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A Synthesis of Symmetrical and Unsymmetrical Pyrazines

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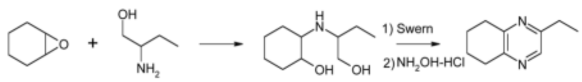

Opening of representative epoxides with 1,2-amino alcohols delivered the amino diols. The product amino diols were then oxidized under Swern conditions. The amino diketones so prepared were not isolated, but were condensed directly with hydroxylamine to give the substituted pyrazines.

Pyrazines are important as intermediates for fragrances,[1] pharmaceuticals,[2] and agricultural chemicals.[3] Remarkably, given the importance of other aromatic heterocycles in medicinal chemistry, there are fewer than 100 trialkyl-substituted pyrazines in the SciFinder database. This is due, not to lack of interest on the part of the pharmaceutical community, but to limited methods for their preparation.[4]

In the course of other work, we had occasion to briefly explore the coupling of epoxides with 1,2-aminodiols. The coupled products could then be oxidized under Swern conditions and condensed with NH_2OH to give pyrazines.[5] Herein we report our results.

Epoxide Opening

It is important to note that the hydrogen bonded amino alcohol is much less nucleophilic, perhaps due to intramolecular hydrogen bonding, than is an isolated amine. We initially had difficulty finding conditions for the epoxide opening. We heated cyclohexene oxide and 2-amino-3-phenyl-1-propanol under solvent-free conditions, but after seven days only starting materials were visible by TLC. While $LiClO_4$ and $BF_3 \cdot OEt_2$ failed to activate the epoxide, the addition of a catalytic amount of $Yb(OTf)_3$ to the reaction[6] facilitated an easy transformation to the amino diol. This is thought to be due to the oxophilicity of the early lanthanides. Further investigations later showed that identical loading of LiBr[7] under solvent-free conditions effected an even faster transformation to the amino diol. When an activated epoxide such as **1b** was used (Entries **3** and **4**, Table 1), additions were carried out without catalyst. Indeed, if catalysts were added, an increased amount of the undesired regioisomer was observed.

Oxidation and Pyrazine Formation

We carried out our initial investigations with 2,2′-bis(cyclohexanol)amine (**3e**). This amino diol provided a fine platform for the elucidation of oxidation strategies. Amino diol **3e** was readily prepared by Taguchi's procedure,[8] combining cyclohexene oxide and aqueous ammonia.

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Supporting Information
General experimental procedures, experimental details, and spectra for all new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

The Jones reagent,[9a] Dess-Martin periodinane,[9b] and the Swern reaction with trifluoroacetic anhydride[9c] each failed to produce the desired amino diketone. The Swern reaction utilizing oxalyl chloride[10] gave some promising results, but incomplete conversion of amino diols (indicated by the presence of amino diol by TLC after workup) proved to be troublesome. When the oxidations were performed at or near the upper temperature limit of −10 °C with an excess of oxidant, the reactions went to completion.

The organic extract from the workup of the oxidation was dried over Na_2SO_4, then directly added to a refluxing solution of ethanolic $NH_2OH{\cdot}HCl$. The reaction flask was fitted with an air condenser which allowed the CH_2Cl_2 to distill out over the course of the cyclization. The brown mixture so produced could then be subjected to acid/base extraction, or evaporated directly onto silica gel for chromatography, to give the product pyrazines (Table 1).

Alternatively, it was not necessary to purify the intermediate amino diol. The amino alcohol **2a** was coupled with the epoxide **1a**. The *crude* amino diol **3a** was carried directly to Swern oxidation, followed by condensation with $NH_2OH{\cdot}HCl$. The overall yield of the pyrazine **4a** from **2a** was slightly improved (10.1% vs. 7.8%) and the procedure was easily scaled.

Conclusion

We have developed what appears to be a versatile route to symmetrical and unsymmetrical pyrazines. It is particularly noteworthy that the Swern oxidation of the aminodiols can be carried out without protection of the basic amines.

