Synthesis of 2-Methylazuleno[1,2-*d*]thiazoles

Kunihide FUJIMORI,* Hiroyuki KITAHASHI, Satoshi KOYAMA, and Kameji YAMANE
Department of Chemistry, Faculty of Science, Shinshu University, Asahi, Matsumoto 390
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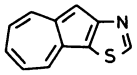
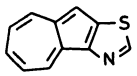
Synopsis. 2-Methylazuleno[1,2-*d*]thiazoles were synthesized from diethyl 2-mercapto-1,3-azulenedicarboxylate, which was prepared by a treatment of diethyl 2-(2-methoxycarbonylethylthio)-1,3-azulenedicarboxylate with sodium ethoxide in five steps.

Among the two possible isomers of azulenothiazoles which are formed by a condensation of thiazole with azulene at the 1,2-position, azuleno[2,1-*d*]thiazole (**I**) as well as its 2-amino and 2-methyl derivatives have been synthesized.[1)]



I



II

We now wish to report the synthesis of azuleno[1,2-*d*]thiazoles (**II**). The reaction of diethyl 2-chloro-1,3-azulenedicarboxylate (**1**)[2)] with methyl 3-mercaptopropionate in pyridine gave diethyl 2-(2-methoxycarbonylethylthio)-1,3-azulenedicarboxylate (**3**) in 93% yield. When the ester **3** was treated with sodium ethoxide in dry ethanol, diethyl 2-mercapto-1,3-azulenedicarboxylate (**4**), a reversal Michael's addition reaction product, was obtained in 96% yield, and methyl acrylate was also detected. The IR and ^{1}H NMR spectra of **4** show an absorption band at 2434 cm^{-1} and a signal at δ=7.71 due to the mercapto group, respectively. Compound **4** has also been obtained by a reaction of **1** with thioacetic acid or hydrogen sulfide in the presence of sodium ethoxide.[3)] However, the present method is unaccompanied by the formation of other by-products, such as thioether or disulfide, and is preferred as a method for the preparation of **4**.

Heating **4** with 100% phosphoric acid at 90°C resulted in deethoxycarbonylation giving ethyl 2-mercapto-1-azulenecarboxylate (**5**) in an almost quantitative yield. Further, the treatment of **5** with acetic anhydride gave 2-(acetylthio)azulene derivative **6** in 91% yield. The nitration of **6** with nitric acid in acetic anhydride at −30°C gave ethyl 2-acetylthio-3-nitro-1-azulenecarboxylate (**7**) in 44% yield. Compound **7**, upon treatment with zinc dust in acetic acid and acetic anhydride at room temperature, gave a mixture of ethyl 2-acetylthio-3-acetylamino-1-azulenecarboxylate (**8**) and ethyl 3-acetylamino-1-azulenecarboxylate (**9**). Compound **8** was treated with a potassium hydroxide solution in tetrahydrofuran–ether, followed by a treatment with hydrochloric acid by cooling with ice under an inert atmosphere to give ethyl 2-methylazuleno[1,2-*d*]thiazole-9-carboxylate (**10**). Furthermore, the demethoxycarbonylation of **10** by heating with 100% phosphoric acid gave 2-methylazuleno[1,2-*d*]thiazole (**11**) in 87% yield. The difference between the vicinal coupling constants, $\Delta J = J_{7,8} - J_{4,5}$, in ^{1}H NMR of **11** is 1.3 Hz, indicating that the 7-membered ring exhibits some bond alternation in analogy with azuleno[2,1-*d*]thiazole.[1)]

The electronic spectra of **10**, **11**, and 2-methylazuleno[2,1-*d*]thiazole[1)] are shown in Fig. 1.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were record-

