

## Two- and Four-Carbon Homologation of Aldehyde by $\text{AgClO}_4$ -Catalyzed Addition of Alkoxyalkenylzirconocene Chloride

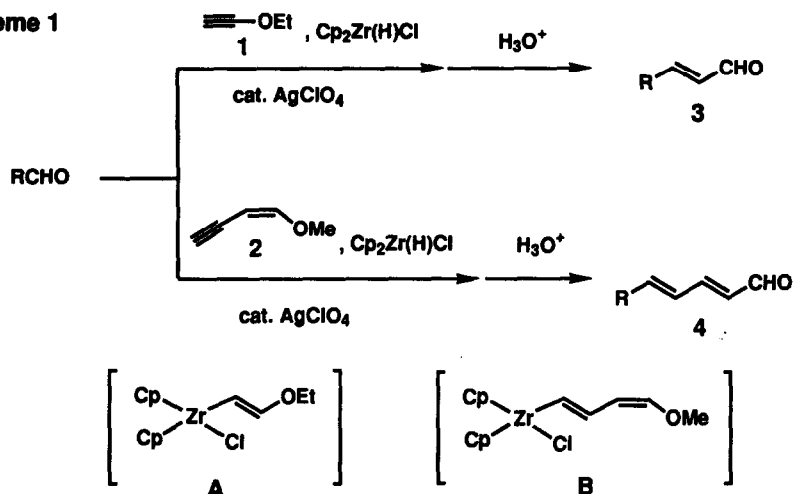
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**Abstract:** Two- and four-carbon homologation of aldehyde is described, which is based on the  $\text{AgClO}_4$ -catalyzed addition of zirconocene complexes, derived from hydrozirconation of 1-ethoxyethyne (1) and (Z)-1-methoxy-1-buten-3-yne (2) with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , followed by acidic hydrolysis.

Structure of conjugated polyene is included as subunit in some important natural products, such as polyene macrolides.<sup>1a)</sup> It is interesting in relation to conducting polymer as well.<sup>1b)</sup> For the selective construction of such structure, it occurred to us that the  $\text{AgClO}_4$ -catalyzed Grignard-type addition of alkenylzirconocene chloride to aldehyde<sup>2)</sup> would be useful provided that the reaction sequence shown in Scheme 1 worked well.

Scheme 1



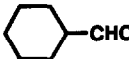
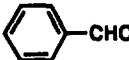
We reasoned that the  $\beta$ -alkoxyalkenylzirconocene chloride A, generated *in situ* by the hydrozirconation of commercially available 1-ethoxyethyne (1),<sup>3,4)</sup> would add to an aldehyde in the presence of catalytic  $\text{AgClO}_4$  to give the corresponding adduct. Subsequent treatment with an acid would then give enal 3, the two-carbon homologue of the starting aldehyde. In a similar manner, we hoped hydrozirconation of a vinylogous alkyne, (Z)-1-methoxy-1-buten-3-yne (2) which is also commercially available,<sup>5)</sup> would generate the  $\delta$ -alkoxydienyl complex B, which would enable the four-carbon homologation to give 4.

In the event, attempts along these lines proved to offer a new approach to aldehyde homologation.<sup>6)</sup>

Addition of 1-ethoxyethyne (1) to a suspension of the  $\text{Cp}_2\text{Zr(H)Cl}$  in  $\text{CH}_2\text{Cl}_2$  gave a clear orange solution in 5–10 min, by which we could judge completion of the hydrozirconation.<sup>3)</sup> To the solution was added an aldehyde followed by 5 mol% of  $\text{AgClO}_4$  as catalyst. Gratifyingly, catalysis by the silver salt was valid also in this case to give the corresponding adduct (room temperature, 30 min), which was subjected to acid hydrolysis (3N HCl) to give the two-carbon homologue of the starting aldehyde. By the similar procedure, use of the enyne 2 enabled the clean four-carbon homologation to give the corresponding dienyl aldehyde.

Table 1 shows the application of these two- and four-carbon homologation procedures to some aldehydes. All reactions proceeded smoothly to give the homologous aldehydes in good to excellent yields. Notably, the products have all (*E*)-geometry as evidenced by 1D and/or 2D-NMR analysis. The chemical and isomeric purity for each product was confirmed to be >95% by capillary GLC analysis (OV-1; 0.25 mm x 50 m).

