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Degradation of aldehydes to one carbon lower homologs

Damien Belotti, Gaëlle Andreatta, Fabienne Pradaux, Samir BouzBouz and Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231-Paris Cedex 05, France

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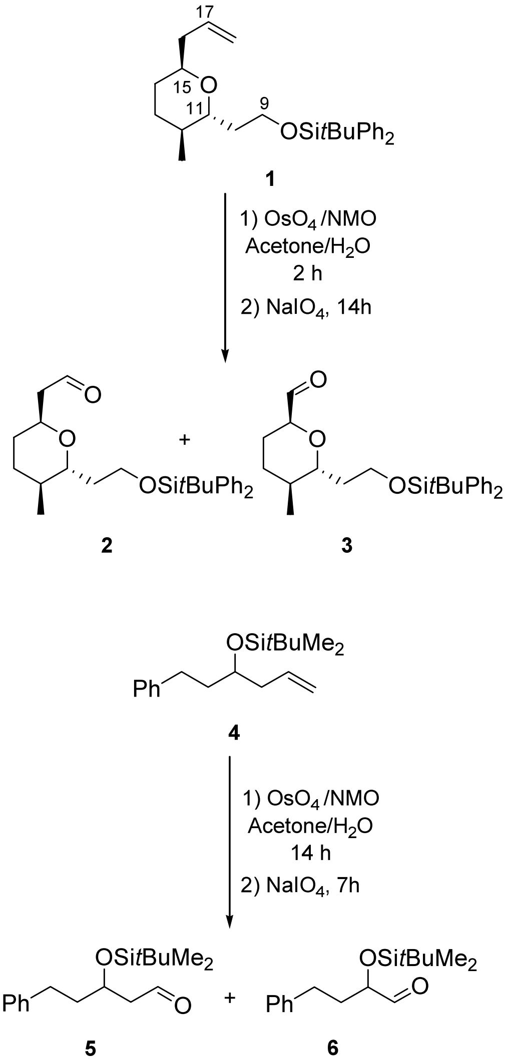
Abstract—Degradation of aldehydes to one carbon lower homologs has been achieved by using a mixture of *N*-methylmorpholine, *N*-methylmorpholine *N*-oxide, a catalytic amount of OsO_4 and $NaIO_4$ in a mixture of acetone/H_2O. © 2003 Elsevier Science Ltd. All rights reserved.

In the aim of synthesizing the C_9–C_{17} fragment of leucascandrolide,[1] we needed to transform compound **1** to aldehyde **2** (Scheme 1). The oxidative cleavage of the double bond by using OsO_4 (0.05 equiv.) in the presence of *N*-methylmorpholine *N*-oxide (NMO) (1.7 equiv.) in a mixture of acetone/H_2O (3/1) followed by the addition of $NaIO_4$ (2 equiv.) was quite surprising as, after 14 hours, a mixture of two aldehydes was obtained: the expected aldehyde **2** in low yield (18%) and the one carbon lower homolog, aldehyde **3**, which was isolated in 20% yield. Under similar conditions, the protected homoallylic alcohol **4** led to two aldehydes **5** and **6**. Aldehyde **5** was isolated in 36% yield and its corresponding lower homolog, aldehyde **6**, was also isolated in 36% yield (Scheme 1).

The α-substituted aldehydes **3** and **6** are probably formed respectively from aldehydes **2** and **5**. Under these oxidative conditions, aldehydes of type **A** are probably in equilibrium with enol intermediates of type **B** in the presence of *N*-methylmorpholine (NMM) liberated in the reaction media. These enol intermediates are then dihydroxylated by NMO/OsO_4 to produce intermediates of type **C** which are probably cleaved by $NaIO_4$ to produce aldehyde **D** (Scheme 2).

To verify this hypothesis, aldehyde **5** was treated with NMM (1 equiv.), NMO (2 equiv.), a catalytic amount of OsO_4 (0.05 equiv.) and $NaIO_4$ (4 equiv.) in acetone/H_2O (10/1) at room temperature. Under these conditions, aldehyde **5** was transformed to **6** in good yield (58%)[2] (Scheme 3).



Scheme 1.

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* Corresponding author. Tel.: +33-1-4079-4429; fax: +33-1-4079-4660; e-mail: janine.cossy@espci.fr

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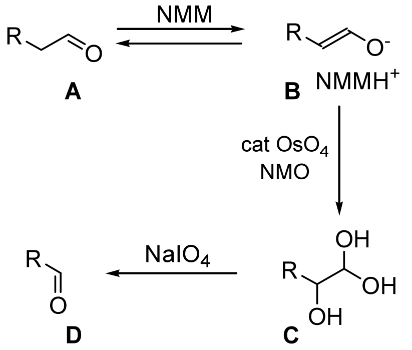
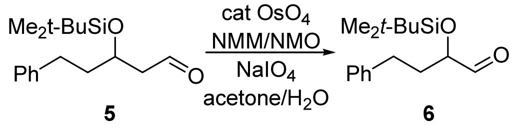


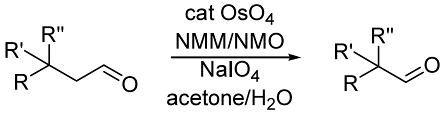
Scheme 2.

