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An efficient one-step chemoselective reduction of alkyl ketones over aryl ketones in β-diketones using LiHMDS and lithium aluminium hydride

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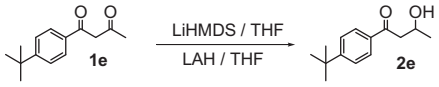
ABSTRACT

β-Hydroxy ketones were synthesized in one-pot from β-diketones by reducing alkyl ketones chemoselectively by keeping aryl ketone intact. Initially, β-diketones were enolized using LiHMDS and later alkyl ketone was chemoselectively reduced efficiently by lithium aluminium hydride. This method produces β- hydroxyl ketones from the corresponding β-diketones in high yield.

Chiral β-hydroxy ketones are useful synthetic intermediates and have been used widely in the synthesis of natural products.[1] β-Hydroxy ketones are very important synthetic intermediates in the synthesis of 1,3-diols, which are basic skeleton of polyene and poly macrolide antibiotics, for example, compactin, Rifamycin,[2] and Lonomycin A,[3] etc.

There are many reported methods to synthesize β-hydroxy ketones, among them traditional aldol condensation, Mukaiyama aldol reactions,[4] and boron mediated aldol condensations[5] of an aldehyde with ketone have been most widely studied. There are methods to synthesize β-hydroxy ketones starting from β-diketones such as ruthenium-BINAP catalyzed hydrogenation,[6] Pt/Al_2O_3 catalyzed hydrogenation,[7] and reduction of both the ketones followed by selective oxidation,[8] but these methods are poor chemo selective and step intensive. Enzymatic chemo selective reduction of β-diketones to β-hydroxy ketones is also reported,[9] this method suffers from long reaction time and tedious work-up. To the best of our knowledge there is only one chemo selective chemical reduction of β-diketones to β-hydroxy ketones using zirconium and hafnium complexes,[10] and this requires the synthesis of these metallocene complexes.

In continuation of our earlier research work,[11] herein we wish to report the efficient one-step, chemoselective reduction of alkyl ketone over aryl ketone using LiHMDS and LAH in β-diketones.



Scheme 1. Synthesis of 1-(4-*tert*-butylphenyl)-3-hydroxybutan-1-one (**2e**).

By applying this methodology a series of β-diketones were chemoselectively reduced to get the β-hydroxy ketones in good yield.

To test our hypothesis, initially we tried a reaction on compound **1e** (Scheme 1) using LiHMDS and LAH and the result was encouraging. Later we tried to optimize the reaction conditions with different reducing agents (Table 1), among them lithium aluminium hydride produced the best results in shorter reaction time (entry 1). DIBAL-H reaction gave only 23% of yield and sodium borohydride did not give any product and starting material remained as such even at room temperature.

After finding the suitable reducing agent the reaction was carried out in different temperatures (Table 1). Reactions at 0, −50 and −78 °C all found to be equally good, reaction at room temperature produced 15% of 1,3-dihydroxy compound.

β-Diketones were synthesized by treating the acid chlorides on the acetophenone enolates by following the procedure reported by Heller et al.[12] Aryl ketones in β-diketones using LiHMDS at 0 °C deprotonate to form enolates and these enolates were chemoselectively reduced by the addition of LAH in one-step (see Fig 1).[13] To test the generality of this method we carried out a number of reactions with different β-diketones and the results are summarized in

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Table 1
Effect of reducing agents and temperature on the yield of **2e**

Entry	Reducing agent	Temp. (°C)	Yield[a]
1	LAH (1 M sol. in THF)	0	81
2	DIBAL-H	0	23
3	LAH (1 M sol. in THF)	−50	75
4	LAH(1 M sol. in THF)	−78	69
5	LAH(1 M sol. in THF)	rt	56

[a] Isolated yield.

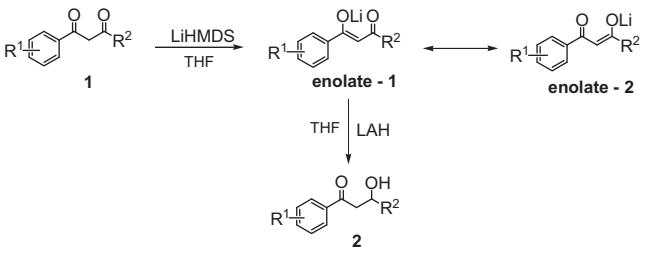

Figure 1. Stabilization of enolate **1** by conjugation with aromatic system.

