The Use of Nafion®-H To Promote Epoxide Cyclizations

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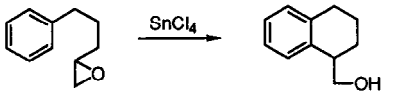
Abstract: Nafion®-H is shown to be an effective promoter of epoxide cyclizations to aromatic positions. The reactions can be done by passing a solution of the epoxide through a column packed with Nafion®-H, or by stirring a mixture of the compound with the acidic promoter and then filtering off the solid and washing it with the appropriate solvent. The solvent mixture that gave the highest yields had a fluorine-containing solvent, and trifluoroethanol in 3–10% amounts seems to be particularly good at maximizing yields. In general, yields are comparable to the same reactions that have been promoted by Lewis acids such as $SnCl_4$ and BF_3•OEt_2, but the workup is significantly easier. Because of the convenience of workup and the fast rates of reaction with this super-acid catalyst, many reactions can be done in a short time period. The reaction mixtures show almost no side products. A biomimetic cyclization was also investigated using the described protocol.

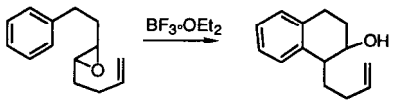
Key words: Nafion®-H, super-acid catalyst, epoxy-arene cyclization

In previous reports, we determined the relative facility of Lewis acid promoted epoxide cyclizations to aromatic positions (epoxy-arene cyclizations; see eq 1 for an example).[1,2]



(1)

Although investigations of such epoxy-arene cyclizations are newer than the well-studied epoxy-ene cyclizations,[2] these reactions have already been used as key steps in the syntheses of important natural products such as pseudopterosin A[3] and edulone A.[4] In very recent studies, we compared the relative facility of epoxy-arene and epoxy-ene cyclizations in compounds which could competitively cyclize to either a double bond or aromatic position (eq 2).[5]

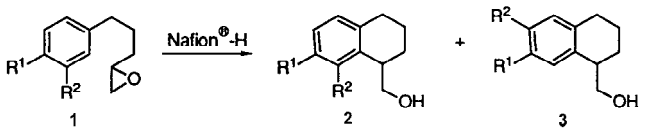


(2)

In a preliminary communication emphasizing the analytical chemistry of a related approach, we reported that Nafion®-H, a polymeric super acid,[6] promoted a single epoxy-arene cyclization that was previously done with a Lewis acid.[1a] (Table, **1a** → **2a**) We herein report a series of epoxides that have been cyclized by a modified protocol using Nafion®-H.[7] The reactions with the polymeric acid require essentially no workup or sophisticated glassware, are done quickly, and often have simpler product mixtures than the Lewis acid promoted reactions. The yields for the two processes are comparable.

The Table shows the results of epoxy-arene cyclizations promoted by Nafion®-H. In most cases, the reactions were done by passing a solution of approximately 20 mg of epoxide (diluted to 10% by volume with solvent) through an 8 mm i.d. × 10 cm column packed with 100 mesh Nafion®-H powder. The product was collected in a 20–50 mL beaker, the solvent was allowed to evaporate, and the product was analyzed by GC, GCMS and NMR. The solvent mixtures that gave the highest yields had 3–10% 2,2,2-trifluoroethanol (TFE) in them. Typical solvent mixtures were CH_2Cl_2/$FCCl_3$/TFE 62:28:10 for **1b** and **f** and a 69:28:3 mixture for **1a** and **g**. The fluorinated solvents were necessary to elute the maximum amount of product possible, as discussed earlier for **1a** (the only epoxide cyclization reaction reported earlier).[6]

Table. Epoxide Cyclization Products



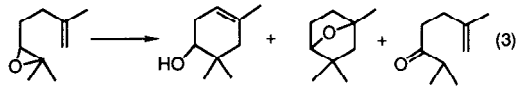
Entry	Epoxide	R^1	R^2	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	**1a**	H	H	88	–
2	**1b**	OMe	H	77	–
3	**1c**	Me	H	72[b]	–
4	**1d**	F	H	58	–
5	**1e**	Cl	H	42	–
6	**1f**	H	OMe	31	43
7	**1g**	H	Me	35[b]	43[b]

[a] GC yield unless otherwise specified.
[b] Distilled yield.

