Preparation of New Nitrogen-Bridged Heterocycles. 55.[1] Reinvestigation of the Bromination/Dehydrobromination of Ethyl 3-[2-(Methylthio)indolizin-3-yl]acrylate Derivatives

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The bromination/dehydrobromination reactions of ethyl 3-[1-alkoxycarbonyl-2-(methylthio)indolizin-3-yl]acrylates were reinvestigated. Reactions of the title compounds with two equivalents of bromine, followed by heating of the resulting reaction mixture and then treatment with a base gave the unexpected dialkyl 7-bromothieno[2,3-*b*]indolizine-2,9-dicarboxylates, while similar reactions using benzyltrimethylammonium tribromide as a brominating agent afforded only non-brominated thieno[2,3-*b*]indolizine derivatives, which were converted to the corresponding 7-bromo derivatives upon further treatment with bromine.

Key words 3-vinylindolizine; thieno[2,3-*b*]indolizine; bromination; intramolecular cyclization; X-ray analysis

In our previous paper[2] we described that addition of bromine to some ethyl 2-[2-(methylthio)indolizin-3-yl]acrylates and subsequent treatment of the resulting adducts with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) gave various types of products depending upon the substituents on the indolizine ring. However, similar treatment of one compound, ethyl 3-[1-ethoxycarbonyl-2-(methylthio)indolizin-3-yl]acrylate (**1a**, see Chart 1), afforded only a complex mixture and no significant product could be isolated from it. Since we were particularly interested in the variability of this reaction, we planned a reinvestigation of this bromination/dehydrobromination involving the use of another brominating agent.

Since the reaction of an equimolar mixture of ethyl 3-[1-ethoxycarbonyl-2-(methylthio)indolizin-3-yl]acrylate (**1a**) and bromine did not provide any significant product,[2] we first investigated the amount of bromine used in this reaction. Addition of two equivalents of bromine to a chloroform–benzene (1 : 1) solution of **1a** at room temperature, followed by refluxing the resulting solution for 4 h and then treatment with DBU to remove hydrogen bromide generated gave a new compound, diethyl 7-bromothieno[2,3-*b*]indolizine-2,9-dicarboxylate (**2a**) in 54% yield. Product **2b** was obtained in 15% yield from similar reactions of **1b** with two equivalents of bromine. Next, the use of benzyltrimethylammonium tribromide (**3**)[3] as a brominating agent in place of bromine was examined. Treatment of **1a**, **b** with an equimolar amount of **3**, followed by heating of the resulting mixtures and then treatment with DBU afforded diethyl and 2-ethyl 9-methyl thieno[3,4-*b*]indolizine-2,9-dicarboxylates (**4a**, **b**) in 59 and 37% yields, respectively. On the other hand, similar treatment of ethyl [1-cyano-2-(methylthio)indolizin-3-yl]acrylate (**1c**) with **3** yielded only ethyl 2-bromo-3-[1-cyano-2-(methylthio)indolizin-3-yl]acrylate (**5c**) in 66% yield, but thieno[2,3-*b*]indolizine such as **4a**, **b** was not formed at all.[4] The use of excess **3** was also ineffective for forming dialkyl 7-bromothieno[2,3-*b*]indolizine-2,9-dicarboxylates (**2a**, **b**). Interestingly, similar reactions of **4a**, **b** with an equivalent of bromine provided the corresponding 7-bromo derivatives **2a**, **b** in 68 and 39% yields, respectively. These results are shown in Chart 1.

Elemental analyses of the new products **2a**, **b** and **4a**, **b** were well in accord with our proposed compositions and IR spectra showed an aromatic ester carbonyl band near 1700 cm^{-1}. In comparison with the chemical shifts and signal patterns of known thieno[2,3-*b*]indolizine derivatives,[5—8] ^{1}H-NMR spectra of **2a**, **b** clearly exhibited the signals for the 3-, 5-, 6-, and 8-protons and of two alkoxycarbonyl groups, but not the 7-proton signal. On the other hand, those of **4a**, **b** showed the continuous four proton signals on the pyridine ring. Furthermore, the absence of the methylthio signal also supported the thieno[3,4-*b*]indolizine structure in products **2a**, **b** and **4a**, **b**. The structure for **2a**, diethyl 7-bromothieno[2,3-*b*]indolizine-2,9-dicarboxylate, was confirmed by X-ray analysis. The ORTEP drawing[9] of **2a** is shown in Fig. 1.

