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High-Intensity Ultrasound-Promoted Reformatsky Reactions

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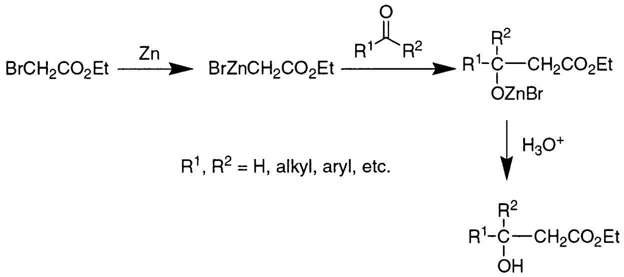
Reformatsky reactions of a phenyl ketone, an α-bromoester, zinc dust, and a catalytic amount of iodine in dioxane under high-intensity ultrasound (HIU) irradiation from an ultrasonic probe give high yields of *β*-hydroxyesters in short reaction times. A series of alkyl phenyl ketones with increasing steric demands of the alkyl group are evaluated as potential electrophiles for the reactions with several α-bromoesters, also having increasing steric demands. The Reformatsky reaction under HIU is found to be concentration dependent.

Introduction

A classic reaction in organic chemistry is the zinc-induced formation of *β*-hydroxyesters from α-haloesters and aldehydes or ketones known as the Reformatsky reaction (Scheme 1).[1] The scope of the Reformatsky reaction has progressed through the years and is the subject of several reviews.[2−5] An underlying problem with the classical protocol of using zinc dust is its low reactivity. It is necessary to "activate" the zinc dust to initiate the reaction. Control of the resulting exothermic reaction has also been a problem. Improvements in yields of the Reformatsky reaction have been achieved when freshly prepared zinc powder,[6] a heated column of zinc dust,[7] a trimethyl borate−THF solvent system,[8] a copper−zinc couple,[9] acid-washed zinc,[10] and trimethylchlorosilane[11] were utilized.

In some instances, ultrasonic irradiation can be utilized to advantage as an alternative for organic reactions ordinarily accomplished by heating.[12,13] Han and Boudjouk[14] reported that the use of a low-intensity ultrasonic (LIU) laboratory cleaning bath greatly improved the rates and yields for Reformatsky reactions of simple aldehydes and ketones with ethyl bromoacetate. However, the zinc dust still had to be "activated" using the "Cava" method,[15] and the reported conditions called for dried, distilled dioxane as the optimal solvent.

SCHEME 1. Reformatsky Reaction



LIU from an ultrasonic cleaner has considerably less power when compared to high-intensity ultrasound (HIU) from a direct immersion horn.[16] This can lead to reproducibility problems due to the lower power involved for LIU.[17] We now report results from our study of HIU-promoted Reformatsky reactions.

Results and Discussion

The HIU Reformatsky reactions were conducted in a 20 °C thermostated cooling bath to control the exothermic reaction and cool the contents from frictional heating produced from the direct introduction of high-intensity ultrasound irradiation. The reaction flask was partially immersed in the cooling bath during ultrasonication, and the in situ temperature was 41−42 °C as determined by a calorimetry experiment. The HIU Reformatsky reactions were performed with unactivated zinc, a phenyl ketone, 1.5 equiv of the α-bromoester, and a catalytic amount of iodine (0.2 equiv) in undistilled, reagent-grade dioxane. A series of six ketones, **1**−**6** (Chart 1), with increasing steric demands were evaluated as potential electrophiles for reactions with α-bromoesters (ethyl bromoacetate, ethyl α-bromopropionate, and ethyl α-bromoisobutyrate), also with increasing degrees of steric bulk.

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[1] Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210.
[2] Shriner, R. L. *Org. React.* **1942**, *1*, 1.
[3] Gaudemar, M. *Organomet. Chem. Rev., A* **1972**, *8*, 183.
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[8] Rathke, M. W.; Lambert, A. *J. Org. Chem.* **1970**, *35*, 3966.
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[12] Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, K., Eds.; Pergamon: New York, 1991; Vol. 2, pp 277−299.
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[14] Han, B.-H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030.
[15] Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikanthan, M. W.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992.
[16] Suslick, K. S.; Flint, E. B. In *Experimental Organometallic Chemistry*; Wayda, A., Darenbourg, M. Y., Eds.; American Chemical Society: Washington DC, 1987; p 195.
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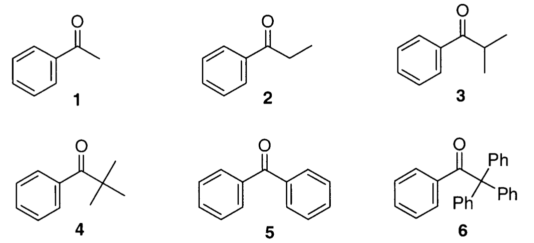
10.1021/jo0261395 CCC: $25.00

CHART 1. Structures of the Phenyl Ketones



For acetophenone (**1**) and propiophenone (**2**), reactions with ethyl bromoacetate proceeded in less than 5 min to provide very high to quantitative yields of the corresponding β-hydroxyesters (Table 1) after minimal purification. Increasing the steric bulk of the α-bromoester component in the series ethyl bromoacetate < ethyl α-bromopropionate < ethyl α-bromoisobutyrate had no effect on the reaction time or yield for either ketone reactant (entries 1−6). When ethyl chloroacetate was used as the α-haloester component with **1**, no reaction took place even after HIU irradiation for 60 min.

