The Reformatsky Reaction in a Continuous Flow System. An Improved Procedure for Preparation of β-Hydroxy Esters

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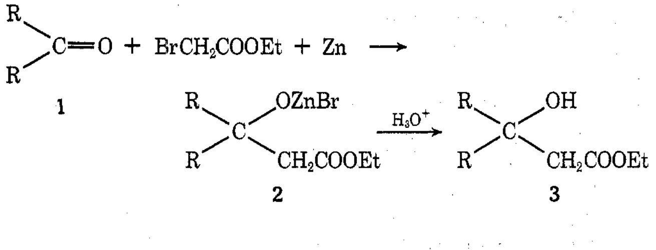
The Reformatsky synthesis of β-hydroxy esters[2] is unfortunately subject to a number of competing side reactions, including self-condensation of the α-bromo ester and carbonyl components, as well as elimination or retrograde aldol condensation of the intermediate β-alkoxyzinc ester,[3] which cause yields in this process to be highly variable. Much of the difficulty associated with the Reformatsky reaction may be traced to the fact that, although heat is generally required to initiate it, once started it becomes vigorously exothermic, often requiring careful moderation. This problem and attendant side reactions become particularly severe on a large scale, and have prompted us to search for a suitable modification of the conventional procedure.

Of the several published improvements for conducting the Reformatsky reaction,[4] that by Rathke and Lindert,[5] in which the reaction is carried out at room temperature in trimethyl borate–tetrahydrofuran (TMB–THF) solvent, appears to offer special promise. Our own approach to this problem, dictated in part by the need for large quantities of β-hydroxy esters, has been based upon the supposition that a continuous-flow system, having a minimum contact of starting materials and product in the reaction zone, would both enhance the yield and avoid the repetition of a batch procedure.

The procedure found to be most effective involved the dropwise addition of a 1:2 molar mixture of the carbonyl component (1) and ethyl bromoacetate in benzene to a benzene-presaturated column containing granular zinc. The apparatus for this purpose is shown in Figure 1. Sufficient heat was applied to the column to maintain a gentle benzene reflux at the head of the column. The resulting zinc alkoxide 2 is delivered by the column as a pale yellow benzene solution, and successive washings of this solution with 15% sulfuric acid, saturated sodium bicarbonate solution, and brine gave the hydroxy ester 3 in high yield.

The results are summarized in Table I. It can be seen that yields from the present procedure represent substantial improvements over those obtained by conventional methods and compare favorably with those of Rathke and Lindert.[5]



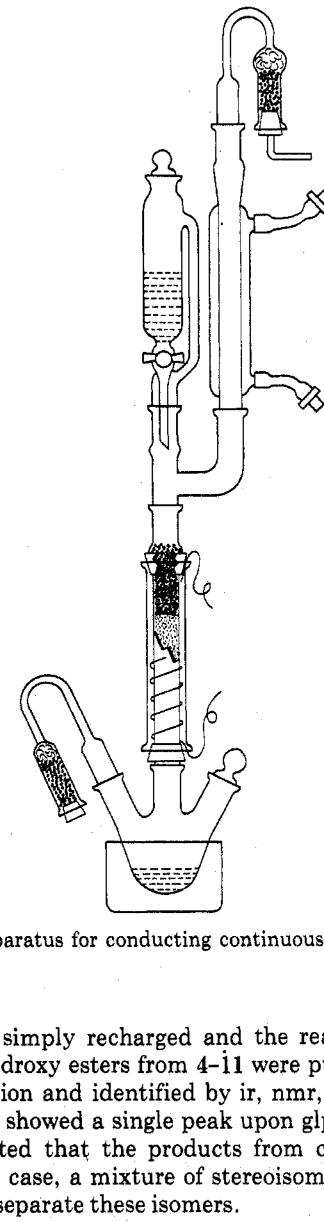


Figure 1. Apparatus for conducting continuous-flow Reformatsky reaction.

It is also noteworthy that successive addition of different carbonyl components in admixture with ethyl bromoacetate to the same column resulted in no detectable cross-contamination of hydroxy esters. Reactions ranging in scale from 0.2 (1-butanal) to 1.6 *M* (cyclopentanone) were carried out without difficulty, the former requiring 0.6 hr and the latter 32 hr (optimum through-put was 60 ml of solution per hour). As the zinc becomes depleted the column can be simply recharged and the reaction resumed.

Product hydroxy esters from 4–11 were purified by short-path distillation and identified by ir, nmr, and mass spectral data. All showed a single peak upon glpc, but nmr evidence indicated that the products from compounds 8–11 were, in each case, a mixture of stereoisomers. No attempt was made to separate these isomers.

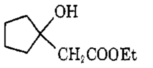
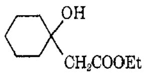
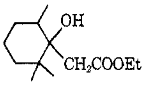
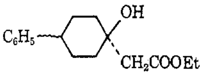
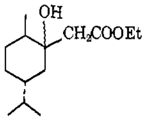
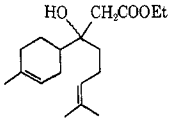
The continuous-flow Reformatsky reaction in a heated column of granular zinc offers several advantages over alternative modes, especially in regard to the extreme tractability of the reaction and the virtual absence of by-products. Hindered ketones such as 2,2,6-trimethylcyclohexanone, which give low yields of hydroxy ester in a conventional procedure, show only moderate improvement in the present variation.

