HETEROCYCLES, Vol 20, No 7, 1983

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

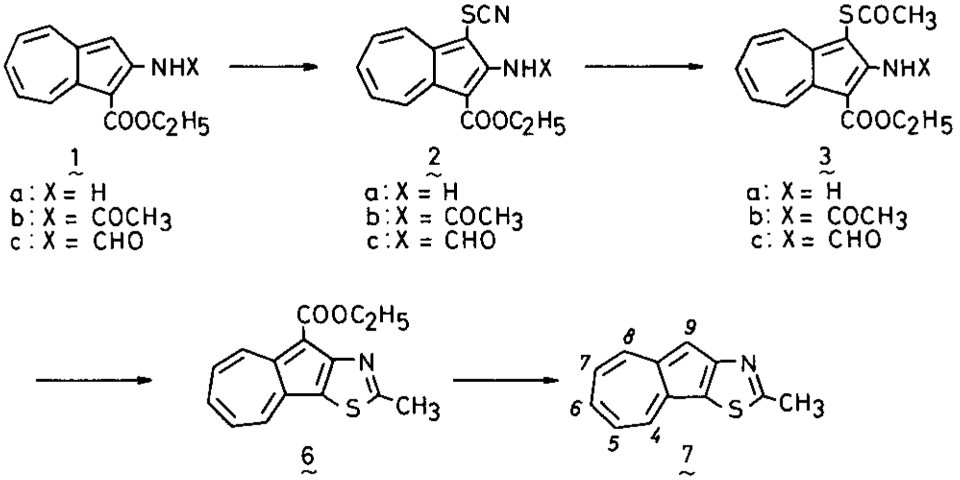
Kameji YAMANE,* Kunihide FUJIMORI,* Shuji ICHIKAWA, Shiro MIYOSHI,
and Kenichi HASHIZUME
Department of Chemistry, Faculty of Science, Shinshu University
Asahi, Matsumoto 390, Japan

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.



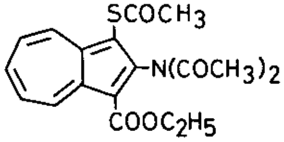
1
a: X = H
b: X = $COCH_3$
c: X = CHO

2
a: X = H
b: X = $COCH_3$
c: X = CHO

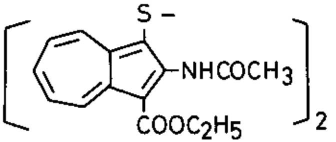
3
a: X = H
b: X = $COCH_3$
c: X = CHO

6

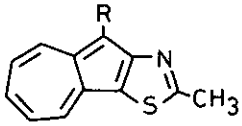
7



4

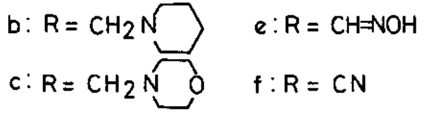


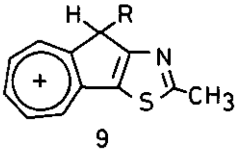
5



8

a: R = $CH_2N(CH_3)_2$ d: R = CHO





9

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); ^{1}H 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 ^{1}H NMR: 1.34(3H, t, J= 7.5Hz, $OCH_2C\underline{H}_3$), 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, $OC\underline{H}_2CH_3$), 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) ^{1}H NMR: 1.52(3H, t, J= 7.5Hz, $OCH_2C\underline{H}_3$), 2.99(3H, s, $C\underline{H}_3$-2), 4.57(2H, q, J= 7.5Hz, $OC\underline{H}_2CH_3$), 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) ^{1}H NMR: 2.92(3H, s, $C\underline{H}_3$-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) ^{1}H NMR: 2.32(6H, s, $CH_2N(C\underline{H}_3)_2$), 2.93(3H, s, $C\underline{H}_3$-2), 4.11(2H, s, $C\underline{H}_2N(CH_3)_2$), 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) ^{1}H 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, $C\underline{H}_3$-2), 4.17(2H, s, $C\underline{H}_2N=$), 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, $C\underline{H}_2$-2', 6'), 2.94(3H, s, $C\underline{H}_3$-2), 3.5-3.7(4H, m, $C\underline{H}_2$-3', 5'), 4.19(2H, s, $C\underline{H}_2N=$), 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, $C\underline{H}_3$-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, $C\underline{H}O$)

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, $C\underline{H}_3$-2), 3.12(1H, s, $CH=NO\underline{H}$), 7.1-7.7(3H, m, H-5,6,7), 8.26(1H, d, J= 8.6Hz, H-4), 8.83(1H, s, $C\underline{H}=NOH$), 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, $C\underline{H}_3$-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)

ACKNOWLEDGMENT The present work was supported by a Grant-in-Aid for Scientific Research No. 00547021 from the Ministry fo Education, Science and Culture. The authors are indebted to Dr. Masafumi Yasunami of Tohoku University for his kind measurement of the ^{13}C NMR spectra and to Sankyo Co. Ltd., for obtaining the mass spectral data and elemental analytical data.

REFERENCES AND NOTE

1. T. Morita, T. Nakadate, and K. Takase, *Heterocycles*, **15**, 835-838 (1980).
2. K. Yamane, K. Fujimori, and T. Takeuchi, *Bull. Chem. Soc. Jpn.*, **54**, 2537-2538 (1981).
3. K. Yamane, K. Fujimori, and S. Ichikawa, *Chem. Lett.*, 707-708 (1982).
4. T. Nozoe, T. Asao, and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **46**, 3161, 3164 (1973).
5. All new compounds described in this paper gave satisfactory elemental analytical data.

Received, 11th March, 1983