N-Bis(methylthio)methylene Derivatives. 5 [1]. New Synthesis of 2-Aminoindolizine and Related Compounds *via* a Formal [3 + 3] Cycloaddition Reaction Using *N*-Bis(ethoxycarbonylmethylthio)methylenephenylsulfonamides

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Reaction of pyridinium *N*-ylide **5a** with *N*-bis(ethoxycarbonyl)methylthio)(*p*-substituted-phenyl)sulfonamides **2a,c** in the presence of triethylamine as a base in ethanol gave diethyl 2-(*p*-substituted-phenylsulfonyl)aminoindolizine-1,3-dicarboxylates **9a,b** *via* a new formal [3 + 3] cycloaddition reaction. In a similar manner, 2-sulfonylaminopyrrolo[2,1-*a*]isoquinoline derivatives **11a-e** were also obtained by the reaction of **2a-c** and **4a,b** with the corresponding isoquinoline *N*-ylides **10a,b** with good results.

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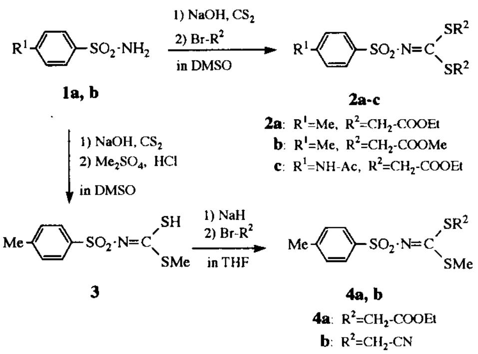
N-Bis(alkylthio)methylenesulfonamides, which are prepared by the condensation of the corresponding sulfonamides with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide and by successive treatment of the intermediates with the appropriate alkyl reagents, are extremely interesting electrophilic reagents for the introduction of not only an aminomethylene group into amine and active methylene compounds but a C = N fragment in the synthesis of heterocyclic compounds [2,3]. Despite numerous reports concerning the utility of these compounds as electrophiles, to our the best knowledge, no synthetic methodology for the preparation of heterocycles by use of α-thiocarbanion of the alkylthio group in the above *N*-bis(alkylthio)methylene compounds exist in the literature. In general, α-thiocarbanions are prepared under strong basic conditions except sulfonyl or sulfinyl group [4,5]. The presence of an electron withdrawing group in methylthio groups like alkyl *S*-substituted thioglycolates which are important reagents for the various types of selective carbon-carbon bond formation in organic synthesis provides an easy method of preparation of α-thiocarbanion species [6].

In an extension of our work on the *N*-bis(alkylthio)methylene compounds [1], we now wish to report the synthesis of 2-aminoindolizines and -pyrrolo[2,1-*a*]isoquinoline derivatives by the reaction of the above reagents with pyridinium and isoquinolinium *N*-ylides. This is the first example of the synthesis of indolizine derivatives *via* a formal [3 + 3] cycloaddition reaction by use of the character of both the α-thiocarbanion and the electrophilic carbon atom of an imino group in *N*-bis(alkylthio)methylene derivatives.

The *N*-bis(alkylthio)methylenephenylsulfonamide derivatives used in this paper were prepared by the method shown in Scheme 1.

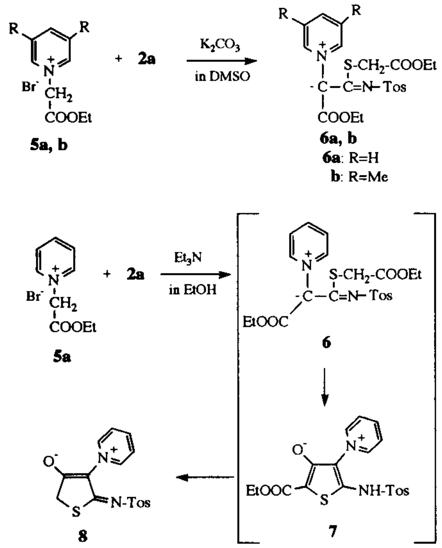
The reaction of **2a** with 1-ethoxycarbonylmethylpyridinium bromide (**5a**) in the presence of potassium carbonate in dimethyl sulfoxide for 10 hours gave the corresponding new pyridinium *N*-ylide **6a** in 69% yield. The reaction of **2a** with **5b** also afforded pyridinium *N*-ylide **6b** in 46% yield. When **5a** was allowed to react with **2a** in the presence of the triethylamine under refluxing conditions, thiophene derivative **8** was obtained in 26% yield. Its structure, a new betaine compound, 3-pyridinium thiophenolate was determined by the spectral data and elemental analysis. The outline of the reaction pathway is shown in Scheme 2.