Table 1. Two- and four-carbon homologation of aldehyde.<sup>7)</sup>

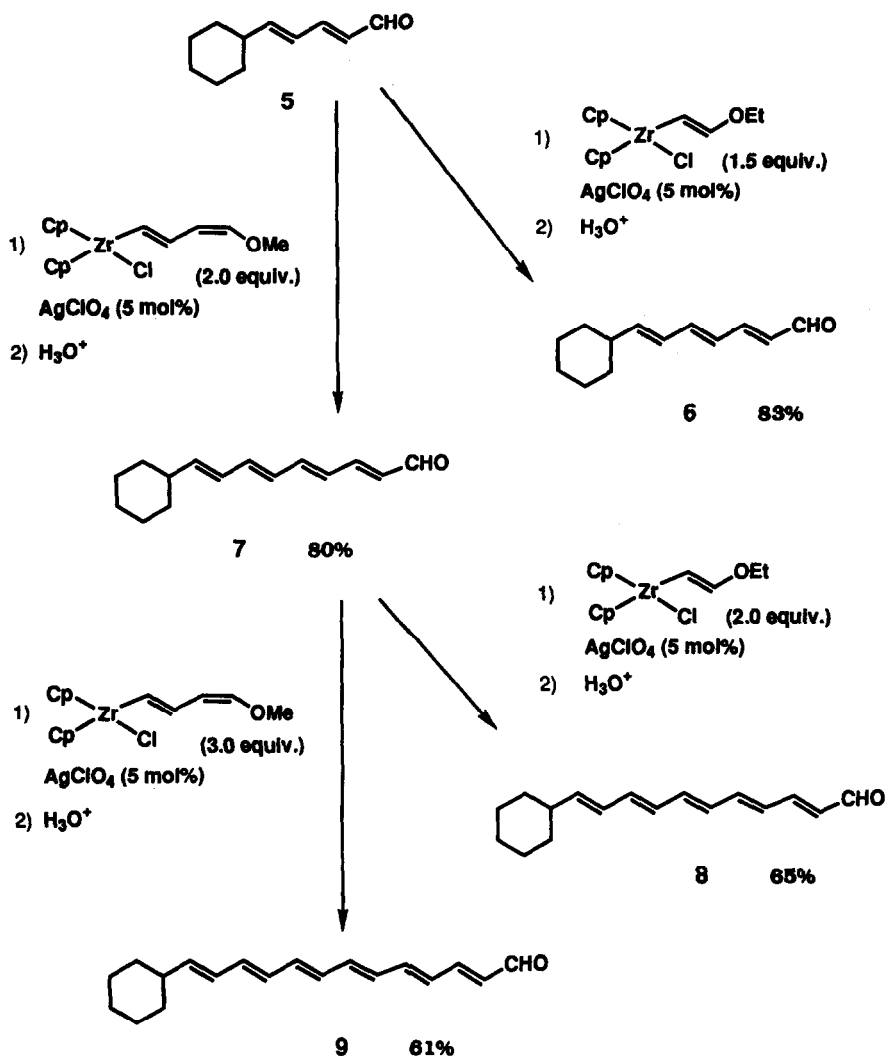
| $\text{RCHO} \xrightarrow[2) \text{H}_3\text{O}^+]{1) \begin{array}{c} \text{Cp} \quad \text{Cp} \\ \diagup \quad \diagdown \\ \text{Zr} \\ \diagdown \quad \diagup \\ \text{Cl} \quad \text{R}' \end{array}, \text{cat. AgClO}_4} \text{R}(\text{CH=CH})_n\text{CHO}$ |                                                                                     | $\begin{array}{l} n = 1, \text{R}' = \text{OEt} \\ n = 2, \text{R}' = (\text{Z})\text{-CH=CH-OMe} \end{array}$ |                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| Run                                                                                                                                                                                                                                                                    | Aldehyde                                                                            | Two-carbon homologation <sup>a)</sup><br>R' = OEt, $n = 1$                                                     | Four-carbon homologation <sup>a)</sup><br>R' = (Z)-CH=CH-OMe, $n = 2$ |
|                                                                                                                                                                                                                                                                        |                                                                                     | Yield / % <sup>b)</sup>                                                                                        | Yield / % <sup>b)</sup>                                               |
| 1                                                                                                                                                                                                                                                                      |  | 90                                                                                                             | 89                                                                    |
| 2                                                                                                                                                                                                                                                                      |  | 89                                                                                                             | 90                                                                    |
| 3                                                                                                                                                                                                                                                                      |  | 94                                                                                                             | 90                                                                    |
| 4                                                                                                                                                                                                                                                                      |  | 90                                                                                                             | 66                                                                    |
| 5                                                                                                                                                                                                                                                                      | $\text{MeO}_2\text{C}(\text{CH}_2)_8\text{CHO}$                                     | 89                                                                                                             | 80                                                                    |

a) For detailed reaction procedure, see text. b) Isolated yield.

