Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2293-2296, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00246-8

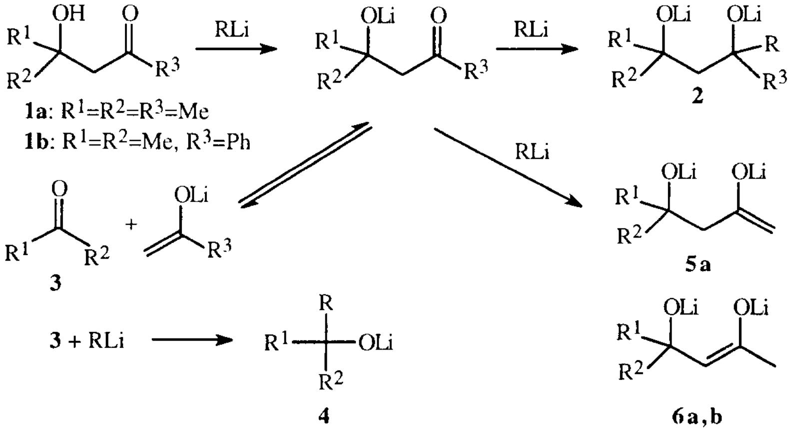
Organo Cerium Reagents in Organic Chemistry: General Method of Synthesis of Alkyl Substituted 1,3-Diols by RLi-CeCl3 Addition to β-Hydroxyketones.

Giuseppe Bartoli*, Marcella Bosco, Jacco Van Beek[1], Letizia Sambri
Dipartimento di Chimica Organica "A. Mangini", I-40136 Bologna, Italy.

Enrico Marcantoni
Dipartimento di Scienze Chimiche, Via S.Agostino 1, I-62032 Camerino (MC), Italy.

Abstract: Organocerium compounds (RLi-CeCl$_3$) are able to transfer an alkyl group to the carbonylic function of a β-hydroxyketone giving alkyl substituted 1,3-diols in excellent yields. The use of these not sophisticated reagents is essential to depress undesired dimetallation and retroaldol side processes.

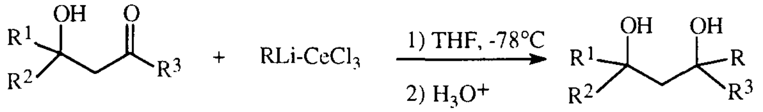
Alkyl substituted 1,3-diols represent a very important class of intermediates in organic chemistry. The most straighforward approach to their synthesis involves the nucleophilic addition of a RLi to the carbonyl function of the lithium salt of a β-hydroxyketone. However, this reaction has been in practice applied only to the synthesis of 2,4-dimethyl-2,4-pentanediol from 4-hydroxy-4-methyl-2-pentanone (**1a**) and methyl lithium[2], since a competitive retroaldol process can very likely occur with less reactive organometallic derivatives or less stable aldol substrates (see Scheme 1). We examined in more detail this procedure and we found that actually a lot of serious drawbacks exist in most cases. For example, the reaction of **1a** with n-BuLi gave the expected 1,3-diol in 60% yield together with retroaldol product **4** (8%) and starting material **1a** (10%)[3]. The recovery of **1a** can be ascribed to a double deprotonation process which leads to enolates **5** and **6**[4].



Scheme 1

Furthermore, the retroaldol process became competitive and the tertiary alcohol from **4** was recovered in 35% yield in the reaction of **1a** with a more stabilized carbanionic system such as phenylethynyl lithium. Analogous results were observed in the reaction of the less stable aldol 1-phenyl-3-hydroxy-3-methyl-1-butanone, (**1b**)[5], with both MeLi and n-BuLi when retroaldol process accounted for the 25% and 40% of the reaction respectively.

Our recent results on the ability of organocerium compounds to transfer an alkyl group to electrophilic substrates having active hydrogens such as 1,3-diketones[6] and α-diphenylphosphinoyl ketones[7] strongly advised us of making use of these easy available reagents to resolve the problem of direct alkylation of β-hydroxy ketones. However some literature suggestions were not encouraging from a practical point of view. Shibasaki[8] found that dialkynyl cerium reagents are able to introduce an alkynyl chain at the carbonylic function of a cycloheptanone framework having a non protected hydroxymethyl group in α position. Although the conversion yields were high, the total ones were generally low (30-40%) even by using a dramatic excess of the organometallic reagent (twentyfold). We wish to report now that an appropriate use of the organocerium reagent can lead to very excellent results. In fact, when a β-hydroxy ketone **1a-d** is allowed to react at -78°C in THF with a monoalkyl cerium derivative prepared from RLi and $CeCl_3$, according to Imamoto procedure, the usual work up of the reaction gives the expected alkyl 1,3-diol in high to quantitative yields (see Table 1).



