DOI: 10.1002/ejoc.200901202

Reduction of Alkynyl α-Hydroxy Esters: Stereoselective α-Ketol Rearrangement

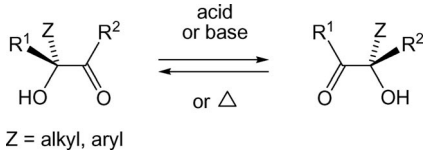
Thomas Hameury,[a] Véronique Bellosta,*[a] Jérôme Guillemont,[b] Luc Van Hijfte,[b] and Janine Cossy*[a]

Keywords: Rearrangement / Hydrides / Diastereoselectivity / α-Ketol

The α-ketol rearrangement of tertiary α-hydroxy esters induced by $LiAlH_4$/acid treatment provides α-hydroxy ketones in good yields and high diastereoselectivity. A mechanism is proposed for this reaction as well as a model to explain the diastereoselectivity of the rearrangement.

Introduction

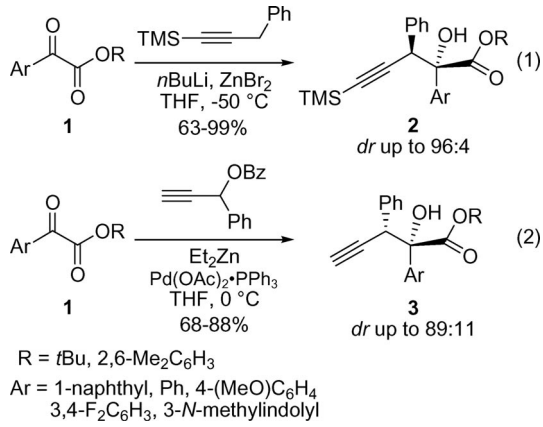
Treatment of α-hydroxy aldehydes and α-hydroxy ketones with base, Brønsted acid, Lewis acid, or by heating, can induce a 1,2-shift of an alkyl or aryl substituent (Scheme 1).[1–3] Under these conditions, both isomers are in equilibrium, and the more stable α-hydroxy carbonyl compound is formed. This transformation, called α-ketol or acyloin rearrangement, has been applied to the synthesis of many polycyclic compounds.[4] In the case of tertiary α-hydroxy aldehydes (R^2 = H), the rearrangement proceeds with total conversion to the thermodynamically favored α-hydroxy ketone.



Scheme 1. α-Ketol rearrangement.

Recently, we reported on the synthesis of tertiary 2,3-diaryl-2-hydroxypentynoates **2** and **3** by diastereodivergent addition of allenylzincs to aryl glyoxylates **1** (Scheme 2).[5] Depending on the conditions used to generate the allenylzinc species [Scheme 2, Equation (1) and (2)], diastereomeric homopropargylic alcohols **2** and **3** were produced in good yields and diastereoselectivities. In order to utilize this method to prepare biologically active compounds, the synthetic potential of these tertiary alcohols was investigated through diverse transformations.

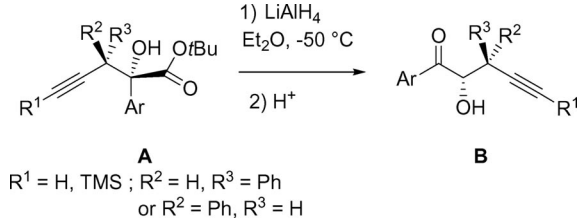
[a] Laboratory of Organic Chemistry, ESPCI ParisTech, CNRS, 10 rue Vauquelin 75231 Paris Cedex 05, France
Fax: +33-1-40794660
E-mail: janine.cossy@espci.fr
[b] Tibotec, a Division of Janssen-Cilag SAS, Janssen-Cilag Research Center, Campus de Maigremont, 27106 Val de Reuil, France
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901202.



Scheme 2. Diastereoselective addition of allenylzincs to aryl glyoxylates.

Results and Discussion

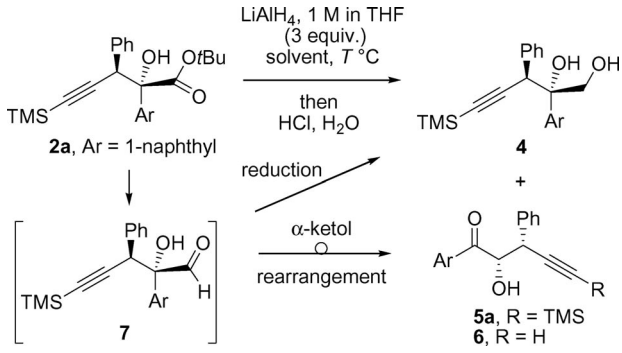
The reactivity of these 2,3-diaryl-2-hydroxypentynoates was examined. Here, we would like to report that tertiary 2,3-diaryl-2-hydroxypentynoates of type **A** were rearranged stereoselectively to 1,3-diaryl-2-hydroxypentynones of type **B** through an α-ketol rearrangement by reduction followed by acid treatment (Scheme 3).



