A Rapid and Efficient Method for the Reduction of Quinoxalines

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Mono and di-substituted alkyl and aryl quinoxalines are rapidly reduced in high yield to their respective 1,2,3,4-tetrahydro-derivatives by borane in THF solution. In the case of the 2,3-di-substituted compounds, reduction is stereoselective yielding exclusively the *cis*-isomers. Sodium borohydride in acetic acid also reduces alkyl and aryl quinoxalines, but proceeds with lower yields and often produces side products. Sodium borohydride in ethanol reduces quinoxaline and 2-methylquinoxaline in high yield; however, the reaction is very slow, whereas 2,3-dialkyl and 2-aryl quinoxalines are not efficiently reduced by sodium borohydride in ethanol.

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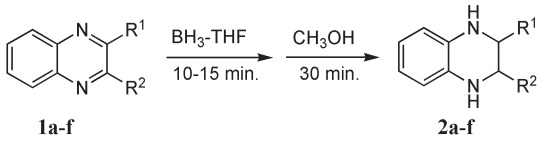
General interest in tetrahydroquinoxaline derivatives is due to their biological activities. Compounds that possess this ring system have recently been studied as potential vasorelaxants [1], anticonvulsants [2] and anti-HIV agents [3]. One approach to obtaining these compounds is direct reduction of the parent quinoxalines. Classical reagents for the conversion of quinoxalines to 1,2,3,4-tetrahydroquinoxalines include lithium aluminum hydride [4] and catalytic hydrogenation [4, 5]. Both methods proceed with moderate to good yields but require substantial purification procedures and extended reaction times. In fact, we found a significant amount of starting quinoxaline unconsumed by LAH even after increasing the stipulated reaction time to six to twelve hours. More recently, the use of titanium chloride [6] or indium powder [7], yields mixtures of stereoisomers and offer no experimental improvement. We were considerably more intrigued by sporadic reports over the last three decades that featured the use of various boron reagents for the reduction of the diazine ring in the quinoxaline system. However, results from these prior studies were somewhat difficult to interpret. For example, pyridine-borane in acetic acid solution at room temperature after seven hours was shown to reduce **1a** in 95% yield, while trimethylamine-borane was apparently ineffective [8]. Subsequently, 2-aminopyrimidine-borane was used for this same transformation [9] but the reported yield was only 54%. Use of the borohydride ion has a similar history. In 1973, Rao stated [10] that quinoxaline was unaffected by sodium borohydride in methanol, but showed that this reagent in acetic acid reduced quinoxalines in moderate to good yields, in the presence of an electron-withdrawing substituent on the fused benzene ring. Later papers demonstrated that both potassium borohydride in carboxylic acid media [11] and sodium cyanoborohydride with benzyl chloroformate in methanol [12] effectively reduced **1a** but were accompanied by, respectively, alkyaltion or acylation at nitrogen.

Scheme 1



We report herein that borane in THF rapidly converts **1a-f** to **2a-f** (Scheme 1). As demonstrated in Table I, the reactions proceed in excellent yields and the reductions involving **1c** and **1f** are highly stereoselective, resulting in the syn addition of hydrogen to give **2c** and **2f**. We also examined sodium borohydride as a reducing agent for **1a-f** and are now able to clarify prior ambiguities. In ethanol, sodium borohydride slowly reduces **1a** and **1b** to give excellent yields of **2a** and **2b**. In addition, we have extended the procedure of Rao [10] by using sodium borohydride in acetic acid to reduce simple alkyl and aryl quinoxalines in moderate to good yields. Data for the sodium borohydride reductions is summarized in Table II.

High yields and fast reaction times render borane-THF a superior reagent for the transformation of **1** to **2**. Solutions of borane-THF can be generated from the addition of iodomethane to lithium borohydride [13] and this technique (Method A) produces products that are indistinguishable from those obtained from commercially available borane-THF solutions (Method B). In the two cases examined (Table I) the non-optimized yields of **2c** and **2f** prepared using Method A are marginally higher than those obtained for the identical products

Table I

Reduction of Quinoxalines **1a-f** with BH_3-THF (Methods A and B)

Compound	R^1	R^2	Yield (%) [a]	M^+ (m/z)	Mp (°C)
2a	H	H	91	134 ($C_8H_{10}N_2$)	96-97
2b	CH_3	H	99	148 ($C_9H_{12}N_2$)	68-69
2c	CH_3	CH_3	88 (79) [b]	162 ($C_{10}H_{14}N_2$)	103-104 [c]
2d	Phenyl	H	81	210 ($C_{14}H_{14}N_2$)	65-66
2e	2-Thienyl	H	90	216 ($C_{12}H_{12}N_2S$)	81-82
2f	Phenyl	Phenyl	81 (74) [b]	286 ($C_{20}H_{18}N_2$)	145-146

[a] isolated products from Method A, yields from Method B in parenthesis; [b] product was exclusively the *cis* isomer; [c] for product from Method B, mp 109-111 °C

