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$FeCl_3$-mediated efficient method for the synthesis of tetrahydropyran derivatives via cross-cyclization of epoxides and homoallylic alcohols

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Abstract

Background: An efficient methodology for the synthesis of tetrahydropyran derivatives has been developed under mild reaction conditions. The reactions were carried out using epoxides and homoallylic alcohols as reactants and ferric chloride as catalyst. All the reactions were done at room temperature in methylene dichloride.

Results: In all cases, the reactions proceeded efficiently at ambient temperature under mild conditions showing the generality of the reaction. The reaction also proceeded well with the cyclic epoxide 1,2-dihydronaphthalene oxide to give the corresponding spirotetrahydropyrans in good yield. The proton on the carbon bearing the halide group (4-H) (δ 3.80, J = 4.46 and 11.80 Hz) shows NOE with the proton on the carbons bearing the benzyl group (2-H) (δ 3.46, J = 11.80 Hz) and the proton on the carbon bearing the methyl group (6-H) (δ 3.40, J = 11.80 Hz). This confirms that the protons 2-H, 4-H, and 6-H are on the same side and occupy the axial position of a chair conformation.

Conclusion: The attractive features of this process are mild reaction conditions, which are environmentally friendly, inexpensive reagents, with short reaction times, and cleaner reactions with improved yields, which make it a useful process for the synthesis of tetrahydropyran derivatives.

Keywords: Epoxides, Homoallylic alcohols, Ferric chloride, Tetrahydropyran

Background

Substituted tetrahydropyrans are the common structural motif of many natural products [1,2] such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins, acutiphycins,and apicularens. Despite their potential importance to construct structurally complex molecules, the synthesis of dihydropyrans remains underutilized. Although several methods are reported [3-19], many of these procedures involve extended reaction timings and the use of expensive reagents. So, the development of efficient and versatile catalytic methods would be a preferable approach especially that low cost, environmental friendly and mild conditions are in high demand. In this respect, ferric chloride has been found as potential Lewis acid in various organic reactions [16,17,20-23]. Because of the numerous advantages, we undertook a study of the utility of the ferric chloride for the tetrahydropyran synthesis. Epoxides are the most convenient starting materials for the preparation of various compounds because of their ease of formation, wide reactivity, and ability to undergo regioselective ring opening reactions which contribute largely to their synthetic value [24-29]. In this report, we describe a simple and efficient protocol for the cyclization reactions of commercially available ferric-mediated reaction of epoxides and homoallylic alcohols to produce tetrahydropyrans.

Methods

All reactions were carried out under an inert atmosphere of nitrogen in oven-dried glassware with magnetic stirring, unless otherwise noted. DCM was distilled from calcium hydride prior to use. Ferric chloride was purchased from a commercial supplier. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates (F254 pre-coated glass plates) using UV light as

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visualizing agent and p-Anisaldehyde and heat as a developing agent. Flash chromatography was performed on silica gel (100–200 mesh). ^{1}H and ^{13}C NMR spectra were obtained at 100, 200 or 400 MHz at 298 K, unless otherwise indicated. Abbreviations for multiplicity are as follows: d indicates doublet, t indicates triplet, q indicates quartet, m indicates multiplet, dd indicates doublet of doublet, and dt indicates doublet of triplet. Chemical shifts are reported in ppm referenced to the internal solvent residual of $CDCl_3$ at 7.27 ppm for 1H NMR and 77.1 ppm for ^{13}C NMR, respectively. IR spectra were obtained on an FT-IR spectrophotometer using NaCl plates. Mass spectrometry data were obtained by ESI mass spectrometer.

Results and discussions

In order to delineate the standard operating conditions, a mixture of styrene oxide and 3-buten-1-ol was treated with ferric chloride in dry methylene dichloride. The mixture was stirred at room temperature for 1 h and after work-up; the crude product was purified over silica gel to provide the product in 70% yield. By spectroscopic analysis, the product was confirmed as 3a by comparing with the literature data (Scheme 1).

This methodology has been generalized by reacting a series of epoxides with homoallylic alcohols to give the corresponding tetrahydropyran derivatives in excellent yields ranging from 80% to 95% as illustrated in Figure 1. The corresponding dihydropyran derivatives in good yields range from 65% to 80% (Figure 1). In all cases, the reactions proceeded efficiently at ambient temperature under mild conditions showing the generality of the reaction. The reaction also proceeded well with the cyclic epoxide 1,2-dihydronaphthalene oxide to give the corresponding spirotetrahydropyrans in good yield (Figure 1, entries 7 to 9).