Scheme 3. Rearrangement of 2,3-diaryl-2-hydroxypentynoates.

When α-hydroxy ester **2a** was treated with 3 equiv. of $LiAlH_4$ (1 M in THF) in Et_2O[6] at 0 °C, and then with aqueous HCl (1 M), diol **4** was isolated in 89% yield along with

Table 1. Optimization of the conditions for the formation of α-hydroxy ketones **5a** and **6**.



Entry	Solvent	Temp., time	Ratio (**5a** + **6**)/**4**[a]	**5a**[b] [%]	**6**[b] [%]	**4**[b] [%]
1	Et_2O/THF 4:1	0 °C, 3 h	1:10.1	10	0	89
2	Et_2O/THF 4:1	–78 °C, 1 h then –78 to 0 °C over 3 h	2.9:1	25	17	21
3	THF	–78 °C, 1.5 h then –78 to 0 °C over 3 h	1:4.1	6	0	48
4	Et_2O/THF 4:1	–50 °C, 48 h	7.8:1	59	12	15

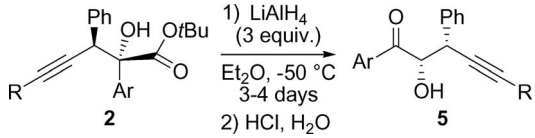
[a] Determined from ^{1}H NMR spectra of the crude mixture. [b] Isolated yield.

the unexpected rearranged α-hydroxy ketone **5a**. Although **5a** was obtained in poor yield (10% yield), the *syn* diastereoselectivity was excellent (*dr* > 95:5, determined from ^{1}H NMR spectra of the crude mixture) (Table 1, Entry 1). Compounds **4** and **5a** could come from the same α-hydroxy aldehyde intermediate **7**, which can be reduced to produce **4** or rearranged to α-ketol **5a**. Intrigued by the stereoselective transformation of **2a** to compound **5a**, and in order to increase its yield, a screening of the conditions was undertaken. The results are reported in Table 1. It should be noted that compound **6**, resulting from the in situ desilylation of the rearranged product **5a**, was also observed during this screening of conditions.

It was noticed that lowering the temperature had a large impact on the outcome of the reaction, with the ratio of (**5a** + **6**)/**4** being inverted in favor of the rearranged products. Indeed, keeping the reaction at –78 °C for 1 h before warming it up to 0 °C, and then treating it with HCl (1 M) provided the rearranged α-hydroxy ketones **5a** and **6** as the major products (Table 1, Entry 2).[7] The addition of a 1 M solution of $LiAlH_4$ in THF to a solution of **2a** in Et_2O, resulted in a 4:1 mixture of Et_2O/THF. However, the use of THF as the only solvent under similar conditions led predominantly to diol **4** (Table 1, Entry 3). The reaction was slow at –78 °C and did not go to completion; however, –50 °C turned out to be a good compromise, as after two days, the rearranged α-hydroxy ketones **5a** and **6** were isolated in good yield (71%), accompanied with only 15% of diol **4** (Table 1, Entry 4).[8]

These latter conditions were then applied to α-hydroxy esters **2** and **3** and the results are summarized in Tables 2 and 3, respectively. In all cases, the rearranged products were obtained in good yields and with excellent diastereoselectivities (*dr* > 95:5, determined from ^{1}H NMR spectra of the crude mixture). Compounds **2** provided specifically the *syn* α-hydroxy ketones **5**, whereas esters **3** gave the *anti* products **8**. Furthermore, the presence of electron-donating or -withdrawing groups on the aromatic ring at C2 did not have any influence on the rearrangement as the rearranged products **5** were obtained in good yields (Table 2, Entries 4 and 5).

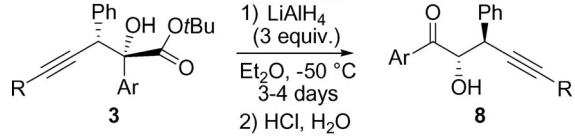
Table 2. Rearrangement of α-hydroxy esters **2**.



Entry	**2**	Ar	R	**5**	Yield [%]
1	**2a**	1-naphthyl	TMS	**5a**	78[a]
2	**2b**	phenyl	TMS	**5b**	43[b]
3	**2c**	phenyl	H	**5c**	74
4	**2d**	4-(MeO)C_6H_4	H	**5d**	97
5	**2e**	3,4-$F_2C_6H_3$	H	**5e**	70

[a] Traces of compounds **4** and **6** were also observed. [b] Desilylated compound **5c** was isolated in 10% yield.