1 **7**

substrate	R in $RLi\text{-}CeCl_3$	product	yields
1a: $R^1=R^2=R^3=Me$	Me	**7aa**	97%
	n-Bu	**7ab**	95%
	Ph	**7ac**	95%
	Ph-≡	**7ad**	95%
	t-Bu	**7ae**	80%
1b: $R^1=R^2=Me$, $R^3=Ph$	Me	**7ac**	83%
	n-Bu	**7bb**	90%
	Ph	**7bc**	86%
1c: $R^1=Me$, $R^2=n\text{-}Bu$, $R^3=Ph$	Ph	**7ca**	85%
1d: $R^1=R^3=Me$, $R^2=n\text{-}Bu$	n-Bu	**7da**[a]	90%

a) As a mixtures of the two possible diastereoisomers.

Table 1

The reaction works well with various $RCeCl_2$ (where R is both a stabilized and a non stabilized carbanionic moiety) with the only exception of vinyl reagents, whose reactions give polymeric products. A typical procedure follows: a THF (15 ml) solution of β-hydroxyketone (3 mmol) was added dropwise at -78°C to a suspension of $RCeCl_2$ (12 mmol) in THF (40 ml) prepared from RLi (1 eq) and dry $CeCl_3$ (1 eq.). The reaction was stirred at this temperature for 1 h and then quenched with 10% aqueous acetic acid. Usual work up gave the crude product which was purified by flash chromatography on a short silica gel column (hexane/ethyl acetate:2/1)[9]. The reaction requires an excess (though a non dramatic one: 4-5 eq.) of metallorganic reagent. However, this is a constant finding in organocerium chemistry when the substrate carries more than one heteroatom[7b,10]. Use of the monoalkyl derivative ($RCeCl_2$) is essential. Dialkyl or trialkyl derivatives gave less satisfactory results. Moreover, Grignard reagents-$CeCl_3$ complexes do not react under the same experimental conditions.Temperature increase and prolonged reaction times promote the retroaldol reaction. On the other hand, we recently reported that Grignard reagents are able to alkylate 1,3-diketones in the presence of $CeCl_3$ to give β-hydroxy ketones[6]. Starting materials **1b-d** were prepared in very good yields according to this procedure[11].

This peculiar behaviour of organocerium reagents offers the possibility of combining the two reactions in a unique protocol for introducing different alkyl chains to both the carbonylic functions of a 1,3-diketone through a two steps sequence by utilizing in each step organocerium complexes as the alkylating agent, but with different modality of use and preparation.

In conclusion, a simple and efficient new method for the synthesis of difficulty available polyalkyl substituted 1,3-diols which utilizes easy accessible starting materials and not sophisticated organometallic reagents is given. Further studies are in progress in our laboratory to apply this method to the construction of enantiomerically pure 1,3- dihydroxy compounds, which are useful building blocks[12] and catalysts[13] in asymmetric synthesis.

This work has been carried out in the frame of the "Progetto di Finanziamento Triennale, Ateneo di Bologna"

REFERENCES AND NOTES.

1. Erasmus student 1995 from the Department of Organic Chemistry, University of Nijmegen, The Netherland.
2. Corey, E.J.; Barrette, E.P.; Magriotis, P.A. *Tetrahedron Lett.* **1985**, 5855.
3. The reactions were carried out by adding dropwise a diethyl ether solution of the ketone to a 2M organolithium solution containing a 5 equivalent excess of the metallating agent in order to largely favour the nucleophilic bimolecular addition over the monomolecular retroaldolic process.
4. Martin, V.A.; Murray, D.H.; Pratt, N.E.; Zhao, Y.; Albizati, K.F. *J.Am.Chem.Soc.* **1990,** 112, 6965.
5. Smith, A.B.; Levenberg, P.A. *Synthesis*, **1981**, 567.
6. Bartoli,G.; Marcantoni, E.; Petrini, M. *Angew.Chem.Inter.Ed. Eng.*,**1993**, *32*, 1061.
7. a) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Tetrahedron Lett.* **1994**, *35*, 8453; b) Bartoli, G.; Marcantoni, E.; Sambri, L.; Tamburini, M. *Angew.Chem.Inter.Ed. Eng.*,**1995**, *34*, 2046.
8. Sugita, K.; Shigeno, K.; Neville, C.; Sasai, H.; Shibasaki, M. *Syn.Lett.* **1994**, 325.
9. ^1H NMR and ^{13}C NMR data for unknown 1,3 diols follow:
   7ab: ^1H NMR (200 MHz, $CDCl_3$): δ=3.62 (bs, 1H), 3.48 (bs, 2H), 1.79 (d,1H, J=15Hz), 1.63 (d,1H, J=15Hz),1.40-1.20 (m, 12H), 0.91 (t, 3H, J=7.5 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ=74.4 (s), 72.3 (s), 50.3 (t), 45.1 (t), 32.6 (q), 31.7 (q), 29.0 (q), 26.5 (t), 23.4 (t), 14.2 (q).