The stereochemistry assignment of 3b was based on the^{1}H NMR spectrum and NOE experiment. From the NOE, it is seen that the proton on the carbon bearing the halide group (4-H) (δ 3.80, J = 4.46 and 11.80 Hz) shows NOE with the proton on the carbons bearing the benzyl group (2-H) (δ 3.46, J = 11.80 Hz) and the proton on the carbon bearing the methyl group (6-H) (δ 3.40, J = 11.80 Hz). This confirms that the protons 2-H, 4-H, and 6-H are on the same side and occupy the axial position of a chair conformation. This observation is consistent with vicinal ^{3}J couplings and unequivocally confirms a 'R' configuration at C-4 position. The predominant formation of a single stereoisomer is probably due to thermodynamic factors (Figure 2).

Experimental

General procedure

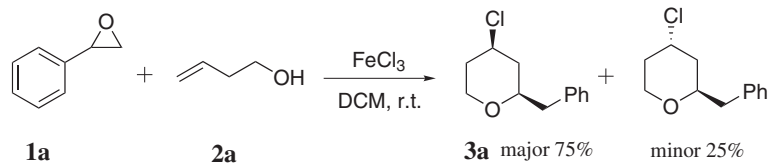
To a stirred solution of 3-buten-1-ol (290 mg, 4 mmol) and styrene oxide (720 mg, 6 mmol) in dry methylene dichloride (20 mL), anhydrous ferric chloride (1.3 g, 8 mmol) was added at room temperature. The mixture was stirred under a nitrogen atmosphere for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding crushed ice and extracted with methylene dichloride (2 × 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel (ethyl acetate-hexane, 3:7). Both diastereomers of 6a were obtained in a 3:1 ratio. All the products were characterized by their spectral data.

(2R, 4R)-2-benzyl-4-chlorotetrahydro-2H-pyran (cis) (3a)

IR (neat): υ 2960, 2843, 1495, 1453, 1103, 1074, 764, 741 cm−1;1H NMR (400 MHz, $CDCl_3$): δ 7.24 to 7.40 (m, 5H), 3.95 to 4.10 (m, 2H), 3.45 to 3.55 (m, 1H), 3.42 (dt, 1H, J = 2.0, 12.1 Hz), 3.0 (dd, 1H, J = 6.8, 13.8 Hz), 2.75 (dd, 1H, J = 6.5, 13.8 Hz), 2.10 to 2.20 (m, 2H), 1.92 (dt, 1H, J = 4.7, 12.0 Hz), 1.65 (q, 1H, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 129.5, 128.1, 126.7, 78.4, 67.3, 55.6, 42.1, 42.6, 37.5. Analysis calculated for C12H15ClO: C, 68.41; H, 7.18. Found: C, 67.97; H, 7.71.

(Trans) (3a)

IR (neat): υ 3025, 2948, 2846, 1494, 1451, 762, 753, 691 cm−^{1};^{1}H NMR (400 MHz, CDCl3): δ 7.20 to 7.30 (m, 5H), 4.52 to 4.59 (m, 1H), 4.02 to 4.10 (m, 1H), 3.95 (dt, 1H, J = 2.0, 11.7 Hz), 3.86 (dd, 1H J = 5.0, 12.0 Hz), 2.90 (dd, 1H, J = 7.4, 13.8 Hz), 2.70 (dd, 1H, J = 5.9, 13.8 Hz), 2.02 to 2.10 (m, 1H), 1.75 to 2.02 (m, 3H);^{13}C NMR (100 MHz, CDCl3): δ 138.1, 129.3, 128.3, 126.5, 72.2, 62.6, 56.3, 42.2, 39.0, 33.8.



Scheme 1 (2*R*, 4*R*)-2-benzyl-4-chlorotetrahydro-2*H*-pyran (*cis*) (3a).

Entry	Epoxide	Alcohol	Products[a,b]	Yield (%)[c]
1	**1a**	**2a**	**3a** (cis/trans=3:1)	95
2	**1a**		**3b**	93
3	**1a**		**3c**	88
4	**1b**		**3d** (cis/trans=4:1)	86
5	**1b**		**3e**	90
6	**1b**		**3f**	80
7	**1c**		**3g**	90
8	**1c**		**3h**	89
9	**1c**		**3i**	85
10	**1d**		**3j**	92

a: All the products were characterized by 1H NMR, IR and mass spectroscopy
b: The minor isomers of THP products were not isolated
c: Yields are Isolated after column chromatography

Figure 1 Ferric chloride-meditated cross-cyclization of epixodes and homoallylic alcohols.

