HETEROCYCLES, Vol. 56, 2002, pp. 497-501, Received, 30th May, 2001

A SIMPLE AND FACILE SYNTHESIS OF AZULENO[1,2-*d*]-PYRAZOLES FROM 1-ACETYL-2-METHOXYAZULENE

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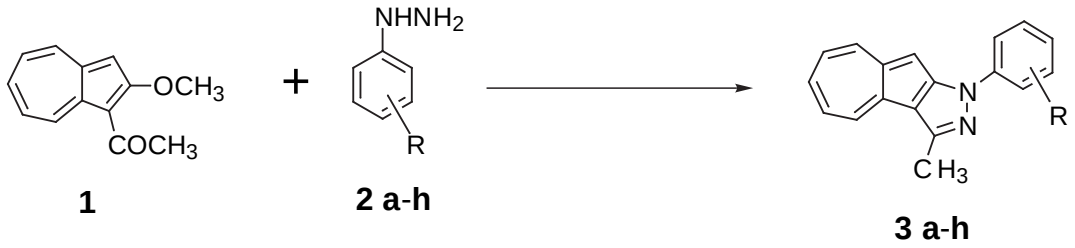
Dedicated to Professor James P. Kutney on the occasion of his 77th birthday.

Abstract - 1-Acetyl-2-methoxyazulene (**1**) reacted with arylhydrazines (**2a-h**) under refluxing in ethanol to give 1-aryl-3-methylazuleno[1,2-*d*]pyrazoles (**3a-h**) in moderate to high yields, except for the low yield of azuleno[1,2-*d*]pyrazole (**3g**).

A variety of heterocycle-fused azulenes have so far been obtained on the viewpoints of chemical properties and physiological activities by several synthetic methods.[1-4] In a previous paper, we reported that 1-acetyl-2-(bromomethyl)azulene reacted with anilines to give 2-aryl-3-methylazuleno[1,2-*c*]pyrroles.[5] On the other hand, it was reported that diethyl 2-methoxyazulene-1,3-dicarboxylate[6] was treated with nitrogen nucleophiles, such as methylamine and phenylhydrazine, to yield nucleophilic substitution products at the 2-position. In connection with our studies on the synthetic utilities of 1-acetylazulenes, this paper describes briefly with the preparation of 1-aryl-3-methylazuleno[1,2-*d*]pyrazoles by the reactions of 1-acetyl-2-methoxyazulene with arylhydrazines.

When a solution of 1-acetyl-2-methoxyazulene (**1**) and phenylhydrazine (**2a**) (1.5 eq) in absolute ethanol was refluxed for 12 h, 3-methy-1-phenylazuleno[1,2-*d*]pyrazole (**3a**) was obtained as violet needles, mp 93-94 ^{o}C, in an excellent yield. Compound (**3a**) gave satisfactory elemental analysis and spectral data. The reactions with methyl-, methoxy-, and chloro-substituted phenylhydrazines (**2b-h**) were also carried out in a similar manner to give readily the corresponding azuleno[1,2-*d*]pyrazoles (**3b-h**) in good yields, except for the reaction with (2-chlorophenyl)hydrazine (**2g**). The results are summarized in Table 1.



1 **2 a-h** **3 a-h**

Scheme 1

Table 1. Reactions of 1-Acetyl-2-methoxyazulene (**1**) with Arylhydrazines (**2a-h**)

Hydrazine		Time	Product	
	R	h	**3**	Yield / %
2a	H	12	**3a**	89
2b	2-CH_3	10	**3b**	73
2c	3-CH_3	12	**3c**	62
2d	4-CH_3	6	**3d**	79
2e	2-OCH_3	12	**3e**	64
2f	4-OCH_3	12	**3f**	71
2g	2-Cl	12	**3g**	34
2h	4-Cl	6	**3h**	87

It is thought that the reactions proceed *via* the hydrazone formation by the condensation of the acetyl group of azulene (**1**) with arylhydrazines followed by the cyclization at the 2-position bearing the methoxyl substituent. The low yield of compound (**3g**) might be due to steric hindeance of the chlorine atom at the cyclization step. As an example of the pyrazole-fused azulenes, previously, it was reported that 5-acetylazulene reacted with hydrazine to afford azuleno[5,6-*d*]pyrazoles.[7] The present work provides the first example of the synthesis of pyrazole-fused azulenes on the five-membered ring. The compound (**1**) will be a valuable synthon for the preparation of a variety of heterocycle-fused azulenes.