In contrast, LIU irradiation of **1** and ethyl bromoacetate following the Han and Boudjouk method[14] in dried, distilled dioxane in an ultrasonic cleaning bath for 30 min gave only 8−33% yields[18] of β-hydroxyester **7**, with the remainder being recovered reactants.

Benzophenone (**5**) exhibited reactivity similar to those of **1** and **2** under HIU irradiation with short reaction times (5 min) and very high yields (entries 13−15). When ethyl chloroacetate was used as the α-haloester component with **5**, no reaction took place under HIU irradiation for 5 or 60 min. Thus, α-chloroesters are judged to be ineffective α-haloester components for HIU-promoted Reformatsky reactions.

Isobutyrophenone (**3**) required a longer reaction time under HIU irradiation to induce complete consumption of the ketone reactant. Both ethyl bromoacetate and ethyl α-bromopropionate gave quantitative yields of β-hydroxyesters from **3** after 35 min of irradiation (entries 7 and 8). With ethyl α-bromoisobutyrate as the α-bromoester component, β-lactone **19** was isolated in 66% yield (entry 9) after 35 min of HIU irradiation.[19] A mechanism for the formation of **19** is shown in Scheme 2. Subsequently, it was observed that after 5 min of HIU treatment, the crude product mixture, as determined by ^{1}H NMR spectroscopy, consisted of **19** and the corresponding β-hydroxyester in a 4:1 ratio together with unreacted starting materials.

For the even more hindered pivalophenone (**4**), reaction with ethyl bromoacetate gave a high yield of the β-hydroxyester after irradiation for 35 min (entry 10). Reaction of **4** with ethyl α-bromopropionate for 35 min gave a mixture of products (entry 11). As determined by ^{1}H NMR and IR spectroscopy and GC, the mixture was mainly recovered pivalophenone and the corresponding β-lactone **20**. Increasing the reaction time from 35 to 70 min gave the same results. The most hindered ester, ethyl α-bromoisobutyrate, did not react with **4** (entry 12).

The very hindered phenyl trityl ketone (**6**) gave no reaction with even the simplest α-bromoester, ethyl bromoacetate, after 60 min of HIU irradiation (entry 16).

Since it appeared that steric factors were responsible for the formation of β-lactone **19** from isobutyrophenone (**3**), the effect of alkyl α-bromoester variation (alkyl = methyl, ethyl, isopropyl, and *tert*-butyl) was determined. Results are shown in Table 2. Increasing the size of the ester alkyl group from Me to *t*-Bu had no significant effect in the α-bromoacetate series with 95−100% yields of the β-hydroxyester isolated after HIU treatment for 35 min (entries 1−4). However, for a corresponding α-bromoisobutyrate series, sensitivity to the identity of the ester alkyl group was observed. The methyl ester gave the β-lactone adduct **19** as the only product in an isolated 74% yield (entry 6) compared with a 66% isolated yield of **19** from the ethyl ester (entry 7). Increasing the bulk with an isopropyl ester resulted in a mixture of products (entry 8). Analysis of the crude product by ^{1}H NMR and IR spectroscopy and GC showed an approximately equal mixture of β-lactone **19**, the corresponding β-hydroxyester **24**, and unreacted **3**. With the bulkiest *tert*-butyl ester, no β-lactone product was observed (entry 9). Analysis of the crude product by ^{1}H NMR and IR spectroscopy and GC showed a mixture of β-hydroxyester **25** in 58−62% GC yield and unreacted **3**. Increasing the reaction time from 35 to 70 min had no effect on the reactant consumption or product distribution.

Stereochemistry. Considerable research has been performed on the stereochemistry of the thermal Reformatsky reaction.[21] With DL-ethyl α-bromopropionate as the α-bromoester component, a mixture of diastereoisomeric β-hydroxyesters is possible. Analysis by ^{1}H NMR spectroscopy reveals complementary sets of signals for the pair of diastereomers produced during the addition reaction. These stereoisomers are designated *threo* and *erythro* (Scheme 3), and their ratio is determined by integration of the ^{1}H NMR spectrum. Jacques and coworkers[22] report a 3:2 *threo:erythro* ratio for reactions of **1** and **2** with ethyl bromoacetate. The diastereomer ratio for HIU-promoted Reformatsky reactions of **1** and **2** with ethyl bromoacetate (entries 2 and 5, Table 1, respectively) was found to be the same as in the thermal reactions.[22] From **3** and ethyl bromoacetate (entry 8, Table 1), a 1:4 *threo*:*erythro* ratio was observed for the HIU-promoted Reformatsky reaction.

Concentration Dependence Studies. During the course of this study, it was noted that Reformatsky reactions under HIU are concentration dependent. Performance of several different reactions using varying concentrations of reactants led to the realization that minimal reactant concentrations were required for the reaction to proceed efficiently. This concentration dependence was observed also with other ketones.[23] The concentration dependence is illustrated by the data in Table 3. Entry 1 represents the standard HIU conditions with THF as the solvent and gives a 93% yield of

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(18) Han and Boudjouk report formation of a 90% yield of β-hydroxyester **7** from **1** after 30 min of LIU irradiation.[14]

(19) Schick and co-workers[20] report the formation of both β-lactone and β-hydroxyester products in reactions of **2**, phenyl propyl ketone, butyl phenyl ketone, or **5** with ethyl α-bromoisobutyrate and zinc in DMF.

