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$ZrCl_4$ mediated cyclization between epoxides and homopropargylic alcohols: synthesis of 4-chloro-5,6-dihydro-2*H*-pyran derivatives☆

J. S. Yadav, K. Rajasekhar and M. S. R. Murty*

Division of Organic Chemistry-I, Discovery Laboratory, Indian Institute of Chemical Technology, Hyderabad 500007, India

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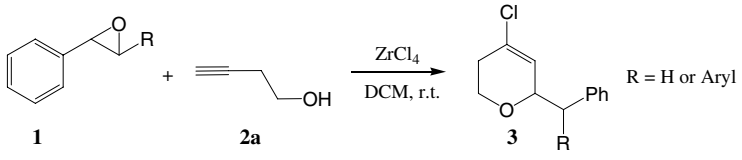
Abstract—Epoxides undergo cyclization with homopropargylic alcohols in the presence of zirconium tetrachloride under mild conditions to afford the corresponding dihydropyran derivatives in excellent yields under mild conditions.

1. Introduction

Substituted dihydropyrans are key intermediates for the synthesis of many natural products.[1] The olefin function particularly has great synthetic value for further functionalization to obtain polysubstituted tetrahydropyrans from dihydropyrans.[2] Despite their potential importance to construct structurally complex molecules, the synthesis of dihydropyrans remains under utilized. Although other methods are available,[3] their importance prompted us to study extensively the synthesis of dihydropyran derivatives. However, the development of efficient and versatile catalytic methods would be a preferable approach. Epoxides are convenient starting materials because of their ease of formation, wide reactivity and ability to undergo regioselective ring-opening reactions.[4] $ZrCl_4$ has been used for various epoxide ring-opening reactions giving the products in good yield.[5] Recently, we reported the formation of tetrahydropyrans through the cyclization reaction between epoxides and homoallylic alcohols.[6] In continuing our research on the synthesis of pyran ring systems, in this report we further extend the work on the synthesis of dihydropyran derivatives through the cyclization between epoxides and homopropargylic alcohols using zirconium tetrachloride.

In order to delineate the standard operating conditions, a mixture of styrene oxide and 3-butyn-1-ol was treated with zirconium tetrachloride in dry methylene chloride. The mixture was stirred at room temperature for 30 min 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[3b] (Scheme 1).

With these encouraging results, the reaction was performed with a wide range of epoxides and all reacted smoothly with 3-butyn-1-ol under similar conditions to



Scheme 1.

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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: msrmurty@iict.res.in

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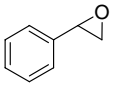
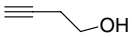
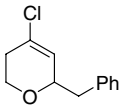
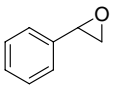
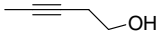
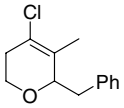
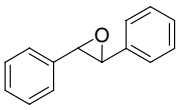
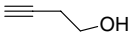
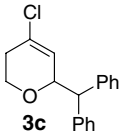
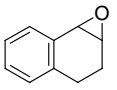
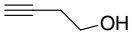
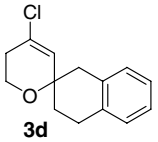
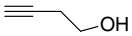
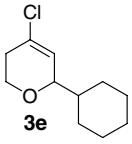
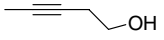
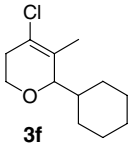
Table 1. $ZrCl_4$ mediated cyclization of epoxides with homopropargylic alcohols

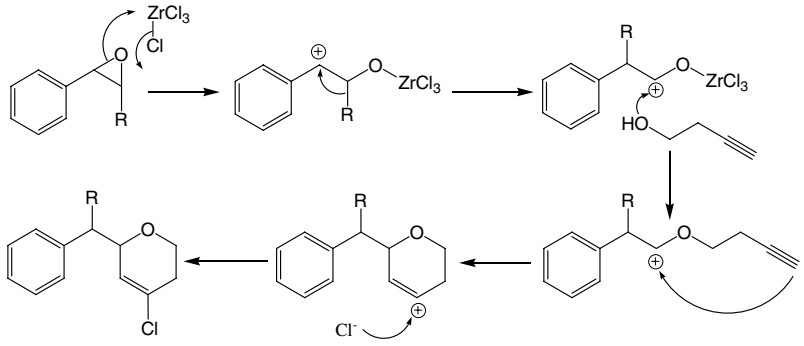
Entry	Epoxide	Alcohol	Products[a]	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	80
2	 **1a**	 **2b**	 **3b**	68
3	 **1b**	 **2a**	 **3c**	65
4	 **1c**	 **2a**	 **3d**	77
5	 **1d**	 **2a**	 **3e**	67
6	 **1d**	 **2b**	 **3f**	65

[a] All the products were characterized by ^1H NMR and mass spectroscopy.
[b] Isolated yields after column chromatography.

afford the corresponding dihydropyran derivatives in good yields ranging from 65–80% (Table 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 spiro dihydropyran in good yield (entry 4).

