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REGIOSELECTIVE SYNTHESIS OF 2,6-DICHLOROQUINOXALINE AND 2-CHLORO-6-IODOQUINOXALINE

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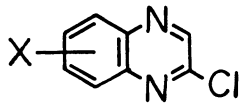
Facile regioselective synthesis of 2,6-dichloroquinoxaline and 2-chloro-6-iodoquinoxaline is described. Electrophilic substitution reaction of 2(1H)-quinoxalinone with chloride and iodide ion in 95% sulfuric acid occurred at 6-position exclusively.

Recently, monosubstituted derivatives of 2-chloroquinoxaline (A) have been used as intermediates for the synthesis of pharmaceutical and agricultural chemicals[1,2] and attracting much effort for their synthesis.



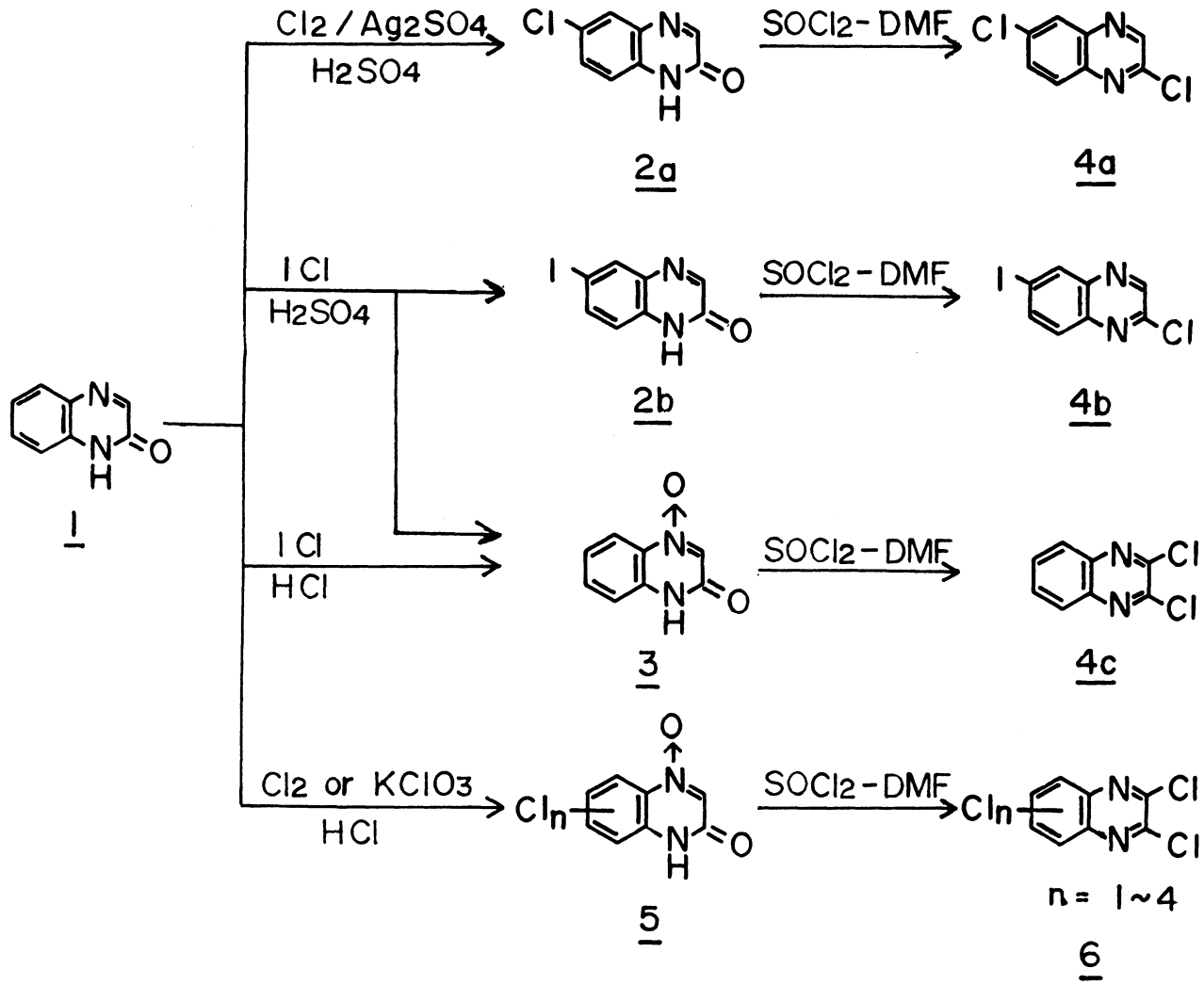
A X; F, Cl, Br, I, NO_2

Direct halogenation of 2(1H)-quinoxalinone (1) with chlorine or bromine in acetic acid has been known to occur at 7-position.[3] Meanwhile, 2-chloro-6-bromoquinoxaline has been synthesized by the reaction of bromine with 1 in the presence of silver sulfate[2] but the extensive study to prepare 2,6-dichloroquinoxaline (4a) has not been reported.

Now we elaborated facile methods for regioselective syntheses of 4a and 2-chloro-6-iodoquinoxaline (4b) from 1 with direct halogenation followed by Vilsmeier reaction.