An optimized procedure is as follows. When a 22.5 mg sample of **1a** was passed through the column (with CH_2Cl_2/$FCCl_3$/TFE, 25 mL, 50:47:3), an 88% GC yield of **2a** resulted. This procedure worked well with ~20 mg quantities of epoxide. We also stirred 150 mg of epoxide **1a** in 113 mg of Nafion®-H and 14 mL of the same solvent. After 1 hour, the mixture was filtered and the product was purified by column chromatography (CH_2Cl_2/hexane 1:1) giving 89 mg (78% isolated yield, ≥92% pure). When **1g** was treated similarly (using CH_2Cl_2 with 3% TFE) the two desired products (arising from cyclization *ortho* and *para* to the methyl group) were isolated in 78% distilled yield, and they were the only products detectable by capillary GC. The volatile crude products of reactions done on epoxides **1a**,**b**,**f** and **g** were at least 95% pure by capillary GC. This is a notable advantage to this method compared to using Lewis acids, where small amounts of halohydrin and other side products are more prominent.[1b,c] Also, the use of Lewis acids requires a complex workup, usually including a mineral acid wash

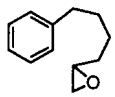
(to dissolve the Lewis acid), a basic wash (to remove acid), a neutral wash, and drying. With this polymeric acid promoter, these operations are circumvented. Also, no effort was made to dry the solvents such as is necessary when using Lewis acids.[1b,c]

The cyclization of **4** (eq 3) was probably the first biomimetic epoxide cyclization prepared in the literature.[8] We treated this epoxide with Nafion®-H and compared the products (**5**/**6**/**7** 1:0.16:1.4) to those formed by BF_3•OEt_2 initiated cyclization. Using Nafion®-H, more ketone **7** formed than with the BF_3•OEt_2 promoted reaction **5**/**6**/**7** (1.3:1:1.2).[8] However, Nafion®-H still promoted the desired reaction.



4 **5** **6** **7**

In earlier work utilizing Lewis acid promoters, 1,2-epoxy-6-phenylhexane **(8)** cyclized to produce a seven-membered ring.[1a] We could not produce any cyclization product using our Nafion®-H procedures. In this case, the product was a highly viscous oil, and only a small percentage of the material could be distilled, even at high vacuum. We thus suspect that dimerization, trimerization, etc. were faster than cyclization under our Nafion®-H conditions.



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In summary, we demonstrated that the use of Nafion®-H offers some significant advantages over the use of standard Lewis acids for some epoxide cyclization reactions. Specifically, the minimum of side products and ease of use and workup are attractive features of this chemistry.

The equipment used has been described elsewhere.[5a] All compounds in the Table have been characterized and reported by us before.[1a–c] However, the work was done before we had access to ^{13}C NMR spectroscopy. Therefore, we have included ^{13}C NMR data on all of these compounds except for **1d** and **3g** (reasons for these exceptions are included in the experimental data). ^{13}C NMR spectra are referenced to the center peak of $CDCl_3$ set at $\delta = 77.0$. Reagent TFE, CH_2Cl_2 and $FCCl_3$ were used as provided from the suppliers without drying or purification. Nafion®-H (100 mesh) was purchased by C.G. Processing, Inc. Compound purities are >95% unless specified otherwise.

General Synthesis of Epoxides:

The epoxides **1a–g** were made by treating the Grignard of (2-bromoethyl)benzene (or substituted analogs) with allyl bromide and then treating the aryl-ene product with MCPBA as described previously.[1a–c] When the alkyl bromide was not available, it was synthesized from the phenethyl alcohol by making the tosylate and treating the tosylate with LiBr. Most spectral data for the compounds are included in cited articles, but ^{13}C NMR and mass spectral data are included below.

1,2-Epoxy-5-phenylpentane **(1a)**:[1a]
^{13}C NMR ($CDCl_3$): δ = 27.5, 31.8, 35.4, 46.7, 51.9, 125.7, 128.1, 128.2, 141.8.
MS: *m/z* (%) = 162 (3), 128 (27), 104 (100), 91 (58).

