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Studies on Mesoionic Compounds. XIV.[1] Synthesis of Mesoionic 1,3-Thiazolium-4-thiolates

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Two approaches to 3-alkyl-2,5-diphenyl-1,3-thiazolium-4-thiolate (**4**) are described: (1) exchange of the exocyclic oxygen atom of the mesoionic 4-olate (**6**) with sulfur *via* O-methylation and (2) base-catalyzed thiation of the *N*-alkyl-1,3-thiazolium compound (**3**). The mesoionic thiazoles underwent cycloaddition with dimethyl acetylenedicarboxylate to give thermally stable bicyclic compounds **8**.

Keywords——N-alkylation; cycloaddition; dimethyl acetylenedicarboxylate; mesoionic compound; 1,3-thiazole

Although the preparation of mesoionic 1,3-thiazoles bearing an exocyclic nitrogen or oxygen atom is well documented,[2] the sulfur analogs, especially the 1,3-thiazolium-4-thiolate system, have not been synthesized, except for the recently reported 2-amino derivative **1** which was obtained from a 1,3-dithiolium-4-olate by a ring interconversion method.[3] The result was not unexpected in this particular system. The well-known standard synthetic methods for mesoionic azoles,[2,3] direct ring closure and ring interconversion by the use of reactive dipolarophiles, are hardly applicable since the precursors required for these approaches are either not available or are limited in available ring substitution patterns. Therefore, for the present study on the synthesis of the title compound, we directed our attention to the direct thiation of *N*-alkylthiazolium compounds and the exchange of exocyclic oxygen for sulfur, both of which have already been reported by us as being highly effective in the 1,2,3-thiadiazole system.[1,4]

2,5-Diphenyl-1,3-thiazole (**2**) was reacted with methyl *p*-toluenesulfonate, and the *N*-methyl compound **3a**, obtained in 80% yield, was treated with sulfur and sodium hydride in the presence of *N*,*N*-dimethylformamide at $-50\,^{\circ}C$ to room temperature. The thiation product was purified by silica gel chromatography followed by crystallization from 2-propanol to afford the 4-thiolate (**4a**) as deep orange crystals in 60% yield. The structure of **4a** was supported by the spectral data (proton nuclear magnetic resonance (^{1}H-NMR) δ: 4.68 for N–Me; mass spectra (MS) *m/e* (base peak): 118 due to $PhC\equiv\overset{+}{N}Me$) and by the formation of the 4-methylthiothiazolium iodide (**5**) in quantitative yield on treatment with methyl iodide. By using the same technique, the 4-ethyl and 4-benzyl derivatives (**4b**, **c**) were obtained from **2** in overall yields of 30 and 40% respectively.

With ready access to the mesoionic 1,3-thiazolium-4-thiolates **4** from 2,5-diphenyl-1,3-thiazole, we next applied the thiation procedure to 2,3-dimethyl-5-phenyl- and 3,5-dimethyl-2-phenyl-1,3-thiazolium tosylates. Unfortunately, however, the result of the thiation was disappointing; a complex mixture of products was obtained and no mesoionic compound could be detected. Failure of the thiation with these dimethyl compounds is presumably due to a fragmentation of the substrates initiated by prior deprotonation of the ring methyl group.

As an alternative approach, exchange of the exocyclic oxygen atom of 1,3-thiazolium-4-

olate with sulfur was investigated. 2,5-Diphenyl-3-methyl-1,3-thiazolium-4-olate (**6**) was prepared after the method of Ohta[2e] in 14% yield by starting with the condensation of *N*-methylthiobenzamide with α-bromophenylacetic acid, followed by ring closure of the *S*-alkylated intermediate with acetic anhydride. Treatment of **6** with trimethyloxonium tetrafluoroborate afforded 4-methoxythiazolium compound **7** in 78% yield, and this was reacted with sodium hydrosulfide in methanol to produce the 4-thiolate **4a** in 44% yield in addition to the 4-olate **6** in 33% yield. Thus, this approach to **4a** was less efficient than the previous one involving direct thiation.

