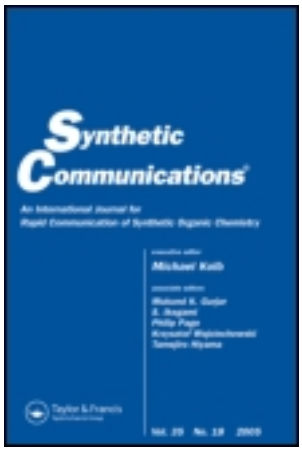

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A Convenient Preparation of Tetrahydrofuran-Based Diamines

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A Convenient Preparation of Tetrahydrofuran-Based Diamines†

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ABSTRACT

A convenient, three-step preparation of tetrahydrofuran-based diamines as combinatorial building blocks from 3,4-epoxytetrahydrofuran is described.

Key Words: Tetrahydrofuran; Diamines; Amino groups.

As combinatorial chemistry plays an important role in new drug discovery,[1,2] there is a growing need for a wide variety of structurally diversified amines as combinatorial building blocks for the use in the library construction in the effort to develop new therapeutically significant molecules. In view of the fact that the tetrahydrofuran ring is a ubiquitous motif, which can be found in many natural products with antitumor, antibiotic, and other biological

†Dedicated to the memory of Mom for her initiation and inspiration.

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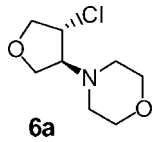
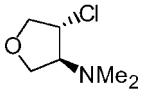
activities (e.g., burseran,[3] asiminocin,[4] and teurilene[5]), we were interested in the conjunction of different substituted amino groups with this important ring to construct a series of new tetrahydrofuran-based diamines **1a**–**1i** (Table 1). In this article, we report a convenient, three-step preparative route to these new diamines from commercially available 3,4-epoxytetrahydrofuran, as shown in Sch. 1.

Thus, epoxide ring opening of commercially available 3,4-epoxytetrahydrofuran (**2**)[a] with morpholine or dimethylamine readily afforded the vicinal amino alcohol **3a** or **3b**, respectively. Mesylation of the amino alcohols with methanesulfonyl chloride and triethylamine in THF and subsequent treatment with various amines smoothly furnished the corresponding vicinal diamines **1a**–**1i** in yields ranging from 55% to 87%. The results are summarized in Table 1. The one-pot, two-step conversion of the amino alcohols to the diamines proceeded with retention of configuration[6,7] presumably through a symmetric aziridinium species **5**, providing racemic trans isomers. It was important to add a certain amount of water just after addition of the amine in order to facilitate the diamine formation step in cases where neat amine was used (entries 3–5 and 7–9).[7a] Water may accelerate the formation of the aziridinium intermediate **5**. There was no nucleophilic attack on **5** by water. However, when CH_2Cl_2 was used in place of THF as solvent, a small amount of the byproduct **6a** or **6b**, resulting from nucleophilic attack of chloride, was detected in the crude product. The diamine **1e** was formed from selective substitution by the more nucleophilic thiol function instead of the amino group of 2-aminoethanethiol (entry 5). The assignment of its structure was further confirmed by acetylation with acetyl chloride and triethylamine in CH_2Cl_2 and NMR analysis of the corresponding acetamide.



6a



6b

In summary, a convenient and practical preparation of a series of tetrahydrofuran-based diamines has been achieved in three steps from commercially

[a]3,4-Epoxytetrahydrofuran is available from Acros Organics now. This epoxide was also prepared in this laboratory by treatment of 2,5-dihydrofuran with urea hydrogen peroxide addition compound and phthalic anhydride in ethyl acetate at room temperature.

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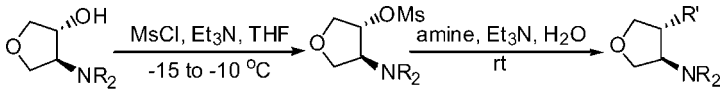
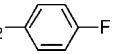
Table 1. One-pot preparation of tetrahydrofuran-based diamines from amino alcohols.



3a,3b **4a,4b** **1a-1i**

Entry	NR_2	R′	Diamine[a]	Yield (%)[b]	B.p. (°C/mmHg)	Purity (%)[c]
1[d]		NH_2	**1a**	55	138–139/3.2	97
2[d]		$NHCH_3$	**1b**	58	131–133/2.5	96
3		$NHCH_2CH{=}CH_2$	**1c**	65	140–142/2.4	96
4			**1d**	60	112–114/0.4	95
5		$SCH_2CH_2NH_2$	**1e**	59	150–152/0.2	97
6[d]	NMe_2	NH_2	**1f**	57	45–46/0.3	98
7	NMe_2	$NHCH_2CH_2OMe$	**1g**	64	95–97/0.4	97
8	NMe_2		**1h**	84	72–74/0.3	99
9	NMe_2		**1i**	87	155–157/1.6	97

[a]Purified by vacuum distillation.
[b]Yields refer to single runs and are given for isolated products.
[c]Determined by GC analysis.
[d]With 28% aqueous ammonia solution or 40% aqueous methylamine solution, water was not added.

