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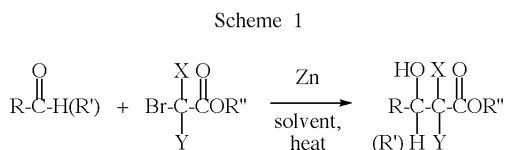
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Reactions of *sym*-(keto)dibenzo-16-crown-5 with ethyl  $\alpha$ -bromoesters, zinc dust and iodine in dioxane and/or tetrahydrofuran under irradiation by high intensity ultrasound (HIU) provide  $\beta$ -hydroxy lariat ether esters in 79-91% yields. HIU-promoted Reformatsky reactions offer several advantages over customary thermal reaction conditions.

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### Introduction.

The Reformatsky reaction of aldehydes and ketones with  $\alpha$ -haloesters and zinc dust is the most generally applicable route to  $\beta$ -hydroxyesters [1] (Scheme 1). Progress in improving the yields of such reactions has been obtained by the use of freshly activated zinc powder [2], a heated column of zinc dust [3], a trimethyl borate-THF solvent system [4], a copper-zinc couple [5], acid-washed zinc [6], and trimethylchlorosilane [7]. In addition, irradiation with low intensity ultrasound (LIU) in an ultrasonic cleaning bath has been reported to enhance both the rates and yields for reactions of simple aldehydes and ketones with ethyl bromoacetate, activated zinc and a catalytic amount of iodine [8].



We have initiated a general investigation of high intensity ultrasound (HIU) applications in organic synthesis. The HIU is produced by a horn that is in direct contact with the reaction solution [9]. We now report results for the HIU Reformatsky reactions of *sym*-(keto)dibenzo-16-crown-5 (**1**) with ethyl  $\alpha$ -bromoesters. Of particular interest was the influence of structural variation within the ethyl  $\alpha$ -bromoester component.

### Results and Discussion.

Results from reactions of eight ethyl  $\alpha$ -bromoesters with lariat ether ketone **1**, unactivated zinc dust and iodine in unpurified dioxane and/or in dry tetrahydrofuran under HIU irradiation (Scheme 2) are recorded in Table 1. Structural variations in the  $\alpha$ -bromoester reactant included replacing one of the  $\alpha$ -hydrogens in ethyl bromoacetate with methyl, ethyl, propyl and phenyl groups and with fluorine and replacing both  $\alpha$ -hydrogens with methyl

groups and with fluorines. Stoichiometries for the reactions were adjusted to provide for complete consumption of **1**. Progress of a reaction was monitored by thin layer chromatography of the reaction mixture.

Reaction of **1** with ethyl bromoacetate, zinc and iodine in dioxane (an "optimum" solvent for sonochemical Reformatsky reactions [8]) with HIU irradiation for five minutes gave a 90% isolated yield of  $\beta$ -hydroxyester **2a** (Entry 1). Changing the solvent to tetrahydrofuran had no observable effect on the reaction rate or efficiency (Entry 2). In contrast, LIU irradiation of the same reactants in dioxane and in tetrahydrofuran in an ultrasonic cleaning bath for five and 30 minutes gave only recovered reactants. Therefore, only HIU was utilized in further evaluation of the sonochemical Reformatsky reactions of **1** with the  $\alpha$ -bromoesters.

Introduction of methyl, ethyl and propyl groups at the  $\alpha$ -position of the bromoester had no observable effect on the rate or yield of the HIU Reformatsky reactions of **1** in

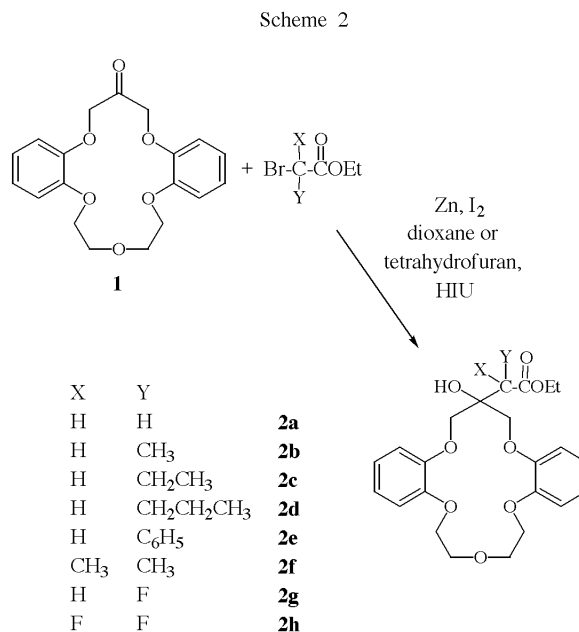


Table 1  
Sonochemical Reformatsky Reactions of Lariat Ether Ketone **1**,  
BrC(X)(Y)CO<sub>2</sub>Et, Zinc and Iodine

