Approach to Substituted Methylcarbapenems and Benzocarbacephems by Radical Cyclization Using Cp_2TiCl

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Abstract: The reductive radical cyclization of 4-(1-methyl-2-phenyloxiranyl)-β-lactams has been achieved using titanocene monochloride. The reaction was regioselective and diastereoselective to afford carbapenems and benzocarbacephems. A rearrangement of β-hydroxy-β-phenylketones to give benzaldehyde was observed when the nitrile function was used as radical acceptor.

Key words: radical cyclization, titanocene chloride, methylcarbapenem, benzocarbacephem antibiotics, lactams

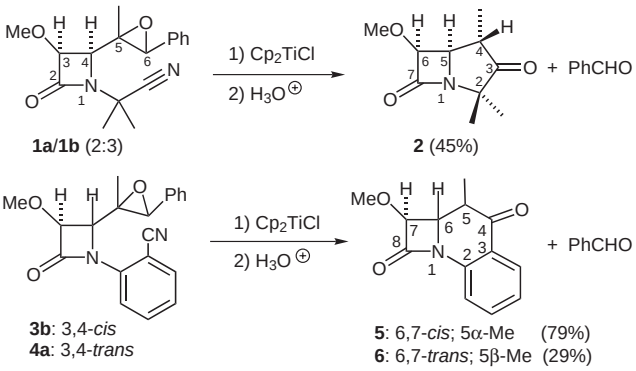
Titanium(III) chloride has been extensively used as a mild and useful reagent for various chemical transformations such as reduction of aromatic aldehydes,[1] glycosyl halides,[2] vicinal dihalides,[3] and sulfoxides.[4] In particular, bis(cyclopentadienyl)titanium(III) chloride is a well-known titanocene(III) reagent that is useful in promoting radical carbon–carbon bond formation. Many of the reported reactions involve either carbonyl compounds,[5] epoxides[6] or alkyl halides[7] as radical precursors. Alkenes, alkynes,[6] carbonyl compounds[8] and the cyano group[9] have been reported as radical acceptors.

Nowadays, radical cyclization of epoxides using titanocene(III) species leading to the synthesis of a number of naturally occurring compounds and related products has attracted much attention.

In previous articles[10] on the Cp_2TiCl-promoted reductive ring opening of enantiomerically pure 4-epoxy-2-azetidinones via single-electron transfer, we described the cyclization of benzyl and tertiary alkyl radicals to conjugated esters and aldehydes as a new approach to polycyclic β-lactams.

In order to extend the application of these reactions to polar multiple bonds, we have also applied this methodology to δ- and ε-epoxynitrile-2-azetidinones[11] and, surprisingly, benzaldehyde elimination was observed during our study on the cyclization of the epoxynitriles with Cp_2TiCl (Scheme 1).[12]

When a 2:3 diastereomeric mixture of racemic epoxynitriles **1a**/**1b** in THF was slowly added to a green solution of Cp_2TiCl in THF, 4α-methylcarbapenem **2** and benzaldehyde were obtained as reaction products.[13] Similar behavior was observed when we explored the 6-*exo* radical



1a/**1b** (2:3) **2** (45%)

3b: 3,4-*cis*
4a: 3,4-*trans*

5: 6,7-*cis*; 5α-Me (79%)
6: 6,7-*trans*; 5β-Me (29%)

Scheme 1 Reaction of epoxynitriles **1a**/**1b**, **3b**, and **4a** with Cp_2TiCl (**a** = 5α,6α-epoxy, **b** = 5β,6β-epoxy)

process from each one of the pure epoxybenzonitrile-2-azetidinones **3** and **4** (Scheme 1), which afforded benzaldehyde and the 5-methylbenzocarbacephems **5** and **6**, respectively.

Benzaldehyde elimination was also observed when the green solution of Cp_2TiCl was added to the epoxides solutions (normal way), but in this case bigger amounts of untransformed starting materials were recovered.

The structures proposed for the reaction products **2**, **5** and **6** were rigorously established by IR, ^1H NMR and ^{13}C NMR (including 2D experiments) and MS spectroscopy.[14]

The evolution of the epoxides **3** and **4** can be explained as shown in Scheme 2 (a similar scheme can be depicted for the transformation of **1** into the bicyclic lactam **2**).

