SYNTHESIS OF NOVEL 6-SUBSTITUTED 2-CHLORO-3-METHYLQUINOXALINES

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Abstract - Facile synthesis of novel 6-substituted 2-chloro-3-methylquinoxalines (4a-d) is described. Intramolecular cyclization reaction of 4-substituted 2-nitroacetoacetanilides (1a-d) in basic conditions afforded 6-substituted 2(1H)-quinoxalinone-4-oxides (2a-d) and in situ, which could be converted into novel 6-substituted 3-methyl-2(1H)-quinoxalinones (3a-d) using ethyl acetoacetate. 3a-d were chlorinated with phosphoryl chloride to afford 4a-d.

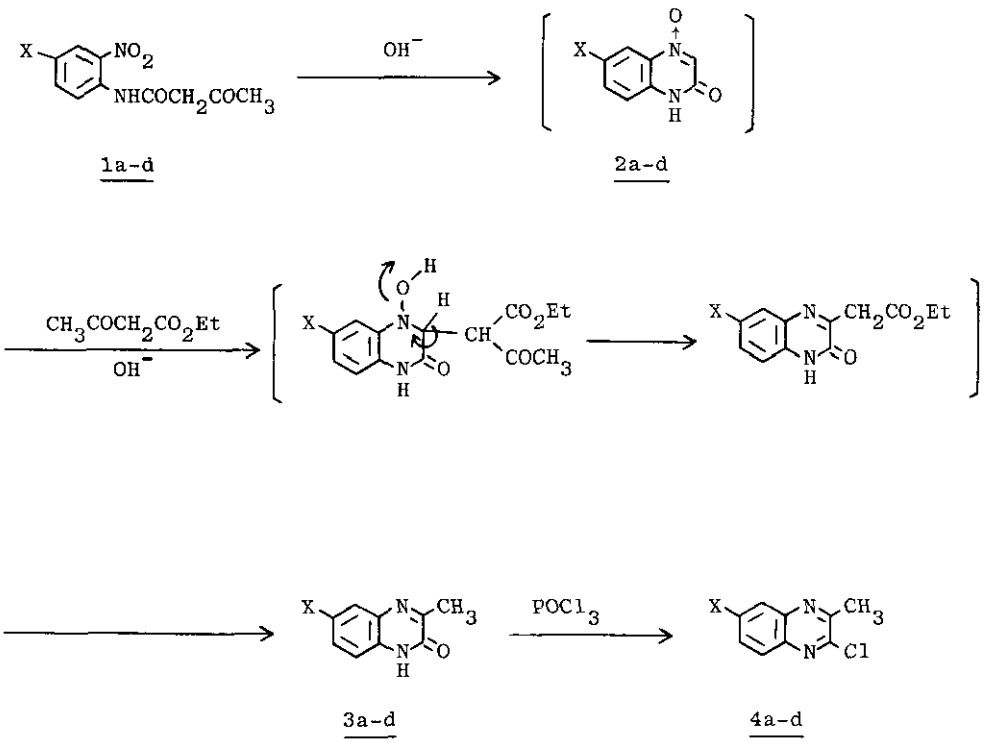
Generally, unsubstituted 3-methyl-2(1H)-quinoxalinone could be synthesized by the reaction of o-phenylenediamine with pyruvic acid.[1] However, the condensation of 4-substituted o-phenylenediamine with pyruvic acid gave a mixture of 6- and 7-substituted 3-methyl-2(1H)-quinoxalinone. On the other hand, Tennant has reported that unsubstituted 3-methyl-2(1H)-quinoxalinone has been obtained from 2(1H)-quinoxalinone-4-oxide.[2] But the yield was not satisfactory because of several by-products and of some steps to prepare 3-methyl-2(1H)-quinoxalinone. The extensive study to prepare 6-substituted 3-methyl-2(1H)-quinoxalinones (3a-d) from 4-substituted 2-nitroacetoacetanilides (1a-d), particularly in one pot reaction, has not been reported.

In connection with our synthetic and biological studies, a method for the synthesis of 6-substituted 2-chloro-3-methylquinoxalines (4a-d) was required.

Now we elaborated a facile method for the synthesis of 3a-d via 6-substituted 2(1H)-quinoxalinone-4-oxides (2a-d) from 1a-d in one pot reaction, since 3a-d would be easily converted into 4a-d.

