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A NEW SOLVENT FOR THE REACTION OF CHLORINATION OF HYDROXYQUINOXALINE DERIVATIVES WITH VILSMEIER REAGENT

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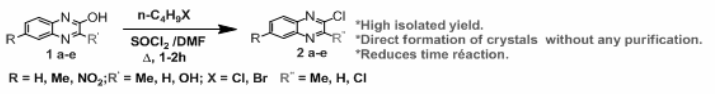
A new efficient procedure for the chlorination of hydroxyquinoxaline derivatives into the corresponding chlorides is described. It has been found that the use of 1-chlorobutane produces the highest yield, reduces the time of reaction and facilitates direct formation of crystals without any purification.



INTRODUCTION

Quinoxaline derivatives represent one of the most biologically active classes of compounds,[1,2] possessing a wide and diverse spectrum of pharmacological properties,[3-7] such as antibiotic, antiviral, anti-cancer and anti-inflammatory activities.[8-11] Besides this, halogenoquinoxalines are extensively utilized heterocyclic, due to their ready availability as well as their stability, which makes them useful precursors in dyes, pharmaceuticals, and agrochemical industries.[12]

Synthetic strategies of substituted halogenated quinoxalines have previously been developed by several workers: Phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride (PCl_5) are the most common agent used.[13] Recently, Zimcik[14] reported the synthesis of 2,3-dichloroquinoxaline derivatives from 2,3-dihydroxyquinoxalines using thionyl chloride in the presence of small amounts of N,N-dimethylformamide (DMF). Similarly, as described by Tanaka[15] and Romer[16] the synthesis of halogenated quinoxaline is performed with an excess of thionyl chloride ($SOCl_2$) and N,N-DMF in 1,4-dioxane or dichloroethane as solvent, respectively. Nevertheless, most of these methods suffer from unsatisfactory product yields, critical product isolation procedures, expensive and harsh reaction conditions.

In this work, different 2,3-dichloroquinoxaline and 2-chloroquinoxaline derivatives were synthesized using a similar approach of generating the Vilsmeier reagent *in situ*. In order to improve the yield and time reaction for the chlorination of hydroxyquinoxaline derivatives, the Tanaka method[15] has been modified, by using 1-chlorobutane or 1-bromobutane as a solvent with different quantities of DMF (Figure 1).

RESULTS AND DISCUSSION

The synthesis of quinoxaline derivatives **1b-d** is summarized in Scheme 2. Hydroxyquinoxaline derivatives were synthesized by a one-step reaction of several substituted *o*-phenylenediamine with oxalic acid, or pyruvic acid, in accordance with the procedure reported in the literature.[17] (Figure 2)

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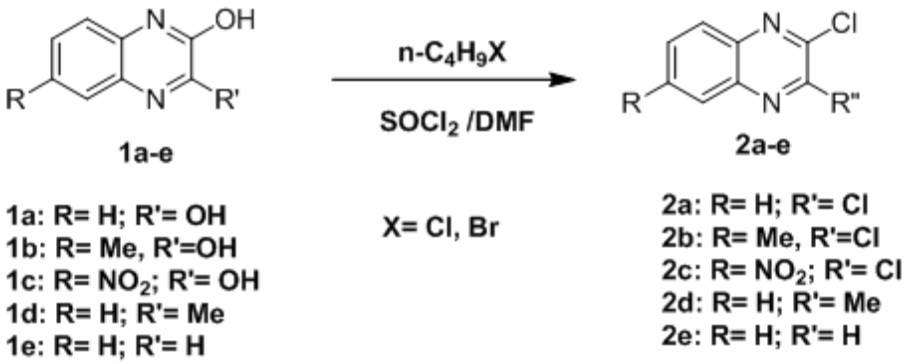


Fig. 1 – Chlorination of hydroxyquioxaline derivatives **1a-e**.

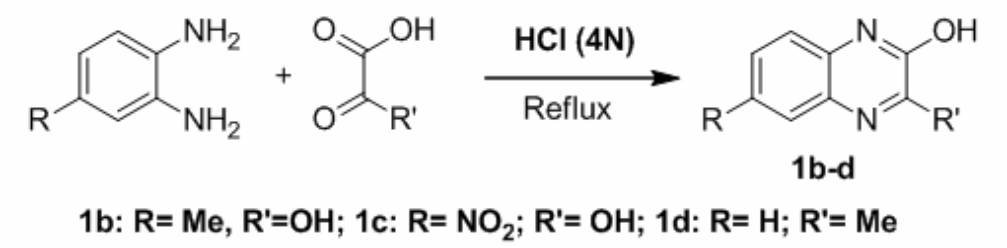
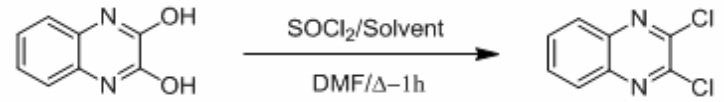


Fig. 2 – Preparation methods of hydroxyquinoxaline derivatives **1b-d**.

