

Remote Reformatsky Reaction: Reaction of β -, γ -, and δ -Zinc Esters with Aldehydes

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Ethyl β -, γ -, and δ -zinc esters react with aldehydes to provide ethyl γ -, δ -, and ϵ -hydroxy esters.

Generally alkylzinc reagents are unreactive towards aldehydes under normal conditions. For the reaction to proceed, special circumstances are required involving either the organozinc reagent (highly polarised or polarizable organozincs, *e.g.*, α -zinc esters, allylzincs,¹ and 1,1-dichloro-2,2,2-trifluoroethylzinc)² or the reaction conditions (in the presence of Lewis acids or bases, *e.g.*, $\text{BF}_3\text{-OEt}_2$ for 1-magnesia-1-zincalkanes³ and amines and glyoximes for dialkylzincs).⁴

Propylzinc iodide (**1a**) and the β - and γ -zinc esters (**1b**) and (**1c**), generated *in situ* in toluene–DMA (*N,N*-dimethylacetamide, see footnote a, Table 1)⁵ do not react with benzaldehyde at room temperature or even at 60 °C. Lewis acids or bases (*e.g.*, *N,N*-dimethyl-2-hydroxyethylamine, 1-phenylethylamine, or $\text{BF}_3\text{-OEt}_2$) were ineffective. After many attempts, we found that trimethylsilyl chloride (TMSCl) was effective in promoting the reaction, the relative amounts

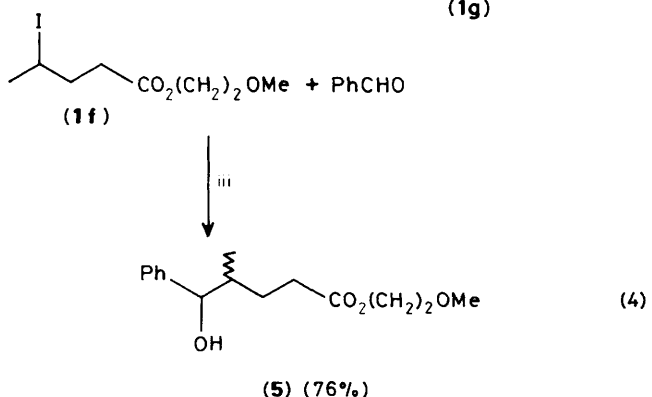
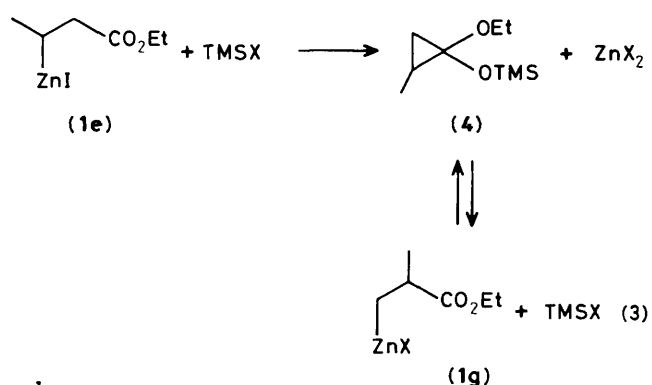
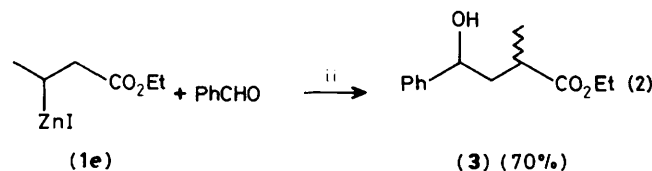
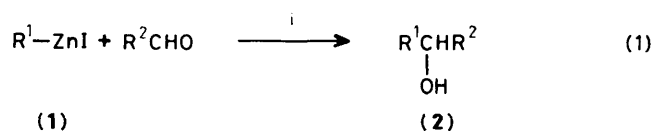
of TMSCl and DMA being decisive [reaction (1)]. An equivalent amount of TMSCl and DMA is sufficient, but we usually used a slight excess of TMSCl. Smaller proportions of TMSCl lead to dramatic decreases in yields. Typical examples are shown in Table 1.

