A Practical Method for the Reformatsky Reaction of Aldehydes

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Abstract: Reformaksky reaction of aliphatic aldehydes has been performed successfully by the addition of BF_3•OEt_2 to a stirred suspension of aldehyde, bromo ester and Zn dust in aqueous THF. For aromatic aldehydes, addition of benzoyl peroxide is also required to effect the reaction.

Key words: aqueous condition, boron trifluoride etherate, stereoselectivity, chemoselectivity, radical chain mechanism.

Carbon−carbon bond formation is the essence of synthetic organic chemistry. In this regard numerous reactions involving the addition of an organic halide to an electrophile in presence of active metals are widely applied in organic synthesis.[1] Consequently, there has been tremendous development of strategies allowing the reactions between functionalized organometallics and carbonyls. Among them, metal-mediated Reformatsky reaction has been traditionally considered as an important homologation reaction as this produces a versatile and exploitable functionality like δ-hydroxy ester. In view of this, there has been continuous effort till recently[2] for the development of practically viable methodologies to carry out this reaction. Thus, a variety of metal-mediated Reformatsky reactions have been reported using Zn,[2b] Ge,[2c] In,[2d] Sn,[2e] Zn-Cu couple,[2f] ultrasound[2g] etc. However, the use of Zn metal is more advantageous as powdered Zn is easily available at low cost, with reasonably good reactivity and hence amenable for handling in practical scale. It is noteworthy that there has been a tremendous development of organozinc reagents and their extensive utilization in organic synthesis.[3]

In synthetic organic chemistry efforts are directed towards the development of the reactions in wet solvent, aqueous medium or salt solution,[4,5] with a view to impart practical viability. Morever, organic reactions in aqueous media without using harmful solvents are of great current interest specially in relation with the present environmental concerns. Regarding Reformatsky reaction, the first examples in aqueous medium were reported in 1985 using (bromomethyl)acrylic acid and metallic Zn to prepare α-methylene-γ-butyrolactones.[4a] Normal α-halocarboxylic esters did not react under these conditions. Since the substrate of this reaction is an allylic halide, the reaction should be regarded as an allylation reaction rather than a Reformatsky reaction.

A direct Reformatsky-type reaction took place when an aromatic aldehyde was reacted with an α-bromo ester in water, mediated either by zinc or tin. However, the reaction gave only a low yield of the product and aliphatic aldehydes failed to react.[5a] Subsequently, Reformatsky reaction has been effected with low to moderate yield of the required product when aromatic aldehydes were reacted with bromo esters in water mediated by In.[4b] In this case also, aliphatic aldehydes failed to react. Recently, Zn-mediated Reformatsky reaction has been performed with a variety of aromatic aldehydes but with few aliphatic ones, in the presence of saturated aqueous NH_4Cl solution and other additives but in majority of the cases the yield are not appreciable.[2h] However, this method gave relatively poor yield of the desired product when ethyl bromoacetate was treated with the aliphatic aldehydes.

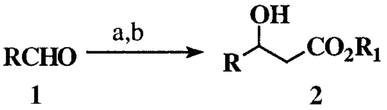
During our ongoing program on the synthesis of bioactive compounds, we have done Zn-mediated allylation of chiral aliphatic carbonyls[7a-c] in the presence of water following Luche's procedure.[6] Simultaneously, we utilized this methodology for the propargylation of the carbonyls.[7a,b] However, our efforts to carry out Reformatsky addition of ethyl bromoacetate to several aliphatic as well as aromatic aldehydes using this procedure proved unsuccessful. We then found that the addition of BF_3•OEt_2 instead of saturated aqueous NH_4Cl solution to a stirred suspension of Zn dust, an aldehyde and ethyl bromoacetate in aqueous THF (containing approx. 2% water) produced much more encouraging results (Scheme). Several aliphatic and aromatic aldehydes were chosen as representative examples. For aliphatic aldehydes (Table, Entries a−f), Reformatsky reaction has been effected smoothly at reasonably faster rate showing their disappearance (TLC) within 1−4 hours. Unfortunately, for aromatic aldehydes (Table, Entries g−k), the results are not appreciable even after stirring the mixture under these reaction conditions for a longer duration (40 h). We then observed that the addition of a catalytic amount of benzoyl peroxide and increased quantity of both Zn dust and bromo ester effected a substantial progress of reaction which goes to completion within 7−9 hours.

