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An Efficient Synthesis of 2-Quinoxalinecarboxylic Acid

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Abstract:

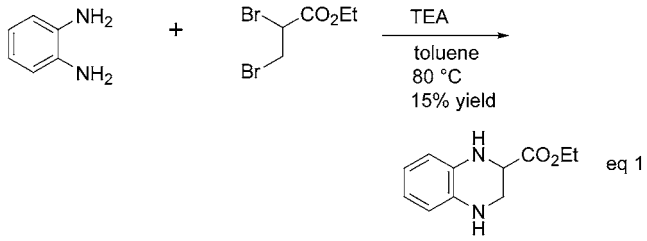
Development of a cost efficient and scaleable process for 2-quinoxalinecarboxylic acid is described. The primarily goals of the development work were to improve the overall yield of the process, to minimize the use of environmentally unacceptable materials, and to obtain a material with a high level of purity. A variety of approaches were examined, and the most efficient method was a condensation of *o*-phenylenediamine with a monosaccharide followed by a mild peroxide oxidation.

Introduction

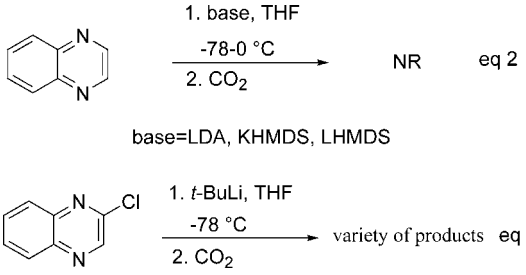
The 2-substituted quinoxaline skeleton is a relatively unexploited heterocycle in drug discovery. Only a few examples of its use are found in the literature.[1−3] The synthesis of 2-quinoxalinecarboxylic acid has been reported many times in the chemical literature, as early as 1935.[4] Other synthetic methods for the preparation of quinoxalinecarboxylic acid include the oxidation of a nitroalkyl[4] or alkenyl[5] substituent, usually with potassium permanganate- or silver(I)-mediated hydrolysis of a tribromomethyl side chain.[7] Synthesis utilizing biocatalytic oxidation of 2-methylquinoxaline has also been described.[8] A latent form of carboxylic functionality is the 2-furyl group, which can easily and quantitatively be cleaved by potassium permanganate to yield the corresponding quinoxalinecarboxylic acid.[4] Another approach, which has had the most success, involves the reaction of *o*-phenylenediamine with monosaccharides[9a−d] followed by the oxidation of the resulting condensed product.[10,11] However, the yield of the condensation step has been poor (∼15−30%). In some other publications, the hydrazone/osazone[7] of a sugar is utilized. For example, fructose was converted to the fructose osazone/hydrazone and condensed with *o*-phenylenediamine to provide a moderate yield of the quinoxaline skeleton. While some of these methods worked rather well, they required materials that would be difficult to handle on large scale, namely the hydrazine starting materials. In addition to the handling of the toxic starting materials, large quantities of the hydrazone would be present in the waste stream.

Results

In the development of an efficient route to 2-quinoxalinecarboxylic acid, we examined a number of different approaches. One of the first routes investigated the straightforward approach of alkylating *o*-phenylenediamine with ethyl 2,3-dibromopropanoate in the presence of triethylamine (TEA, eq 1). Unfortunately, the reaction resulted in an unacceptable yield of material that required a difficult purification.



Deprotonation of quinoxaline with a variety of bases (lithium diisopropylamide (LDA), potassium and lithium bis(trimethylsilyl)amide (KHMDS and LHMDS, respectively)) with subsequent quench using carbon dioxide failed to provide any desired quinoxalinecarboxylic acid (eq 2). In a similar approach, 2-chloroquinoxaline was submitted to conditions of lithium−halogen exchange (eq 3). Under these conditions, the starting material was consumed with no detection of the desired quinoxalinecarboxylic acid.



