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Reaction of Methylcerium Reagent with Tertiary Amides: Synthesis of Saturated and Unsaturated Ketones from Tertiary Amides

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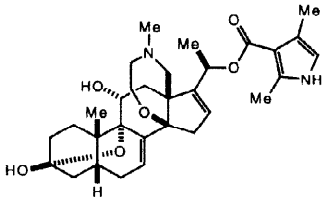
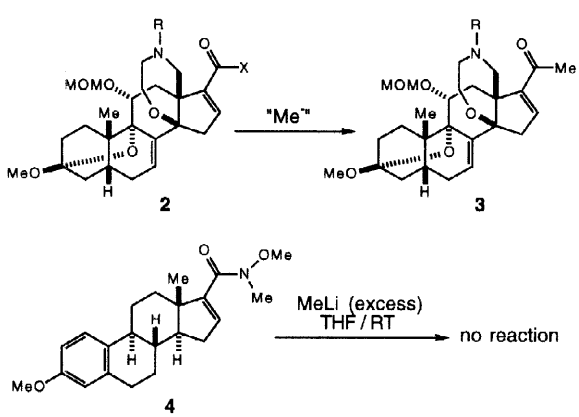
Abstract: The reaction of $CeCl_3$•MeLi to tertiary amides has been studied. The reagent prepared from cerium(III) chloride and methyllithium at 0 °C adds cleanly to morpholine amides to give the corresponding methyl ketones. Even in the presence of a large excess of the reagent, no tertiary alcohol formation is observed, indicating that the tetrahedral intermediates are stable under the reaction conditions employed.

In conjunction with the ongoing studies toward a total synthesis of batrachotoxin (**1**) in this laboratory,[1] we needed to transform the carboxylic acid **2** (X=OH) or its derivative into the corresponding methyl ketone **3**. An inherent problem in this transformation is over-addition of a nucleophile to the electrophile. There are a number of elegant solutions to overcome this difficulty. Among them, the method developed by Weinreb occupies a unique position: *N*-methoxy-*N*-methylamides (Weinreb amides) are shown to react cleanly with both Grignard and organolithium reagents to form ketones without contamination of tertiary alcohols.[2] This method had appeared to meet our need ideally. Unfortunately, however, the amide **4**, derived estrone, did not react even with a large excess of methyllithium at room temperature. In this communication, we report a solution to this problem by using an organocerium reagent.



1 : Batrachotoxin



2 **3** **4**

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Imamoto reported that the treatment of $CeCl_3$ with MeLi (1 equiv) results in the generation of an organocerium species, putatively described as "$MeCeCl_2$", with attenuated basicity and high oxophilicity.[3-5] In our experience, however, the organocerium species generated under the originally reported conditions presented technical difficulties such as poor reproducibility in the reaction with tertiary amides. This problem was overcome by using "$MeCeCl_2$" prepared with the following procedure.[6]

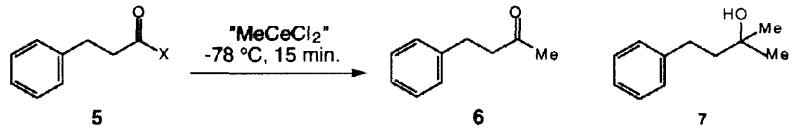
Preparation of "$MeCeCl_2$" solution. Pulverized dry $CeCl_3$[7] (592 mg, 2.40 mmol) was placed in a dry flask under an atmosphere of nitrogen, and anhydrous THF (10 mL) was introduced. The resulting white slurry was then cooled to -78 °C, and methyllithium (1.4 M, 1.8 mL, 1 equiv) was added dropwise, whereupon the color of suspension turned from white to pale yellow. After stirring for 10 minutes at this temperature, the reaction mixture was warmed to 0 °C and stirred at the same temperature for 10 minutes, during which time the color of the reaction mixture turned from pale yellow to dark yellow. This mixture was cooled to -78 °C without stirring, and the supernatant was used for the studies. This dark yellow solution is approximately 0.2 M in active methylating species.[8]

The reactivity of "$MeCeCl_2$" was examined against the tertiary amides prepared from dihydrocinnamic acid and secondary alkylamines (Table 1). With one equivalent of "$MeCeCl_2$" against the substrate $X=N(Me)_2$ (entry 1), the methyl ketone **6** was obtained in 70% yield, along with 30% of the unreacted starting material but no tertiary alcohol **7**. This result indicates that the tetrahedral intermediate exhibits a unique stability under the reaction conditions employed. It is worthwhile noting that the corresponding tetrahedral intermediate derived from methyl dihydrocinnamate is not stable under the reaction conditions; i.e., the reaction of methyl dihydrocinnamate with "$MeCeCl_2$" (1 equiv) yielded **7**, along with the starting ester but none of **6**.

The observed stability of the tetrahedral intermediate was encouraging, but an additional improvement was required to apply this chemistry for practical purposes; the tertiary amide derived from dimethylamine was completely consumed with 3 equivalents of the reagents to yield **6**, but accompanied by a substantial amount of the tertiary alcohol **7** (entry 2). Efforts were then made to tune the reactivity of the tertiary amides by changing their dialkylamine. Presumably due to an increase in the steric bulkiness, a change of dimethylamine to diethylamine (entry 3,4) resulted in deactivation of the amide carbonyl, and perhaps destabilization of the tetrahedral intermediate as well, giving a worse ratio of **6**:**7**. Interestingly, the tertiary amide derived from diisopropylamine was completely inert even in the presence of 3 equivalents of reagent (entry 5).