Intramolecular cyclization reactions of 1a-d were carried out in sodium hydroxide solution at 65 °C to form 2a-d as intermediates, which were in situ treated with

ethyl acetoacetate to obtain 3a-d in 68(3a), 72(3b), 65(3c), and 68%(3d) yields, respectively. When ethyl acetoacetate was not applied to this reaction, the intermediates 2a-d could be isolated in 84(2a), 86(2b), 81(2c), and 83%(2d) yields, respectively. In the above reactions, ethyl acetoacetate reacted at 3-position of 2a-d to result in dehydration, deacetylation, and decarboxylation successively. Other kinds of active methylene compounds such as acetone, diketene, and diethyl malonate were applied to this reaction in order to examine their reactivities. When acetone and diketene were used, the same product as the above was obtained in low yield together with several by-products. On the other hand, diethyl malonate did not react with 2a-d at all. Ethyl acetoacetate was a suitable reagent to synthesize 3a-d from 2a-d in situ.



X: a= F, b= Cl, c= Br, d= CF_3

Scheme 1.

Generally, 2(1H)-quinoxalinone derivatives, which have no substituent at 3-position, can be chlorinated using either thionyl chloride in the presence of a catalytic amount of dimethyl formamide or phosphoryl chloride to obtain the corresponding 2-chloroquinoxaline derivatives. The chlorination is smoothly carried out in either case. However, when the Vilsmeier reagent prepared from an excess of thionyl chloride and a catalytic amount of dimethyl formamide in situ was used to chlorinate 3a-d, their chlorinations were unsuccessful because of the presence of the methyl group at 3-position, and these reactions provided the polymerized and unidentified materials. The chlorinations of 3a-d to 4a-d were conveniently accomplished using phosphoryl chloride in 77(4a), 89(4b), 83(4c), and 71%(4d) yields, respectively. Reaction pathway and products are shown in Scheme 1. Compounds 3a-d and 4a-d are new, and, especially, 4a-d can be used as important intermediates of pharmaceutical and agricultural chemicals.[3,4] Physical data of 3a-d and 4a-d are summarized in Table 1.

Table 1. Physical Data of 3a-d and 4a-d

A) 6-Substituted 3-Methyl-2(1H)-quinoxalinones (3a-d)

Compound	X	Formula	mp(°C)	Analyses(%) Calcd. / Found		
				C	H	N
3a	F	$C_9H_7N_2OF$	263-264	60.66 60.46	3.96 3.91	15.72 15.61
3b	Cl	$C_9H_7N_2OCl$	257-258	55.55 55.40	3.63 3.61	14.40 14.31
3c	Br	$C_9H_7N_2OBr$	264-265	45.21 45.01	2.95 2.92	11.72 11.59
3d	CF_3	$C_{10}H_7N_2OF_3$	193-194	52.63 52.51	3.09 3.07	12.28 12.19

B) 6-Substituted 3-Methyl-2-chloroquinoxalines (4a-d)

4a	F	$C_9H_6N_2ClF$	142-144	54.98 54.87	3.08 3.05	14.25 14.19
4b	Cl	$C_9H_6N_2Cl_2$	128-129	50.73 50.61	2.84 2.82	13.15 13.02
4c	Br	$C_9H_6N_2BrCl$	125-126	41.98 41.85	2.35 2.29	10.88 10.78
4d	CF_3	$C_{10}H_6N_2ClF_3$	113-114	48.70 48.61	2.45 2.42	11.36 11.30

EXPERIMENTAL SECTION

Pmr spectra were obtained on a JEOL FX-90 Spectrometer locked on the tetramethylsilane as an internal reference. Ir spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA 3500 and DX-300, JMA 3100. Elemental analyses were measured on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione). Chemical purities were determined on a Shimazu Liquid Chromatograph LC-3A. All melting points are uncorrected.

General procedure for the synthesis of 3a-d from 1a-d. 1a-d (345 mmol) were dissolved in toluene (150 ml) and added dropwise to a solution of 18% sodium hydroxide (1500 ml) with continuous stirring at 65 °C over a period of 15 min. After completion of the addition, stirring was continued at 65 °C for 1.0 h. Next ethyl acetoacetate (690 mmol) was added dropwise to the resulting slurry solution at 65 °C over a period of 10 min. After stirring at 65 °C for 1.0 h, the resulting by-product was filtered off and the toluene layer was separated. The aqueous layer was acidified with 6N hydrochloric acid below 10 °C. The resulting solid was collected and washed with water and then dried in vacuo to afford 3a-d. Purification of 3a-d was carried out by the recrystallization of their sodium salts from water.

3a; ir(KBr): 2870, 1662, 1493, 1411, 1254, 900, 811, and 584 cm^{-1}. ms m/z 178(M^+, base peak) and 150.