Table 1

Optimization of reaction conditions [a]



Entry	DMF (mol %)	Solvent	Time(h)	Yield (%)
1	4	Dioxane	3	85[15]
2	10	1,2-Dichloroethane	2	95[16]
3	4	1-Chlorobutane	1	50
4	4.5	1-Chlorobutane	1	55
5	5	1-Chlorobutane	1	76
6	5.5	1-Chlorobutane	1	98
7	6	1-Chlorobutane	1	95 [b, c]
8	4	1-Bromobutane	3	33[c]
9	4.5	1-Bromobutane	3	42[c]
10	5	1-Bromobutane	3	65[c]
11	5.5	1-Bromobutane	3	93[c]
12	6	1-Bromobutane	3	90[b, c]

[a] Reaction conditions: 2,3-dihydroxyquinoxaline (3.1mmol), solvent (5mL), thionyl chloride (2equiv.), reflux (79-100 °C).
[b] excess of DMF.
[c] Recristallized in Toluene.

Table 2

Chlorination of hydroxyquioxaline derivatives **1a-e**

Entry	Substrate	Product	1,2-dichloroethane[16]		1-chlorobutane		1-bromobutane	
			Time(h)	Yield (%)	Time(h)	Yield (%)	Time(h)	Yield (%)
1	1a	2 a	2	95 [c]	1	98	3	93
2	1b	2b	2	93 [c]	1	96	3	92

Table 2 (continued)

3	1c	2c	4	99 [c]	2	93	3	70
4	1d	2d	-	-	15 min	25 [a, b]	-	-
5	1e	2e	-	-	15 min	35 [a,b]	-	-

[a] after 20 min the reaction mixture became dark and the chlorination is not completed.
[b] conditions: 0°C, 25°C, 79-100°C.
[c] Recrystallized from CH_3CN/H_2O.

This paper investigates the optimization of chlorination reaction conditions reported by Tanaka in 1992. 2,3-Dihydroxyquinoxaline **1a** was mixed with 2.0 equiv of thionyl chloride in 1-chlorobutane as solvent, and 4 mol% of DMF. The mixture was smoothly transformed leading to a maximum yield of 50% in 1 hour. Increasing the amount of DMF to 5.5 mol% is obviously favorable to improve the yield up to 98 % (Table 1, entry 6). The same procedure was applied for the chlorination reactions in 1-bromobutane (Table 1, entries 8–12). On the other hand, lowering the amount of DMF less than 4 mol% is obviously unfavorable for this reaction, and subsequently no reaction occurred in the absence of DMF under the same conditions.

2,3-Dichloroquinoxalines **2b–c** were readily formed by the drop wise addition of catalytic amounts (5.5mol%) of DMF to the corresponding 2,3-dihydroxyquinoxalines **1b–c** in 1-chlorobutane and thionyl chloride (Table 2). It has been found that the use of 5.5mol% of N,N-DMF produces the best yield, time. On the other hand, 1-chlorobutane facilitates direct production of crystals without any purification. These products can be prepared in 1-bromobutane as solvent, the desired 2,3-dichloroquinoxaline **2a-c** were formed by heating the reaction mixture to reflux during 3 hours, the mixture was cooled to ambient temperature, followed by concentration to dryness. The resulting products were purified by recrystallization of the crude product in toluene or CH_3CN/H_2O yielding 70% to 93%. Also, it should be mentioned that other alkyl halides were tested as solvent, but only trace of desired halogenated quinoxaline was obtained. Other typical reaction parameters, such as reaction temperature and concentration of the reactant, were also investigated in this chemical transformation; however, no significant improvement in yield was obtained.

Compared to 1,2-dichloroethane[16], it has been found that the use of 1-chlorobutane reduces time reaction to half as illustrated in table 2, and facilitates direct formation of crystals without any purification. Also, the incorporation of halogen substituted solvent decreases reaction time in the order Cl < Br.

However, various attempts to chlorinate 2-hydroxy-3-methylquinoxaline (**1d**) or 2-hydroxy quinoxaline (**1e**) with thionyl chloride and DMF in 1-chlorobutane under different conditions gave only 25% to 35 % of the halogenated quinoxalines **2d-e** during 15 min (Table 2). A slightly brownish powder appeared during the heating, which become dark and the chlorinated derivative disappeared after 30 min. The same reaction was repeated at 0 °C and 25 °C, traces of solid were obtained after 24 hours.

During this investigation, a new method has been established to improve the yield and gain time for the synthesis of 2,3-dichloroquinoxaline. Also, the results show that the nature of the functional group on the aromatic ring of the substrate exerted a strong influence on the time and the reaction yield (the presence of an electron-withdrawing functional group (NO_2) increases time). It can be concluded that the type of alkyl halides and the quantity of DMF have a great influence on yield and reducing time. For example, chlorination of **1a** take 1 hour in 1-Chlorobutane instead of 3 hours in 1,4-dioxane and 2 hours in 1,2-dichloethane.

