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Exceptionally Facile Reduction of Carboxylic Esters to Aldehydes by Lithium Aluminum Hydride in the Presence of Diethylamine[1]

Summary: Both aliphatic and aromatic carboxylic esters are readily reduced to the corresponding aldehydes by lithium aluminum hydride in the presence of excess diethylamine in pentane in excellent yields at room temperature.

Sir: The development of a simple synthetic route to aldehydes from readily available carboxylic acid derivatives is an important goal in organic chemistry. Many useful reducing agents have been reported, especially for the transformation of carboxylic esters to the corresponding aldehydes, e.g., lithium tri-*tert*-butoxyaluminum hydride,[2] diisobutylaluminum hydride,[3] sodium aluminum hydride,[4] and bis(4-methyl-1-piperazinyl)aluminum hydride.[5] However, these reagents cannot achieve a very general reduction of both aliphatic and aromatic carboxylic esters.

In the course of exploring a practical method for reduction of such derivatives to aldehydes by using lithium aluminum hydride (LAH) itself, we have found that this reagent in the presence of excess diethylamine effects the desired transformation in high yields.

LAH possesses 4 equiv of hydride, and all are strong enough to reduce carboxylic esters to their final alcohol stages. However, in the presence of excess diethylamine (DEA), only one hydride equivalent is available for reduction, while the other hydrides (AlH_3) are held in the stable alane–amine complex, which precipitates from pentane solution.

This system reduces aliphatic carboxylic esters examined to aldehydes in yields of 90–96%, regardless of structural type. Even aliphatic diesters such as diethyl sebacate (**1**) and diethyl adipate (**2**) are converted into the dialdehydes with 2 equiv of LAH in yields of 94–97%. α,β-Unsaturated esters such as ethyl acrylate (**3**), ethyl crotonate (**4**), and ethyl cinnamate (**5**) are readily converted into the corresponding olefinic aldehydes in yields of 93–94%.

The reduction of aromatic esters **6** by this system works equally well, giving yields of 92–94% within 0.5 h at room temperature (Chart I).

The reaction also provides a simple procedure for the isolation of the aldehydes products. Thus, the filtration of the alane–amine complex that precipitates at 0 °C, followed by hydrolysis, affords a very good yield of aldehydes.

Chart I

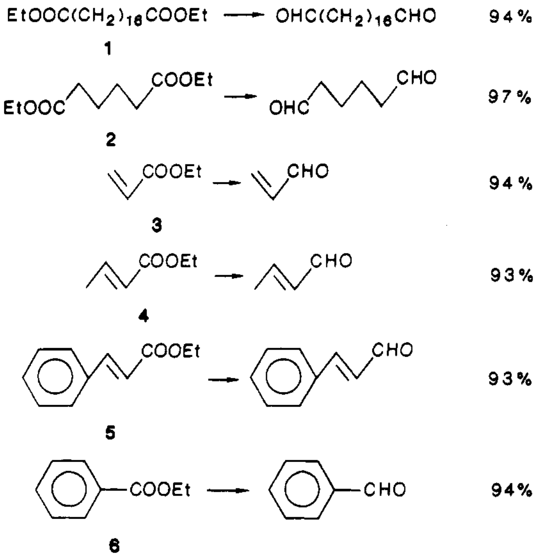

Table I. Yields of Aldehydes in the Reduction of Representative Carboxylic Esters with Lithium Aluminum Hydride in the Presence of Excess Diethylamine[a] in Pentane at Room Temperature[b]

ester	reaction time (h)	yield of aldehyde (%)[c]
phenyl acetate	3	90
isopropyl acetate	1	93
ethyl butyrate	0.5	95
ethyl isobutyrate	0.5	93
ethyl isovalerate	2	93
ethyl caproate	1	96 (84)[d]
ethyl caprylate	2	94
ethyl caprate	3	93
methyl laurate	6	93 (85)[d]
ethyl stearate	6	91
diethyl adipate	1	97
diethyl sebacate	3	94
ethyl acrylate	2	94
ethyl crotonate	3	93
ethyl cinnamate	6	93 (79)[d,e]
methyl benzoate	0.5	92
ethyl benzoate	0.5	94 (84)[d]

[a] 100% excess amine used. [b] Treated with 1 equiv of reagent for monocarboxylic and 2 equiv for dicarboxylic esters. [c] Analysis with 2,4-dinitrophenylhydrazine. [d] Isolated yield. [e] No saturated products on the double bond were detected.

The following procedure for the reduction of ethyl caproate is illustrative. An oven-dried 25-mL flask, fitted with a side arm and a bent adaptor connected to a mercury bubbler, was charged with 5 mL of 1 M LAH solution in THF (5 mmol).[6] THF was pumped off, and then 5 mL of pentane and 0.73 g of diethylamine (10 mmol, 100% excess) were injected. To this slurry was added 0.72 g (5 mmol) of neat ethyl caproate, and the reaction mixture was stirred for 1 h at room temperature. Analysis with 2,4-dinitrophenylhydrazine indicated a yield of 96%.

