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Titanium-Mediated Reaction of Cycloheptatriene with Aldehydes : A New 'Electron-Reversed' Approach to the Functionalization of Seven-Membered Ring

Jan Szymoniak, Didier Felix and Claude Moïse*

Laboratoire de Synthèse et d'Electrosynthèse Organométalliques associé au CNRS, Faculté des Sciences, 6 bd Gabriel,
21000 Dijon, France.

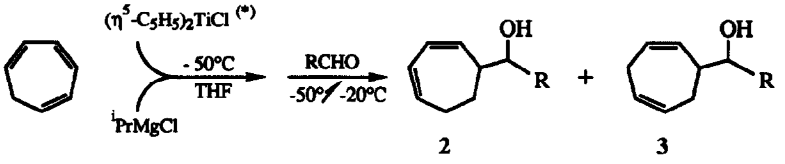
Abstract : The cycloheptenyl-η^3-allyltitanium species prepared starting from cycloheptatriene by the action of titanocene dichloride and an alkyl Grignard reagent, undergo in situ addition to aldehydes to produce a mixture of isomeric 1,4- and 1,3-cycloheptadienyl alkyl (aryl) carbinols, 3 and 2 respectively. The increasing 3/2 ratio with the increase of steric hindrance in aldehyde was observed. The reaction opens a simple way to the variously functionalized 1,4-cycloheptadienes, some of which are closely related to biologically active compounds.

If appropriately functionalized, the seven-membered rings provide interesting and useful building blocks for e.g. (+)-Prelog–Djerassi lactone[1] macrolide antibiotics[1,2] or sugars.[3] However, until recently there was a lack of general methods for the selective functionalization of this ring. Among the methodologies developed, those using organometallic chemistry usually involve a nucleophile addition to the cationic cycloheptadiene-iron[4] or-molybdenum[5] complexes and also palladium -catalyzed nucleophile 1,4-addition reactions to cyclohepta-1,3-diene.[6] The structural limitations of this approach are obvious. They could be overcome by developing a complementary 'reversed polarity' strategy of functionalization of the seven-membered ring. The purpose of this Letter is to report on the preliminary developments of such a strategy : the addition of aldehydes to a nucleophile synthon derived from cycloheptatriene.

The archetype for the conversion of a triene to an allylic anion equivalent could involve the formation of cycloheptenyl-η^3-allyltitanocenes related to the well known simpler η^3–allyltitanocene complexes. The latter may be readily obtained starting from a diene in the presence of titanocene dichloride and an alkyl Grignard reagent. The striking feature of these complexes lies in that they add to aldehydes in a highly regio- and stereocontrolled fashion.[7] However, to the best of our knowledge, there are no precedents for the use of alkenyl-η^3-allyltitanocenes as nucleophile reagents. Thus, we first established the experimental conditions required.

The cycloheptenyl-η^3-allyltitanium complexes have been formed in a one-pot reaction including two successive reduction steps. In a representative procedure, a THF solution of titanocene dichloride (5 mmoles) was treated under argon at room temperature with an equivalent of isopropylmagnesium chloride (2M solution in THF). After stirring for 0.5 h at rt, the green solution of

(η^5-C_5H_5)$_2$TiCl was cooled to -50°C. Freshly distilled cycloheptatriene (1.5 eq.) and a second portion of organomagnesium reagent (1 eq.) were successively added. After 10 min at -50°C, the aldehyde was added to this solution of allyltitanium complex and the mixture was allowed to warm gradually to -20°C (0.5 h). Finally, basic workup (Na_2CO_3 aq.) was followed by extraction with ether and flash chromatography separation over SiO_2.



(*) = (η^5-C_5H_5)$_2$TiCl_2 + ^{i}PrMgCl, r.t.

Table 1

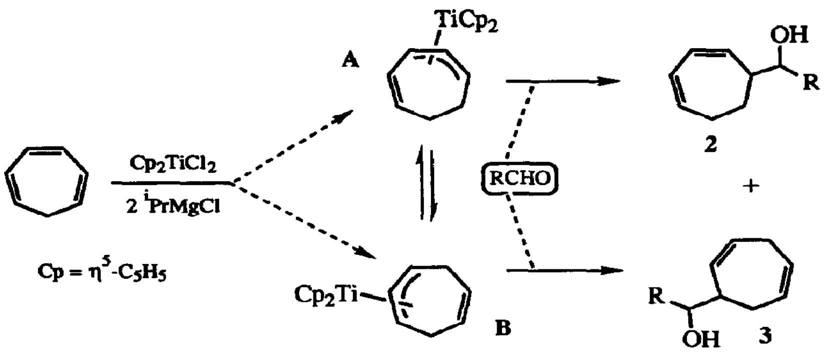
RCHO 1	R	3/2 ratio (yield of 3)	d.e. in 2[9] (%)
1a	C_6H_5	1.44 (42)	60
1b	C_2H_5	2.03 (50)	57
1c	n-C_5H_{11}	1.88 (48)	60
1d	$(CH_3)_2CH$	3 (55)	59
1e	$(CH_3)_3C$	24 (73)	56

The results of the reactions employing aldehydes **1a-e** are summarized in Table 1. Only two among the three possible isomeric homoallylic alcohols, namely **2** and **3**, were formed in each case.[8] As can be seen in Table 1, the **3/2** ratio increases in a significant manner with the increasing steric hindrance in the aliphatic alkyl chain. Analysis of the crude product mixture by 400 MHz ^1H NMR spectroscopy indicated the presence of only one diastereomeric product **3**. The stereochemical purity of **3** was confirmed by ^{13}C NMR spectroscopy and gas chromatography. Unlike for the regioisomer **3**, an almost equal mixture[9] of both diastereomers **2** was detected by GC-coupled mass spectroscopy. Furthermore, Collins reagent oxidation of homoallyl alcohol **2a** provided 2,4-cycloheptadienyl phenyl ketone as the sole product.

