The Synthesis of 2-Styrylazulene and Its Derivatives by the Condensation of 2-Methylazulene Derivatives with Benzaldehydes

Motoyasu SAITO, Tadayoshi MORITA, and Kahei TAKASE*

Department of Chemistry, Faculty of Science, Tohoku University, Aramaki-aza-Aoba, Sendai 980

(Received March 10, 1980)

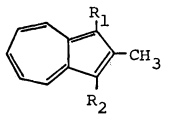
The reaction of 2-methylazulene derivatives, such as dimethyl 2-methylazulene-1,3-dicarboxylate, methyl 3-cyano-2-methylazulene-1-carboxylate, and 1-cyano- and 1-carbamoyl-2-methylazulenes, with benzaldehyde in the presence of alkoxide resulted in condensation to give 2-styrylazulene derivatives. 2-Styrylazulene, a parent hydrocarbon, and its *p*-nitro and *p*-dimethylamino derivatives were also synthesized.

Styrylazulenes are important azulenic compounds analogous to stilbene and interesting for their chemical and physical properties. Of the five possible position isomers, 1-,[1] 5-,[2] and 6-styrylazulenes,[2] and some derivatives of 4-,[3] and 5-styrylazulenes[4] have been synthesized.

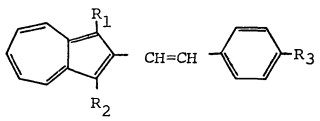
On the other hand, we have found that 2-methylazulene derivatives with electron-withdrawing substituents, such as an alkoxycarbonyl or cyano group, at the 1 (and/or 3)-position easily condensed with benzaldehyde in the presence of alkoxide to give 2-styrylazulene derivatives; an outline of a part of these results has been reported in a preliminary communication.[5] This paper will describe the details of the synthesis of 2-styrylazulene (**1**) and its derivatives by the condensation of 2-methylazulene derivatives with benzaldehydes.

Results and Discussion

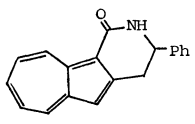
2-Methylazulene (**2**) and its derivatives, such as dimethyl 2-methylazulene-1,3-dicarboxylate (**3**), methyl 3-cyano-2-methylazulene-1-carboxylate (**4**), and 1-cyano- (**5**) and 1-carbamoyl-2-methylazulenes (**6**), were prepared, and the condensation reactions of these azulenes with benzaldehyde were examined, in order to synthesize 2-styrylazulenes. The treatment of **2** with benzaldehyde in the presence of sodium ethoxide gave no condensation product. In contrast with this, the treatment of **3** and **4** with benzaldehyde in the presence of sodium methoxide or ethoxide at room temperature resulted in condensation to give 3-methoxycarbonyl- (**7**) and 3-cyano-2-styrylazulene-1-carboxylic acids (**8**) in excellent yields respectively. In a similar manner, **5** gave 1-cyano-2-styrylazulene (**9**) in a good yield. The condensation of **6** with benzaldehyde was not easy, so it proceeded under reflux to give 1-carbamoyl-2-styrylazulene (**10**) in only a low yield of 14%. The structures of **7**, **8**, **9**, and **10** were determined on the basis of the chemical evidence described below, as well as the spectral data. Compounds **7** and **8** are acidic enough to be soluble in an aq sodium hydrogen carbonate solution and gave methyl esters (**11** and **12**) on methylation with diazomethane. The treatment of **7** and **8** with phosphoric acid[6] resulted in decarboxylation to give methyl 2-styrylazulene-1-carboxylate (**13**) and **9** respectively. Further, on treatment with concd sulfuric acid at 100 °C,[6] **9** gave **10**, together with a lactam, judging from the IR spectrum, which exhibits the $\nu_{C=O}$ of amide at 1639 cm^{-1}, compatible with that at 1642 cm^{-1} in 1-carbamoyl-2-methylazulene.[6] The NMR spectral data are also consistent with the assigned structure. The configuration of the ethylenic linkage in the 2-styrylazulenes obtained here is established to be *trans* on the basis of the IR and NMR spectral data.[5] The formation of the hydrolized carboxylic acids, **7** and **8**, even though the reaction was carried out under anhydrous media, is presumed to be *via* lactone-type intermediates.[5]