*1,2-Epoxy-5-(*p-*methoxyphenyl)pentane* **(1b)**:[1b]
^{13}C NMR ($CDCl_3$): δ = 27.0, 31.9, 34.6, 46.9, 52.1, 55.2, 113.7, 129.2, 134.0, 157.7.
MS: *m/z* (%) = 192 (19), 134 (89), 121 (100), 91 (26).

*1,2-Epoxy-5-(*p-*tolyl)pentane* **(1c)**:[1b]
^{13}C NMR ($CDCl_3$): δ = 20.9, 27.7, 31.9, 35.0, 46.9, 52.1, 128.2, 128.9, 135.2, 138.8.
MS: *m/z* (%) = 176 (9), 145 (45), 118 (100), 105 (53), 91 (28).

*1,2-Epoxy-5-(*p-*fluorophenyl)pentane* **(1d)**:[1b]
This was characterized earlier, including combustion analysis, and was consumed and not available for ^{13}C NMR spectroscopy. ^{13}C NMR data of the cyclization product **2d** is given below.

*1,2-Epoxy-5-(*p-*chlorophenyl)pentane* **(1e)**:[1b]
^{13}C NMR ($CDCl_3$): δ = 27.5, 31.7, 34.7, 46.8, 52.0, 128.2, 128.5, 131.3, 140.3.
MS: *m/z* (%) = 198 (1.5), 196 (5), 140 (33), 138 (100), 125 (46), 103 (26).

*1,2-Epoxy-5-(*m-*methoxyphenyl)pentane* (**1f**):[1c]
^{13}C NMR ($CDCl_3$): δ = 27.6, 32.0, 35.6, 47.0, 52.2, 55.1, 111.1, 114.2, 120.8, 129.3, 143.6, 159.6.
MS: *m/z* (%) = 192 (25), 161 (32), 134 (100), 121 (28), 115 (41), 91 (46).

*1,2-Epoxy-5-(*m-*tolyl)pentane* **(1g)**:[1c]
^{13}C NMR ($CDCl_3$): δ = 21.2, 27.6, 31.8, 35.3, 46.7, 51.9, 125.2, 126.4, 128.1, 129.1, 137.6, 141.8.
MS: *m/z* (%) = 176 (5), 145 (29), 118 (100), 117 (34), 105 (35).

Epoxide Cyclizations:

The reaction of **1a** was optimized with respect to residence time (on a packed column) and solvent composition on a 22.5 mg-scale (3.6 mmol) reaction using a 8 mm i.d. × 10 cm column packed with Nafion®-H, and collecting 25 mL of effluent. The solvent had 3% TFE (CH_2Cl_2/$FCCl_3$/TFE 50:47:3), the residence time on the column was 7 min, and the yield was 19.8 mg (88%, GC yield with 6-methoxy-1-tetralone as the internal standard). When the residence time was 30, 15, and 6 min, 76, 82, and 63% yields resulted respectively. With 5% TFE, the yield was 80% and with no TFE (CH_2Cl_2/$FCCl_3$ 50:50) it was 69%. Thus the best yield we could obtain was 88% compared to 91% using $SnCl_4$ as the cyclization promoter in anhyd CH_2Cl_2.[1c]

A 150-mg scale reaction was performed as described in the text. In a large scale reaction, **1a** (1.46 g, 90 mmol) was stirred for 3.5 h in a mixture of CH_2Cl_2 (289 mL), TFE (11 mL), and Nafion®-H (0.980 g). The Nafion®-H was filtered off through very fine filter paper and the filtrate was washed with 5% $NaHCO_3$ and concentrated. The desired product was distilled at 82–84 °C/0.02 Torr using a short-path still, giving 0.813 g of >95% pure **2a** (56%).
^{13}C NMR ($CDCl_3$): δ = 19.5, 24.9, 29.6, 40.1, 66.9, 125.5, 126.0, 128.6, 129.2, 136.6, 138.0.
MS: *m/z* (%) = 162 (14), 131 (100), 129 (31), 128 (59), 127 (31), 115 (26), 91 (31).

