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CONJUGATE HYDROBORATION-REDUCTION AND ORGANOLITHIUM ADDITIONS TO ACYLKETENE ACETALS. SYNTHESIS OF MONOPROTECTED β-DICARBONYLS[1]

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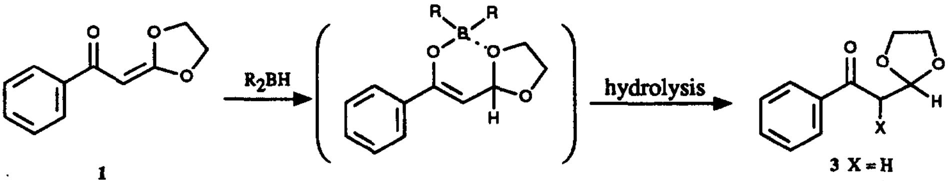
Summary: Hydride and organolithium additions to acylketene acetals are presented. Results indicate conjugate addition to be the dominant reaction pathway, resulting in the formation of monoprotected β-diketones and β-ketoaldehydes.

As part of our studies on the chemistry of enantiomerically pure cyclic ketene acetals,[2] we recently began to explore the reactivity of acylketene acetals.[3] Herein, we report our initial results which indicate that conjugate addition is the preferred mode of attack by both organolithium reagents and borane reducing agents.

Acylketene acetals **1** and **2** were prepared from acetophenone and cyclohexanone, respectively, via β-keto methyl ester formation (NaH, $(CH_3O)_2C{=}O$), transesterification with β-chloroethanol ($Ti(O\text{-}iPr)_4$[4]), and cyclization with K_2CO_3 in DMF.[5] The overall yield of **1** from acetophenone and **2** from cyclohexanone is 57% and 42%, respectively.

Addition of borane-THF complex[6] at -78°C to compound **1** for 30 minutes followed by protic quench yielded β-keto acetal **3** in 70% isolated yield. Workup with D_2O resulted in the introduction of a single deuterium atom at the α-position (**4**) thereby indicating the intermediacy of a boron enolate. This conjugate hydroboration-reduction pathway, although uncommon, has been observed.[7]

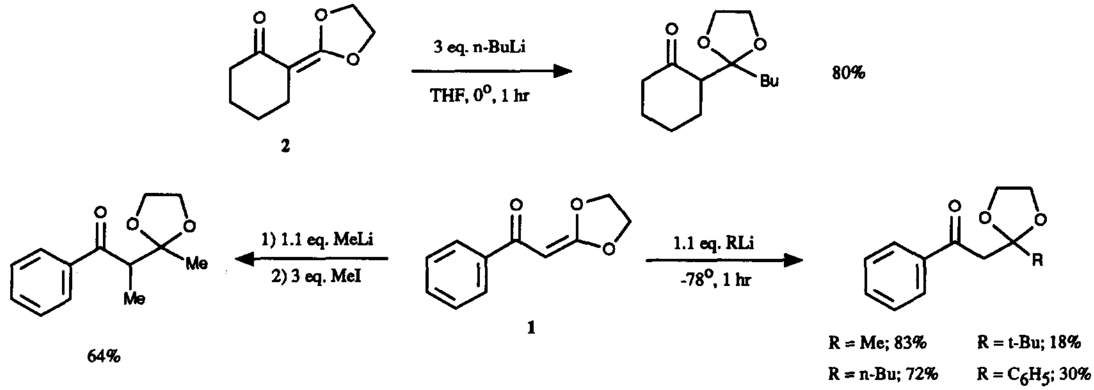


1

3 X = H
4 X = D

Reactions of organolithium reagents with **1** and **2** show predominant 1,4 reactivity without the use of copper salts or other reagents to activate the enone system toward conjugate addition. As shown below, all organolithium reagents react with **1** to give very good to modest yields of only 1,4 adduct with no evidence of 1,2 adduct. These initial reactions have not been optimized and unreacted starting material is easily isolated. Similar results occur with **2** albeit at higher temperature and with an excess of organolithium reagent. The intermediacy of a lithium enolate allows for effective alkylation of the α-carbon.

The results of these reactions indicate that monoprotected β-diketones, compounds which are not so easily or selectively produced, are available through this methodology. Furthermore, the reduction of β-ketal carbonyls bearing enantiomerically pure centers in the ketal moiety has been shown to yield β-ketal alcohols with excellent diastereoselectivity.[8] Thus, extention of the present conjugate addition/alkylation



methodology, employing *enantiomerically pure* acylketene acetals as substrates, followed by diastereoselective reduction of the resultant β-keto ketal and ketal removal, will allow for the enantioselective synthesis of β-hydroxy carbonyl products. These experiments are underway and will be reported in due course.

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