An Efficient Synthesis of α-Branched Enones

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Dedicated to Professor Clayton A. Heathcock for his many significant contributions to the art of synthesis and on the occasion of his retirement

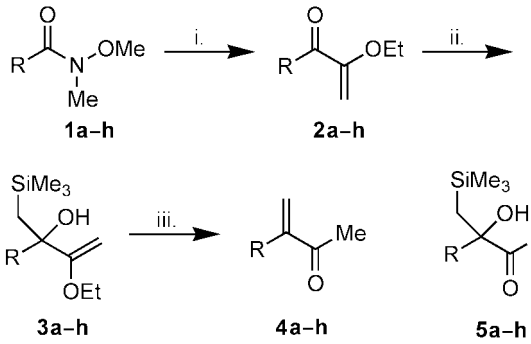
Abstract: A new method for preparing α-branched enones from carboxylic acid derivatives is reported. The procedure commenced by the reaction of *N*,*O*-dimethylamides with a masked acyl anion equivalent, followed by the addition of (trimethylsilyl-methyl)cerium dichloride to give intermediates that undergo Lewis acid mediated olefination to produce enol ethers that are then hydrolyzed to afford simple α-branched enones in high overall yields.

Key words: enones, Peterson olefination, titanium, acyl anion equivalents, homologation

In the context of designing novel approaches to complex natural products using ring-closing metathesis as a key step, we had occasion to require a procedure that allowed for the synthesis of α-substituted enones from carboxylic acid derivatives. A survey of the literature revealed that there were few such methods of general applicability.[1] We were thus encouraged to develop a new synthetic method for effecting such a construction and now report a convenient three-step preparation of α-branched enones from carboxylic acid derivatives.

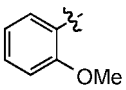
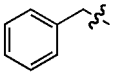
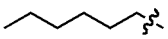
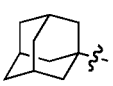
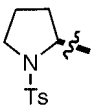
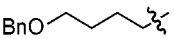
The starting point for our synthesis of α-branched enones was the series of *N*,*O*-dimethylamides (**1a**–**h**), which were prepared from the corresponding acid,[2] acid chloride,[3] or ester[4] according to standard methods. Treatment of amides **1a**–**h** with the lithium anion of ethyl vinyl ether[5] afforded the intermediate enones **2a**–**h** in high yield (Scheme 1, Table 1).[6] Addition of the organocerium reagent derived from transmetallation of commercially available (trimethylsilylmethyl)lithium with anhydrous $CeCl_3$ provided the corresponding tertiary alcohols **3a**–**h**. Use of the cerium reagent was critical to obtaining good yields in this addition.[7]

The stage was then set for forming the desired enones by elimination of trimethylsilanol by a Peterson olefination protocol,[8] followed by acid-catalyzed hydrolysis of the enol ether moiety. Experiments to induce the elimination were first performed under standard basic conditions (NaH/HMPA or KH) leading to the desired enones in modest yields (40–62%) along with some unidentifiable side-products. Attempts to effect the elimination under acidic conditions (e.g., H_2SO_4 or HF) were unsuccessful as hydrolysis of the enol ether function occurred competitively with elimination to give **5a**–**h**. Once the enol ether was transformed into a carbonyl group, the elimination of the elements of TMS-OH was substantially more difficult. Only ketones **5a**,**b** could be converted to the desired enones, while protodesilylation of **3a**–**h** was an unavoidable side reaction when HF was used.



Scheme 1 *Reagents and conditions*: i. 2-Ethoxyvinyllithium, THF, –78 °C; ii. $Cl_2CeCH_2SiMe_3$, PhMe, –78 °C; iii. $TiCl_4$, 2,6-lutidine, CH_2Cl_2, –45 °C, then H_3O^+.

Table 1 Preparation of α-Branched Enones **4a**–**h** from Carboxylic Acid Derivatives **1a**–**h**

Entry	R =	Yield (%) **2**	Yield (%) **3**	Yield (%) **4**
a		88	93	72[9]
b		81	89	88[1,9]
c		80	76	82[9]
d		95	94	86[9]
e		88	81	83[10]
f[a]		93 (91)	98 (99)	93 (93)[12]
g		69	93	63[11]
h		87	94	82[12]

[a] Reaction conducted on 0.4 mmol and 4.0 mmol scales with identical yields (4.0 mmol scale yields given in parentheses).