2: R_1= R_2= H
3: R_1= R_2= CO_2Me
4: R_1= CO_2Me, R_2= CN
5: R_1= CN, R_2= H
6: R_1= $CONH_2$, R_2= H



1: R_1= R_2= R_3= H
7: R_1= CO_2H, R_2= CO_2Me, R_3= H
8: R_1= CO_2H, R_2= CN, R_3= H
9: R_1= CN, R_2= R_3= H
10: R_1= $CONH_2$, R_2= R_3= H
11: R_1= R_2= CO_2Me, R_3= H
12: R_1= CO_2Me, R_2= CN, R_3= H
13: R_1= CO_2Me, R_2= R_3= H
15: R_1= CN, R_2= H, R_3= NO_2
16: R_1= CN, R_2= H, R_3= NMe_2
17: R_1= R_2= H, R_3= NO_2
18: R_1= R_2= H, R_3= NMe_2
19: R_1= $CONH_2$, R_2= H, R_3= NO_2
20: R_1= $CONH_2$, R_2= H, R_3= NMe_2



14

Fig. 1.

The fact that **3**, **4**, and **5** easily reacted with benzaldehyde in the presence of alkoxide to give the condensation products indicates that the methyl group at the 2-position in these compounds is acidic enough to yield the carbanion, which can react with benzaldehyde, by means of alkoxide. For this reason, it seems that the electronic effects, that is, the mesomeric and inductive effects of the electron-withdrawing methoxycarbonyl or cyano substituent at the 1 (and/or 3)position of the azulene ring, contribute to the activation of the methyl proton. Such condensation also took place when other aromatic aldehydes were used. Thus, the treatment of **5** with *p*-nitro- and *p*-dimethylaminobenzaldehydes in the presence of sodium ethoxide gave 1-cyano-2-(*p*-nitrostyryl)- (**15**) and 1-cyano-2-(*p*-dimethylaminostyryl)azulenes (**16**) respectively, although in the latter case, the reaction was not easy, but did proceed by heating under reflux.

A parent hydrocarbon, **1**, could be obtained from

7 in an 88% yield on hydrolysis with aq ethanolic alkali and the subsequent decarboxylation of the resulting dicarboxylic acid by heating with phosphoric acid. Further, **1** was also obtained from **10** by decarbamoylation[6] on treatment with phosphoric acid. 2-(*p*-Nitrostyryl)- (**17**) and 2-(*p*-dimethylaminostyryl)azulene (**18**) could also be synthesized as follows: the treatment of **15** and **16** with concd sulfuric acid afforded carbamoyl derivatives (**19** and **20**), accompanied by the formation of small amounts of **17** and **18** respectively. Further, the treatment of **19** and **20** with phosphoric acid resulted in decarbamoylation to give **17** and **18** respectively in good yields.

Experimental

All the melting points are uncorrected. The IR spectra were taken on a Shimadzu IR-27 infracord spectrophotometer, and the electronic spectra, on a Hitachi EPS-3 spectrophotometer. The NMR spectra were recorded with a Varian A-60D spectrometer. Compounds **4**, **5**, and **6** were prepared according to a method previously reported.[6]

*Dimethyl 2-Methylazulene-1,3-dicarboxylate (**3**).* This compound was prepared by a procedure similar to that used for the preparation of ethyl methyl 2-methylazulene-1,3-dicarboxylate.[6] A mixture of 940 mg (5 mmol) of 3-acetyl-2*H*-cyclohepta[*b*]furan-2-one[6] and 1.32 g (10 mmol) of dimethyl malonate in a sodium methoxide solution, prepared from 460 mg of sodium and 50 ml of anhydrous methanol, was treated in a manner similar to that previously described.[6] The part insoluble in an aq potassium carbonate solution gave 160 mg (13%) of methyl 3-acetyl-2-hydroxyazulene-1-carboxylate as yellow needles; mp 201—202 °C (from benzene). IR (KBr): 3440, 1670, 1127, and 1053 cm^{-1}. Found: C, 68.62; H, 5.02%. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95%.

The part soluble in an aq potassium carbonate solution gave 640 mg (52%) of 3-methoxycarbonyl-2-methylazulene-1-carboxylic acid as pale red crystals; mp 209 °C (dec). The treatment of this acid with diazomethane in a manner similar to that previously described[6] gave 595 mg of **3** as red needles; mp 112—115 °C (from methanol). λ_{max}^{MeOH} 237 nm (log ε 4.50), 270 (4.38), 295 (4.57), 305 (4.66), 343 (3.90), 371 (3.93), and 490 (2.95); IR (KBr): 1690, 1233, and 1080 cm^{-1}. Found: C, 70.01; H, 5.51%. Calcd for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46%.

