

SYNTHESIS AND CYCLOADDITION REACTION OF 2a,4,5-TRIAZABENZ [cd] -
AZULENE DERIVATIVES

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Abstract - 2a,4,5-Triazabenz [cd] azulene derivatives (2) were synthesized by the reaction of 8-hydrazino-3-phenyl-1-azaazulenes (1) with triethyl orthoformate. 2-Chloro substituted compound (2b) was easily hydrolyzed on silica gel and gave (2-chloro-8-imino-3-phenyl-1-aza-1,8-dihydroazulen-1-yl) form-aldehyde oxime. Reaction of 2a with dimethyl acetylenedicarboxylate gave dimethyl 1-phenyl-2a,5-diazabenz [cd] azulene-3,4-dicarboxylate and dimethyl (1-cyano-3-phenyl-1,8-dihydro-1-azaazulen-8-ylideneamino)maleate.

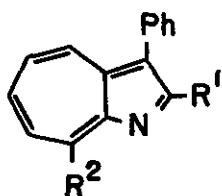
Some full conjugated peri-condensed azaazulenes¹⁻⁵ including cyclazine systems⁶⁻¹² have been investigated because of the interest concerning their physical and chemical properties. Regarding the research on cyclohepta[ef]-cycl[3.2.2]azine system, we carried out the synthesis of 2a,4,5-triazabenz [cd] azulene derivatives (2a,b) and the reaction of 2a with dimethyl acetylenedicarboxylate (DMAD).

Heating of a mixture of 8-hydrazino-3-phenyl-1-azaazulene¹³ (1a) and triethyl orthoformate in the presence of p-toluenesulfonic acid for 30 min gave 1-phenyl-2a,4,5-triazabenz [cd] azulene (2a) in 96% yield. The compound 2a was slightly unstable, and showed slight contamination after chromatographic separation and recrystallization. The ¹H NMR spectrum of 2a reveals signals at δ 5.56 (dd, J=11.0 and 7.3 Hz, H-7), 6.05 (dd, J=12.2 and 7.3 Hz, H-8), 6.16 (d, J=12.2 Hz, H-9), 6.45 (d, J=11.0 Hz, H-6), 7.06 (s, H-2), 7.25-7.50 (m, phenyl), and 8.02 (s, H-3). The signals of the seven-membered ring protons resonated at considerably high field and have large divergences of the coupling constants ($J_{6-7} \sim J_{7-8} = 3.7$ Hz, $J_{7-8} \sim J_{8-9} = 4.9$ Hz). The results indicate a high degree of

bond alternation in the seven-membered ring as in the cases of 2a-aza-,² 2a,5-diaza-,³ and 2,2a,4,5-tetraazabenz [cd] azulenes.⁴

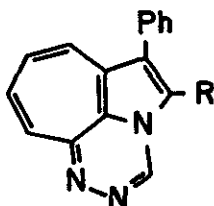
When 1b was treated with triethyl orthoformate, 2b was obtained in only 9% yield and (2-chloro-8-imino-3-phenyl-1-aza-1,8-dihydroazulen-1-yl)formaldehyde oxime [3, MS m/z 297 (M⁺)], which would be a hydrolyzed product of 2b, was obtained in 64% yield instead. Compound 2b was hydrolyzed on silica gel to give 3 in a good yield. In the IR spectrum of 3, characteristic absorptions assignable to an oxime are seen at 3190 (OH) 1650 cm⁻¹ (C=N). Its ¹H NMR spectrum shows a signal of a sharp singlet at δ 8.29 (CH=N) and signals of two 1H broad singlets at δ 10.18 (NH) and 10.59 (OH).

The reaction of 2a with DMAD in hot acetonitrile for 2 h gave dimethyl 1-phenyl-2a,5-diazabenz [cd] azulene-3,4-dicarboxylate (4) (4%), dimethyl (1-cyano-3-phenyl-1,8-dihydro-1-azaazulen-8-ylideneamino)maleate (5) (5%), and some undefined compounds. When the reaction was carried out in hot xylene, the compound 5 was isolated in a 19% yield. In the mass spectrum of 4, a molecular peak is