Although the reductive opening of the oxiranyl ring with titanocene monochloride (Scheme 2) should take place with the formation of the best stabilized benzylic radical intermediate **I** (or the equivalent from **1**) the evolution to the lactams **2**, **5**, and **6** reflects the reversibility of the oxirane ring opening because these cyclic products should come from the less stable tertiary homobenzylic radical **II**. This radical should be more reactive and have better accessibility to the cyano group than the benzylic radical **I**, driving the equilibrium towards the observed products. However, this behavior was not observed when the homobenzylic radical was secondary as we have recently observed,[11] perhaps because it is not enough stabilized to be in an appreciable amount in equilibrium with the benzylic radical. In that case, the cyclization products came only from the addition of the benzylic radical to the cyano group.

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The radical **II** cyclizes to the radical **III**, followed by coupling to the titanocene(III) chloride present in the reaction medium [**IV**, pathway (a)] and then, after hydrolysis, gaves the β-hydroxyketones **7** which rearrange to the products **2**, **5**, or **6** with loss of benzaldehyde. Otherwise, the radical **III**, in equilibrium with the alkoxy radical **V** [pathway (b)], may lose benzaldehyde through a typical β-cleavage generating a new radical **VI**. This stabilized radical can further be coupled with titanocene(III) chloride available in the reaction medium to give the organometallic species **VII**. Finally, decomposition with aqueous KH_2PO_4 and work-up can provide the β-lactams **2**, **5**, and **6**.

It is noteworthy that, contrary to the results we obtained in the reactions of other 4-(1-methyl-2-phenyloxiranyl)-2-azetidinones with Cp_2TiCl (not yet published), we have not observed in the above reactions the β-lactam ring opening by evolution of the homobenzylic radical **II** as shown in Scheme 2.

The thermodynamic stability can explain the diastereoselectivity observed in the cyclization products through pathways (a) or (b) so we carried out a molecular modeling study to determine the difference of energy minima between each pair of diastereomers.[15] It showed that the energy differences are 0.6 (for **2**), 2.5 (for **5**) and 1.2 (for **6**) kcal/mol, with the products with *trans*-arrangement of H4 and H5 (or H5 and H6) being more stable. We presume that the benzaldehyde elimination should proceed via the ionic pathway (a) because in pathway (b) the presence of the titanium(III) chloride in the reaction medium should give rise to the reduction or to the intramolecular coupling of benzaldehyde.[1]

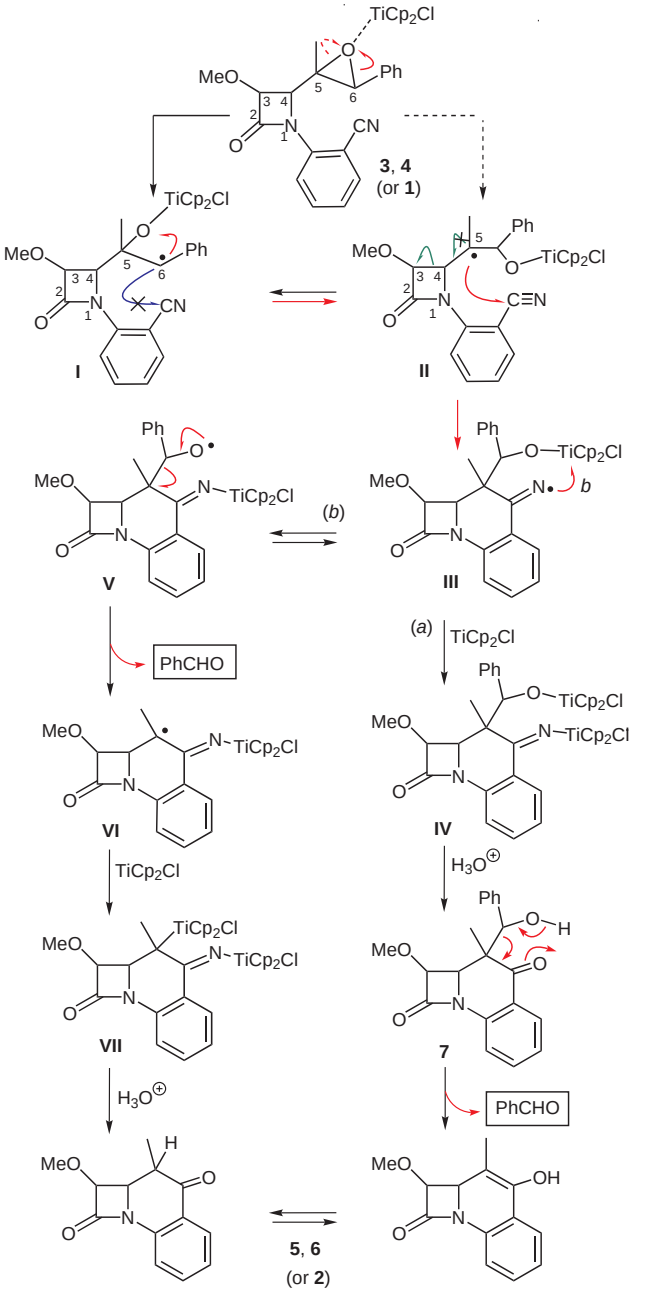
Further evidence for this hypothesis was obtained from the reaction of epoxyaldehydes **8** with Cp_2TiCl (Scheme 3).