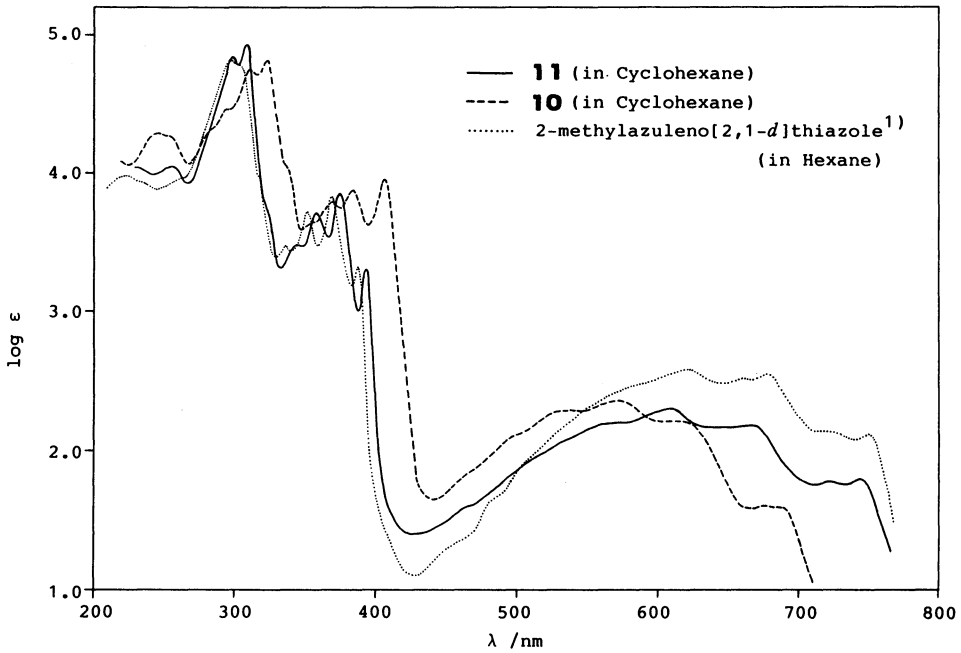


Fig. 1. Electronic spectra of **10**, **11**, and 2-methylazuleno[2,1-*d*]thiazole.

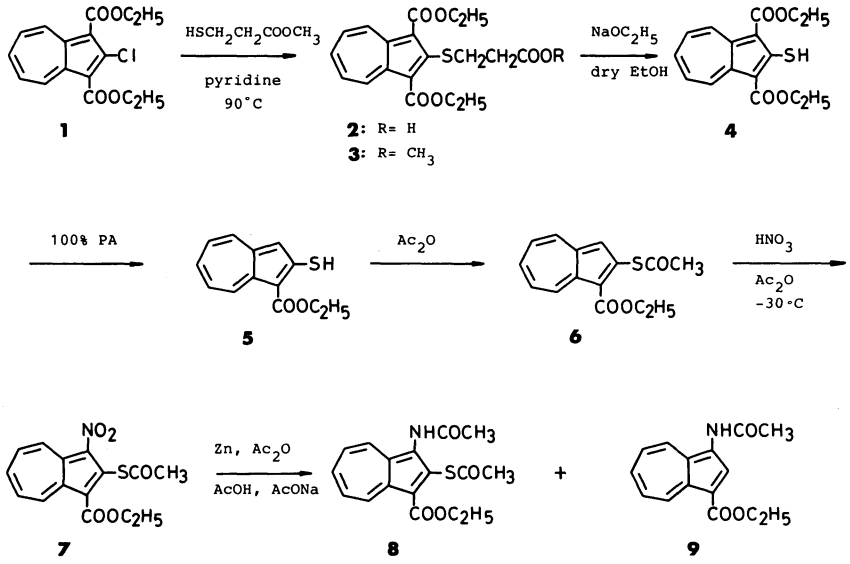


Fig. 2.