*3-Methoxycarbonyl-2-styrylazulene-1-carboxylic Acid (**7**).* To a sodium methoxide solution, prepared from 300 mg of sodium and 15 ml of anhydrous methanol, 1.29 g (5 mmol) of **3** and 900 mg (8.5 mmol) of benzaldehyde were added; the mixture was stirred for 5 h and then allowed to stand overnight at room temp. The reaction mixture was diluted with 100 ml of water and shaken with ether. The ether layer was washed with water and concentrated to recover 340 mg of **3**. The combined aq solution was acidified with with 6 M (1M=1 mol dm^{-3}) hydrochloric acid, and the crystals thus separated out were collected to give 1.10 g (90%) of **7** as red prisms; mp 177—178 °C (from methanol). λ_{max}^{MeOH} 233 nm (log ε 4.50), 295 (4.50), 338 (4.71), 404 (4.20), and 540 (2.75). Found: C, 76.19; H, 4.97%. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85%.

*3-Cyano-2-styrylazulene-1-carboxylic Acid (**8**).* A mixture of 900 mg (4 mmol) of **4** and 720 mg (6.8 mmol) of benzaldehyde in a sodium ethoxide solution, prepared from 280 mg of sodium and 20 ml of anhydrous ethanol, was treated in a manner similar to that described above to give 1.17 g (98%) of **8** as reddish brown prisms: mp 238—239 °C (from ethanol). λ_{max}^{MeOH} 230 nm (log ε 4.46), 340 (4.76), 409 (4.23), and 560 (2.72). Found: C, 79.88; H, 4.48; N, 4.69%. Calcd for $C_{20}H_{13}O_2N$: C, 80.25; H, 4.38; N, 4.68%.

*1-Cyano-2-styrylazulene (**9**). a)*: A mixture of 165 mg (1 mmol) of **5** and 180 mg (1.7 mmol) of benzaldehyde in a sodium ethoxide solution, prepared from 70 mg of sodium and 5 ml of ethanol, was stirred for 5 h and then allowed to stand overinght at room temp. The reaction mixture was subsequently diluted with 50 ml of water and extracted with chloroform. After the evaporation of the solvent from the extract, the residue was chromatographed (alumina, benzene) to give 170 mg (67%) of **9** as green needles; mp 119—120 °C (from benzene–cyclohexane). λ_{max}^{MeOH} 231 nm (log ε 4.27), 323 (4.75), 335 (4.83), 388 (4.15), 408 (4,43), 433 (4.42), 558 (2.72), 589 (2.75), and 653 (2.42). Found: C, 90.01; H, 5.15; N, 5.38%. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49%.

b): A mixture of 220 mg o **8** and 3 ml of 85% phosphoric acid was heated at 100 °C for 30 min; then it was poured into ice water and extracted with chloroform. The extract was worked up as has been described above to give 160 mg (85%) of **9** as green needles; mp 119—120 °C.

*1-Carbamoyl-2-styrylazulene (**10**).* A mixture of 50 mg (0.27 mmol) of **6** and 80 mg (0.76 mmol) of benzaldehyde in a sodium ethoxide solution, prepared from 70 mg of sodium and 3 ml of ethanol, was heated under reflux for 5.5 h. The reaction mixture was then diluted with 20 ml of water and extracted with chloroform. After the evaporation of the solvent from the extract, the residue was chromatographed (silica gel, benzene) to give 10 mg (14%) of **10** as green needles; mp 207—208 °C (from benzene). λ_{max}^{MeOH} 318 nm (log ε 4.64), 327 (4.72), 405 (4.38), and 426 (4.26). Found: C, 83.46; H, 5.82; N, 4.85%. Calcd for $C_{19}H_{15}ON$: C, 83.49; H, 5.53; N, 5.13%.

*Dimethyl 2-Styrylazulene-1,3-dicarboxylate (**11**).* To a suspension of 300 mg of **7** in 20 ml of ether, 5 ml of an ethereal solution of diazomethane was added, after which the mixture was stirred for 3 h and allowed to stand overnight in a refrigerator. After the evaporation of the solvent, the residue was chromatographed (alumina, benzene) to give 300 mg (96%) of **11** as red scales; mp 136—137 °C (from methanol). λ_{max}^{MeOH} 233 nm (log ε 4.59), 294 (4.58), 338 (4.80), 404 (4.31), and 540 (2.81). Found: C, 76.21; H, 5.50%. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24%.