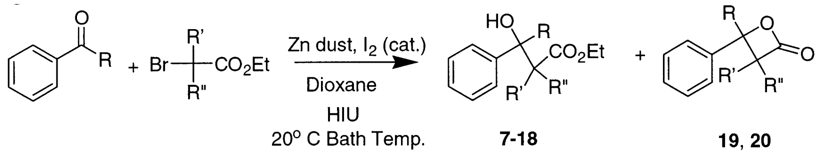
(20) Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K.; Kunath, A. *J. Org. Chem.* **1994**, *59*, 3161.

(21) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Wiley: New York, 1983; Vol. 3, p 144.

(22) Canceill, J.; Basselier, J. J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 1024.

(23) Ross, N. A.; Bartsch, R. A. *J. Heterocycl. Chem.* **2001**, *38*, 1255.

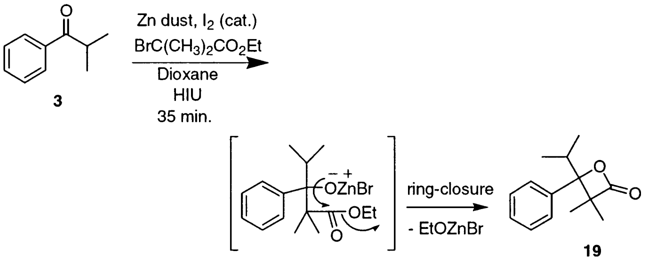
TABLE 1. HIU-Promoted Reformatsky Reactions of α-Bromoesters with Phenyl Ketones 1−6



entry	PhC(O)R	R′R″CBrCO$_2$Et		reaction time	product	yield[a] (%)	
	R	R′	R″	(min)		β-hydroxyester	β-lactone
1	Me	H	H	5	**7**	93	0
2	Me	Me	H	5	**8**	99[b]	0
3	Me	Me	Me	5	**9**	100	0
4	Et	H	H	5	**10**	99	0
5	Et	Me	H	5	**11**	96[b]	0
6	Et	Me	Me	5	**12**	99	0
7	*i*-Pr	H	H	35	**13**	100	0
8	*i*-Pr	Me	H	35	**14**	100[c]	0
9	*i*-Pr	Me	Me	35	**19**	0	66
10	*t*-Bu	H	H	35	**15**	94	0
11	*t*-Bu	Me	H	35, 70	**20**	0	26, 23[d]
12	*t*-Bu	Me	Me	35	NR[e]		
13	Ph	H	H	5	**16**	95	0
14	Ph	Me	H	5	**17**	99	0
15	Ph	Me	Me	10	**18**	100	0
16	Tr[f]	H	H	60	NR[e]		

[a] Isolated yield. [b] A 3:2 mixture of *threo*/*erythro* diastereomers. [c] A 1:4 mixture of *threo*/*erythro* diastereomers. [d] GC yield of crude reaction product after workup (unreacted pivalophenone present). [e] No reaction, only recovered ketone starting material. [f] Tr = Trityl.

SCHEME 2. Mechanism for Formation of β-Lactone 19



β-hydroxyester **7** from sonication of **1** and ethyl bromoacetate for 5 min when the weight percent of zinc was 4.1. Reducing the concentrations of the reactants uniformly by one-third reduced the yield from 93% to 78% (entry 2). Further reduction resulted in inhibition of the reaction, and only unreacted starting materials were recovered (entries 3 and 4). Changing the solvent from THF to dioxane had no effect on the reaction in the case where the weight percent of zinc was 1.4 (entry 4). These results reveal that only a small difference in the weight percent of zinc (0.8) makes a difference as to whether the reaction proceeds.

The concentration dependence may be attributed to the zinc density.[24] For the successful reactions, the amounts of zinc were 4.1 (entry 1) and 3.0 (entry 2) wt %. Decreasing the amount of zinc to 2.2 wt % (entry 3) and lower (entry 4) gave no reaction. Apparently, below a minimal zinc density, metal collisions are minimized, which slows or halts surface activation of the metal.

Comparison with Thermal Reactions. The conventional thermal Reformatsky reaction involves refluxing the mixture in benzene or diethyl ether and gives modest to low yields for a variety of β-hydroxyesters.[2] In this work, dried, distilled THF and undistilled, reagent-grade dioxane were utilized as solvents for thermal reactions with ethyl bromoacetate to allow for direct comparison with the HIU experiments, since THF and dioxane are equally compatible solvents for HIU-induced Reformatsky reactions. Thermal reactions were performed with **1** and ethyl bromoacetate in both refluxing THF and dioxane. From reaction in THF for 20 h, a 58% GC yield of β-hydroxyester **7** was observed together with unconsumed ketone reactant. The reaction in refluxing dioxane failed completely, and no product was detected by ^{1}H NMR spectroscopic analysis of the crude product mixture. Thermal reactions were also performed with **5** and ethyl bromoacetate at reflux in both anhydrous THF and reagent-grade dioxane. From reaction in THF at reflux for 20 h, a 65% GC yield of the β-hydroxyester **18** was obtained together with unconsumed ketone reactant. Reaction in refluxing dioxane for 23 h gave a 9% GC yield in the crude product mixture, with the majority being unreacted ketone reactant.

