JOC*Note*

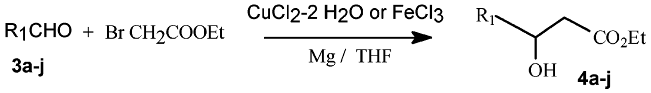
A Simple and Efficient Procedure of Low Valent Iron- or Copper-Mediated Reformatsky Reaction of Aldehydes

Angshuman Chattopadhyay* and Akhil Kr. Dubey

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai-400 085, India

achat@apsara.barc.ernet.in

Received May 29, 2007

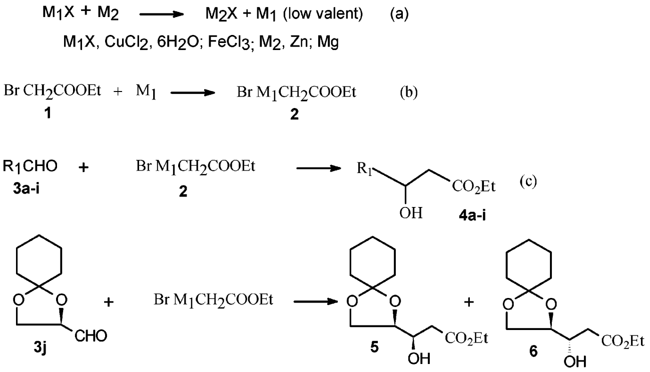


An operationally simple and very efficient procedure of Reformatsky reaction of aldehydes has been carried out in THF in the presence of low valent iron or copper which were prepared *in situ* employing a bimetal redox strategy through reduction of FeCl$_3$ or CuCl$_2$−2H$_2$O with magnesium.

Metal-mediated carbon−carbon bond formation is an important strategy in organic synthesis. In this regard, considerable attention has been focused over the ages toward exploring the potentials of various metals in promoting varieties of Barbier type addition of organic halides to electrophiles.[1] It is well-known that to mediate any reaction a metal needs to be in an active form under the reaction conditions.[2] Nevertheless, for all metal-promoted additions the electronic configuration and the active state of a metal contribute significantly regarding the efficacy and operational procedure of the reactions, in addition to its role in directing the stereoselectivity in the case of asymmetric additions. In this perspective, there is a scope for exploring the potential of metals of various active forms to participate in Barbier type additions to carbonyls and simultaneously investigating the mechanism of such reactions.

Reformatsky reaction is a classic example of Barbier type carbon−carbon bond forming reactions in organic synthesis producing a synthetically exploitable structural unit, β-hydroxy propionic acid esters *via* the reaction of a α-bromoester with an aldehyde.[3] The scope of this reaction has been reviewed over the ages.[4] Because of the importance of β-hydroxy esters, the Reformatsky products, as useful components for the synthesis of natural products such as macrolides and polyether antibiotics,[5] there has been continuous effort until recently for the development of practically viable methodologies to carry out these reactions.[4,6] Hence, a variety of strategies have emerged until recently to perform this reaction using metal mediators like Zn,[6a] Ge,[6b] In,[6c] Sn,[6d] Zn−Cu couple,[6e] ultrasound approach,[6f,i] catalyzed with Co(I),[6j] Fe,[6k] Ni,[6l] etc.

SCHEME 1



Earlier, we developed a useful procedure for zinc-mediated Reformatsky reaction of aldehydes where active metal was produced by surface erosion on treatment with a Lewis acid.[7] Recently, we have developed a practical method of crotylation of aldehydes in distilled THF through mediation of metals like Fe, Cu, and Co in their low valent form.[8] The metals were prepared in an active form *in situ* following a bimetal redox strategy (step a, Scheme 1) by stirring a mixture of the corresponding metal salt and a reducing metal (zinc dust) in THF in the presence of the reactants. It is well-known that, for all such metal-mediated additions of organic halides, the prime requisite is the ability of a metal in its active form to insert into the carbon−halogen bond to produce the organometallic (as in step b, Scheme 1), which then undergoes nucleophilic addition to carbonyls (as in step c, Scheme 1). Our next venture was to explore the viability and efficacy of this strategy to perform Reformatsky reaction of aldehydes taking into account the fact that zinc Reformatsky reagents derived from α-halo esters exist as C-metalated structures.[9] In this pursuit, our aim was to attempt this reaction with a variety of aldehydes using similar combinations of metals/metal salts.