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(Trimethylsilylmethyl)titanium dichloride has been used in a process that results in the methylenation of aldehydes via an intermediate titanium-alkoxide.[13] This reaction inspired us to examine the use of titanium based reagents to induce the elimination of **3a**–**h**. After some experimentation, we found that the alcohols **3a**–**h** could be rapidly and cleanly converted to the corresponding enones **4a**–**h** by addition of a pre-mixed solution of $TiCl_4$ and 2,6-lutidine at –45 °C, followed by an aqueous acid workup. Use of 2,6-lutidine as an acid scavenger was generally essential to maintaining the integrity of the enol ether function during the elimination step. Only **5a**,**b** could be converted into **4a**,**b**. We were unable to transform **5c**–**h** into **4c**–**h** under these conditions, presumably because generation of a β-silyl carbocation adjacent to a carbonyl via loss of the hydroxyl group is unfavorable in substrates without additional carbocation stabilizing functionalities like an aromatic ring.

As is evident from examination of the entries in Table 1, the method may be successfully applied to substrates with varying degrees of branching in the α-position, as well as those having protected amine and alcohol functions. Less than 3% epimerization occurred during the conversion of **1g** to **4g**, so the method is applicable to the preparation of stereochemically pure enones.[14] Additionally, the scale of the reaction sequence can be increased with ease and with nearly identical yields to the small scale trials as was demonstrated by the conversion of **1f** to **4f** on 4 mmol scale. We also found that the efficiency of the three-step process can be improved with only a slight (<10%) decrease in the overall yield by directly treating the cerium alkoxide intermediates obtained by addition of (trimethylsilylmethyl)cerium dichloride to **2a**–**h**, with a pre-mixed solution of $TiCl_4$ and 2,6-lutidine at –45 °C. For substrates that are incompatible with $TiCl_4$, standard KH-mediated olefination conditions[8a] can be employed, although increased reaction times are required and slightly lower yields of the products may be obtained.

In summary, a concise new method for preparing α-branched enones from carboxylic acid derivatives has been developed. Application of this method to the preparation of intermediates suitable for subsequent ring-closing metathesis and to natural products synthesis is currently under investigation. The results of these studies will be reported in due course.

Representative Procedure for the Preparation of 2a–h

A solution of *tert*-BuLi (1.5 M in pentane, 10.8 mL, 16.2 mmol) was added dropwise to a stirred solution of freshly distilled ethyl vinyl ether (1.28 g, 17.8 mmol) in THF (20 mL) at –78 °C. The resulting bright yellow solution was stirred at –78 °C for 10 min, and then placed into a 0 °C bath. After 5 min, the solution was recooled to –78 °C, and a solution of **1f** (1.21 g, 5.40 mmol) in THF (27 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 2 h, whereupon MeOH (ca. 10 mL) was added and the reaction mixture was warmed to r.t. by removal of the cooling bath. The reaction mixture was subsequently washed with H_2O (75 mL), and the resulting aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with pentane–Et_2O (3:1, containing 2% v/v Et_3N) to afford 1.15 g (91%) of pure enol ether **2f** as a clear oil.

Representative Procedure for the Preparation of 3a–h

Anhyd $CeCl_3$ (2.02 g, 8.20 mmol) was suspended in PhMe (41 mL) and the mixture was sonicated for 1 h. The resulting finely divided suspension was cooled to –78 °C, and then treated with a solution of $LiCH_2TMS$ (0.95 M in pentane, 8.4 mL, 8.0 mmol) via syringe. The resulting slurry was stirred for 1 h at –78 °C, whereupon a solution of enol ether **2f** (0.91 g, 3.90 mmol) in PhMe (5 mL) was added via cannula. The reaction mixture was stirred at –78 °C for 2 h, and then MeOH (ca. 5 mL) was added. The reaction mixture was allowed to warm to r.t. by removal of the cooling bath, and then filtered through a plug of Celite, and the filtrate was subsequently washed with H_2O (100 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude residue that was purified by flash chromatography eluting with pentane–Et_2O (4:1, containing 2% v/v Et_3N) to afford 1.25 g (99%) of pure alcohol **3f** as a clear oil.