*Methyl 3-Cyano-2-styrylazulene-1-carboxylate (**12**).* The treatment of 200 mg of **8** with diazomethane in a manner similar to that described above gave 190 mg (91%) of **12** as red needles; mp 149—150 °C (from cyclohexane). λ_{max}^{MeOH} 232 nm (log ε 4.06), 291 (4.31), 342 (4.77), and 410 (4.35). Found: C, 80.54; H, 4.97; N, 4.47%. Calcd for $C_{21}H_{15}O_2N$: C, 80.49; H, 4.83; N, 4.47%.

*Methyl 2-Styrylazulene-1-carboxylate (**13**).* A mixture of 50 mg of **7** and 1 ml of 100% phosphoric acid was heated at 100 °C for 3 min; then it was poured into 10 ml of ice water and extracted with chloroform. After the evaporation of the solvent, the residue was chromatographed (alumina, benzene) to 35 mg (81%) of **13** as green needles; mp 88—89 °C (from methanol). λ_{max}^{MeOH} 335 nm (log ε 4.50), 402 (4.05), 424 (3.90), and 574 (2.86). Found: C, 83.02; H, 5.52%. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59%.

*Treatment of **9** with Sulfuric Acid.* A mixture of 510 mg of **9** and 4 ml of 80% sulfuric acid was heated at 100 °C for 1 h; then it was poured into 80 ml of ice water and extracted with chloroform. After the evaporation of the solvent from the extract, the residue was chromatographed

(alumina, benzene, and chloroform). The first fraction, eluted with benzene, recovered 32 mg of **9**. The second fraction, eluted with benzene, gave 95 mg (19%) of **14** as reddish violet prisms; mp 204—205 °C (from benzene). λ_{max}^{MeOH} 299 nm (log ε 4.65), 358 (3.91), and 376 (3.95). NMR ($CDCl_3$) δ 3.34 (d, J=8.0 Hz, $CHC\underline{H}_2$), 4.94 (t, J=8.0 Hz, $C\underline{H}CH_2$), 5.80 (br s, N$\underline{H}$), 7.05 (s, H-3), 7.4—7.8 (m H-5, -7), 7.38 (br s, C_6H_5), 8.33 (br d, J=9 Hz, H-4), 9.70 (br d, J=9 Hz, H-8). Found: C, 83.46; H, 5.54; N, 5.05%. Calcd for $C_{19}H_{15}ON$: C, 83.49; H, 5.53; N, 5.13%. The third fraction, eluted with chloroform, gave 210 mg (41%) of **10** as green needles; mp 207—208 °C.

*2-Styrylazulene (**1**).* *a)*: A solution of 1.00 g of **7** dissolved in a mixture of 10 ml of a 10% aq potassium hydroxide solution and 100 ml of ethanol, was heated under reflux for 40 min. The subsequent acidification of the solution with 1 M hydrochloric acid separated out 920 mg of 2-styrylazulene-1,3-dicarboxylic acid. A mixture of the acid and 5 ml of 85% phosphoric acid was heated at 100 °C for 15 min and then poured into 100 ml of ice water and extracted with chloroform. After the evaporation of the solvent from the extract, the residue was chromatographed (alumina, benzene) to give 610 mg (88%) of **1** as green scales; mp 207—208 °C (from cyclohexane). Found: C, 93.95; H, 6.11%. Calcd for $C_{18}H_{14}$: C, 93.87; H, 6.13%.

b): A mixture of 80 mg of **10** and 1 ml of 85% phosphoric acid was heated at 100 °C for 1 h; then it was diluted with 20 ml of water and extracted with chloroform. After the evaporation of the solvent, the residue was chromatographed (alumina, benzene) to give 40 mg (59%) of **1** as green scales; mp 207—208 °C.

*1-Cyano-2-(*p*-nitrostyryl)azulene (**15**).* A mixture of 166 mg (1 mmol) of **5** and 226 mg (1.5 mmol) of *p*-nitrobenzaldehyde in a sodium ethoxide solution, prepared from 53 mg of sodium and 3 ml of ethanol, was stirred for 20 h at 0—10 °C; then it was diluted with 20 ml of water and extracted with chloroform. The extract was washed with water and concentrated, and the residue was chromatographed (alumina, benzene) to give 75 mg (25%) of **15** as bluish green needles; mp 227—228 °C (from benzene). λ_{max}^{MeOH} 233 nm (log ε 4.27), 286 (4.20), 333 (4.72), 404 (4.59), and 424 (4.48). Found: C, 75.51; H, 4.07; N, 9.16%. Calcd for $C_{19}H_{12}O_2N_2$: C, 75.99; H, 4.03; N, 9.33%.

