Synthesis of 2,3-Dichloroquinoxalines *via* Vilsmeier Reagent Chlorination

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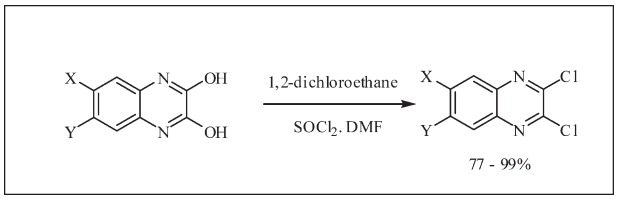

A convenient and high-yielding synthesis of 2,3-dichloroquinoxalines from the corresponding 2,3-dihydroxyquinoxalines has been developed. Treatment of a slurry of the 2,3-dihydroxyquinoxaline **1a–j** with *N*,*N*-dimethylformamide in the presence of excess thionylchloride in 1,2-dichloroethane results in the rapid and high-yielding formation of the 2,3-dichloroquinoxaline derivatives **2a–j**. Simplified workup and purification procedures for these compounds are also described.

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INTRODUCTION

The chemistry of 2,3-dichloroquinoxalines has received considerable attention in the past [1]. This class of compounds has previously been shown to exhibit a broad range of biological activity. For example, various derivatives of 2,3-dichloroquinoxalines have been shown to exhibit fungicidal and bactericidal activity [2]. They have also shown utility in industrial applications such as use as reactive dyes for fibers [3].

These dichloroquinoxaline compounds have traditionally been prepared by chlorination of the corresponding quinoxaline 2,3-diones (2,3-dihydroxyquinoxalines) with phosphorous-based chlorinating reagents. Phosphorus oxychloride ($POCl_3$) is the most common agent used, usually in the presence of an initiator such as *N*,*N*-dimethylaniline [4], or phosphorus pentachloride (PCl_5). However, the hazards of handling phosphorus oxychloride or phosphorus pentachloride are not to be taken lightly. Moreover, phosphorus containing waste streams is becoming increasingly difficult to dispose of in industrial settings.

Recently, Zimcik and coworkers [5] reported the synthesis of 2,3-dichloro-6,7-dicyanoquinoxaline from 2,3-dihy-droxy-6,7-dicyanoquinoxaline, using thionyl chloride in the presence of small amounts of *N*,*N*-dimethylformamide (DMF). Similarly, Tanaka and coworkers [6] has reported the synthesis of 2,3-dichloro-6-trifluoromethylquinoxaline from 2,3-dihydroxy-6-trifluoromethylquinoxaline with an excess of thionyl chloride ($SOCl_2$) in *N*,*N*-DMF as the solvent. In both of these cases, the actual chlorinating reagent is undoubtedly the Vilsmeier reagent, generated *in situ* from the reaction of *N*,*N*-DMF with thionyl chloride.

We have recently synthesized a series of 2,3-dichloroquinoxalines using a similar approach of generating the Vilsmeier reagent *in situ* by the addition of catalytic amounts of *N*,*N*-DMF to a slurry of 2,3-dihydroxyquinoxalines and thionyl chloride in 1,2-dichloroethane. Inspired by these earlier reports, we herein report the general utility of this reaction protocol and give experimental details for simplified workup and purification procedures for the synthesis of 2,3-dichloroquinoxalines *via* chlorination of 2,3-dihydroxyquinoxalines with the Vilsmeier reagent.

RESULTS AND DISCUSSION

2,3-Dichloroquinoxalines, **2** (Scheme 1), can be readily prepared by chlorination of 2,3-dihydroxyquinoxalines, **1**, which in turn can be prepared by the

Scheme 1

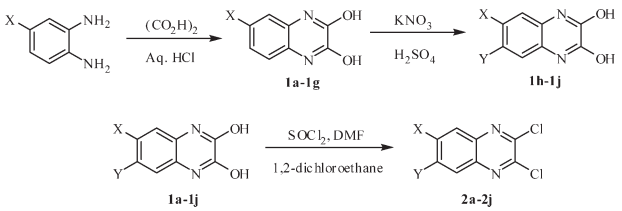

Table 1

Physical and analytical data of compounds **2a–j**.