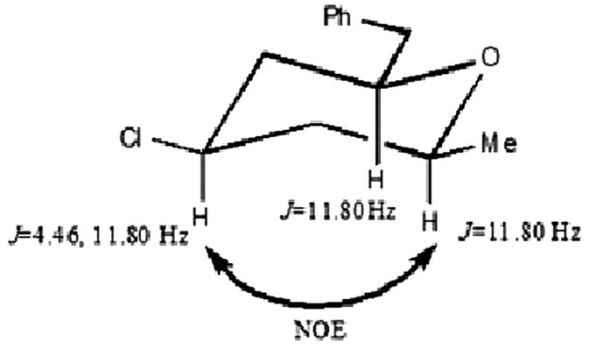


Figure 2 (2*R*, 4*R*, 6*S*)-2-Bbenzyl-4-chloro-6-methyltetrahydro-2*H*-pyran (3b). ^{1}H NMR (200 MHz, CDCl3): δ 7.10 to7.30 (m, 5H), 3.80 to 4.00 (m, 1H), 3.30 to 3.50 (m, 2H), 2.95 (dd, 1H, J = 5.9, 13.3 Hz), 2.65 (dd, 1H, J = 6.6, 13.3 Hz), 2.05 (dt, 2H, J = 2.2, 12.6 Hz), 1.40 to 1.60 (m, 2H), 1.20 (d, 3H, J = 5.9 Hz); EIMS *m/z*: 224 (10) M^+, 150 (15), 133 (100), 97 (30), 69 (85), 41 (35). Analysis calculated for $C_{13}H_{17}ClO$ (224.73): C, 69.48; H, 7.62%. Found: C, 69.56; H, 7.87%.

(2R, 4R, 6S)-2-Bbenzyl-4-chloro-6-methyltetrahydro-2H-pyran (3b)

1H NMR (200 MHz, CDCl3): δ 7.10 to 7.30 (m, 5H), 3.80to 4.00 (m, 1H), 3.30 to 3.50 (m, 2H), 2.95 (dd, 1H, J = 5.9, 13.3 Hz), 2.65 (dd, 1H, J = 6.6, 13.3 Hz), 2.05 (dt, 2H, J = 2.2, 12.6 Hz), 1.40 to 1.60 (m, 2H), 1.20 (d, 3H, J = 5.9 Hz); EIMS *m/z*: 224 (10) M^+, 150 (15), 133 (100), 97 (30), 69 (85), 41 (35). Analysis calculated for C13H17ClO (224.73): C, 69.48; H, 7.62%. Found: C, 69.56; H, 7.87%.

(2R, 4S, 6R)-2-benzyl-4-chloro-6-phenyltetrahydro-2H-pyran (cis) (3d)

IR (neat): υ 3021, 2956, 2852, 1596, 1492, 1445, 746, 695 cm−1,1H NMR (200 MHz, $CDCl_3$): δ 7.20 to 7.36 (m, 10H), 3.95 to 4.10 (m, 4H), 3.46 (dt, 1H, J = 2.0, 8.4 Hz), 2.05 to 2.20 (m, 2H), 1.80 to 1.90 (m, 1H), 1.55 to 1.65 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 141.7, 128.6, 128.6, 128.4, 128.3, 126.7, 126.4, 78.9, 67.2, 57.4, 56.1, 41.5, 36.9. EIMS *m/z*: 286 M^+.

(Trans) (3d)

IR (neat): υ 3085, 3059, 2961, 2805, 1594, 1491, 750, 698 cm−1,1H NMR (400 MHz, $CDCl_3$): δ 7.10 to 7.30 (m, 10H), 4.52 (dt, 1H, J = 8.0 Hz), 4.53 (singlet (s), 1H), 3.92 (triplet (t), 1H, J = 12.0 Hz), 3.75to 3.85 (m, 2H), 1.92 to 1.99 (m, 1H), 1.65to 1.75 (m, 3H);^{13}C NMR (100 MHz, CDCl3): δ 142.1, 124.0, 128.6, 128.4, 128.3, 126.5, 126.3, 73.3, 62.5, 57.1, 56.6, 38.2, 33.6. EIMS *m/z*: 286 M^+. Analysis calculated for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.62; H, 7.09.

