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

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The treatment of 2-iminothieno[3,2-α]indolizine derivatives with potassium tert-butoxide generated exclusively potassium 1-(2-cyanovinyl)indolizine-2-thiolates through the ring opening of the initially formed thio-2-imide ions. These 2-indolizinethiolates reacted with various alkylating agents to give the corresponding 5-alkylated 1-vinylindolizine derivatives, and 2-acetonithio- 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-aryloxythieno[3,2-α]indolizines in high yields with the elimination of a methylene compound.

Keywords: indolizine; thieno[3,2-α]indolizine; thieno[3,2-α]indolizine; ring transformation; alkylation; intramolecular Michael addition

In previous papers2) 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 appropriate 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 thieno[3,2-α]-indolizine-2-imide ion, generated by treatment of the corresponding 2-iminothieno[3,2-α]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.2a,3) In this paper we wish to describe facile preparations of 2-alkylthio-1-(2-cyanovinyl)indolizines through the reactions of 2-iminothieno[3,2-α]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-α]indolizine derivatives.

Results and Discussion

Reactions of 2-iminothieno[3,2-α]indolizines with Some

Alkylation Agents in the Presence of a Strong Base

When the alkylation reaction of diethyl 2-iminothieno[3,2-α]-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 thieno[3,2-α]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 ('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-iminothieno[3,2-α]indolizines 4 strongly suggested the existence of an equilibrium between the thieno[3,2-α]indolizine-2-imide ion 5 and the 1-(2-cyanovinyl)-2-indolizinethiolate ion 6, and the exclusive

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formation of 3a, b by the soft-soft interaction\textsuperscript{5) of alkylating agents 2a, b with the latter ion 6.

Since it was anticipated that the alkylation of 2-iminothio][3,2-α]indolizine in the presence of a base would lead to various S-functionalized 1-(2-cyano vinyl)indolizine derivatives, which are potential precursors for further condensed heterocycles, we next examined the reactions of 2-iminothio][3,2-α]indolizine derivatives with other alkyl halides. However, the treatment of diethyl 2-iminothio][3,2-α]indolizine-3,9-dicarboxylic hydrochlorides 1a, b\textsuperscript{20) with potassium tert-butoxide followed by the addition of chloroacetone 2c did not afford the initially expected 2-acetylthio-1-vinylindolizine derivatives such as 3 or 2-(acetonylthio)thio][3,2-α]indolizine such as 4, but gave ethyl 2-acetylthio][3,2-α]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-phenylphenoxy chloride (2h) yielded the same types of products 7b–f, h–l in 73–96% yields (Chart 2). Furthermore, the gas chromatographic monitoring of some reaction solutions clearly showed the generation of a methane compound, ethyl cyanoacetate (10) in them. In contrast with the smooth transformation of 2-acetylthio- and 2-phenacylthio-1-vinylindolizine inter-

mediates to the corresponding thieno[3,2-α]indolizines 7a–l, however, the alkaline treatment of 2-ethoxycarbonyl-

methylthio-3-vinylindolizine 3a did not give any thieno-

formation of 3,2-α]indolizine.

The structures of products 7a–l were determined by physical and spectral means and from mechanistic con-

siderations. For example, the 1-H-NMR spectrum (see Table I) of compound 7a showed signals at 6 7.71 (1H, dt, J = 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 1766 and 1640 cm\textsuperscript{–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-cyano vinyl)-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-cyano vinyl)indolizines 3 nor N-alkylated 2-iminothio][3,2-α]indolizines 4. Eventually, the products 7a–l were concluded to be ethyl 2-acetylthio][3,2-α]indolizine-8-carboxylate derivatives on
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a) Compounds 3a—1 were obtained as yellow needles.

**Chart 3**

![Chart showing the reaction scheme](image)

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

Compounds 7a—1 must have been obtained via the intramolecular Michael addition of the anion 8 generated in situ from S-alkylated 2-(2-cyano-2-ethoxy-carbonylvinyl)indolo-zine 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-acylami-thoxy-3-(2-cyano-2-ethoxy-carbonylvinyl)indolizines to 2-acylfluoro-[2,3-b]indolizines and the same methyl compound 10 in the presence of a base, and the ease of elimination of a methylene compound is also well known in some aromatization reactions. 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 thiено[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-ethoxy-carbonyl-methoxy-3-(2,2-disubstituted vinyl)indolizine derivatives.

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 1H-NMR spectra were determined with a Varian EM360A spectrometer in deuterochloroform 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 Shimazu GC-4BP instrument with a column (3mm i.d. x 2.25 m) packed with Celite containing diethyl glycol succinate (30 weight %).

Reactions of 2-imino-thieno[3,2-a]indolizines with Some Alkylation Agents in the Presence of a Strong Base

General Method: A dimethylformamide solution (10 ml) of diethyl-2-imino-thieno[3,2-a]indolizine-3,5-dicarboxylic hydrochloride (1.0) 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) 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-α]indolizines 7α–I could be obtained similarly, but prolonged reaction times were required because of the extremely low solubility in ethanol of 1α, 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 1α, b.

The formation of ethyl cyanoacetate 10 in the reactions of 1α, b with 2c–h could be detected by gas chromatographic monitoring (H2 carrier gas, oven temperature 110 °C) of the reaction solutions.

Some physical and spectral data for thieno[3,2-α]indolizines 7α–I are summarized in Tables I and II, and those for 1-vinylindolizines 3α, b are as follows: 3α: yield, 92%, yellow needles, mp 103–106 °C. IR (KBr): 2213 (CN), 1734, 1723, 1680 (CO)cm⁻¹. 1H-NMR (CDCl3) δ: 1.15, 1.40, 1.47 (each 3H, t, J = 7.0 Hz, OCH₂CH₃), 3.67 (2H, s, SCH₂), 4.07, 4.39, and 4.49 (each 2H, q, J = 7.0 Hz, OCH₂CH₃), 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 C₁₉H₁₇N₂O₃S. 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. 107 °C).

References and Notes
1) For part XXXII of this series, see A. Kakehi, S. Ito, Heterocycles, 36, 1195 (1993).
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.