Compound	X	Y	Time (h)	Mp (°C)	Yield (%)
2a	H	H	2	100–102[a]	95
2b	NO_2	H	4	152–153[a]	99
2c	Cl	H	4	144[a]	99
2d	CH_3	H	2	113–114[a]	93
2e	F	H	2	143–145[b]	98
2f	CN	H	2	239–240[b]	77
2g	CF_3	H	2	91–93[b]	81
2h	CH_3	NO_2	2	134–136[b]	95
2i	Cl	NO_2	0.5	135–137[b]	93
2j	NO_2	NO_2	0.5	210–212[b]	92

[a] Recrystallized from CH_3CN/H_2O.
[b] Filtered through SiO_2 with CH_2Cl_2.

condensation of commercially available 1,2-phenylenediamines with oxalic acid in aqueous hydrochloric acid (HCl) [1]. Mono and dinitroquinoxalines **1b** and **1h–1j** were prepared by nitration of the parent dihydroxyquinoxaline with one or two equivalents of potassium nitrate (KNO_3) in sulfuric acid (H_2SO_4) [7].

We have found that 2,3-dichloroquinoxalines **2a–2j** are readily formed by the drop wise addition of catalytic amounts of *N*,*N*-DMF (10 mol %) to slurry of the corresponding 2,3-dihydroxyquinoxalines **1a–1j** in 1,2-dichloroethene and an excess (2.5–3.0 molar equivalents) of thionyl chloride (Table 1).

In all cases, the desired 2,3-dichloroquinoxaline was rapidly formed by bringing the reaction mixture to reflux. After complete conversion, the reaction mixture was cooled to ambient temperature, followed by concentration to dryness. Purification of the desired product can then be readily accomplished by recrystallization of the crude product from acetonitrile/water, giving the desired 2,3-dichloroquinoxaline in high yield and purity. Alternatively, and particularly convenient for larger scale reactions, the residual material obtained after evaporation of the excess thionyl chloride and 1,2-dichloroethane can be purified by slurrying the initially isolated residue in water, followed by filtration and re-dissolving the crude product into methylene chloride (CH_2Cl_2) and filtering through a plug of silica gel.

There are several advantages to this method over those previously reported. First is that $SOCl_2$/DMF is considerably less expensive and less hazardous than using $POCl_3$/*N*,*N*-dimethylaniline. Also, in general, the reaction requires much shorter reaction times. For example, in our experiments, chlorination of **1c** with $POCl_3$/*N*,*N*-dimethylaniline required refluxing for 6 days for complete conversion and **2c** was obtained in 76% yield. In contrast, chlorination of **1c** with $SOCl_2$/DMF in 1,2-dichloroethane led to complete reaction within 4 h, giving a near quantitative yield of **2c**.

EXPERIMENTAL

General experimental procedures. All solvents and reagents were reagent grade and were used without further purification. ^1H and ^{13}C NMR spectra were obtained on a Varian XM-300 NMR. All yields reported are those of isolated material judged homogeneous by ^1H NMR.

General procedure for the synthesis of 2,3-dihydroxyquinoxalines 1a–j. ***2,3-Dihydroxyquinoxline (1a).*** A solution of oxalic acid (27.1 g, 0.215 mol) in 4*N* aqueous HCl (50 mL) was added to a solution of 1,2-diaminobenzene (20.9 g, 0.193 mol) in 4*N* HCl (150 mL), and the resulting solution was heated to reflux for 2 h. The reaction mixture was cooled to ambient temperature, and the resulting precipitate was isolated by filtration, washed with water, and dried, giving 30.5 g (98%) of **1a** as an off white powder, mp >300°C: ^1H NMR (DMSO-d_6): δ 11.90 (s, 2H), 7.13–7.04 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 155.12, 125.52, 122.91, 115.06.

General procedure for the nitration of 2,3-dihydroxyquinoxalines 1h–j. ***2,3-Dihydroxy-6-nitro-7-methylquinoxaline (1h).*** To a solution of 2,3-dihydroxy-6-methylquinoxaline (10.0 g, 0.0574 mol) in H_2SO_4 (124 mL) at 0°C was added, in several portions, KNO_3 (6.39 g, 0.0632 mol), and the resulting solution was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was carefully poured into 500 mL of ice/water, stirred 30 min, filtered, washed with water and dried, giving 12.2 g (96%) of **1h** as a pale yellow solid, mp >300°C. ^1H NMR (DMSO-d_6): δ 12.20 (s, 1H), 12.02 (s, 1H), 7.72 (s, 1H), 6.95 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 155.10, 154.47, 142.21, 130.10, 128.69, 124.05, 117.70, 111.60, 20.31.

