Synthesis of 1,2,5a-Triazacyclohept[*a*]azulen-5(2*H*)-ones

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Synopsis. Reactions of 2-hydrazino-1-azaazulenes with acetylacetone gave 2-(3,5-dimethyl-1-pyrazolyl)-1-azaazulenes. Cyclizations of diethyl (1-azaazulen-2-yl)hydrazinomethylenemalonates in refluxing *t*-butylbenzene or on silica gel gave 1,2,5a-triazacyclohept[*a*]azulen-5(2*H*)-ones.

The chemistry of azaazulenes has attracted considerable attention because of their interesting chemical behavior and physicochemical properties.[1] Although many studies regarding hetero-annulated 1-azaazulenes have been made,[2-9] azepine-annulated 1-azaazulene, which would have a 16π-electronic antiaromaticity, has not been synthesized. In this paper, an attempt to synthesize of 1,2,5a-triazacyclohept[*a*]azulene is described. Although the conversion to a full conjugated 16π-electronic system was not successful, the publication of the synthesis of a novel tricyclic 1,2,5a-triazacyclohept[*a*]azulen-5(2*H*)-one seemed worthwhile, which is considered to be precursor of 1,2,5a-triazacyclohept[*a*]azulene.

It is known that hydrazino-substituted heterocycles have often been used in the synthetic design of annulated triazepines.[10-12] We therefore employed 2-hydrazino-1-azaazulenes[13] (**1**) as starting materials.

The treatment of **1a** and **1b** with acetylacetone (AA) gave 2-(3,5-dimethyl-1-pyrazolyl)-1-azaazulenes (**2a** and **2b**) in good yields, respectively. Compounds **2a** and **2b** were identical with the products derived from 2-chloro-1-azaazulenes (**3a** and **3b**) and 3,5-dimethylpyrazole, respectively.

Reaction of **1a** with ethyl acetoacetate (EAA) gave **4** as orange prisms in 63% yield, which was assigned as 2-(3-methyl-5-oxo-3-pyrazolin-1-yl)-1-azaazulene on the basis of the spectroscopic data as well as elemental analysis.

Since a direct construction of the triazepine ring using **1** and AA or EAA was unsuccessful, we carried out the synthesis and cyclizations of diethyl (1-azaazulen-2-yl)hydrazinomethylenemalonate (**5**).

The treatment of **1** with diethyl ethoxymethylenemalonate (DEEM) in refluxing ethanol gave **5** in good yields. Heating of **5a** in *t*-butylbenzene under reflux for 30 min gave **6a** in 92.5% yield, which was assigned as ethyl 2,5-dihydro-5-oxo-1,2,5a-triazacyclohept[*a*]-azulene-4-carboxylate on the basis of the spectroscopic data as well as HRMS. Compound **6a** was also obtained in 56% yield through a treatment of **5a** with silica gel for 7 d. In the ^{1}H NMR spectrum of **6a**, a low-field resonated 1H multiplet, owing to a deshielding effect of C-5 carbonyl, was observed at δ 9.20—9.27, which could be assigned to the C-6 proton. Other signals were observed at δ 7.23 (s, H-11), 7.75—7.95 (m, H-3, 7, 8, and 9), and 8.41 (d, J=10.4 Hz, H-10) together with ethyl ester signals.[14]

The treatment of **5b** in refluxing *t*-butylbenzene gave **6b**, but a treatment of **5b** with silica gel did not.

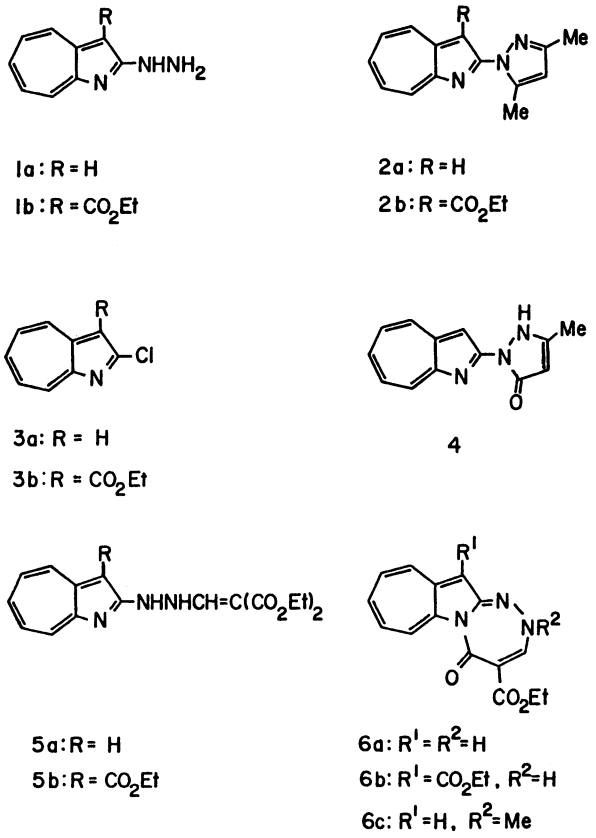

Fig. 1.