A trimethyl borate−THF solvent system[8] has been shown to improve the conventional Reformatsky reaction. Reaction at room temperature reduces base-catalyzed side reactions of the starting materials that were at least partially responsible for the low yields.[25] Reactions of **1** with the three ethyl α-bromoesters, zinc dust, and trimethyl borate−THF (1:1) were conducted for 20 h at room temperature. The results (Table 4) show that, as the bulkiness of the α-bromoester increases on going from ethyl bromoacetate to ethyl α-bromopropionate, the β-hydroxyester yield drops from 76% to 40%. With ethyl α-bromoisobutyrate, only a trace (~3%) of the β-hydroxyester product was detected by GC analysis of the crude reaction mixture. Reaction of **5**, ethyl bromoacetate, zinc dust, and trimethyl borate−THF (1:1) for 20 h at room

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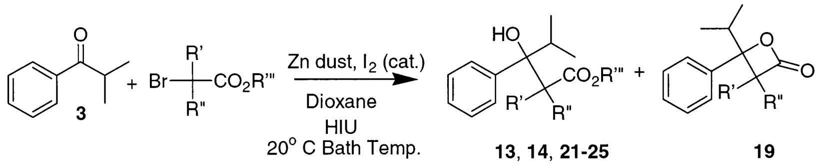
[24] Suslick, K. S. Department of Chemistry, University of Illinois, Urbana-Champaign. Personal communication, 2001.

[25] Hussey, A. S.; Newman, M. S. *J. Am. Chem. Soc.* **1948**, *70*, 3024.

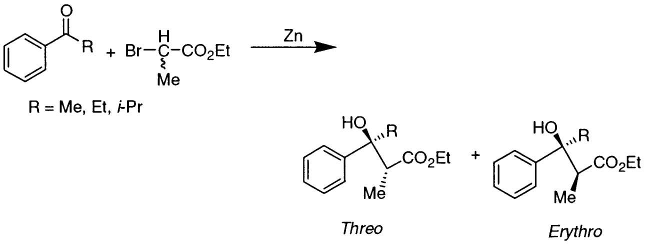
TABLE 2. HIU-Promoted Reformatsky Reactions of α-Bromoesters and Isobutyrophenone (3)



entry	R′	R″	R‴	reaction time (min)	product	yield[a] (%) β-hydroxyester	β-lactone
1	H	H	Me	35	**21**	100	0
2	H	H	Et	35	**13**	100	0
3	H	H	*i*-Pr	35	**22**	97	0
4	H	H	*t*-Bu	35	**23**	95	0
5	Me	H	Et	35	**14**	100	0
6	Me	Me	Me	35	**19**	0	74
7	Me	Me	Et	35	**19**	0	66
8	Me	Me	*i*-Pr	35	**24** + **19**	34[b]	30[b]
9	Me	Me	*t*-Bu	35, 70	**25**[c]	58, 62[b]	0

[a] Isolated yield. [b] GC yields in crude reaction mixture after workup. Unreacted isobutyrophenone present. [c] A small amount of **25** was isolated from the unreacted ketone in the product by recrystallization from hexane.

SCHEME 3. Diastereomeric β-Hydroxyesters Produced in Reformatsky Reactions with DL-Ethyl α-Bromopropionate



temperature was also attempted. No product formation was evident by ^{1}H NMR spectroscopic analysis.

Conclusions

Irradiation of a mixture of a phenyl ketone, an α-bromoester, zinc dust, and iodine in dioxane with an HIU horn gave very high yields of β-hydroxyesters in short reaction times. Only when the reactants became extremely bulky did the HIU-promoted Reformatsky reaction fail. It was not necessary to activate the zinc, and undistilled, reagent-grade dioxane was used. These factors, as well minimal purification of the crude products, make the HIU method attractive for performing Reformatsky reactions.

Experimental Section

Materials. The ketones and α-haloesters were used as obtained from commercial sources unless otherwise stated. Zinc dust (99.9%) was used directly unless otherwise noted. THF was distilled from sodium−benzophenone ketyl radical. Iodine crystals and trimethyl borate were used directly as obtained from commercial sources. Reagent-grade dioxane was stored over activated 4 Å molecular sieves and used without distillation unless specified. The methyl and isopropyl α-bromoisobutyrate esters were synthesized from the commercially available α-bromo-α-methylpropionyl bromide using a standard procedure.[26]

Physical and Analytical Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 499.7 and 125.7 MHz, respectively, in deuteriochloroform. Chemical shifts are given in δ values (ppm) with TMS as the internal standard. HIU irradiation was provided by an ultrasonic processor probe system (20 kHz, 600 W, 13 mm tip diameter at a power level of 7) from that was modified in-house for insertion into 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 °C circulating temperature bath. LIU was produced with an ultrasonic laboratory cleaner (40 kHz, 100 W). GC analysis was performed with a 30 m × 0.32 mm × 0.25 mm capillary column using a temperature ramp program from 45 to 250 °C at 10 °C/min. Elemental analyses were performed by Desert Analytics, Inc. (Tucson, AZ).

