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Reformatsky reaction of α-chloroesters with carbonyl compounds with commercially available zinc

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The condensation of α-chloroesters with aliphatic as well as aromatic ketones with commercially available zinc without any external metal additives is described.

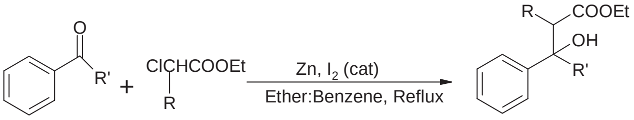
Keywords: Reformatsky reaction, α-chloroesters, carbonyl compounds, zinc

The reaction between α-bromoesters, zinc metal and carbonyl compound was formulated by Refomatsky in 1887[1] and its utility in carbon carbon bond formation is recognised as a powerful tool in organic synthesis.[2] Reformatsky reactions have subsequently been performed on a wide variety of substrates such as imines,[3] nitriles.[4] The reaction has also been performed in an electrochemical manner using a zinc-copper couple.[5] In connection with our ongoing program on C–C bond formation employing the Reformatsky reaction,[6-9] we faced problems procuring ethyl bromoacetate. It was then decided to look into the reaction of readily available with ethyl chloroacetate with zinc under Reformatsky conditions. A literature survey revealed almost non-existence of report on chloroesters being employed in Reformatsky reaction. The use of α-iodoesters and α-chloroesters in the Reformatsky reaction is seldom reported whereas α-chloroester condensations have been carried on a few aldehydes and aliphatic ketones[10] and substituted benzaldehydes.[11] However, it has been reported that presence of Cu along with Zn is a prerequisite for α-chloroesters to participate in the Refomatsky reaction.[12] This reaction has also been performed with Rieke zinc but the yields of the reaction are moderate to very low[13] to be of any utility on a preparative scale. The utility of α-chloroester to participate in the Reformatsky reaction seems almost non-existent inspite of its ready availability, stability cost-effectiveness as well as its less hazardous nature as compared to the corresponding bromoesters.

We now report the condensation of α-chloroesters with aliphatic as well as aromatic ketones with commercially available zinc without any external metal additives. The reaction involves the use of combination of benzene and ether (1:1) as the solvent system. The reaction was monitored by using TLC and generally took 6–8 h. A wide variety of ketones ranging from aliphatic to aromatic ketones when subjected to ethyl chloroacetate and zinc furnished the corresponding adduct in good to excellent yields.

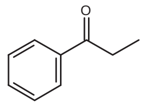
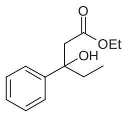
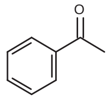
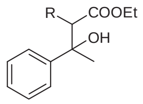
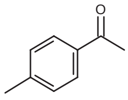
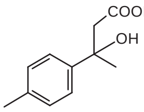
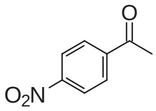
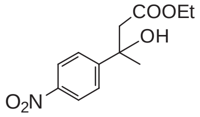
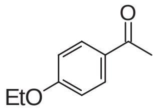
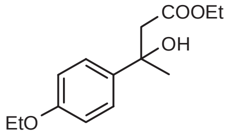
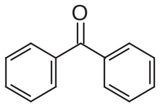
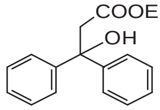
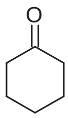
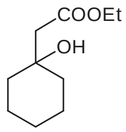
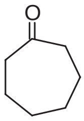
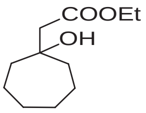
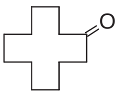
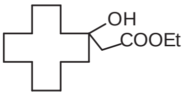
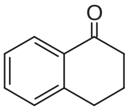
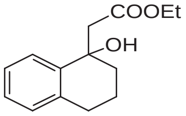
Experimental

To a suspension of zinc[14] (1.63 g, 25 mmol supplied by Loba, India) in benzene ether (1:1, 5 ml) was added acetophenone (1 g, 8.33 mmol) followed by ethyl chloroacetate (1.224 g, 10 mmol) in benzene ether (1:1, 5 ml). A crystal of iodine was added and the reaction mixture was refluxed for 6 h (80^{0}C, oil bath temp). After completion (TLC), the reaction mixture was cooled and quenched with 10% HCl (15 ml). The product was extracted with ethyl acetate (2×25 ml) and washed with water (3×10 ml). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and solvent removed under vacuum. The residue thus obtained was purified by column chromatography (SiO_2) using 5% ethyl acetate-pet ether as the eluent. It is evident from the table that α-chloroesters participate well in the reaction to furnish the corresponding alcohols in synthetically useful yields. A point worth of note is that even α-substituted chloroesters participates efficiently as compared to α-chloroacetate (entry **2b**).



Scheme 1

Table 1 Yield obtained in reaction using α-chloroesters

SL. No:	Substrate	Product	Yield
1			83%[15]
2			R= H 71%[1a] R= Me 70%[1a]
3			72%[18]
4			73%[16]
5			82%
6			69%[21]
7			66%[19]
8			74%[19]
9			86%
10			75%[17]

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Conclusion

We have demonstrated that α-chloroesters serve as good reagents for C–C bond formation with commercially available zinc. The obvious advantages of chloroesters over bromoesters in term of handling, stability, cheap-availability should make the present protocol an attractive simple and convenient alternative to practicing organic chemists.

Entry **5**: Ethyl 3-(4′-ethoxyphenyl) 3-hydroxy butyrate: ^{1}H NMR: 7.33 (d, 2H, J = 8Hz), 6.82 (d, 2H, J= 8Hz), 4.26 (b, 1H), 4.03 (m, 4H), 2.93(d, 1H, J=16Hz), 2.73 (d, 1H, J=16Hz), 1.51 (s, 3H), 1.41(t, 3H, J=6Hz) and 1.15(t, 3H, J=7Hz). ^{13}C NMR: 172.3(s), 157.5(s), 138.7(s), 125.3(d), 113.8(d), 72.1(s), 63.0(t), 60.2(t), 46.3(t), 30.4(q), 14.6(q), and 13.8(q). IR (Neat) cm^{-1}: 3390, 2978, 1712, 1604, 1514 and 1478. Mass (*m/z*): 252(m+), 234, 206, 189, 165, 149 and 134. Elemental analysis C 66.8, H 8.3 (calculated C 66.7, H 8.0)

Entry **9**: Ethyl 2-(1′-hydroxy cyclododecyl) acetate: ^{1}H NMR: 4.15(q, 2H, J=7Hz), 3.5(b, 1H), 2.4(s, 2H) and 1.2-1.65(m, 25H). ^{13}C NMR: 172.5(s), 73.2(s), 60.0(t), 43.8(t), 34.0 (t), 26.1(t), 25.2(t), 22.2(t), 21.8(t), 19.3(t) and 13.9 (q). IR ($CHCl_3$) cm^{-1}: 3510, 2932, 2862, 1710, 1470, 1446, 1398, and 1370. Mass (*m/z*): 270(m+), 252, 241, 225, 207, 182, 143 and 130. Elemental analysis C 71.2, H 11.1 (calculated C 71.0, H 11.2).

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14. Zinc activation: 50gm of zinc (supplied by Loba, India) was washed with distilled water (2×50ml). After decanting the water layer it was treated with 5% dil. HCl (2×30ml) with vigorous stirring. The acid was decanted and the zinc was treated with distilled water (3×50ml). It was then treated with acetone to remove the traces of water (2×50ml). The zinc was then dried in an oven for 8 h at 100°C.
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