Experimental Section

Amino diols 3b

In a 25 mL round bottom flask, (*R*)-(−)-2-amino-1-butanol (**2b**) (2.00 g, 23.5 mmol) was added to cyclohexene oxide (**1a**) (2.31 g, 23.6 mmol). To this was then added LiBr (102 mg, 5 mol %). The flask was sealed and the reaction was heated to 70 °C for 2 days, and then subjected to bulb-to-bulb distillation (100 °C, 2 mmHg) to remove unreacted amino alcohol and epoxide. The residue was chromatographed over basic alumina with a gradient of acetone in CH_2Cl_2 (0–60% in 20% increments) that had been saturated with NH_4OH. The eluent was dried over Na_2SO_4, filtered with CH_2Cl_2, and concentrated to give the diastereomeric mixture of amino diols **3b** (3.12 g, 70% yield) as a viscous, pale yellow oil. TLC: R_f = 0.43 (5:44:1 MeOH/CH_2Cl_2/NH_4OH); IR (film): 3364, 2931, 2858, and 1450 cm^{-1}; ^1H NMR (CD_3OD) δ 0.93 (t, *J* = 7.41 Hz, 3H), 1.11 (m, 1H), 1.27 (m, 3H), 1.52 (m, 2H), 1.69 (m, 2H), 1.94 (m, 2H), 2.38 (m, 1H), 2.60 (m, 1H), 3.23 (m, 1H), 3.48 (m, 2H); ^{13}C NMR (CD_3OD)[13] δ d 10.12, 11.03, 58.36, 59.06, 61.88, 62.32, 74.72, 75.02; u 24.13, 25.62, 25.79, 26.38, 31.65, 32.00, 35.21, 35.30, 62.68, 64.81; HRMS calcd for $C_{10}H_{21}NNaO_2$: 210.147, obsd: 210.147 [M+Na].

Pyrazine 4b

Oxalyl chloride (2.13 g, 14.0 mmol) diluted to 10 mL with CH_2Cl_2 was added to a 100 mL round bottom flask in a −40 °C bath. To this was added DMSO (1.31 g, 16.9 mmol, diluted to 10 mL with CH_2Cl_2) over the course of one min (gas evolution). Amino diols **3b** (200 mg, 1.07 mmol, in 10 mL CH_2Cl_2) were then added. The reaction was allowed to proceed with the temperature being kept between −20 °C and −40 °C. After 2 h, 5 mL of triethylamine (35.8 mmol) was added (exotherm) to give a turbid yellow solution. The mixture was allowed to warm to 0 °C over the course of 30 min, and the mixture was then partitioned between water and CH_2Cl_2. The combined organic extract was dried over Na_2SO_4. TLC indicated the absence of amino diols **3b**. The CH_2Cl_2 solution was decanted into a 250 mL round bottom flask, to which was added 20 mL of absolute EtOH and

$NH_2OH·HCl$ (88 mg, 1.27 mmol). The round bottom flask was fitted with a distillation apparatus and the mixture was heated until the bulk of the CH_2Cl_2 had distilled out. The mixture was then kept at reflux for two hours with an air condenser. The brown mixture was then concentrated onto flash silica gel and chromatographed on flash silica gel with a MTBE/PE gradient to give 88 mg of crude pyrazine **4b**. This was then further purified via TLC mesh chromatography (1:1 MTBE/PE) to give 25 mg of analytically pure pyrazine **4b** as a pale yellow oil, 15% yield overall from **3b**. TLC R_f = 0.43 (MTBE); IR: 2937, 1651, 1463, and 1386 cm^{-1}; ^1H NMR (CD_3OD) δ 1.26 (t, J = 7.6 Hz, 3H), 1.88 (m, 4H), 2.73 (q, J = 7.6 Hz, 2H), 2.89 (m, 4H), 8.16 (s, 1H); ^{13}C NMR (CD_3OD) δ d 14.03, 140.44; u 22.69, 28.46, 31.55, 31.97, 149.95, 151.84, 155.29; HRMS calcd for $C_{10}H_{15}N_2$: 163.124, obsd: 163.123 [M+].

Telescoped procedure: Pyrazine 4a—In a 25 mL sealed tube, *S*-(−)-2-amino-3-phenyl-1-propanol (**2a**) (3.0 g, 20 mmol) was combined with cyclohexene oxide (**1a**) (3.9 g, 40 mmol). LiBr (50 mg) was added and the flask was sealed. The reaction was maintained at 80 °C for 4 days, at which point the mixture was cooled to room temperature. NMR of the reaction mixture indicated complete consumption of **2a**. A 2.0 g portion of the reaction mixture was dissolved into 15 mL CH_2Cl_2 and carried on to the oxidation/cyclization protocol.