EXPERIMENTAL

Melting points were measured using a melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-84005 PC spectro-photometer in KBr discs (υ max in cm^{-1}). ^1H NMR and ^{13}C NMR spectra in $CDCl_3$ and DMSO were recorded on a Bruker Avance DPX instrument at 350 MHz and 100 MHz, respectively; chemical shifts are recorded in δ values and coupling constants *J* in Hz. Hydroxyquinoxalines derivatives **1a** and **1e** were commercially available (Sigma-Aldrich). According to the literature methods,[17] the quinoxaline derivatives (**1b-d)** were synthesized using several substituted *o*-phenylenediamines with oxalic acid, or pyruvic acid.

General procedure for the chlorination of dihydroxy-quinoxalines in 1-chlorobutane:

N,N-Dimethylformamide (0.5 mg, 0.0673 mmol) was added dropwise to a slurry of 2,3-dihydroxyquinoxaline (2.0 g,

12.3 mmol) and thionyl chloride (2.92 g, 24.6 mmol) in 1-chlorobutane (20 mL). The mixture was refluxed for 1h. Then cooled to ambient temperature, the obtained needles were filtered, washed with ethyl ether, and dried.

*2,3-Dichloroquinoxaline (**2a**)*: white needles, yield 98%; mp 100–102 °C(lit. [16] m.p. 100–102 °C); FT-IR (KBr, cm^{-1}): 3049, 1618, 1562,753; ^{1}H NMR (350 MHz, $CDCl_3$): δ 8.07–8.02 (m, 2H, ArH), 7.85–7.80 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): 143.3, 140.9, 131.6, 127.8. Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 48.28; H, 2.03; N, 14.07. Found: C, 47.52; H, 1.89; N, 14.15.

*2,3-Dichloro-6-methylquinoxaline (**2b**)*: Gray needles; yield 96%; mp 112–114 °C(lit. [16] m.p. 113–114 °C) FT-IR (KBr): 2927, 1625,826; ^{1}H NMR (350 MHz, $CDCl_3$): δ 7.92 (d, *J*= 8.5, 1H, ArH), 7.80 (s, 1H, ArH), 7.63 (dd, *J*= 8.5, *J*= 1.5, 1H, ArH), 2.60 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 145.5, 144.6, 142.4, 141.0, 139.3, 133.7, 127.9, 127.4, 22.1; Anal. Calcd. for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84; N, 13.14. Found: C, 50.57; H, 2.59; N, 12.90.

*2,3-Dichloro-6-nitroquinoxaline (**2c**)*: pink needles; yield 93%; mp 152–153 °C (lit. [16] m.p. 152–153 °C); FT-IR (KBr): 3485,3095 ,733; ^{1}H NMR (350 MHz, $CDCl_3$): δ 7.87 (d, *J*= 9.0, 1H, ArH), 7.76 (s, 1H, ArH), 7.70 (dd, *J*= 9.0, *J*= 2.0, 1H, ArH); ^{13}C NMR ($CDCl_3$): 143.3, 140.9, 131.6, 127.8. Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 39.37; H, 1.23; N, 12.21. Found: C, 38.92; H, 1.08; N, 12.54.

General procedure for the chlorination of mono hydroxy quinoxalines in 1-chlorobutane:

0.13 mL of N,N-dimethylformamide was added dropwise to a slurry monohydroxy quinoxaline **1d-e** (0.5g, 3.1 mmol) and thionyl chloride (0.73 g, 6.2 mmol) in 1-chlorobutane (5 mL). The resulting reaction mixture was refluxed for 15 min., and then evaporated to dryness under reduced pressure to leave a solid. The residue was taken up in a minimum of CH_2Cl_2, filtered and washed with CH_2Cl_2. Concentration then give the halogenated derivatives.

2-Chloro-3-methyl quinoxaline (**2d**): pink needles; yield 35%; mp 87–88 °C (lit. [18] m.p. 83–87 °C); ^{1}H NMR (350 MHz, $CDCl_3$): δ 8.07-7.97 (m, 2H, ArH); 7.80-7.73 (m, 2H, ArH); 2.86 (s, 3H, CH_3).

Chloroquinoxaline (**2e**): white needles; yield 35%; mp 48 °C (lit. [19] m.p. 46–47 °C); ^{1}H NMR (350 MHz, $CDCl_3$): δ 8.10 (s, 1H, H_3), 7.75 (dd, 1H, ArH),7.55 (ddd, H, ArH); 7.30 (m, 2H, ArH).

General procedure for the chlorination of 2,3-dihydroxy-quinoxalines in 1-bromobutane:

To a suspension of 2,3-dichloroquinoxalines **2a-c** (0.5 g, 3.1 mmol) in bromobutane (5 mL) were added DMF (0.12 mg, 0.00168 mmol) and thionyl chloride (0.73 g, 6.2 mmol). The mixture was heated at 100 °C for 3 hours with stirring and then evaporated to dryness under reduced pressure to leave a solid. The residual solid was recrystallized from toluene to give needles.

CONCLUSION

It is very interesting to conclude that thionyl chloride combined with DMF in 1-chlorobutane on the chlorination reaction is a useful method, applicable to all types of 2,3-dihydroxy quinoxaline. The obtained results correlate well with estimates by other methods such as good yield, faster reaction times, and direct formation of crystals.

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