General Procedure for Reformatsky Reactions under HIU Irradiation. The 25 mL, four-armed sonochemical reaction flask capped with rubber septa was flushed with nitrogen for several minutes. Zinc dust (1.18 g, 18 mmol) and iodine (0.50 g, 2.0 mmol) were added to the flask. Half of the dioxane (12.5 mL) was added, and nitrogen was bubbled through the solution. The ketone (10 mmol) and α-bromoester (15 mmol) were added, followed by the remaining solvent (12.5 mL). The flask was attached to the probe, and the lower portion was immersed in a 20 °C ethylene glycol/water (1:1) constant-temperature bath. The reaction mixture was sonicated for the specified period in a 6 s pulse mode.

At the end of the reaction period, the flask was detached from the probe and the contents were poured into a beaker containing distilled water/ice (200 mL). The mixture was transferred to a 1 L separatory funnel. The beaker was rinsed with 2% aq HCl (100 mL), and the rinsings were added to the separatory funnel. The sonochemical flask was rinsed with CH_2Cl_2, and the rinsings were added to the separatory funnel. The mixture in the separatory funnel was extracted with CH_2Cl_2 (2 × 200 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was dried in vacuo to give the crude product that was subjected to short-path column chromatography on alumina with EtOAc or EtOAc/hexanes as eluent and, if necessary, Kugelrohr evaporation of the remaining volatile impurities under high vacuum (0.3 Torr) to give the β-hydroxyester.

For reactions conducted in the 15 mL, four-armed sonochemical flask, a total of 12.5 mL of solvent was utilized.

Ethyl 3-hydroxy-3-phenylbutyrate (**7**)[2] was prepared from **1** in 93% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent: colorless oil; IR (neat) 3502, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 2.87 (dd, J = 15.9, 15.9 Hz, 2H), 4.04 (q, J = 7.1 Hz,

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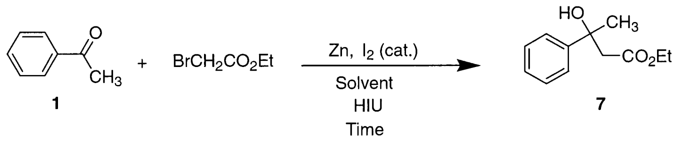
[26] Allen, F. C.; Kalm, M. J. *Organic Syntheses*; Wiley & Sons: New York, 1963; Collect. Vol. IV, p 608.

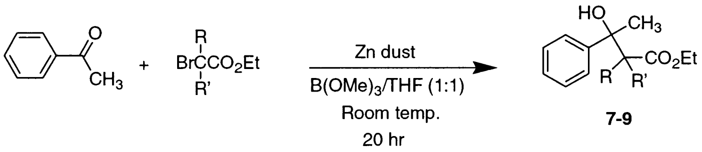
TABLE 3. Concentration Effect in HIU-Promoted Reformatsky Reactions



entry	solvent	solvent vol (mL)	zinc concn (wt %)	ketone concn (M)	isolated yield (%)	reaction time (min)
1	THF[a]	25	4.1	0.400	93	5
2	THF[a]	12.5	3.0	0.266	78	5
3	THF[a]	12.5	2.2	0.191	NR[c]	5
4	THF[a] or dioxane[b]	25	1.4	0.116	NR[c]	30

[a] Distilled from Na−benzophenone ketyl. [b] Undistilled, reagent-grade. [c] No reaction.

TABLE 4. Thermal Reformatsky Reactions Conducted in a Trimethyl Borate−THF Solvent System



entry	R	R′	product	yield[a] (%)
1	H	H	**7**	76[b]
2	Me	H	**8**	40
3	Me	Me	**9**	3

[a] GC yield in the crude reaction mixture after workup (incomplete reaction). [b] Isolated yield.

2H), 4.40 (s, 1H), 7.19−7.24 (m, 1H), 7.28−7.35 (m, 2H), 7.41−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 30.5, 46.3, 60.6, 72.6, 124.3, 126.7, 128.0, 146.8, 172.5. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.55.

Ethyl 3-hydroxy-2-methyl-3-phenylbutyrate (**8**)[2] was prepared from **1** in 99% yield as a 60:40 mixture of *threo*/*erythro* diastereomers after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 100 °C ot (oven temperature): clear oil; IR (neat) 3502, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, $J = 7.1$ Hz, *threo*), 1.29 (t, $J = 7.1$ Hz, *erythro*, *threo* + *erythro* = 3H), 0.95 (d, $J = 7.2$ Hz, *erythro*), 1.33 (d, $J = 7.1$, *threo*, *threo* + *erythro* = 3H), 1.45 (s, *threo*), 1.56 (s, *erythro*, *threo* + *erythro* = 3H), 2.83 (q, $J = 7.1$ Hz, *erythro*), 3.0 (q, $J = 7.2$ Hz, *threo*, *threo* + *erythro* = 1H), 3.82−3.93 (m, *threo*), 4.15−4.27 (m, *erythro*, *threo* + *erythro* = 2H), 3.94 (s, *erythro*), 4.09 (s, *threo*, *threo* + *erythro* = 1H), 7.16−7.25 (m, 1H), 7.27−7.38 (m, 2H), 7.38−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.6, 13.7, 14.0, 26.7, 29.8, 48.4, 49.2, 60.3, 60.7, 74.2, 74.5, 124.6, 124.8, 126.5, 126.6, 127.9, 128.0, 145.0, 147.5, 176.6, 177.1. Anal. Calcd for $C_{13}H_{18}O_3\cdot 2H_2O$: C, 69.16; H, 8.21. Found: C, 69.52; H, 7.85. (The presence of H_2O in the analytical sample was evident in its ^{1}H NMR spectrum.)

