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CONJUGATE ADDITION REACTIONS OF ENANTIOMERICALLY PURE ACYLKETENE ACETALS AND ETHYLLITHIUM. A PRONOUNCED SALT EFFECT.

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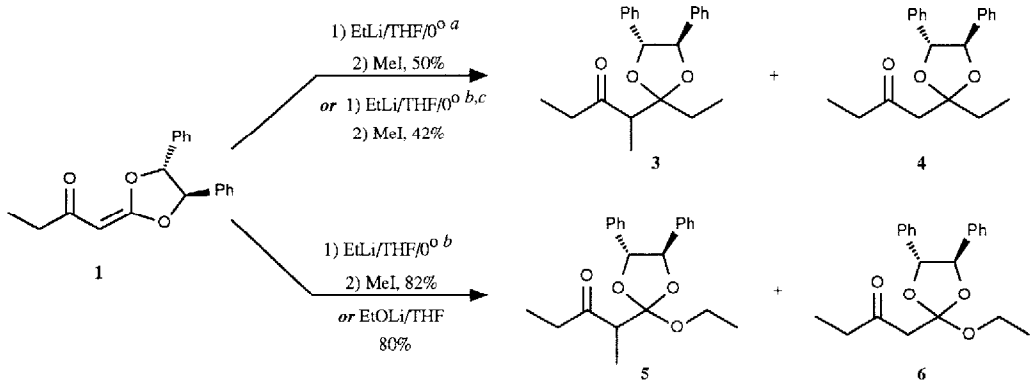
Abstract: *The order of addition of salt-free ethyllithium/benzene solution to enantiomerically pure acylketene acetal* ***1*** *dictates the product formed in a chemospecific manner. Introduction of lithium bromide removes the distinction.*

As part of our continuing studies on the chemistry of enantiomerically pure cyclic ketene acetals,[1] we recently began to explore the reactivity of acylketene acetals.[2] Herein, we report the unusual reactivity of ethyllithium solutions with homochiral acylketene acetal **1**.[3]

Ethyllithium is commonly prepared by one of three methods. We chose not to employ the gaseous reagent ethyl chloride.[4] Rather, we utilized both a modified version of the method of Gronert and Streitwieser[5] (C_2H_5Br/Li in pentane, remove LiBr, remove solvent, store in benzene) and the method of Masamune and Choy[6] (C_2H_5Br/Li in Et_2O at -30°). Titration[7] of the C_2H_5Li/benzene solution prepared immediately after sublimation[8] of solid C_2H_5Li indicated that other basic materials were at a minimum. However, repetition of the titration after storage of the solution at low temperature for one week indicated approximately one half of the basic materials in the solution were not alkyllithium. We assume these to be LiOH (from water intrusion) and LiOEt (from oxygen intrusion). The C_2H_5Li/Et_2O solution showed varying amounts of non-alkyllithium base immediately after formation. This was attributed to the propensity of the solution to decompose to LiOEt at temperatures above -20°C.[9]

The addition of the C_2H_5Li/benzene solution to a cooled (0°C) THF solution of acylketene acetal **1**, followed by quench with CH_3I, afforded desired product **3** in 42% yield as a greater than 10 to 1 diastereomeric mixture of products. Compound **4** was also routinely isolated in small amounts. When the reaction was performed via an inverse addition protocol; i.e., addition of a THF solution of **1** to a 0°C solution of C_2H_5Li/benzene in THF, followed by CH_3I quench, two new products were formed in a combined 82% yield. There was no indication of compounds **3** and **4** in this latter reaction. The structures of **5** and **6** were confirmed when a solution of $LiOC_2H_5$ in THF was treated with **1**, followed by CH_3I, to afford, in 80% yield, the orthoester products.

The reactions with C_2H_5Li/Et_2O showed no indication of orthoester product formation, regardless of the order of addition. Finally, repetition of the C_2H_5Li/benzene inverse addition reaction, *in the presence of lithium bromide*, afforded ketal products **3** and **4** in comparable yield to the normal addition reaction.



[a] Reaction occurs by addition of EtLi to a 0° THF solution of acylketene acetal.

[b] Reaction occurs by addition of THF solution of acylketene acetal to a 0° THF solution of EtLi. [c] Added LiBr.

The origin of this dramatic effect is unclear. It is well known that ethyllithium exists as an aggregate in solution and that alkoxides can enter the aggregate with a concomitant change in chemical properties.[11,12] Lithium halides have also been implicated in the attenuation of reactivity.[10] In the present case, it would appear as if lithium bromide allows for a significant reactivity difference between ethyl and ethoxide anions, in favor of ethyl, regardless of solvent or order of addition. Without lithium bromide, inverse addition promotes ethoxide to the more reactive role with **1**.

The production of **5** and **6** in good yield allows for a new approach to the synthesis of β-hydroxy acids. Reduction of the ketone functionality of these molecules, followed by formal hydrolysis of the orthoester group, would yield the desired compounds. Since **1** is available in enantiomerically pure form, this approach could afford homochiral material via a route that does not involve a classical aldol reaction.[11] These experiments are currently under study, and will be reported in due course.

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