Scheme 1

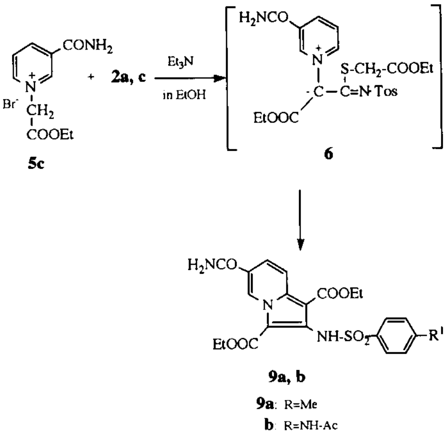


Next, 1-ethoxycarbonylmethyl-3-carbamoylpyridinium bromide (**5c**), obtained from nicotinamide and ethyl bromoacetate, was allowed to react with **2a** in the presence of triethylamine in ethanol giving the desired cyclized product, diethyl 6-carbamoyl-2-*p*-toluenesulfonylaminoindolizine-1,3-dicarboxylate (**9a**), in 37% yield [7]. The nuclear magnetic resonance (nmr) spectrum of **9a** revealed signals of three aromatic protons due to the indolizine ring at 7.70 ppm (doublet, J = 9.6 Hz, 4-H), 8.10 ppm (doublet, J = 9.6 Hz, 5-H), and 8.30 ppm (singlet 7-H). From its nmr and ir spectra and elemental analysis of this compound, the structure was assigned as **9a**. Diethyl 2-(*p*-acetylaminophenylsulfonyl)amino-6-carbamoylindolizine-1,3-dicarboxylate (**9b**) was also obtained from **5c** and *N*-bis(ethoxycarbonylmethyl)methylene-*p*-acetylaminophenylsulfonamide (**2c**), in 27% yield. The outline of the reaction pathway for the formation of **9** is shown in Scheme 4. It seems reasonable that the initially formed intermediate, pyridinium *N*-ylide, by the addition-elimination reaction of nucleophilic attack of the ylide carbanion into **5**, undergoes successively nucleophilic addition of an α-thiocarbanion into the 2-position of the pyridinium group, then that of dehydration, and finally the elimination of the sulfur atom to give **9**. In the case of the condensation of the ester group and the active methylene of ethoxycarbonylmethyl group gives the corresponding thiophene derivative **8**.

Scheme 2

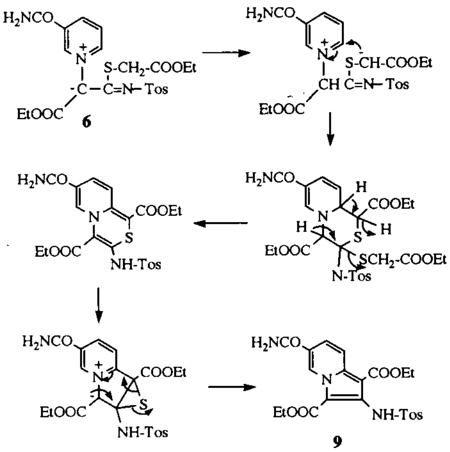


Scheme 3

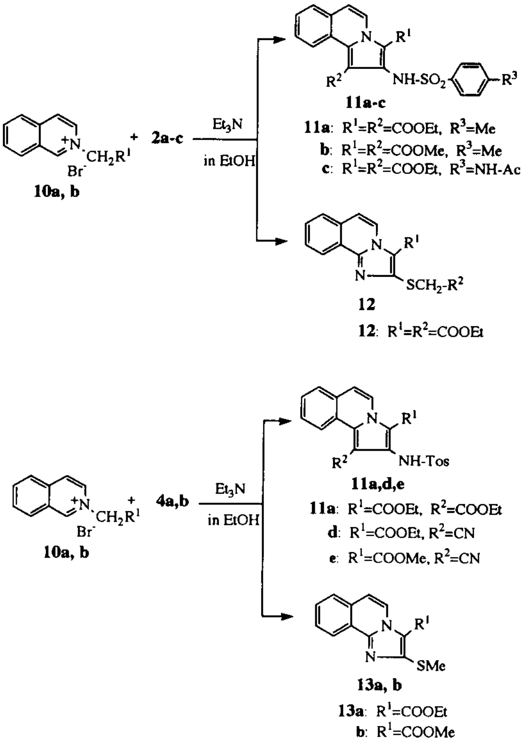


When compound **2a** was allowed to react with 2-ethoxycarbonylmethylisoquinolinium bromide **10a** under similar condition to that described for the preparation of 2-tosylaminoindolizines, the expected cycloaddition product, diethyl 2-tosylaminopyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (**11a**) was obtained in 24% yield along with ethyl 2-ethoxycarbonylmethylthioimidazo[2,1-*a*]isoquinoline-3-carboxylate (**12**) in 24% yield which is formed by 1,5-dipolar cycloaddition of the tosylamino group to the 1-position of the isoquinolinium ring. In a manner similar, **10b** was allowed to react with **2b** to give the corresponding **11b** in 24% yield. In this reaction, imidazo[2,1-*a*]isoquinoline derivatives were not detected in the reaction mixture. On the other hand, the reaction of **2c** with **10a** under the same reaction conditions gave 2-phenylsulfonylaminopyrrolo[2,1-*a*]isoquinoline derivative **11c** in 37% yield. In this reaction, imidazo[2,1-*a*]isoquinoline derivative **12** was obtained in 4.5% yield, because of the lower nucleophilicity of amido group due to the *p*-amino group.

Scheme 4. Reaction Pathway of The Formation of 2-Aminoindolizines



Scheme 5



The reaction of **10a** with the *N*-(methylthio)(ethoxycarbonylmethyl)methylene derivative **4a** afforded a mixture of **11a** and **13a** in 14 and 24% yields, respectively. Compound **4b** also reacted with **10a** to afford a mixture of 1-cyano-2-(*p*-toluenesulfonyl)aminopyrrolo[2,1-*a*]isoquinoline **11d** and **13a** which were separated by alumina column chromatography from the crude reaction mixture. The reaction of **10b** with **4b** was also carried out under the same reaction conditions to give a mixture of **11e** and **13b** in 12 and 19% yields, respectively.

In conclusion, *N*-bis(ethoxycarbonylmethylthio)methylene-*p*-toluenesulfonamides **2a-c, 4a,b** shown in this paper are very useful and convenient to react with a 1,3-dipolar reagent for the synthesis 2-aminoindolizine and pyrrolo[2,1-*a*]isoquinoline derivatives. Further studies of the new synthesis of heterocyclic compounds using **2** are in progress [8].