(2S, 4R)-4-chloro-2-(diphenylmethyl)-tetrahydro-2H-pyran (3e)

1H NMR (200 MHz, $CDCl_3$): δ 7.10 to 7.30 (m, 10H), 3.85 to 4.00 (m, 3H), 3.40to 3.50 (m, 1H), 2.10 (dt, 1H, J = 1.4, 2.2 Hz), 1.92 (dt, 1H, J = 1.4, 2.2 Hz), 1.40to 1.56 (m, 2H), 1.18 (d, 3H, J = 6.6 Hz); EIMS*m/z*: 300 (10) M^+, 166 (45), 134 (100), 98 (25), 69 (70), 41 (30). Analysis calculated for $C_{19}H_{21}ClO$ (300.82): C, 75.86; H, 7.04%. Found: C, 76.15; H, 7.23%.

(2S, 4S, 6R)-4-chloro-2-(diphenylmethyl)-6-phenyltetrahydro-2H-pyran (3f)

1H NMR (200 MHz, $CDCl_3$): δ 7.15to 7.45 (m, 15H), 4.50 (dd, 1H, J = 11.2, 12.8 Hz), 4.15 to 4.30 (m, 2H), 4.10 (d, 1H, J = 7.2 Hz), 2.40 to 2.55 (m, 1H), 1.60 to 2.10 (m, 3H);^{13}C NMR (200 MHz, CDCl3): δ 40.8, 43.8, 44.3, 56.1, 77.0, 78.7, 125.5, 125.8, 126.4, 126.6, 127.4, 127.7, 128.1, 128.3, 128.5, 128.6, 129.1; EIMS *m/z*: 362 (10) M^+, 271 (10), 236 (10), 165(40), 130 (40), 116 (30), 103 (100), 90 (30), 66 (20), 50 (15). Analysis calculated for C24H23ClO (362.89): C, 79.43; H, 6.39. Found: C, 79.69; H, 6.62.

(2R, 4'R)-4'-chloro-3,3',4,4',5',6'-hexahydro-1H-spiro-[naphthalene-2,2'-pyran] (3g)

1H NMR (200 MHz, $CDCl_3$): δ 6.88 to 7.02 (m, 4H), 4.12 to 4.25 (m, 1H), 3.80 (dd, 1H, J = 2.0, 2.7 Hz), 3.65 (dd, 1H, J = 2.0, 2.7 Hz), 2.84 to 2.97 (m, 1H), 2.68 to 2.76 (s, 2H), 2.55 to 2.64 (m, 1H), 1.96 to 2.16 (m, 2H), 1.56 to 1.92 (m, 4H); EIMS *m/z*: 236 (25) M^+, 201 (80), 129 (55), 104 (100), 91 (35), 55 (70); Analysis calculated for $C_{14}H_{17}ClO$ (236.74): C, 71.03; H, 7.24%. Found: C, 71.46; H, 7.32%.

(2R,4'R,6'S)-4'-chloro-6'-methyl-3,3',4,4',5',6'-hexahydro-1H-spiro-[naphthalene-2,2'-pyran] (3h)

1H NMR (200 MHz, $CDCl_3$): δ 6.90 to 7.05 (m, 4H), 4.15 to 4.25 (m, 1H), 3.65 to3.85 (m, 1H), 2.50 to 3.02 (m, 4H), 2.01 to 2.12 (m, 2H), 1.45 to 1.90 (m, 4H), 1.17 (d, 3H, J = 5.9 Hz). EIMS *m/z*: 250 (15) M^+, 216 (100), 215 (20), 129 (25), 104 (50), 91 (10), 42 (10). Analysis calculated for $C_{15}H_{19}ClO$ (250.76): C, 71.84; H, 7.64%. Found: C, 71.95; H, 7.85%.

Conclusion

In summary, we have described a simple and highly efficient protocol for the preparation of tetrahydropyran derivatives through the reaction between epoxides and homoallylic alcohols using ferric chloride. The attractive features of this process are mild reaction conditions, which are environmentally friendly, inexpensive reagents, with short reaction times, and cleaner reactions with improved yields, which make it a useful process for the synthesis of tetrahydropyran derivatives.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
NS, carried out synthesis of tetrahydropyran derivatives, CMRJ, participated in the design of the study and performed the spectral analysis. MJ, conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

Authors' information
NS and CMRJ are research scholars and MJ is professor from the Department of Biochemistry, Faculty of Science, Kakatiya University, Warangal Andra Pradesh, 506 009, India.

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