Entry	X	Y	Product	Solvent	Reaction time, min.	Isolated yield, %
1[a]	H	H	<b>2a</b>	dioxane	5	90
2[a]	H	H	<b>2a</b>	tetrahydrofuran	5	89
3[b]	H	CH <sub>3</sub>	<b>2b</b>	dioxane	5	91
4[b]	H	C <sub>2</sub> H <sub>5</sub>	<b>2c</b>	dioxane	5	88
5[b]	H	C <sub>3</sub> H <sub>7</sub>	<b>2d</b>	dioxane	5	91
6[c]	H	C <sub>6</sub> H <sub>5</sub>	<b>2e</b>	dioxane	50	79
7[b]	CH <sub>3</sub>	CH <sub>3</sub>	<b>2f</b>	dioxane	5	79
8[b]	H	F	<b>2g</b>	dioxane	5	79
9[b]	F	F	<b>2h</b>	tetrahydrofuran[d]	60	85

[a] Molar ratio of **1**:ethyl bromoacetate:zinc:iodine = 1.0:1.5:1.8:0.2; [b] Molar ratio of **1**:ethyl  $\alpha$ -bromoester:zinc:iodine = 1.0:-2.5:3.0:0.33; [c] Molar ratio of **1**:ethyl  $\alpha$ -bromophenylacetate :zinc:iodine = 1.0:4.0:4.0:0.44; [d] There was no reaction with HIU irradiation for 60 minutes in dioxane.

dioxane (entries 3-5, respectively). Thus 88-91% yields of the  $\beta$ -hydroxyesters **2b-2d** were obtained in five minutes. However, when one of the  $\alpha$ -hydrogens in ethyl bromoacetate was replaced with a phenyl group, consumption of **1** in dioxane took 50 minutes and the yield of  $\beta$ -hydroxyester **2e** diminished to 79%. With replacement of both  $\alpha$ -hydrogens in ethyl bromoacetate by methyl groups, a 79% yield of the  $\beta$ -hydroxyester **2f** was obtained after five minutes of HIU irradiation in dioxane.

To probe the effect of replacing one of the  $\alpha$ -hydrogens of ethyl bromoacetate with a strongly electron-withdrawing substituent, the HIU sonochemical Reformatsky reaction of **1** with ethyl bromodifluoroacetate was conducted in dioxane. A 79% yield of the monofluorinated  $\beta$ -hydroxyester **2g** was realized in five minutes.

Based upon the successful HIU sonochemical reactions of lariat ether ketone **1** with a variety of ethyl  $\alpha$ -bromoesters in dioxane to produce  $\beta$ -hydroxyesters **2a-2g**, it was surprising to recover only unreacted starting materials from irradiation of **1** with ethyl bromodifluoroacetate in dioxane for 60 minutes. However, changing the solvent to tetrahydrofuran and HIU irradiation under the same conditions gave an 85% yield of difluorinated  $\beta$ -hydroxyester **2h** after a 60-minute irradiation. At this stage, the reason for ineffectiveness of the reaction in dioxane is not apparent.

For comparison with thermal Reformatsky reactions, mixtures of **1** with three ethyl  $\alpha$ -bromoesters, unactivated zinc dust and iodine in dioxane were refluxed. The reaction mixtures were monitored by thin layer chromatography for consumption of **1**. With ethyl

bromoacetate, a 79% yield of  $\beta$ -hydroxyester **2a** was obtained after one hour. From ethyl  $\alpha$ -bromopropanoate, refluxing for 20 hours gave a 53% yield of  $\beta$ -hydroxyester **2b**. With the even more hindered ethyl  $\alpha$ -bromoisobutyrate, a 53% yield of  $\beta$ -hydroxyester **2f** was obtained after refluxing overnight. For each of these three  $\alpha$ -bromoesters, the analogous HIU Reformatsky reaction provided a higher yield of the  $\beta$ -hydroxyester product in five minutes (Table 1).