Table 2. Almost all the substrates reacted smoothly and produced β-hydroxy ketones in good yield. Chemoselective reduction of alkyl ketones was further confirmed by the NOE experiment in compounds **2a, 2c, 2k,** and **2m**. Substrates having the highly electron withdrawing groups did not work (entries 4 and 14) and starting material was intact even at room temperature. In a few cases very small amount of 1,3-dihydroxy compounds was observed, when reactions continued for more than 45 min after adding LAH.

In summary, we have developed an efficient, simple, fast one-step method for chemoselective reduction of alkyl ketones in the presence of aryl ketone in β-diketones using LiHMDS and LAH. This method will help researchers to prepare various β-hydroxy ketones, which are basic skeleton of many natural products and important synthetic intermediates in the synthesis of 1,3-diols.

Acknowledgments

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Supplementary data

Supplementary data (Copies of ^{1}H NMR and ^{13}C NMR of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.057.

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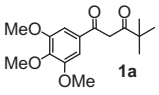
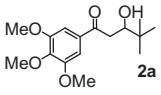
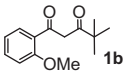
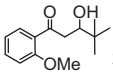
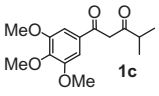
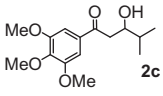
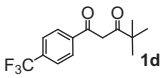
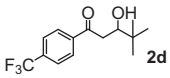
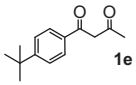
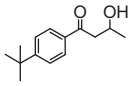
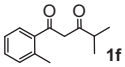
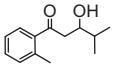
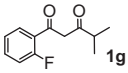
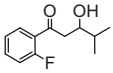
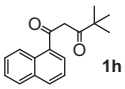
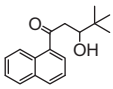
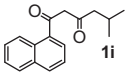
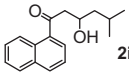
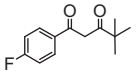
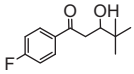
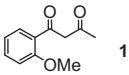
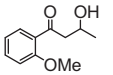
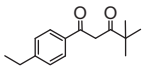
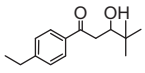
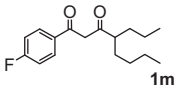
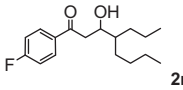
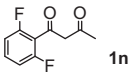
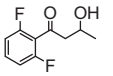
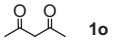
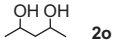
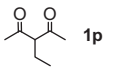
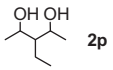
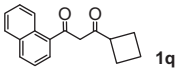
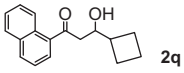
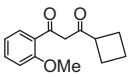
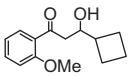
Table 2
Chemoselective reduction of β-diketones

Entry	Substrate	Product	Yield[a] (%)
1	 1a	 2a	80
2	 1b	 2b	78
3	 1c	 2c	75
4	 1d	 2d	0
5	 1e	 2e	81
6	 1f	 2f	72
7	 1g	 2g	70
8	 1h	 2h	76
9	 1i	 2i	78
10	 1j	 2j	72
11	 1k	 2k	80
12	 1l	 2l	74
13	 1m	 2m	70
14	 1n	 2n	0
15	 1o	 2o	78
16	 1p	 2p	82
17	 1q	 2q	72
18	 1r	 2r	68

[a] Isolated Yield.

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13. *General procedure for chemoselective reduction of β-diketones*: LiHMDS (2.5 mmol) was added to the solution of β-diketone (2.3 mmol) in THF (10 mL) at 0 °C. After stirring at this temperature for 30 minutes LAH (4.6 mmol, 1 M solution in THF) was added at 0 °C and stirred at this temperature for 30 min., Reaction was monitored by TLC, after completion of the reaction, reaction mixture was quenched with cold water (4 mL) and the resulting solid was filtered through celite bed and washed with ethyl acetate (20 mL). Filtrate was dried over anhydrous Na_2SO_4, and purification of crude by column chromatography on silica gel (10% ethyl acetate in pet ether) afforded the pure product.