Possible mechanisms for the formation of products **2a**, **b**, **4a**, **b**, and **5c** are shown in Chart 2. The routes to 3-vinylindolizine (**5c**) and non-brominated thieno[3,4-*b*]indolizines (**4a**, **b**) were the same as those shown in our previous paper.[2] However, it was clear this time that these processes are thermally promoted reactions and the use of a base such as DBU is not necessarily essential. Some routes in which thiophene

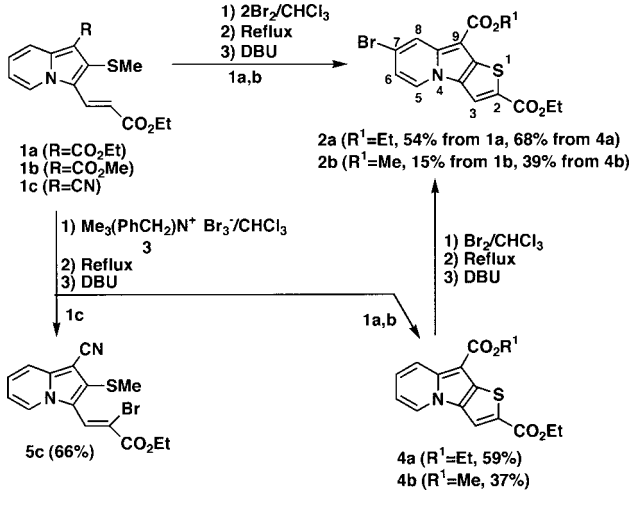

Chart 1

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ring was formed by an intramolecular radical or electrophilic attack on the sulfur atom in sulfides followed by the elimination of a substituent on the sulfur atom are documented.[10—16] Our method for the thiophene ring formation using vinyl-substituted sulfides such as **1a**, **b** and bromine or benzyltrimethylammonium tribromide (**3**) can be performed under milder conditions and is very simple, though the yields were moderate. These methods may be useful tools in fused thiophene synthesis. On the other hand, 7-bromothieno[3,4-*b*]indolizines (**2a**, **b**) must be formed *via* the addition of bromine to the double bond at the 7- and 8-positions of thieno[3,4-*b*]indolizines (**4a**, **b**), followed by the dehydrobromination from the resulting adducts **8** with the recovery of the aromatic character. An alternative path *via* arenium intermediates such as **9**, an aromatic electrophilic substitution of **4a**, **b** by bromine, is negligible, because the most electron-rich position of thieno[3,4-*b*]indolizine is the 6-carbon and not the 7-carbon.[17] Maybe, the electrophilic substitution of **3a**, **b** should provide the 6-bromo derivatives *via* an arenium intermediate such as **10**.

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 were determined with a Hitachi R-600 (60 MHz) or Bruker DRX-500 (500 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 IR spectrophotometer.

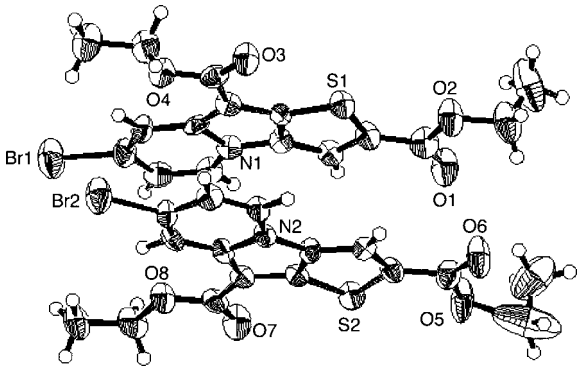

Fig. 1. ORTEP Drawing of **2a**

Preparations of Ethyl 3-[2-(Methylthio)indolizine-3-yl]acrylate Derivatives Compounds (**1a**—**c**) were synthesized from the *S*-alkylations of pyridinium 1-[3-ethoxycarbonyl-1-[methylthio(thiocarbonyl)]allylides with ethyl bromoacetate, methyl bromoacetate, and bromoacetonitrile followed by dehydrobromination with DBU and then dehydrogenation of the resulting pyridinium salts with chloranil, according to our previous procedure.[2] Some data for the new compound **1b** are as follows.