EXPERIMENTAL

All the melting points were determined with a Yanagimoto MP JP-3 apparatus and are uncorrected. The IR spectra were taken on a JASCO IRA-1 spectrophotometer. The NMR spectra were recorded with a JEOL JNM-EX 300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C). The MS spectra were

obtained by a JEOL JMX-DX 303HF instrument. All the elemental analyses were performed at the Instrumental Analysis Center, Kumamoto University. Merck Kieselgel 60 was used for column chromatography.

Materials. 1-Acetyl-2-methoxyazulene (**1**) was prepared according to the method described in the literature.[8]

Reactions of 1-Acetyl-2-methoyazulene (1) with Phenylhydrazines (2a-h). A mixed solution of 1-acetyl-2-methoxyazulene (**1**) (40 mg, 0.2 mmol) and arylhydrazine (**2a-h**) (0.3 mmol) in absolute ethanol (10 mL) was refluxed for 6-12 h. The reaction mixture was diluted with water (25 mL) and extracted with benzene (2 10 mL). After drying over sodium sulfate, the evaporated residue was chromatographed on silica gel column with benzene to give 1-aryl-3-methylazuleno[1,2-*d*]pyrazoles (**3a-h**).

3-Methyl-1-phenylazuleno[1,2-*d*]pyrazoles (3a). Violet needles (from benzene); yield 46 mg (89%); mp 93-94 °C; ^{1}H NMR ($CDCl_3$) δ 2.68 (3H, s, CH_3), 6.97 (1H, t, *J* = 9.6 Hz, 4'-H), 7.03 (1H, s, 9-H), 7.11 (2H, dd, *J* = 9.6, 7.5 Hz, 3',5'-H), 7.25 (1H, dd, *J* = 10.5, 9.0 Hz, 6-H), 7.37 (2H, m, 5,7-H), 7.79 (2H, d, *J* = 7.5 Hz, 2',6'-H), 7.98 (1H, d, *J* = 11.1 Hz, 8-H), 8.01 (1H, d, *J* = 9.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 99.5 (=CH-), 118.4 (=CH-), 121.2 (=C<), 124.5 (=CH-), 124.6 (=CH-), 125.8 (=CH-), 129.2 (=CH-), 129.3 (=CH-), 131.4 (=C<), 133.4 (=CH-), 135.5 (=CH-), 140.8 (=C<), 143.8 (=C<), 145.4 (=C<), 149.4 (=C<). MS (EI) *m/z* 258 (M^+). *Anal*. Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.96; H, 5.26; N, 10.69.

3-Methyl-1-(2-methylphenyl)azuleno[1,2-*d*]pyrazoles (3b). Violet oil; yield 40 mg (73%); ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s, 2'-CH_3), 2.76 (3H, s, 3-CH_3), 6.76 (1H, s, 9-H), 7.00 (1H, dd, *J* = 9.9, 9.6 Hz, 6-H), 7.14-7.29 (5H, m), 7.37-7.43 (1H, m), 8.00 (1H, d, *J* = 10.5 Hz, 8-H), 8.12 (1H, d, *J* = 9.4 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (3-CH_3), 18.4 (2'-CH_3), 98.8 (=CH-), 119.9 (=C<), 124.3 (=CH-), 125.7 (=CH-), 126.2 (=CH-), 126.5 (=CH-), 127.8 (=CH-), 128.8 (=CH-), 131.4 (=CH-), 132.2 (=C<), 133.0 (=CH-), 133.9 (=C<), 135.2 (=CH-), 139.3 (=C<), 143.1 (=C<), 145.3 (=C<), 152.6 (=C<). MS (EI) *m/z* 272 (M^+, 100), 230 (18). HRMS Calcd for $C_{19}H_{16}N_2$: M, 272.1314. Found: *m/z* 272.1315.