The tertiary amides derived from 5- and 6-membered cyclic alkylamines met our need beautifully (entry 6-11). Even with 3 equivalents of reagent, there was no double-addition product detected for these cases. To the best of our knowledge, this is the first demonstration of conversion of simple tertiary amides into ketones by organocerium species without over-reaction.[9] It should be emphasized that, to stop the reaction at the mono-addition stage, this reaction does not require the carefully controlled addition of an exact amount of organometallic to the substrate, which obviously adds an experimental convenience. Interestingly, this beneficial effect is not observed for the case of 7-membered amides (entry 13).

Table 1. Additions of "$MeCeCl_2$" to tertiary amides derived from dihydrocinnamic acid.[a]



5 6 7

entry	amine (X)	"$MeCeCl_2$" (equiv)	yield of **6** (%)	ratio (**6**:**7**)
1	dimethylamine	1	70[b]	100:0
2	"	3	60	70:30
3	diethylamine	1	20[b]	50:50
4	"	3	30	70:30
5	diisopropylamine	3	no reaction	
6	pyrrolidine	1	85	100:0
8	piperidine	1	80[b]	100:0
9	"	3	95	100:0
10	morpholine	1	80[b]	100:0
11	"	3	94	100:0
12	hexamethyleneimine	1	95[b]	100:0
13	"	3	90	60:40

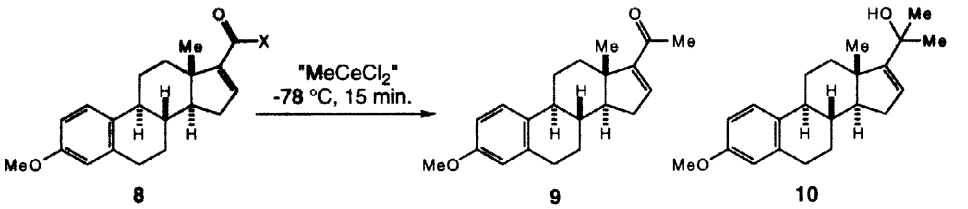
[a]Reactions were conducted in THF at -78 °C and quenched with MeOH after 15 min at -78 °C. [b]The starting material was recovered.

In order to extend this chemistry to the batrachotoxin synthesis, we tested the reactivity of "$MeCeCl_2$" against sterically crowded α,β-unsaturated amides and used the amides derived from estrone as model substrates (Table 2).[10] Unlike the saturated amides shown in Table 1, the α,β-unsaturated amides derived from pyrrolidine and piperidine exhibited a marked decrease in the reactivity against "$MeCeCl_2$"; the reaction was not completed even after 1 hour (entry 1, 2). Nevertheless, it was encouraging that there was no tertiary alcohol **10** detected even under these conditions. In contrast, the tertiary amide derived from morpholine exhibited an outstanding reactivity toward the reagent; this amide was completely consumed with 3 equivalents of the reagent within 5 minutes, to yield the enone **9** in greater than 95% yield with no contamination of **10** (entry 3). The dramatic enhancement of reactivity could be attributed to the fact that "$MeCeCl_2$" acts as a Lewis acid, coordinating to the morpholine oxygen atom, decreasing the basicity of morpholine nitrogen and thereby increasing the electrophilicity of amide carbonyl. Significantly, no tertiary alcohol was detected even in the presence of 10 equivalents of the reagent, indicating that the tetrahedral intermediate derived from the morpholine amide is perfectly stable under the reaction conditions (entry 4).

The method reported appears to have an excellent applicability. Indeed, it has been successfully applied for the transformation of **2**→**3** required for the batrachotoxin[11] and has also been extended to some other organocerium species.[12]

Acknowledgment: Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged.

Table 2. Additions of "$MeCeCl_2$" to tertiary amides derived from esterone.[a]



entry	cyclic amine (X)	"$MeCeCl_2$" (equiv)	time (min.)	yield of **9** (%)	ratio (**9:10**)
1	pyrrolidine	3	60	40 (70[b])	100:0
2	piperidine	3	60	40 (80[b])	100:0
3	morpholine	3	5	95	100:0
4	"	10	15	95	100:0

[a]Reactions were conducted in THF at -78 °C and quenched with MeOH after 60, 15, or 5 min. at -78 °C. [b]Yield based on the recovered starting material.

References and Notes

1. For synthetic work from this laboratory, see: (a) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35* 8333. (b) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett.* **1994**, *35*, 8377.

2. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

3. (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (d) Imamoto, T. *Pure & Appl. Chem.* **1990**, *62*, 747.

4. For a review of the use of organolanthanides in organic synthesis, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

5. For an attempt to characterize the composition of organocerium reagents, see: Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569.

6. For ultrasound-assisted preparation of organocerium reagent, see: Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759.

7. The efficiency of the reaction is highly dependent on preparing finely powdered anhydrous $CeCl_3$. Anhydrous $CeCl_3$ purchased from Aldrich was pulverized with a mortar in a dry box and activated at 90 °C under high vacuum for 2 hours. For a procedure of drying $CeCl_3 \cdot 7H_2O$, see: Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787.

8. The concentration of active methylating species was estimated by exhaustive methylation of methyl dihydrocinnamate; 0.61 mmol of this ester was completely consumed by 6.1 mL of the "$MeCeCl_2$" solution to yield the tertiary alcohol quantitatively.

9. For the reaction of alkyllanthanum triflate with hindered tertiary amides, see: Collins, S.; Hong, Y.; Hoover, G. J.; Veit, J. R. *J. Org. Chem.* **1990**, *55*, 3565.

10. This substrate was prepared from estrone by adopting the method reported by Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

11. Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y., submitted for publication.

12. The reaction of other THF-soluble alkyl and alkenyl cerium species, including the reagent prepared from butyllithium and 1-ethoxyvinyllithium, has been studied thus far: Kurosu, M.; Marcin, L. R.; Kishi, Y., unpublished results.