The reaction of a 1:2 diastereomeric mixture of epoxyaldehydes **8a**/**8b** with Cp_2TiCl, under the reported reaction conditions, gave a mixture of the bicyclic β-lactams **9a**/**9b**, from which the pure compound **9b** could be isolated by column chromatography.[14]

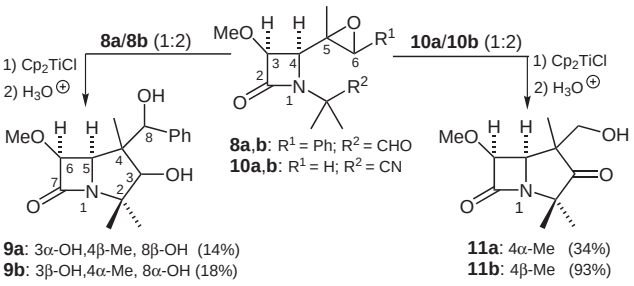
Epoxyaldehydes **8a** and **8b** upon treatment with Cp_2TiCl could also progress through radical intermediates related to **III**–**V** (Scheme 4) but the presence of the hydroxybenzyl group in β-lactams **9a** and **9b** rules out the alternative pathway (b).

Finally, in order to investigate the flexibility in the rearrangement of hydroxybenzylketones in carbapenem systems we carried out the reaction of the epoxynitriles **10a**,**b** with Cp_2TiCl (Scheme 3).

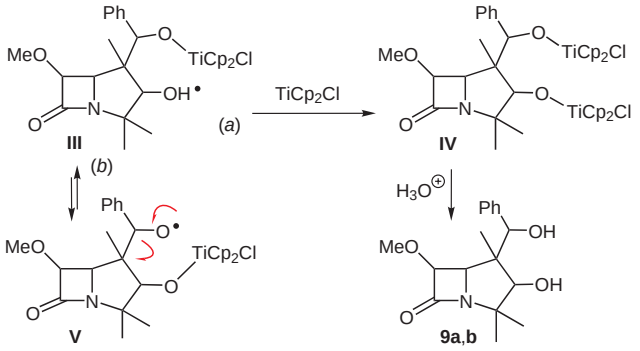
In this case, the cyclization of the tertiary radical at C5 generated from a 1:2 mixture of epoxynitriles **10a**,**b** with Cp_2TiCl, afforded a mixture of the corresponding carbapenems **11a**/**11b**, from which the pure compound **11b** could be isolated by column chromatography.[14] The hydroxyl IR absorption bands as well as the presence of a typical AB system for an hydroxymethylene group in the



Scheme 2 Proposed mechanisms explaining the formation of compounds **5**, **6**, and benzaldehyde



Scheme 3 Reaction of epoxides **8a**/**8b** and **10a**/**10b** with Cp_2TiCl (**a** = 5α,6α-epoxy, **b** = 5β,6β-epoxy)



Scheme 4 Proposed mechanism explaining the formation of compounds **9a**,**b**

^{1}H NMR spectra of compounds **11a** and **11b**, indicates that the rearrangement of these β-hydroxyketones has not occurred.

