Pergamon

Tetrahedron Letters 42 (2001) 8833–8835

TETRAHEDRON
LETTERS

Addition of organocerium reagents to homoallyl alcohols

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Received 12 October 2001

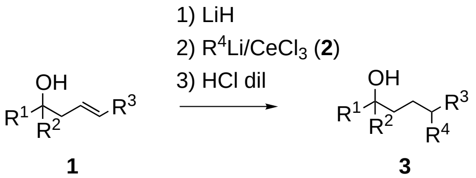
Abstract—Alkylcerium reagents and hydride ions add to multiple bonds of homoallyl alcohols under mild conditions, leading to saturated alcohols in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

We were recently interested in the reaction of allyl alcohols with organocerium regents:[1,2] inexpensive, non-toxic and non-basic organometallic reagents introduced about 20 years ago.[3–6]

Addition of organometallic reagents to a double bond always represented an unreachable target for organic chemists, since carbon–carbon double bonds are generally inert toward nucleophilic attack. Few reactants and substrates are reported to give fair yields in extreme reaction conditions and most examples are restricted to allyl alcohols.[7–11] Much more rare reactions involving homoallyl alcohols (the reaction of allyl Grignard reagent with 1,1-diphenyl-3-buten-1-ol,[12] 3-cyclopenten-1-ol and 3-cyclohexen-1-ol,[13] the titanium-mediated addition of alanes or organolithiums,[14] and, more recently, the zirconium-catalyzed carbomagnesation)[15] always give low yields and conspicuous amounts of regioisomers, stereoisomers and elimination product mixtures.

Organocerium reagents promise to be more widely applicable and efficient than previous reported procedures as in the case of homoallyl alcohols.

Table 1. Reactions of homoallyl alcohols with organocerium reagents



Entry	Product	R^1	R^2	R^3	Reagent	R^4	Reaction time (h)	Yield (%)
1	**1a**	H	Ph	H	**2a**	H	72	86
2	**1a**	H	Ph	H	**2b**	Me	72	94
3	**1a**	H	Ph	H	**2c**	Ph	24	85
4	**1a**	H	Ph	H	**2d**	Bu	24	86
5	**1b**	Et	Ph	H	**2b**	Me	72	93
6	**1c**	H	Ph	Ph	**2d**	Bu	72	90[a]
7	**1d**	H	Pr	Ph	**2d**	Bu	72	14[b,c]

[a] 68/32 Isomer ratio.
[b] 66/34 Isomer ratio.
[c] Together with 47% yield of 1-phenyl-1,3-heptadiene.

Keywords: cerium reagents; unsaturated alcohols; alkylation reactions.

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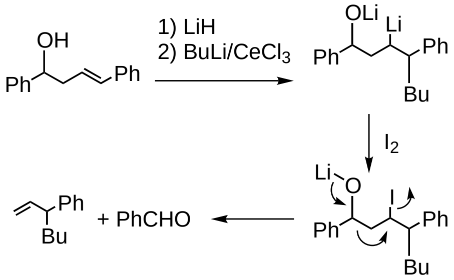
PII: S0040-4039(01)01917-7

Addition of organocerium reagents to homoallyl alcohols was carried out under the same reaction conditions previously set up for allyl alcohols.[2]

As shown in Table 1, these conditions can be efficiently extended to the present reaction, but reaction times are considerably longer than with allyl alcohols.

The combination of both organolithiums and lithium aluminium hydride with cerium chloride works very well. Products are obtained in good or satisfactory yields and chromatographic separation of the product was often unnecessary.[†]

Conversely from allyl alcohols, where addition depends on substituents on the double bond,[1] the alkyl framework of the organocerium reagent always binds to the double bond terminus farthest from the alcohol function. Spectroscopic and chemical evidences support this unexpected finding. The product arising from the reaction of 1,4-diphenyl-3-buten-1-ol (**1c**) and butylcerium (**2d**) shows a peak at 2.81 in the ^{1}H spectrum, the integration of which accounts for a benzylic proton. ^{13}C NMR spectrum confirms this assignment: the signal at 31.6 ppm accounts for a benzylic CH as demonstrated by a DEPT experiment. Moreover, we found[2] that addition of iodine should result in decomposition to alkene and aldehyde according to the pathway depicted in Scheme 1. The reaction of **1c** and **2d** was treated with iodine[‡] and the product distribution confirms that the alkyl framework is bound to the double-bond terminus farthest from the alcohol function.



Scheme 1.