Based on the encouraging results we encountered for crotylation[8] of aldehydes with FeCl$_3$ (97%, Aldrich) and CuCl$_2$−

---

(1) (a) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164. (b) Rieke, R. D. *Science* **1989**, *246*, 1260. (c) Erdik, E. *Tetrahedron* **1987**, *43*, 2203.

(2) *Active Metals*; Fürstner, A. Ed.; VCH Publishers: Weinheim, Germany, 1996.

(3) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210.

(4) (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423. (c) Shriner, R. L. *Org. React.* **1942**, *1*, 1. (d) Ribeiro, C. m. R.; de Farias, F. M. C. *Mini-Rev. Org. Chem.* **2006**, *3*, 1−10. (e) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325 and references cited therein.

(5) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990.

(6) (a) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 542. (b) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691 and references cited therein. (c) Chao, L.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (d) Harda, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 161. (e) Santanielo, E.; Manzocchi, A. *Synthesis* **1977**, 698. (f) Han, B.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (g) Bieber, L. W.; Malvestiti, I.; Storch, E. C. *J. Org. Chem.* **1997**, *62*, 9065 and references cited therein. (h) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1991**, *56*, 4333. (i) Ross, N. A.; Bartsch, R. A. *Org. Chem.* **2003**, *68*, 360. (j) Lombardo, L.; Gualandi, A.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 465. (k) Durandetti, M.; Perichon, J. *Synthesis* **2006**, 1542. (l) Durandetti, M.; Gosmini, C.; Perichon, J. *Tetrahedron* **2007**, *63*, 1146.

(7) Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561.

(8) Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett.* **2006**, *47*, 4701.

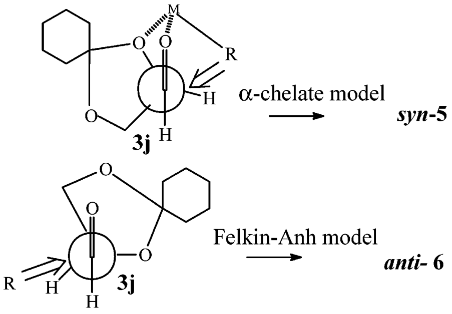
(9) (a) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron Lett.* **1982**, *23*, 3945. (b) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron* **1984**, *40*, 2781. (c) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M. *Organometallics* **1984**, *3*, 1403. (d) Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 553.

10.1021/jo0710984 CCC: $37.00

TABLE 1. Low Valent Cu- and Fe-Mediated Reformatsky Reaction of Aldehydes

entry	aldehyde	metal salt/metal	time hr	product	% yield	product ratio
A	heptanal **3a**	Cu salt/Mg	6	**4a**[a]	72.8	
B	heptanal **3a**	Fe salt/Mg	3.5	**4a**[a]	81.5	
C	isobutanal **3b**	Cu salt/Mg	6	**4b**[a]	73.7	
D	isobutanal **3b**	Fe salt/Mg	4	**4b**[a]	82.6	
E	dodecanal **3c**	Cu salt/Mg	7	**4c**[a]	73.8	
F	dodecanal **3c**	Fe salt/Mg	3	**4c**[a]	84.8	
G	benzaldehyde **3d**	Cu salt/Mg	8	**4d**[a]	72.5	
H	benzaldehyde **3d**	Fe salt/Mg	5.5	**4d**[a]	79.6	
I	4-methoxybenzaldehyde **3e**	Cu salt/Mg	7	**4e**[a]	71.8	
J	4-methoxybenzaldehyde **3e**	Fe salt/Mg	3.5	**4e**[a]	81.8	
K	3,4-dimethoxybenzaldehyde **3f**	Cu salt/Mg	7.5	**4f**	75.2	
L	3,4-dimethoxybenzaldehyde **3f**	Fe salt/Mg	4	**4f**	84.2	
M	4-phenylbenzaldehyde **3g**	Cu salt/Mg	6	**4g**	78.9	
N	4-phenylbenzaldehyde **3g**	Fe salt/Mg	3	**4g**	86.2	
O	4-isopropylbenzaldehyde **3h**	Cu salt/Mg	7	**4h**	73.4	
P	4-isopropylbenzaldehyde **3h**	Fe salt/Mg	4	**4h**	80.2	
Q	3-methoxybenzaldehyde **3i**	Cu salt/Mg	7	**4i**	75.3	
R	3-methoxybenzaldehyde **3i**	Fe salt/Mg	3.5	**4i**	78.9	
S	(*R*)-2,3-cyclohexylideneglyceral **3j**	Cu salt/Mg	6	**5**[a] and **6**[a]	77.7	**5**/**6** :: 63.2:36.8[b]
T	(*R*)-2,3-cyclohexylideneglyceral **3j**	Fe salt/Mg	4	**5**[a] and **6**[a]	81.5	**5**/**6** :: 53.4:46.6[b]

[a] The compounds were characterized from their spectral data (ref 7). [b] The ratios were determined after separation of the diastereoisomers by column chromatography.