The presence of the benzyl group in the hydroxybenzylketones **7** (Scheme 2) may probably be the reason for the elimination of benzaldehyde in the radical cyclization of epoxynitriles **1**, **3**, and **4**. The C4–C8 bond energies in compounds **11a** and **11b** with a hydroxymethyl group at C4 are larger than those of the β-hydroxy-β-phenylketones **7**.

In summary, we have analyzed the reactivity of 4-(1-methyl-2-phenyloxiranyl)-β-lactams with Cp_2TiCl using cyano and formyl groups as radical aceptors and the shared aspect for these reactions is the regioselectivity in the homolytic cleavage C5–O of the oxirane ring. The benzaldehyde elimination observed in the above examples can be exploited as a new route to 4-methylcarbapenems (stable antibiotics to kidney dehydropeptidase)[16] and 5-substituted benzocarbacephems (β-lactamase inhibitors).[17] Further studies on the mechanistic and stereochemical implications of this reaction are underway and will be reported in due course.

Acknowledgment

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(12) The stereochemistry depicted in Schemes 1 and 3 for the oxirane ring in epoxides **1a**,**b**, **8a**,**b**, and **10a**,**b** were tentatively proposed by comparison of the respective polarities and ^{1}H NMR data with those of pure 4-(1-methyl-2-phenyloxiranyl)-β-lactams **Ia** and **Ib** (Figure 1).[10b] This will be described elsewhere.

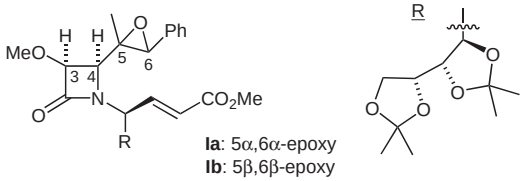

Figure 1

(13) **Typical Procedure**
A solution of the specific epoxide (1.0 mmol) in THF (17.0 mL) was added dropwise to a green suspension of Cp_2TiCl, generated from titanocene dichloride (548 mg, 2.2 mmol) and activated zinc granules (262 mg, 4.0 mmol), in anhyd and strictly deoxygenated THF (12.5 mL). The reaction mixture was stirred at r.t. until a color change from green to orange was observed, and then the reaction was quenched with 10% v/v aq KH_2PO_4 (30.0 mL). The aqueous phase was extracted with EtOAc and the organic combined extracts were filtered through Celite®, dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude material obtained was purified by column chromatography on silica gel.
(14) All these compounds are racemic mixtures but only one stereoisomer is depicted for simplicity. The C3-, C4- or C5-configuration for bi- or tricyclic β-lactams is based on spectroscopic data and the configuration proposed for the starting material. This will be described elsewhere.
Selected Data for Cyclization Products
Carbapenem **2**: R_f = 0.50 (7:3 benzene–EtOAc). IR (neat): ν = 3500, 1774, 1755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (3 H, s), 1.53 (3 H, s), 1.21 (3 H, d, *J* = 7.1 Hz), 2.73 (1 H, dq, *J* = 7.1, 8.7 Hz), 3.52 (3 H, s), 3.62 (1 H, dd, *J* = 4.0, 8.7 Hz), 4.68 (1 H, d, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 21.0, 23.4, 41.0, 58.9, 59.1, 64.4, 83.4, 170.9, 218.0. HRMS–FAB: *m/z* calcd for $C_{10}H_{15}NO_3Na$ [M$^+$ + 23]: 220.0944; found: 220.0949.
Benzocarbacephem **5**: R_f = 0.28 (95:5 benzene–EtOAc). IR (neat): ν = 1759, 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (3 H, d, *J* = 6.5 Hz), 3.01 (1 H, dq, *J* = 6.5, 12.8 Hz), 3.68 (3 H, s), 3.98 (1 H, dd, *J* = 4.5, 12.8 Hz), 4.79 (1 H, d,

J = 4.5 Hz), 7.21 (1 H, dt, *J* = 1.2, 7.9 Hz), 7.52 (1 H, dt, *J* = 1.4, 7.9 Hz), 7.55 (1 H, dd, *J* = 1.2, 7.9 Hz), 7.95 (1 H, dd, *J* = 1.4, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 40.5, 57.7, 59.5, 84.9, 119.4, 123.2, 124.7, 127.7, 134.9, 138.0, 163.7, 194.8. HRMS–FAB: *m/z* calcd for $C_{13}H_{13}NO_3Na$ [M^+ + Na]: 254.0788; found: 254.0795.