3-Methyl-1-(3-methylphenyl)azuleno[1,2-*d*]pyrazoles (3c). Violet oil; yield 34 mg (62%); ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s, 3'-CH_3), 2.71 (3H, s, 3-CH_3), 6.93 (1H, d, *J* = 7.5 Hz, 4'-H), 7.02-7.14 (2H, m), 7.09 (1H, s, 9-H), 7.22-7.32 (2H, m), 7.58 (1H, d, *J* = 8.1 Hz, 6'-H), 7.65 (1H, s, 2'-H), 8.03 (1H, d, *J* = 10.2 Hz, 8-H), 8.07 (1H, d, *J* = 9.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (3-CH_3), 21.6 (3'-CH_3), 99.7 (=CH-), 115.4 (=CH-), 119.2 (=CH-), 121.1 (=C<), 124.6 (=CH-), 125.5 (=CH-), 125.8 (=CH-), 129.1 (=CH-), 129.2 (=CH-), 131.5 (=C<), 133.4 (=CH-), 135.5 (=CH-),

139.4 (=C<), 140.7 (=C<), 143.8 (=C<), 145.5 (=C<), 149.5 (=C<). MS (EI) *m/z* 272 (M^+). HRMS Calcd for $C_{19}H_{16}N_2$: M, 272.1314. Found: *m/z* 272.1315.

3-Methyl-1-(4-methylphenyl)azuleno[1,2-*d*]pyrazoles (3d). Violet needles (from benzene); yield 43 mg (79%); mp 127-128 °C; ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s, 4'-CH_3), 2.74 (3H, s, 3-CH_3), 7.03 (1H, dd, *J* = 10.5, 9.6 Hz, 7-H), 7.11 (1H, s, 9-H), 7.16 (1H, dd, *J* = 10.0, 9.6 Hz, 5-H), 7.20 (2H, d, *J* = 8.2 Hz, 3',5'-H), 7.31 (1H, dd, *J* = 9.9, 9.6 Hz, 6-H), 7.71 (2H, d, *J* = 7.2 Hz, 2',6'-H), 8.06 (1H, d, *J* = 10.5 Hz, 8-H), 8.09 (1H, d, *J* = 10.0 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.1 (3-CH_3), 20.9 (4'-CH_3), 99.6 (=CH-), 118.5 (=CH-), 124.6 (=CH-), 125.8 (=CH-), 128.3 (=C<), 129.1 (=CH-), 129.9 (=CH-), 131.6 (=C<), 133.3 (=CH-), 134.4 (=C<), 135.5 (=CH-), 138.6 (=C<), 143.6 (=C<), 145.5 (=C<), 149.5 (=C<). *Anal*. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.59; H, 5.85; N, 10.15.

1-(2-Methoxylphenyl)-3-methylazuleno[1,2-*d*]pyrazoles (3e). Violet oil; yield 37 mg (64%); ^{1}H NMR ($CDCl_3$) δ 2.76 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 6.83 (1H, s, 9-H), 6.96-7.03 (3H, m), 7.15-7.31 (3H, m), 7.58 (1H, d, *J* = 9.1 Hz, 6'-H), 8.02 (1H, d, *J* = 10.5 Hz, 8-H), 8.10 (1H, d, *J* = 9.1 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 55.7 (OCH_3), 100.9 (=CH-), 112.2 (=CH-), 121.0 (=CH-), 124.0 (=CH-), 125.5 (=CH-), 126.6 (=CH-), 127.8 (=CH-), 128.3 (=CH-), 128.6 (=CH-), 129.8 (=C<), 132.1 (=C<), 132.8 (=CH-), 135.3 (=C<), 143.7 (=C<), 144.7 (=C<), 152.5 (=C<), 152.9 (=C<). MS (EI) *m/z* 288 (M^+). HRMS Calcd for $C_{19}H_{16}N_2O$: M, 288.1263. Found: *m/z* 288.1258.