It has been generally observed that the reaction rate for aromatic aldehydes is slower as compared with that of aliphatic aldehydes. This is in sharp contrast with all the available reports where majority of the Reformatsky reactions under wet condition have been performed smoothly with aromatic aldehydes rather than aliphatic ones. In our case, for aliphtic aldehydes the reactions are clean and high yielding for the expected products without any prominent dehydration of the resulting β-hydroxy esters. For aromatic aldehydes that we have utilized, the general yields are appreciable but slightly lower as compared to

Table Reformatsky Reactions of Aldehydes

Entry	RCHO	$BrCH_2CO_2R_1$	Additive	Time (h)	Yield (%)
a	isobutanal	R_1 = Et	none	1–2	92
b	(*R*)-2,3-*O*-cyclohexylidene glyceraldehyde	R_1 = Me	none	2–3	81
c	citronellal	R_1 = Et	none	3–4	70
d	heptanal	R_1 = Et	none	3–4	88
e	decanal	R_1 = Et	none	3–4	85
f	dodecanal	R_1 = Et	none	3–4	84
g	benzaldehyde	R_1 = Et	Bz_2O_2	7–8	81
h	4-chlorobenzaldehyde	R_1 = Et	Bz_2O_2	8–9	76
i	4-methoxybenzaldehyde	R_1 = Et	Bz_2O_2	8–9	75
j	2-methoxybenzaldehyde	R_1 = Et	Bz_2O_2	8–9	66
k	1-naphthaldehyde	R_1 = Et	Bz_2O_2	7–8	78

the average cases for aliphatic ones. This is probably due to the formation of slight amount of side products caused by prolonged stirring of the mixture in the presence of Lewis acid. However, there is considerable improvement in the yields of the Reformatsky products of the aldehydes (Table, Entries g, h and i) as compared to those in a reported procedure.[2h] To our delight, when (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (Table, Entry b), a potentially useful chiron[7a,c] was used as substrate no deketalization was observed. This is certainly advantageous for the subsequent synthetic maneuvre as this requires selective exploitation of all the hydroxyl functionalities of the resulting product. Furthermore, the addition has been found to be highly *anti* selective (*syn*:*anti* = 2:98) by treating methyl bromoacetate with **1b** under similar condition. This was evident by isolation of both diastereomers of the product by column chromatography and comparing their NMR data with those of the reported ones.[8]



Reagents and conditions: a) Zn, $BrCH_2CO_2R_1$, BF_3•OEt_2, aq THF; b) Bz_2O_2

Scheme

From the above observations the mechanism of this methodology remains inconclusive. However, the rate of Zn insertion into the carbon–halide bond is a crucial factor that depends on the reaction condition and mode of Zn activation. Hence, it can be concluded that the addition of saturated aqueous NH_4Cl solution can not make Zn dust sufficiently active to react with ethyl bromoacetate which has comparatively much less reactivity than those of allylic or propargylic bromides. The enhancement of the activity of Zn dust in this case has been caused due to the chemical erosion of the Zn surface after the addition of Lewis acid (BF_3•OEt_2). However, the failure of the aromatic aldehydes to undergo Reformatsky reaction in presence of such eroded Zn only, led to the speculation that the reaction subsequently does not propagate through ionic mechanism. The presence of the radical chain mechanism[2h] deserves consideration as the reactions have been facilitated considerably by the addition of benzoyl peroxide. Nevertheless, the sluggishness of the reaction of aromatic aldehydes under this condition with respect to the aliphatic ones still remains a problem. Moreover, when several aliphatic and aromatic ketones were tried we found them to be totally unreactive under this condition. Hence, our method presents a good application for conducting chemoselective Reformatsky reaction of aldehydes in the presence of ketones.

In summary, a practical method for Reformatsky reaction has been developed under aqueous condition. The novelty of this method is due to its operational simplicity and practical viability. Moreover, this appears to be a unique procedure in the presence of water which is smoothly applicable for aliphatic aldehydes whose availability in different functional and stereochemical combination is very well documented.

