*a*]indolizines **7a**—**l**, however, the alkaline treatment of 2-ethoxycarbonylmethylthio-3-vinylindolizine **3a** did not give any thieno-[3,2-*a*]indolizine.

The structures of products **7a**—**l** were determined by physical and spectral means and from mechanistic considerations. For example, the ^{1}H-NMR spectrum (see Table I) of compound **7a** showed signals at δ 7.16 (1H, dt, $J=7.0$, 7.0, 2.0 Hz, 6-H), 7.39 (1H, br t, $J=9.0$, 7.0 Hz, 5-H), 7.92 (1H, br d, $J=9.0$ Hz, 4-H), and 9.71 (1H, br d, $J=7.0$ Hz, 7-H) due to four protons on the pyridine ring, at δ 2.64 (3H, s) due to an acetyl group, and at δ 8.06 (1H, s) due to the vinyl proton on the thiophene ring, together with proton signals of an ethoxycarbonyl group at δ 1.46 (3H, t, $J=7.0$ Hz) and 4.46 (2H, q, $J=7.0$ Hz). The IR spectrum of **7a** exhibited two carbonyl absorption bands at 1676 and 1640 cm^{-1} but no cyano absorption bands. The absence of any methylene groups derived from the alkylating agents **2c**—**h** employed here and of any cyano groups attributable to the 1-(2-cyanovinyl)-2-indolizinethiolate structure **6** in the ^{1}H-NMR (Table I) and IR spectra (Table II) showed clearly that these compounds **7a**—**l** are neither *S*-alkylated 1-(2-cyanovinyl)indolizines **3** nor *N*-alkylated 2-iminothiino[3,2-*a*]indolizines **4**. Eventually, the products **7a**—**l** were concluded to be ethyl 2-acylthieno[3,2-*a*]indolizine-8-carboxylate derivatives on

TABLE II. Physical and Analytical Data for Thieno[3,2-*a*]indolizines (**7**)

Compd. 7[a)]	1	2	Yield (%)	Melting point (°C)	IR (KBr) ν_{CO} cm^{-1}		Formula	Analysis (%) Calcd C	H	N	Found C	H	N
7a	**1a**	**2c**	54	188—190	1676	1640	$C_{15}H_{13}NO_3S$	62.70	4.56	4.87	62.58	4.64	4.91
7b	**1a**	**2d**	75	78—80	1688	1649	$C_{20}H_{15}NO_3S$	68.75	4.33	4.01	68.53	4.63	3.89
7c	**1a**	**2e**	96	222—224	1676	1607	$C_{20}H_{14}ClNO_3S$	62.58	3.68	3.65	62.73	3.64	3.55
7d	**1a**	**2f**	96	179—181	1688	1617	$C_{20}H_{14}BrNO_3S$	56.09	3.29	3.27	56.10	3.30	3.25
7e	**1a**	**2g**	73	219—222	1680	1617	$C_{21}H_{17}NO_3S$	69.40	4.72	3.85	69.26	4.80	3.83
7f	**1a**	**2h**	87	216—218	1676	1615	$C_{26}H_{19}NO_3S$	73.39	4.50	3.29	73.13	4.61	3.44
7g	**1b**	**2c**	80	136—138	1676	1640	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44	64.83	5.69	4.09
7h	**1b**	**2d**	89	147—149	1690	1632	$C_{22}H_{19}NO_3S$	70.00	5.07	3.71	70.18	5.03	3.57
7i	**1b**	**2e**	94	175—177	1686	1618	$C_{22}H_{18}ClNO_3S$	64.15	4.40	3.40	64.31	4.36	3.28
7j	**1b**	**2f**	93	199—201	1686	1618	$C_{22}H_{18}BrNO_3S$	57.90	3.98	3.07	57.72	3.93	2.90
7k	**1b**	**2g**	81	86—88	1682	1606	$C_{23}H_{21}NO_3S$	70.56	5.41	3.58	70.36	5.62	3.56
7l	**1b**	**2h**	95	202—204	1682	1620	$C_{28}H_{23}NO_3S$	74.15	5.11	3.09	73.96	5.05	2.96

a) Compounds **3a**—**l** were obtained as yellow needles.

