Tetrahedron Letters,Vol.25,No.38,pp 4233-4236,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

ORGANOCERIUM REAGENTS. NUCLEOPHILIC ADDITION TO EASILY ENOLIZABLE KETONES

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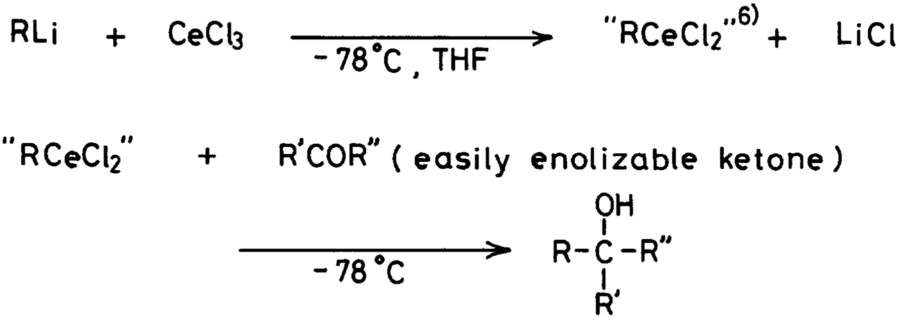
Summary: Organocerium reagents, prepared from organolithiums and anhydrous cerium (III) chloride, react cleanly with easily enolizable ketones to afford the addition products in good to excellent yields.

The nucleophilic addition of Grignard or lithium reagents to carbonyl compounds is undoubtedly one of the most versatile reactions in synthetic organic chemistry.[1)] However, it is also well known that the reaction of easily enolizable carbonyl compounds such as β,γ-enones results mainly in the formation of enolates owing to the strong basicity of the reagents and consequently the desired addition products can not be obtained in satisfactory yields. Despite its synthetic utility, the efforts to circumvent this problem have only been described in a few literatures.[2-4)] We have found that organocerium reagents react cleanly with easily enolizable ketones to afford the addition products in good to excellent yields.

The organocerium reagents could be conveniently generated by the reaction of organolithium reagents with anhydrous cerium (III) chloride at -78°C in tetrahydrofuran.[5)] The reagents were then allowed to react with several ketones which are susceptible to enolization. At the same time the ketones were treated also with the corresponding Grignard or lithium reagents for comparison.

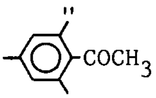
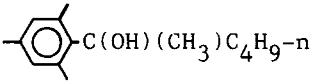
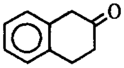
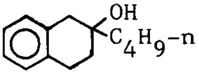
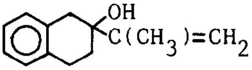
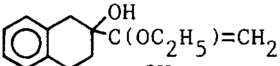
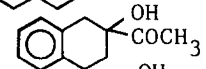
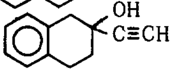
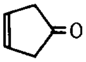
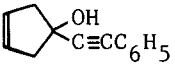


$$\mathrm{RLi} + \mathrm{CeCl_3} \xrightarrow[-78^\circ\mathrm{C,\ THF}]{} \text{"}\mathrm{RCeCl_2}\text{"}^{6)} + \mathrm{LiCl}$$

$$\text{"}\mathrm{RCeCl_2}\text{"} + \mathrm{R'COR''}\ \text{(easily enolizable ketone)} \xrightarrow[-78^\circ\mathrm{C}]{} \mathrm{R{-}\overset{\displaystyle OH}{\underset{\displaystyle R'}{C}}{-}R''}$$

As is shown in Table 1, cerium reagents gave rise to the addition products in high yields. The results are in sharp contrast to those obtained using the Grignard or lithium reagents. It should be emphasized that organocerium

Table 1. Comparison of the Reactivity of Organocerium, Grignard, and Organolithium Reagents with Readily Enolizable ketones

