Radical Cyclization of Epoxynitriles Mediated by Titanocene Chloride

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Abstract: The reductive radical cyclization of β -, γ -, δ - and ϵ -epoxynitriles has been achieved using titanocene chloride. The reaction was regioselective and afforded cyclic β -hydroxyketones in good yield. The catalytic version of this radical cyclization is also reported.

Key words: radical cyclization, titanocene chloride, epoxynitrile, cyclobutanone, cycloheptanone

Radical additions to polar multiple bonds have been scarcely explored, and few of them have been exploited in organic syntheses.¹ Radical cyclization onto nitriles is a slow process; the available kinetic data are restricted to the 5-*exo*-intermolecular addition of a radical onto nitrile to give a cyclic iminyl radical.²



Scheme 1 Radical addition to C=N triple bond

The process, as shown in Scheme 1, is slower than that corresponding to the 5-hexenyl $(2.5 \times 10^5 \text{ s}^{-1})$ or 5-hexynyl radical $(1 \times 10^4 \text{ s}^{-1})$ ² Though the 5-*exo*-cylization is not reversible, in some cases, e.g. ring strain or formation of stabilized radical, could be give nitrile translocation.³ We have not found examples of 3-exo- and 4-exo-cyclizations of radical onto nitriles. The 6-exo-4a and 7-exoprocesses^{4b} have been reported scarcely, and often these reactions fail due to competition from faster 1,5-hydrogen transfer processes. The 5-exo-radical cyclization onto nitrile has been the most studied.⁴ The examples reported are based on the creation of the radical from halides or selenides with tributyltin hydride⁴ or the reductive coupling of ketonitriles using a one-electron reducing agent.⁵ Recently, K. Itoh et al.⁶ have reported the Cp₂TiPh mediated reductive cyclization of cyanoketones in the 5- and 6-exomodes to provide an entry to 5- and 6-membered a-hydroxycycloalkanones. The reaction was more efficient in providing bicyclic than monocyclic hydroxyketones; attempts to achieve 7-exo-cyclization failed. Those authors attributed a key role to the coordination of the Cp₂TiPh to

SYNLETT 2004, No. 6, pp 1011–1014 Advanced online publication: 01.04.2004 DOI: 10.1055/s-2004-822901; Art ID: G35703ST © Georg Thieme Verlag Stuttgart · New York the cyano group. However, Cp_2TiCl failed in those cyclizations. T. Hirao has developed a catalytic version of this reaction promoted by $Cp_2TiCl/Me_3SiCl/Zn.^7$

To our knowledge, they have not been studies before relative to the intramolecular reductive coupling of epoxynitriles.

To realize the radical addition to nitriles, we next investigated the reaction of $Cp_2TiCl_{,8}$ generated in situ from Cp_2TiCl_2 and Zn in THF at room temperature, with two series of epoxynitriles with different tethers between the two functional groups. (Figure 1 and Figure 2) Compounds 2–5 were obtained from 3-methyl-3-buten-1-ol and 4-methyl-3-penten-1-ol, and compound 1 from heptanaldehyde by standard procedures. This will be described elsewhere. The radical reactions were carried out by slowly adding the reagent to the epoxynitrile.⁹ The results, which afforded monocyclic compounds, are summarized in Figure 1.

We started our investigation with epoxynitrile 1: instead of the expected cyclization product, which would be a cyclopropanone, we obtained allylic alcohol **1a**, with one carbon less than the starting material. This product must be generated after homolytic cleavage of the oxirane by β fragmentation, with loss of the CN group. The fragmentation could be either homolytic, or heterolytic via two-electron reduction of the epoxide. The reaction deserves further study.