Furthermore, higher homologues are also available by reiterating these homologation processes as shown in Scheme 2. Dienal **5**, prepared by the four-carbon homologation of cyclohexanecarboxaldehyde (run 2 in Table 1; see also typical procedure), was converted to trienal **6** and tetraenal **7** in high yields. Pentaenal **8** and hexaenal **9** were also easily prepared, although some excess of alkoxyalkenylzirconocene chloride was necessary in order to gain reasonable yields.

These homologation processes offer a high-yield and expeditious entry into conjugated polyenals.

**Scheme 2**



Typical procedure is described for the preparation of **5** by the four-carbon homologation of cyclohexanecarboxaldehyde: A solution of (Z)-1-methoxy-1-buten-3-yne (**2**) (0.82 M in CH<sub>2</sub>Cl<sub>2</sub>, 16 mL, 13 mmol) was added to Cp<sub>2</sub>Zr(H)Cl (3.26 g, 12.6 mmol) at 0 °C under N<sub>2</sub> (exothermic!). During warming to room temperature, the zirconocene complex gradually dissolved to give a clear red solution (10 min). Cyclohexanecarboxaldehyde (954 mg, 8.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added followed by AgClO<sub>4</sub> (89 mg, 430 μmol, 5 mol%). After 30 min, the reaction mixture was diluted with Et<sub>2</sub>O, to which sat. NaHCO<sub>3</sub> aqueous solution. The mixture was filtered through a Celite pad, and the products were extracted with Et<sub>2</sub>O (10 mL x 3). To the combined ethereal solution was added 3N HCl (60 mL) and the two-phase mixture was stirred under N<sub>2</sub> for 1.5 h. After separation, the organic layer was washed with sat. NaHCO<sub>3</sub> aqueous solution and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Purification with silica-gel column chromatography (hexane/EtOAc = 95/5) gave **5** (1.25 g, 90%; 96% isomeric purity by GLC).

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## References and Notes

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2. Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* *in press*; Maeta, H.; Suzuki, K. *ibid.* *in press*.
3. Hydrozirconation of **1** was reported: Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168–3170. For general review on hydrozirconation, see Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340.
4. 1-Ethoxyethyne (**1**) was purchased from Fluka as ca. 40% solution in hexane which was used as such. For preparation of **1**, see Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Shaw, B. L. *Org. Synth.*; Col. Vol. IV, pp 404–407.
5. Enyne **2** is available from Aldrich as 50 wt % solution in methanol–water. For preparation of anhydrous **2** and its utilization, see Corey, E. J.; Albright, J. O. *J. Org. Chem.* **1983**, *48*, 2114–2115. The stock solution of **2** in CH<sub>2</sub>Cl<sub>2</sub> (0.82 M) was stable at 0 °C for at least 2 months.
6. Selected recent examples for the synthesis of unsaturated aldehyde, see Rein, T.; Åkermark, B.; Helquist, P. *Acta Chem. Scand., Ser. B* **1988**, *42*, 569–572; Contreras, B.; Duhamel, L.; Plé, G. *Synth. Commun.* **1990**, *20*, 2983–2990; Yahata, N.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3601–3605; Duhamel, L.; Guillemont, J.; Gallic, Y. L.; Plé, G.; Poirier, J.-M.; Ramondenc, Y.; Chabardes, P. *Tetrahedron Lett.* **1990**, *31*, 3129–3132; Lewis, N.; McKen, P. W.; Taylor, R. J. K. *Synlett* **1991**, 898–900; Belosludtsev, Y. Y.; Borer, B. C.; Taylor, R. J. K. *Synthesis* **1991**, 320–322; Bäckvall, J.-E.; Ericsson, A. M.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1992**, *33*, 131–134.
7. All new compounds were fully characterized by <sup>1</sup>H-, <sup>13</sup>C NMR, IR, and HRMS.

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