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on a JASCO IRA-2 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-FX-90Q (90 MHz) spectrometer with tetra-methylsilane as an internal standard. Mass (ms) spectra were recorded on a JEOL-01SG mass spectrometer.

N-Bis(ethoxycarbonylmethylthio)methylene-*p*-toluenesulfonamide (**2a**).

Half of a solution of 30% sodium hydroxide solution (sodium hydroxide, 8.0 g) was added into the solution of 17.212 g (0.10 mole) of *p*-toluenesulfonamide in 100 ml of dimethyl sulfoxide and the mixture was stirred for 20 minutes at 0°. Then, 4.56 g (0.06 mole) of carbon disulfide was slowly added to above a mixture with stirring at 0° over a period of 20 minutes and stirring was continued for 20 minutes at same the temperature. The remaining half of the solution of sodium hydroxide was added to the above reaction mixture and stirring was continued for 10 minutes. Then, 4.56 g (0.06 mole) of carbon disulfide was again slowly added to the above reaction mixture and stirring was continued for 1 hour at room temperature. To the reaction product of carbon disulfide (disodium *p*-toluenesulfonamide-*N*-dithiocarboxylate) in the solution of dimethyl sulfoxide, 33.401 g (0.2 mole) of ethyl bromoacetate was slowly added dropwise while the reaction mixture was stirred vigorously at room temperature. After stirring for 2 hours, the reaction mixture was poured into 500 ml of ice water and then was allowed to stand for 3 hours. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 39.127 g (0.933 mole, 93%) of colorless needles, mp 75-76° [lit [2], mp 79°]. If the precipitate did not appear, the reaction mixture was extracted with 200 ml of benzene. The organic layer was washed with water several times and dried over anhydrous sodium sulfate. After evaporation of the solvent, 100 ml of hexane was added to the above residue and the crystallized product was collected by filtration, ir (potassium bromide): ν max 1740 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 227 (3.97), 258 (4.27); ^{1}H-nmr (deuteriochloroform): δ 1.23 (6H, t, J = 7.0 Hz, O-CH$_2$C*H*$_3$), 2.43 (3H, s, *p*-Me), 3.87 (4H, s, -CH$_2$-), 4.12 (4H, q, J = 7.0 Hz, O-CH$_2$-), 7.30 (2H, d, J = 8.1 Hz, phenyl-H), 7.83 (2H, d, J = 8.1 Hz, phenyl-H).

N-Bis(methoxycarbonylmethylthio)methylene-*p*-toluenesulfonamide (**2b**).

This compound (18.62 g, 0.0475 mole) was prepared in 95% yield from 8.61 g (0.05 mole) of **1a**, 4.57 g (0.06 mole) of carbon disulfide, 4.00 g (0.10 mole) of sodium hydroxide, and 15.30 g (0.10 mole) of methyl bromoacetate in a manner similar to that described for the preparation of **2a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 90-92°; ir (potassium bromide): ν max 1740 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 227 (4.05), 257 (4.30); ^{1}H-nmr (deuteriochloroform): δ 2.43 (3H, s, *p*-Me), 3.66 (6H, s, OMe), 3.87 (4H, s, 2 x -CH$_2$-S), 7.30 (2H, d, J = 8.4 Hz, 3, 5-H), 7.83 (2H, d, J = 8.4 Hz, 2, 6-H); ms: m/z 391 (M$^+$, 3), 286 (16), 260 (26), 303 (100), 91 (99).

Anal. Calcd. for $C_{14}H_{17}O_6NS_3$ = 391.477: C, 43.00; H, 4.38; N, 3.58; S, 24.57. Found: C, 42.71; H, 4.23; N, 3.67; S, 24.49.

N-Bis(ethoxycarbonylmethylthio)methylene-*p*-acetylaminophenylsulfonamide (**2c**).

This compound (43.479 g, 0.094 mole) was prepared in 94% yield from *p*-acetylaminophenylsulfonamide (21.42 g, 0.1 mole), 9.135 g (0.12 mole) of carbon disulfide, and 33.401 g (0.2 mole) of ethyl bromoacetate in a manner similar to that described for **2a**. The crude product was purified by the chromatography on an alumina column using dichloromethane as the eluent to give colorless needles, mp 104-106°; ir (potassium bromide): ν max 3360 (NH), 1745, 1718, 1702 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 265 (4.36); ^{1}H-nmr (deuteriochloroform): δ 1.24 (6H, t, J = 7.3, O-CH$_2$C*H*$_3$), 2.21 (3H, s, CO-Me), 3.87 (6H, s, OMe), 4.14 (4H, q, J = 7.3 Hz, O-C*H*$_2$CH$_3$), 7.64 (2H, d, J = 9.2 Hz, 3, 5-H), 7.88 (2H, d, J = 9.2 Hz, 2, 6-H); ms: m/z 462 (M$^+$, 2), 317 (9), 198 (48), 106 (50), 103 (100).

Anal. Calcd. for $C_{17}H_{22}N_2O_7S_3$ = 462.56: C, 44.14; H, 4.80; N, 6.06; S, 20.80. Found: C, 43.87; H, 4.67; N, 6.10; S, 20.89.

N-(Ethoxycarbonylmethylthio)(methylthio)methylene-*p*-toluenesulfonamide (**4a**).