In the ^{13}C NMR spectrum of **6b**, signals of seven membered carbons (C-6, 7, 8, 9, and 10) are observed at δ 134—140. In its ^{1}H NMR spectrum, signals of H-6 and 10 were observed at δ 8.96 (dd, J=6.8 and 2.4 Hz) and 9.01 (d, J=12.2 Hz), respectively, which were deshielded by the carbonyl group at C-5 and ester group at C-11, respectively. Other signals of seven-membered ring protons (H-7, 8, and 9) were observed at δ 7.90—8.15 (m). Although these observations suggest that **6b** should be fundamentally aromatic, the large divergence of the coupling constants ($J_{6\text{-}7}$—$J_{9\text{-}10}$=5.4 Hz) shows that the contribution of heptafulvene form should be considerably large.

Compounds **6a** and **6b** were somewhat decomposed and changed to unidentified reddish violet compounds by prolonged heating or prolonged contact with silica gel.

For leading to full conjugated system, acetylation and methylation of **6a** were attempted. The treatment of **6a** with acetic anhydride gave no distinct product. The treatment of **6a** with methyl iodide in the presence of a base gave **6c**, which was assigned as an *N*-methylated product on the basis of the spectroscopic data; no *O*-methylated compound was obtained. *N*-Methyl protons appeared at δ 4.11 in the ^{1}H NMR

spectrum of **6c** and *N*-methyl carbon at δ 41.2 in its ^{13}C NMR spectrum.

Reactions and successive cyclizations of diethyl ethoxymethylenemalonate and heterocycles have been exclusively used for the preparation of fused pyrimidines.[9,15,16] Now we extended the reaction for the preparation of fused triazepine, as described above.

Experimental

Melting points were uncorrected. ^1H NMR spectra (250 MHz) and ^{13}C NMR spectra (62.87 MHz) were recorded on a Hitachi R-250H spectrometer using deuteriochloroform as a solvent (tetramethylsilane as an internal standard), unless otherwise stated. IR spectra were recorded for Nujol mulls with a Hitachi 270-50 infrared spectrophotometer. Mass spectra were determined with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. High-resolution mass spectra were obtained on the same instrument. Column chromatography was performed on Kieselgel 60.

Reaction of 1 with AA. a) A mixture of **1a** (318 mg, 2 mmol) and AA (405 mg, 4 mmol) in ethanol (30 ml) was refluxed for 3 h and evaporated. Chromatography of the residue with chloroform-ethyl acetate (1 : 1) gave **2a** (430 mg, 96%), which was crystallized from cyclohexane to give orange needles (359 mg, 80%), mp 86—88 °C, ^1H NMR δ=2.36 (3H, s, Me), 2.87 (3H, s, Me), 6.06 (1H, s, H-4′), 7.58 (1H, s, H-3), 7.50—7.75 (3H, m, H-5, 6, and 7), 8.39 (1H, d, J=9.8 Hz, H-4), 8.45—8.53 (1H, m, H-8). Found: C, 75.45; H, 5.94; N, 18.65%. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82%.

When above reaction was carried out in refluxing benzene or acetic acid, **2a** was obtained in 95% and 91%, respectively.

b) A mixture of **1b** (463 mg, 2 mmol), AA (452 mmol, 4.5 mmol), and trifluoroacetic acid (0.1 ml) in ethanol (30 ml) was refluxed for 20 h and evaporated. Chromatography of the residue with chloroform gave **2b** (512 mg, 87%) as yellow oil. ^1H NMR (60 MHz) δ=1.25 (3H, t, Me), 2.32 (3H, s, Me), 2.47 (3H, s, Me), 4.28 (2H, q, OCH_2), 5.96 (1H, s, H-4′), 7.58—7.96 (3H, m, H-5, 6, and 7), 8.45—8.70 (1H, m, H-8), 9.05—9.25 (1H, m, H-4); IR 1702 cm^{-1} (ester C=O). Picrate of **2b**, yellow scales (from ethanol), mp 151—153 °C, Found: C, 52.61; H, 3.77; N, 16.13%. Calcd for $C_{23}H_{20}N_6O_9$: C, 52.67; H, 3.84, N, 16.02%.