Experimental Section

Materials. 1-Butanal, cyclopentanone, cyclohexanone, benzaldehyde, 2,2,6-trimethylcyclohexanone, and ethyl bromoacetate were obtained from commercial sources; they were distilled prior to use and checked for purity by glpc. 4-Phenylcyclohexanone was prepared by the method of Ungnade.[6] (−)-Carvomenthone was prepared from (+)-carvone following the procedure of Rothman and Day.[7] 1-Methyl-4-(5-methylhex-4-enoyl)cyclohexene was obtained by the route of Vig, *et al.*[8] Granular zinc (20 mesh) was activated prior to use by washing with 2% hydrochloric acid, water, 95% ethanol, acetone, and anhydrous ether; it was then dried *in vacuo* at 100° for 0.2 hr. Glc analysis was carried out on an Aerograph Autoprep 700 using a 5 ft × 0.25 in. column of 10% SE-30 on Chromosorb W.

Reactions Using Zinc Column. The following procedure for the conversion of cyclopentanone to ethyl (1-hydroxycyclopentyl)-acetate (5) is representative. The apparatus shown in Figure 1 was charged with 110 g (1.7 g-atoms) of zinc and sufficient glass helices to form a bed 4 cm deep above the zinc (total bed length was *ca.* 20 cm). The column was saturated with 15 ml of dry ben-

Table I
Reformatsky Reaction of Carbonyl Compounds with Zinc and Ethyl Bromoacetate

Carbonyl compd	Product	Bp, °C (mm)[a]	Yield, %		
			Zinc column[b]	Conventional method	TMB-THF method[c]
1-Butanal (**4**)	$CH_3(CH_2)_2CH(OH)CH_2COOEt$	45 (0.02)	89	69[d]	97
Cyclopentanone (**5**)		57 (0.03)	95	50[c]	93
Cyclohexanone (**6**)		66 (0.03)	93	56[e]	85
Benzaldehyde (**7**)	$C_6H_5CH(OH)CH_2COOEt$	95 (0.02)	94	61[e]	95
2,2,6-Trimethylcyclohexanone (**8**)		73 (0.02)	49	20[f]	
4-Phenylcyclohexanone (**9**)		70 (0.02)	96		
(−)-Carvomenthone (**10**)		126 (0.02)	83		
1-Methyl-4-(5-methylhex-4-enoyl)cyclohexene (**11**)		118 (0.02)	86		

[a] Analyzed sample. [b] Based upon glpc analysis using internal standards. [c] Data from ref 5. [d] Data from ref 4. [e] Data from ref 2. [f] This work.

zene and heated until refluxing benzene was just visible above the head of the column bed. A solution of 12.2 g (0.146 mol) of cyclopentanone and 48.6 (0.291 mol) of ethyl bromoacetate in 200 ml of dry benzene was added dropwise from the funnel at *ca.* 1 ml/min. The heat applied to the column was decreased by 25% soon after addition commenced to maintain a gentle reflux at the column head. After addition was complete, the column was flushed with 50 ml of benzene. The pale yellow solution which had collected was poured into 300 ml of ice-cold 15% sulfuric acid, and the mixture was shaken until the colorless precipitate had dissolved. The organic layer was separated and washed successively with saturated sodium bicarbonate solution and saturated sodium chloride solution. The benzene extract was dried ($MgSO_4$), the solvent was removed *in vacuo*, and the residue was distilled to give 23.6 g (95%) of **5**, bp 53-57° (0.03 mm).

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Registry No. 4, 2305-25-1; **5**, 3197-76-0; **6**, 5326-50-1; **7**, 5764-85-2; **8**, 42908-40-7; 1-butanal, 123-72-8; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; 2,2,6-trimethylcyclohexanone, 2408-37-9; zinc, 7440-66-6; ethyl bromoacetate, 105-36-2.

References and Notes

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Synthesis of Menthyl- and Neomenthyldiphenylphosphine. Epimeric, Chiral, Tertiary Phosphine Ligands for Asymmetric Synthesis

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During the past several years the hydrogenation of unsaturated organic substrates using soluble transition-metal complexes as catalysts has been extensively studied. Numerous publications testify to the intrinsic interest and utility of homogeneous reducing systems.[1] Such systems are ideally suited for the introduction of chiral ligands which convey upon the transition metal complex the potential for diastereomeric interactions with unsaturated organic substrates, thus making asymmetric synthesis possible.[2] The realization of asymmetric synthesis in homogeneous hydrogenations,[3] hydrosilylations,[4] and hydroformylations[5] has been the subject of several recent papers.

In this paper we report details of the synthetic procedures for neomenthyldiphenylphosphine (NMDPP) and menthyldiphenylphosphine (MDPP), chiral tertiary phos-