The most remarkable drawback of this reaction is elimination to alkene in the presence of substituents enhancing allylic proton acidity. In fact, allowing 1,2-diphenyl-3-buten-1-ol (**1e**) to react both with methylcerium (**2b**) and **2d**, the exclusive formation of 1,2-diphenyl-1,3-butadiene was observed.[¶] Despite the declared non-basicity of cerium reagents (at least for a 1/1 ratio between cerium chloride and organolithium),[2] we observed that the elimination prevailing over addition was very likely caused by the low tendency of double bond to undergo nucleophilic attack and by the simultaneous presence of allylic and benzylic protons. Moreover, 1-phenyl-1,3-heptadiene is exclusively recovered in the reaction of **2b** with 1-phenyl-1-hepten-4-ol (**1d**), while reaction of **1d** with **2d** led to a mixture of addition and elimination products (Table 1, entry 7), probably due to a higher basicity of the methyl complex with respect to the butyl one. Finally, from reaction of **1c** and **2d** the expected addition product was recovered in very high yield (Table 1, entry 6), very likely because phenyl group is less encumbering that an alkyl chain.

In conclusion, the addition of organoceriums to homoallyl alcohols appears to be a valid improvement in the field of nucleophilic addition to functionalized double bonds. In fact, this reaction employs easily available starting materials and mild experimental conditions. However, a question arises from this reaction: are organoceriums completely nucleophilic and non-basic reagents? The answer seems to be 'no', when nucleophilic attack is very fast, it largely prevails over proton abstraction, but in stressing the reaction conditions also cerium reagents can act as a base.

[†] **General procedure**: Cerium(III) chloride was dried according to the classical procedure.[6] The resulting white THF slurry was then cooled to −78°C and the titrated organolithium reagent (16.5 mmol) was added dropwise from a syringe [or lithium aluminium hydride (7.5 mmol) was poured in] and the mixture allowed to stir for 2 h. Lithium hydride (5.5 mmol) was poured into a THF solution of homoallyl alcohol **la**–**e** (5 mmol) with stirring at 0°C under a nitrogen atmosphere. After 1.5 h the mixture was syringed into the organocerium reagent with stirring at −78°C under a nitrogen atmosphere. The reaction was allowed to stand in a freezer for the requested time (Table 1) before quenching with 4% HCl solution, extraction with diethyl ether, and washing with water. The dried (Na_2SO_4) extracts were concentrated under reduced pressure and characterized without further purification except for reaction of entry 7 in Table 1, which was purified by flash chromatography on a silica gel column [light petroleum (40–60°C)/diethyl ether, 7:3 as eluant]. Yields of the recovered products are listed in Table 1. All compounds gave satisfactory microanalyses and were fully characterised by NMR, and mass spectroscopy. 1-Phenyl-1-pentanol,[16] 3-phenyl-3-heptanol,[17] 1-phenyl-1,3-heptadiene,[18] 1,2-diphenyl-1,3-butadiene,[19] 1-phenyl-1-octanol,[20] 1-phenyl-1-butanol,[21] 1,4-diphenyl-1-butanol[22] gave physical data identical to those reported in the literature. 1,4-Diphenyl-1-octanol (68/32 mixture of diastereomers, determined by GC): oil. δ_H 0.73 (t, 3H, CH_3, $J=$ 6.45), 0.85–1.30 (m, 8H), 1.55–1.90 (m, 2H), 2.00 (brs, 1H, OH), 2.81 6.80–7.30 (m, 10H, Ar); m/z (%): (major isomer) 264 (M^+-18, 1), 176 (73), 133 (7), 107 (100), 92 (55), 91 (77), 79 (39), 77 (28). (Minor isomer) 281 (M^+-1, 1), 264 (1), 176 (60), 133 (6), 107 (100), 92 (53), 91 (76), 79 (42), 77 (28). 7-Phenyl-4-undecanol: (66/34 mixture of diastereomers, determined by GC): oil. δ_H 0.60–0.95 (m, 6H, $2CH_3$), 1.00–1.50 (m, 12H), 1.55–1.95 (m, 2H), 2.57 (tt, 1H, $J_1=6.21$, $J_2=3.63$), 3.55–3.75 (m, 1H, CHOH), 7.10–7.40 (m, 5H, ArH); m/z (%): (major isomer) 230 (M^+-18, 7), 173 (10), 160 (100), 117 (48), 104 (77), 91 (68). (Minor isomer) 230 (M^+-18, 39), 173 (59), 160 (19), 117 (53), 104 (30), 91 (100).

[‡] When formation of 1,4-diphenyl-1-octanol was detected by GC/MS, a THF solution of iodine (16 mmol) was added. The reaction was allowed to stand in freezer overnight and then treated with HCl (4%) and extracted with ether. The organic layer was washed with a $NaHSO_3$ solution and water, dried (Na_2SO_4). GC/MS analysis showed benzaldehyde and 3-phenyl-1-heptene [$m/z=174$ (M^+), 117 (base), 104, 91].

[¶] Elimination does not take place before addition of organocerium reagent. In fact **1c**–**e** are quantitatively recovered after allowing them to react for 24 h with lithium hydride, instead of the 1.5 h generally used for the preparation of the lithium alcoholate.

Acknowledgements

A.T. thanks the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for his educational grant.

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