Reaction of 3 with 3,5-Dimethylpyrazole. A mixture of **3a** (146 mg, 1mmol) and 3,5-dimethylpyrazole (120 mg, 1.25 mmol) in 1-butanol was refluxed for 17 h and evaporated. To the residue water was added, and the mixture was neutralized with sodium hydrogencarbonate and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residue with chloroform gave **2a** (38%).

Similar treatment of **3b** with 3,5-dimethylpyrazole gave **2b** in a 54% yield.

Reaction of 1a with EAA. A solution of **1a** (318 mg, 2 mmol) and EAA (390 mg, 3 mmol) in ethanol (30 ml) was refluxed for 5 h and evaporated. Chromatography of the residue with ethyl acetate gave **4** (0.284 mg, 63%), which was crystallized from hexane to give orange prisms (37%), mp 198—200 °C; ^1H NMR δ=2.31 (3H, s, Me), 5.46 (1H, s, H-4′), 7.46 (1H, s, H-3), 7.60—7.80 (3H, m, H-5, 6, and 7), 8.35—8.41 (1H, m, H-4), 8.41 (1H, d, J=9.8 Hz, H-8);[14] IR 3250—2800 (NH), 1646 cm^{-1} (amido C=O). Found: C, 69.48; H, 4.96; N, 18.71%. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65%.

Reaction of 1 with DEEM. A solution of **1a** (318 mg, 2 mmol) and DEEM (451 mg, 2.1 mmol) in ethanol (30 ml) was refluxed for 1 h and evaporated. The residue was crystallized from cyclohexane-dichloromethane to give **5a** (602 mg, 92%) as red needles, mp 163—165 °C; ^1H NMR δ=1.25 (3H, t, J=7.0 Hz, Me), 1.38 (3H, t, J=7.0 Hz, Me), 4.19 (2H, q, J=7.0 Hz, OCH_2), 4.30 (2H, q, J=7.0 Hz, OCH_2), 6.28 (1H, s, H-3), 6.63—7.00 (4H, m, H-4, 5, 6, and 7), 7.23 (d, J=11.6 Hz, H-8), 8.46 (d, J=10.4 Hz, =CHNH), 11.60 (bd, J=10.4 Hz, =CHNH, exch.);[14] IR 3200—2650 (NH), 1674 (ester C=O), and 1634 cm^{-1} (C=N). Found: C, 62.13; H, 5.90; N, 12.71%. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76%.

In a similar manner, reaction of **1b** (463 mg, 2.0 mmol) and DEEM (895 mg, 4.14 mmol) in refluxing ethanol (40 ml) for 30 min gave **5b** (774 mg, 96%), which was crystallized to give yellow needles (592 mg, 74%), mp 119—121 °C; ^1H NMR δ=1.35 (3H, t, J=7.3 Hz, Me), 1.40 (3H, t, J=6.7 Hz, Me), 1.52 (3H, t, J=7.3 Hz, Me), 4.36 (2H, q, J=6.7 Hz, OCH_2), 4.40 (2H, q, J=7.3 Hz, OCH_2), 4.53 (2H, q, J=7.3 Hz, OCH_2), 7.75—7.85 (3H, m, H-5, 6, and 7), 8.28—8.35 (1H, m, H-8), 8.81 (1H, d, J=3.1 Hz, =CHNH), 8.96 (1H, d, J=3.1 Hz, =CHNH), 9.20 (1H, d, J=9.15 Hz, H-4), 10.09 (1H, bs, NH); IR 3328 (NH), 3200—2650 (NH), 1714 and 1664 (ester C=O), and 1604 cm^{-1} (C=N). Found: C, 59.91; H, 5.83; N, 10.28%. Calcd for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.77; N, 10.47%.