Ethyl 3-hydroxy-2,2-dimethyl-3-phenylbutyrate (**9**) was prepared from **1** in 100% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 110 °C ot: colorless oil; IR (neat) 3482, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.15 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.61 (s, 3H), 4.08−4.18 (m, 2H), 4.52 (s, 1H), 7.19−7.26 (m, 1H), 7.27−7.32 (m, 2H), 7.41−7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.5, 21.6, 24.8, 49.9, 60.9, 76.9, 126.7, 127.0, 127.1, 143.4, 178.4. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.85; H, 8.58.

Ethyl 3-hydroxy-3-phenylpentanoate (**10**)[2,4] was prepared from **2** in 99% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent: colorless oil; IR (neat) 3503, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (t, $J = 7.4$ Hz, 3H), 1.08 (t, $J = 7.2$ Hz, 3H), 1.72−1.89 (m, 2H), 2.87 (dd, $J = 15.7$, 15.7 Hz, 2H), 4.01 (q, $J = 7.1$ Hz, 2H), 4.34 (s, 1H), 7.16−7.25 (m, 1H), 7.27−7.36 (m, 2H), 7.36−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.7, 13.9, 35.8, 44.9, 60.6, 75.1, 125.1, 126.6, 128.0, 145.1, 172.9. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.91; H, 8.31.

Ethyl 3-hydroxy-2-methyl-3-phenylpentanoate (**11**) was prepared from **2** in 96% yield as a 3:2 mixture of *threo*/*erythro* diastereomers, after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 110 °C ot: clear oil; IR (neat) 3497, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.61−0.72 (m, 3H), 0.84−0.98 (m, 3H), 1.32 (t, $J = 7.2$ Hz, *erythro*, 1H), 1.36 (d, $J = 7.1$ Hz, *threo*, 2H), 1.61−1.81 (m, 1H), 1.85−1.98 (m, 1H), 2.86 (q, $J = 7.1$ Hz, *erythro*), 3.05 (q, $J = 7.2$ Hz, *threo*, *threo* + *erythro* = 1H), 3.75 (s, *erythro*), 4.06 (s, *threo*, *threo* + *erythro* = 1H), 3.77−3.94 (m, *threo*), 4.17−4.30 (m, *erythro*, *threo* + *erythro* = 2H), 7.14−7.26 (m, 1H), 7.28−7.37 (m, 2H), 7.37−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.4, 7.8, 11.9, 12.6, 13.7, 14.1, 31.4, 34.4, 47.5, 48.8, 60.3, 60.7, 76.9, 77.1, 125.4, 125.5, 126.3, 126.5, 127.8, 127.9, 142.5, 145.2, 176.9, 177.6. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.79; H, 8.27.

Ethyl 3-hydroxy-2,2-dimethyl-3-phenylpentanoate (**12**) was prepared from **2** in 99% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 110 °C ot: colorless oil; IR (neat) 3472, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, $J = 7.3$ Hz, 3H), 1.1 (s, 3H), 1.16 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.97 (doublet of sextets, 2H), 4.08−4.19 (m, 2H), 4.40 (s, 1H), 7.20−7.26 (m, 1H), 7.28−7.34 (m, 2H), 7.38−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.9, 13.9, 21.4, 21.8, 28.2, 50.3, 61.0, 79.8, 126.6, 127.1, 128.0, 140.1, 178.8. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.91; H, 8.86.

Ethyl 3-hydroxy-4-methyl-3-phenylpentanoate (**13**) was prepared from **3** in 100% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent: colorless oil; IR (neat) 3496, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H), 1.03 (t, $J = 7.1$ Hz, 3H), 1.94 (septet, $J = 6.7$ Hz, 1H), 2.92 (dd, $J = 15.6$, 15.6 Hz, 2H), 3.89−4.01 (m, 2H), 4.32 (s, 1H), 7.15−7.24 (m, 1H), 7.26−7.34 (m, 2H), 7.34−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 16.8, 17.1, 38.6, 42.3, 60.5, 77.2, 125.7, 126.6, 127.7, 144.8, 173.3.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.82; H, 8.59.