Another approach employing 2-chloroquinoxaline was to displace the chloride with a nitrile. A neat mixture of

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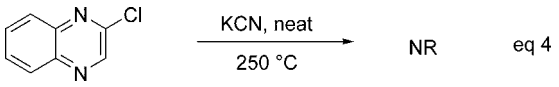
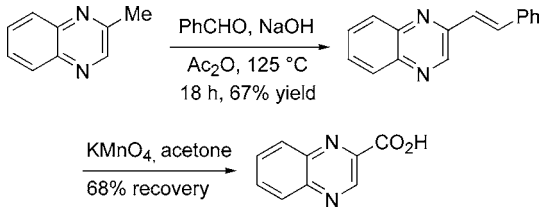
potassium cyanide and 2-chloroquinoxaline was heated to 250 °C with only starting material being observed.



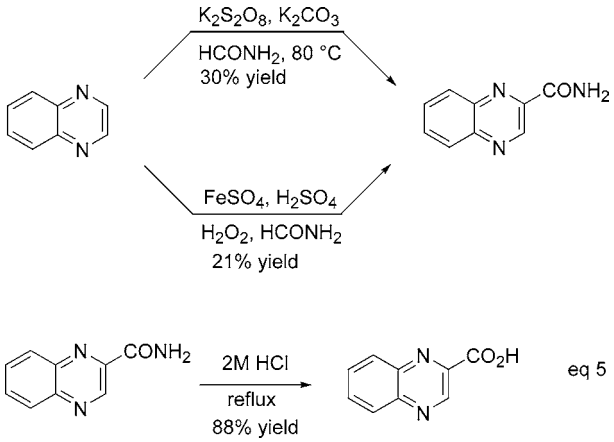
Direct chemical oxidation of 2-methylquinoxaline generally provides pyrazine dicarboxylic acid; however, an earlier report described a procedure that converted a styryl group to a carboxylic acid (Scheme 1). Condensation of 2-methylquinoxaline with benzaldehyde provided the styryl derivative.[6] At this stage, potassium permanganate was used to cleave oxidatively the olefin to provide the desired product. Unfortunately, oxidation only provided a 68% recovery of material that required further purification (50−70% purity).

Scheme 1



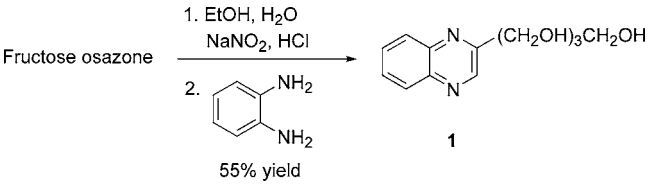
A final attempt to functionalize quinoxaline was investigated. In this approach, the literature cites methods where acyl radicals add to quinoxaline to provide the desired quinoxalinecarboxylic acid derivative in good yields.[13] In our hands, the yield rarely exceeded 30% (Scheme 2). The resulting amide was easily hydrolyzed to provide the desired acid (eq 5).

Scheme 2



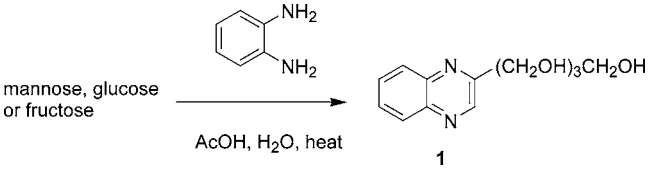
The approach that had the most success was an improved route using the procedures[9−11] that used *o*-phenylenediamine and a monosaccharide. The earliest reports found that when *o*-phenylenediamine was mixed with glucose,[9a] fructose,[9b,c] or mannose,[9d] a crystalline product was formed. The elemental analysis matched the expected condensation product. However, the yields have been poor (∼15−30%). In later publications,[12] some preparations utilized the osazone or hydrazone of a hexose. Fructose was converted to the fructose osazone and condensed with *o*-phenylenediamine to provide a moderate yield of the quinoxaline skeleton (Scheme 3). While some of these methods worked rather well, the additional steps and potential hazardous reagents made this approach less attractive. With these issues in mind, a decision was made to optimize the route that employed an unmodified sugar and *o*-phenylenediamine.

