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Synthesis of β-hydroxy esters using highly active manganese ☆

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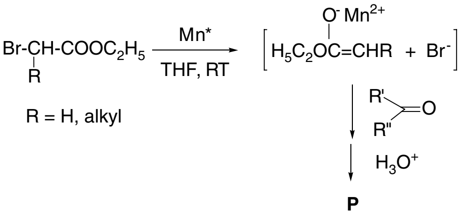
Abstract—A modified Reformatsky reaction is reported using highly reactive manganese (Mn*). The active manganese was found to readily react with α-haloester in the presence of aldehydes and ketones to yield the corresponding β-hydroxy esters. The reaction is carried out at room temperature in the absence of Lewis acid or trapping agents.

The Reformatsky reaction is one of the standard methods for preparing β-hydroxy esters[1]. The reaction typically utilized refluxing benzene or benzene/ether solvents and is characterized by difficulty of initiation and modest yields. Another major problem is the control of the very exothermic reaction. Several attempts have been put forth[2] to improve the reaction condition including use of Rieke zinc,[3] trimethyl borate/THF, or continuous-flow procedure requiring refluxing benzene.[4,5] Most recently, high intensity ultrasound-promoted Reformatsky reactions using α-bromoester, zinc dust and a catalytic amount of iodine were reported in high yields of β-hydroxy esters.[6] Moreover, a variety of metals or metal salts other than zinc have been studied in order to extend the scope and selectivity.[7–13]

However, the study of the reaction using manganese has been limited. In fact, there was only one report,[14] where the employed procedure required the presence of a stoichiometric amount of a trapping agent such as acetic anhydride and Lewis acid such as zinc chloride. In the absence of acetic anhydride or Lewis acid, the yields are very low. Therefore, in the course of our studies on the chemistry of active manganese, we attempted to study the reaction in detail using manganese (Scheme 1). We now wish to report our positive results and improvements on the Reformatsky reaction using active manganese.



Scheme 1.

The active manganese was prepared following the procedure published previously.[15,16] The basic procedure involves the reduction of an anhydrous manganese salt with lithium and naphthalene in THF under argon atmosphere at room temperature.

Initially, active manganese was simply treated with a α-bromoester followed by addition of the carbonyl compound at room temperature. But the results were found to be disappointing. Once the reaction started, there was considerable difficulty in moderating the exothermic reaction as expected. Also, the reaction was complicated by the formation of homo-coupling products. Lowering the reaction temperature resulted in lower yields. However, we found that the activated manganese would react rapidly with the α-bromoester in the presence of the carbonyl compounds in THF producing high yields of the corresponding addition product.[17] The reaction was completed in 1–2 h at room temperature. The results are summarized in Table 1.

Active manganese (Mn*) prepared from MnBr$_2$ or MnCl$_2$ is extremely reactive towards ketones and aldehydes yielding pinacols. This precluded its use in this

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☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.11.045

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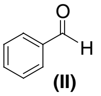
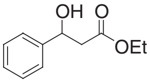
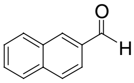
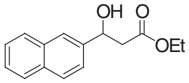
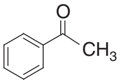
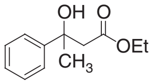
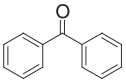
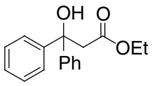
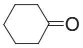
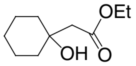
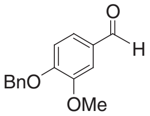
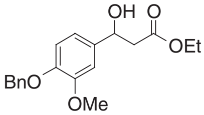
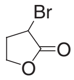
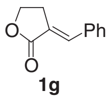
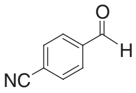
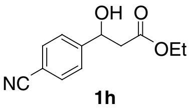
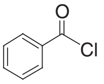
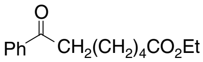
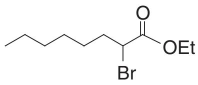
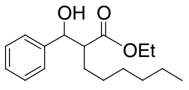
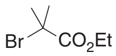
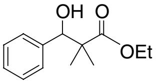
Table 1. Reactions of α-bromoester with carbonyl compounds using Mn*