7-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol (2b):[1b]

Prepared by eluting **1b** (41 mg, 7.5 mmol) in solvent (1 mL, CH_2Cl_2/$FCCl_3$/TFE 50:40:10) through Nafion®-H (2.0 g) packed in a giant pipet. The volatile crude product distribution was >97% **2b**, and the GC yield was 77%.

^{13}C NMR ($CDCl_3$): δ = 20.0, 25.1, 28.8, 40.5, 55.2, 67.1, 112.1, 113.6, 129.2, 130.1, 137.7, 157.5.
MS: *m/z* (%) = 192 (23), 161 (100), 158 (30), 115 (75).

7-Methyl-1,2,3,4-tetrahydronaphthalene-1-methanol (2c):[1b]
Prepared by stirring **1c** (306 mg, 1.7 mmol) in a mixture of CH_2Cl_2 (72 mL), TFE (3 mL), and Nafion®-H (292 mg). After 2.5 h, the Nafion®-H was removed by filtration through very fine filter paper, and the filtrate was rotary evaporated. Kugelrohr distillation (78–100°C/0.025 Torr gave 0.219 g (72%) of **2c**, which contained no impurities, according to capillary GC and ^{13}C NMR.
^{13}C NMR ($CDCl_3$): δ = 19.8, 21.0, 25.2, 29.2, 40.2, 67.1, 127.0, 129.2, 135.0, 136.4.
MS: *m/z* (%) = 176 (16), 145 (100), 129 (27), 128 (29), 115 (35).

7-Fluoro-1,2,3,4-tetrahydronaphthalene-1-methanol (2d):[1b]
Prepared from **1d** by the HPLC column cyclization method[6] using CH_2Cl_2/$FCCl_3$/TFE (62:28:10) (58% GC yield). The major impurities identified by GCMS were a 2:1 mixture of unreacted epoxide and the aldehyde[1b] resulting from epoxide rearrangement.
^{13}C NMR ($CDCl_3$): δ = 19.9, 25.0, 29.0, 40.4, 66.9, 113.1 (d, *J* = 22 Hz), 114. 8 (d, *J* = 20 Hz), 130.5 (d, *J* = 27 Hz), 133.5, 138.7 (d, *J* = 7 Hz), 160.9 (d, *J* = 242 Hz).
MS: *m/z* (%) = 180 (17), 149 (100), 147 (35), 146 (37), 133 (30), 109 (47).

7-Chloro-1,2,3,4-tetrahydronaphthalene-1-methanol (2e):[1b]
Prepared by cyclizing **1e** (2 mg) by the HPLC method[6] in CH_2Cl_2/$FCCl_3$/TFE (69:28:3) (42% GC yield). Major impurities were unreacted **2e** and the aldehyde reported earlier.[1b]
^{13}C NMR ($CDCl_3$): δ = 19.7, 24.9, 29.1, 40.2, 66.9, 126.2, 128.5, 130.6, 131.1, 136.5, 138.7.
MS: *m/z* (%) = 198 (7), 196 (21), 165 (100), 130 (47), 129 (58), 128 (44), 127 (36), 115 (25).

8-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol (2f):[1c]
Formed in 31% GC yield during the reaction of **1f** with Nafion®-H, along with a 43% yield of **3f**. The products were separated by HPLC using a 10 mm i.d. × 25 cm column packed with 10 μm silica gel using hexane/EtOAc (80:20), **2f** eluted first (mp 72–73°C)[1c] (followed by **3f**).

2f:
^{13}C NMR ($CDCl_3$): δ = 18.2, 24.5, 29.4, 35.2, 55.3, 65.7, 107.3, 121.8, 125.7, 126.6, 139.2, 157.4.
MS: *m/z* (%) = 192 (14), 161 (100), 115 (41).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol **(3f)**:[1c]
Purified by HPLC of the above cyclization mixture was characterized earlier (and made independently), including derivative mp[1c].
^{13}C NMR ($CDCl_3$): δ = 19.7, 25.3, 30.0, 39.5, 55.2, 67.1, 112.0, 113.8, 128.7, 129.6, 139.4, 157.7.
MS: *m/z* (%) = 192 (11), 161 (100), 115 (66).