Next, cycloaddition reaction of **4** with dimethyl acetylenedicarboxylate was attempted. By carrying out the reaction in refluxing benzene, the 1 : 1 adduct **8** was obtained in 47—72% yields. Noteworthy here is the thermal stability of **8**, in contrast to the cycloadduct of 2,3-diphenyl-1,3-thiazolium-4-olate and dimethyl acetylenedicarboxylate, which is not isolable, spontaneously eliminating sulfur or phenyl isocyanate to give a pyridone or thiophene derivative.[5] In the electron impact MS of **8**, the observed fragmentation patterns were essentially the same as those of the parent mesoionic compounds.

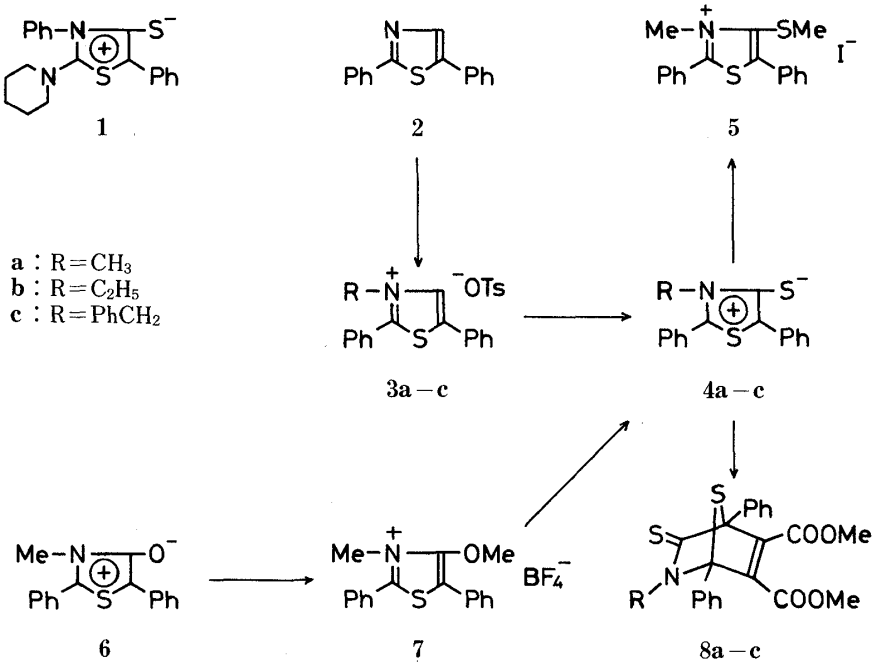

Chart 1

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco IRA-1 grating spectrophotometer. ^{1}H-NMR spectra were taken on a JEOL PMX-60 spectrometer in deuteriochloroform unless otherwise noted, and chemical shifts are expressed in ppm downfield from internal tetramethylsilane. MS were obtained on a JEOL D-300 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this university. For column chromatography, Merck Silica gel 60 (70—200 or 230—400 mesh) was used. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in work-up, and removal of the solvent was performed with a rotary evaporator.

3-Methyl-2,5-diphenyl-1,3-thiazolium Tosylate (3a)——A mixture of **2**[6] (474 mg, 2 mmol) and methyl *p*-toluenesulfonate (745 mg, 4 mmol) was heated at 100 °C with stirring. After 2 h, the mixture was allowed to cool to room temperature, and the solid product was washed with ether and recrystallized from iso-PrOH to give **3a** (680 mg, 80%) as colorless plates, mp 166—167 °C. *Anal.* Calcd for $C_{23}H_{21}NO_3S_2$: C, 65.22; H, 5.00; N, 3.31. Found: C, 64.94; H, 5.02; N, 3.23. ^{1}H-NMR (CD_3OD) δ: 2.32 (3H, s, ArMe), 4.23 (3H, s, NMe), 7.1—7.7 (14H, m, ArH), 8.75 (1H, s, 4-H).

3-Methyl-2,5-diphenyl-1,3-thiazolium-4-thiolate (4a)——a) A mixture of **3a** (847 mg, 2 mmol), sulfur (512 mg, 2 mmol) and NaH (60% dispersion in mineral oil, 240 mg, 6 mmol) was cooled to −50 °C under a nitrogen atmosphere, and dry dimethylformamide (DMF) (10 ml) was introduced dropwise. The reaction mixture was stirred and allowed to warm to room temperature, and after continued stirring for 2 h it was concentrated under reduced pressure at below 60 °C. The residue was extracted with MeOH (10 ml × 2), and the extract was concentrated to give an orange-red oil, which was subjected to column chromatography (silica gel, 20 g; solvent, benzene). The solid eluate was recrystallized from iso-PrOH to afford **4a** (343 mg, 60%) as deep orange needles, mp 190—192 °C. *Anal.* Calcd for $C_{16}H_{13}NS_2$: C, 67.81; H, 4.62; N, 4.94. Found: C, 67.51; H, 4.61; N, 4.89. IR (KBr): 1220 cm^{-1}. ^{1}H-NMR δ: 4.68 (3H, s, NMe), 7.1—8.3 (10H, m, Ph). MS *m/e* (relative intensity): 283 (M^+, 100), 121 ($PhCS^+$, 25), 118 ($PhC\equiv\overset{+}{N}Me$, 100), 77 ($Ph^+$, 70).