During the course of these investigations, the HIU Reformatsky reactions were found to be concentration dependent. Results for five reactions of lariat ether ketone **1** with 1.5 equivalents of ethyl bromoacetate, 1.8 equivalents of zinc dust and 0.2 equivalents of iodine in tetrahydrofuran are presented in Table 2. As shown in entries 1 and 2, the HIU Reformatsky reactions gave 89 and 91% yields of  $\beta$ -hydroxyester **2a** in five minutes when the concentration of **1** was 0.400 and 0.333 molar. On the other hand, when the concentration of **1** was reduced to 0.266 and 0.116 molar (entries 3 and 4, respectively), only unreacted starting materials were recovered after HIU irradiation for five minutes. The same result was obtained when the reaction time at the 0.12 molar concentration was increased to 30 minutes. When the concentration of **1** was 0.266 molar and the amounts of ethyl bromoacetate, zinc dust and iodine were doubled, a five-minute irradiation did produce some product. By <sup>1</sup>H nmr spectroscopy, it was estimated that about 10% of the crude product mixture was  $\beta$ -hydroxyester **2a**.

Table 2  
Concentration Effects in Sonochemical Reformatsky Reactions  
of Lariat Ether Ketone **1**, Ethyl Bromoacetate, Zinc and  
Iodine in Tetrahydrofuran[a]

Entry	Flask size, ml	Zinc, wt. %	[ <b>1</b> ], molar	Reaction time, min.	Isolated yield, %
1	25	3.9	0.400	5	89
2	15	3.4	0.333	5	91
3	15	2.9	0.266	5	NR[b]
4	25	1.4	0.116	5 and 30	NR
5[c]	15	5.2	0.266	5	10[d]

[a] Equivalents of **1** (1.0), ethyl bromoacetate (1.5), zinc dust (1.8) and iodine (0.2); [b] NR = no reaction; [c] Molar ratios of ethyl bromoacetate, zinc and iodine to **1** were doubled; [d] Estimated by <sup>1</sup>H nmr spectroscopy of the crude reaction mixture.

This concentration dependence is attributed to the zinc density. For the successful reactions, the amounts of zinc were 3.9% (entry 1) and 3.4% (entry 2) by weight. Decreasing the amount of zinc to 2.9% (entry 3) and lower (entry 4) gave no reaction. Apparently, below a minimal zinc density, the metal collisions are insufficient to activate the metal surface and maintain the reaction.

In conclusion, we have shown that irradiation with HIU is an effective means of producing 79-91% yields of Reformatsky reaction products from lariat ether ketone **1** and  $\alpha$ -bromoesters. The reactions are much more rapid and produce higher yields of  $\beta$ -hydroxyesters than thermal reactions conducted with the same reactants at reflux. Activation of the zinc dust is avoided and reagent-grade dioxane may be used without purification as the solvent.

Studies designed to explore additional applications of HIU in organic synthesis are underway in our laboratories.

#### EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus. Infrared (ir) spectra were measured with a Perkin Elmer Model 1600 FTIR spectrometer as films on NaCl plates or as deposits from dichloromethane solutions on NaCl plates. Proton nuclear magnetic resonance ( $^1\text{H}$  nmr) spectra were recorded on a Bruker AF-300 instrument (300.133 MHz). Chemical shifts are given in  $\delta$  values (ppm) with tetramethylsilane as the internal standard.

The ethyl  $\alpha$ -bromoesters were used as obtained from commercial sources with the exception of ethyl  $\alpha$ -bromophenylacetate, which was synthesized from its commercially available carboxylic acid. *sym*-(Keto)dibenzo-16-crown-5 (**1**) was prepared by a reported method [10]. Tetrahydrofuran was distilled from sodium-benzophenone ketyl radical. Zinc dust (Fisher, 99.9%) was used as received. Iodine crystals (Mallinckrodt) were used as received. Reagent-grade dioxane was stored over activated 4 Å molecular sieves. Elemental analyses were performed by Desert Analytics Laboratories of Tucson, AZ.

HIU was generated with an ultrasonic processor probe system (20 kHz, 600 watts, 13 mm tip diameter at a power level of 7) from Sonics & Materials, Inc. that was modified in-house for insertion into the sonochemical vessel and a custom-designed and fabricated, four-armed, 15- or 25-ml glass sonochemical reaction vessel. During irradiation, the reaction vessel was cooled in a 20° circulating temperature bath. Monitoring of the temperature of the reaction mixture during irradiation revealed that it increased from 20° to 41-42° with dioxane solvent and 35-36° for THF solvent within five minutes and then remained constant.