Table II

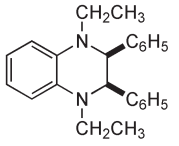
Reduction of Quinoxalines **1a-f** with $NaBH_4$ in Various Solvents

Compound	R^1	R^2	EtOH [a] (% Yield)	AcOH [b] (% Yield)
2a	H	H	99	77
2b	CH_3	H	92	81
2c	CH_3	CH_3	25 [c,d]	71 [c]
2d	Phenyl	H	30 [d]	66
2e	2-Thienyl	H	30 [d]	79
3	Phenyl	Phenyl	-	77 [e]

[a] Method C;[b] Method D;[c] product contains both *cis* and *trans* isomers;[d] estimated from product mixture by ^{1}H NMR;[e] isolated product is **3**.

using Method B. The high purity (> 97%) of all products isolated from the borane-THF reductions using either method is confirmed by GC/MS analysis with one exception. Compound **2c**, when prepared by Method A, shows starting material to be present (*ca*. 10%). This problem is not encountered when using Method B. It should be noted, that in either case **2c** is identical to *cis*-1,2,3,4-tetrahydro-2,3-dimethylquinoxaline prepared by reduction with LAH using the procedure of DeSelms and Mosher [4].

The use of sodium borohydride in acetic acid (Method D) is complicated by the fact that reduction of **1c** under these conditions led to a mixture of stereoisomers. The isomers are readily distinguished in the ^{1}H NMR spectrum by the methine protons, which occur at δ 3.1 (*trans*) and δ 3.5 (*cis*). Integration of these signals indicates that the mixture is predominantly composed of the *cis*-isomer (87%). Moreover, reduction of **1f** in acetic acid media did not lead to **2f**, but rather gave rise to **3**, in 77% yield. The nonequivalence of the ethylene protons in the ^{1}H NMR spectrum of this compound is presumably due to slow conformational changes caused by the bulky substituents.



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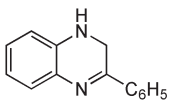
Addition of one equivalent of acetic acid to sodium or lithium borohydride in ethereal solvents yields hydrogen and either $MB(OAc)_4$ or $MBH(OAc)_3$ [13]. The latter was considered to be the active reducing agent in prior studies involving conditions similar to those described in Table II [14]. In any case, it is obvious from the difference in stereochemical outcomes for the reduction of **1c**, that $NaBH_4$ in glacial acetic acid is a considerably different reagent than borane-THF. It is possible that quinoxaline is protonated by acetic acid prior to reduction in a manner resembling that suggested by Gribble [15] for the reduction of indole in this medium. Like **1f** in this study, the reduction of indole was accompanied by alkylation at nitrogen when $NaBH_4$-HOAc was used. No alkylated products are formed when borane-THF is used as the reducing agent.

Reaction of **1a** or **1b** with sodium borohydride in ethanol (Method C) is extremely slow, requiring five days and a large excess of reducing agent for the complete consumption of the starting material in both cases. It is not a useful method for the reduction of **1c-e**. Reaction of **1c** is incomplete after five days. The ^{1}H NMR spectrum indicates only 25% of the staring material is converted to products, which include both *cis* and *trans* stereoisomers in this case. Treatment of **1d** with excess borohydride for five days leads to a mixture at least three components. The ^{1}H NMR spectrum shows signals characteristic of 1,2-dihydro-3-phenylquinoxaline, **4** [16], and **2d**, as well as, the starting



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material. Analogous results are produced by the reaction of **1e** under these conditions. We did not attempt to separate the mixtures, nor did we attempt to use **1f** as a substrate.

In conclusion, borane-THF, either generated *in-situ* from iodomethane and lithium borohydride, or from commercially available solutions in THF is a rapid, efficient and stereoselective reagent for the complete reduction of the diazine ring in the quinoxaline system.

EXPERIMENTAL

Quinoxalines were purchased from the Aldrich Chemical Co. and used as received with the exception of **1e** which was prepared from 2-thienylglyoxal [17] by the method of Billman [18]. NMR spectra were obtained from a JEOL spectrometer nominally operating at 500 MHz for hydrogen and 125 MHz for carbon 13. FTIR spectra were obtained as solutions in CH_2Cl_2 using a Nicolet Impact 400 spectrometer. Mass Spectra were obtained using a Hewlett-Packard 5973 MSD instrument.

General Procedure for the Reduction to 1,2,3,4-Tetrahydroquinoxalines (**2a-f**) Using Borane-THF.

Method A.

