

Synthesis of β,γ -Unsaturated Ketones via Cerium-Mediated Addition of Organolithiums to Silylated Enaminones

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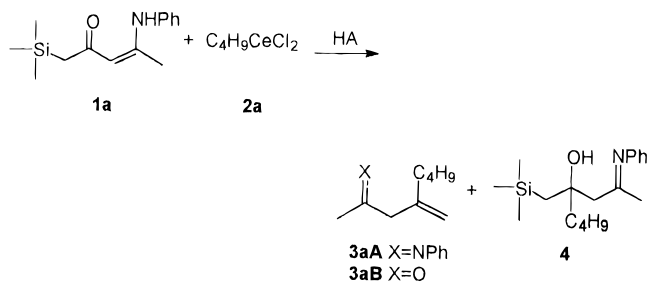
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β,γ -Unsaturated ketones serve as versatile intermediates in organic synthesis.¹ Their preparation is often complicated by a proclivity toward prototropic rearrangement to produce mixtures of conjugated and unconjugated ketones.² Many synthetic approaches to β,γ -unsaturated ketones have been attempted. Among these are direct oxidation of homoallylic alcohols,³ Claisen rearrangement of α -alkoxy ketone enolates,⁴ acylation of olefins,⁵ allylation of borolanes,⁶ and reaction of butenediylmagnesium with esters.⁷ However, each suffers from tedious procedures or limited applicability. In view of the synthetic importance of β,γ -unsaturated ketones, it was desirable to develop convenient methodologies for their synthesis from readily available starting materials.

Previously, we developed a method for the almost exclusive regiocontrolled alkylation of acyclic enaminones (β -*N*-monoalkylamino α,β -unsaturated ketones) at the α' and γ positions.⁸ More recently, the method was extended to the preparation of α' - and γ -(trimethylsilyl) enaminones by addition of trimethylchlorosilane to *N*, α' - and *N*, γ -dianions of enaminones, respectively.⁹ In addition, we discovered that the use of "dry"¹⁰ cerium(III) chloride allows the addition of organolithiums to enaminones.¹¹ As part of these investigations we report now a

Table 1. Quenching of the Reaction between Butylcerium Chloride (2a) and 1-(Trimethylsilyl)-4-(*N*-phenylamino)pent-3-en-2-one (1a) with Various Acidic Solutions



HA	3a ^a (%)	4 ^a (%)
HCl 10%	100 ^b	0
CH ₃ COOH 10%	96 ^c	4
CH ₃ COOH 5%	47 ^c	53
CH ₃ COOH/CH ₃ COONa	traces	>99

^a GC ratios. ^b Detected as 3aB. ^c Detected as 3aA.

facile and convenient synthesis of β,γ -unsaturated ketones via silanol elimination from the adduct between α' -(trimethylsilyl) enaminones and organocerium reagents.

Results and Discussion

1-(Trimethylsilyl)-4-(*N*-phenylamino)pent-3-en-2-one (**1a**) was added at -78 °C to an excess of butylcerium chloride (**2a**) prepared from equimolecular amounts of "dry" cerium(III) chloride and organolithiums. After 2 h, the reaction mixture was quenched with acid.

The acidic quenching is a cornerstone of the procedure for the following reasons: (i) silanol elimination is promoted, (ii) cerous salts are dissolved, (iii) acidic hydrolysis of the silyl group is avoided.⁹

Some acidic quenching protocols were tested to find the optimum conditions. All quenched mixtures were submitted to GC/MS analysis. The results, collected in Table 1, demonstrate that silanol elimination is acid catalyzed and precedes hydrolysis of the silyl group.

Unfortunately, attempts to isolate the silanol intermediate **4** (the sole product obtained in the reaction quenched with acetic acid/sodium acetate buffer) were unsuccessful (decomposition on silica gel, neutral alumina or Florisil during chromatography) but its presence was easily verified by MS and NMR analysis of the crude reaction mixture.¹²

The reaction of the trimethylsilyl derivatives and organocerium reagents followed by hydrolysis to the β,γ -unsaturated ketone with 10% HCl solution is quite general (Table 2).

If primary alkylceriums and phenylcerium are employed, all reactions proceed in high yield, while secondary and tertiary alkylcerium reagents do not react (Table 2, entries 3 and 4).

Since substituents on C-1 make the α' -(trimethylsilyl) enaminones prone to rapid hydrolysis of the silyl group,⁹ a one-pot reaction was carried out by adding the organocerium compound to the mixture of trimethylchlorosilane and the *N*, α' -dianion of C-1 substituted enaminone (Table 2, entry 13).

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(1) Ohtsuka, Y.; Sasahara, T. and Oishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 1106 and references therein.