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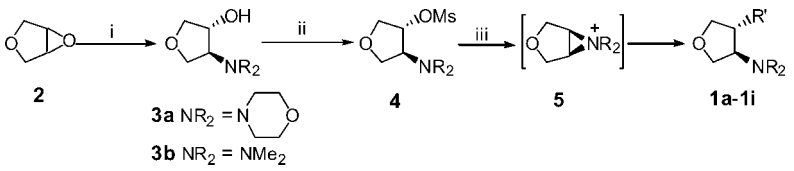

Scheme 1. Reaction conditions: (i) for **3a**, morpholine (1.5 eq.), 75–80°C; for **3b**, 40% aqueous Me_2NH solution (2 eq.), 55–60°C; (ii) MsCl (1.1 eq.), Et_3N (2 eq.), THF, −15 to −10°C; (iii) amine (2 eq.), Et_3N (2 eq.), H_2O, rt.

available 3,4-epoxytetrahydrofuran with good overall yields. This efficient sequence should prove useful in the synthesis of other related substituted vicinal diamines.

EXPERIMENTAL

All reagents and solvents were purchased from Acros or Aldrich and used without further purification. GC was performed using a Hewlett–Packard 5890A chromatograph equipped with a flame ionization detector. NMR spectra were obtained with a Varian Gemini 300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as the internal standard. Melting points were taken in glass capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected.

***trans*-3-Hydroxy-4-morpholinotetrahydrofuran (3a).** A 500-mL, three-necked, round-bottomed flask, equipped with a thermometer, a condenser, a mechanic stirrer, and an addition funnel, was charged with morpholine (152 mL, 1.74 mol, 1.5 eq.). The flask was heated to 75–80°C, and 3,4-epoxytetrahydrofuran (100 g, 1.16 mol) was added dropwise with agitation under nitrogen over a period of 30 min. The mixture was then agitated at 75–80°C for 3 hr when GC analysis indicated the complete consumption of the starting material. Excess morpholine was removed under reduced pressure and the brown oily residue was subjected to vacuum distillation to give 169 g (84%) of *trans*-3-hydroxy-4-morpholinotetrahydrofuran (**3a**) as a white solid: mp 51–53°C, bp 145–147°C/0.5–0.6 mmHg; 98% GC purity; ^{1}H NMR ($CDCl_3$) δ 4.40 (m, 1H), 4.11 (m, 1H), 3.94 (m, 1H), 3.73 (m, 5H), 3.67 (m, 1H), 2.82 (m, 1H), 2.62 (m, 2H), 2.48 (m, 2H), 1.89 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 73.3, 71.6, 66.8, 63.2, 54.9, 72.2; Anal. calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.41; H, 9.01; N, 7.92.

***trans*-3-(Dimethylamino)-4-hydroxytetrahydrofuran (3b).** A 5-L, three-necked, round-bottomed flask, equipped with a thermometer, a condenser, a mechanic stirrer, and an addition funnel, was charged with 40% aqueous

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dimethylamine solution (2.3 L, 18.32 mol, 2 eq.). The solution was heated to 50°C, and 3,4-epoxytetrahydrofuran (790 g, 9.17 mol) was added dropwise with agitation under nitrogen, while the temperature being maintained at 50–55°C. After addition, the mixture was agitated at 50–55°C under nitrogen overnight. Excess dimethylamine and water were removed under reduced pressure and the pale brown liquid residue was subjected to vacuum distillation to give 1.08 kg (90%) of *trans*-3-(dimethylamino)-4-hydroxytetrahydrofuran (**3b**) as a pale yellow liquid: bp 95–98°C/0.4 mmHg; 99% GC purity; ^{1}H NMR ($CDCl_3$) δ 3.91 (m, 2H), 3.81 (m, 3H), 3.06 (m, 1H), 2.27 (s, 6H), 1.98 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 72.9, 71.6, 67.5, 66.1, 39.7; Anal. calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.11; H, 9.89; N, 10.91.