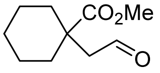
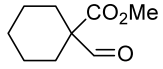
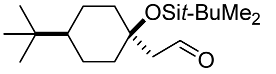
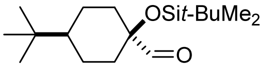
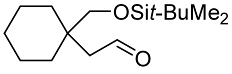
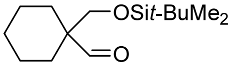
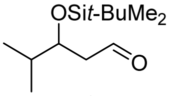
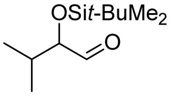
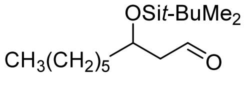
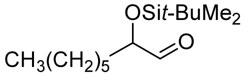
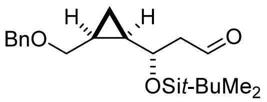
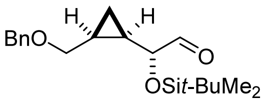
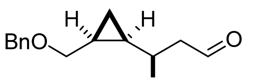
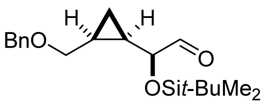


Scheme 3.

This oxidative one-pot process transformation of aldehydes to one carbon lower homologs is not a common process. A complete degradation of unbranched aldehydes to acetaldehyde and formate units has been previously observed by using copper-catalyzed oxidation[3] but, to our knowledge, only one method which corresponds to the degradation of aldehydes to one carbon lower homologs has been reported in the litterature.[4] This process consists in the treatment of an aldehyde with iodine bromide followed by the treatment of the resulting α-bromoaldehyde with potassium hydroxide, and the obtained hydrate of α-hydroxyaldehyde was cleaved by sodium periodate. This procedure was applied to the degradation of the side chain of cholanic aldehyde.[4]

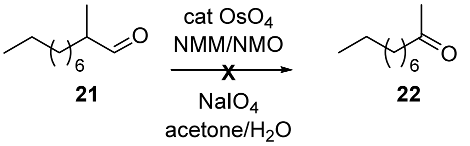
Table 1. Degradation of aldehydes to one carbon lower homologs



Entry	Starting Material	Product	Yield
1	 **7**	 **14**	61%
2	 **8**	 **15**	50%
3	 **9**	 **16**	68%
4	 **10**	 **17**	58%
5	 **11**	 **18**	80%
6	 **12**	 **19**	60%
7	 **13**	 **20**	62%

Due to the importance of α-substituted aldehydes in synthesis, the easy NMM/NMO/OsO_4 and $NaIO_4$ one-pot procedure for the oxidative cleavage of aldehydes has been applied to aldehydes **7–13**. The results are reported in Table 1.

When aldehydes **7–13** were treated by NMM/NMO/OsO_4 and $NaIO_4$, the respective one carbon lower homologs **14–20** were isolated in yields higher than 50%. It is worth noting that the presence of a quaternary center (compounds **14–16**) as well as the presence of a protected hydroxy group (compounds **17–20**) avoids further enolisation in aldehydes **14–20**. It has been also verified that an α-alkyl substituted aldehyde such as **21** was not transformed to ketone **22** under these oxidative conditions (Scheme 4).



Scheme 4.

These oxidative conditions are very mild as a *t*-butyldimethylsilyl protecting group was tolerated. Furthermore, no epimerization of the stereogenic center was observed when α-substituted aldehydes were formed from β-substituted aldehydes (Table 1, entries 6 and 7).

α-Substituted aldehydes and particularly chiral α-hydroxyaldehydes can be prepared very easily by degradation of protected β-hydroxyaldehydes. These latter compounds are very useful synthons and their use in the elaboration of biological active compounds will be reported in due course.

References

1. (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–59; (b) Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1989**, *72*, 237–245.
2. **General procedure**: To a stirred solution of β-substituted aldehyde (2 mmol), *N*-methylmorpholine (0.22 mL, 2 mmol) and *N*-methylmorpholine *N*-oxide (0.47 g, 4 mmol) in acetone/water (30 mL/3 mL) were added a 4% osmium tetroxide solution in water (0.64 mL, 0.1 mmol of OsO_4) and, after 10 min, sodium periodate (1.71 g, 8 mmol). The resulting suspension was stirred for 24 h (TLC or GC/MS monitoring) and then filtered through Celite, which was washed with acetone. The solvent was evaporated in vacuo and the residue was taken up with ethyl acetate (50 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the α-substituted aldehyde.
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4. (a) Yanuka, Y.; Katz, R.; Sarel, S. *J. Chem. Soc., Chem. Commun*. **1968**, 851–852; (b) Yanuka, Y.; Katz, R.; Sarel, S. *Tetrahedron Lett*. **1970**, *11*, 5229–5232.