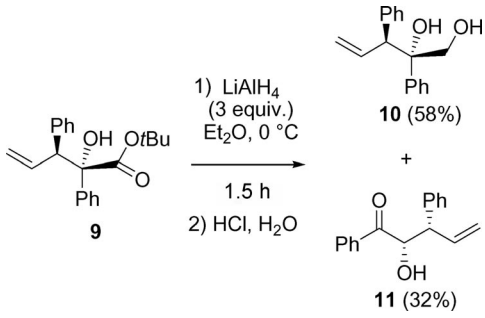
Table 3. Rearrangement of α-hydroxy esters **3**.



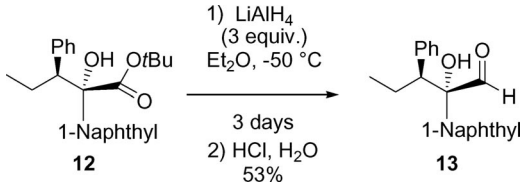
Entry	**3**	Ar	R	**8**	Yield [%]
1	**3a**	1-naphthyl	H	**8a**	50
2	**3b**	phenyl	TMS	**8b**	67
3	**3c**	phenyl	H	**8c**	96

Similarly, treatment of homoallylic alcohol **9** with $LiAlH_4$ (1 M in THF) at 0 °C afforded a mixture of diol **10** and the rearranged compound **11** in 58% and 32% yields respectively, after acid treatment (Scheme 4). However, when compound **12** was submitted to $LiAlH_4$ (1 M in THF)

in Et_2O at –50 °C for three days and then HCl treatment, α-hydroxy aldehyde **13** was isolated in 53% yield and no rearranged product was detected (Scheme 5). Aldehyde **13** did not undergo a spontaneous α-ketol rearrangement, and it was revealed to be stable during the acidic workup as well as on silica gel. These results showed that the migrating carbon has to be in a propargylic or an allylic position for the α-ketol rearrangement to proceed.[9]

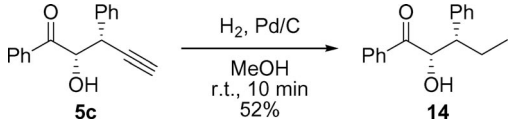


Scheme 4. Reactivity of allylic hydroxy ester **9**.



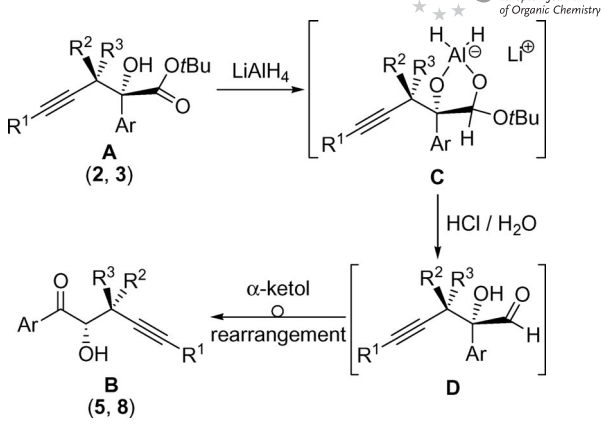
Scheme 5. Reactivity of hydroxy ester **12**.

The *syn* relative stereochemistry in compound **5c** was established after hydrogenation of the alkyne (Scheme 6). α-Hydroxy ketone **14** was isolated and the spectroscopic data were in accordance with those described in the literature.[10]



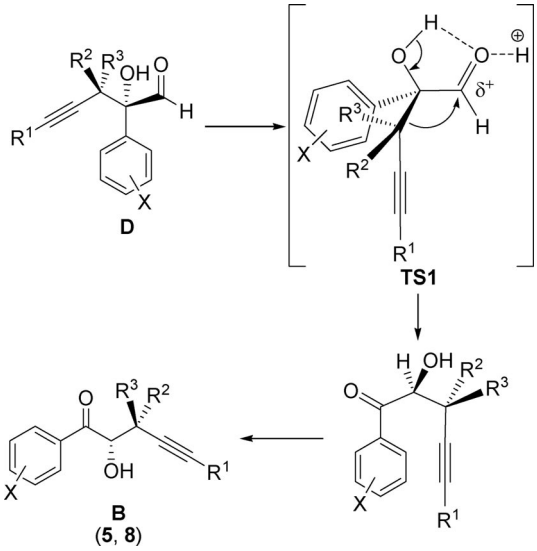
Scheme 6. Determination of the *syn* relative stereochemistry in **5c**.

