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Titanocene(III) mediated 8-*endo* radical cyclizations for the synthesis of eight-membered cyclic ethers

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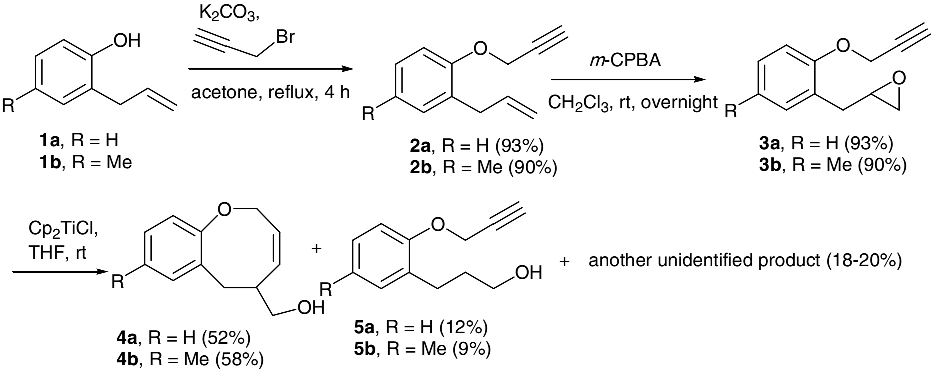
Abstract—Titanocene(III) chloride (Cp_2TiCl) mediated 8-*endo* radical cyclizations towards the synthesis of eight-membered cyclic ethers have been described. Titanocene(III) chloride was prepared in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and activated zinc dust in THF.

The synthesis of medium and large-sized ring ethers is a highly challenging problem to organic chemists due to their widespread occurrence in natural products such as brevetoxin-A, ciguatoxin, prelaureatin, laurallene, helianane, heliannuol and radulanin-E. Several methods[1] have been developed for constructing medium-sized rings including ring-closing metathesis (RCM). Radical cyclization reactions have become an invaluable tool in synthetic organic chemistry, especially in the synthesis of complex natural products, due to the mildness of their generation and predictable behaviour in many organic transformations.[2] In continuation of our study[3] on titanocene(III) chloride (Cp_2TiCl) mediated radical cyclization reactions for the synthesis of five- and six-membered oxygen heterocycles and related natural products, we report here, for the first time, titanocene(III) mediated 8-*endo* radical cyclizations towards the synthesis of eight-membered ethers in good yields. Cp_2TiCl was prepared[4] in situ from commercially available Cp_2TiCl_2 and activated zinc dust in THF. When we had almost completed our study, a report appeared[5] on 7-*endo* radical cyclizations catalyzed by titanocene(III). Thus, 2-allyl phenol **1a**, prepared from allyl phenyl ether via Claisen rearrangement, was treated with propargyl bromide in the presence of K_2CO_3 to yield **2a** in excellent yield (Scheme 1). The propargyl ether **2a** on treatment with *m*-CPBA in CH_2Cl_2 afforded the epoxide **3a** in excellent yield. The epoxide **3a** on treatment with



Scheme 1.

Keywords: Titanocene(III) chloride; 8-*endo* Radical cyclization; Cyclic ethers.

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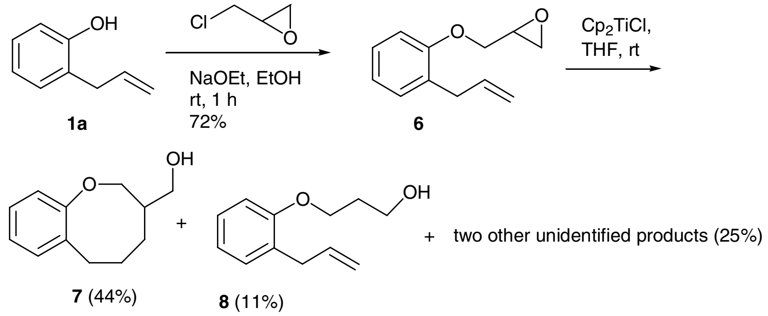

Scheme 2.

Cp_2TiCl in THF under argon afforded[6] the eight-membered ether **4a** in moderate yield (52%) along with the reduced product **5a** (9–12%) and an unidentified product (18–20%). The methyl substituted derivative **4b** (58%) was prepared in a similar manner.

On the other hand, 2-allyl phenol **1a** was transformed into **6** in a single-step using epichlorohydrin (Scheme 2). Reductive opening of the epoxide **6** using Cp_2TiCl in THF under argon afforded the eight-membered ether **7** (44%) along with the reduced product **8** (11%) and two other unidentified products (25%).

In conclusion, we have developed a new methodology to construct eight-membered ring ethers via radical cyclization of epoxides using titanocene(III) chloride as the radical source. Further studies are in progress to extend this protocol for the construction of higher-membered heterocyclic rings and its application to the synthesis of natural products and will be reported elsewhere.

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6. Typical experimental procedure for the radical cyclization reaction: a solution of titanocene dichloride (498 mg, 2 mmol) in dry THF (25 mL) was stirred with activated zinc dust (393 mg, 6 mmol) for 1 h under argon. The resulting green solution was then transferred through a cannula to a dropping funnel and was added dropwise to a magnetically stirred solution of epoxy propargylic ether **3a** (188 mg, 1 mmol) in dry THF (35 mL) at room temperature under argon over 8 h. The reaction mixture was stirred for an additional 6 h and then decomposed with a saturated aqueous solution of NaH_2PO_4. The volatiles were removed under reduced pressure and the residue obtained was extracted with diethyl ether (3 × 50 mL). The combined ether layer was washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the product which was chromatographed over silica gel (60–120 mesh) using 10% ethyl acetate in light petroleum as eluent to yield **4a** (52%) as a viscous oil along with the reduced product **5a** (12%) and another unidentified product (18%). Spectral data of **4a**: IR (neat): 3398, 2920, 2856, 1490, 1207, 1006, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.58 (dd, $J = 15.7$, 10.9 Hz, 1H), 3.22 (dd, $J = 15.7$, 4.9 Hz, 1H), 3.64–3.79 (m, 3H), 4.46 (dd, $J = 15.5$, 4.8 Hz, 1H), 4.94 (dd, $J = 15.5$, 2.4, Hz, 1H), 5.43–5.49 (m, 1H), 5.55–5.62 (m, 1H), 7.00–7.08 (m, 3H), 7.15–7.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.6, 40.7, 67.2, 72.7, 122.7, 124.0, 126.7, 127.5, 130.7, 133.1, 133.4, 156.9. HRMS

calcd for $[C_{12}H_{14}O_2+Na]^+$ 213.0892, found 213.0880. Spectral data of **7**: IR (neat): 3398, 2922, 2873, 1488, 1218, 1008, 744 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.43–1.56 (m, 2H), 1.61–1.72 (m, 2H), 1.99–2.04 (m, 1H), 2.65–2.72 (m, 1H), 2.83–2.88 (m, 1H), 3.41 (d, $J = 6.3$ Hz, 2H), 3.85 (t, $J = 11.2$ Hz, 1H), 4.24 (dd, $J = 11.2$, 4.3 Hz, 1H), 7.01–7.21 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 30.2, 30.3, 30.8, 40.5, 65.0, 78.0, 121.2, 124.2, 127.5, 129.6, 136.7, 157.0. HRMS calcd for $[C_{12}H_{16}O_2+Na]^+$ 215.1047, found 215.1049.