Ethyl 3-hydroxy-2,4-dimethyl-3-phenylpentanoate (14) was prepared from **3** in 100% yield as a 1:4 mixture of *threo*/*erythro* diastereomers, after chromatography on alumina with EtOAc as eluent and flash Kugelrohr distillation up to 100 °C ot: colorless oil; IR (neat) 3496, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.69 (d, $J = 6.7$ Hz, *threo*), 0.77 (d, $J = 6.6$ Hz, *erythro*, *threo* + *erythro* = 3H), 0.81 (d, $J = 7.0$ Hz, *threo*), 0.86 (d, $J = 6.8$ Hz, *erythro*, *threo* + *erythro* = 3H), 0.95 (t, $J = 7.1$ Hz, *threo*), 1.28 (t, $J = 7.1$ Hz, *erythro*, *threo* + *erythro* = 3H), 1.01 (d, $J = 7.1$ Hz, *erythro*), 1.37 (d, $J = 7.1$ Hz, *threo*, + *erythro* = 3H), 1.99 (septet, $J = 6.8$ Hz, *erythro*), 2.16 (septet, $J = 6.9$ Hz, *threo*, *threo* + *erythro* = 1H), 3.25 (q, $J = 7.1$ Hz, *erythro*), 3.39 (q, $J = 7.1$ Hz, *threo*, *threo* + *erythro* = 1H), 3.78−3.92 (m, *threo*), 4.11−4.28 (m, *erythro*, *threo* + *erythro* = 2H), 3.98 (s, *erythro*, 0.8H), 7.13−7.26 (m, 1H), 7.26−7.35 (m, 2H), 7.34−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.5, 13.2, 13.7, 14.0, 16.6, 17.0, 17.2, 18.0, 33.2, 37.6, 44.2, 45.1, 60.4, 60.8, 78.6, 79.3, 126.3, 126.4, 126.7, 126.8, 127.2, 127.4, 140.6, 142.8, 177.3, 177.4. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.80; H, 8.70.

Ethyl 3-hydroxy-4,4-dimethyl-3-phenylpentanoate (15) was prepared from **4** in 94% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 110 °C ot: colorless oil; IR (neat) 3488, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9H), 1.01 (t, $J = 7.2$ Hz, 3H), 3.05 (dd, $J = 15.7$, 15.7 Hz, 2H), 3.93 (q, $J = 7.1$ Hz, 2H), 4.38 (s, 1H), 7.13−7.23 (m, 1H), 7.23−7.30 (m, 2H), 7.30−7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 25.4, 37.9, 39.9, 60.5, 77.3, 126.5, 127.0, 127.3, 143.6, 173.8. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.05; H, 9.00.

Ethyl 3-hydroxy-3,3-diphenylpropionate (16)[2,4] was prepared from **5** in 95% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent: white solid; mp 78−79 °C; IR (deposit from CH_2Cl_2 onto a NaCl plate) 3476, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, $J = 7.1$ Hz, 3H), 3.25 (s, 2H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.10 (s, 1H), 7.15−7.23 (m, 2H), 7.23−7.32 (m, 4H), 7.38−7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9, 45.5, 60.9, 76.3, 125.6, 127.0, 128.1, 145.9, 172.7. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.71; H, 6.47.

Ethyl 3-hydroxy-2-methyl-3,3-diphenylpropionate (17) was prepared from **5** in 99% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent: white solid; mp 90−93 °C; IR (deposit from CH_2Cl_2 onto a NaCl plate) 3489, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, $J = 7.1$ Hz, 3H), 1.16 (d, 7.1 Hz, 3H), 3.65 (q, $J = 7.2$ Hz, 1H), 3.95−4.10 (m, 2H), 4.73 (s, 1H), 7.07−7.18 (m, 2H), 7.21−7.31 (m, 4H), 7.44−7.49 (m, 2H), 7.53−7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.8, 13.8, 46.8, 60.7, 78.0, 125.2, 125.3, 126.5, 126.8, 128.0, 128.1, 144.1, 147.5, 177.3. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.40; H, 7.01.

Ethyl 3-hydroxy-2,2-dimethyl-3,3-diphenylpropionate (18) was prepared from **5** in 100% yield after chromatography on alumina with EtOAc/hexanes (1:1) as eluent and flash Kugelrohr distillation up to 125 °C ot: opaque oil; IR (neat) 3556, 3468, 1732, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.33 (s, 6H), 4.18 (q, $J = 7.1$ Hz, 2H), 5.13 (s, 1H), 7.17−7.27 (m, 6H), 7.31−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9, 24.0, 48.9, 61.3, 82.1, 126.8, 127.1, 128.2, 128.6, 145.5, 179.6. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.85; H, 7.35.

4-Isopropyl-3,3-dimethyl-4-phenyloxetan-2-one (19) was prepared from **3** in 74% yield (from the methyl ester) or 66% yield (from the ethyl ester) after recrystallization from hexanes: white solid; mp 68−70 °C; IR (deposit from CH_2Cl_2 onto a NaCl plate) 1807, 1207, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 7.0$ Hz, 3H), 1.05 (s, 3H), 1.56 (s, 3H), 2.46 (septet, $J = 6.7$ Hz, 1H), 6.85−7.04 (m, 1H), 7.29−7.36 (m, 2H), 7.36−7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.3, 18.1, 18.3, 22.9, 34.7, 56.7, 91.2, 126.2, 126.5, 127.1, 127.4, 128.2, 135.2, 175.4. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.32; H, 8.24.

Methyl 3-hydroxy-4-methyl-3-phenylpentanoate (21) was prepared from **3** in 100% yield after chromatography on alumina with EtOAc as eluent: colorless oil; IR (neat) 3500, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 1.94 (septet, $J = 6.8$ Hz, 1H), 2.5 (dd, $J = 15.9$, 15.9 Hz, 2H), 3.48 (s, 3H), 4.31 (s, 1H), 7.15−7.22 (m, 1H), 7.25−7.32 (m, 2H), 7.35−7.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 17.0, 38.5, 41.9, 51.5, 77.0, 125.5, 126.5, 127.6, 144.7, 173.7. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.37; H, 8.06.

