Pergamon

Tetrahedron Letters 40 (1999) 6485–6487

TETRAHEDRON
LETTERS

Reaction of α,β-unsaturated ketones with $LiAlH_4$ under oxygen: synthesis of 1,3-diols

Aurelio G. Csákÿ,* Natalia Máximo, Joaquín Plumet * and Ainhoa Rámila

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

Received 10 June 1999; accepted 29 June 1999

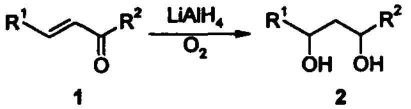
Abstract

1,3-Diols have been obtained by the reaction of α,β-unsaturated ketones with $LiAlH_4$ in THF under a dry oxygen atmosphere. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: diols; ketones; oxygenation; reduction.

1,3-Diols have attracted considerable attention in recent times due to the ubiquitous presence of this moiety in macrolide antibiotics.[1] Consequently, a wide variety of synthetic methods have been developed for these targets.[2] However, most of these procedures require several steps for the preparation of the starting materials, which poses an inherent difficulty from the large-scale synthesis standpoint. We wish to report herein a new procedure for the synthesis of 1,3-diols based on the reaction of the easy-to-prepare α,β-unsaturated ketones[3] **1** with $LiAlH_4$.

Portionwise addition of solid $LiAlH_4$ (6.0 mol) to a 0.2 M solution of compounds **1** (1.0 mol) in THF under dry oxygen (0°C, 1.5 h) and hydrolysis (H_2O) resulted in the isolation of the 1,3-diols **2** (Scheme 1, Table 1).



Scheme 1.

Additional experiments carried out with compound **1a** put forward that the unsaturated alcohol **3a** and the saturated alcohol **4a** can be isolated by carrying out the reaction under an argon atmosphere and quenching with water prior to bubbling oxygen into the reaction mixture. Furthermore, 1,3-diol **2a** was also isolated from the reaction of **3a**[4] with $LiAlH_4$ under the same reaction conditions (vide supra). On the other hand, when the reaction was carried out with less than 6.0 equiv. of $LiAlH_4$, longer reaction times were required to ensue full conversion, and only **3a** (95% yield) was isolated when 1.0 equiv. of $LiAlH_4$

---

* Corresponding authors.

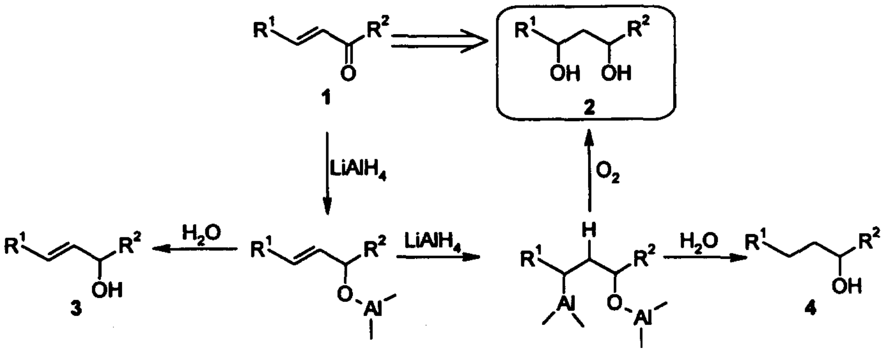
PII: S0040-4039(99)01270-8

Table 1
Reaction of the α,β-unsaturated ketones **1** with $LiAlH_4$

Entry	1	R^1	R^2	2 (%)[a]
1	**1a**	Ph	Ph	**2a** (90)
2	**1b**	2-Furyl	2-Furyl	**2b** (85)
3	**1c**	Ph	2-Furyl	**2c** (85)
4	**1d**	2-Furyl	Ph	**2d** (80)
5	**1e**	2-Thienyl	2-Furyl	**2e** (85)
6	**1f**	Ph	CH_3	**2f** (80)

(a) Isolated yield after silica-gel chromatography (hexane-EtOAc)

was used. These observations allowed the proposal of a reaction course (Scheme 2) based on an initial 1,2-reduction of the carbonyl group of compounds **1** followed by an intermolecular hydroalumination process of the C=C bond of the intermediate allylic alkoxides.[5]



Scheme 2.

Compounds **2** were obtained as an equimolecular mixture of *syn* and *anti* diastereomers, which were separated by crystallization in hexane–ethyl acetate (**2a–e**) or chromatography (**2f**, silica gel, hexane:ethyl acetate 80:20). Compounds **2** can be deracemized by means of known procedures.[6,7]

In summary, the herein reported procedure constitutes the one-pot transformation of an α,β-unsaturated ketone into a 1,3-diol, which is without precedent in the literature consulted.

Acknowledgements

DGYCT (project PB-960641) is gratefully ackowledged for financial support.

References

1. (a) *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040.
2. See for instance: (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635–645. (b) Enders, D.; Hundertmark, T.; Lampe, C.; Jegelka, U.; Scharfbillig, I. *Eur. J. Chem.* **1998**, 2839–2849 and references cited therein.
3. Compounds **1b–e** were prepared by the addition of the corresponding aldehyde (10 mmol) at 0°C to a solution of the corresponding methylketone (10 mmol) in a mixture of EtOH (50 mL) and H_2O (30 mL) containing NaOH (3 mmol). The solution was stirred from 0°C to rt for 24 h. Compounds **1b–e** precipitated out of the solution upon addition of water

(20 mL) and cooling the mixture at 0°C. This procedure can be easily scaled to the multi-gram synthesis of these starting materials.

4. Prepared by the reaction of **1a** with 1.0 equiv. of $LiAlH_4$ in THF at 0°C under Ar (3 h) followed by addition of water and extraction with Et_2O.
5. For the hydroalumination of C=C bonds, see: Eisch, J. J In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8, Chapter 3.11. See also: (a) Snyder, E. I. *J. Org. Chem.* **1967**, *32*, 3531–3534. (b) Borden, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 2197–2198.
6. For a deracemization procedure of 1,3-diols, see: Harada, T.; Shintani, T.; Oku, A. *J. Am. Chem. Soc.* **1995**, *117*, 12346–12347.
7. For the spontaneous resolution of racemic 1,3-diphenylpropane-1,3-diol, see: Dale, J. *Chem. Soc.* **1961**, 910–922.