(2) Pollack, R. M.; Bounds, P. L.; Bevis C. L. In *The Chemistry of Enones* Part 1; Patai, S., and Zappoport, Z., Eds.; John Wiley & Sons: New York, 1989; p 599.

(3) Zaidlewicz, M. *Synthesis* **1988**, 701.

(4) Kacinsky, J. L. C. and Solomon, R. G. *J. Org. Chem.* **1984**, *51*, 1393.

(5) a) Beak, P.; Berger, K. R. *J. Am. Chem. Soc.* **1980**, *102*, 3848.

(b) Kang, K.-T.; U, J. S. *Synth Commun.* **1994**, *24*, 1507.

(6) Brown, H. C.; Soundararajan, R. *Tetrahedron Lett.* **1994**, *35*, 6963.

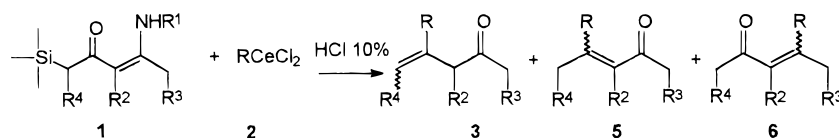
(7) Rieke, R. D.; Sell, M. S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 3429.

(8) Bartoli, G.; Bosco, M.; Cimarelli, C.; Dalpozzo, R.; Guerra, M.; Palmieri, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 649.

(9) Bartoli, G.; Bosco, M.; Dalpozzo R.; De Nino, A.; Iantorno, E.; Tagarelli, A.; Palmieri, G. *Tetrahedron* **1996**, *52*, 9179.

(10) The water molecule found in "dry" cerium(III) chloride seems to have no effect on the reagent, since the whole organolithium reagent should be destroyed by this adventitious water. cf. Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.

(11) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Chem. Eur. J.* **1996**, *2*, 913.

Table 2. Reaction of α' -(Trimethylsilyl) Enaminones with Organocerium Reagents at -78°C and Quenched with 10% Hydrochloric Acid

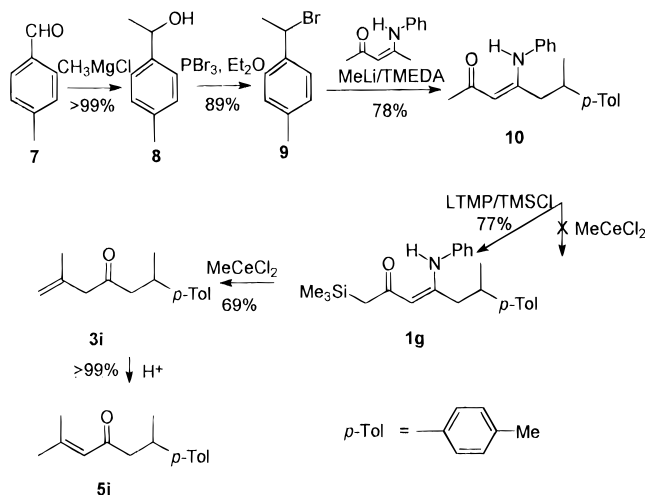
entry	enaminone	R ¹	R ²	R ³	R ⁴	cerium reagent	R	product (%)		
								3	5	6
1	1a	Ph	H	H	H	2a	C ₄ H ₉	a (77)		
2	1a	Ph	H	H	H	2b	C ₆ H ₁₃	b (71)		
3	1a	Ph	H	H	H	2c	<i>s</i> -C ₄ H ₉	c (traces) ^a		
4	1a	Ph	H	H	H	2d	<i>t</i> -C ₄ H ₉	d (0) ^a		
5	1a	Ph	H	H	H	2e	CH ₃	e (87)		
6	1a	Ph	H	H	H	2f	Ph	f (72)		
7	1c	<i>i</i> -C ₃ H ₇	H	H	H	2a	C ₄ H ₉	a (12)		a (48)
8	1d	Me	H	H	H	2a	C ₄ H ₉			a (65)
9	1e	Ph	H	C ₄ H ₉	H	2a	C ₄ H ₉	g (70)		
10	1f	Me	H	C ₄ H ₉	H	2a	C ₄ H ₉			h (67)
11	1g	Ph	H	MeCH- <i>p</i> -Tol	H	2e	CH ₃	i (69)		
12	1h	Ph	CH ₂ Ph	H	H	2a	C ₄ H ₉		j (84)	
13	1i	Ph	H	H	C ₄ H ₉	2a	C ₄ H ₉	k (45) ^b		

^a The only recovered product was 2,4-pentanedione from complete hydrolysis of starting material. ^b Overall yield based on 2-(*N*-phenylamino)non-2-en-4-one.