M = Fe, Cu ; R = CH_2CO_2Et

FIGURE 1.

$2H_2O$ (Aldrich) [$E°_{Fe=Fe^{2+}+2e}$ +0.441 and $E°_{Fe^{2+}=Fe^{3+}+e}$ −0.771 V; $E°_{Cu=Cu^{2+}+2e}$ −0.337 V], we have chosen these two salts in combination with either of two reducing metals *viz* Zn dust (SRL India, $E°_{Zn=Zn^{2+}+2e}$ +0.761) and magnesium turning (SRL India, $E°_{Mg=Mg^{2+}+2e}$ +2.37) to perform a Reformatsky reaction. Three classes of aldehyde substrates were chosen, viz aliphatic (**3a**−**c**), aromatic (**3d**−**i**), and chiral (**3j**),[10] in order to explore the generality of this strategy. In all these heterogeneous reactions, aldehyde was treated with an excess amount of ethyl 2-bromoacetate (Aldrich, 2 equiv), metal salt (3 equiv), and metal (3 equiv) to ensure their progress at a faster rate.

Unlike our earlier experience with crotylation of aldehydes, all Reformatsky reactions using zinc dust as a reducing metal [Zn/$CuCl_2$−$2H_2O$ or Zn/$FeCl_3$] were found to be highly disappointing and their progresses were too little (vide TLC) to be reported even after stirring the mixtures for 30 h. However, to our delight the reactions involving magnesium as a reducing metal showed results that were very promising with a total consumption of aldehydes **3a**−**j** after stirring the reaction mixtures for some time as shown in Table 1.

Interestingly, the reactivity of magnesium as an efficient reducing agent for all these carbon−carbon bond forming reactions in Table 1 under somewhat moist reaction conditions[11] is worth noting. In addition, for all these cases magnesium turnings were found to be more reactive than zinc dust despite having much less available surface area which may be explained as being due to higher values of $\Delta E°_{Mg-Fe(III)}$ and $\Delta E°_{Mg-Cu(II)}$ compared to $\Delta E°_{Zn-Fe(III)}$ and $\Delta E°_{Zn-Cu(II)}$, respectively. Of the two successful bimetal redox systems involving magnesium, the combination of Mg/$FeCl_3$ was found to be more efficient compared to Mg/$CuCl_2$−$2H_2O$ for all substrates (**3a**−**j**) used here as was evident from the fact that the former gave the desired products with better yields and in less reaction time (entries B, D, F, H, J, L, N, P, R, T, Table 1). As with the case of crotylation earlier,[8] the relative sluggishness of the Cu-promoted Reformatsky reaction could also be explained from the probable loss of its activity caused by a reduction of available surface area of active metals because of its tendency for sintering on prolonged stirring. Interestingly, the additions to chiral aldehyde **3j** mediated with both Fe and Cu (entries S and T, Table 1) took place smoothly and efficiently but with poorer selectivity compared to our earlier procedure,[7] thereby making both *syn*-**5** and *anti*-**6** diastereomers in substantial amounts. The predominant formation of *syn*-**5** for both cases (entries S, T, Table 1) gave sufficient evidence of the formation of organocopper and organoiron reagents **2**, as indicated in Scheme 1, and during their additions to **3j**, the possibility of nucleophilic attack through the α-chelate transition state is enhanced as per literature precedence[12] with respect to that *via* the Felkin−Anh model (Figure 1).

Thus, a very practical method of Reformatsky reaction of aldehydes has been developed through judicious exploitation of spontaneously occurring bimetal redox reactions under moist conditions. The efficacy of this method is due to its operational

---

(10) (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585. (b) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104.

(11) Distilled THF generally has some reasonable amount of moisture. The partial (Cu) and good (Fe) solubility of the metal salts in distilled THF which always contains some amount of moisture facilitates bimetal redox reactions and subsequent Reformatsky reactions. Similar to that observed earlier,[8] in anhydrous THF no reaction took place presumably due to very poor solubility of these metal salts.