Benzocarbacephem **6**: R_f = 0.25 (95:5 benzene–EtOAc). IR (neat): ν = 1761, 1684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (3 H, d, *J* = 6.6 Hz), 2.76 (1 H, dq, *J* = 6.6, 12.9 Hz), 3.60 (3 H, s), 3.88 (1 H, dd, *J* = 2.0, 12.9 Hz), 4.66 (1 H, d, *J* = 2.0 Hz), 7.19 (1 H, dt, *J* = 1.0, 7.9 Hz), 7.57 (1 H, dt, *J* = 1.5, 7.9 Hz), 7.65 (1 H, dd, *J* = 1.0, 7.9 Hz), 7.91 (1 H, dd, *J* = 1.5, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 43.9, 58.1, 61.4, 90.3, 118.7, 121.9, 124.5, 127.9, 135.2, 138.3, 161.3, 193.3. HRMS–FAB: *m/z* calcd for $C_{13}H_{13}NO_3Na$ [M^+ + Na]: 254.0788; found: 254.0800.

Carbapenem **9a** (from enriched mixtures): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (3 H, s), 1.23 (3 H, s), 1.47 (3 H, s), 2.63 (3 H, s), 2.79 (1 H, s), 3.56 (1 H, d, *J* = 4.0 Hz), 4.21 (1 H, d, *J* = 4.0 Hz), 4.76 (1 H, s), 7.24–7.39 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.1, 19.3, 29.5, 58.5, 58.9, 59.1, 62.9, 82.4, 83.9, 127.5, 127.9, 141.3, 171.3.

Carbapenem **9b**: R_f = 0.37 (1:1 hexane–EtOAc). IR (neat): ν = 3411, 1731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (3 H, s), 1.28 (3 H, s), 1.42 (3 H, s), 2.55 (3 H, s), 3.25 (1 H, s), 3.71 (1 H, d, *J* = 4.3 Hz), 4.39 (1 H, d, *J* = 4.3 Hz), 4.60 (1 H, s), 7.24–7.39 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.4, 19.1, 29.7, 52.7, 53.4, 58.7, 59.1, 59.2, 78.9, 83.6, 126.8, 128.3, 141.1, 170.6. HRMS–FAB: *m/z* calcd for $C_{17}H_{24}NO_4$ [M^+ + 1]: 306.1700; found: 306.1722.

Carbapenem **11a** (from enriched mixtures): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (3 H, s), 1.10 (3 H, s), 1.64 (3 H, s), 2.12 (1 H, br s), 3.51 (3 H, s), 4.07 (1 H, d, *J* = 4.5 Hz), 4.29 (2 H, d, *J* = 1.9 Hz), 4.75 (1 H, d, *J* = 4.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 21.8, 23.3, 54.6, 55.7, 59.2, 65.0, 66.9, 84.7, 171.0, 221.4.

Carbapenem **11b**: R_f = 0.34 (1:1 benzene–EtOAc). IR (neat): ν = 3473, 1746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (3 H, s), 1.17 (3 H, s), 1.62 (3 H, s), 2.12 (1 H, br s), 3.51 (3 H, s), 3.61 (1 H, d, *J* = 11.1 Hz), 3.85 (1 H, d, *J* = 11.1 Hz), 4.12 (1 H, d, *J* = 4.5 Hz), 4.77 (1 H, d, *J* = 4.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 21.7, 23.1, 54.6, 55.7, 59.2, 64.0, 65.2, 84.7, 171.0, 221.4. HRMS–FAB: *m/z* calcd for $C_{11}H_{17}NO_4Na$ [M^+ + 23]: 250.1055; found: 250.1050.

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