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THE FACILE SYNTHESIS OF QUINOXALINYL-2-OXYPHENOLS

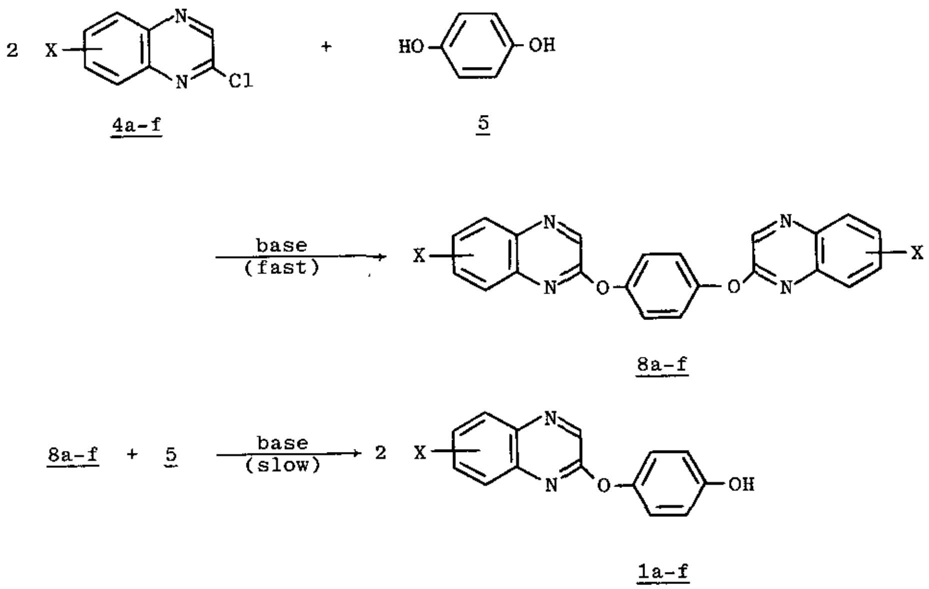
Gozyo Sakata,* Kenzi Makino, and Isao Hashiba
Central Research Institute, Nissan Chemical Ind., LTD.
Tsuboi-cho, Funabashi, Chiba 274, Japan

Abstract - Facile synthesis of quinoxalinyl-2-oxyphenols are described. The condensation of 2-chloroquinoxalines with three molar equivalent of dihydroxybenzene in basic medium gave preferentially quinoxalinyl-2-oxyphenols, which involves nucleophilic cleavage of the initially formed bis(quinoxalinyl-2-oxy)benzenes by an excess of dihydroxybenzene.

Recently, several derivatives of 4-(quinoxalinyl-2-oxy)phenol (1a-f), 3-(quinoxalinyl-2-oxy)phenol (2a-f) and 2-(quinoxalinyl-2-oxy)phenol (3a-f) are used as intermediates for the synthesis of agricultural chemicals. For instance, they can be easily converted into 2-(quinoxalinyl-2-oxyphenoxy)propanoic acids and O-(quinoxalinyl-2-oxyphenyl)thiophosphate derivatives, which are attracted special interest as a new type of selective herbicide and excellent insecticide,[1,2] respectively.

In connection with our synthetic and biological studies, a facile method for the synthesis of 1a-f, 2a-f and 3a-f was required. In this paper, we wish to report the condensation reaction of substituted 2-chloroquinoxalines (4a-f) with dihydroxybenzene such as hydroquinone (5), resorcinol (6) and catechol (7), to synthesize 1a-f, 2a-f and 3a-f. They are new compounds and reactions for the synthesis of them have not been reported.

When 2,6-dichloroquinoxaline (4c) and three molar equivalent of 5 were refluxed in the presence of anhydrous potassium carbonate in dimethylformamide, 4-(6-chloroquinoxalinyl-2-oxy)phenol (1c) and small amount of 1,4-bis(6-chloroquinoxalinyl-2-oxy)benzene (8c) were obtained. In the analysis of this reaction with HPLC method, it became clear that 8c was formed as main product in early stage and cleavaged to 1c with an excess of 5. This reaction sequence was supported by the fact that 1c is also obtained by the *reaction of 8c with one molar* equivalent of 5 in the same reaction condition. Also, the same result was obtained in the case of 4-(6-fluoroquinoxalinyl-2-oxy)phenol (1b) and they are shown in Scheme 1.