Ketone	Reagent	Conditions	Product	Yield[a]
$(C_6H_5CH_2)_2CO$	$n\text{-}C_4H_9CeCl_2$	-78°C, 3 h	$(C_6H_5CH_2)_2C(OH)C_4H_9\text{-}n$	96
"	$n\text{-}C_4H_9MgBr$	-78°C,3h,0°C,1h	"	20
"	$t\text{-}C_4H_9CeCl_2$	-78°C, 3 h	$(C_6H_5CH_2)_2C(OH)C_4H_9\text{-}t$	65
"	$t\text{-}C_4H_9MgCl$	0°C, 8 h	"	trace
"	$HC{\equiv}CCeCl_2$	-78°C, 3 h	$(C_6H_5CH_2)_2C(OH)C{\equiv}CH$	95
"	$HC{\equiv}CLi$	-78°C, 3 h	"	60
	$n\text{-}C_4H_9CeCl_2$	-78°C, 4 h		57
"	$n\text{-}C_4H_9MgBr$	0°C, 8 h	"	10[b]
"	$n\text{-}C_4H_9Li$	-78°C, 5 h	"	10[b]
	$n\text{-}C_4H_9CeCl_2$	-78°C, 3 h		88
"	$n\text{-}C_4H_9MgBr$	0°C, 4 h	"	6
"	$CH_2{=}C(CH_3)CeCl_2$	-78°C, 2 h		88
"	$CH_2{=}C(CH_3)Li$	-78°C, 4 h	"	12
"	$CH_2{=}C(OC_2H_5)CeCl_2$	-78°C, 4 h		75
"	$CH_2{=}C(OC_2H_5)CeCl_2$	-78°C, 4 h		70[c]
"	$HC{\equiv}CCeCl_2$	-78°C, 3 h		89
"	$HC{\equiv}CLi$	-78°C, 3 h	"	10
	$C_6H_5C{\equiv}CCeCl_2$	-78°C, 3 h		89
"	$C_6H_5C{\equiv}CLi$	-78°C, 3 h	"	30
$p\text{-}BrC_6H_4COCH_2Br$	$C_6H_5C{\equiv}CCeCl_2$	-78°C, 1 h	$p\text{-}BrC_6H_4C(OH)(CH_2Br)C{\equiv}CC_6H_5$	95
"	$C_6H_5C{\equiv}CMgBr$	-78°C,2h,0°C,2h	"	18
"	$C_6H_5C{\equiv}CLi$	-78°C, 4 h	"	trace
CH_3COCH_2Br	$C_6H_5C{\equiv}CCeCl_2$	-78°C, 3 h	$CH_3C(OH)(CH_2Br)C{\equiv}CC_6H_5$	95
"	$C_6H_5C{\equiv}CMgBr$	-78°C, 2 h	"	7

a) Isolated yield unless otherwise stated.

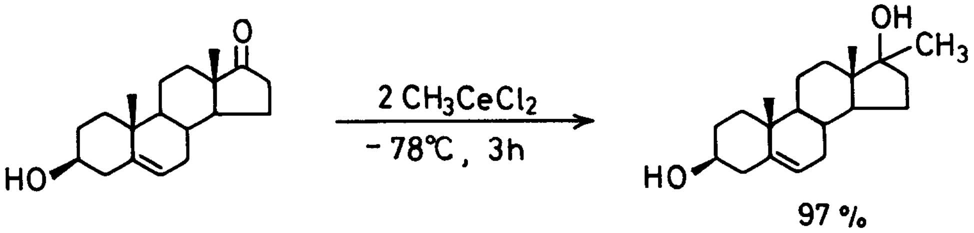
b) Determined by ^1H NMR.

c) After hydrolysis with 2 N HCl in one pot.

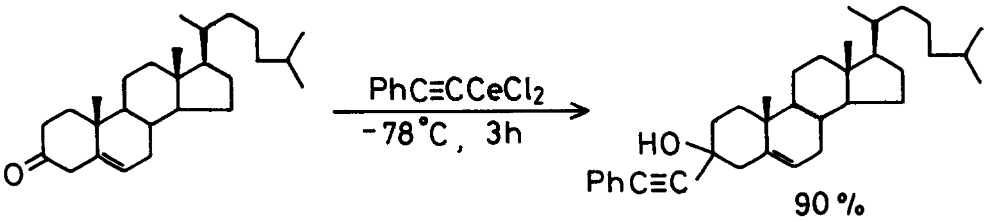
reagents are distinctly less basic than Grignard or lithium reagents, and that they exhibit a pronounced affinity for carbonyl groups. These characteristic reactivities of cerium reagents may be mainly ascribed to strong oxaphilicity of trivalent cerium.

The method exploited here has following characteristic features. 1) The reagents can be conveniently generated; commercially available cerium chloride ($CeCl_3 \cdot 7H_2O$) is easily rendered anhydrous by drying at 140°C in vacuo and the subsequent transmetallation is conducted simply. 2) Not only alkyl- but also alkenyl and alkynylcerium reagents can be generated. 3) The reactions proceed cleanly to produce the addition products in satisfactory yields. 4) The method is applicable to extremely enolizable ketones including α-bromoketones.