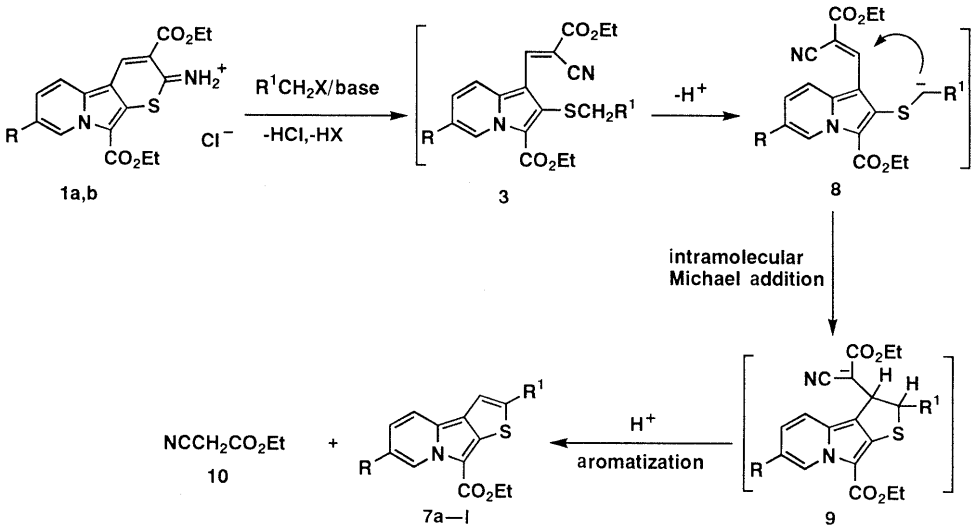


Chart 3

the basis of their spectral and analytical results and from a mechanistic consideration of the reaction (Chart 3).

Compounds **7a**—**l** must have been obtained *via* the intramolecular Michael addition of the anion **8** generated *in situ* from *S*-alkylated 2-(2-cyano-2-ethoxycarbonylvinyl)indolizine **3**, once formed, under the reaction conditions employed here, followed by the aromatization of the resulting 2,3-dihydrothieno[3,2-*a*]indolizine **9** with the elimination of **10**. A similar mechanism has already been proposed in the transformation from 2-acylmethoxy-3-(2-cyano-2-ethoxycarbonylvinyl)indolizines to 2-acylfuro-[2,3-*b*]indolizines and the same methylene compound **10** in the presence of a base,[6)] and the ease of elimination of a methylene compound is also well known in some aromatization reactions.[7)] This reaction is, however, the first example of an application for the construction of a thiophene ring, and also for the preparation of 3-unsubstituted thieno[3,2-*a*]indolizine derivatives. On the other hand, the failure to obtain the corresponding thieno[3,2-*a*]indolizine derivative by the alkaline treatment of the indolizine **3a** may be owing to insufficient stabilization of the carbanion intermediates such as **8** of the ester functionality compared with the keto group. Similar behavior has been observed in furan ring formation by the alkaline treatment of 2-ethoxycarbonylmethoxy-3-(2,2-disubstituted vinyl)indolizine derivatives.[6)]

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The microanalyses were carried out on a Perkin–Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Varian EM360A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 infrared spectrophotometer. The gas chromatography was carried out on a Shimadzu GC-4BPT instrument with a column (3 mm i.d. × 2.25 m) packed with Celite containing diethylene glycol succinate (30 weight %).

Reactions of 2-Iminothiino[3,2-*a*]indolizines with Some Alkylating Agents in the Presence of a Strong Base General Method: A dimethylformamide solution (10 ml) of diethyl 2-iminothiino[3,2-*a*]indolizine-3,9-dicarboxylate hydrochloride (**1**,[2a)] 1 mmol) and potassium *tert*-butoxide (2.5 mmol) was heated in a water bath (60—80 °C) for 20 min, then an alkylating agent (**2**, 1.2 mmol)[8)] was added and the reaction was allowed to continue for 2 h under the same conditions. The reaction mixture was poured into 20 ml of water. The precipitates were collected by suction, dried and then dissolved in chloroform (3 ml). The chloroform solution

was separated by column chromatography on alumina using chloroform as an eluent. The chloroform layer was evaporated and the crude product was recrystallized from ethanol.