General procedure for the chlorination of dihydroxyquinoxalines. ***2,3-Dichloroquinoxaline (2a).*** *N*,*N*-Dimethylformamide (0.045 g, 0.00062 mol, 0.1 eq) was added dropwise to a slurry of 2,3-dihydroxyquinoxaline (2.0 g, 0.012 mol) and thionyl chloride (3.7 g, 0.031 mol) in 1,2-dichloroethane (20 mL). The resulting reaction mixture was heated to reflux for 2 h then concentrated to dryness. The residue was dissolved in 1,2-dichloroethane (25 mL) and concentrated to dryness. The resulting solid was recrystallized from CH_3CN/H_2O, giving 2.3 g (95%) of **2a** as fine, off white needles, mp 100–102°C; ^1H NMR ($CDCl_3$): δ 8.10–8.06 (m, 2H), 7.98–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) 144.50, 139.92, 131.67, 127.81. *Anal*. Calcd. for $C_8H_4Cl_2N_2$: C, 48.28; H, 2.03; N, 14.07. Found: C, 47.87; H, 2.1; N, 14.00.

2,3-Dichloro-6-nitroquinoxaline (2b). This compound was prepared from *N*,*N*-DMF (0.11 g, 0.0014 mol), 2,3-dihydroxy-6-nitroquinoxaline (3.0 g, 0.0145 mol) and thionylchloride (4.31 g, 0.035 mol) in 1,2-dichloroethane (30 mL) as previously described, to give 3.52 g (99%) of **2b** after recrystallization (CH_3CN/H_2O) as a tan powder, mp 152–153°C; ^1H NMR (DMSO-d_6) (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 9.2, 2,5 Hz, 1H), 8.28 (d, J = 9.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) 148.18, 148.07, 147.28, 142.3, 138.83, 129.68, 124.74, 123.67. *Anal*. Calcd. for $C_8H_3Cl_2N_3O_2$: C, 39.37; H, 1.24; N, 17.22. Found: C, 39.11; H, 1.03; N, 16.99.

2,3,6-Trichloroquinoxaline (2c). This compound was prepared from *N*,*N*-DMF (0.074 g, 0.001 mol), 6-chloro-2,3-dihydroxyquinoxaline (2.0 g, 0.0102 mol), and thionylchloride (3.02 g, 0.025 mol) in 1,2-dichloroethane (10 mL) after 4 h reflux to give 3.52 g (99%) of **2c** after recrystallization from

CH_3CN/H_2O as yellow needles, mp 144°C; ^{1}H NMR (DMSO-d_6) 8.23 (d, J = 2.2 Hz, 1H), 8.12 (d, J = 8.9 Hz, 1H), 7.98 (dd, J = 9.0, 2.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) 145.87, 145.05, 140.28, 138.67, 135.91, 132.10, 129.57, 126.72, 126.72. *Anal*. Calcd. for $C_8H_3Cl_3N_2$: C, 41.15; H, 1.30; N, 12.00. Found: C, 40.83; H, 1.22; N, 12.20.

2,3-Dichloro-6-methylquinoxaline (2d). This compound was prepared from *N*,*N*-DMF (0.083 g, 0.0011 mol), 2,3-dihydroxy-6-methylquinoxaline (2.0 g, 0.012 mol) and thionyl chloride (3.38 g, 0.028 mol) in 1,2-dichloroethane (20 mL) after 2 h at reflux. Recrystallized from CH_3CN/H_2O to give 2.25 g (93%) of **2d** as fine, light tan colored needles, mp 113–114°C; ^{1}H NMR (DMSO-d_6): δ 7.94 (d, J = 8.3 Hz, 1H), 7.82 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 144.27, 143.39, 142.33, 139.97, 138.34, 133.72, 127.30, 126.54, 21.30. *Anal*. Calcd. for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84; N, 13.15. Found: C, 50.37; H, 2.88; N, 13.22.

2,3-Dichloro-6-fluoroquinoxaline (2e). This compound was prepared from *N*,*N*-DMF (0.41 g, 0.0056 mol), 6-fluoro-3-dihydroxyquinoxaline (10.0 g, 0.0555 mol) and thionyl chloride (16.5 g, 0.139 mol) in 1,2-dichloroethane (50 mL), and the resulting reaction mixture was heated at reflux for 2 h. The resulting solution was cooled to room temperature and concentrated to dryness. The resulting solid was slurried in water (150 mL) for 30 min, then filtered and dried. The residue was taken up in a minimum of CH_2Cl_2 and filtered through a short column of silica gel, eluting with CH_2Cl_2. Concentration then gave 11.75 g (98%) of **2e** as a pale yellow solid, mp 143–145°C; ^{1}H NMR (DMSO-d_6): δ 8.18 (dd, J = 9.2, 5.6 Hz, 1H), 7.95 (dd, J = 9.2, 2.7 Hz, 1H), 7.88 (dd, J = 8.4, 2.7 Hz, 1H). *Anal*. Calcd. for $C_8H_3Cl_2FN_2$: C, 44.27; H, 1.39; N, 12.91. Found: C, 44.03; H, 1.33; N, 12.88.