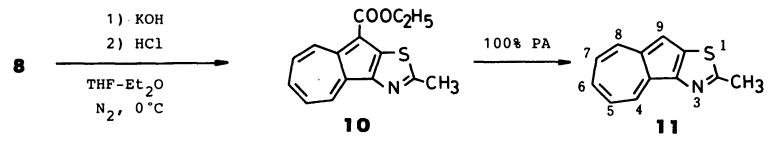


Fig. 3.

ed with a JEOL 90Q spectrometer using tetramethylsilane as an internal standard. The IR spectra were taken on a Hitachi 345 infrared spectrometer and the electronic absorption spectra were measured with a Hitachi 200-20 spectrometer.

Diethyl 2-(2-Methoxycarbonylethylthio)-1,3-azulenedicarboxylate (3). A mixture of diethyl 2-chloro-1,3-azulenedicarboxylate (**1**) (600 mg) and methyl 3-mercaptopropionate (310 mg) in pyridine (30 ml) was heated at 90°C for 1 h. After cooling, the reaction mixture was poured into water and extracted with dichloromethane. The dichloromethane layer was washed with 3M sulfuric acid and water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column with benzene. The red effluent was freed from the solvent to give **3** (711 mg, 93%) as red micro needles; mp 70.5—71°C; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.49 (6H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.61 (2H, t, J=7.7 Hz, $SCH_2C\underline{H}_2COOMe$), 3.34 (2H, t, J=7.7Hz, $SC\underline{H}_2CH_2COOMe$), 3.64 (3H, s, $SCH_2CH_2COOC\underline{H}_3$), 4.51 (4H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.4—7.9 (3H, m, H-5,6,7), and 9.17 (2H, dm, J=9.6 Hz, H-4,8). Found: C, 61.35; H, 5.56; S, 8.24%. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.68; S, 8.21%. The second red effluent gave a trace of diethyl 2-(2-carboxyethylthio)-1,3-azulenedicarboxylate (**2**) as a red solid; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.50 (6H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.66 (2H, t, J=7.7 Hz, $SCH_2C\underline{H}_2COOH$), 3.33 (2H, t, J=7.7 Hz, $SC\underline{H}_2CH_2COOH$), 4.51 (4H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), and 10.7 (1H, bs, $COO\underline{H}$).

Diethyl 2-Mercapto-1,3-azulenedicarboxylate (4). Into a solution of **3** (6.25 g) in anhydrous ethyl alcohol (100 ml), a sodium ethoxide solution which was prepared from sodium metal (583 mg) and anhydrous ethanol (50 ml) was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water, neutralized with 2M hydrochloric acid (1 M=1 mol dm^{-3}), and extracted with benzene. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column. From the benzene effluent, **4** was obtained as orange needles (4.69 g, 96%); mp 88.5—89°C (lit, 3, 85—86°C); ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.53 (6H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 4.51 (4H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.71 (1H, s, S$\underline{H}$), 7.5—7.8 (3H, m, H-5,6,7), and 9,3—9.5 (2H, m, H-4,8); IR (KBr) 2434 cm^{-1} (SH). (Found: C, 63.38; H, 5.39; S, 10.36%).

Ethyl 2-Mercapto-1-azulenecarboxylate (5). A mixture of **4** (3.93 g) and 100% phosphoric acid (50 ml) was heated for 30 min at 90°C. After cooling, the reaction mixture was poured into water and extracted with benzene. The extract was washed with water, dried, and evaporated. The residue was chromatographed on a silica-gel column with benzene–hexane (1:1). The red effluent was freed from the solvent to give **5** (3.00 g, ca. 100%) as red oil; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.49 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 4.47 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 5.35 (1H, s, S$\underline{H}$), 7.30 (1H, s, H-3), 7.1—7.7 (3H, m, H-5,6,7), 8.02 (1H, dm, J=9.8 Hz, H-4), and 9.24 (1H, dm, J=9.8 Hz, H-8). Found: C, 67.00, H, 5.10; S, 13.85%. Calcd for $C_{13}H_{12}O_2S$: C, 67.24; H, 5.17; S, 13.81%. From the purple effluent, a trace of 2-mercaptoazulene[3] was obtained as bluish purple crystals; mp 112—113°C; IR (KBr) 2538 cm^{-1} (SH); ^{1}H NMR (90 MHz, in $CDCl_3$) δ=3.87 (1H, s, S$\underline{H}$), 7.11 (2H, s, H-1,3), 6.9—7.6 (3H, m, H-5,6,7), and 8.04 (2H, dm, J=9.7 Hz, H-4,8); ^{13}C NMR (22.5 MHz, in $CDCl_3$) δ=116.8, 124.5, 133.1, 135.4, 140.7, and 140.9.