General Procedure for Reactions of **1** with Ethyl  $\alpha$ -Bromoesters under HIU Irradiation.

A special sonochemical flask (20 cm high, 2 cm id with four side arms capped with rubber septa) was flushed with nitrogen for 10 minutes. Zinc dust (1.96 g, 30 mmol) and iodine (0.83 g, 3.3 mmol) were added to the flask. Half of the solvent (dioxane or tetrahydrofuran, 12.5 ml) was added and nitrogen was bubbled through the solution. Lariat ether ketone **1** (3.44 g, 10.0 mmol) and the ethyl  $\alpha$ -bromoester (25.0 mmol) and then the remaining 12.5 ml of solvent were added. The flask was attached to the probe and the lower portion was immersed in a 20° ethylene glycol/water (1:1) constant temperature bath. The reaction mixture was sonicated in a six-second pulse mode. At the end of the reaction, the flask was detached from the probe and the contents were poured into ice-water (200 ml) in a beaker. The mixture was transferred to a 1000-ml separatory funnel. The beaker was rinsed with 100 ml of 2% hydrochloric acid and the rinsings were added to the separatory funnel. The sonochemical flask was rinsed with dichloromethane and the rinsings were added to the separatory funnel. The mixture in the separatory funnel was

extracted with dichloromethane (2 x 400 ml). The combined dichloromethane layers were dried over magnesium sulfate and evaporated *in vacuo*. The residue was dried *in vacuo* to give the crude product.

For reactions conducted in the 15-ml sonochemical flask (19 cm high, 2 cm id with four side arms), a total of 15 ml of solvent was utilized.

*sym*-(Hydroxy)(methylenecarboethoxy)dibenzo-16-crown-5 (**2a**).

This compound was obtained in 90% yield as a white solid with mp 87-89° after chromatography on alumina with ethyl acetate as eluent; ir: 3474 (OH), 1729 (C=O), 1123, 1044 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  1.19-1.24 (t, 3H), 3.06 (s, 2H), 3.88-3.91 (m, 4H), 4.11-4.22 (m, 11H), 6.82-6.97 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{28}\text{O}_8$ : C, 63.88; H, 6.53. Found: C, 63.59; H, 6.72.

*sym*-(Hydroxy)( $\alpha$ -methylmethylenecarboethoxy)dibenzo-16-crown-5 (**2b**).

This compound was obtained in 91% yield as a white solid with mp 78-80° after chromatography on alumina with ethyl acetate as eluent and crystallization from hexanes; ir: 3482 (OH), 1727 (C=O), 1123, 1045 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.19-1.28 (t, 3H), 1.34-1.39 (d, 3H), 3.29-3.37 (q, 1H), 3.85-3.93 (m, 4H), 4.06-4.28 (m, 10H), 4.40-4.44 (d, 1H), 6.81-6.99 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{24}\text{H}_{30}\text{O}_8$ : C, 64.56; H, 6.77. Found: C, 64.53; H, 6.59.

*sym*-( $\alpha$ -Ethylmethylenecarboethoxy)(hydroxy)dibenzo-16-crown-5 (**2c**).

This compound was obtained in 88% yield as a white solid with mp 94-96° after chromatography on alumina with ethyl acetate as eluent and crystallization from hexanes followed by recrystallization from ethyl acetate-hexanes; ir: 3489 (OH), 1724 (C=O), 1123, 1045 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.94-0.98 (t, 3H), 1.21-1.25 (t, 3H), 1.75-1.86 (m, 2H), 3.15-3.20 (dd, 1H), 3.86-4.03 (m, 5H), 4.06-4.37 (m, 10H), 6.82-6.98 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{26}\text{H}_{32}\text{O}_8$ : C, 65.20; H, 7.00. Found: C, 65.45; H, 7.24.

*sym*-(Hydroxy)( $\alpha$ -propylmethylenecarboethoxy)dibenzo-16-crown-5 (**2d**).