A 300 ml, three-necked, round-bottomed flask was fitted with a magnetic stirrer, a pressure-equalizing dropping funnel, and a combined inlet-outlet assembly connected to a nitrogen source. The flask was charged with 1.50 g (0.0625 mole) of sodium hydride (a batch of 3.0 g of a 50% sodium hydride dispersion in mineral oil was washed with hexane to remove the mineral oil immediately prior to use), the apparatus was flushed with nitrogen, and 100 ml of tetrahydrofuran was added. The suspension was stirred and cooled in an ice bath under a static nitrogen atmosphere. A solution of 13.5 g (0.05 mole) of methyl *N*-*p*-toluenesulfonyldithiocarbamete **3** in 20 ml of tetrahydrofuran was added over a 20 minutes period. The formation of the sodium salt was complete when hydrogen evolution ceases. Stirring and cooling were continued for 20 minutes, after which a solution of 10.0 g (0.06 mole) of ethyl bromoacetate in 20 ml of tetrahydrofuran was slowly added. The contents of the flask were stirred at room temperature for 1 hour. The reaction mixture was poured into 1000 ml of ice water and was extracted with dichloromethane. The organic extracts was washed with 100 ml of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure gave a caramel oil which was crystallized by addition 10 ml of ethanol. The product was collected by the filtration. The product was recrystallized from methanol to give 6.99 g (0.02 mole, 40%) of colorless needles, mp 87-89°; ir (potassium bromide): ν max 1740 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 305 (4.05), 435 (4.31); ^{1}H-nmr (deuteriochloroform): δ 1.19 (3H, t, J = 7.1 Hz, O-CH$_2$C*H*$_3$), 2.43 (3H, s, *p*-Me), 2.63 (3H, s, SMe), 3.94 (2H, s, S-CH$_2$-), 4.05 (2H, q, J = 7.1 Hz, O-CH$_2$-CH$_3$), 7.29 (2H, d, J = 8.4 Hz, 2′, 6′-H), 7.83 (2H, d, J = 8.4 Hz, 3′, 5′-H).

Anal. Calcd. for $C_{13}H_{17}NO_4S_3$: C, 44.94; H, 4.93; N, 4.03; S, 27.68. Found: C, 44.79; H, 4.84; N, 4.07; S, 27.80.

N-(α-Cyanomethyl)(α-methylthuio)methylene-*p*-toluenesulfonamide (**4b**).

This compound (0.565 g, 1.88 mmoles) was prepared in 11% from 4.5 g (17 mmoles) of **3** and 3.33 g (20 mmoles) of bromoacetonitrile in a manner similar to that described for the synthesis of **4a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 147-149°; ir (potassium bromide): ν max 2240 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.44 (3H, s, *p*-Me), 2.64 (3H, s, SMe), 3.79 (2H, s, S-CH$_2$-), 7.32 (2H, d, J = 8.5 Hs, 3, 5-H), 7.88 (2H, d, J = 8.5 Hz, 2, 6-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S_3$: C, 43.98; H, 4.03; N, 9.33; S, 32.02. Found: C, 43.85; H, 3.97; N, 9.35; S, 31.71.

α-Ethoxycarbonyl-α-[(ethoxycarbonylmethylthio)(*p*-toluenesulfonylimino)methyl]pyridinium Methylide (**6a**).

A mixture of 0.419 g (1.0 mmole) of **5a**, 0.365 g (1.5 mmoles) of **2a**, 0.207 g (1.5 mmoles) of potassium carbonate, and 15 ml of dimethyl sulfoxide was stirred at room temperature for 50 hours. The reaction mixture was poured into 100 ml of ice water and acidified with 10% hydrochloric acid solution. The mixture was extracted with 20 ml of dichloromethane three times. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent by evaporating gave a brown residue. The residue was separated by alumina column chromatography. After eluation with benzene, the product was eluted using ethanol to give 0.320 g (69%) of yellow crystals. This compound was recrystallized from ethanol to give pure yellow needles, mp 151-152°; ir (potassium bromide): ν max 1735, 1675 (COOEt) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 225 (4.12), 258 (4.04), 303 (4.35); ^{1}H-nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.3 Hz, O-CH$_2$C*H*$_3$), 1.18 (3H, t, J = 7.3 Hz, O-CH$_2$C*H*$_3$), 2.35 (3H, s, *p*-Me), 3.38 (2H, s, S-CH$_2$-), 3.96 (2H, q, J = 7.3 Hz, O-C*H*$_2$CH$_3$), 4.15 (2H, q, J = 7.3 Hz, O-C*H*$_2$CH$_3$), 7.14 (2H, d, J = 8.2 Hz, 3′,5′-H), 7.60 (2H, d, J = 8.2 Hz, 2′, 6′-H), 7.74 (2H, m, 3, 5-H), 8.31 (1H, m, 4-H), 8.66 (2H, m, 2, 6-H).

Anal. Calcd. for $C_{21}H_{24}N_2O_6S_2$: C, 54.29; H, 5.21; N, 6.03; S, 13.80. Found: C, 54.05; H, 5.10; N, 6.03; S, 13.82.

α-Ethoxycarbonyl-α-[(ethoxycarbonylmethylthio)(*p*-tolenesulfonylimino)methyl]-3,5-dimethylpyridinium Methylide (**6b**).

This compound (0.31 g, 0.826 mmole) was prepared in 46% yield from 0.839 g (2.0 mmoles) of **5b** and 0.548 g (2.0 mmoles) of **2a** in a manner similar to that described for the synthesis of **5a**. An analytical sample was recrystallized from 2-propanol to give lemon yellow needles, mp 181-182°; ir (potassium bromide): ν max 1750, 1675 (COOEt) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 223 (4.16), 302 (4.36); ^{1}H-nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.3 Hz, O-CH$_2$C*H*$_3$), 1.21 (3H, t, J = 7.3 Hz, O-CH$_2$C*H*$_3$), 2.35 (3H, s, *p*-Me), 2.50 (3H, 3-Me or 5-Me), 2.51 (3H, s, 5-Me or 3-Me), 3.39 (2H, s, S-CH$_2$-), 3.96 (2H, q, J = 7.3 Hz, O-C*H*$_2$CH$_3$), 4.16 (2H, q, O-C*H*$_2$CH$_3$), 7.13 (2H, d, J = 8.3 Hz, 3′, 5′-H), 7.60 (2H, d, J = 8.3 Hz, 2′, 6′-H), 7.85 (1H, bs, 4-H), 8.27 (2H, bs, 2, 6-H).