Reaction (2) is interesting. The β -methyl group of the β -zinc ester (**1e**) migrates to the position α to the ester group in the product. A plausible rationale for this behaviour is shown in reaction (3), which involves an isomerization of (**1e**) to (**1g**)^{6a,c} via the cyclopropane (**4**).^{5c} Judging from our previous observations, this isomerization seems to take place only in the presence of TMSCl; (**1e**) undergoes allylation and acylation retaining the methyl group β to the carbonyl group.^{5c,5d} The β -zinc esters (**1b**), (**1e**), and (**1g**), may partly owe their low reactivity to the formation of cyclopropanes [Table 1, entry 3 and reaction (2)]. In contrast with (**1e**), (**1f**)

Table 1. Reactions of organozinc reagents R^1ZnI (**1**) with aldehydes R^2CHO to give alcohols $R^1CH(OH)R^2$ (**2**).^a

Entry	Organozinc (1) R^1	Aldehyde R^2CHO R^2	Conditions		% Isolated yield of (2) ^b
			$\theta/^\circ C^c$	t/h	
1	(1a) Pr^n	C_5H_{11}	60	4	66
2	(1a) Pr^n	Ph	—	5	95
3	(1b) $(CH_2)_2CO_2Et$	Ph	60	4	95
4	(1c) $(CH_2)_3CO_2Et$	Bu ^t	—	3 days	40
5	(1c) $(CH_2)_3CO_2Et$	<i>o</i> -MeOC ₆ H ₄	—	3	97
6	(1c) $(CH_2)_3CO_2Et$	<i>p</i> -FC ₆ H ₄	—	18	88
7	(1c) $(CH_2)_3CO_2Et$	PhCH=CH	—	4.5	68 ^d
8	(1d) $(CH_2)_4CO_2Et$	C_5H_{11}	60	6	22 ^e
9	(1d) $(CH_2)_4CO_2Et$	Ph	—	18	80

^a The organozinc reagent (**1**) [prepared from the iodide R^1I (1.5 mmol) and Zn–Cu (1.55 mmol) in toluene (3 ml)–DMA (2 mmol) at 60 °C for 3–4 h] was treated with TMSCl (3 mmol, room temp., 10 min) and then with the aldehyde (1.0 mmol) under the conditions indicated. ^b Yields are for materials purified by column chromatography over silica gel and based on aldehyde. ^c Room temperature unless indicated otherwise. ^d Together with PhCH(CH₂CHO)CH₂CH₂CH₂CO₂Et (10%). ^e Together with $C_5H_{11}CH(OH)CHBuCHO$ (55%).



Reagents and conditions: i, TMSCl, toluene–DMA, then H_3O^+ ; ii, 60 °C, 17 h, then H_3O^+ ; iii, room temp., 6 h, then H_3O^+ .

reacts with aldehydes to provide products without methyl group migration [reaction (4)]. A mixture of two diastereoisomers (**5**) was isolated in 76% yield (*syn:anti* = 1:2.3).[†]

Finally the effect of co-solvents on the reaction should be noted. For the zincation of iodides, the use of a co-solvent, such as *N*-methylpyrrolidone (NMP), *N*-methyloxazolidin-2-one, *N,N*-dimethylbenzamide, *N,N*-dimethylacetamide (DMA), or hexamethylphosphoric triamide (HMPA), in a slight excess with respect to iodide, is essential. These co-solvents greatly affect the rate of reaction of (**1**) with aldehydes; *N*-methyloxazolidin-2-one and NMP accelerate the reaction, as compared with DMA and *N,N*-dimethylbenzamide. On the other hand, HMPA drastically retards the reaction. For example, the reaction of (**1c**) and *p*-fluorobenzaldehyde in toluene–HMPA results in recovery of the aldehyde even after 24 h.

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[†] The corresponding ethyl ester showed similar results (*syn:anti* = 1:2).