Compound 2 was treated with Cp2TiCl to explore the possibility of cyclobutanone formation. The hydroxycyclobutanone 2a was obtained cleanly in 73% yield. We next examined the 5-exo- and 6-exo-cyclization of the nitriles 3 and 4. Compounds 3 and 4 afforded the hydroxycyclopentanone 3a and the hydroxycyclohexanone 4a, respectively, in an exclusive way. A catalytic version of the reaction with titanocene dichloride has been carried out with epoxynitrile 4, following the conditions reported by A. Gansäuer et al.,¹⁰ which employ a 5% of Cp₂TiCl₂ as reagent and collidine hydrochloride as a source of protons. After 4 days the hydroxyketone 4a was obtained as the unique product of the reaction, however the conversion was low (37%).¹¹ This result demonstrates a free radical mechanism. The 7-exo-cyclization was carried out with epoxynitrile 5, which also afforded a cyclic compound, the hydroxycycloheptanone 5a (45% yield), together with the acyclic unsaturated hydroxynitrile **5b**, and its reduction product 5c in a 1:2 ratio and 27% yield. When the reaction was carried out by addition of





Figure 1 Cycloalkanones from epoxynitriles

compound **5** to the Cp₂TiCl, the ratio of the products was inverted (**5a** 30% and **5b:5c** 62%, 1:2). This means that an excess of Ti(III) promotes the coupling of this species with the carbon radical instead of the coupling with the cyano group (Scheme 2).

A common aspect for all reactions with titanocene dichloride is the regioselectivity in the homolytic cleavage of the oxirane ring.

In order to broaden the radical cyclization study and to find synthetic applications for this method, we accomplished the cyclization of a series of cyclic epoxynitriles that might afford interesting bicyclic compounds that would find use as intermediates in the synthesis of the natural products.

Compound **6** was obtained from commercial 3,7-dimethyl-2,6-octadienenitrile, and compounds **7–10** from α cyclocitral¹² by standard procedures, to be described elsewhere.¹³



Scheme 2 Reaction mechanism of Cp₂TiCl with epoxynitriles

Attempts to obtain the desired bicyclo[4.1.0]heptanone from epoxynitrile **6** with Cp₂TiCl were unfruitful. The only product obtained was the unsaturated cyanoalcohol **6a**. It is interesting to note that in this case β -elimination corresponded to the hydrogen instead of the cyano group, as we observed for compound **1**. The 4-*exo*-cyclization of compound **7** was very clean and afforded **7a** as a single diastereoisomer in good yield (89%). Similarly, the epoxynitrile **8** afforded only cyclized products by the 5*exo*-mode: the hydroxy ketones **8a** and **8b** (ratio 5:1) in 80% yield.

The behaviour of the epoxynitrile **9** against Cp_2TiCl , slightly different from its parent compound, gave the desired bicyclic compound **9a** (43%), together with the cyanoalcohol **9b** (36%).¹⁴

It should be noted that the *cis*-fused isomer was the major compound obtained from **8** and the *trans*-fused isomer was the exclusive isomer from **9**.

Furthermore, the reaction of the ε -epoxynitrile **10** did not give the desired 7-*exo* reductive cyclization product. Instead, the cyanoalcohol **10a** was obtained. This result contrasts with the result obtained for the acyclic epoxynitrile **5**.

The present epoxynitrile cyclization is a novel and powerful route to β -hydroxycycloalkanones. The synthetic versatility of this method was demonstrated in the preparation of bicyclic compounds. Also remarkable is the easy and high yield synthesis of cyclobutanones and cycloheptanones by this intramolecular radical addition, for which there are few preparation methods in the literature.



Figure 2 Bicyclic hydroxycycloalkanones from epoxynitriles

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- (9) General Procedure. A mixture of Cp₂TiCl₂ (2.2 mmol) and Zn (3 mmol) in strictly deoxygenated THF (4 mL) was stirred at r.t. until the red solution turned green. In a separate flask, the epoxy nitrile (1 mmol) was dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added via cannula to the epoxide solution. After 30 min, an excess of sat. NaH₂PO₃ was added, and the mixture was stirred for 20 min. The product was extracted into Et₂O and washed with sat. NaHCO₃ and H₂O. After removal of the solvent, the crude product was purified by flash chromatography.
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- (11) Catalytic Radical Reaction. General Procedure. To a mixture of collidine hydrochloride (2.5 mmol), epoxy nitrile (1.0 mmol), and Zn (2.0 mmol) in THF (10 mL) was added titanocene dichloride (0.05 mmol), and the resulting mixture was stirred at r.t. After addition of Et_2O , the mixture was washed with H_2O , 2 N HCl, H_2O , sat. aq NaHCO₃, and H_2O , and dried. After removal of the solvent, the crude product was purified by flash chromatography on silica gel.
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- (13) The structure of epoxynitriles 6–10, in which the oxiranic oxygen and the side chain are *cis*, is based on spectroscopic data and comparison with the model compound I, whose structure was determined by X-ray crystallography (Figure 3): Mori, K.; Aki, S.; Kido, M. *Liebigs Ann. Chem.* 1993, 83.