1-(4-Methoxylphenyl)-3-methylazuleno[1,2-*d*]pyrazoles (3f). Violet needles (from benzene); yield 41 mg (71%); mp 101-103 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.83 (1H, s, 9-H), 6.93 (2H, d, *J* = 9.0 Hz, 3',5'-H), 7.02 (1H, dd, *J* = 10.8, 9.6 Hz, 7-H), 7.15 (1H, dd, *J* = 9.9, 9.6 Hz, 5-H), 7.29 (1H, dd, *J* = 9.9, 9.6 Hz, 6-H), 7.71 (2H, d, *J* = 9.0 Hz, 2',6'-H), 8.03 (1H, d, *J* = 10.8 Hz, 8-H), 8.07 (1H, d, *J* = 9.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 55.5 (OCH_3), 99.3 (=CH-), 114.6 (=CH-), 120.1 (=CH-), 120.9 (=C<), 124.5 (=CH-), 125.8 (=CH-), 128.9 (=CH-), 131.8 (=C<), 133.2 (=CH-), 134.6 (=C<), 135.4 (=CH-), 143.4 (=C<), 145.5 (=C<), 149.5 (=C<), 157.0 (=C<). *Anal*. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.44; H, 5.57; N, 9.78.

1-(2-Chlorophenyl)-3-methylazuleno[1,2-*d*]pyrazoles (3g). Violet needles (from benzene); yield 20 mg (34%); mp 98-99 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s, CH_3), 6.84 (1H, s, 9-H), 7.04-7.16 (2H, m), 7.21-7.33 (3H, m), 7.46 (1H, dd, *J* = 7.7, 1.7 Hz, 3'-H), 7.55 (1H, dd, *J* = 8.0, 1.6 Hz, 6'-H), 8.02 (1H, d, *J* = 10.5 Hz, 8-H), 8.13 (1H, d, *J* = 8.7 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 100.0 (=CH-), 120.3 (=C<), 124.4 (=CH-), 125.7 (=CH-), 127.5 (=CH-), 128.3 (=CH-), 128.4 (=CH-), 128.9 (=C<), 129.2 (=CH-), 130.6 (=CH-), 131.9 (=C<), 133.4 (=CH-), 135.5 (=CH-), 138.3 (=C<),

144.2 (=C<), 145.1 (=C<), 152.6 (=C<). *Anal*. Calcd for $C_{18}H_{13}N_2Cl$: C, 73.84; H, 4.48; N, 9.57. Found: C, 73.59 H, 4.38; N, 9.55.

1-(4-Chlorophenyl)-3-methylazuleno[1,2-*d*]pyrazoles (3h). Violet needles (from benzene); yield 51 mg (87%); mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s, CH_3), 7.06 (1H, s, 9-H), 7.09-7.23 (3H, m), 7.36 (2H, d, *J* = 8.9 Hz, 3',5'-H), 7.74 (2H, d, *J* = 9.0 Hz, 2',6'-H), 8.08 (1H, d, *J* = 10.5 Hz, 8-H), 8.12 (1H, d, *J* = 9.9 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 99.2 (=CH-), 119.4 (=C<), 124.8 (=CH-), 126.0 (=CH), 128.3 (=CH-), 129.4 (=CH-), 129.6 (=CH-), 129.7 (=C<), 131.4 (=C<), 133.8 (=CH-), 135.8 (=CH-), 139.5 (=C<), 144.2 (=C<), 145.7 (=C<), 149.3 (=C<). *Anal*. Calcd for $C_{18}H_{13}N_2Cl$: C, 73.84; H, 4.48; N, 9.57. Found: C, 73.78; H, 4.45; N, 9.36.

REFERENCES

1. T. Morita, T. Nakadate, and K. Takase, *Heterocycles*, 1981, **15**, 835.
2. K. Fujimori, T. Fujita, K. Yamane, M. Yasunami, and K. Takase, *Chem. Lett.*, 1983, 1721.
3. K. Yamane, K. Fujimori, S. Ichikawa, S. Miyoshi, and K. Hashizume, *Heterocycles*, 1983, **20**, 1263.
4. K. Fujimori, H. Fukazawa, Y. Nezu, K. Yamane, M. Yasunami, and K. Takase, *Chem. Lett.*, 1986, 1021.
5. D.-L. Wang and K. Imafuku, *Heterocycles*, 2001, **54**, 647.
6. T. Nozoe, K. Takase, and N. Shimazaki, *Bull. Chem. Soc. Jpn*., 1964, **37**, 1664.
7. T. Nozow, K. Takase, and M. Tada, *Bull. Chem. Soc. Jpn*., 1963, **36**, 1016.
8. T. Nozoe, H. Wakabayashi, K. Shindo, S. Ishikawa, C.-P. Wu, and P.-W. Yang, *Heterocycles*, 1991, **32**, 213.