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Vinylalumination of Activated Carbonyl Compounds

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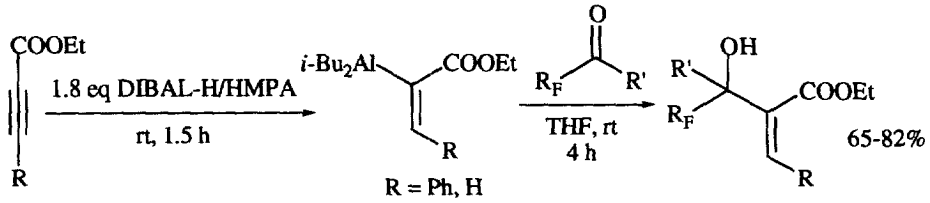
Abstract: [α-(Ethoxycarbonyl)vinyl]diisobutylaluminum and its β-methyl and -phenyl analogs react with activated ketones, such as α-keto esters, α-acyl cyanides, and α-acetylenic ketones to provide the corresponding α-hydroxyalkenylated products in high yields.

key words: vinylalumination, α-keto esters, acyl cyanides, acetylenic ketones

The reaction of an activated olefin with aldehydes or imines in the presence of a trialkylamine or -phosphine, the Morita-Baylis-Hillman reaction, has attracted wide interest among organic chemists.[2] This simple reaction which has been accommodated in certain undergraduate curriculum[3] does not need any sophisticated instrumentation or techniques. The product hydroxyalkene has been employed in the synthesis of valuable compounds.[2] There are several drawbacks for this otherwise simple reaction. One of the shortcomings is its impractical slow rate, often requiring two or more weeks for completion. Another disadvantage is the inconsistent yield of products. In addition, the procedure is not applicable to β-substituted alkenes and requires extreme conditions for the reaction of ketones.[2] Nevertheless, activated carbonyls, such as perfluorinated ketones[4] or α-keto esters[5] react readily.

We recognized that a few other classes of activated carbonyl compounds, such as α-acetylenic ketones and α-acylcyanides[6] also should undergo Morita-Baylis-Hillman reaction. Accordingly, we treated 3-butyn-2-one and pyruvonitrile with methyl acrylate in the presence of 10% 1,4-diazabicyclo[2.2.2]octane (Dabco). Surprisingly, both of these classes of carbonyl compounds failed to undergo the expected reaction.[7]

Vinylalumination of carbonyl compounds with [α-(ethoxycarbonyl)vinyl]diisobutylaluminum has been established as an alternative to Morita-Baylis-Hillman reaction.[8] Recently, we synthesized a series of fluoro-organic molecules using this procedure (eq 1).[9] During this project, we observed that alkyl and aryl fluoroalkyl ketones



(1)

underwent vinylalumination without Lewis acid catalysis. On this basis, we anticipated that the above activated ketones also should undergo reaction with [α-(ethoxycarbonyl)vinyl]diisobutylaluminum. Indeed, all of the

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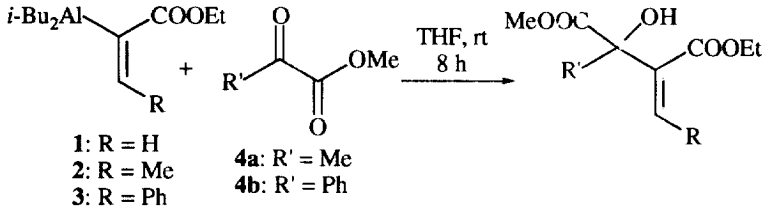
three classes of ketones underwent facile reaction without Lewis acid catalysis and, upon hydrolysis, provided the product hydroxyalkenes in moderate to high yields. Our results are presented below.

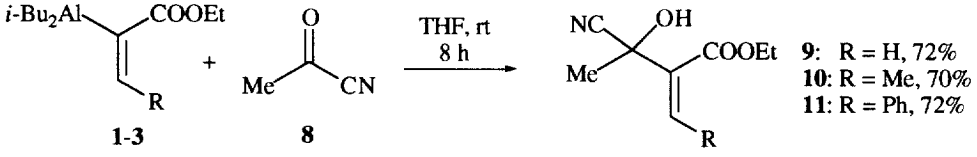
The reaction of ethylpropiolate in THF with 1.5 equiv DIBAL-H-HMPA in hexanes at 0 °C provided the [α-(ethoxycarbonyl)vinyl]diisobutylaluminum (**1**).[9] Methyl pyruvate (**4a**) was added to this reagent at rt and the reaction, followed by gas chromatography, was complete within 8 h. Hydrolysis using 0.5 *M* HCl, followed by chromatography provided 65% of the product **5a** (eq 2). An aromatic keto ester, methyl benzoyl formate (**4b**), also underwent ready reaction with **1** to form the product **5b** in 70% yield. We then extended this reaction to the β-substituted vinylaluminums. [α-(Ethoxycarbonyl)-β-methylvinyl]diisobutylaluminum (**2**) also reacted with **4a** and **4b** smoothly to provide the corresponding hydroxyalkenyl diester products **6a** and **6b**, respectively. The β-phenylvinyldiisobutylaluminum reagent **3** provided the products **7a** and **7b** from the α-keto esters **4a** and **4b**, respectively. It is noteworthy that unlike the Morita-Baylis-Hillman reaction, the vinylalumination is very facile with both aliphatic and aromatic keto esters and the yields of the products are consistent.



