THE SYNTHESIS AND SEVERAL REACTIONS OF 2-METHYLAZULENO[2,1-d]-THIAZOLE

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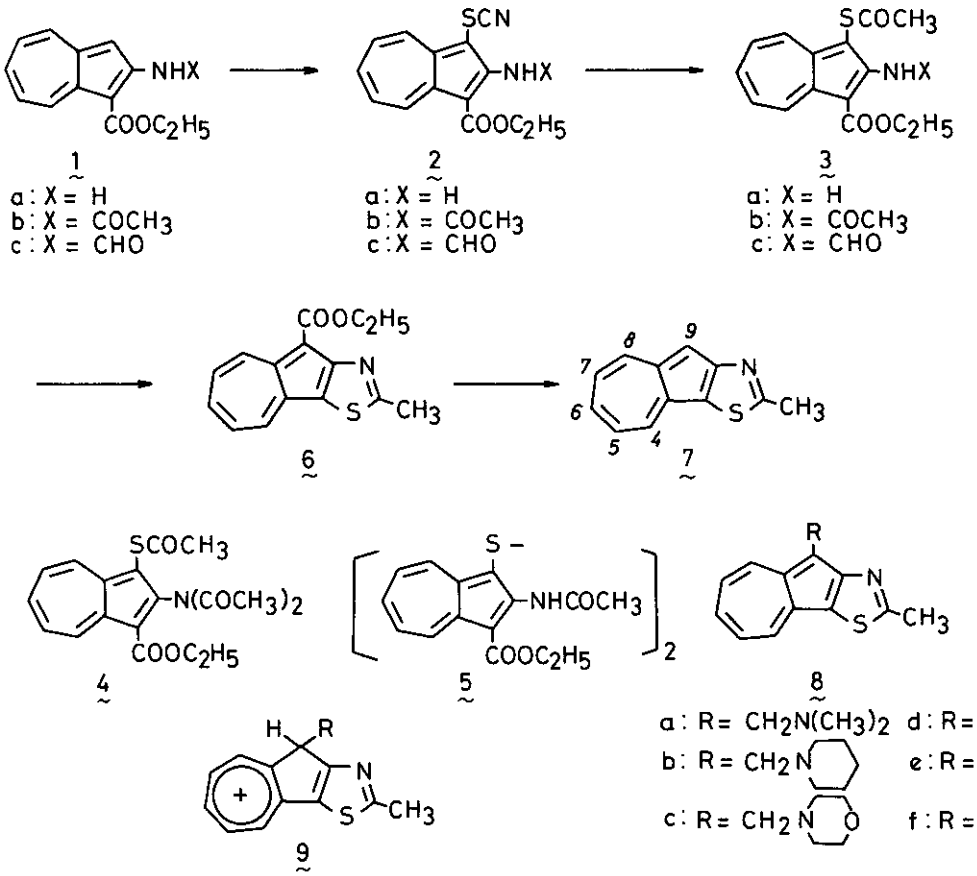
Abstract: 2-Methylazuleno[2,1-d]thiazole was synthesized from 2-amino, 2-formylamino, and 2-acetylamino derivatives of ethyl azulene-1-carboxylate in four steps. The 9-dimethylaminomethyl, 9-piperidinomethyl, and 9-morpholinomethyl derivatives were prepared by Mannich reaction of 2-methylazuleno[2,1-d]thiazole. The Vilsmeyer-Haack reaction of 2-methylazuleno[2,1-d]thiazole gave the 9-formyl derivative, and dehydration of its oxime afforded the 9-cyano derivative.

Many compounds fused heterocycles with the five-membered ring of azulene are known.[1] We have reported the syntheses of azuleno[2,1-b]thiophene[2] and azuleno[2,1-d]-thiazole.[3] In this paper, we wish to report the synthesis of 2-methylazuleno-[2,1-d]thiazole and its several reactions.