(12) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636.

simplicity which only requires stirring the reaction mixture at ambient temperature without the use of any additional energy source like heating or sonication, its generality as evident from its success with varied kinds of aldehydes, and very importantly its economical viability due to the use of inexpensive and commercially available chemicals (magnesium turning and hydrated metal salts) to effect this C−C bond formation. Recently, several Reformatsky type additions of α-haloesters to carbonyl substrates were reported using Co(I),[6j] Fe,[6k] and Ni[6l] as catalysts which were also prepared employing the bimetal redox strategy. However, in view of the fact that these reactions need to be performed under specialized conditions such as in a highly anhydrous medium,[6j] at higher temperature,[6k] or through the use of a metal−ligand complex to effect a bimetal redox reaction,[6k,l] our present protocol is comparably much simpler and more straightforward. Presently, investigation on the viability as well as efficacy of a few more C−C bond forming reactions employing this strategy is in progress.

Experimental Section

General Procedure of Reformatsky Reaction: To a well stirred mixture of aldehyde **3** (0.01mol), ethyl 2-bromoacetate **2** (3.34 g, 0.02 mol), and metal salt [$CuCl_2-2H_2O$ (5.1 g, 0.03 mol) or $FeCl_3$ (4.86 g, 0.03 mol)] in THF (75 mL) was added Mg turnings (768 mg, 0.032 mol) in one lot. The mixture was stirred at ambient temperature for the period shown in Table 1. The reaction mixture was then treated successively with water (50 mL) and EtOAc (100 mL), stirred for 10 min more, and then filtered. The filtrate was treated with 2% aqueous HCl to dissolve a small amount of suspended particles. The organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine and then dried. Solvent removal and column chromatography of the residue (silica gel, 0−20% EtOAc in petroleum ether) afforded the desired Reformatsky products in pure form.

Ethyl 3-(3,4-Dimethoxyphenyl)-3-hydroxypropionate (4f). ^1H NMR($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 2.73 (m, 2H), 2.8 (bs, 1H), 3.8 (s, 6H), 4.14 (m, 2H), 5.04 (m, 1H), 6.7−6.9 (m, 3H). ^{13}C NMR($CDCl_3$): 13.9, 43.6, 55.5, 55.6, 60.5, 70.0, 108.9, 110.9, 117.8, 135.7, 148.2, 148.8, 171.9. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.68; H, 6.90.

Ethyl 3-(4-Phenylphenyl)-3-hydroxypropionate (4g). ^1H NMR-($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 1.9 (bs, 1H), 2.8 (m, 2H), 4.2 (q, J = 7 Hz, 2H), 5.2 (m, 1H), 7.0−7.7 (m, 8H), 8.1(m, 1H). ^{13}C NMR($CDCl_3$): 14.2, 43.4, 61.0, 70.2, 126.2, 127.1, 127.3, 128.5, 128.8, 129.0. 129.5, 130.2, 130.8, 133.7, 140.7, 141.6, 172.5. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.28; H, 6.99.

Ethyl 3-(4-Isopropylphenyl)-3-hydroxypropionate (4h). ^1H NMR($CDCl_3$): δ 1.22−1.31 (m, 9H), 2.7 (m, 2H), 2.91 (q, J= 6.8 Hz, 1H), 3.2 (bs, 1H), 4.21 (q, J= 7.2 Hz, 2H), 5.45 (m, 1H), 7.1−7.5 (m, 4H). ^{13}C NMR($CDCl_3$): 14.1, 24.0, 33.8, 43.5, 61.8, 70.2, 125.8, 126.5, 140.2, 148.4, 172.4. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.43; H, 8.33.

Ethyl 3-(3-Methoxyphenyl)-3-hydroxypropionate (4i). ^1H NMR ($CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 2.82 (m, 2H), 3.90 (s, 3H, overlapped with a bs, 1H), 4.17 (q, J = 7.2 Hz, 2H), 5.09 (m, 1H), 6.7−6.9 (m, 3H), 7.25 (m, 1H). ^{13}C NMR($CDCl_3$): 14.1, 43.6, 55.1, 60.8, 70.2, 111.1, 113.2, 118.0, 129.4, 144.6, 159.7, 172.1. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.43.

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **4f−i**. The material is available free of charge via the Internet at http://pubs.acs.org.

JO0710984