The formation of ketones **5** and **8** in the presence of an excess of $LiAlH_4$, implies that the rearrangement did not proceed in the reaction media, but probably during the workup under acidic conditions. We postulated that the reduction of hydroxy ester **A** would provide α-hydroxy aldehyde **D** after hydrolysis of the intermediate **C**, which would be stable at –50 °C (Scheme 7). Aldehyde **D** would then undergo an α-ketol rearrangement leading to the more stable α-hydroxy ketone **B**. The isolation of aldehyde **13** (Scheme 5) is in accordance with this pathway, as intermediate **C** prevents the reduction of the masked carbonyl in the presence of $LiAlH_4$.



Scheme 7. Proposed mechanism for the reductive α-ketol rearrangement.

In order to explain the excellent diastereoselectivity observed after treatment of compounds **2** and **3** with $LiAlH_4$ followed by an HCl workup, the aldehyde intermediate **D** can be considered. The co-planarity of the two carbon–oxygen bonds due to hydrogen bonding, as shown in **TS1**, would direct the propargylic group to the *Si* face of the aldehyde (Scheme 8).[1] The 1,2-shift occurs with retention of configuration of the migrating carbon, to produce the *syn*- or *anti*-hydroxy ketone stereoselectively. However, an acidic activation of the aldehyde cannot be excluded.



Scheme 8. Possible explanation for the diastereoselectivity.

Conclusions

We have demonstrated that 2,3-diaryl-2-hydroxypentynoates can be transformed to α-ketols in a highly stereoselective fashion, through reduction by using $LiAlH_4$ and subsequent rearrangement of the resulting α-hydroxy aldehyde under acidic conditions. The use of this rearrangement for synthesizing biologically active compounds is in progress in our laboratory and will be reported in due course.

Supporting Information (see also the footnote on the first page of this article): General experimental procedure and characterization data for α-ketols **5** and **8**.

Acknowledgments

Tibotec, a division of Janssen-Cilag SAS, is gratefully acknowledged for financial support (grant to T. H.).

[1] L. A. Paquette, J. E. Hofferberth, *Org. React.* **2003**, *62*, 477–567.
[2] T.-F. Yang, Z.-N. Zhang, C.-H. Tseng, L.-H. Chen, *Tetrahedron Lett.* **2005**, *46*, 1917–1920.
[3] 1,2-Rearrangement of α-siloxy aldehydes: a) T. Ooi, K. Ohmatsu, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 2410–2411; b) K. Ohmatsu, T. Tanaka, T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2008**, *47*, 5203–5206.
[4] Examples of synthetic applications: a) J. L. Wood, B. M. Stoltz, S. N. Goodman, K. Onwueme, *J. Am. Chem. Soc.* **1997**, *119*, 9652–9661; b) J. Liu, L. N. Mander, A. C. Willis, *Tetrahedron* **1998**, *54*, 11637–11650; c) Q. Zeng, S. Bailey, T.-Z. Wang, L. A. Paquette, *J. Org. Chem.* **1998**, *63*, 137–143; d) L. A. Paquette, J. E. Hofferberth, *J. Org. Chem.* **2003**, *68*, 2266–2275; e) B. Gerard, G. Jones II, J. A. Porco Jr., *J. Am. Chem. Soc.* **2004**, *126*, 13620–13621; f) B. Gerard, S. Sangji, D. O'Leary, J. A. Porco Jr., *J. Am. Chem. Soc.* **2006**, *128*, 7754–7756; g) B. Gerard, R. Cencic, J. Pelletier, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2007**, *46*, 7831–7834; h) T. E. Adams, M. El Sous, B. C. Hawkins, S. Hirner, G. Holloway, M. L. Khoo, D. J. Owen, G. P. Savage, P. J. Scammells, M. A. Rizzacasa, *J. Am. Chem. Soc.* **2009**, *131*, 1607–1616.
[5] T. Hameury, J. Guillemont, L. Van Hijfte, V. Bellosta, J. Cossy, *Org. Lett.* **2009**, *11*, 2397–2400.
[6] The use of $LiAlH_4$ (1 M in THF) in Et_2O corresponds to a 4:1 mixture of Et_2O/THF.
[7] When compound **2a** was treated under the same conditions of temperature (1 h at –78 °C, then warming up to 0 °C over 3 h), but with only 1.2 equiv. of $LiAlH_4$, the ratio (**5a** + **6**)/**4** was 1:1.7.
[8] Similar results were observed when the reaction mixture was hydrolyzed with the following basic aqueous treatment: for 1 g of $LiAlH_4$, 1 mL H_2O, then 2 mL aqueous NaOH 10%, then 3 mL H_2O.
[9] For similar observations, see: X. Creary, P. A. Inocencio, T. L. Underiner, R. Kostromin, *J. Org. Chem.* **1985**, *50*, 1932–1938.
[10] L. Carde, D. H. Davies, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2455–2463.

Received: October 21, 2009
Published Online: December 18, 2009