Synthesis of 2-methylazuleno[2,1-d]thiazole (7)

The reaction of ethyl 2-acethylaminoazulene-1-carboxylate (1b) with thiocyanogen bromide yielded the 3-thiocyano compound (2b). Compound 2b, on treatment with zinc dust in acetic acid and acetic anhydride at room temperature, gave the S-acetyl compound (3b) in 92% yield. When this reductive acetylation was conducted by heating under reflux, 2b did not afford 3b, but the triacetyl compound 4 as violet oily substance. Compound 3b was converted to the disulfide 5b on treatment with activated alumina, while it gave ethyl 2-methylazuleno[2,1-d]thiazole-9-carboxylate (6) on treatment with a potassium hydroxide solution in tetrahydrofuran-ether, followed by treatment with hydrochloric acid by cooling with ice under an inert atmosphere. Demethoxycarbonylation of 6 by heating with 100% phosphoric acid gave 2-methylazuleno-[2,1-d]thiazole (7) in an almost quantitative yield. Thiocyanation of ethyl 2-aminoazulene-1-carboxylate (1a) gave 3-thiocyano compound (2a) (93% yield), which was

then reduced with zinc dust in acetic acid and acetic anhydride to give S-acetyl compound (3a) (76% yield), and heating of the latter with formic acid gave 6 (40% yield). Ethyl 2-formylaminoazulene-1-carboxylate (1c)[4] was converted to the 3-thiocyano compound (2c) and then the S-acetyl compound (3c) in a similar manner as in the case of 1a and 1b. The thiazole formation reaction of 3c gave 6 in a 92% yield.



Reactions of 2-Methylazuleno[2,1-d]thiazole (7)

The reaction of 7 with electrophilic reagents afforded 9-position substituents, that was accounted for by considering the carbonium ion (9) as an intermediate. Mannich reaction of 7 gave 9-dimethylaminomethyl (8a) (ca. 100% yield), 9-piperidinomethyl (8b) (99% yield), and 9-morpholinomethyl derivative (8c) (57% yield). Further, Vilsmeyer-Haack reaction of 7 yielded 9-formyl compound (8d) (99% yield). The oxime (8e) of 8d was dehydrated by heating with acetic anhydride at 110°C to give 9-cyano derivative (8f) (83% yield). The physical properties and spectral data of 2-methylazuleno[2,1-d]thiazoles are shown in Table 1.

Table 1. The Physical Properties and Spectral Data of 4, 6, 7, and 8a-f.

Compound	IR(KBr) cm^{-1}; ES λmax nm(log ε); ^1H NMR(in $CDCl_3$) δ ppm; ^{13}C NMR(in $CDCl_3$) δ ppm
4	violet oil IR($CHCl_3$): 2997, 1705, 1415, 1239, 1138 ^1H NMR: 1.34(3H, t, J= 7.5Hz, $OCH_2\underline{CH_3}$), 2.27(6H, s, $N(COC\underline{H_3})_2$), 2.43(3H, s, $SCOC\underline{H_3}$), 4.37(2H, q, J= 7.5Hz, $OC\underline{H_2}CH_3$), 7.4-8.0(3H, m, H-5,6,7), 8.48(1H, d, J= 10.0Hz, H-4), 9.75(1H, d, J= 10.3Hz, H-8)
6	greenish blue needles; mp 102-103°C IR: 2968, 1682, 1432, 1242, 1216, 1122, 780, 730, 610 ES(in n-hexane): 212(4.32), 254(3.97), 260(3.97), 300(4.45)(sh), 311(4.73), 3.24(4.77), 363(3.73)(sh), 382(3.89), 402(3.64), 585(3.54) ^1H NMR: 1.52(3H, t, J= 7.5Hz, $OCH_2\underline{CH_3}$), 2.99(3H, s, $\underline{CH_3}$-2), 4.57(2H, q, J= 7.5Hz, $OC\underline{H_2}CH_3$), 7.2-7.8(3H, m, H-5,6,7), 8.32(1H, d, J= 8.9Hz, H-4), 9.71(1H, d, J= 10.1Hz, H-8) ^{13}C NMR: 14.8(q), 21.1(q), 60.3(t), 106.2(s), 124.3(s), 126.8(d), 128.1(d), 132.4(s), 134.9(d), 137.9(d), 138.4(d), 144.5(s), 164.8(s), 165.8(s), 176.1(s)
7	dark blue needles; mp 89.5-90°C IR: 1573, 1431, 1172, 792 ES(in n-hexane): 222(3.98), 296(4.81), 301(4.79), 335(3.47), 367(3.82), 385(3.42), 621(2.59) ^1H NMR: 2.92(3H, s, $\underline{CH_3}$-2), 7.08(1H, dd, J= 10.0, 9.8Hz, H-5 or 7), 7.12 (1H, dd, J= 9.8, 9.4Hz, H-7 or 5), 7.51(1H, dd, J= 9.8, 9.8Hz, H-6), 7.53 (1H, s, H-9), 8.22(1H, d, J= 9.4Hz, H-4 or 8), 8.31(1H, d, J= 10.0Hz, H-8 or 4) ^{13}C NMR: 21.3(q), 106.8(d), 122.8(d), 123.01(s), 123.02(d), 130.0(s), 133.2(d), 136.2(d), 137.5(d), 142.5(s), 166.5(s), 174.4(s)
8a	bluish green needles; mp 85-86°C IR: 2972, 2947, 2863, 2825 ES(in CH_3OH): 222(4.03), 257(3.97), 300(4.83), 306(4.79)(sh), 352(3.69), 368(3.83), 608(2.56), 650(2.50)(sh), 720(2.12)(sh) ^1H NMR: 2.32(6H, s, $CH_2N(C\underline{H_3})_2$), 2.93(3H, s, $\underline{CH_3}$-2), 4.11(2H, s, $C\underline{H_2}N(CH_3)_2$), 6.9-7.6(3H, m, H-5,6,7), 8.11(1H, d, J= 9.0Hz, H-4), 8.51(1H, d, J= 10.3Hz, H-8)
8b	green needles; mp 106-107°C IR: 2931, 2743 ES(in CH_3OH): 220(4.05), 257(3.97), 301(4.84), 306(4.80), 352(3.71), 368(3.83), 378(3.36)(sh), 610(2.59), 663(2.50)(sh), 733(2.12)(sh) ^1H NMR: 1.2-1.7(6H, m, $C\underline{H_2}$-3', 4', 5'), 2.3-2.6(4H, m, $C\underline{H_2}$-2', 6'), 2.93 (3H, s, $\underline{CH_3}$-2), 4.17(2H, s, $C\underline{H_2}N$=), 6.9-7.6(3H, m, H-5,6,7), 8.10(1H, d, J= 8.4Hz, H-4), 8.55(1H, d, J= 9.9Hz, H-8)
8c	green needles; mp 105-106°C IR: 2905, 2860