5a: R = H, R' = Me, 65%
5b: R = H, R' = Ph, 70%
6a: R = Me, R' = Me, 70%
6b: R = Me, R' = Ph, 60%
7a: R = Ph, R' = Me, 65%
7b: R = Ph, R' = Ph, 75%

(2)

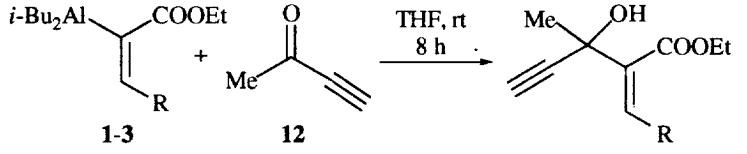
The scope of this reaction was then expanded to include acyl cyanides. No difficulty was experienced in condensing pyruvonitrile with all of the three vinyl aluminum reagents **1-3** (eq 3). The reactions were complete within 8 h and acidic work up provided the α-alkenyl-β-cyano-β-hydroxy esters in 70-72% yields. The Morita-Baylis-Hillman reaction of this class of carbonyl compounds is too slow to be of any practical use.



9: R = H, 72%
10: R = Me, 70%
11: R = Ph, 72%

(3)

The inclusion of α-acetylenic ketones in our scheme further widened the value of the vinylalumination procedure. Reagents **1-3** reacted comfortably with 3-butyn-2-one without any Lewis acid catalysis. However, the products were isolated in only 45-51% yields. Lewis acid catalysis with BF_3•EE did not improve the yields.



13: R = H, 51%
14: R = Me, 45%
15: R = Ph, 46%

(4)

All of the above reactions provide multifunctional molecules which can be converted to several other useful synthons. For example, lithium aluminum hydride reduction or hydrolysis of **5-7** should provide a triol or a hydroxy dicarboxylic acid, respectively. Hydrolysis or reduction of **9-11** should provide the corresponding hydroxyalkenyl diacid or amino diol, respectively. The olefinic group could also be transformed into various other functional groups.

In conclusion, as portrayed above, activated carbonyl compounds, such as α-keto esters, acyl cyanides, and α-acetylenic ketones undergo facile condensation with unsubstituted and β-methyl or -phenyl substituted [α-(ethoxycarbonyl)vinyl]diisobutylaluminum to provide the corresponding hydroxyalkenyl products in moderate to high yields. These multifunctionalized molecules should find applications in organic syntheses. This procedure is widely applicable compared to the Morita-Baylis-Hillman protocol. Currently, we are examining the conditions to improve the yields of this vinylalumination reaction. Further, we are investigating the reactions of enolizable and non-enolizable α-dicarbonyl compounds. The preliminary results are very encouraging.

A typical experimental procedure is as follows. To a stirred solution of HMPA (2.69 g, 2.6 mL 15 mmol) in anhydrous THF (25 mL), 7.5 mL of 1*M* DIBAL-H (7.5 mmol) in hexanes was added at 0 °C and stirred for 0.5 h. Ethyl propiolate (0.49 g, 0.51 mL, 5 mmol) was then added and stirred at 0 °C for 1 h, when the colorless mixture turned yellow. This was followed by the slow addition of the activated ketone (10 mmol) dissolved in 5 mL of dry THF. The orange mixture was warmed to rt and stirred for 8 h, quenched with 50 mL of 0.5 *M* HCl at 0 °C, and extracted with ethyl ether (3x50 mL). The combined ether layers were washed with saturated $NaHCO_3$ solution (30 mL) and dried over anhydrous $MgSO_4$. Removal of the solvents and purification by column chromatography over silica gel (hexane:ethyl acetate :: 90:10) provided the product.

The procedure is similar for the preparation and reaction of **2** and **3** except that two equiv of DIBAL-H was used and the mixture was stirred at rt (1.5 h for **2** and 4 h for **3**) prior to the addition of the activated ketone.

