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New Reduction of Divinylketones to Rearranged Polyenyl Ethers under Luche Conditions.

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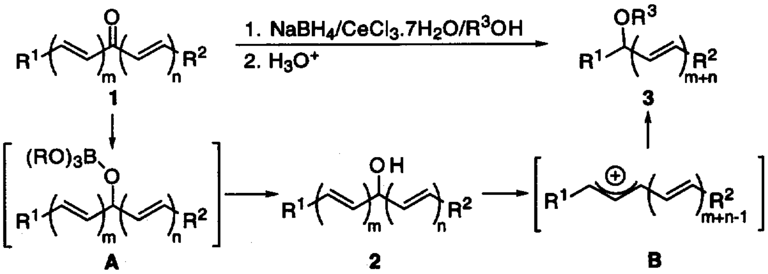
Abstract

The reduction of some substituted divinylketones under Luche conditions (sodium borohydride and cerium trichloride) using different alcohols as solvents affords rearranged polyenyl alkyl ethers in good yields.

Keywords: Divinyl ketones; Reduction; Cerium and compounds; Polyenyl ethers

The reduction of carbonyl compounds by metal hydrides is a versatile synthetic tool and is ubiquitous in organic synthesis.[1] However, the reduction of α,β-unsaturated ketones can follow two pathways: addition to the carbonyl group or addition to the conjugated double bond.[2] The need for the selective 1,2-reduction of enones has led to the development of several specific reagent combinations. The most widely accepted of these involves sodium borohydride in the presence of cerium trichloride. The success of this reagent, developed by Luche et al.,[3] may be explained by considering the active species as an alkoxyborohydride in combination with a hard cerium cation which coordinates to the carbonyl to enhance 1,2-selectivity. The mechanistic study of the role of the lanthanide cation has suggested that it catalyzes decomposition of borohydride by the hydroxylic solvent to afford alkoxyborohydrides.[4]

In order to prepare the alcohol **2a** we carried out the reduction of dibenzylideneacetone[5] **1a** with $NaBH_4$ in the presence of $CeCl_3.7H_2O$ using MeOH as solvent. After acidic work up and chromatographic purification only the dienyl methyl ether **3a** was isolated instead of the expected alcohol **2a** (Scheme 1 and Table 1, entry 1). It is interesting to note that the process is completely regio- and stereoselective and only the conjugated *E,E* isomer of dienyl ether **3a** was formed.



Scheme 1

In light of the unexpected outcome of this reaction, we investigated the possibility of preparing several alkyl dienyl ethers using different alcohols as solvents. So, treatment of **1a** under the reaction conditions described above in the presence of other alcohols led to the corresponding dienyl ethers **3b-f** (entries 2-6).[6] As the solubility of the ketone and the cerium salt in the corresponding alcohol decreased, the reaction times were longer (from 15 min for methanol to several hours for benzyl alcohol). On the other hand, starting from **1b-c**, a mixture of regioisomers **3g-h** was obtained (entries 7 and 8), probably due to the similar electronic stabilization

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of the two different γ-positions. The regioselectivity observed in the case of ketone **1d** is noteworthy, isomer **3i** being the major product which could be isolated (entry 9). In addition, we extended the scope of this reaction to the preparation of other polyenyl ethers with different numbers of conjugated double bonds. So, ketones **1e** and **1f** under Luche conditions afforded trienyl and tetraenyl alkyl ethers **3j-k** in good yields (entries 10 and 11). It is interesting to note that only the more stable isomers, with the extended conjugation, were obtained.

Table 1. Rearranged polyenyl ethers **3** from divinyl ketones **1**.

Entry	Starting ketone	R^1	R^2	m	n	R^3	Product[a]	Yield (%)[b]
1	**1a**	Ph	Ph	1	1	Me	**3a**	86
2	**1a**	Ph	Ph	1	1	Et	**3b**	77
3	**1a**	Ph	Ph	1	1	^{i}Pr	**3c**	70
4	**1a**	Ph	Ph	1	1	C_8H_{17}	**3d**	66
5	**1a**	Ph	Ph	1	1	$CH_2CH{=}CH_2$	**3e**	75
6	**1a**	Ph	Ph	1	1	CH_2Ph	**3f**	73
7	**1b**	Ph	4-$MeOC_6H_4$	1	1	Me	**3g**[c]	78
8	**1c**	Ph	4-ClC_6H_4	1	1	Me	**3h**[c]	78
9	**1d**	Ph	2-Fu[d]	1	1	Me	**3i**	79
10	**1e**	Ph	Ph	1	2	Me	**3j**	76
11	**1f**	Ph	Ph	2	2	Me	**3k**	83

[a] All products were fully characterized by spectroscopic methods (IR, MS, ^1H and ^{13}C NMR). [b] Isolated yield based on the starting ketone **1**. [c] Isolated as a mixture of regioisomers. [d] 2-Fu = 2-furyl

On the basis of the experimental data, we propose that the first step is the reduction of the divinylketones **1** by the alkoxyborohydride $(RO)_3BH$ to generate the borate **A** which after acidic cleavage of the B-O bond affords the corresponding alcohol. In the acidic reaction conditions alcohol **2** could undergo loss of water to give rise to the allylic cation **B**, which is able to react with the nucleophilic solvent to afford the dienyl alkyl ethers **3**. Although in this kind of reaction two regioisomeric products are usually formed by intermolecular nucleophilic attack,[7] in our case, the attack of ROH is regioselective at γ-positions affording dienyl rather than allyl ethers, presumably due to the high degree of conjugation. In order to clarify the reaction pathway, when the reaction of **1a** with the mixture $NaBH_4/CeCl_3$ was worked up in a neutral or basic medium, only the allyl alcohol **2a** was isolated. Interestingly, the treatment of **2a** with $CeCl_3.7H_2O$ in MeOH generated the ether **3a** quantitatively. This result supports the idea that a free OH is needed to obtain the alkyl ether instead of the alcohol.

In summary, we have extended the use of the reduction of divinylketones with $NaBH_4+CeCl_3.7H_2O$. This transformation affords a preparation of polyenyl ethers from readily available starting materials in a regio- and diastereoselective way and could be useful for the synthesis of conjugated polyenyl natural products.

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References and Notes

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[5] Divinyl ketones **1** were prepared by aldol condensations following standard procedures. See: Thebtaranonth, C.; Thebtaranonth, Y. In The Chemistry of Enones. Patai, S.; Rappoport, Z., Eds. New York: John Wiley and Sons, 1989; Chapter 7.

[6] Typical procedure: An Erlenmeyer flask was charged with $CeCl_3.7H_2O$ (5 mmol), divinyl ketone (5 mmol) and the corresponding alcohol (20 g). The mixture was stirred for 10 min (in some cases the ketone or the cerium salt were not completely dissolved). The flask was immersed in an ice bath, and $NaBH_4$ (5 mmol) was added in portions over 5 min. Hydrogen evolved with elevation of temperature to 20°C. After the mixture was stirred for an additional time (from 15 min in the case of methanol until several hours with benzyl alcohol), the resulting grey suspension was concentrated to about 5 ml under reduced pressure. The residue was stirred with HCl 1N (20 ml), the inorganic salts were dissolved and the mixture was extracted with ether (3 x 30 ml). The combined extracts were dried over Na_2SO_4 and the solvent evaporated. Chromatography purification yielded pure dienyl alkyl ethers.

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