Next, we examined the reaction of cerium reagents with a few steroids possessing an enolizable functionality such as cyclopentanone or β,γ-enone moiety. Dehydroisoandrosterone was, on treatment with methylcerium reagent, converted into 17-methyl-5-androstene-3,17-diol[7] in almost quantitative yield. This result is superior over that obtained by the use of methylmagnesium iodide (65% yield).[8] In addition, it may be favorably compared with the similar reaction of β-acetoxy-5-androsten-17-one with methylzirconium tributoxide in that the addition product was produced in the yield of ca. 80%.[2]



5-Cholesten-3-one was also readily subjected to nucleophilic addition with a cerium reagent to yield an ethynyl alcohol derivative as a sole product.[9]



We believe that organocerium reagents have potential synthetic utility in their applicability to a variety of organic syntheses.

<u>General Procedure for the Generation of Organocerium Reagents and Reactions with Carbonyl Compounds.</u> Cerium chloride ($CeCl_3 \cdot 7H_2O$)(480 mg, 1.3 mmol) was placed in a 30 mL two-necked flask and was heated with stirring at 140°C in vacuo (0.1 Torr) for 2 h and cooled.[10] Dry tetrahydrofuran (4 mL) was added with stirring under argon and stirring was continued for 2 h. The resulted suspension was then cooled to -78°C, and organolithium compound

(1.2 mmol)11) was added with stirring, whereupon the color of the suspension turned from white to yellow or orange. After being kept at the same temperature for 0.5 h, carbonyl compound (1.0 mmol) in tetrahydrofuran (2 mL) was added and the mixture was stirred for 3~4 h. Then, the reaction mixture was treated with sat. NH_4Cl solution, filtered through cerite, and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4, evaporated in vacuo, and the residue was subjected to preparative layer chromatography on silica gel to give the addition product.

Acknowledgment: Financial support for this work from Yamada Science Foundation and the Ministry of Education, Japanese Government (Grant-in-aid, No. 58540300) is gratefully acknowledged.

Reference and Notes

1) For excellent reviews, see: a) D. Seyferth, A. G. Davies, E. O. Fisher, J. F. Normant, and O. A. Reutov, "Organometallic Chemistry Reviews", Vol.3, Elsevier, Amsterdam (1977). b) J. C. Stowell, "Carbanion in Organic Synthesis", Wiley, New York (1979). c) R. L. Augustine, "Carbon-Carbon Bond Formation", Vol. 1, Marcel Dekker, New York (1979). d) E. Negishi, "Organometallics in Organic Synthesis", Vol. 1, Wiley, New York (1980).
2) B. Weidmann, C. D. Maycock, and D. Seebach, Helv. Chim. Acta, 64, 1552 (1981).
3) B. Weidmann and D. Seebach, Angew. Chem., Int. Ed. Engl., 22, 31 (1983).
4) D. Seebach, B. Weidmann, and L. Widler, "Modern Synthetic Method" Vol. 3. Verlag, Frankfurt, 1983. p. 217.
5) Trivalent σ-bonded organometallic compounds of lanthanide elements such as lutetium, ytterbium, erbium, and samarium have been synthesized by the reaction of lanthanide (III) chloride with organolithiums. H. Schumann, J. Müller, N. Bruncks, H. Lauke, J. Pickardt, H. Schwartz, and K. Eckart, Organometallics, 3, 69 (1984) and references cited therein.
6) This formulation merely expresses the basic stoichiometry, and some other species including "ate" complexes may be present in equilibrium.
7) The product contained only a single isomer (mp. 201-202 °C), as judged from ^1H and ^{13}C NMR spectra.
8) K. Miescher and W. Klarer, Helv. Chim. Acta, 22, 962 (1935).
9) The isolated product (mp. 154-155 °C) was a single isomer, as judged from ^1H and ^{13}C spectra.
10) Cooling to room temperature is essential to obtain satisfactory results.
11) The reagents prepared from $CeCl_3$ and organolithium compounds in a molar ratio of 1:3 may also give satisfactory results. However, the use of catalytic amount of $CeCl_3$ (5~10 mole %) results in poor yields.

(Received in Japan 4 June 1984)