

Reactive barium-promoted Reformatsky-type reaction of α -chloroketones with aldehydes

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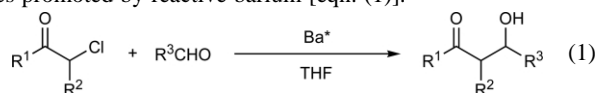
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Received (in Cambridge, UK) 14th November 2003, Accepted 14th January 2004

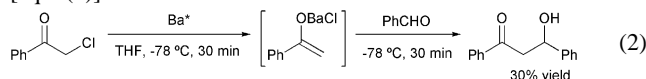
First published as an Advance Article on the web 3rd February 2004

A Reformatsky-type aldol reaction of α -chloroketones with aldehydes has been achieved using reactive barium as a low-valent metal in THF; this one-pot process is more effective for obtaining the desired β -hydroxy ketones in high yields than the stepwise process in which barium enolates are prepared prior to the reaction with aldehydes.

Allylic barium reagents¹ are well-known to be easily prepared by treatment of the corresponding allylic chlorides with *in situ*-generated reactive Rieke barium^{1,2} and they exhibit stereochemical stability and regioselectivity which are markedly different from those of ordinary allylic Grignard or lithium reagents. It is well established that an allylic magnesium reagent gives the γ -substituted product predominantly in the reaction with carbonyl compounds,³ while the allylic barium reagent reacts with remarkable α -selectivity and retains the configuration of the starting chlorides.¹ Interest in the origin of the exceptional regioselectivity and configurational stability led us to further investigate the nature of related barium reagents and their reactions. We report here a novel Reformatsky-type reaction of α -chloroketones with aldehydes promoted by reactive barium [eqn. (1)].



Aldol condensation of ketone enolates with aldehydes provides a beneficial route to β -hydroxy ketones.⁴ Although the Lewis acid-catalyzed Mukaiyama-type aldol reaction of silyl enol ethers or ketene silyl acetals has been extensively studied and numerous excellent Lewis acid catalysts have been developed,⁵ this method is inconvenient in that it requires the masked enolates to be prepared from the corresponding ketones in advance. Alternatively, a Reformatsky-type reaction (a one-pot process), in which a mixture of α -haloketone and aldehyde is treated with a low-valent metal,⁶ seems to be more convenient from a practical point of view.⁷ Prior to the development of the one-pot Reformatsky-type reaction, we attempted a stepwise Reformatsky-type reaction of barium enolate,⁸ derived from 2-chloroacetophenone and reactive barium in THF, with benzaldehyde at -78°C for 3 h; however, the desired aldol adduct was obtained in only 30% yield, probably because of the concomitant homocoupling reaction of the α -chloroketone [eqn. (2)].



Thus, we examined an alternative one-pot Reformatsky-type reaction so as to diminish the side reaction and, in fact, higher yields were obtained in this process. For example, the same aldol adduct was formed in 59% yield when a 1:1 mixture of 2-chloroacetophenone and benzaldehyde was treated with 2 equiv. of reactive barium in THF at -78°C for 3 h (entry 1, Table 1). Increases in the amounts of α -chloroketone and reactive barium improved the chemical yield (entry 2). We next performed the aldol reaction with various aldehydes under the optimized reaction conditions and the results are summarized in Table 1. Not only aromatic aldehydes, but α,β -unsaturated aldehydes and aliphatic aldehydes also showed reactivity toward the *in situ*-generated barium enolate though the chemical yields were not satisfactory

Table 1 Reactive barium-promoted Reformatsky-type reaction of 2-chloroacetophenone with various aldehydes^a

Entry	RCHO	Yield (%) ^b
1 ^c	PhCHO	59
2 ^d	PhCHO	64
3 ^e	4-MeOC ₆ H ₄ CHO	63
4	4-FC ₆ H ₄ CHO	75
5	2-C ₁₀ H ₇ CHO	68
6	(<i>E</i>)-PhCH=CHCHO	28
7	Ph(CH ₂) ₂ CHO	40

^a Unless otherwise noted, the reaction was carried out using 2-chloroacetophenone (2 equiv.), aldehyde (1 equiv.), and reactive barium (2 equiv.) in dry THF at -78°C for 3 h. ^b Isolated yield. ^c 1 equiv. of 2-chloroacetophenone and 2 equiv. of reactive barium were used. ^d 2 equiv. of 2-chloroacetophenone and 4 equiv. of reactive barium were used. ^e 0.5 equiv. of 2-chloroacetophenone and 1 equiv. of reactive barium were used. The yield was calculated based on the molar amount of 2-chloroacetophenone.