Figure 3

(14) (a) The stereochemistry of the bicyclic hydroxyketone **7a** was established by ¹H NMR and ¹³C NMR spectra, H-C correlations and NOE experiments. The hydroxyketone **8a** was reported by: Fernández-Mateos, A.; Pascual Coca, G.; Rubio González, R.; Tapia Hernández, C. *J. Org. Chem.* **1996**, *61*, 9097; the stereochemistry of hydroxyketone **9a** was determined by ¹H NMR and ¹³C NMR spectra. (b) **2- Methyl-1-nonen-3-ol (1a)**: IR (film): 3370, 1653 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.88$ (3 H, t, *J* = 7.0 Hz), 1.20–1.60 (10 H, m), 1.72 (3 H, s), 4.05 (1 H, t, *J* = 6.5 Hz), 4.83 (1 H, s),

4.93 (1 H, s) ppm. 13 C NMR (CDCl₃): $\delta = 13.98$, 17.41, 22.53, 25.49, 29.16, 31.74, 34.95, 75.97, 110.80, 147.67 ppm. MS (EI): m/z (%) = 156 (3) [M⁺], 113 (11), 99 (11), 94 (12), 86 (18), 71 (100), 55 (20). HRMS (IE): 156.1511 (M⁺, C₁₀H₂₀O), calcd 156.1514. **2-Hydroxymethyl-2-methyl-cyclobutanone (2a)**: IR (film): 3461, 1775 cm⁻¹. 11 H NMR (CDCl₃): $\delta = 1.18$ (3 H, s), 1.75 (1 H, m), 2.20 (1 H, m), 2.99 (2 H, m), 3.53 (1 H, d, J = 15.0 Hz), 3.69 (1 H, d, J = 15.0 Hz) ppm. 13 C NMR (CDCl₃): $\delta = 17.76$, 21.25, 43.16, 65.75, 66.00, 215.21 ppm. MS (EI): m/z (%) = 96 (6) [M⁺ - 16], 85 (7), 69 (44), 57 (100). HRMS (IE): 114.0678 (M⁺, C₆H₁₀O₂), calcd 114.0680.

2-Hydroxymethyl-2-methyl-cyclopentanone (3a): IR (film): 3445, 1732 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.98$ (3 H, s), 1.60–2.40 (6 H, m), 3.42 (1 H, d, J = 10.9 Hz), 3.58 (1 H, d, J = 10.9 Hz) ppm. ¹³C NMR (CDCl₃): $\delta = 18.74$, 19.20, 33.05, 38.29, 50.24, 66.91, 224.31 ppm. MS (EI): m/z = 128(9) [M⁺], 110 (9), 97 (9), 82 (27), 69(89), 57 (100). HRMS (IE): 128.0836 (M⁺, C₇H₁₂O₂), calcd 128.0837.

2-Hydroxymethyl-2-methyl-cyclohexanone (4a): IR (film): 3443, 1703 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 1.11$ (3 H, s), 1.50–2.00 (6 H, m), 2.24 (1 H, dt, $J_1 = 4.2$ Hz, $J_2 = 14.0$ Hz), 2.46 (1 H, ddd, $J_1 = 6.0$ Hz, $J_2 = 12.5$ Hz, $J_3 = 14.2$ Hz), 3.47 (2 H, dd, $J_1 = 12.0$ Hz, $J_2 = 17.0$ Hz) ppm. ¹³C NMR (CDCl₃): $\delta = 20.12$, 20.69, 27.19, 35.50, 38.89, 50.10, 68.85, 217.88 ppm. MS (EI): m/z (%) = 124 (27) [M⁺ – 18], 112 (36), 97 (18), 82 (100), 69 (50), 55 (97). HRMS (IE): 142.1001 (M⁺, C₈H₁₄O₂), calcd 142.0994.