Scheme 3



To this end, the synthesis of the quinoxaline ring system was approached from the condensation of fructose, glucose, or mannose with *o*-phenylenediamine (Scheme 4). A variety of conditions were investigated to optimize this transformation (Table 1). Conditions found in Table 1 were conducted on 3−6 g of the appropriate sugar.

Scheme 4



Initial investigations duplicated the reported low yields of the desired polyhydroxylated quinoxaline. The reaction provided even lower yields of product when conducted at >80 °C (entries 1, 2). Stronger acids such as trifluoroacetic acid (entry 5) and hydrochloric acid failed to yield any desired product. Variations on the equivalents of sugar and phenylenediamine, as well as the rate of addition, did not significantly improve the yields. The optimum temperature for this condensation was briefly examined. After 1.5 h at 60 °C, no desired product was observed (entry 4). Only after heating to 80 °C was the product formed, and heating at 80 °C for an extended period of time led to the best yield for a single addition of fructose (entry 7).The next step of the synthesis of 2-quinoxalinecarboxylic acid was the oxidation of the polyhydroxylated side chain. Initial attempts utilizing basic hydrogen peroxide provided only a 30% yield of the desired acid. After additional experiments, the yields were increased to 70% (based on 1.5 g of the desired polyhydroxylated quinoxaline; a 60% yield was obtained on an 8.5 g reaction). One of the reasons for the yield improvement can be attributed to the purity of the starting material used in the peroxide oxidation. Subsequent oxidations from

Scheme 5

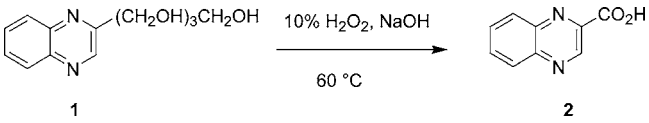


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Table 1. **Conditions examined for the preparation of 2-tetrahydrobutylquinoxaline**

entry	phenylenediamine (equiv)	sugar (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	1	mannose (1)	H_2O/50% AcOH (10:1)	reflux	2	8
2	1	glucose (1)	10% AcOH	reflux	2	11
3	1	glucose (1)	H_2O/50% AcOH (10:1)	80	2	31
4	1	fructose (1)	H_2O/50% AcOH (10:1)	60	1.5	NR
5	2	fructose (1)	H_2O/50% TFA (4:1)	80	2	decomp
6	1	fructose (2)	H_2O/ 50% AcOH (10:1)	80	2	25
7	1	fructose (1)	H_2O/ 50% AcOH (10:1)	80	18	46

material obtained from the fructose osazone path failed to provide a reliable yield. However, material arising from the fructose approach appears to be of higher quality, thereby resulting in better yields in the following oxidation. It should be also mentioned that the original side-chain oxidation reported the addition of sodium hydroxide to a solution of 2-tetrahydroxybutylquinoxaline in 6% hydrogen peroxide at 70 °C.[11] However, this order of addition resulted in an exothermic reaction with severe foaming that was difficult to control. Alternatively, if 30% hydrogen peroxide was slowly added to a solution of the quinoxaline in aqueous sodium hydroxide, minimal foaming was observed, but the reaction was still quite exothermic. It was envisaged that the excessive foaming formation resulted from the excess hydrogen peroxide (14 volumes based on 2-tetrahydroxybutylquinoxaline). To examine this possibility, the amount of hydrogen peroxide was halved to 7 volumes to provide crude 2-quinoxalinecarboxylic acid (57% yield, based on 5 g of 2-tetrahydroxybutylquinoxaline). Under these conditions, the mixture did not foam excessively, but the reaction was still slightly exothermic. The amount of 30% hydrogen peroxide was halved again to 3.5 volumes to afford a 57% yield of the crude acid. No significant exotherm event or foaming problems were encountered under these conditions, and the product was formed in comparable purity and yield.