Cyclization of 5a. a) A solution of **5a** (1.00 g, 3.04 mmol) in *t*-butylbenzene (10 ml) was refluxed for 30 min and evaporated. The residue was chromatographed with acetone to give **6a** (796 mg, 92.5%), which was crystallized from cyclohexane-dichloromethane to give red needles (650 mg, 76%), mp 232—234 °C; ^1H NMR δ=1.18 (3H, t, J=6.7 Hz, Me), 4.14 (2H, q, J=6.7 Hz, OCH_2), 7.23 (1H, s, H-11), 7.75—7.95 (3H, m, H-7, 8, and 9), 7.87 (1H, s, H-3), 8.41 (1H, d, J=10.4 Hz, H-10), 9.20-9.27 (1H, m, H-6);[14] IR 3150 (NH), 1722 (ester C=O), 1630 (amido C=O), and 1615 (C=N); MS *m/z* (rel intensity) 283 (M^+; 100), 238 (77), 237 (68), 211 (55), 129 (16), and 102 (36). HRMS Found: *m/z* 283.0954. Calcd for $C_{15}H_{13}N_3O_3$: M, 283.0956.

b) A mixture of **5a** (250 mg, 0.76 mmol) and silica gel (5.0 g) in chloroform (50 ml) was left to stand at room temperature for 7 d and then chromatographed. Elution with chloroform-ethyl acetate (1 : 1) gave recovered **5a** (25 mg, 10%). Elution with acetone gave **6a** (120 mg, 56%).

Cyclization of 5b. A solution of **5b** (402 mg, 1.00 mmol) and *t*-butylbenzene (10 ml) was refluxed for 40 min and cooled. The precipitate was collected by filtration to give **6b** (262 mg, 74%), which was crystallized from cyclohexane-dichloromethane to give red needles (185 mg, 52%), mp 186—188 °C; ^1H NMR δ=1.34 (3H, t, J=7.3 Hz, Me), 1.39 (3H, t, J=7.3 Hz, Me), 4.31 (2H, q, J=7.3 Hz, OCH_2), 4.48 (2H, q, J=7.3 Hz, OCH_2), 7.90—8.15 (3H, m, H-7, 8, and 9), 7.99 (1H, s, H-3), 8.96 (1H, dd, J=6.8 and 2.4 Hz, H-6), 9.01 (1H, d, J=12.2 Hz, H-10), and 9.50 (1H, bs, NH); ^{13}C NMR δ=14.14 (q), 14.55 (q), 59.34 (t), 61.53 (t), 93.18 (s), 106.34 (s), 134.45 (d), 134.72 (d), 134.87 (d), 135.80 (d), 139.47 (d), 144.03 (s), 146.31 (d), 149.45 (s), 151.51 (s), 162.06 (s), 163.26 (s), 163.84 (s); IR 3200—2650 (NH), 1734, 1710 (ester C=O), 1630 (amido C=O), and 1610 cm-1 (C=N); MS *m/z* (rel intensity) 355 (M^+; 100), 310 (22), 309 (38), 264 (71), 237 (94), 129 (22), and 110 (31). HRMS Found: *m/z* 355.1087. Calcd for $C_{18}H_{17}N_3O_5$: M, 355.1167.

Methylation of 6a. To the mixture of **6a** (100 mg, 0.35 mmol) and potassium hydroxide 180 mg, 3.2 mmol) in 90% aq ethanol (50 ml), methyl iodide (500 mg) was added, and the mixture was refluxed for 16 h and evaporated. The residue was dissolved in water, neutralized with 1M hydrochloric acid (1M=1 mol dm^{-3}), and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was chromatographed with chloroform-ethyl acetate (1 : 1) gave **6c** (25 mg, 24%), which was crystallized from hexane-dichloromethane to give orange needles (18 mg, 17%), mp 173—174 °C, ^1H NMR δ=1.38 (3H, t, J=7.3 Hz, Me), 4.11 (3H, s, NMe), 4.35 (2H, q, J=7.3 Hz, OCH_2), 7.63—7.83 (3H, m, H-7, 8, and 9), 7.97 (1H, s, H-11), 8.10 (1H, s,

H-3), 8.52 (2H, d, J=9.2 Hz, H-6 and 10); ^{13}C NMR δ=14.42 (q), 41.21 (q), 60.11 (t), 100.25 (s), 104.84 (d), 129.32 (d), 129.77 (d), 134.15 (d), 134.61 (d), 135.98 (d), 146.75 (s), 148.21 (d), 154.76 (s), 155.53 (s), 160.85 (s), 162.01 (s); IR 1716 (ester C=O) and 1668 cm-1 (amido C=O); MS m/z (rel intensity) 297 (M^+; 65), 268 (20), 224 (55), 223 (42), 195 (100), 184 (74), 171 (78), 144 (44), 129 (53), and 102 (29). HRMS Found: m/z 297.1112. Calcd for $C_{16}H_{15}N_3O_3$: M, 297.1109.

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