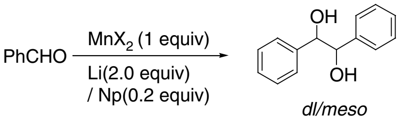
Entry	α-Bromoesters	Carbonyl compound	Product[a]	Yield (%)[b]
1	$BrCH_2COOEt$ **I**	 **(II)**	 **1a**	90
2	**I**		 **1b**	85
3	**I**		 **1c**	86
4	**I**		 **1d**	82
5	**I**		 **1e**	91
6	**I**		 **1f**	79
7		**II**	 **1g**	90
8	**I**		 **1h**	86
9	$C_2H_5O_2C(CH_2)_6Br$		 $PhC(O)CH_2(CH_2)_4CO_2Et$ **1i**	68
10		**II**	 **1j**	70
11		**II**	 **1k**	58

[a] All products are fully characterized (^1H, ^{13}C NMR and MS) and match literatures.

[b] Isolate yield (based on electrophiles).

reaction. However, Mn* prepared from MnI_2 is much less reactive allowing the formation of the Reformatsky reagent in preference to pinacol formation. Accordingly, MnI_2 proved to be ideal for this reaction (Table 2).

Table 2. Reactivity study of Mn* on halides



MnX_2	Conditions (°C/time)	Yield[a] (%)
$MnCl_2$	rt/30 min	86
$MnBr_2$	rt/overnight	89
MnI_2	rt/24 h	80

[a] Isolate yield (based on aldehyde).

The reactivity of the organomanganese reagents was examined with several aldehydes and ketones. The corresponding β-hydroxyester products were obtained in high yields (entries 1–8). It is noteworthy that this reaction exhibits tolerance of functional groups on the aromatic ring including cyano and methoxy. Significantly, a α-bromolactone was also found to readily react and undergo a mixed aldol condensation (entry 7). For all cases, the reaction was conducted in absence of any Lewis acid, which is required for zinc enolates prepared from α-haloketones. Organomanganese compounds in which the ester group is farther removed from the carbanion centre can also be prepared and the reaction with benzoyl chloride gave a modest yield (entry 9). This would not be possible for the lithium or magnesium reagents. Secondary and tertiary manganese enolates were also tested with aldehydes and were shown to provide the corresponding products readily (entries 10 and 11). The activated manganese will also react with α-chloroesters in THF. However, the yields are only in the modest range.

In summary, manganese ester enolates were readily prepared for the Reformatsky reaction via direct oxidative addition of highly active Rieke manganese to α-haloesters, lactone and alkyl halides with remote ester groups. The resulting reagents demonstrated excellent addition reactions with various electrophiles such as aldehydes and ketones. The employed procedure does not require any special preparation or complicated work-up process. The wide range of haloesters that can be used in this reaction offers the synthetic chemist an important new tool.

Supporting Information

Typical procedure for synthesis of β-hydroxy esters using active manganese. Characterization information including ^{1}H NMR, ^{13}C NMR spectra and/or MS/IR data for all products (**1a**–**k**). The supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

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17. The following is a representative procedure: Ethyl α-bromoacetate (60 mmol) and benzaldehyde (58 mmol) were weighed separately. To the black slurry of active manganese in THF (30 mL) was added the mixture of benzaldehyde and ethyl α-bromoacetate drop by drop over 25 min. The addition was conducted at 0 °C and the entire system was kept under argon. The reaction mixture was stirred at room temperature for about an hour after the addition was completed. The reaction was then quenched with 2 N hydrochloric acid (20 mL) or saturated ammonium chloride and the organic layer was separated from the acidic aqueous layer. The aqueous layer was extracted with ether (3 × 20 mL) and the combined organic phase was washed twice with saturated sodium hydrogen carbonate (10 mL) and water (10 mL). The ether extract was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated, resulting in a pale yellow liquid. The crude product was subjected to GLC, which showed no by-products. The crude product was purified by vacuum distillation or column chromatography yielding 90% of the corresponding compound.