Conclusions

A cost-efficient and scaleable synthesis of 2-quinoxalinecarboxylic acid utilizes a two-step process. The first step of the process involves a condensation reaction of D-fructose with *o*-phenylenediamine in the presence of 50% acetic acid to construct the quinoxaline skeleton. After a detailed investigation on this process, the best yield was obtained when the reaction temperature was kept at 80 °C. The second step of the process involves an oxidation of the side chain of **1** using 30% basic hydrogen peroxide as an oxidant. A modification in the order of addition of the reagents and their concentration proved to be critical to minimize the amount of foaming and the exothermic event. The exothermic event and foaming problems were completely eliminated when a minimum amount of hydrogen peroxide was used in the reaction. In summary, a large quantity of quinoxalinecarboxylic acid was synthesized via a two-step process in a 22% overall yield starting from reasonably priced starting materials. It is worth noting that no further purification process was performed on the final product since this procedure provides the product with an acceptable level of purity (>95%).

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received. Proton nuclear magnetic resonance spectra were obtained on a Bruker AC-300 spectrometer at 300 MHz using dimethyl sulfoxide as the solvent. Carbon nuclear magnetic resonance spectra were obtained on a Bruker AMX-300 at 75 MHz using dimethyl sulfoxide as the solvent. The melting points were obtained on a Thomas-Hoover capillary melting point apparatus.

Preparation of 2-Tetrahydroxybutylquinoxaline (1). 1,2-Phenylenediamine (450 g, 4.16 mol) was placed in a 5-L three-neck round-bottom flask equipped with a mechanical stirrer and thermocouple. Aqueous acetic acid (2.0 L, 10% solution) was added to the reactor, and the mixture was stirred for 30 min. D-Fructose (750 g, 4.16 mol) was added portionwise over 20 min. The mixture was heated to 80 °C and stirred for 18 h at 80 °C. The reaction mixture was cooled to 10 °C for 5 h. The solids were filtered through Shark skin filter paper using a Büchner funnel. The solids were washed with water (2 × 500 mL). A rubber dam was placed over the funnel, and the funnel was kept under vacuum for 3 h. The light-brown solids were placed in a vacuum oven for 18 h (oven temp = 60 °C, 1 mmHg). The desired product was obtained in a 40% yield (400 g); mp 181−184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.05−8.11 (m, 2H), 5.63 (d, 2H), 5.17 (d, 1H), 4.74 (d, 1H), 4.64 (d, 1H), 4.42 (t, 1H), 3.65−3.72 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.4, 145.2, 141.0, 140.8, 129.9, 129.2, 128.8, 128.6, 74.3, 72.5, 71.2, 63.5.

Preparation of 2-Quinoxalinecarboxylic acid (2). In a 5-L four-neck round-bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser, and liquid addition funnel, sodium hydroxide (155.4 g, 3.88 mol, pellets) was dissolved in water (1575 mL). Once the internal temperature reached 40 °C, 2-tetrahydroxybutylquinoxaline (70.0 g, 280 mmol) was added, and the suspension was stirred for 45 min. A 30% solution of hydrogen peroxide (130 mL) was introduced into the reaction mixture over a 15 min period (no change in internal temperature was observed). The reaction mixture was slowly heated to 60 °C over a period of 3 h. *Slowly*, the remainder of the 30% hydrogen peroxide solution (115 mL) was added over a period of 45 min (maximum temperature reached was 91 °C). The reaction mixture was stirred for an additional 30 min. The reaction mixture was then refluxed for 15 min. The reaction was cooled to 80 °C, and the liquid was decanted away from the tar-like material. The tar-like

material was discarded. The reaction was allowed to cool to room temperature. The pH of the solution was adjusted to 2 with concentrated hydrochloric acid. The mixture was allowed to stand overnight at room temperature. The off-white solids were filtered through Shark skin filter paper and washed with water (2 × 100 mL). A rubber dam was placed over the funnel, and the funnel was kept under vacuum for 3 h. The off-white solids were placed in a vacuum oven for 18 h (oven temp = 60 °C, 1 mmHg). The desired product was obtained in a 53% yield (25.7 g); mp 209−210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.20−8.31 (m, 2H), 7.91−8.08 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.3, 145.2, 143.6, 142.8, 140.8, 132.4, 131.3, 103.1, 129.0, 128.2.

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