3b; ir(KBr): 2845, 1661, 1562, 1480, 1399, 1200, 1078, 933, 895, 810, 721, 583, and 541 cm^{-1}. ms m/z 194(M^+, base peak), 166, and 131.

3c; ir(KBr): 2845, 1662, 1560, 1478, 1399, 1277, 1200, 928, 890, 812, 720, 582, and 521 cm^{-1}. ms m/z 238(M^+, base peak), 210, and 131.

3d; ir(KBr): 2865, 1664, 1618, 1570, 1350, 1319, 1281, 1263, 1211, 1174, 1135, 1114, 1068, 908, 820, 651, 589, and 521 cm^{-1}. ms m/z 228(M^+, base peak), 200, and 131.

The chlorinations of 3a-d to 4a-d. Suspensions of 3a-d were refluxed in a large excess of phosphoryl chloride for 40 min. After removal of excess phosphoryl chloride under reduced pressure, crude dark product was poured onto ice-water and stirred for 10 min. The resulting solid was collected and washed with 1% sodium hydroxide solution, next with water and dried in vacuo. Purification was carried out with column chromatography (silica gel, $CHCl_3$) to afford 4a-d.

4a; ir(KBr): 3430, 2940, 1618, 1482, 1311, 1198, 1150, and 1041 cm^{-1}. pmr($CDCl_3$) δ 2.80(3H, s) and 7.25-8.20(3H, m). ms m/z 196(M^+, base peak), 161, 134, and 120.

4b; ir(KBr): 3025, 1598, 1475, 1371, 1310, 1171, 1135, 1042, 919, 890, and 832 cm^{-1}.

pmr($CDCl_3$) δ 2.78(3H, s), 7.55(1H, d d, J= 9.0, 2.4 Hz), 7.85(1H, d, J= 9.0 Hz), and 7.92(1H, d, J= 2.4 Hz). ms m/z 212(M^+, base peak), 177, and 136.

4c; ir(KBr): 3040, 1600, 1479, 1374, 1311, 1172, 1142, 1045, 912, and 835 cm^{-1}. pmr($CDCl_3$) δ 2.79(3H, s), 7.78(2H, bs), and 8.15(1H, bs). ms m/z 256(M^+, base peak), 221, and 142.

4d; ir(KBr): 3425, 1390, 1358, 1324, 1302, 1282, 1262, 1191, 1150, 1126, 1047, 929, and 852 cm^{-1}. pmr($CDCl_3$) δ 2.82(3H, s), 7.85(1H, d d, J= 8.8, 2.4 Hz), 8.08(1H, d, J= 8.8 Hz), and 8.32(1H, d, J= 2.4 Hz). ms m/z 246(M^+, base peak), 211, and 170.

The isolation of 2a-d. 2a-d could be obtained by heating of 1a-d in sodium hydroxide solution. 2a, 2b, and 2c; mp >300 °C. 2d; mp 280-281 °C.

2a; ir(KBr): 3400, 3050, 1650, 1532, 1485, 1424, 1250, 1202, 1131, 1002, 884, 860, 838, 734, 644, 544, and 515 cm^{-1}. ms m/z 180(M^+, base peak), 164, 150, 136, 109, and 97. Found: C, 53.21; H, 2.75; N, 15.50%. Calcd for $C_8H_5N_2O_2F$: C, 53.35; H, 2.80; N, 15.56%.

2b; ir(KBr): 3425, 3050, 1660, 1519, 1472, 1418, 1252, 1157, 1130, 1002, 836, 524, and 510 cm^{-1}. ms m/z 196(M^+, base peak), 180, 166, 152, 125, and 105. Found: C, 48.71; H, 2.49; N, 14.19%. Calcd for $C_8H_5N_2O_2Cl$: C, 48.87; H, 2.56; N, 14.25%.

2c; ms m/z 240(M^+, base peak), 224, 210, 196. Found: C, 39.61; H, 2.05; N, 11.50%. Calcd for $C_8H_5N_2O_2Br$: C, 39.85; H, 2.09; N, 11.62%.

2d; ir(KBr): 2920, 1670, 1632, 1532, 1450, 1372, 1354, 1318, 1262, 1233, 1145, 1110, 912, 848, 683, and 509 cm^{-1}. ms m/z 230(M^+, base peak), 214, 211, 200, 186, 167, 136, and 105. Found: C, 46.87; H, 2.18; N, 12.08%. Calcd for $C_9H_5N_2O_2F_3$: C, 46.96; H, 2.19; N, 12.17%.

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