The following procedure was used for a larger scale reaction. In the assembly previously described, 50 mL of 1 M LAH solution in THF (50 mmol) was charged. The THF solvent was pumped off, and then 7.3 g of diethylamine in 50 mL of pentane was added. To this slurry was injected ethyl caproate (7.21 g, 50 mmol), and the slurry was stirred vigorously for 1 h at room temperature. The reaction mixture was then cooled to 0 °C, and the pre-

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(6) The concentration of LAH solution in THF was measured gasometrically by hydrolysis of an aliquot of the solution with a hydrolyzing mixture of THF–2 N HCl (1:1).

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cipitate was filtered and washed with cold pentane several times. The separated liquid portion was hydrolyzed with 50 mL of 2 N HCl solution by stirring vigorously for 6 h at room temperature. The mixture was saturated with NaCl. The separated layer was subjected to fractional distillation, providing 4.2 g of caproaldehyde (84%): bp 130–131 °C; n^{20}_D 1.4034.

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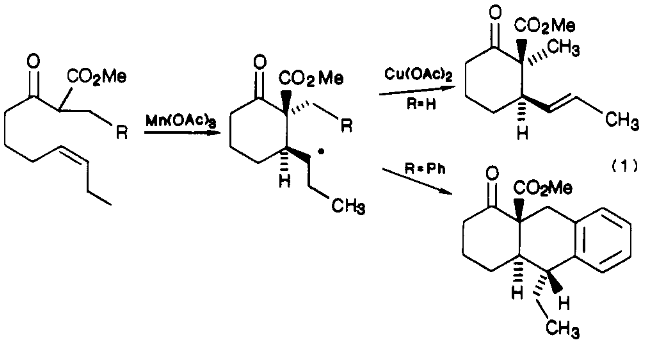
Manganese(III)-Based Oxidative Free Radical Cyclizations. 5. Termination of Polycyclization by Oxidative β-Hydride Elimination[1]

Summary: Oxidative free radical cyclization of β-keto esters such as **1a** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ leads to bicyclic products such as **6a** in excellent yield. The key steps are oxidation of **1a** to **2a** by $Mn(OAc)_3 \cdot 2H_2O$, two successive free radical cyclizations to give **4a**, and oxidative β-hydride elimination by $Cu(OAc)_2 \cdot H_2O$ to give **6a**.

Sir: Free radical cyclizations of alkenes have recently been developed into a powerful method for the synthesis of polycyclic compounds.[3] Typically these cyclizations are terminated reductively by hydrogen atom transfer. Development of methods for oxidative termination promises to increase the scope of these cyclizations since more highly functionalized products will be produced.[4,5] We have recently described manganese(III)-based oxidative free radical cyclizations which are initiated by oxidation of a β-dicarbonyl compound with $Mn(OAc)_3 \cdot 2H_2O$.[1] The resulting radical adds to a double bond to give a monocyclic radical which is either oxidized to an alkene by $Cu(OAc)_2 \cdot H_2O$[1a,c,d] or undergoes a second cyclization by adding to a proximate aromatic ring to give a cyclohexadienyl radical, which is oxidized and loses a proton to regenerate the aromatic ring.[1a,c] (see eq 1).



(1)

We report here a new class of oxidative cyclizations in which two sequential cyclizations to double bonds generate a bicyclic cyclopentylmethyl radical, which is then oxidized to generate an *exo*-methylenecyclopentane. Reaction of β-keto ester **1a**,[6a] as a 0.1 M solution in acetic acid, with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ for 26 h at room temperature gave an 86% yield of **6a**,[11] mp 71.8–72.5 °C. Oxidation of the β-keto ester of **1a** by $Mn(OAc)_3 \cdot 2H_2O$ gives the radical **2a** (Scheme I), probably as a manganese complex.[1d] Cyclization proceeds as expected for this class of stabilized radicals to give exclusively the tertiary cyclohexyl radical **3a**.[1] The primary cyclopentylmethyl radical **7a** is not formed. It is also possible that the double bond is involved in the rate-limiting oxidation of **1a**. If this were the case **3a** might be formed by the addition of the double bond to the manganese enolate of **1a** without the intermediacy of **2a**. Oxidative free radical cyclizations of β-keto esters with $Mn(OAc)_3 \cdot 2H_2O$ do not follow the cyclization rules developed for normal radical cyclizations.[12] Although the detailed mechanism is not known, these oxidative cyclizations are nevertheless quite predictable and consistent.

The monocyclic radical **3a** is a normal alkyl radical, not perturbed by stabilizing groups or manganese, which cyclizes, as expected,[3c,d,12] to give exclusively the cyclopentylmethyl radical **4a**. Cyclopentylmethyl radical **4a** undergoes the expected reaction[13] with $Cu(OAc)_2 \cdot H_2O$ to give organocopper intermediate **5a**, which undergoes facile β-hydride elimination to give **6a**. The success of this reaction depends upon the fact that cyclization of **3a** to give **4a** is faster than the oxidation of **3a** by either $Mn(OAc)_3 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$.

Primary radicals are oxidized very slowly by $Mn(OAc)_3 \cdot 2H_2O$.[14] The unsaturated product **6a** is formed in only ≈20% yield in the absence of $Cu(OAc)_2 \cdot H_2O$. The major products are oligomer and a mixture of saturated products formed from **4a** by abstraction of a hydrogen atom from the medium.

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