2-Hydroxymethyl-2-methyl-cycloheptanone (5a): IR (film): 3447, 1694 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 1.14$ (3 H, s), 1.40-1.80 (8 H, m), 2.43 (1 H, m), 2.63 (1 H, m), 3.37 (1 H, d, J = 11.0 Hz), 3.71 (1 H, d, J = 11.0 Hz) ppm. ¹³C NMR $(CDCl_3): \delta = 21.20, 24.70, 26.21, 30.55, 34.96, 41.10, 51.98,$ 69.54, 219.68 ppm. MS (EI): *m*/*z* (%) = 156 (5) [M⁺], 138 (36), 126 (11), 109 (14), 95 (23), 81 (24), 69(79), 56 (100). HRMS (IE): 156.1154 (M⁺, C₉H₁₆O₂), calcd 156.1150. 7-Hydroxymethyl-7-heptenenitrile (5b) and 8-hydroxy-7-methyl-octanenitrile (5c): IR (film): 3432, 2926, 2861, 2247, 1715, 1653, 1464, 1427, 1375 cm⁻¹. ¹H NMR (CDCl₃): δ 0.89 (3 H, d, *J* = 6.7 Hz), 1.00–2.10 (20 H, m), 2.34 (4 H, br s), 3.39 (1 H, dd, $J_1 = 6.4$ Hz, $J_2 = 10.4$ Hz), $3.46 (1 \text{ H}, \text{ dd}, J_1 = 6 \text{ Hz}, J_2 = 10.4 \text{ Hz}), 4.84 (1 \text{ H}, \text{ s}), 5.01$ (1 H, s) ppm. ¹³C NMR (CDCl₃): δ = 16.45, 17.01 (2 C), 25.13, 25.22, 26.05, 26.76, 28.26, 28.84, 32.47, 32.71, 35.52, 65.64, 68.00, 109.53, 119.67, 119.74, 148.42 ppm. (1SR,5RS)-2,2-Dimethyl-5-hydroxy-6-methylencyclohexanecarbonitrile (6a): IR (film): 3435, 2241 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 1.00 (3 \text{ H, s}), 1.17 (3 \text{ H, s}), 1.40-1.80$ (4 H, m), 3.48 (1 H, s), 4.40 (1 H, m), 5.23 (2 H, s) ppm. ¹³C NMR (CDCl₃): δ = 21.78, 29.06, 29.56, 32.91, 35.58,

43.83, 70.30, 112.96, 118.58, 142.31 ppm. MS (EI): m/z (%) = 165 (2) [M⁺], 150 (98), 134 (10), 107 (11), 97 (12), 85 (16), 69 (100). HRMS (IE): 165.1152 (M⁺, C₁₀H₁₅NO), calcd 165.1154.