Representative Procedure for the Preparation of 4a–h

Freshly distilled 2,6-lutidine (1.22 g, 11.4 mmol) in CH_2Cl_2 (60 mL) was cooled to –45 °C, whereupon freshly distilled $TiCl_4$ (1.08 g, 5.70 mmol) was added dropwise via syringe. The resulting bright yellow solution was stirred at –45 °C for 15 min, and then a solution of **3f** (1.23 g, 3.80 mmol) in CH_2Cl_2 (15 mL) was added via cannula. The resulting dark brown solution was stirred at –45 °C for 2.5 h, whereupon aq 1 N HCl (ca. 10 mL) was added, and the cooling bath was removed. The mixture was stirred at r.t. for an additional 10 min, and then washed with H_2O (100 mL). The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude residue that was purified by flash chromatography eluting with pentane–Et_2O (4:1) to afford 0.72 g (93%) of pure enone **4f**[12] as a light yellow oil.

General Procedure for the Preparation of 4a–h Directly from 2a–h

Anhyd $CeCl_3$ (1.9 mmol) was suspended in PhMe (10 mL) and the mixture was sonicated for 1 h. The resulting finely divided suspension was cooled to –78 °C, and then treated with a solution of $LiCH_2TMS$ (0.95 M in pentane, 1.8 mmol) via syringe. The resulting slurry was stirred for 1 h at –78 °C, whereupon a solution of enol ether **2a**–**h** (0.9 mmol) in PhMe (3 mL) was added via cannula. The resulting mixture was stirred at –78 °C until the reaction was judged complete by TLC (2–12 h), and then transferred to a –45 °C bath. The reaction mixture was allowed to equilibrate to this temperature over a period of 10 min, and then treated with a pre-mixed solution of freshly distilled 2,6-lutidine (7.2 mmol) and $TiCl_4$ (3.6 mmol) in PhMe (7 mL) at –45 °C via cannula. The resulting dark brown solution was stirred at –45 °C until the reaction was judged complete by TLC (2–4 h), whereupon aq 1 N HCl (ca. 5 mL) was added and the reaction mixture was warmed to r.t. by removal of the cooling bath. The mixture was stirred at r.t. for an additional 10 min, and then isolated and purified by flash chromatography[15] as previously described to give pure enones **4a**–**h** as light yellow or colorless oils.

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(12) Characterization data for new enones **4b**, **4f**, and **4h**. Enone **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–6.86 (comp, 4 H), 6.04 (d, *J* = 1.2 Hz, 1 H), 5.65 (d, *J* = 1.2 Hz, 1 H), 3.76 (s, 3 H), 2.26 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3, 156.8, 148.4, 130.5, 130.1, 128.0, 124. 0, 121.2, 111.0, 55.7, 27.4. MS (CI): *m/z* = 177 [M + H$^+$]. IR (neat): 2939, 1698, 1600, 1491, 1243, 1170, 1026 cm^{-1}. Enone **4f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (s, 1 H), 5.23 (s, 1 H), 2.23 (s, 3 H), 2.00–1.96 (comp, 3 H), 1.80 (d, *J* = 2.9 Hz, 6 H), 1.73–1.64 (comp, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 159.1, 120.1, 40.9, 37.7, 37.0, 30.3, 28.8. MS (CI): *m/z* = 205 [M + H$^+$]. IR (neat): 2906, 1676, 1265, 1135 cm^{-1}. Enone **4h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (comp, 5 H), 6.00 (s, 1 H), 5.77–5.76 (m, 1 H), 4.50 (s, 2 H), 3.48 (t, *J* = 6.5 Hz, 2 H), 2.33 (s, 3 H), 2.30–2.25 (comp, 2 H), 1.67–1.58 (comp, 2 H), 1.55–1.45 (comp, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 149.2, 138.8, 128.6, 127.9, 127.7, 125.3, 73.1, 70.4, 30.5, 29.7, 26.2, 25.2. MS (CI): *m/z* = 233 [M + H$^+$]. IR (neat): 2937, 2860, 1678, 1454, 1365, 1104 cm^{-1}.

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(14) The **4g** produced from enantiomerically pure (>99% ee) proline had an enantiomeric ratio of >97:3; Chiralcel OD column, flowrate = 1.0 mL/min, gradient elution (1 to 3% *i*-PrOH/hexanes over 60 min).

(15) Enone **4d** was most conveniently purified by distillation at 90–93 °C (10 mm Hg).