Anal. Calcd. for $C_{23}H_{28}N_2O_6S_2$: C, 56.08; H, 5.73; N, 5.69; S, 13.02. Found: C, 56.03; H, 5.76; N, 5.70; S, 12.97.

2-*p*-Toluenesulfonylimino-3-pyridinio-2,5-dihydrothiophen-4-olate (**8**).

A solution of 1.678 g (4.0 mmoles) of **5a**, 0.984 g (4.0 mmoles) of **2a**, and 4 ml of triethylamine in ethanol was refluxed for 26 hours. After evaporation of the solvent and excess triethylamine, the residue was washed with 10% hydrochloric acid and extracted with 30 ml of dichloromethane. The organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed by alumina column using a mixture of ethyl acetate and ethanol (4:1) as an eluent to give 0.355 g (1.03 mmoles, 26%) of pale yellow crystals. An analytical sample was recrystallized ethanol to give pale yellow needles, mp 168-170°; ir (potassium bromide): ν max 1620, 1580 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 220 (4.12), 254 (4.31), 306 (4.36), 360 (3.70); ^{1}H-nmr (deuteriochloroform): δ 2.39 (3H, s, *p*-Me), 3.66 (2H, s, 2-CH$_2$), 7.23 (2H, J = 8.0 Hz, 3′, 5′-H), 7.83 (2H, d, J = 8.0 Hz, 2′, 6′-H), 7.84 (2H, m, 3, 5-H), 8.19 (1H, m, 4-H), 8.85 (2H, m, 2, 6-H); ms: m/z 346 (M$^+$, 60), 191 (43), 155 (23), 149 (38), 145 (26), 91 (77), 44 (100).

Anal. Calcd. for $C_{16}H_{14}N_2O_3S_2$ = 346.43: C, 55.47; H, 4.07; N, 8.09; S, 18.51. Found: C, 55.43; H, 4.08; N, 8.02; S, 18.65.

Diethyl 6-Carbamoyl-2-*p*-toluenesulfonylaminoindolizine-1,3-dicarboxylate (**9a**).

A solution of 0.550 g (2.0 mmoles) of 3-carbamoyl-1-ethoxycarbonylmethylpyridinium bromide (**5c**), 0.839 g (2.0 mmoles) of **2a**, and 1 ml of triethylamine in 20 ml of ethanol was refluxed for 20 hours. After removal of solvent and excess triethylamine, 100 ml of water was added to the residue and was acidified with 10% hydrochloric acid. The brown caramel oil was separated and crystallized by adding 10 ml of ethanol. The crystallized product was collected by filtrate to give 0.351 g (0.642 mmole, 37%) of **9a**. This compound was recrystallized from ethanol to give colorless needles, mp 223-225°; ir (potassium bromide): ν max 3420, 3260, 3160 (NH), 1690, 1665, 1620 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 230 (4.37), 264 (4.68), 327 (4.07); ^{1}H-nmr (deuteriochloroform): δ 1.28 (3H, t, J = 7.3 Hz, OCH$_2$C*H*$_3$), 1.44 (3H, t, J = 7.3 Hz, OCH$_2$C*H*$_3$), 2.37 (3H, s, *p*-Me), 4.17 (2H, q, J = 7.3 Hz, O-CH$_2$-), 4.38 (2H, q, J = 7.3 Hz, O-CH$_2$-), 6.14 (2H, bs, NH$_2$), 7.16 (2H, d, J = 8.3 Hz, 2′, 6′-H), 7.49 (2H, d, J = 8.3 Hz, 3′, 4′-H), 7.70 (1H, d, J = 9.6 Hz, 4-H), 8.10 (1H, d, J = 9.6 Hz, 5-H), 8.30 (1H, s, 7-H), 9.92 (1H, s, NH); ms: m/z 473 (M$^+$, 2), 472 (M$^+$-1, 9), 318 (16), 300 (13), 201 (13), 136 (36), 106 (13), 105 (98), 91 (43), 77 (58), 44 (100), 40 (46).

Anal: Calcd. for $C_{22}H_{23}N_3O_7S$ = 473.484: C, 55.80; H, 4.90; N, 8.87; S, 6.77. Found: C, 55.49; H, 4.87; N, 8.87; S, 6.71.

Diethyl 2-(*p*-Acetylamino)phenylsulfonylamino-6-carbamoylindolizine-1,3-dicarboxylate (**9b**).

This compound (0.141 g, 0.273 mmole) was prepared in 27% yield from 0.462 g (1.0 mmole) of **2c** and 0.275 g (1.0 mmole) of **5c** in a manner similar to that described for the synthesis of **9a**.

An analytical sample was recrystallized from ethanol to give lemon yellow needles, mp 228-230°; ir (potassium bromide): ν max 3600-3300 (broad, NH_2, NH), 1690, 1670, 1630 (CO) cm^{-1}; uv (ethanol, insufficient solubility): λ max nm 257, 325, λ min nm 225, 305; ^{1}H-nmr (deuteriochloroform + trifluoroacetic acid (one position)): δ 1.33 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.45 (3H, t, J = 7.3 Hz, OCH_2CH_3), 2.31 (3H, s, N-COMe), 4.22 (2H, q, J = 7.3 Hz, O-CH_2-), 4.39 (2H, q, J = 7.3 Hz, O-CH_2-), 7.56 (4H, bs, phenyl-H), 7.75 (1H, dd, J = 0.9, 9.7 Hz, 7-H), 8.17 (1H, dd, J = 0.9, 9.7 Hz, 8-H), 10.00 (1H, m, 5-H).