8-Methyl-1,2,3,4-tetrahydronaphthalene-1-methanol (2g):[1c]
Prepared in a 35% distilled yield along with a 43% distilled yield of **3g** as follows. **1g** (0.3511 g, 1.9 mmol) was stirred along with CH_2Cl_2 (79 mL), TFE (4 mL), and Nafion®-H (325 mg). The Nafion®-H was removed by filtration through very fine filter paper and the filtrate was concentrated by rotary evaporation. The volatile crude product mixture was 98% **2g** and **3g** by capillary GC. The product was purified by Kugelrohr distillation (90–100°C/ 0.025–0.04 Torr) to give 0.275 g (78%) of distillate which was exclusively **2g** and **3g** by capillary GC. HPLC (as described above) using trace hexane in EtOAc/EtOH (85:15) did not cleanly separate the 6- and 8-isomers but **3g** eluted first in an unsymmetrical peak and we did isolate pure **3g** by peak shaving (see below). **2g** could not be isolated pure even by HPLC.[1c] It was isolated as a 72:28 **2g**/**3g** mixture, and its ^{13}C NMR peaks were assigned from NMR of this mixture by subtracting the peaks from the 6-methyl isomer.
^{13}C NMR ($CDCl_3$): δ = 17.8, 19.0, 23.9, 29.5, 37.6, 64.3, 126.0, 127.1, 127.9, 135.0, 136.6, 137.8.
MS: *m/z* (%) = 176 (10), 145 (100), 129 (34), 128 (31), 115 (35).

6-Methyl-1,2,3,4-tetrahydronaphthalene-1-methanol **(3g)**:[1c]
Isolated by HPLC.
^{13}C NMR ($CDCl_3$): δ = 19.8, 20.9, 25.3, 29.7, 39.9, 67.1, 126.6, 128.6, 130.0, 133.5, 135.6, 137.8.
MS: *m/z* (%) = 176 (7), 145 (100), 129 (27), 128 (31), 115 (32).

Geraniolene Epoxide (4):[8]
Synthesized as described by Goldsmith.[8]
^{13}C NMR ($CDCl_3$): δ = 19.4, 23.1, 25.5, 27.8, 35.2, 58.9, 64.7, 111.0, 145.5 (94% pure).
The epoxide was cyclized with BF_3•OEt_2 as previously reported[8], and the products were isolated by preparative GC.[8] The isolated products were identified using the reported ^{1}H NMR and IR data[8] and they were compared by GCMS to the products formed from Nafion®-H promoted cyclizations performed on a 2 mg scale by the column method using CH_2Cl_2/$FCCl_3$/TFE (77.5:22.5:0.5). This solvent system gave the fewest side products.

1,2-Epoxy-6-phenylhexane (8):[1a]
Prepared as reported earlier.[1a]
^{13}C NMR ($CDCl_3$): δ = 25.5, 31.1, 32.2, 35.7, 46.9, 52.1, 125.6, 128.1, 128.2, 142.2.
The compound (223 mg, 1.27 mmol) was stirred in CH_2Cl_2/$ClCF_3$/TFE (50 mL, 5:4.5:5) and Nafion®-H (343 mg). The reaction was followed by GC, but few new volatile products appeared, and the peaks grew smaller. When 157 mg of **8** was treated similarly, the viscous product was Kugelrohr distilled (up to 130°C/0.08 Torr), yielding only 39 mg of distillate, which did not show the ^{1}H NMR (or GCMS) peaks expected of the desired cyclization product (at δ = 3.6–4.0).[1a]

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(7) In the preliminary report,[6] an HPLC column was packed with Nafion®-H powder and the epoxide was passed through the HPLC column. An analytical column was attached directly after the reactor column, and the reactant and product were separated and analyzed using the tandem analytical column. Although this two-column approach was very efficient, we have abandoned it because the powdered Nafion®-H HPLC column packing material eventually swells and plugs the column when using the solvent mixture that gives the highest yields. We now prefer the non-HPLC method described herein.
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A regioisomer of **5** (2,2,4-trimethylcyclohex-3-en-1-ol) was treated as though it was **5** in Goldsmith's calculation of the ratio of products. We did not detect this isomer in our Nafion®-H reaction products by capillary GC. We did detect it in the $BF_3 \cdot OEt_2$ cyclization products.