2,3-Dichloro-6-cyanoquinoxaline (2f). *N*,*N*-dimethylformamide (0.039 g, 0.0005 mol) was added dropwise to a slurry of 6-cyano-2,3-dihydroxyquinoxaline (1.0 g, 0.0054 mol) and thionyl chloride (1.6 g, 0.013 mol) in 1,2-dichloroethane (5 mL), and the resulting solution was heated at reflux for 2 h. The solution was cooled and concentrated. The residue was slurried in water (50 mL) for 30 min, then filtered and dried. The residue was taken up in a minimum of CH_2Cl_2 and filtered through a short column of silica gel, eluting with CH_2Cl_2. Concentration gave 0.92 g (77%) of **2f** as a light gray powder, mp 239–240°C; ^{1}H NMR ($CDCl_3$): δ 8.40 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H); 7.97 (dd, J = 8.7, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 147.58, 146.71, 141.42, 139.03, 133.74, 132.49, 129.35, 117.47, 113.51. *Anal*. Calcd. for $C_9H_3Cl_2N_3$: C, 48.25; H, 1.35; N, 18.76. Found: C, 48.22; H, 1.15; N, 18.57.

2,3-Dichloro-6-trifluoromethylquinoxaline (2g). This compound was prepared from *N*,*N*-DMF (0.19 g, 0.0026 mol), 2,3-dihydroxy-6-trifluoromethylquinoxaline (6.0 g, 0.026 mol) and thionyl chloride (7.8 g, 0.065 mol) in 1,2-dichloroethane (50 mL) after 2 h reflux to give 5.62 g (81%) of **2g** after filtration through a short column of silica gel, eluting with CH_2Cl_2, mp 91–93°C; ^{1}H NMR (DMSO-d_6): δ 8.50 (bs, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.20 (dd, J = 8.8, 2.0 Hz, 1H). *Anal*. Calcd. for $C_9H_3Cl_2F_3N_2$: C, 40.48; H, 1.13; N, 10.49. Found: C, 40.20; H, 1.15; N, 10.50.

2,3-Dichloro-7-methyl-6-nitroquinoxaline (2h). This compound was prepared from *N*,*N*-DMF (0.072 g, 0.00090 mol), 2,3-dihydroxy-6-nitro-7-methylquinoxaline (2.0 g, 0.00090 mol) and thionyl chloride (2.69 g, 0.023 mol) in 1,2-dichloroethane (5 mL) after 2 h at reflux to give 5.62 g (81%) of **2h** after filtration through a short column of silica gel, eluting with CH_2Cl_2, mp 134–136°C; ^{1}H NMR (DMSO-d_6): δ 8.66 (s, 1H), 8.18 (s, 1H), 2.67 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 150.56, 147.81, 146.48, 140.94, 137.57, 134.57, 130.88, 123.65, 19.00. *Anal*. Calcd. for $C_9H_5Cl_2N_3O_2$: C, 41.89; H, 1.95; N, 16.28. Found: C, 41.93; H, 1.22; N, 16.50.

2,3,6-Trichloro-7-nitroquinoxaline (2i). This compound was prepared from *N*,*N*-DMF (0.364 g, 0.0050 mol), 2,3-dihydroxy-6-chloro-7-nitroquinoxaline (12.0 g, 0.0498 mol) and thionyl chloride (14.8 g, 0.124 mol) in 1,2-dichloroethane (50 mL) after 30 min at reflux to give 12.8 g (93%) of **2i** as a golden yellow powder after filtration through short column of silica gel, eluting with CH_2Cl_2, mp 135–137°C; ^{1}H NMR (DMSO-d_6): δ 8.89 (s, 1H), 8.58 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 148.72, 148.58, 147.62, 140.88, 138.01, 130.35, 126.02, 124.72. *Anal*. Calcd. for $C_8H_2Cl_3N_3O_2$: C, 34.50; H, 0.72; N, 15.09. Found: C, 34.52; H, 0.81; N, 15.11.

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