(1SR,5RS,6SR)-5-Hydroxy-2,2,6-trimethyl-bicyclo [4.2.0]octan-7-one (7a): Mp 91-94 °C. IR (film): 3482. 1769 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.92$ (3 H, s), 1.00 (3 H, s), 1.18 (3 H, s), 1.22 (1 H, m), 1.62 (1 H, m), 1.78 (3 H, m), 2.68 (1 H, dd, $J_1 = 9.0$ Hz, $J_2 = 16.4$ Hz), 3.06 (1 H, dd, $J_1 = 10.6$ Hz, $J_2 = 16.4$ Hz), 3.83 (1 H, br s) ppm. ¹³C NMR $(CDCl_3): \delta = 20.94, 26.70, 27.86, 28.93, 29.39, 29.49, 43.23,$ 47.71, 64.59, 69.99, 212.04 ppm. MS (EI): m/z (%) = 182 (2) [M⁺], 167 (15), 140 (8), 122 (69), 107(60), 84 (100), 69(31). HRMS (IE): 182.1302 (M^+ , $C_{11}H_{18}O_2$), calcd 182.1307. (3aSR,7RS,7aRS)-7-Hydroxy-4,4,7a-trimethyloctahydro-inden-1-one (8b): IR (film): 3479, 1738 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.94$ (3 H, s), 0.96 (3 H, s), 1.05 (3 H, s), 2.35 (2 H, m), 3.69 (1 H, dd, $J_1 = 4.8$ Hz, $J_2 = 11.1$ Hz) ppm. ¹³C NMR (CDCl₃): δ = 10.32, 19.26, 21.49, 26.48, 31.39, 31.90, 39.22, 51.47, 52.27, 76.63, 222.89 ppm. MS (EI): m/z (%) = 196 (12) [M⁺], 181 (14), 140 (53), 123 (15), 97 (100), 81 (22), 69(15), 55 (24). HRMS (IE): 196.1460 $(M^+, C_{12}H_{20}O_2)$, calcd 196.1463. (4aSR,8RS,8aRS) 8-Hydroxy-5,5,8a-trimethyloctahydro-naphthalen-1-one (9a): IR (film): 3567, 1694 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.89$ (3 H, s), 0.94 (3 H, s), 1.20 (3 H, s), 1.20-1.80 (7 H, m), 2.00-2.20 (2 H, m), 2.54 (2 H, m), 3.86 (1 H, m) ppm. ¹³C NMR (CDCl₃): δ = 13.29, 20.67, 22.08, 25.25, 25.68, 32.70, 34.05, 37.71, 39.58, 52.12, 54.19, 73.40, 218.09 ppm. MS (EI): m/z (%) = 210 (7) [M⁺], 192 (20), 185 (5), 167 (5), 154 (16), 136 (11), 121 (8), 111 (100), 95 (11), 81 (16), 69 (20), 55 (52). HRMS (IE): 210.3124 (M⁺, C₁₃H₂₂O₂), calcd 210.3126. (1RS,5RS)-4-(5-Hydroxy-2,2,6-trimethyl-cyclohexyl)**butyronitrile (9b)**: IR (film): 3447, 2247 cm⁻¹. ¹H NMR $(CDCl_3)$: $\delta = 0.85 (3 H, s), 0.89 (3 H, s), 0.90 (3 H, d, J = 7.4)$ Hz), 1.10–1.60 (10 H, m), 2.35 (2 H, t, *J* = 6.2 Hz), 3.67 (1 H, m) ppm. ¹³C NMR (CDCl₃): $\delta = 8.67, 17.44, 23.33, 24.28$ (2 C), 26.04, 26.96, 31.45 (2 C), 33.12, 35.62, 47.49, 73.74, 119.55 ppm. MS (EI): m/z (%) = 209(23) [M⁺], 159 (17), 136 (17), 125 (18), 110 (24), 97 (31), 81(32), 69 (57), 55 (100). HRMS (IE): 209.1780 (M⁺, C₁₃H₂₃NO), calcd 209.1779. (1RS,5RS) 5-(5-Hydroxy-2,2,6-trimethyl-cyclohexyl)pentanonitrile (10a): IR (film): 3432, 2247 cm⁻¹. ¹H NMR

pentanonitrile (10a): IR (film): 3432, 2247 cm⁻¹. ¹H NMR (CDCl₃): $\delta = 0.81$ (3 H, s), 0.83 (3 H, s), 0.85 (3 H, d, J = 7.4 Hz), 1.10-1.70 (11 H, m), 2.04 (1 H, m), 2.32 (2 H, t, J = 7.0 Hz), 3.63 (1 H, br s) ppm. MS (EI): m/z (%) = 205(45) [M⁺] 149 (95), 123 (47), 95 (36), 81 (100). HRMS (IE): 223.1931 (M⁺, C₁₄H₂₅NO), calcd 223.1936.