(entries 6 and 7). In the reaction with an α,β -unsaturated aldehyde, 1,2-addition took place exclusively (entry 6). In the case of *p*-anisaldehyde, employment of a 1:2 mixture of 2-chloroacetophenone and the aldehyde was more effective for obtaining a high yield (entry 3).

The utility of the present reactive barium-promoted Reformatsky-type reaction was further demonstrated by using an α -chloroketone possessing an alkyl substituent at the α -position, which is an interesting substrate from the viewpoint of *anti/syn* diastereoselectivity. Thus, when a mixture of 2-chlorocyclohexanone (2 equiv.) and benzaldehyde (1 equiv.) was exposed to 2 equiv. of reactive barium, the desired aldol adduct was formed in

Table 2 Reactive barium-promoted diastereoselective Reformatsky-type reaction of 2-chlorocyclohexanone with various aldehydes^a

Entry	RCHO	Yield (%) ^b	<i>anti/syn</i> ^c
1 ^d	PhCHO	50	58:42
2	PhCHO	68	67:33
3	4-MeOC ₆ H ₄ CHO	59	83:17
4 ^e	4-FC ₆ H ₄ CHO	75	71:29
5	1-C ₁₀ H ₇ CHO	62	70:30
6 ^e	2-C ₁₀ H ₇ CHO	58	67:33
7	(<i>E</i>)-PhCH=CHCHO	58	61:39
8	Ph(CH ₂) ₂ CHO	52	71:29

^a Unless otherwise noted, the reaction was carried out using 2-chlorocyclohexanone (2 equiv.), aldehyde (1 equiv.), and reactive barium (2 equiv.) in dry THF at -78°C for 3 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d 4 equiv. of lithium biphenylide were used instead of reactive barium. ^e 1.5 equiv. of 2-chlorocyclohexanone and 1.5 equiv. of reactive barium were used.

68% yield with an *anti/syn* ratio of 67:33 (entry 2 in Table 2).[†] This *anti* selectivity is higher than that shown by the reaction promoted by lithium biphenylide¹⁰ (entry 1). From other aldehydes including α,β -unsaturated aldehydes and aliphatic aldehydes, the corresponding aldol adducts were obtained in moderate to good yields with *anti*-diastereoselectivity (entries 3–8).

In summary, we have achieved a novel, one-pot Reformatsky-type reaction of α -chloroketones with aldehydes using reactive barium as a promoter. This procedure is superior to the corresponding stepwise version with respect to chemical yield and can produce a variety of β -hydroxy ketones with *anti*-selectivity. Further work is now in progress on related reactions using barium reagents.

We gratefully acknowledge financial support from the Forum on Iodine Utilization (FIU).

Notes and references

[†] Typical procedure for Reformatsky-type reaction of aldehydes with 2-chlorocyclohexanone promoted by reactive barium: Synthesis of 2-(hydroxyphenylmethyl)cyclohexanone (entry 2 in Table 2). An oven-dried, 20 mL, two-necked round-bottomed flask equipped with a Teflon[®]-coated magnetic stirring bar was flushed with argon. Freshly cut lithium (14 mg, 2.0 mmol) and biphenyl (323 mg, 2.1 mmol) were put into the apparatus and covered with dry THF (5 mL), and the mixture was stirred for 2 h at 20–25 °C (lithium was completely consumed). Anhydrous BaI₂ (426 mg, 1.2 mmol) was placed in a separate oven-dried, 20 mL flask also equipped with a Teflon[®]-coated magnetic stirring bar under an argon atmosphere; this was covered with dry THF (5 mL), and stirred for 5 min at room temperature. To the solution of BaI₂ in THF was added at room temperature a solution of the lithium biphenylide in THF under an argon stream. The reaction mixture was stirred for 1 h at room temperature. A solution of 2-chlorocyclohexanone (114 μ L, 1.00 mmol) and benzaldehyde (51 μ L, 0.50 mmol) in dry THF (2 mL) was added dropwise to the resulting dark brown suspension of reactive barium (1.0 mmol) in THF (10 mL) at –78 °C. After being stirred for 3 h at this temperature, the mixture was treated with a saturated NH₄Cl aqueous solution (10 mL) at –78 °C and the aqueous layer was extracted with diethyl ether (10 mL). The combined organic extracts were washed with 1 N sodium thiosulfate solution (20 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo* after filtration. The residual crude product was purified by column chromatography on silica gel to give a mixture of the aldol adducts (69 mg, 68% yield) as a colorless oil. The *anti/syn* ratio was determined to be 67:33 by ¹H NMR analysis. Spectral data (TLC, IR, ¹H NMR, and ¹³C NMR) of the *syn* and *anti* isomers indicated good agreement with the reported data.⁹

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