Prototropic rearrangement to the more stable α,β -unsaturated isomer was observed when the reaction mixture was allowed to remain in acidic media or on prolonged contact with silica gel.¹³ This rearrangement is very fast with α -substituted enaminones, and we were not able to isolate the corresponding β,γ -unsaturated isomer (Table 2, entry 12).

To ensure 1,2-addition to the carbonyl moiety, a phenyl substituent is required on the nitrogen atom. With branched substituents, a mixture of 1,2- and 1,4-addition products is observed (Table 2, entry 7), and with *N*-methyleneaminones, only the conjugated product is recovered (Table 2, entries 8 and 10). These results are in agreement with those previously reported for the reaction with simple enaminones.¹¹

However, the present reaction shows some relevant differences in comparison with the reaction of simple enaminones.¹¹ In particular, a branched chain bound to the nitrogen atom (Table 2, entry 7) or a chain lengthening at C-5 (Table 2, entries 9–11) leads to good reactivity, and the expected ketones are isolated in high yield. Moreover, cerium reagents derived from organolithiums are ineffective. For example, the methylmagnesium–cerium chloride complex and the more reactive allylmagnesium–cerium chloride complex did not give the corresponding β,γ -unsaturated ketone. Acetylac-

Scheme 1

etone, resulting from complete hydrolysis of 1a, was the only isolable product.

Reasons for this different behavior cannot be easily rationalized. Some influence of the silicon atom on the π system of the enaminone can be tentatively invoked.

Nevertheless, our findings complement the previously reported spectrum of reactivity of organoceriums and enaminones,¹¹ since the facile prototropic rearrangement allows for the preparation of the α,β -unsaturated ketones not available by that methodology.¹¹

The total synthesis of (\pm)-*ar*-turmerone (5i, Scheme 1),¹⁴ the chief component of the essential oil from rhizomes of *Curcuma longa*, is an example of how the present methodology complements the reported one.¹¹ Turmerone is a sesquiterpenoid ketone used in the perfume chemistry, and it also displays antitumor properties.

It should be noted that the reaction of methylcerium chloride with enaminone 10 might be expected to furnish

(12) To develop methodology for the preparation of β -hydroxy- γ -silyl ketones, the reaction of butylcerium chloride with the hydrolytically more stable 1-(*tert*-butyldimethylsilyl)-4-(*N*-phenylamino)pent-3-en-2-one (1b) was carried out and quenched with acetic acid/sodium acetate buffer. The MS–FAB and ¹H NMR analyses of the crude reaction mixture showed only the corresponding *N*-phenylimino derivative of 4-[(*tert*-butyldimethylsilyl)methyl]oct-3-en-2-one: *t*_R 10.14 min; *m/z* 329 (M⁺), 272, 214, 200, 118, 77, 73 (100); FAB–MS *m/z* (*v*⁺) 330 (MH⁺), 314, 272, 214, 118, 73 (100); ¹H NMR relevant peaks δ 0.34 (s, 6H), 1.72 and 1.22 (s, 9H), 2.00 and 2.03 (s, 2H), 2.13 and 2.14 (s, 3H), 6.04 and 6.06 (s, 1H). Chromatography of the mixture caused the imino function to be hydrolyzed (82% yield of recovered ketone). The same product was obtained in comparable yields (89%, *EZ* ratio 1.8/1) by quenching of the reaction with 10% HCl solution.

(13) The crude product 3a allowed to stand on silica gel overnight was almost quantitatively converted into 5a.

(14) Rupe, H. and Gassman, A. *Helv. Chim. Acta* **1936**, *19*, 569.

turmerone directly, but because of the lengthened alkyl chain at the γ position the reaction fails (vide supra). Alternatively, alkylation at the α' -position of 4-(*N*-methylamino)pent-3-en-2-one employing LTMP as a base⁸ followed by conjugate addition of the cerium reagent occurs in very low yields. Our procedure furnishes **5i** in 37% overall yield¹⁵ in a six-step sequence from inexpensive *p*-methylbenzaldehyde.

In conclusion, an efficient synthesis of β,γ -unsaturated ketones is now available from readily available starting materials. Moreover, this procedure can be used to prepare α,β -unsaturated ketones by mediated addition of cerium reagents to enaminones. Studies are in progress to bypass the drawback of α' -substituted silylated enaminones by using the Peterson reagent and cerium(III) chloride.

Experimental Section

THF was dried by refluxing over sodium wire until the blue color of benzophenone ketyl persisted and then distilling into a dry receiver under nitrogen atmosphere.