This compound was obtained in 91% yield as a white solid with mp 74-75° after chromatography on alumina with ethyl acetate as eluent and crystallization from ethyl acetate-hexanes; ir: 3488 (OH), 1724 (C=O), 1123, 1044 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.92-0.97 (t, 3H), 1.20-1.25 (t, 3H), 1.28-1.39 (m, 2H), 1.71-1.82 (m, 2H), 3.26-3.31 (dd, 1H), 3.85-3.93 (m, 5H), 4.04-4.18 (m, 7H), 4.27-4.37 (m, 3H), 6.82-6.99 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{26}\text{H}_{34}\text{O}_8$ : C, 65.81; H, 7.22. Found: C, 66.09; H, 7.32.

*sym*-(Hydroxy)( $\alpha$ -phenylmethylenecarboethoxy)dibenzo-16-crown-5 (**2e**).

This compound was obtained in 79% yield as a white solid with mp 169-170° after chromatography on alumina with ethyl acetate as eluent and crystallization from ethyl acetate-hexanes followed by recrystallization from ethyl acetate; ir: 3517 (OH), 1727

(C=O), 1254 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.11-1.16 (t, 3H), 3.66-3.69 (d, 1H), 3.88-4.25 (m, 12H), 4.50 (s, 1H) 4.57-4.60 (d, 1H), 4.92 (s, 1H), 6.60-6.63 (m, 1H), 6.78-6.88 (m, 5H), 6.98-7.07 (m, 2H), 7.26-7.28 (m 3H), 7.56-7.59 (m, 2H).

*Anal.* Calcd. for  $\text{C}_{29}\text{H}_{32}\text{O}_8$ : C, 68.49; H, 6.34. Found: C, 68.44; H, 6.48.

*sym*-( $\alpha,\alpha$ -Dimethylmethylenecarboethoxy)(hydroxy)dibenzo-16-crown-5 (**2f**).

This compound was obtained in 79% yield as a white solid with mp 99-101° after chromatography on alumina with ethyl acetate as eluent and crystallization from hexanes; ir: 3530, 3397 (OH), 1719, 1700 (C=O), 1125, 1045 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.18-1.23 (t, 3H), 1.47 (s, 6H), 3.87-3.89 (m, 4H), 4.10-4.25 (m, 8H), 4.39-4.42 (d, 2H), 6.78-6.96 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{32}\text{O}_8$ : C, 65.20; H, 7.00. Found: C, 65.26; H, 7.01.

*sym*-( $\alpha$ -Fluoromethylenecarboethoxy)(hydroxy)dibenzo-16-crown-5 (**2g**).

This compound was obtained in 79% yield as a white solid with mp 97-98° after chromatography on alumina with ethyl acetate as eluent and crystallization from hexanes followed by recrystallization from ethyl acetate/hexanes; ir: 3486 (OH), 1748 (C=O), 1124, 1046 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.21-1.32 (t, 3H), 3.75 (s, 1H), 3.89-3.92 (m, 4H), 4.12-4.25 (m, 10H), 5.26-5.42 (d, 1H), 6.83-6.99 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{27}\text{FO}_8$ : C, 61.33; H, 6.04. Found: C, 61.33; H, 6.07.

*sym*-( $\alpha,\alpha$ -Difluoromethylenecarboethoxy)(hydroxy)dibenzo-16-crown-5 (**2h**).

This compound was obtained in 85% yield as a white solid with mp 72-74° after chromatography on alumina with ethyl acetate as eluent and crystallization from hexanes; ir: 3510 (OH), 1762 (C=O), 1125, 1047 (C-O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  1.27-1.32 (t, 3H), 3.89-3.92 (m, 4H), 4.09-4.22 (m, 5H), 4.30-4.48 (m, 4H), 4.49-4.53 (d, 2H), 6.84-6.99 (m, 8H).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{26}\text{F}_2\text{O}_8$ : C, 58.97; H, 5.59. Found: C, 59.15; H, 5.80.

General Procedure for Thermal Reformatsky Reactions of **1** and Ethyl  $\alpha$ -Bromoesters.

Two necks of a 50-ml, three-necked flask fitted with a reflux condenser were capped with rubber septa and the flask was flushed with nitrogen for 10 minutes. Zinc dust (1.96 g, 30 mmol) and iodine (0.83 g, 3.3 mmol) were added. Half (12.5 ml) of the dioxane solvent was added. Lariat ether ketone **1** (3.44 g, 10.0 mmol) and the ethyl  $\alpha$ -bromoester (25.0 mmol) were added followed by the remaining solvent (12.5 ml). The reaction mixture was refluxed. Work-up was performed as described above.

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