Under a nitrogen atmosphere, iodomethane (3.1 mmol) was added to a stirred mixture of lithium borohydride (3.4 mmol) and anhydrous THF (5 ml) in a water bath at room temperature. After 10 minutes vigorous effervescence had completely ceased and **1** (1.0 mmol) in anhydrous THF (10 ml) was added *via* syringe and stirred for 10-15 minutes. To the resulting solution, methanol (5 ml) was added (vigorous effervescence) and the solution was stirred for an additional 30 minutes. The solvents were evaporated and the residue was dissolved in methanol (10 ml) and evaporated. The residue was taken up in dichloromethane (15 ml) and aqueous NaOH (3 *M*, 30 ml). After separation, the aqueous layer was thoroughly extracted with additional dichloromethane (4 x 15 ml). The combined organic layers were dried with potassium carbonate, filtered and evaporated. The materials obtained were either solids, which were not further purified, or viscous oils, which crystallized upon triturating with pentane. Compounds were then analyzed by GC/MS and part of this data is presented in Table I. The physical and spectroscopic properties of compounds **2a** [19], **2b** [20], **2c** [4], **2d** [16] and **2f** [4] are consistent with those previously reported.

Method B.

To a stirred THF (5 ml) solution of **1** (1.0 mmol) under a nitrogen atmosphere in a water bath at ambient temperature was added borane THF solution (2.5 ml, 1.0 *M*). After 15 minutes methanol (5 ml) was added (vigorous effervescence) and the clear solution was stirred for 30 minutes. Further treatment was identical to that given above in Method A. Characterization of compounds **2c** and **2d** [21] prepared by this method is fully consistent with data obtained using Method A.

1,2,3,4-Tetrahydro-2-(2'-thienyl)quinoxaline (**2e**).

This compound, prepared by Method A, was shown to be 97.5 % pure by gc/ms, mp 86-87 °C; ir: NH 3390 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.41-3.43 (dd, 1H, *trans* 3-H, J = 7.5, 12.5 Hz), 3.53-3.55 (dd, 1H, *cis* 3-H, J = 2.9, 12.5 Hz), 3.95 (br s, 2H, N-H), 4.82-4.84 (dd, 1H, 2-H, J = 2.9, 7.5 Hz), 6.5-7.3 (m, 7H, ArH); ^{13}C nmr: δ 49.5, 50.7, 114.9, 119.2, 124.2, 125.0, 126.8, 128.6, 129.2, 130.0, 133.1, 145.7; ms: m/z 216 (M^+), 133 (M^+- C_4H_3S), 97 (C_5H_5S).

Anal. Calcd. for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.26; H, 5.23; N, 12.57.

General Procedure for the Reduction of Quinoxalines Using Sodium Borohydride in Ethanol.

Method C.

Solid sodium borohydride (2.5 mmol) was added to a stirred mixture of the quinoxaline (1.0 mmol) in ethanol (10 ml). The reaction was purged with nitrogen, attached to mineral oil bubbler and stirred for three days at ambient temperature. A second portion of sodium borohydride (2.5 mmol) was added along with 10 ml of ethanol. The mixture was purged with nitrogen and stirring was continued for an additional 2-3 days. The solvent was evaporated and the residue partitioned between aqueous NaOH (3 *M*, 30 ml) and dichloromethane (15 ml). The aqueous layer was extracted with dichloromethane (4 x 15 ml) and the combined organic layers were dried, filtered and evaporated. The residue was dissolved in $CDCl_3$ and evaluated by ^1H NMR spectroscopy.

Method D.

Reductions using sodium borohydride in acetic acid generally followed the procedure of Rao [10], but CH_2Cl_2 rather than chloroform was used for extractions and aqueous acetic acid solutions were made basic prior to extraction. Product identity was confirmed by comparison of physical and spectroscopic data with literature values.

1,4-Diethyl-2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline (**3**).

Sodium borohydride was added in small portions to a well-stirred solution **1f** (0.232 g, 0.82 mmol) in glacial acetic acid (20 ml) at 10-15 °C until TLC (CH_2Cl_2/EtOAc, 3:1) indicated the starting material was completely consumed. Water (80 ml) was added and the solution was extracted with CH_2Cl_2 (30 ml). The aqueous layer was made basic with solid NaOH and extracted (3 x 15 ml). The combined organic layers were dried and the solvent was evaporated. The residue was purified by silica gel chromatography (eluted with hexanes/EtOAc, 10:1) to give 0.214 g of a waxy solid (77%), mp 130-133; ^1H nmr (deuteriochloroform): δ 0.90-1.00 (m, 6H, N-Et), 3.09-3.10 (m, 2H, N-Et), 3.37-3.38 (m, 2H, N-Et), 4.21 (s, 2H, *cis* CH), 6.75-7.26 (m, 14H, ArH); ^{13}C nmr: δ 11.0, 43.2, 64.9, 111.8, 118.0, 127.3, 127.5, 129.5, 135.2, 139.3; ms: m/z 342 (M^+), 313 (M^+- C_2H_5), 91 (C_7H_7).

Anal. Calcd. for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.35; H, 7.35; N, 8.05.

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[21] For example, compound **2d** was prepared by *Method B* in 74% yield, mp 145 °C. *Anal*. Calcd. for $C_{14}H_{14}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.47; H, 6.02; N, 9.37.