ES(in CH_3OH): 222(4.04), 255(3.96), 300(4.83), 352(3.68), 368(3.81), 380(3.24)(sh), 610(2.58), 654(2.55), 720(2.22)
^1H NMR: 2.4-2.6(4H, m, CH_2-2', 6'), 2.94(3H, s, CH_3-2), 3.5-3.7(4H, m, CH_2-3', 5'), 4.19(2H, s, CH_2N=), 6.9-7.6(3H, m, H-5,6,7), 8.15(1H, d, J= 9.3Hz, H-4), 8.54(1H, d, J= 10.0Hz, H-8)

8d dark blue prisms; mp 153-154 °C

IR: 1628
ES(in CH_3OH): 220(4.34), 235(4.27), 264(4.13), 322(4.59)(sh), 334(4.70), 379(3.83), 399(3.87), 413(2.84), 548(3.66)
^1H NMR: 2.92(3H, s, CH_3-2), 7.2-7.8(3H, m, H-5,6,7), 8.12(1H, d, J= 8.5Hz, H-4), 9.44(1H, d, J= 9.8Hz, H-8), 10.55(1H, s, CHO)

8e greenish brown prisms; mp 227-228 °C

IR: 3313, 1583
ES(in CH_3OH): 234(4.35), 256(4.16), 319(4.65), 387(3.81), 404(3.76), 420 (3.58), 524(2.50), 630(2.54), 680(2.45)(sh)
^1H NMR: 2.95(3H, s, CH_3-2), 3.12(1H, s, CH=NOH), 7.1-7.7(3H, m, H-5,6,7), 8.26(1H, d, J= 8.6Hz, H-4), 8.83(1H, s, CH=NOH), 8.99(1H, d, J= 10.0Hz, H-8)

8f green needles; mp 196-197 °C

IR: 2173
ES(in CH_3OH): 208(4.42), 226(4.16)(sh), 256(4.00)(sh), 308(4.81), 320(4.84), 360(3.82)(sh), 374(3.94), 388(3.63)(sh), 548(2.66), 590(2.64)(sh)
^1H NMR: 2.97(3H, s, CH_3-2), 7.3-7.9(3H, m, H-5,6,7), 8.27(1H, d, J= 8.2Hz, H-4), 8.51(1H, d, J= 9.8Hz, H-8)

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