In the reactions in which ethanolic sodium ethoxide was used as a base under heating, the corresponding thieno[3,2-*a*]indolizines **7a**—**l** could be obtained similarly, but prolonged reaction times were required because of the extremely low solubility in ethanol of **1a**, **b**. Furthermore, the use of excess potassium *tert*-butoxide (2.5—4.0 eq) gave satisfactory results in these reactions, but the use of stoichiometric amounts (2 eq) of the base always afforded the reduced yields of **7**, together with considerable amount of the free base of **1a**, **b**.

The formation of ethyl cyanoacetate **10** in the reactions of **1a**, **b** with **2c**—**h** could be detected by gas chromatographic monitoring (H_2 carrier gas, oven temperature 110 °C) of the reaction solutions.

Some physical and spectral data for thieno[3,2-*a*]indolizines **7a**—**l** are sammarized in Tables I and II, and those for 1-vinylindolizines **3a**, **b** are as follows: **3a**: yield, 92%, yellow needles, mp 103—106 °C. IR (KBr): 2213 (CN), 1734, 1723, 1680 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15, 1.40, 1.47 (each 3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 3.67 (2H, s, SCH_2), 4.07, 4.39, and 4.49 (each 2H, q, J=7.0 Hz, $OC\underline{H_2}CH_3$), 7.11 (1H, dt, J=7.0, 7.0, 2.0 Hz, 6-H), 7.53 (1H, br t, J=9.0, 7.0 Hz, 7-H), 8.05 (1H, br d, J=9.0 Hz, 8-H), 8.95 (1H, s, vinyl-H), 9.68 (1H, br d, J=7.0 Hz, 6-H). *Anal.* Calcd for $C_{21}H_{22}N_2O_6S$: C, 58.59; H, 5.15; N, 6.51. Found: C, 58.57; H, 5.20; N, 6.48. **3b**: yield, 89%, yellow needles, mp 107 °C (lit.[4] 107 °C).

References and Notes

1) For part XXXII of this series, see A. Kakehi, S. Ito, *Heterocycles*, **36**, 1195 (1993).
2) *a*) A. Kakehi, S. Ito, T. Ohizumi, T. Maeda, *J. Org. Chem.*, **47**, 369 (1982); *b*) A. Kakehi, S. Ito, S. Matsumoto, Y. Morimoto, *Chem. Lett.*, **1987**, 2043; *c*) A. Kakehi, S. Ito, T. Fujii, Y. Morimoto, S. Matsumoto, M. Shiohara, *Bull. Chem. Soc. Jpn.*, **62**, 119 (1989); *d*) A. Kakehi, S. Ito, S. Hatanaka, *Chem. Lett.*, **1989**, 2229; *e*) A. Kakehi, S. Ito, N. Yamada, K. Yamaguchi, *Chem. Pharm. Bull.*, **38**, 1527 (1990); *f*) A. Kakehi, S. Ito, T. Fujii, T. Sakurai, K. Urushido, S. Hatanaka, T. Mabuchi, S. Matsushita, *Bull. Chem. Soc. Jpn.*, **63**, 3571 (1990); *g*) A. Kakehi, S. Ito, T. Sakurai, K. Urushido, H. Isawa, M. Enomoto, *ibid.*, **64**, 3289 (1991); *h*) A. Kakehi, S. Ito, J. Hakui, H. Fukazawa, *ibid.*, **65**, 1244 (1992).
3) A. Kakehi, S. Ito, N. Yamada, K. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **63**, 829 (1990).
4) A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima, T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978).
5) T.-L. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York, 1977, p. 126.
6) A. Kakehi, S. Ito, H. Furuta, K. Todoroki, *J. Fac. Eng. Shinshu Univ.*, **58**, 1 (1985).
7) A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima, T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978); A. Kakehi, S. Ito, K. Nagata, N. Kinoshita, N. Kakinuma, *Chem. Pharm. Bull.*, **35**, 156 (1987).
8) In the reaction using methyl iodide (**2b**) as alkylating agent, a flask fitted with a condenser and a large excess of **2b** (1 g) were used.