Anal. Calcd. for $C_{23}H_{24}N_4O_8S$ = 516.509: C, 53.48; H, 4.68; N, 10.85; S, 6.21. Found: C, 53.28; H, 4.60; N, 10.73; S, 6.46.

The Reaction of **2a** with 1-Ethoxycarbonylmethylisoquinolinium Bromide (**10a**).

A solution of 0.444 g (1.50 mmoles) of 3-carbamoyl-1-ethoxycarbonylmethylpyridinium bromide (**10a**), 0.419 g (1.0 mmole) of **2a**, and 1 ml of triethylamine in 20 ml of ethanol was refluxed for 39 hours. After removal of solvent and excess triethylamine, 100 ml of water was added to the residue and was acidified with 10% hydrochloric acid. The brown caramel oil was separated and crystallized by adding 10 ml of ethanol. The crystallized product was collected by filtrate to give 0.754 g (0.365 mmole, 37%) of diethyl 2-*p*-toluenesulfonylaminopyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (**11a**). This compound was recrystallized from ethanol to give colorless needles, mp 175-176°; ir (potassium bromide): ν max 3155 (NH), 1718, 1655 (CO) cm^{-1}; uv (ethanol): λ max nm (log ε) 273 (4.74), 315 (3.96), 342 (3.96), 359 (4.00); ^{1}H-nmr (deuteriochloroform): δ 1.36 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.44 (3H, t, J = 7.3 Hz, OCH_2CH_3), 2.34 (3H, s, *p*-Me), 4.24 (2H, q, J = 7.3 Hz, O-CH_2-), 4.45 (2H, q, J = 7.3 Hz, O-CH_2-), 7.11 (1H, d, J = 7.7 Hz, 6-H), 7.13 (2H, d, J = 8.3 Hz, 2′, 6′-H), 7.50 (2H, d, J = 8.3 Hz, 3′, 4′-H), 7.35-7.75 (3H, m, 7, 8, 9-H), 8.02 (1H, bs, NH), 8.85-8.95 (1H, m, 10-H), 9.02 (1H, d, J = 7.7 Hz, 5-H); ms: m/z 480 (M$^+$, 65), 434 (20), 416 (15), 358 (39), 325 (50), 286 (100), 256 (23), 213 (38), 179 (32), 128 (68), 57 (78), 43 (82).

Anal. Calcd. for $C_{25}H_{24}N_2O_6S$ = 480.524: C, 62.48; H, 5.03; N, 5.83; S, 6.67. Found: C, 62.24; H, 5.06; N, 5.82; S, 6.55.

After removal of the ethanol of the filtrate, the residue was chromatography of alumina column using benzene as an eluent to give 0.153 g (0.318 mmole, 32%) of ethyl 2-ethoxycarbonylmethylthioimidazo[2,1-*a*]isoquinoline-3-carboxylate (**12**). An analytical sample was recrystallized from hexane to give colorless needles, mp 112-114°; ir (potassium bromide): ν max 1730, 1690 (CO) cm^{-1}; uv (ethanol): λ max nm (log ε) 269 (4.75), 313 (4.06); ^{1}H-nmr (deuteriochloroform): δ 1.31 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.49 (3H, t, J = 7.3 Hz, OCH_2CH_3), 4.15 (2H, s, S-CH_2-), 4.26 (2H, q, J = 7.3 Hz, O-CH_2-), 4.46 (2H, q, J = 7.3 Hz, O-CH_2-), 7.18 (1H, dd, J = 0.7, 7.5 Hz, 6-H), 7.57-7.82 (3H, m, 7, 8, 9-H), 8.54-8.64 (1H, m, 10-H), 9.03 (1H, d, J = 7.5 Hz, 5-H); ms: m/z 358 (M$^+$, 85), 313 (14), 285 (100), 255 (22), 239 (25), 155 (18), 128 (32), 57 (25), 43 (20).

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$ = 358.419: C, 60.32; H, 5.06; N, 7.82; S, 8.95. Found: C, 59.92; H, 5.13; N, 7.77; S, 8.96.

Dimethyl 2-(*p*-Toluenesulfonylamino)pyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (**11b**).

A solution of 3.10 g (10.0 mmoles) of 2-methoxycarbonylmethylisoquinolinium bromide (**10b**), 3.91 g (10.0 mmoles) of **2b**, and 1 ml of triethylamine in 100 ml of ethanol was refluxed for 43 hours. After removal of solvent and excess triethylamine, 100 ml of water was added to the residue and was acidified with 10% hydrochloric acid. The mixture was extracted with benzene twice. The combined organic layer were washed with 50 ml of water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on an alumina column by using benzene as an eluent to give 1.08 g (2.39 mmoles, 24%) of **11b**. This compound was recrystallized from methanol to give colorless needles, mp 195-196°; ir (potassium bromide): ν max 3225 (NH), 1715, 1680 (CO) cm^{-1}; uv (ethanol): λ max nm (log ε) 273 (4.45), 326 (3.64), 342 (3.76), 359 (3.80); ^{1}H-nmr (deuteriochloroform): δ 2.34 (3H, s, *p*-Me), 3.76 (3H, s, OMe), 3.95 (3H, s, OMe), 7.07 (1H, d, J = 7.5 Hz, 6-H), 7.13 (2H, d, J = 8.3 Hz, 3′, 5′-H), 7.57 (2H, d, J = 8.3 Hz, 2′, 6′-H), 7.54-7.74 (3H, m, 7, 8, 9-H), 7.93 (1H, bs, NH), 8.79-8.94 (1H, 10-H), 8.97 (1H, d, J = 7.5 Hz, 5-H); ms: m/z 451 (M$^+$-1, 53), 388 (24), 298 (26), 297 (100), 235 (32), 179 (24), 91 (13).