5a: ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.27 (t, *J*= 7.14 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 1.57 (s, 3H, $\mathbf{CH_3}C(OH)COOMe$), 3.73 (s, 3H, $COO\mathbf{CH_3}$), 3.9 (br s, 1H, **OH**, exchangeable with D_2O), 4.19 (m, 2H, $\mathbf{CH_2}CH_3$), 5.93 (s, 1H, **HC**=C<), 6.34 (s, 1H, **HC**=C<). ^{13}C NMR δ ($CDCl_3$) (ppm): 14.05 ($COOCH_2\mathbf{CH_3}$), 23.73 ($\mathbf{CH_3}C(OH)COOMe$), 52.98 (**C**(OH)COOMe), 61.27 ($COO\mathbf{CH_3}$), 73.81 ($\mathbf{CH_2}CH_3$), 125.48 (**C**=CH_2), 141.95 (C=**C**H_2), 166.11 (**C**$OOCH_2CH_3$), 175.40 (**C**$OOCH_3$).

6a: ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.28 (t, *J*= 7.17 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 1.54 (s, 3H, $\mathbf{CH_3}C(OH)COOMe$), 2.00 (d, *J*= 7.17 Hz, 3H, $\mathbf{H_3}C$-C=CH), 3.75 (s, 3H, $COO\mathbf{CH_3}$), 3.79 (br s, 1H, **OH**, exchangeable with D_2O), 4.22 (q, *J*= 7.17 Hz, 2H, $\mathbf{CH_2}CH_3$), 6.35 (q, *J*= 7.20 Hz, 1H, **HC**=C). ^{13}C NMR δ ($CDCl_3$) (ppm): 14.14 ($COOCH_2\mathbf{CH_3}$), 15.64 ($\mathbf{CH_3}$-C=C), 24.36 ($\mathbf{CH_3}C(OH)COOMe$), 53.00 (**C**(OH)COOMe), 60.78 ($COO\mathbf{CH_3}$), 74.92 ($\mathbf{CH_2}CH_3$), 135.17 (**C**=C-CH_3), 135.78 (CH_3**C**=C), 167.08 (**C**$OOCH_2CH_3$), 176.06 (**C**$OOCH_3$).

7a: ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.06 (t, *J*= 7.14 Hz, 3H, $COOCH_2\mathbf{CH_3}$), 1.71 (s, 3H, $\mathbf{CH_3}C(OH)COOMe$), 3.83 (s, 3H, $COO\mathbf{CH_3}$), 3.85 (br s, 1H, **OH**, exchangeable with D_2O), 4.10 (q, *J*= 7.14 Hz, 2H, $\mathbf{CH_2}CH_3$), 7.02 (s, 1H, **H**(Ph)C=C<), 7.3 (m, 5H, Ph). ^{13}C NMR δ ($CDCl_3$) (ppm): 13.64

($COOCH_2CH_3$), 24.74 ($CH_3C(OH)COOMe$), 53.39 (C(OH)), 61.12 ($COOCH_3$), 75.36 (CH_2CH_3), 126.49, 128.22, 128.36, 128.60, 132.99, 135.23, 136.29, 168.29 ($COOCH_2CH_3$), 175.34 ($COOCH_3$).

9: ^1H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.30 (t, *J*= 7.17 Hz, 3H, $COOCH_2CH_3$), 1.78 (s, 3H, $CH_3C(OH)CN$), 4.27 (q, *J*= 7.17 Hz, 2H, CH_2CH_3), 4.82 (br s, 1H, **OH**, exchangeable with D_2O), 6.09 (s, 1H, **HC**=C<), 6.42 (s, 1H, **HC**=C<). ^{13}C NMR δ ($CDCl_3$) (ppm): 13.98 ($COOCH_2CH_3$), 26.69 ($CH_3C(OH)CN$), 62.01 (C(OH)CN), 67.47 (CH_2CH_3), 120.49 (CN), 127.45 ($C=CH_2$), 139.02 ($C=CH_2$), 165.29 ($COOCH_2CH_3$).

13: ^1H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.33 (t, *J*= 7.14 Hz, 3H, $COOCH_2CH_3$), 1.73 (s, 3H, $CH_3C(OH)C{\equiv}C$), 2.53 (s, 1H, **HC**≡C), 4.28 (q, *J*= 7.14 Hz, 2H, CH_2CH_3), 4.82 (br s, 1H, **OH**, exchangeable with D_2O), 6.06 (s, 1H, **HC**=C<), 6.26 (s, 1H, HC=C<). ^{13}C NMR δ ($CDCl_3$) (ppm): 14.10 ($COOCH_2CH_3$), 28.64 ($CH_3C(OH)C{\equiv}CH$), 61.41 (C(OH)C≡CH), 67.95 (CH_2CH_3), 72.34 (-C≡CH) 85.75 (-C≡CH) 124.93 ($C=CH_2$), 142.12 ($C=CH_2$), 166.67 ($COOCH_2CH_3$).

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