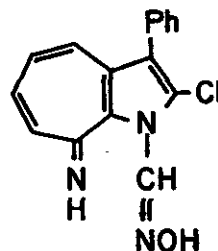
1a: R¹ = H, R² = NHNH₂

1b: R¹ = Cl, R² = NHNH₂

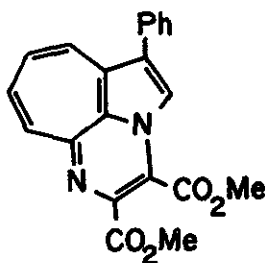


2a: R = H

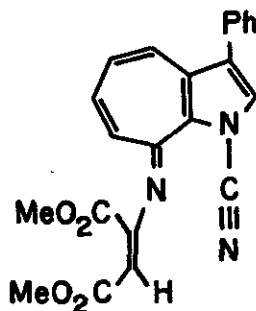
2b: R = Cl



3

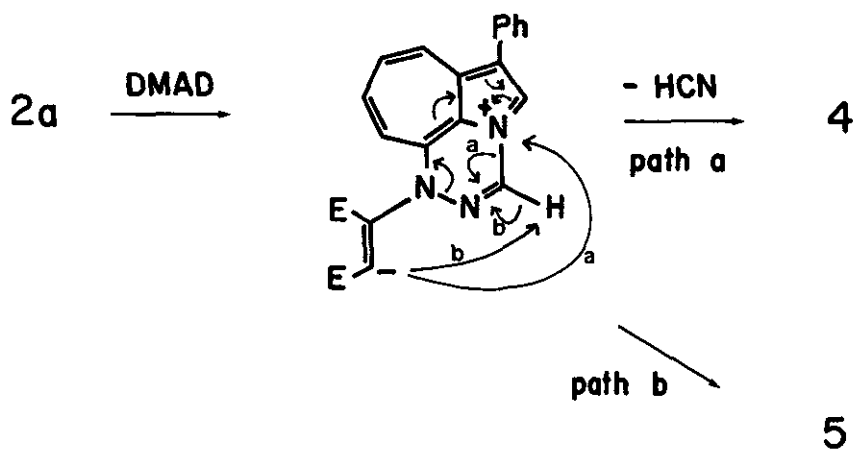


4



5

observed at m/z 360. The ^1H NMR spectrum of **4** shows two methyl ester singlets at δ 3.86 and 3.89, and a 1H singlet assignable to H-2 at δ 8.16, which would be deshielded by the ester group at C-3, together with seven-membered ring protons and phenyl protons. Its IR spectrum shows ester carbonyl absorptions at 1750 and 1700 cm^{-1} . The same compound was obtained on the reaction of 8-amino-3-phenyl-1-azaazulene with DMAD.^{1*} The ^1H NMR spectrum of **5** shows signals at δ 3.68 (s, OMe), 3.91 (s, OMe), 6.91 (s, H-vinyl), 7.00 (dd, $J=10.4$ and 8.9 Hz, H-6), 7.27 (s, H-2), 7.34 (dd, $J=12.2$ and 8.9 Hz, H-5), 7.39-7.51 (m, phenyl), 7.72 (d, $J=12.2$ Hz, H-4), and 7.89 (d, $J=10.4$ Hz, H-7). In its IR spectrum, CN absorption is seen at 2170 cm^{-1} . These results accord with the structures. While 2a,5-diazabenz[cd]azulene reacted with DMAD to give azacyclohepta[ef]-cycl[3.2.2]azine,³ 2a,4,5-triazabenz[cd]azulene gave no corresponding cyclazine but another type of products **4** and **5** instead. This would be caused by the presence of a reactive azine moiety in the latter molecule. A plausible mechanism is shown in the Scheme 1.



Scheme 1

EXPERIMENTAL

Melting points were uncorrected. ^1H NMR spectra were taken on a Hitachi R-250H (250 MHz) spectrometers using deuteriochloroform as a solvent (TMS as an internal standard), unless otherwise stated. IR spectra were recorded for Nujol mulls with a Hitachi 270-50 infrared spectrophotometer.

Syntheses of 2. A mixture of 1a (0.471 g), p-toluenesulfonic acid (0.040 g), and triethyl orthoformate (10 ml) was heated at 140 °C for 30 min. The mixture was evaporated and the residue was chromatographed on silica gel rapidly. Elution with ethanol gave 2a as violet crystals (0.470 g, 96%), which was crystallized from n-hexane-dichloromethane to give violet needles (0.353 g, 72%), mp 200-201 °C (Found: m/z 245.0955. $\text{C}_{18}\text{H}_{11}\text{N}_3$ requires 245.0952); ^1H NMR δ =5.56 (dd, J=11.0 and 7.3 Hz, H-7), 6.05 (dd, J=12.2 and 7.3 Hz, H-8), 6.16 (d, J=12.2 Hz, H-9), 6.45 (d, J=11.0 Hz, H-6), 7.06 (s, H-2), 7.25-7.50 (m, phenyl), and 8.02 (s, H-3); IR 750 and 695 cm^{-1} (phenyl).