Anal. Calcd. for $C_{23}H_{20}N_2O_6S$ = 452.47: C, 61.05; H, 4.46; N, 6.19; S, 7.09. Found: C, 60.94; H, 4.51; N, 6.19; S, 7.02.

Diethyl 2-(*p*-Acetoaminophenylsulfonylamino)pyrrolo[2,1-*a*]isoquinoline-1,3-dicarboxylate (**11c**).

A solution of 0.253 g (0.86 mmole) of 2-ethoxycarbonylmethylisoquinolinium bromide (**10a**), 0.257 g (0.57 mmole) of **2c**, and 0.8 ml of triethylamine in 20 ml of ethanol was refluxed for 48 hours. After removal of solvent and excess triethylamine, 100 ml of water was added to the residue and acidified with 10% hydrochloric acid. The mixture was extracted with benzene twice. The combined organic layers were washed with 50 ml of water, 10% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on an alumina column by using hexane as an eluent to give 0.024 g (0.067 mmole, 12%) of **12**. This compound was recrystallized from ethanol to give colorless needles, mp 112-114°. The second fraction using ethanol as an eluent gave 0.138 g (0.264 mmole, 46%) of **11c** as yellow needles. An analytical sample was recrystallized from ethanol to give yellow needles, mp 205-207°; ir (potassium bromide): ν max 3350, 3265 (NH), 1682 (CO), cm^{-1}; uv (ethanol): λ max nm (log ε) 273 (4.83), 326 (3.94), 342 (4.07), 359 (4.11); ^{1}H-nmr (deuteriochloroform): δ 1.35 (3H, t, J = 7.3 Hz, OCH_2CH_3), 1.45 (3H, t, J = 7.3 Hz, OCH_2CH_3), 2.16 (3H, s, N-COMe), 4.23 (2H, q, J = 7.3 Hz, O-CH_2-), 4.42 (2H, q, J = 7.3 Hz, O-CH_2-), 7.07 (1H, d, J = 7.7 Hz, 6-H), 7.45 (4H, bs, Ph-H), 7.45-7.67 (3H, m, 7, 8, 9-H), 7.69 (1H, bs, NH), 8.05 (1H, bs, NH), 8.79-8.89 (1H, m, 10-H), 8.96 (1H, d, J = 7.7 Hz, 5-H); ms: m/z 523 (M$^+$, 12), 522 (M$^+$-1, 37), 477 (7), 458 (54), 387 (24), 326 (69), 281 (39), 235 (51), 208 (61), 179 (66), 44 (100).

Anal. Calcd. for $C_{26}H_{25}N_3O_7S$ = 523.544: C, 59.64; H, 4.81; N, 8.03; S, 6.12. Found: C, 59.25; H, 4.97; N, 7.88; S, 5.91.

The Reaction of **4a** with 2-Ethoxycarbonylmethylisoquinolinium Bromide (**10a**).

A solution of 0.444 g (1.5 mmoles) of 2-ethoxycarbonylmethylisoquinolinium bromide (**10a**), 0.30 g (1.0 mmole) of **4a** and 1 ml of triethylamine in 20 ml of ethanol was refluxed for 48 hours. After removal of the solvent and excess triethylamine, 50 ml of water was added to the residue and was acidified with 10% hydrochloric acid. The caramel oil product was washed with 5 ml of ethanol to give a crystallized product of a mixture of ethyl 2-

methylthioimidazo[2,1-*a*]isoquinoline-3-carboxylate (**13a**) and ethyl 1-cyano-2-(*p*-toluenesulfonylaminopyrrolo[2,1-*a*]isoquinoline (**11a**) which were easily separated by alumina column chromatography. Benzene elution gave 0.068 g (0.237 mmole, 24%) of **13a** colorless needles, mp 154-155° (lit [1], mp 154°). Ethanol elution gave 0.061 g (0.141 mmole, 14%) of **11a** as colorless needles, mp 175-176°.

The Reaction of 4b with 2-Ethoxycarbonylmethylisoquinolinium Bromide (10a).

A solution of 0.444 g (1.5 mmoles) of 2-ethoxycarbonylmethylisoquinolinium bromide (**10a**), 0.30 g (1.0 mmole) of **4b**, and 1 ml of triethylamine in 20 ml of methanol was refluxed for 51 hours. After removal of the solvent and excess triethylamine, 50 ml of water was added to the residue and was acidified with 10% hydrochloric acid. The caramel oil product was crystallized by treatment with 5 ml of ethanol to give a mixture of ethyl 2-methylthioimidazo[2,1-*a*]isoquinoline-3-carboxylate (**13a**) and ethyl 1-cyano-2-(*p*-toluenesulfonylaminopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**11d**) which were easily separated by chromatography on alumina column. Benzene elution gave 0.068 g (0.237 mmole, 24%) of **13a** as colorless needles, mp 153-155° (lit [1], mp 154°). The ethanol elution gave 0.05 g (0.115 mmole, 12%) of **11d** as colorless needles, mp 206-208°; ir (potassium bromide): ν max 3270 (NH), 2225 (CN), 1682 (CO) cm^{-1} uv (ethanol): λ max nm (log ϵ) 270 (4.78), 315 (4.06), 338 (4.01), 355 (4.00); ^{1}H-nmr (deuteriochloroform): δ 1.38 (3H, t, J = 7.3 Hz, OCH_2CH_3), 2.39 (3H, s, *p*-Me), 4.27 (2H, q, J = 7.3 Hz, O-CH$_2$-), 7.20 (1H, d, J = 7.7 Hz, 6-H), 7.24 (4H, d, J = 8.3 Hz, phenyl-H), 7.66-7.80 (5H, m, phenyl-H, 7, 8, 9-H), 8.07 (1H, bs, NH), 8.99-9.12 (1H, m, 10-H), 9.03 (1H, d, J = 7.7 Hz, 5-H); ms: m/z 433 (M$^+$, 73), 369 (11), 278 (100), 234 (33), 206 (28), 179 (22), 44 (67).