Isopropyl 3-hydroxy-4-methyl-3-phenylpentanoate (22)- was prepared from **3** in 97% yield after chromatography on alumina with EtOAc as eluent and flash Kugelrohr distillation up to 123 °C ot: colorless oil; IR (neat) 3491, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.2$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.3$ Hz, 3H), 1.93 (septet, $J = 6.7$ Hz, 1H), 2.89 (dd, $J = 15.3$, 15.4 Hz, 2H), 4.35 (s, 1H), 4.81 (septet, $J = 6.2$ Hz, 1H), 7.14−7.21 (m, 1H), 7.24−7.32 (m, 2H), 7.36−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.8, 17.0, 21.2, 21.3, 38.5, 42.7, 67.9, 77.2, 125.7, 126.5, 127.6, 144.8, 172.8. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.31; H, 9.05.

***tert*-Butyl 3-hydroxy-4-methyl-3-phenylpentanoate (23)** was prepared from **3** in 95% yield after chromatography on alumina with EtOAc as eluent and flash Kugelrohr distillation up to 100 °C ot: colorless oil; IR (neat) 3486, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.18 (s, 9H), 1.91 (septet, $J = 6.8$ Hz, 1H), 2.83 (dd, $J = 15.1$, 15.1 Hz, 2H), 4.33 (s, 1H), 7.12−7.23 (m, 1H), 7.23−7.33 (m, 2H), 7.36−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.8, 17.0, 27.6, 38.6, 43.7, 77.3, 81.4, 125.9, 126.4, 127.5, 145.0, 172.6. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.91; H, 9.17.

***tert*-Butyl 3-hydroxy-2,2,4-trimethyl-3-phenylpentanoate (25)** was isolated from reaction of **3** and α-bromoisobutyrate in a small amount from the crude product mixture after recrystallization from hexanes: white solid; mp 80−82 °C; IR (deposit from CH_2Cl_2 onto a NaCl plate) 3404, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.65 (d, $J = 6.6$ Hz, 3H), 0.87 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.22 (s, 3H), 1.48 (s, 9H), 2.57 (septet, $J = 6.6$ Hz, 1H), 6.03 (s, 1H), 7.16−7.26 (m, 1H), 7.27−7.37 (m, 2H), 7.37−7.88 (br m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.4, 18.7, 20.2, 25.5, 27.5, 27.6, 33.8, 47.3, 77.0, 81.9, 126.2, 127.0, 127.9, 143.2, 179.7. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.26; H, 9.85.

General Procedure for Reformatsky Reactions under LIU Irradiation. A 50 mL, round-bottom flask was flushed with nitrogen for several minutes. Zinc (Cava-activated or dust) (1.18 g, 18 mmol) and iodine (0.50 g, 2.0 mmol) were added to the flask. Half of the dioxane (12.5 mL) solvent was added. The ketone (10 mmol) and α-bromoester (15 mmol) were added followed by the remaining solvent (12.5 mL). The flask was partially submerged in the ultrasonic cleaning bath in a position of maximum ultrasonic intensity. The reaction mixture was sonicated for the specified period in a continuous irradiation mode and was not thermostated. At the end of the reaction period, the reaction mixture was worked up in the same fashion as reported above for reactions conducted under HIU irradiation, and the crude product was analyzed by ^{1}H NMR spectroscopy and GC.

General Procedure for Thermal Reformatsky Reactions.[4] A 50 mL, three-necked flask equipped with a magnetic stirring bar and a reflux condenser was flushed with nitrogen for several minutes and kept under nitrogen throughout the reaction. Zinc dust (1.18 g, 18 mmol) and iodine (0.50 g, 2.0 mmol) were added. Half of the solvent (12.5 mL) was added, and stirring was initiated. The ketone (10 mmol) and α-bromoester (15 mmol) were added followed by the remaining solvent (12.5 mL). The reaction mixture was refluxed overnight (>19 h) and worked up in the same fashion as reported above for reactions conducted under HIU irradiation, and the crude product was analyzed by ^{1}H NMR spectroscopy and GC.

General Procedure for Thermal Reformatsky Reactions in the Trimethyl Borate−THF System.[8] A 50 mL flask equipped with a magnetic stirring bar was flushed with nitrogen for several minutes and maintained under nitrogen during the reaction. Zinc dust (1.18 g, 18 mmol) was added, and the flask was immersed in a water bath at 25 °C. The ketone (10 mmol), anhydrous THF (12.5 mL), and trimethyl borate (12.5 mL) were added sequentially. Stirring was initiated, and the α-bromoester (15 mmol) was added by syringe. The reaction mixture was stirred overnight (20 h) and then hydrolyzed by addition of a solution of 25 mL of concentrated NH_4OH and 25 mL of MeOH. After addition of CH_2Cl_2 (100 mL) and distilled H_2O (50 mL), the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was dried in vacuo to give the crude product, which was analyzed by ^{1}H NMR spectroscopy and GC.

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