General Procedure for the One-Pot Preparation of Diamines 1a–1i from Amino Alcohol 3a or 3b

To a stirred solution of the amino alcohol **3a** or **3b** (1 mol) in THF (1 L) was added triethylamine (280 mL, 2 mol, 2 eq.). After the mixture was cooled to −15°C, a solution of methanesulfonyl chloride (85 mL, 1.1 mol, 1.1 eq.) in THF (80 mL) was added dropwise with agitation under nitrogen over a period of 1 hr, while the temperature being maintained below −10°C. The mixture was then agitated at −15 to −10°C for 1 hr when TLC and GC analysis showed that the mesylation was complete. Triethylamine (280 mL, 2 mol, 2 eq.), an amine (2 mol, 2 eq.), and water (80 mL) were added in turn with agitation below −10°C. The resulting mixture was then agitated under nitrogen at room temperature overnight. Water (300 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by vacuum distillation. Their yields, boiling points, and purity were listed in Table 1.

1a. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 4.02 (m, 1H), 3.98 (m, 1H), 3.74–3.70 (m, 5H), 3.51 (m, 2H), 2.61 (m, 3H), 2.48 (m, 2H), 1.48 (s, broad, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 72.8, 72.1, 67.5, 64.4, 54.8, 52.7; Anal. calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.67; H, 9.22; N, 16.43.

1b. a pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ 4.05 (m, 2H), 3.77 (m, 4H), 3.66 (m, 2H), 3.23 (m, 1H), 2.78 (m, 1H), 2.67 (m, 2H), 2.51 (m, 2H), 2.48 (s, 3H); Anal. calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74. Found: C, 58.34; H, 9.64.

1c. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 5.88 (m, 1H), 5.19 (dd, J = 1.6, 17.2 Hz, 1H), 5.11 (dd, J = 1.5, 11.8 Hz, 1H), 3.95 (m, 2H), 3.70 (m, 5H), 3.62 (m, 1H), 3.31 (m, 1H), 3.24 (m, 2H), 2.74 (m, 1H), 2.58

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(m, 2H), 2.47 (m, 2H), 1.32 (s, broad, 1H, NH); Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50. Found: C, 62.49; H, 9.29.

1d. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 3.98–3.94 (m, 2H), 3.72 (m, 6H), 3.42 (m, 1H), 2.73 (m, 1H), 2.62 (m, 2H), 2.47 (m, 2H), 2.10 (m, 1H), 1.69 (s, broad, 1H, NH), 0.47 (m, 2H), 0.37 (m, 2H); Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50. Found: C, 62.42; H, 9.39.

1e. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 1H), 3.92 (m, 1H), 3.81 (m, 1H), 3.75 (m, 5H), 3.29 (m, 1H), 2.92 (m, 3H), 2.68 (m, 4H), 2.49 (m, 2H), 1.55 (s, broad, 2H, NH_2); Anal. calcd. for $C_{10}H_{20}N_2O_2S$: C, 51.69; H, 8.68; N, 12.06. Found: C, 51.46; H, 9.02; N, 12.43.

1f. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 2H), 3.68 (m, 1H), 3.49 (m, 2H), 2.51 (m, 1H), 2.29 (s, 6H), 1.45 (s, broad, 2H, NH_2); Anal. calcd. for $C_6H_{14}N_2O$: C, 55.35; H, 10.84. Found: C, 55.65; H, 10.98.

1g. a pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ 3.96–3.92 (m, 2H), 3.70 (m, 1H), 3.62 (m, 1H), 3.49 (t, $J = 7.2$ Hz, 2H), 3.36 (s, 3H), 3.26 (m, 1H), 2.77 (m, 2H), 2.70 (m, 1H), 2.28 (s, 6H), 1.68 (s, broad, 1H, NH); Anal. calcd. for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71. Found: C, 57.74; H, 10.81.

1h. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 3.93–3.91 (m, 2H), 3.68 (m, 2H), 3.38 (m, 1H), 2.67 (m, 1H), 2.20 (s, 6H), 2.13 (m, 1H), 1.81 (s, broad, 1H, NH), 0.47 (m, 2H), 0.36 (m, 2H); Anal. calcd. for $C_9H_{18}N_2O$: C, 63.49; H, 10.66. Found: C, 63.54; H, 10.39.

1i. a colorless liquid; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 3.95–3.88 (m, 2H), 3.74 (d, 2H), 3.68 (m, 2H), 3.24 (m, 1H), 2.69 (m, 1H), 2.24 (s, 6H), 1.31 (s, broad, 1H, NH); Anal. calcd. for $C_{13}H_{19}FN_2O$: C, 65.52; H, 8.04; N, 11.76. Found: C, 65.67; H, 8.29; N, 11.89.

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