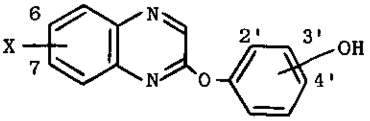
X: a=H, b=6-F, c=6-Cl, d=6-CF_3, e=7-Br, f=6,7-Cl_2

Scheme 1.

When 6 and 7 were allowed to react with 4a-f, 1,3-bis(quinoxalinyl-2-oxy)benzenes (9a-f) and 1,2-bis(quinoxalinyl-2-oxy)benzenes (10a-f) were formed in early stage in a similar manner to the case of the reaction with 5 and the intermediates (9a-f) and (10a-f) this formed underwent the nucleophilic cleavage with excess 6 and 7 to give 2a-f and 3a-f, respectively.

The yield of 1a-f, 2a-f and 3a-f was remarkably affected by the kinds of solvent. When polar and aprotic solvent such as dimethylformamide, 1,3-dimethyl-2-imidazolizinone and dimethyl sulfoxide was used, good yield was obtained. Physical data for 1a-f, 2b,c and 3a-e are listed in Table 1.

Table 1. Physical Data for Quinoxalinyl-2-oxyphenol



A) 1a-f [4'-OH]

Compound (X)	Formula	mp(°C)	Yield(%)	Analyses(%)		Calcd. Found
				C	H	N
1a (H)	$C_{14}H_{10}N_2O_2$	196-197	92	70.59 70.48	4.20 4.18	11.76 11.81
1b (6-F)	$C_{14}H_9N_2O_2F$	185-187	89	65.63 65.48	3.52 3.41	10.94 10.85
1c (6-Cl)	$C_{14}H_9N_2O_2Cl$	186-189	95	61.83 61.88	3.30 3.25	10.28 10.15
1d (6-CF_3)	$C_{15}H_9N_2O_2F_3$	168-170	85	58.82 58.63	2.94 2.76	9.15 9.26
1e (7-Br)	$C_{14}H_9N_2O_2Br$	167-169	82	53.00 52.91	2.84 2.76	8.83 8.61
1f (6,7-Cl_2)	$C_{14}H_8N_2O_2Cl_2$	177-179	78	54.72 54.75	2.61 2.38	9.12 9.06

B) 2b,c [3'-OH]

2b (6-F)	$C_{14}H_9N_2O_2F$	194-195	72	65.63 65.43	3.52 3.29	10.94 10.75
2c (6-Cl)	$C_{14}H_9N_2O_2Cl$	163-165	81	61.83 61.89	3.30 3.32	10.28 10.10

C) 3a-e [2'-OH]

3a (H)	$C_{14}H_{10}N_2O_2$	116-118	64	70.59 70.35	4.20 4.06	11.76 11.68
3b (6-F)	$C_{14}H_9N_2O_2F$	170-173	58	65.63 65.62	3.52 3.45	10.94 10.87
3c (6-Cl)	$C_{14}H_9N_2O_2Cl$	181-183	75	61.83 61.69	3.30 3.27	10.28 10.29
3d (6-CF_3)	$C_{15}H_9N_2O_2F_3$	140-144	73	58.82 58.76	2.94 2.85	9.15 9.07
3e (7-Br)	$C_{14}H_9N_2O_2Br$	179-183	68	53.00 52.91	2.84 2.86	8.83 8.85

EXPERIMENTAL SECTION

Nmr 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 Spectrometer. 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 1a-f, 2a-f and 3a-f. A mixture of dihydroxybenzene 5-7 (164 mmol) and anhydrous potassium carbonate (130 mmol) in DMF (400 ml) was stirred at 100 °C for 1.0 h under N_2 atmosphere. After cooling, substituted 2-chloroquinoxaline 4a-f (45 mmol) was added and stirring was continued at 120 °C for 3.0 h. After the reaction, DMF was evaporated under reduced pressure and the residue was dissolved in 5% NaOH solution (400 ml). Then, insoluble substances were filtered off and the filtrate was acidified with 2N HCl. The resulting solid was collected and washed with hot water to remove the unreacted dihydroxybenzene, next dried in vacuo. They were purified by the recrystallization from EtOH.