Similarly, a solution of 1b (0.542 g), p-toluenesulfonic acid (0.040 g), and triethyl orthoformate (10 ml) in dry xylene (20 ml) was heated for 20 min at 140 °C, and worked up. Chromatography of the residue with chloroform gave 3 (0.367 g, 64%) and 2b (0.048 g, 9%), successively. [3: orange needles (from benzene-dichloromethane), mp 167-168 °C (Found: C, 64.48; H, 3.92; N, 13.27; M⁺, 297. $\text{C}_{18}\text{H}_{12}\text{ClN}_3\text{O}$ requires C, 64.54; H, 4.06; N, 14.11; M, 297); ^1H NMR δ (DMSO- d_6)=7.17 (t, J=9.7 Hz, H-5) 7.35-7.60 (m, H-4 and phenyl), 7.76 (t, J=9.7 Hz, H-6), 7.98 (d, J=9.7 Hz, H-7), 8.29 (s, CH=N), 10.18 (bs, exch., NH), and 10.59 (bs, exch., OH); IR 3190 (broad, OH), 3100-2800 (broad, NH), 1650 and 1630 (C=N), and 695 cm^{-1} (phenyl). 2b: violet prisms (from dichloromethane-n-hexane), mp 212-213 °C (Found: m/z 279.0547. $\text{C}_{18}\text{H}_{10}\text{N}_3^{35}\text{Cl}$ requires 279.0563); ^1H NMR δ =5.60 (dd, J=11.6 and 7.9 Hz, H-7), 6.10 (dd, J=12.2 and 7.9 Hz, H-8), 6.25 (d, J=12.2 Hz, H-9), 6.33 (d, J=11.6 Hz, H-6), 7.25-7.55 (m, phenyl), and 8.10 (s, H-3); IR 690 cm^{-1} (phenyl)].

Hydrolysis of 2b. A mixture of 2b (0.020 g) and silica gel (0.70 g) in chloroform (10 ml) was left to stand at room temperature for 3 d, then filtered. Silica gel was washed with ethanol. Evaporation of the combined solution gave 3 (18 mg, 85%).

Reaction of 2a with DMAD. a) A solution of 2a (0.245 g) and DMAD (0.310 g) in acetonitrile (50 ml) was heated under reflux for 2 h. The solvent was evaporated and the residue was chromatographed. Elution with benzene-chloroform (1:1) gave 4 (0.015 g, 4%), which was crystallized from cyclohexane-

dichloromethane to give violet scales, mp 156-158 °C (Found: C, 69.85; H, 4.43; N, 7.86; M^r, 360. C₂₁H₁₆N₂O₄ requires C, 69.99; H, 4.48; N, 7.77%; M, 360); ¹H NMR δ = 3.86 (s, OMe), 3.89 (s, OMe), 5.58-5.70 (m, H-7), 6.10-6.20 (m, H-8 and 9), 6.70 (d, J=11.0 Hz, H-6), 7.30-7.50 (m, phenyl), and 8.16 (s, H-2); IR 1750, 1700 (C=O), 720, and 695 cm⁻¹ (phenyl). Further elution gave 5 (0.021 g, 5%), which was crystallized from cyclohexane-dichloromethane to give yellow needles, mp 175-176 °C (Found: C, 68.22; H, 4.32; N 10.48; M^r, 387. C₂₂H₁₇N₃O₄ requires C, 68.21; H, 4.42; N, 10.85%; M, 387); ¹H NMR δ = 3.68 (s, OMe), 3.91 (s, OMe), 6.91 (s, H-vinyl), 7.00 (dd, J=10.4 and 8.9 Hz, H-6), 7.27 (s, H-2), 7.34 (dd, J=12.2 and 8.9 Hz, H-5), 7.39-7.51 (m, phenyl), 7.72 (d, J=12.2 Hz, H-4), and 7.89 (d, J=10.4 Hz, H-7); IR 2170 (CN), 1740, 1730 (C=O), 1655 (C=N), and 710 cm⁻¹ (phenyl).

b) A solution of 2a (0.245 g) and DMAD (0.284 g) in dry xylene (30 ml) was heated under reflux for 1 h and worked up as above. Elution with chloroform gave 4 (trace) and 5 (0.075 g, 19%), successively.

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