7ac: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.50-7.40 (m, 2H), 7.38-7.15 (m, 3H), 4.78 (bs, 1H), 2.95 (bs, 1H), 2.20 (d,1H, J=15Hz), 2.11 (d,1H, J=15Hz), 1.52 (s, 3H), 1.25 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (200 MHz, CDCl$_3$): δ=149.0 (s), 128.6 (d), 126.4 (d), 125.0 (d), 75.6 (s), 73.3 (s), 52.8 (t), 34.6 (q), 33.5 (q), 29.8 (q).

7ad: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.45-7.35 (m, 2H), 7.34-7.17 (m, 3H), 4.60 (bs, 1H), 3.14 (bs, 1H), 2.00 (bs, 2H), 1.63 (s, 3H), 1.62 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (200 MHz, CDCl$_3$): δ=149.0 (s), 131.5 (d), 128.4 (d), 128.3 (d), 123.1 (s), 93.9 (s), 84.2 (s), 72.7 (s), 67.7 (s), 52.4 (t), 33.4 (q), 32.9 (q), 29.3 (q).

7ae: ^{1}H NMR (200 MHz, CDCl$_3$): δ= 3.70 (bs, 1H), 3.05 (bs, 1H), 2.00 (d,1H, J=14.6Hz), 1.42 (d,1H, J=14.6Hz), 1.43 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (200 MHz, CDCl$_3$): δ=77.7 (s), 72.2 (s), 45.1 (t), 39.1 (s), 33.7 (q), 30.2 (q), 25.0 (q), 24;5 (q).

7bb: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.45-7.18 (m, 5H), 4.45 (bs, 1H), 2.58 (bs, 1H), 2.15 (bs, 2H), 1.80-1.70 (m, 2H), 1.40-1.10 (m, 7H), 0.80 (t, 3H, J=7.2 Hz), 0.72 (s, 3H); ^{13}C NMR (200 MHz, CDCl$_3$): δ= 149.0 (s), 128.1 (d), 126.2 (d), 125.6 (d), 76.6 (s), 73.3 (s), 52.0 (t), 46.4 (t), 33.9 (q), 33.5 (q), 29.7 (q), 25.1 (t), 23.1 (t), 14.2 (q).

7bc: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.53-7.45 (d, 4H, J=1.4Hz), 7.35-7.22 (m, 4H),7.20-7.15 (m, 2H), 5.22 (bs, 1H), 2.62 (bs, 1H), 2.62 (s, 2H), 1.05 (s, 3H); ^{13}C NMR (200 MHz, CDCl$_3$): δ= 148.4 (s), 128.2 (d), 126.7 (d), 125.9 (d), 78.3 (s), 73.8 (s), 50.6 (t), 31.8 (q).

7ca: ^{1}H NMR (200 MHz, CDCl$_3$): δ=7.53-7.45 (m, 4H), 7.30-7.17 (m, 6H), 2.62 (d,1H, J=10Hz), 2.54 (d,1H, J=10Hz), 1.40-1.02 (m, 6H), 0.91(s, 3H), 0.84 (t, 3H, J=2.0 Hz); ^{13}C NMR (200 MHz, CDCl$_3$): δ= 149.5 (s), 148.2 (s), 128.1 (d), 126.5 (d), 126.4 (d), 125.9 (d), 125.6 (d), 78.2 (s), 75.4(s), 48.7 (t), 44.7 (t), 28.2(q), 26.2 (t), 23.2 (t), 14.1 (q).

7da: It consists of a 1:1 mixture of the two diastereoisomers whose ^{1}H NMR signals can't be assigned. ^{13}C NMR (200 MHz, CDCl$_3$): δ=74.5 (s), 74.4 (s), 48.6 (t), 48.3 (t), 45.8 (t), 44.6 (t), 29.9 (t), 29.4 (q), 28.7 (q), 26.8 (t), 26.4 (t), 23.4 (t), 14.3 (q).

10. a) Denmark, S.E.; Edwards, J.P., Nicaise, O. *J. Org. Chem.*, **1993**, *58*, 569; b) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E.R. *Angew.Chem.Inter.Ed. Eng.*,**1993**, *32,* 418.
11. Compound **1a** is an Aldrich commercial product.
12. Scott, J.W. in "Asymmetric Synthesis", J.D. Morrison and J.W. Scott, ed. Academy Press, New York, 1984, vol. 4, chapter 1.
13. Duthaler, R.O.; Hafner, A. *Chem.Rev.*, **1992**, *92*, 807.

(*Received in UK* 22 *December* 1995; *revised* 5 *February* 1996; *accepted* 9 *February* 1996)