Anal. Calcd. for $C_{23}H_{19}N_3O_4S$ = 433.464: C, 63.73; H, 4.42; N, 9.69. Found: C, 63.33; H, 4.50; N, 9.63.

The Reaction of 4b with 2-Methoxycarbonylmethylisoquinolinium Bromide (10b).

A solution of 0.423 g (1.5 mmoles) of 2-methoxycarbonylmethylisoquinolinium bromide (**10b**), 0.30 g (1.0 mmole) of **4b**, and 1 ml of triethylamine in 20 ml of methanol was refluxed for 51 hours. After removal of the solvent and excess triethylamine, 50 ml of water was added to the residue and acidified with 10% hydrochloric acid. The caramel oil product was crystallized by the treatment with 5 ml of ethanol to give a mixture of ethyl 2-methylthioimidazo[2,1-*a*]isoquinoline-3-carboxylate (**13b**) and methyl 1-cyano-2-(*p*-toluenesulfonylaminopyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**11e**) which easily separated by chromatography on an alumina column. Benzene elution gave 0.032 g (0.118 mmole, 12%) of **13b** as colorless needles, mp 118-120° (lit [1], mp 120°). Methanol elution gave 0.079 g (0.189 mmole, 19%) of **11e** as colorless needles. An analytical sample was recrystallized from methanol to give colorless needles, mp 216-219°; ir (potassium bromide): ν max 3250 (NH), 2225 (CN), 1690 (CO) cm^{-1}; uv (ethanol): λ max nm (log ϵ) 270 (4.78), 315 (4.06), 339 (4.01), 356 (4.00); ^{1}H-nmr (deuteriochloroform): δ 2.40 (3H, s, *p*-Me), 376 (3H, s, OMe), 7.17-7.28 (4H, phenyl-H, 6-H), 7.62-7.73 (5H, m, phenyl-H, 7, 8, 9-H, NH), 8.98-9.08 (1H, m, 10-H), 9.03 (1H, d, J = 7.7 Hz, 5-H); ms: m/z 418 (M$^+$-1, 47), 368 (11), 264 (81), 234 (7), 211 (24), 179 (15), 57 (100), 44 (91).

Anal. Calcd. for $C_{22}H_{17}N_3O_4S$ = 419.438; C, 62.99; H, 4.09; N, 10.02; S, 7.64. Found: C, 62.57; H, 4.20; N, 9.95; S, 7.31.

REFERENCES AND NOTES

[1] Part **1**: Y. Tominaga, S. Motokawa, Y. Shiroshita and A. Hosomi, *J. Heterocyclic Chem.*, **24**, 1365 (1987); Part **2**: Y. Tominaga, M. Hara, H. Honkawa and A. Hosomi, *J. Heterocyclic Chem.*, **27**, 1245 (1990); Part **3**: Y. Tominaga, S. Ohno, S. Kohra, H. Fujito and H. Mazume, *J. Heterocyclic Chem.*, **28**, 1039 (1991); Part **4**: Y. Tominaga, K. Ogata, S. Kohra and A. Hosomi, *Tetrahedron Letters*, **32**, 5987 (1991).

[2] Y. Kuwayama and S. Kataoka, *Yakugaku Zasshi*, **85**, 391 (1965).

[3] R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).

[4] S. P. Tanis, M. C. McMills and P. M. Herrinton, *J. Org. Chem.*, **50**, 5887 (1985).

[5] A. Hosomi, K. Hoashi, K. Ogata, S. Kohra and Y. Tominaga, *Chem. Pharm. Bull.*, **36**, 3736 (1988).

[6] K. Tanaka, N. Yamaguchi, R. Tanigawa and A. Kaji, *Bull. Chem. Soc. Japan*, **52**, 3619 (1979).

[7] Kakehi, *et al.* have reported that alkaline treatment of 1-[2-(substituted methylthio)vinyl]pyridinium bromides, readily obtainable from the *S*-alkylation of pridinium 1-(thiocarbonyl)methylides with various alkyl bromides such as bromoacetonitrile, ethyl bromoacetate, and some phenacyl bromides, gave smoothly 1,9a-dihydro[2,1-*c*][1,4]thiazine derivatives, *via* 1,6-cyclization, which are readily converted to 2-methylthioindolizine derivatives; [a] A. Kakehi, S. Ito, S. Yonezu, K. Maruta, K. Yuito, M. Shiohara and K. Adachi, *Bull. Chem. Soc. Japan*, **60**, 1867 (1987); [b] A. Kakehi, S.Ito, N. Yamada and K. Yamaguchi, *Bull. Chem. Soc. Japan*, **63**, 829 (1990).

[8] The reaction of **2** with malononitrile as an active methylene compound in the presence of potassium carbonate in dimethyl sulfoxide gave 2,4-diaminothiophene derivatives. Details will be published in a forthcoming paper.