Commercial cerium(III) chloride heptahydrate was placed in a flask with a stirring bar. The flask was heated in vacuo in an oil bath to 140 °C/0.2 mmHg for 2 h. Nitrogen was introduced while the flask was still hot. The flask was cooled in an ice bath, and dry THF was introduced from a syringe. The suspension was stirred overnight at room temperature. The resulting white slurry was then cooled at -78 °C and the titred commercial organolithium reagent was added dropwise from a syringe.

2-Benzylacetylacetone was prepared according to Baumstark's procedure.¹⁶

α' -(Trimethylsilyl) enaminones were prepared as previously described.⁹

Acidic Quenching. A THF solution of enaminone **1a** (5 mmol) was added dropwise to the butylcerium chloride (12.5 mmol) with stirring, at -78 °C under a nitrogen atmosphere. After 1 h, samples of the reaction were quenched with 10% HCl, 10% AcOH, 5% AcOH, and AcOH/AcONa (1:1 w/w) solutions. The samples were submitted to GC/MS analyses, and the following plot ratios were obtained:

(15) A number of syntheses have been reported leading to racemic turmerone; see among others: (a) Crawford, R. J.; Erman, W. F.; Broadus, C. D. *J. Am. Chem. Soc.* **1972**, *94*, 4298. (b) Snowden, R. L.; Linder, S. M.; Muller, B. L.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1987**, *70*, 1858. (c) Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, 3817. (d) Hayakawa, S.; Michiue, T.; Okamoto, M.; Hatakejima, S.; Ohta, S. *Heterocycles* **1988**, *27*, 457.

(16) Choudhary, A.; Baumstark, A. *Synthesis*, **1989**, 688.

10% HCl 4-Butylpent-4-en-2-one (**3aA**) (100%): t_R 1.90 min; m/z 140 (M^+), 125, 82, 55, 43 (100).

10% AcOH: **3aA** (96%), phenylimino derivative of 4-(trimethylsilylmethyl)-4-hydroxyoctan-2-one **4**: (53%) t_R 8.49 min; m/z 287 ($M^+ - H_2O$), 272, 214, 118 (100), 77, 73 (4%).

5% AcOH. Phenylimino derivative of 4-butylpent-4-en-2-one (**3aB**) (47%) t_R 6.80 min; m/z 215 (M^+), 200, 172, 158, 118 (100), 77. **4**: (53).

AcOH/AcONa (1:1 w/w): **4** (>99%).

The whole reaction was then quenched with AcOH/AcONa (1:1 w/w). The crude reaction was submitted to GC/MS analysis, which showed the peak at 6.80 min almost exclusively: FAB-MS m/z (ν^+) 306 (MH^+), 288, 248, 133, 118, 73 (100); ¹H NMR relevant peaks δ 0.33 (s, 9H), 2.02 (s, 2H), 2.19 (s, 3H), 2.70 and 2.78 (ABq, 2H, $J = 12.8$ Hz).

After chromatography, the only recovered product submitted to GC/MS analysis showed the peak at 1.90 min and was recognized as 4-butylpent-4-en-2-one **3a** (51% yield).

General Procedure. A THF solution of enaminone **1a-i** (5 mmol) was added dropwise to the organocerium reagent **2a-f** (12.5 mmol) with stirring at -78 °C under a nitrogen atmosphere. After 1 h, the reaction was quenched with 10% HCl solution, extracted with diethyl ether, and washed with water. The dried (Na_2SO_4) extracts were concentrated under reduced pressure and purified by flash chromatography on a silica gel column (light petroleum (40–60 °C)/diethyl ether 9/1 as eluant). Yields of the recovered products are listed in Table 2. All compounds were fully characterized by NMR, IR and mass spectra.

Synthesis of (\pm) *ar*-Turmerone. 4-(*N*-phenylamino)-6-(4-methylphenyl)-1-(trimethylsilyl)hept-3-en-2-one (**1g**) was synthesized according to our procedure⁹ from **10** in 77% yield after a reaction time of 1 h.

β,γ -Unsaturated ketone **3i** was prepared as described above and then was converted to (\pm)-*ar*-turmerone **5i** by stirring the crude mixture overnight with *p*-toluenesulfonic acid (1.2 mmol with respect to methylcerium chloride). The mixture was then poured in a saturated $NaHCO_3$ aqueous solution and extracted with diethyl ether. The dried (Na_2SO_4) extracts were evaporated under reduced pressure and purified by flash chromatography on a silica gel column (light petroleum (40–60 °C)/diethyl ether 9/1 as eluant). Turmerone was isolated in 69% yield based on **1g** and had physical data identical to that reported in the literature.¹⁵

Supporting Information Available: ¹H NMR, IR and m/z spectral data for all new compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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