The mechanism for dihydropyran formation can be explained by opening of the epoxide ring with zirconium tetrachloride followed by the migration of hydrogen (in the case of **1a**, **1c** and **1d**) or the phenyl group (in the case of **1b)** to generate the carbenium species, which is attacked by the homopropargylic alcohol and cyclized to the dihydropyran carbenium species. This is further attacked by the chloride nucleophile to give the 4-chloro-5,6-dihydro-2*H*-pyran derivative (Scheme 2).

In summary, we have described a simple and highly efficient protocol for the preparation of dihydropyran derivatives through the reaction between epoxides and



Scheme 2.

homopropargylic alcohols using zirconium tetrachloride.

2. Representative procedure

To a stirred solution of styrene oxide (240 mg, 2 mmol) and 3-butyn-1-ol (140 mg, 2 mmol) in dry methylene chloride (10 mL) was added zirconium tetrachloride (466 mg, 2 mmol) at room temperature. The mixture was stirred under a nitrogen atmosphere for 30 min. After work-up, the solution was concentrated and the crude mixture was separated by column chromatography over silica gel to give dihydropyran **3** (ethyl acetate–hexane, 3–7).

3. Spectral data

Compound **3b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.18–7.28 (m, 5H), 4.22–4.29 (m, 1H), 3.83 (dt, $J = 1.51$ and 6.79 Hz, 2H), 3.04 (dd, $J = 3.77$ and 10.57 Hz, 1H), 2.84 (dd, $J = 7.55$ and 6.79 Hz, 1H), 2.00–2.12 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 30.95, 36.13, 42.29, 67.17, 81.89, 126.40, 128.30, 129.28, 129.84. EIMS: *m*/*z*: 222 (10) M^+, 187 (10), 131 (25), 103 (100), 91 (50), 77 (15). Anal. Calcd for $C_{13}H_{15}ClO$ (222): C, 70.11; H, 6.79%. Found: C, 70.18; H, 6.72%.

Compound **3c**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.17–7.37 (m, 10H), 5.69–5.73 (m, 1H), 4.79–4.89 (m, 1H), 4.34–4.46 (m, 1H), 3.89–4.07 (m, 2H), 2.49–2.69 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 33.01, 56.35, 64.17, 77.58, 125.53, 126.63, 126.92, 128.84, 128.70, 128.52. EIMS: *m*/*z*: 284 (10) M^+, 249 (15), 167 (100), 153 (10), 139 (20), 117 (15), 105 (60), 77 (50). Anal. Calcd for $C_{18}H_{17}ClO$ (284): C, 75.92; H, 6.02%. Found: C, 75.98; H, 6.13%.

Compound **3d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.03–7.13 (m, 4H), 5.85 (t, $J = 1.75$ Hz, 1H), 3.92 (t, $J = 5.26$ Hz, 2H), 2.70–3.14 (m, 4H), 2.38–2.47 (m, 2H), 1.80–2.09 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.77, 32.22, 33.04, 39.59, 59.49, 73.10, 125.90, 126.02, 128.55, 129.31, 129.75. EIMS: *m*/*z*: 234 (10) M^+, 199 (80), 155 (20), 141 (20), 130 (10), 129 (15), 104 (100), 78 (10). Anal. Calcd for $C_{14}H_{15}ClO$ (234): C, 71.64; H, 6.44%. Found: C, 71.72; H, 6.48%.

Compound **3f**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.24 (d, $J = 4.53$ Hz, 1H), 3.94–4.02 (m, 1H), 3.71–3.81 (m, 1H), 2.71–2.81 (m, 1H), 2.45–2.58 (m, 1H), 2.07–2.09 (m, 3H), 1.55–1.92 (m, 5H), 1.41–1.51 (m, 1H), 1.03–1.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 27.70, 29.32, 28.63, 34.25, 38.40, 43.10, 64.22, 79.83, 125.20, 129.12. EIMS: *m*/*z*: 214 (10) M^+, 179 (15), 131 (100), 83 (10), 67 (40), 55 (20), 41 (40), 39 (20). Anal. Calcd for $C_{12}H_{19}ClO$ (214): C, 67.12; H, 8.92%. Found: C, 67.21; H, 8.98%.

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