All experiments were conducted using unactivated 20 mesh Zn powder. Aqueous THF was used as mentioned in the text. Reagent grade aldehydes and bromo esters were used directly. NMR spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS. IR were recorded on a Perkin-Elmer 837 spectrometer.

Reformatsky Reaction of Aldehydes in the Presence of BF_3•OEt_2; General Procedure

To a well stirred suspension of aldehyde (0.03 mol), Zn dust (9.75 g, 0.15 g-atom for Entries a−f; 11.7 g, 0.18 g-atom for Entries g−k), bromo ester (0.09 mol for Entries a−f; 0.12 mol for Entries g−k) and benzoyl peroxide (10 mol% for Entries g−k) in moist THF (80 mL) was added BF_3•OEt_2 (7.4 mL, 0.06 mol) in portions over a period of 15 min. The mixture was stirred at r.t. for the period as mentioned in the Table. It was then filtered and the residue was washed with EtOAc. The organic layer was washed with dil aq HCl (5%) to dissolve a turbid suspension, H_2O, brine and dried. Solvent removal and column chromatography [silica gel, 0−20% EtOAc in petroleum ether of the residue afforded pure β-hydroxy ester.

Ethyl 3-Hydroxy-4-methylpentanoate (2a)

bp 82−84 °C/10 Torr (Lit[9] bp 79−80 °C/5 Torr).

IR (film): ν = 3479, 1732, 1371 cm^{-1}.

^1H NMR: δ = 4.15 (2H, q, *J* = 6 Hz), 3.6−3.8 (1 H, m), 3.0 (1 H, br s, OH), 2.4 (2 H, d, *J* = 6 Hz), 1.3−1.5 (1 H, m), 1.21 (3 H, t, *J* = 6 Hz), 0.9 (6 H, d, *J* = 6 Hz).

Methyl (4,5-*O*-Cyclohexylidene)-3,4,5-trihydroxypentanoate (2b)

(i) Minor (3*R*, 4*R*)-isomer:

IR (film): ν = 3519, 1731 cm^{-1}.

^1H NMR: δ = 4.0−4.1 (2 H, m), 3.85−3.95 (1 H, m), 3.75−3.85 (1 H, m), 3.68 (3 H, s), 3.4 (1 H, br s, OH), 2.45 (2 H, s), 1.35−1.65 (10 H, m).

(ii) Major (3*S*, 4*R*)-isomer:

IR (film): ν = 3525, 1734 cm^{-1}.

^1H NMR: δ = 3.95−4.1 (2 H, m), 3.8−3.95 (2 H, m), 3.68 (3 H, s), 3.0 (1 H, br s, OH), 2.70 (1 H, dd, *J* = 15.9, 8.0 Hz), 2.44 (1 H, dd, *J* = 15.9, 8.0 Hz), 1.35−1.65 (10 H, m).

Ethyl 3-Hydroxy-5,9-dimethyldec-8-enoate (2c)

IR (film): ν = 3520, 1735, 1376 cm^{-1}.

^1H NMR: δ = 5.1−5.3 (1 H, m), 4.15 (2 H, q, *J* = 6 Hz), 3.6−3.8 (1 H, m), 3.0 (1 H, br s, OH), 1.9−2.5 (4 H, m), 1.65 (3 H, s), 1.58 (3 H, s), 1.2−1.4 (5 H, m), 0.86−1.0 (6 H, m).

Anal. Calcd for $C_{14}H_{26}O_3$: C 69.38, H 10.81. Found: C 69.17, H 10.61.

Ethyl 3-Hydroxynonanoate (2d)

IR (film): ν = 3520, 1735 cm^{-1}.

^1H NMR: δ = 4.15 (2 H, q, *J* = 6 Hz), 3.6−3.8 (1 H, m), 2.8 (1 H, br s, OH), 2.4 (2 H, d, *J* = 6Hz), 1.3−1.4 (10 H, m), 1.21 (3 H, t, *J* = 6 Hz), 0.91 (3 H, t, *J* = 6Hz).

Anal Calcd for $C_{11}H_{22}O_3$: C 65.31, H 10.96. Found: C 65.54, H 10.72.

Ethyl 3-Hydroxydodecanoate (2e)

IR (film): ν = 3520, 1735 cm^{-1}.