Ethyl 3-[1-Methoxycarbonyl-2-(methylthio)indolizine-3-yl]acrylate (**1b**): Yield 47%, yellow needles, mp 97—98 °C, IR (KBr) 1701, 1616 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.39 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.52 (3H, s, SMe), 4.05 (3H, s), 4.39 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.86 (1H, d, J=17.0 Hz, vinyl-H), 7.03 (1H, br t, J=7.0 Hz, 6-H), 7.38 (1H, br q, J=7.0, 9.0 Hz, 7-H), 8.36 (1H, d, J=17.0 Hz, vinyl-H), 8.45 (1H, br d, J=7.0 Hz, 5-H), 8.48 (1H, br d, J=9.0 Hz, 8-H). *Anal.* Calcd for $C_{16}H_{17}N_2O_4S$: C, 60.17; H, 5.39; N, 4.39. Found: C, 60.45; H, 5.31; N, 4.18.

Reactions of Ethyl 3-[2-(Methylthio)indolizine-3-yl]acrylate Derivatives with Brominating Agents General Method A: A chloroform–benzene solution (1 : 1, 20 ml) of 2-methylthio-3-vinylindolizine (**1a**, **b**, 1 mmol) and bromine (2 mmol) was allowed to react under stirring at room temperature until the disappearance of the starting indolizine was confirmed by TLC monitoring (*ca.* 2 h). The resulting solution was heated under reflux for 4 h in a water bath (80 °C). After the addition of DBU (2 mmol) the reaction mixture was stirred for a further 2 h at room temperature. Evaporation of the solvent from the reaction mixture and column chromatographic separation (alumina) of the residue gave the corresponding dialkyl 7-bromothieno[2,3-*b*]indolizine-2,9-dicarboxylates (**2a**, **b**).[18,19]

General Method B: In a similar procedure to that described above (Method A) benzyltrimethylammonium tribromide (**3**, 1 mmol) was used as a brominating agent in place of bromine. The work-ups of the reaction mixtures gave dialkyl thieno[2,3-*b*]indolizine-2,9-dicarboxylates (**4a**, **b**) or ethyl 2-bromo-3-(1-cyano-2-metylthioindolizin-3-yl)acrylate (**5c**). The use of excess benzyltrimethylammonium tribromide (**3**, 2 mmol) in these reactions provided only the same products **4a**, **b** and **5c** but did not afford any 7-bromothieno[3,4-*b*]indolizine derivatives such as **2a**, **b**. The use of DBU was not necessarily essential in the present reactions because these reactions proceeded without a base. DBU acted to remove hydrogen bromide generated by the thermolysis of adducts **6a**—**c** and/or intermediates **7** and **8**.

Some data for the compounds **2a**, **b**, **4a**, **b**, and **5c** are as follows.

Diethyl 7-Bromothieno[2,3-*b*]indolizine-2,9-dicarboxylate (**2a**): Yield 54% (Method A) and 68% (Method B), yellow needles, mp 227—228 °C, IR (KBr) 1701 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) 1.42 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.47 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 4.40 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.43 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.94 (1H, dd, J=7.2, 1.9 Hz, 6-H), 8.03 (1H, s, 3-H), 8.09 (1H, d, J=7.2 Hz, 5-H), 8.49 (1H, br s, 8-H).