Oxalyl chloride (6.87 mL, 80 mmol) was added to 100 mL of CH_2Cl_2 in a 250 mL round bottom flask at −78 °C. DMSO (7 mL, 90 mmol diluted to 20 mL with CH_2Cl_2) over the course of three minutes with gas evolution and apparent exotherm. The crude reaction mixture **3a** (2.0 g in 15 mL CH_2Cl_2) was then added over the course of a minute. The reaction was allowed to proceed with the temperature being kept between −20 °C and −40 °C. After 2h, the reaction was taken back to −78 °C and triethylamine (20 mL, 143 mmol) was then added with accompanying exotherm to give a turbid yellow solution. The mixture was kept at −78 °C for 15 minutes, then allowed to warm to 0 °C over the course of 30 min, at which point the mixture was then partitioned between 75 mL of a 1:1:1 (sat NaCl, H_2O, 15% NaOH) solution and CH_2Cl_2. The combined organic extract was dried over Na_2SO_4. TLC indicated the absence of amino diols **3a**. The CH_2Cl_2 solution was decanted into a 250 mL round bottom flask, to which was added 25 mL of absolute EtOH and $NH_2OH · HCl$ (880 mg, 12.7 mmol). The round bottom flask was fitted with a distillation apparatus and the mixture was heated until the bulk of the CH_2Cl_2 had distilled out. The mixture was then kept at reflux overnight with an air condenser. The resulting black solution was then concentrated onto flash silica gel and filtered through a plug of flash silica gel with 100 mL of MTBE to give 240 mg of crude pyrazine **4a**. This was then subjected to kugelrohr distillation (130 °C, 200 mbar) and the bottoms were chromatographed with a TLC mesh column (10–40% MTBE/PE, 50 mL/10% increment) to give 103 mg of pyrazine 4a as a pale yellow oil, 10.1% yield overall from the starting amino alcohol **2a**.

TLC—R_f = 0.56 (MTBE); IR (film): 2936, 1454, 1387, and 1126 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.73 (m, 4H), 2.75 (m, 4H), 3.93 (s, 2H), 7.10 (m, 5H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ d 126.39, 128.47, 128.64, 128.76, 141.08; u 22.43, 29.52, 31.34, 31.78, 41.51, 138.52, 150.17, 151.95, 152.59; HRMS calcd for $C_{15}H_{15}N_2$: 223.124, obsd: 223.124 [M-H].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

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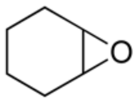
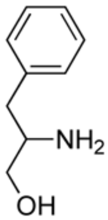
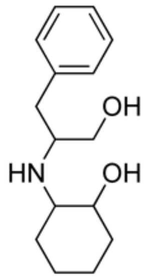
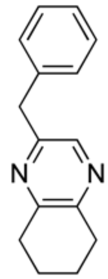
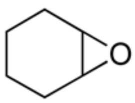
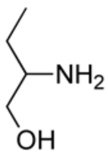
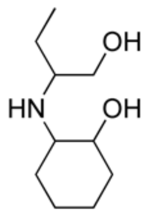
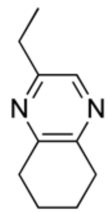
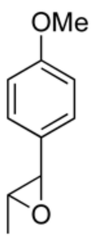
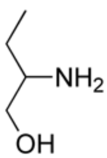
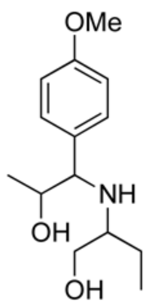
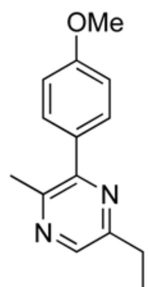
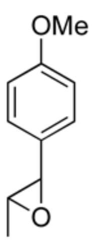
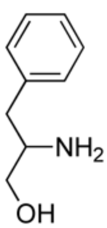
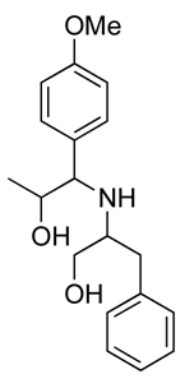
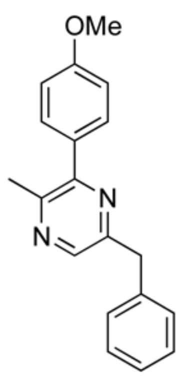
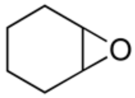
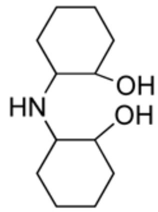
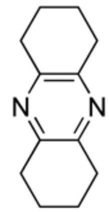
13. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d", from methylene and quaternary carbons as "u".

Table 1

Preparation of Pyrazines

	Epoxide	Amino alcohol	Amino diol (%)	Pyrazine (%)
1	 **1a**	 **2a**	 **3a**	 **4a**
2	 **1a**	 **2b**	 **3b**	 **4b**[a]
3	 **1b**	 **2b**	 **3c**	 **4c**
4	 **1b**	 **2a**	 **3d**	 **4d**

	Epoxide	Amino alcohol	Amino diol (%)	Pyrazine (%)
5	 **1a**	NH_3	 **3e**[b]	 **4e**[c]

[a]Ref. 11.

[b]Ref 8.

[c]Ref 12.