1a; ir(KBr): 3060, 1600, 1570, 1500, 1440, 1400, 1305, 1266, 1209, 1185, 1140, 998, 928, 839, and 762 cm^{-1}. pmr(DMSO-d_6) δ 7.00(2H, d, J= 9.6 Hz), 7.29(2H, d, J= 9.6 Hz), 7.45-8.35(4H, m), 8.93(1H, s), and 9.66(1H, s). ms m/z 238(M^+, base peak), 210, and 182.

1b; ir(KBr): 3175, 1618, 1572, 1500, 1488, 1332, 1309, 1208, 1006, and 838 cm^{-1}. pmr(DMSO-d_6) δ 6.83(2H, d, J= 9.6 Hz), 7.10(2H, d, J= 9.6 Hz), 7.28-7.92(3H, m), 8.73(1H, s), and 9.47(1H, bs).

1c; ir(KBr): 3220, 1600, 1560, 1502, 1439, 1388, 1308, 1208, 932, and 825 cm^{-1}. ms m/z 272(M^+), 244(base peak), 209, 182, and 110.

2b; ir(KBr): 3125, 1600, 1488, 1382, 1302, 1222, 1209, 1148, 1002, 968, 832, and 773 cm^{-1}. pmr(DMSO-d_6) δ 6.50-8.00(7H, m), 8.79(1H, s), and 9.72(1H, bs).

3c; pmr(DMSO-d_6) δ 6.62-7.32(5H, m), 7.53(1H, d d, J= 9.0, 3.0 Hz), 7.66(1H, d, J= 9.0 Hz), 7.99(1H, d, J= 3.0 Hz), and 8.71(1H, s). ms m/z 272(M^+, base peak), 255, 215, 180, 163, and 110.

3d; ms m/z 306(M^+, base peak), 289, 277, 249, and 197.

Preparation of 8c. A mixture of 5 (16.5 g, 150 mmol) and 4c (59.7 g, 300 mmol) in DMF (600 ml) in the presence of anhydrous potassium carbonate (62.2 g, 450 mmol) was stirred at 60 °C for 1.0 h. After cooling, the reaction mixture was poured into ice water (1.5 l). The resulting solid was collected and washed with 5% NaOH, next with water. It was dried in vacuo and purification was carried out to afford 8c in 97% yield. mp 260-261 °C. ir(KBr): 3375, 1600, 1564, 1490, 1439, 1388, 1372, 1302, 1209, 1180, 935, and 828 cm^{-1}. ms m/z 434(M^+, base peak), 406, and 378. Found: C, 60.65; H, 2.58; N, 12.80%. Calcd for $C_{22}H_{12}N_4O_2Cl_2$: C, 60.69; H, 2.76; N, 12.87%.

As the same manner, 8b was synthesized in 92% yield. mp 267-268 °C. ms m/z 402 (M^+, base peak), 374, and 346. Found: C, 65.59; H, 2.76; N, 13.90%. Calcd for $C_{22}H_{12}N_4O_2F_2$: C, 65.67; H, 2.99; N, 13.93%.

Preparation of 1b from 8b. A mixture of 8b (4.0 g, 10 mmol) and 5 (1.32 g, 12 mmol) in DMF (20 ml) in the presence of anhydrous potassium carbonate (3.5 g, 25 mmol) was stirred at 120 °C for 1.0 h. After cooling, the reaction mixture was worked up as mentioned above to afford 1b in 83% yield.

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