b) Trimethyloxonium tetrafluoroborate (222 mg, 1.5 mmol) was added to a solution of **6** (400 mg, 1.5 mmol) in dry dichloromethane (10 ml), and the mixture was stirred at room temperature overnight. Removal of the solvent under reduced pressure afforded a crystalline mass, which was washed with ether and then recrystallized from iso-PrOH to give **7** (430 mg, 78%) as colorless needles, mp 163—164 °C. ^{1}H-NMR (CD_3OD) δ: 3.98 (3H, s, OMe), 4.03 (3H, s, NMe), 7.5—7.9 (10H, m, Ph).

A stirred solution of **7** (185 mg, 0.5 mmol) in MeOH (5 ml) was cooled to −70 °C, and NaSH[7] (34 mg, 0.6 mmol) was added. The mixture was allowed to warm to room temperature and stirring was continued overnight. The solvent was removed under reduced pressure and the oily residue was dissolved in chloroform (30 ml). The solution was washed with water, dried, and concentrated. The residue was subjected to column chromatography (silica gel, 5 g; solvent, benzene) to give **4a** (62 mg, 44%) and **6** (47 mg, 33%).

3-Methyl-2,5-diphenyl-1,3-thiazolium-4-olate (6)——A stirred solution of *N*-methylthiobenzamide (5.0 g, 33 mmol), α-bromophenylacetic acid (7.1 g, 33 mmol) and triethylamine (3.4 g, 34 mmol) in benzene (100 ml) was refluxed for 3 h. The mixture was cooled with ice-water and filtered to remove precipitated triethylamine hydrobromide. The filtrate was concentrated under reduced pressure, and the residue was treated with acetic anhydride (50 ml) at room temperature for 1 h. Removal of unreacted acetic anhydride under reduced pressure afforded an orange-red oil, which was subjected to column chromatography (silica gel, 100 g; solvent, $CHCl_3$) and the solid eluate was recrystallized from iso-PrOH to give **6** as orange needles, mp 161—162 °C. *Anal.* Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 72.17; H, 4.91; N, 5.07. IR (KBr): 1580 cm^{-1}. ^{1}H-NMR δ: 3.71 (3H, s, NMe), 7.51 (5H, s, Ph), 7.2—7.8 (5H, m, Ph). MS *m/e* (relative intensity): 267 (M^+, 55), 118 ($PhC\equiv\overset{+}{N}Me$, 100), 77 ($Ph^+$, 65).

3-Ethyl-2,5-diphenyl-1,3-thiazolium-4-thiolate (4b)——By using the same procedure as described for the preparation of **4a**, **2** (711 mg) was reacted with ethyl *p*-toluenesulfonate at 120 °C for 8 h. The *N*-ethyl product **3b** was without purification subjected to thiation. Purification of **4b** was performed by silica gel chromatography followed by recrystallization from iso-PrOH: orange needles (254 mg, 30%), mp 157—158 °C. *Anal.* Calcd for $C_{17}H_{15}NS_2$: C, 68.65; H, 5.08; N, 4.71. Found: C, 68.76; H, 5.09; N, 4.81. IR (KBr): 1220 cm^{-1}. ^{1}H-NMR δ: 1.48 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 4.68 (2H, q, J=7 Hz, $\underline{CH_2}Me$), 7.1—8.3 (10H, m, Ph). MS *m/e* (relative intensity): 297 (M^+, 85), 166 (25), 132 ($PhC\equiv\overset{+}{N}Et$, 30), 121 ($PhCS^+$, 55), 104 ($PhC\equiv\overset{+}{N}H$, 100), 77 ($Ph^+$, 35).