*1-Cyano-2-(*p*-dimethylaminostyryl)azulene (**16**).* A mixture of 167 mg (1 mmol) of **5** and 255 mg (1.7 mmol) of *p*-dimethylaminobenzaldehyde in a sodium ethoxide solution, prepared from 56 mg of sodium and 3 ml of ethanol, was heated under reflux for 7 h. The reaction mixture was then worked up in a manner similar to that described above, except for the use of chloroform in place of benzene as the solvent for chromatography, to give 113 mg (38%) of **16** as reddish brown needles; mp 196—197 °C (benzene). λ_{max}^{MeOH} 260 nm (log ε 4.17), 307 (4.63), 357 (4.45), and 490 (4.57). Found: C, 84.26; H, 5.91; N, 9.55%. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39%.

*2-(*p*-Nitrostyryl)- (**17**) and 1-Carbamoyl-2-(*p*-nitrostyryl)-azulene (**19**).* *a)*: A mixture of 340 mg of **15** and 4 ml of concd sulfuric acid was heated at 100 °C for 3 h and then diluted with 50 ml of water. The crystals thus separated out were collected and chromatographed (alumina, benzene and chloroform). The first fraction, eluted with benzene, gave 10 mg (3%) of **17** as green prisms; mp 254—256 °C (from chloroform). λ_{max}^{MeOH} 231 nm (log ε 4.07), 282 (4.50), 323 (4.51), 406 (4.60), 425 (4.51), 584 (2.67), and 627 (2.64). Found: C, 78.42; H, 4.61; N, 4.89%. Calcd for $C_{18}H_{13}O_2N$: C, 78.53; H, 4.76; N, 5.09%. The second fraction, eluted with chloroform, gave 230 mg (64%) of **19** as green needles; mp 238—239 °C (from chloroform). λ_{max}^{MeOH} 230 nm (log ε 4.97), 284 (4.50), 327 (4.59), and 404 (4.55). Found: C, 71.64; H, 4.43; N, 8.60%. Calcd for $C_{19}H_{14}O_3N_2$: C, 71.69; H, 4.43; N, 8.80%.

b): A mixture of 260 mg of **19** and 3 ml of 100% phosphoric acid was heated at 100 °C for 3 h and then worked up in a manner similar to that described above to give 69 mg (31%) of **17** as green prisms; mp 254—256 °C.

*2-(*p*-Dimethylaminostyryl)- (**18**) and 1-Carbamoyl-2-(*p*-dimethylaminostyryl)azulene (**20**).* *a)*: A mixture of 310 mg of **16** and 3 ml of 80% sulfuric acid was treated in a manner similar to that described above. The first fraction from chromatography, eluted with benzene, gave 30 mg (11%) of **18** as reddish brown scales; mp 237—238 °C (from benzene). λ_{max}^{MeOH} 262 nm (log ε 4.30), 294 (4.68), 340 (4.56). Found: C, 87.76; H, 7.10; N, 5.00%. Calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12%. The second fraction, eluted with benzene, gave 130 mg (40%) of **20** as brownish green prisms; mp 249—250 °C (from chloroform–ethyl acetate). λ_{max}^{MeOH} 302 nm (log ε 4.50), 352 (4.36), 468 (4.44). Found: 79.38; H, 6.05; N, 8.88%. Calcd for $C_{21}H_{20}ON_2$: C, 79.71; H, 6.37; N, 8.85%.

b): A mixture of 100 mg of **20** and 1 ml of 85% phosphoric acid was heated at 100 °C for 2 h; then it was worked up in a manner similar to that described above to give 48 mg (56%) of **18** as reddish brown scales; mp 237—238 °C.

This research has been financially supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education and by a grant from the Sankyo Co., Ltd.

References

1) R. N. McDonald and W. S. Stewart, *J. Org. Chem.*, **30**, 270 (1965).
2) H. Matsumura and S. Nagamura, *Nippon Kagaku Zasshi*, **85**, 901 (1964).
3) M. Scholz, L. n. Vien, G. Fisher, B. Tschapke, and M. Muhlstädt, *Chem. Ber.*, **100**, 375 (1967).
4) T. Kuraoka, *Nippon Kagaku Zasshi*, **83**, 928 (1962).
5) M. Saito, T. Morita, and K. Takase, *Chem. Lett.*, **1974**, 289.
6) T. Nozoe, K. Takase, T. Nakazawa, and S. Fukuda, *Tetrahedron*, **27**, 3357 (1971).