Ethyl 2-Acetylthio-1-azulenecarboxylate (6). A mixture of **5** (3.00 g) and acetic anhydride (55 ml) was heated for 30 min at 90°C. The reaction mixture was evaporated under reduced pressure, and the residue was diluted with water. The solution was then neutralized with a aqueous sodium carbonate solution and extracted with benzene. The benzene layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column with benzene–hexane (1:1). The purple

effluent gave **6** (3.22 g, 91%) as dark purple prisms; mp 72—73 °C; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.48 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.56 (3H, s, $SCOC\underline{H}_3$), 4.47 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.2—7.8 (3H, m, H-5,6,7), 8.26 (1H, dm, J=9.8 Hz, H-4), and 9.46 (1H, dm, J=9.8 Hz, H-8). Found: C, 65.60; H, 5.15; S, 11.57%. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69%.

Ethyl 2-Acetylthio-3-nitro-1-azulenecarboxylate (7). Into a solution of **6** (500 mg) in acetic anhydride (240 ml) which had been cooled at −30 °C, nitric acid was added, drop by drop; the solution was then stirred for 8 h. The reaction mixture was diluted with water, neutralized with a 6M sodium hydroxide aqueous solution, and extracted with dichloromethane. The extract after being dried and freed from solvent yielded a residue. The residue was chromatographed on a silica-gel column with benzene. The effluent gave **7** (258 mg, 44%) as dark red prisms; mp 144.5—145 °C; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.46 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.56 (3H, s, $SCOC\underline{H}_3$), 4.44 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.7—8.2 (3H, m, H-5,6,7), and 9.5—9.7 (2H, m, H-4,8). Found: C, 56.48; H, 4.08; N, 4.13; S, 9.99%. Calcd for $C_{15}H_{13}NO_5S$: C, 56.41; H, 4.07; N, 4.42; S, 10.04%. From purple effluent, **6** (175 mg, 35%) was recovered.

Ethyl 3-Acetylamino-2-acetylthio-1-azulenecarboxylate (8) and Ethyl 3-Acetylamino-1-azulenecarboxylate (9). A mixture of **7** (300 mg), acetic anhydride (75 ml), sodium acetate (5.28 g), and zinc dust (10.7 g) in acetic acid (75 ml) was stirred for 21 h at room temperature. The reaction mixture was diluted with water and unchanged zinc dust was removed by filtration. The filtrate was neutalized with potassium carbonate and extracted with dichloromethane. The extract was dried and the solvent was removed. The resulting residue was chromatographed on a silica-gel column. **8** (109 mg, 35%, purple needles, mp 113—114 °C); IR (KBr) 3264, 1711, 1684, 1644, and 1528 cm^{-1}; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.45 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.26 (3H, s, $NHCOC\underline{H}_3$), 2.52 (3H, s, $SCOC\underline{H}_3$), 4.45 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 6.90 (1H, bs, $N\underline{H}COCH_3$), 7.1—7.9 (3H, m, H-5,6,7), 8.30 (1H, dm, J=9.6 Hz, H-4), and 9.49 (1H, dm, J=9.6 Hz, H-8). Found: C, 61.50; H, 5.15; N, 4.20; S, 9.65%. Calcd for $C_{17}H_{17}O_4NS$: C, 61.61; H, 5.17; N, 4.23; S, 9.68%. **9** (66 mg, 27%, greenish blue micro needles, mp 181—181.5 °C); IR (KBr) 3266, 1695, 1659, and 1541 cm^{-1}; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.40 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.25 (3H, s, $NHCOC\underline{H}_3$), 4.36 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.0—7.8 (3H, m, H-5,6,7), 7.97 (1H, dm, J=9.6 Hz, H-4), 8.47 (1H, s, H-2), and 9.49 (1H, dm, J=9.6 Hz, H-8); ^{13}C NMR (22.5 MHz, in $CDCl_3$) δ=14.6, 23.7, 59.9, 114.6, 124.0, 125.4, 127.3, 133.3, 133.9, 134.5, 137.9, 138.1, 139.5, 165.2, and 169.2. Found: C, 70.28; H, 5.91; N, 5.52%. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44%.