3-Benzyl-2,5-diphenyl-1,3-thiazolium-4-thiolate (4c)——This compound was obtained from **2** in 40% yield as described above: mp 171—173 °C (iso-PrOH). IR (KBr): 1220 cm^{-1}. *Anal.* Calcd for $C_{22}H_{17}NS_2$: C, 73.50; H, 4.77; N, 3.90. Found: C, 73.80; H, 4.82; N, 3.98. ^{1}H-NMR δ: 5.96 (2H, s, $\underline{CH_2}Ph$), 6.9—8.3 (15H, m, Ph). MS *m/e* (relative intensity): 359 (M^+, 40), 326 (80), 165 (35), 121 ($PhCS^+$, 98), 91 ($\underline{PhCH_2^+}$, 100).

3-Methyl-4-methylthio-2,5-diphenyl-1,3-thiazolium Iodide (5)——A solution of **4a** (7 mg) in methyl iodide (0.5 ml) was stirred at room temperature for 30 min. The solution was concentrated under reduced pressure, and the residual yellow solid was washed with ether and dried to give **5** (9.8 mg), mp 158—159 °C. *Anal.* Calcd for $C_{17}H_{16}INS_2$: C, 47.98; H, 3.79; N, 3.29. Found: C, 47.73; H, 3.93; N, 3.15. ^{1}H-NMR (CD_3OD) δ: 2.46 (3H, s, SMe), 4.21 (3H, s, NMe), 7.3—8.0 (10H, m, Ph).

Reaction of 4 with Dimethyl Acetylenedicarboxylate (Formation of Cycloadduct 8)——A solution of **4a** (142 mg, 0.5 mmol) and dimethyl acetylenedicarboxylate (71 mg, 0.5 mmol) in benzene (3 ml) was heated under reflux for 8 h. The solvent was removed under reduced pressure, and the residue was subjected to chromatography (silica gel, 5 g; solvent, benzene) to give **8a**, which was recrystallized from cyclohexane: yellow prisms (150 mg, 70%), mp 177—178 °C. *Anal.* Calcd for $C_{22}H_{19}NO_4S_2$: C, 62.10; H, 4.50; N, 3.29. Found: C, 62.19; H, 4.49; N, 3.29. IR (KBr): 1710, 1240 cm^{-1}. ^{1}H-NMR δ: 3.70 (3H, s, OMe), 3.87 (3H, s, OMe), 3.8 (3H, br s, NMe), 6.7—7.1 (10H, m, Ph). MS *m/e* (relative intensity): 425 (M^+, 1), 121 ($PhCS^+$, 30), 118 ($PhC\equiv\overset{+}{N}Me$, 100).

By using the same procedure, the following *N*-alkyl derivatives were obtained and characterized by spectral analyses. **8b**: yellow prisms from cyclohexane, mp 141—142 °C (47% yield). *Anal.* Calcd for $C_{23}H_{21}NO_4S_2$: C, 62.85; H, 4.82; N, 3.19. Found: C, 62.95; H, 4.84; N, 3.23. IR (KBr): 1710, 1240 cm^{-1}. ^{1}H-NMR δ: 1.35 (3H, br, CH_3), 3.67 (3H, s, OMe), 3.86 (3H, s, OMe), 4.0 (2H, br, CH_2), 6.7—7.5 (10H, m, Ph). MS *m/e* (relative intensity): 439 (M^+, 2), 132 ($PhC\equiv\overset{+}{N}Et$, 100), 121 ($PhCS^+$, 75), 104 ($PhC\equiv\overset{+}{N}H$, 95). **8c**: yellow needles from benzene, mp 131—132 °C (72%

yield). *Anal.* Calcd for $C_{28}H_{23}NO_4S_2$: C, 67.05; H, 4.62; N, 2.79. Found: C, 66.84; H, 4.59; N, 2.73. IR (KBr): 1710, 1250 cm^{-1}. ^{1}H-NMR δ: 3.65 (3H, s, OMe), 3.80 (3H, s, OMe), 5.4 (2H, br, CH_2), 6.7—7.5 (15H, m, Ph). MS *m/e* (relative intensity): 501 (M^+, 5), 195 ($PhC\equiv\overset{+}{N}HCH_2Ph$, 95), 194 ($PhC\equiv\overset{+}{N}CH_2Ph$, 60), 121 ($PhCS^+$, 100).

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