A solution of 1 in 95% sulfuric acid was treated with chlorine in the presence of silver sulfate and afforded 6-chloro-2(1H)-quinoxalinone (2a), mp 306-308 °C, in 51% yield. When the reaction was carried out in the absence of silver sulfate, the chlorination of 1 did not occur at all. On the other hand, treatment of 1 in 95% sulfuric acid with iodine monochloride gave 6-iodo-2(1H)-quinoxalinone (2b) and 2(1H)-quinoxalinone-4-oxide (3) in 46 and 49%, respectively. In this reaction, iodine acted as an electrophile. Halogenation of 1 with chlorine and bromine in

acetic acid occurred at 7-position,[3] while chlorination in the presence of silver sulfate and iodination using iodine monochloride took place at 6-position in 95% sulfuric acid. Solvent controlled the orientation of electrophilic substitution reaction. 3 can also be derived from N-oxidation of 1. It is assumed that some oxidizing agent is generated *in situ* from iodine monochloride and water contained in 95% sulfuric acid. Actually, only 3 was obtained when 1 was reacted with iodine monochloride in 35% hydrochloric acid. The reaction of chlorine with 1 in 35% hydrochloric acid led to N-oxidation and subsequent mono-, di-, tri-, and tetra-



1 2a 4a 2b 4b 3 4c 5 6

Scheme 1.

chlorination. The same product (5) was obtained by the reaction of potassium chlorate with 1 in 35% hydrochloric acid. The condensation of 4-iodo-o-phenylenediamine with n-butyl glyoxylate under the same conditions to synthesize 6- and 7-chloro-2(1H)-quinoxalinone was not successful, because liberation of iodine occurred intensely.

The Vilsmeier reaction of 2a, 2b, and 3 with thionyl chloride in the presence of a catalytic amount of DMF afforded 4a,[6,7] 4b,[8] and 2,3-dichloroquinoxaline (4c),[9,10] respectively. The same reaction of 5 was also carried out and GC-MS analysis of the product indicated that it (6) consisted of pentachloroquinoxaline (5%), tetrachloroquinoxaline (69%), trichloroquinoxaline (17%), and dichloroquinoxaline (9%).

New compounds are listed in Scheme 1 and their structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, and Mass spectra compared with those of 6- or 7-halo-2-chloroquinoxaline.

References

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6) 2,7-Dichloroquinoxaline or 2,6,7-trichloroquinoxaline was not obtained. By-product was 2-chloroquinoxaline, which was derived from the non-reacted starting material.

7) Compound 4a:[11] total yield 41%, colorless solid, mp 154.0-155.0 °C[4]; ^{1}H-NMR ($CDCl_3$) δ 7.73(1H, d d, J= 8.9, 2.2 Hz), 7.96(1H, d, J= 8.9 Hz), 8.09(1H, d, J= 2.2 Hz), 8.77(1H, s); ^{13}C-NMR($CDCl_3$) δ 128.31(d), 129.68(d), 132.04(d), 136.02(s), 140.51(s), 141.29(s), 145.78(d), 147.61(s); m/z 198(M^+, base peak), 163(M^+-Cl), 136(M^+-Cl-HCN).

8) This new compound was prepared as the following procedure. To a homogenous solution of 1 (2.92 g, 20.0 mmol) in 40 ml of 95% sulfuric acid a solution of iodine monochloride (3.57 g, 22.0 mmol) in 15 ml of carbon tetrachloride was

added dropwise with continuous stirring at room temperature over a period of 30 min. After completion of the addition, stirring was continued for 15 h at room temperature. Then, iodine monochloride (3.57 g, 22.0 mmol) in 15 ml of carbon tetrachloride was further added dropwise at room temperature and the mixture was stirred continuously at room temperature for 5 h. The dark solution was slowly poured onto ice-water. The resulting solid was collected and washed with water and then dried in vacuo. The crude 2b was refluxed with 15 ml of thionyl chloride and a few drops of DMF for 1.5 h. After removal of excess thionyl chloride under reduced pressure, crude product was dissolved in chloroform and washed with 1% sodium hydroxide solution (twice), next with water (twice) and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was purified with column chromatography (silica gel, $CHCl_3$) to afford 2.15 g (37%) of 4b,[11] as a pale-yellow solid, mp 151.5-152.5 °C; ^{1}H-NMR($CDCl_3$) δ 7.75 (1H, d, J= 8.8 Hz), 7.98(1H, d d, J= 8.8, 1.8 Hz), 8.36(1H, d, J= 1.8 Hz), 8.73 (1H, s); ^{13}C-NMR($CDCl_3$) δ 97.46(s), 130.29(d), 137.44(d), 139.12(d), 139.99(s), 142.48(s), 145.35(d), 147.95(s); m/z 290(M^+, base peak), 163(M^+-I), 128 (M^+-I-Cl).

9) This compound was prepared by the reaction of 1 with iodine monochloride in 35% hydrochloric acid or in 95% sulfuric acid followed by Vilsmeier reaction in 71% or 47% yield, respectively.

10) Compound 4c[11] as a colorless solid: mp 150.5-151.5 °C[5]; ^{1}H-NMR($CDCl_3$) δ 7.64-8.10(4H, m); ^{13}C-NMR($CDCl_3$) δ 128.12(d), 131.10(d), 140.47(s), 145.24(s); m/z 198(M^+ base peak), 163(M^+-Cl), 128(M^+-diCl).

11) All compounds gave satisfactory elemental analyses.

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