^1H NMR: δ = 4.15 (2 H, q, *J* = 6 Hz), 3.6−3.8 (1 H, m), 2.9 (1 H, br s, OH), 2.4 (2 H, d, *J* = 6 Hz), 1.3 1.4 (10 H, m), 1.21 (3 H, t, *J* = 6 Hz), 0.91 (3 H, t, *J* = 6 Hz).

Anal. Calcd for $C_{14}H_{28}O_3$: C 68.81, H 11.55. Found: C 68.59, H 11.77.

Ethyl 3-Hydroxytetradecanoate (2f)

IR (film): ν = 3520, 1735 cm^{-1}.

^1H NMR: δ = 4.15 (2 H, q, *J* = 6 Hz), 3.6-3.8 (1 H, m), 2.9 (1 H, br s, OH), 2.4 (2 H, d, *J* = 6Hz), 1.3 1.4 (10 H, m), 1.21 (3 H, t, *J* = 6 Hz), 0.91 (3 H, t, *J* = 6Hz).

Anal. Calcd for $C_{16}H_{32}O_3$: C 70.54, H 11.84. Found: C 70.28, H 11.68.

Ethyl 3-Hydroxy-5-phenylpropanoate (2g)

IR (film): ν = 3480, 3087, 1731, 1603 cm^{-1}.

^1H NMR: δ = 7.1−7.5 (5 H, m), 5.0 (1 H, t, *J* = 5 Hz), 4.15 (2 H, q, *J* = 6 Hz), 2.95 (1 H, br s, OH), 2.55 (2 H, d, *J* = 7 Hz), 1.2 (3 H, t, *J* = 6.5 Hz).

Ethyl 5-[4-Chlorophenyl]-3-hydroxypropanoate (2h)

IR (film): ν = 3470, 3087, 1731, 1603 cm^{-1}.

^1H NMR: δ = 7.3 (2 H, d, *J* = 8.4 Hz), 6.87 (2 H, d, *J* = 8.4 Hz), 5.07 (1 H, t, *J* = 5 Hz), 4.15 (2 H, q, *J* = 6 Hz), 2.95 (1 H, br s, OH), 2.68 (2 H, d, *J* = 7 Hz), 1.21 (3 H, t, *J* = 6.5 Hz).

Ethyl 3-Hydroxy-5-[4-methoxyphenyl]propanoate (2i)

IR (film): ν = 3470, 3087, 1731, 1603 cm^{-1}.

^1H NMR: δ = 7.3 (2 H, d, *J* = 8.4 Hz), 6.87 (2 H, d, *J* = 8.4 Hz), 5.07 (1 H, t, *J* = 5 Hz), 4.15 (2 H, q, *J* = 6 Hz), 3.8 (3 H, s), 2.95 (1 H, br s, OH), 2.66 (2 H, d, *J* = 7 Hz), 1.22 (3 H, t, *J* = 6.5 Hz).

Ethyl 3-Hydroxy-5-[2-methoxyphenyl]propanoate (2j)

IR(film): ν = 3470, 3087, 1731, 1603 cm^{-1}.

^1H NMR: δ = 7.4−6.8 (4 H, m), 5.37 (1 H, t, *J* = 5 Hz), 4.15 (2 H, q, *J* = 6 Hz), 3.8 (3 H, s), 2.95 (1 H, br s, OH), 2.66 (2 H, d, *J* = 7 Hz), 1.24 (3 H, t, *J* = 6.5 Hz).

Anal. Calcd for $C_{12}H_{16}O_4$: C 64.27, H 7.19. Found: C 64.55, H 7.42.

Ethyl 3-Hydroxy-3-[1-naphthalyl]propanoate (2k)

IR(film): ν = 3466, 3067, 1735, 1623 cm^{-1}.

^1H NMR: δ = 8.2−7.2 (7 H, m), 5.79 (1 H, t, *J* = 5 Hz), 4.15 (2 H, q, *J* = 6 Hz), 3.29 (1 H, br s, OH), 2.68 (2 H, d, *J* = 7 Hz), 1.24 (3 H, t, *J* = 6.5 Hz).

Anal. Calcd for $C_{15}H_{16}O_3$: C 73.75, H 6.60. Found: C 73.38, H 6.38.

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