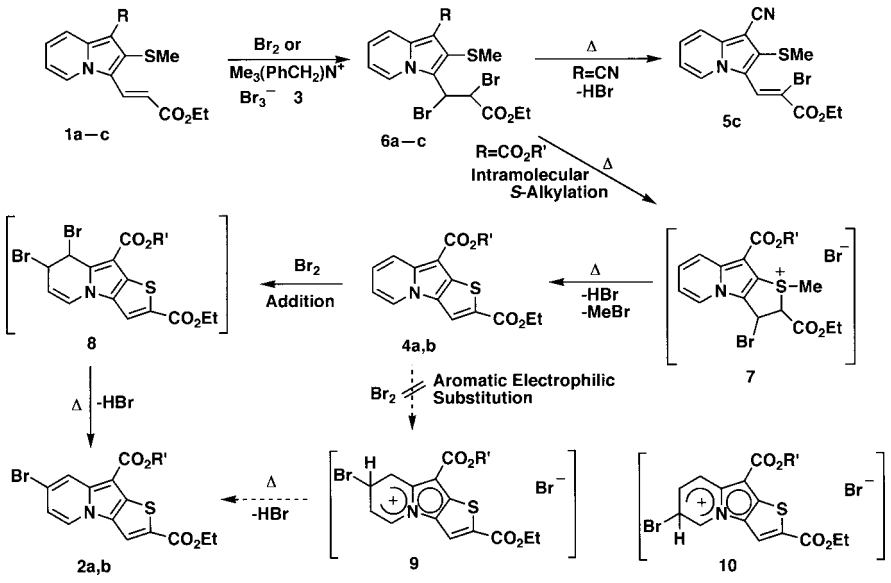

Chart 2

Anal. Calcd for $C_{16}H_{14}BrNO_4S$: C, 48.50; H, 3.56; N, 3.53. Found: C, 48.72; H, 3.58; N, 3.29.

2-Ethyl 9-Methyl 7-Bromothieno[2,3-*b*]indolizine-2,9-dicarboxylate (**2b**): yield 15% (Method A) and 39% (Method B), yellow needles, mp 242—243 °C, IR (KBr) 1697 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.43 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 4.02 (3H, s, OMe), 4.42 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.05 (1H, dd, J=7.0, 2.0 Hz, 6-H), 7.95 (1H, d, J=7.0 Hz, 5-H), 8.10 (1H, s, 3-H), 8.40 (1H, br s, 8-H). *Anal.* Calcd for $C_{15}H_{12}BrNO_4S$: C, 47.13; H, 3.16; N, 3.66. Found: C, 47.32; H, 3.15; N, 3.48.

Diethyl Thieno[2,3-*b*]indolizine-2,9-dicarboxylate (**4a**): 59% (Method B), yellow needles, mp 161—162 °C, IR (KBr) 1709 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.43 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.49 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 4.45 (4H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.92 (1H, br t, J=7.0 Hz, 6-H), 7.33 (1H, br q, J=9.0, 7.0 Hz, 7-H), 8.14 (1H, s, 3-H), 8.35 (1H, br d, J=9.0 Hz, 8-H), 8.39 (1H, br d, J=7.0 Hz, 5-H). *Anal.* Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.65; H, 4.70; N, 4.38.

2-Ethyl 9-Methyl Thieno[2,3-*b*]indolizine-2,9-dicarboxylate (**4b**): 37% (Method B), yellow needles, mp 178—179 °C, IR (KBr) 1676 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.43 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 4.00 (3H, s, $OC\underline{H}_3$), 4.45 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.88 (1H, br t, J=7.0 Hz, 6-H), 7.30 (1H, br q, J=9.0, 7.0 Hz, 7-H), 8.10 (1H, s, 3-H), 8.30 (1H, br d, J=9.0 Hz, 8-H), 8.32 (1H, br d, J=7.0 Hz, 5-H). *Anal.* Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62. Found: C, 59.47; H, 4.35; N, 4.51.

Ethyl 2-Bromo-3-(1-cyano-2-metylthioindolizin-3-yl)acrylate (**5c**): Yield 66% (Method B), yellow needles, mp 137—138 °C (lit.[2] 135—137 °C).

Crystallography of Diethyl 7-Bromothieno[2,3-*b*]indolizine-2,9-dicarboxylate (2a) A single crystal (0.04×0.18×0.46 mm) grown from chloroform was used for unit-cell determination and data collection on a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **2a**: $C_{16}H_{14}BrNO_4S$; M=396.25; monoclinic, space group $P1$ (#2), Z=4 with a=12.497 (4) Å, b=14.507 (3) Å, c=9.031 (2) Å; α=92.28 (2)°, β=92.37 (2)°, γ=80.78 (2)°; V=1613.7 (7) Å^3, and D_{calc}=1.631 g/cm^3. All calculations were performed using the TEXSAN package.[20] The structure was solved by a direct method (SIR).[21] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotopically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.060 and 0.051, respectively, for 2515 (I>2.00σ(I)) observed reflections.

References and Notes

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18) These compounds are useful substrates for some carbon–carbon bond formation reactions such as Heck reaction. See: Dieck H. A., Heck R. F., *J. Am. Chem. Soc.*, **96**, 1133—1136 (1974).
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