The formation in each case of isomeric alcohols **2** and **3** reveals the concomitant existence of two precursor allyltitanium complexes, **A** and **B** respectively (Scheme 1). An equilibrium between them, perturbated by the reacting aldehyde, can be assumed on account of the variable **3/2** product ratio. In this context, the total absence of the second regioisomer related to complex **A** can be readily explained by the loss of conjugation which would occur during the formation of this product.

A high regiocontrol has been exercised in the kinetically determined addition step. Particularly, the increase of the **3/2** product ratio with the increasing steric hindrance in the aldehyde R group implies that the steric requirements should be more severe on the route leading from **A** to **2** than on that leading from **B** to **3**. Because of the supposed reactant-like transition state for this reaction[10], the latter assumption implies a larger steric hindrance for **A** than for **B**. The reason for this can be easily understood. When a vinyl group is attached to the terminal position of an allyl system, both fragments should be situated in the same plane in order to maximize the resonance energy. This tendency exhibited by **A** to a planar arrangement of five of the seven carbon atoms of the ring results in its higher steric hindrance compared to **B**. Finally, the equilibrium between complexes **A** and **B** appears to be controlled by two competing electronic and steric factors.

Scheme 1



Since the increasing size of the reacting electrophile perturbated more and more the **B**/**A** equilibrium (in favour of the less hindered complex **B**), the protonation of the complex mixture should reveal the real **B**/**A** value. We have undertaken such an experiment by trapping the complex mixture with gaseous HCl. The ratio of the resulting diene products (1,4-cycloheptadiene vs 1,3 cycloheptadiene) was determined by ^{1}H NMR and gas chromatography. The value obtained for the **B** /**A** ratio, was 0.82. It was significantly lower than any of the ratios from table 1. Unlike the seven-membered ring based alkenyl-η^3-allyltitanium complexes, the protonation of analogous complex derived from a linear triene afforded exclusively the conjugated diene analogous to **2** [11]. This dichotomy ilustrates the importance of the steric factor in the above cyclic series.

In conclusion, we have demonstrated the feasibility of preparing the η^3-allyltitanium complexes starting from cycloheptatriene, and of using them as nucleophiles in the addition with aldehydes. This methodology constitutes the first straight entry into 1,4-cycloheptadienes substituted at the 6-position, closely related to some biologically active molecules.[12] Studies aimed at improving the 1,4- vs 1,3-products ratio, and also exploring other electrophiles are currently underway.

References and Notes

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8. All new compounds were fully characterized by spectroscopic methods. For example:
   2e: IR (neat) 3475, 1650, 1610; ^{1}H NMR (C_6D_6) δ 0.89 (s, 9H), 1.39 (d, J = 6.7 Hz, 1H, D_2O exchangeable), 1.53-1.63 (m, 1H; H-5 decoupling : ddd, J = 13.1, 9.6, 4.2 Hz), 1.66-1.74 (m, 1H), 2.12-2.22 (m, 1H), 2.39-2.50 (m, 1H), 2.66 (m, 1H), 2.86 (d, J = 6.7 Hz, 1H), 5.74-5.84 (m, 3H), 5.86-5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.7, 29.4, 32.6, 36.2, 41.9, 84.7, 124.5, 127.8, 132.5, 135.6; DEPT ^{13}C NMR - disappearence of 36.2; MS (identical for both diasteromers) m/z 180 (M^+, 20), 123 (100), 105, 95, 79.
   3e : IR (neat) 3417, 2957, 1648; ^{1}H NMR (C_6D_6) δ 0.92 (s, 9H), 1.58 (br s, 1H, D_2O exchangeable), 1.96-2.11 (m, 3H), 2.16-2.24 (m, 1H, coupled with H-1), 3.25 (br s, 1H), 3.42 (m, 1H), 5.50 (ddd, J = 11.5, 6.9, 6.0 Hz, 1H, coupled with H-7), 5.63 (dddd, J = 11.5, 6.0, 6.0, 2.3 Hz, 1H), 5.73 (dddd, J = 11.5, 6.2, 6.0, 2.3 Hz);5.91 (dd, J = 11.5, 6.0 Hz, 1H); ^{13} C NMR ($CDCl_3$) δ 26.5, 26.6, 27.3, 36.2, 41.3, 83.4, 130.4, 130.9, 131.8, 134.2; DEPT ^{13}C NMR - disappearence of 36.2; MS m/z 123 (M^+-CMe_3), 105, 94, 79 (100).
9. The diastereomeric ratio was determined by gas chromatography.
10. An pericyclic six-membered early transition state was generally postulated for the exothermic allyltitanation process; see for example, Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics*, **1988**, *7*, 2289-2293.
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