Ethyl 2-Methylazuleno[1,2-*d*]thiazole-9-carboxylate (10). To a solution of **8** (78 mg) in tetrahydrofuran (7 ml) and ether (14 ml) which had been cooled in an ice bath, a solution of potassium hydroxide (148 mg) in water (7 ml) was added, drop by drop, under an atmosphere of nitrogen, after which the solution was stirred for 20 min. Further, hydrochloric acid (7 ml) was added and then the solution was stirred for 12 h at room temperature. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was washed with water, and evaporated. The residue was chromatographed on a silica-gel column with benzene-ethyl acetate (9:1). The purple effluent was freed from the solvent to give **10** (42 mg, 41%) as purple prisms; mp 107.5—108 °C; IR (KBr) 1683, 1437, 1417, and 1196 cm^{-1}; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=1.51 (3H, t, J=7.2 Hz, $COOCH_2C\underline{H}_3$), 2.96 (3H, s, $C\underline{H}_3$-2), 4.52 (2H, q, J=7.2 Hz, $COOC\underline{H}_2CH_3$), 7.4—8.0 (3H, m, H-5,6,7), 8.97 (1H, dm, J=9.0 Hz, H-4), and 9.68 (1H, dm, J=10.3 Hz, H-8); ^{13}C NMR (22.5 MHz, in $CDCl_3$) δ=14.7, 20.5, 60.3, 106.4, 127.6, 128.2, 131.6, 133.7, 137.2, 138.6, 142.2, 146.8, 148.6, 164.2, and 168.2. Found: C, 66.68; H, 4.80; N, 5.23; S, 11.95%. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82%.

2-Methylazuleno[1,2-*d*]thiazole (11). A mixture of **10** (23 mg) and 100% phosphoric acid (5 ml) was heated for 1 h at 90 °C. After cooling, the reaction mixture was diluted with water and extracted with benzene. The dried extract was evaporated to give a residue. The residue was chromatographed on a silica-gel column with benzene. The blue effluent was from the solvent to give **12** (15 mg, 87%) as deep blue prisms; mp 139—139.5 °C; IR (KBr) 1574, 1514, 1378, 1146, and 786 cm^{-1}; ^{1}H NMR (90 MHz, in $CDCl_3$) δ=2.90 (3H, s, $C\underline{H}_3$-2), 7.0—7.7 (3H, m, H-5,6,7), 7.33 (1H, s, H-9), 8.22 (1H, dm, J=10.3 Hz, H-8), and 8.81 (1H, dm, J=9.0 Hz, H-4); ^{13}C NMR (22.5 MHz, in $CDCl_3$) δ=20.6, 105.7, 122.8, 123.5, 128.0, 131.9, 136.5, 136.8, 140.4, 144.2, 150.1, and 166.0. Found: C, 72.55; H, 4.47; N, 6.72; S, 16.20%. Calcd for $C_{12}H_9NS$: C, 72.32; H, 4.55; N, 7.03, S, 16.09%.

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