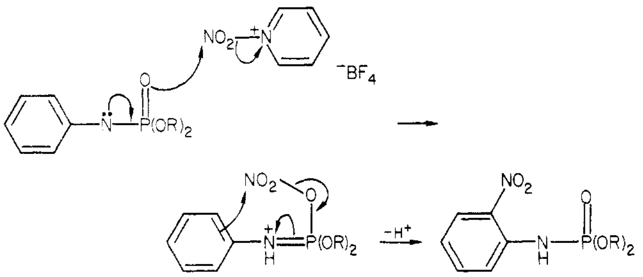
Scheme I



in isomer percentages of $\pm$3%. Our lower limit of detectability as determined from trial runs is 2%.

The first striking feature of the data in Table I is the large difference in isomer ratios obtained for the present work on **3** as opposed to the earlier published results.[3] We do not observe the large proportion of ortho isomer, and indeed the system shows a substantial preference for the meta product, consistent with reaction via the N-protonated form. It appears that in the earlier work,[3] the substrates were nitrated at least partially as free bases, thus giving an anomalously high amount of ortho product.[8]

There is little effect on the product ratios when the (OR)$_2$ group on phosphorus is changed from (OEt)$_2$ to (OCH$_3$)$_2$ as shown by results for **3** and **4**.

The minor increase in the amount of meta nitration product for **5** relative to **4** may reflect the increased stability of the N-protonated species in **5** which would be expected on the basis of the electron-donating inductive effect of the CH$_3$ group.

Interestingly, the thioamidate **6** shows essentially *no meta* nitration, indicating that introduction of the sulfur atom converts the substituent into an ortho–para director, and no appreciable reaction occurs via the N-protonated conjugate acid. If protonation on sulfur does occur, the directing effects of this substituent suggest that the N lone pair is not significantly involved in conjugative interactions with it.

Aprotic Nitrations. Nitration of **3** via the pyridine–nitronium tetrafluoroborate complex[6] gives dramatically different isomer distributions, namely, 66% ortho, 7% meta, and 27% para product. These findings are rather similar to those reported[3] for **3** when nitration is performed in acetic anhydride, and the reaction via the conjugate acid of **3** is not possible.

In conclusion, it appears that phosphoramidate nitrations in protic media lead to a predominance of meta product, indicating that the reaction occurs via the N-protonated form. There is no need to postulate a special "ortho" mechanism as was done previously,[3] since the ortho products are in fact formed to a minimal extent.

In aprotic media, however, there is a tendency for ortho product predominance over the para product in excess of the statistical value of 2. It is known[6] that the *N*-nitropyridinium ions themselves participate in the rate-determining transition state of transfer nitrations, rather than "free" nitronium ions. To rationalize the preferred ortho pathway, one could suggest a mechanism such as that outlined in Scheme I. An analogous pathway could be suggested for the nitration of **3** in acetic anhydride, with N$_2$O$_5$ believed to be the electrophile.[1,9]

Experimental Section

Materials **3–6** were prepared via published methods.[3,5] The nitration reactions and subsequent hydrolyses to the nitroaniline derivatives were carried out in a manner similar to that reported previously by Modro and Pioch.[3] Our quantitative separations were obtained on silica gel 60 F$_{254}$ 20 × 20 cm preparative TLC plates obtained from Merck, Darmstadt, Germany. The solvent system was a 50:50 volume mixture of diethyl ether and low-boiling (30–60 °C) petroleum ether.

Yields of separated products are greater than 80% in all cases. Authentic samples of all the nitroanilines were obtained from Aldrich Chemical Corp., Milwaukee WI.

^{1}H NMR spectra of the products (nitroanilines) were compared to those of authentic samples on Varian T-60, XL-100, and XL-200 NMR spectrometers with CDCl$_3$ as the solvent and Me$_4$Si as an internal reference.

It was also shown that when no nitric acid was added, starting materials **3–6** could be recovered quantitatively from the sulfuric acid solutions under the conditions of the nitration reaction. This proves that there is no nitroaniline in the reaction product which arises from nitration of an initially hydrolyzed starting material.

Nitrations using the pyridine–nitronium tetrafluoroborate complex were carried out according to the published method,[6] modified as described below.

To a flask under an N$_2$ atmosphere at 0 °C were added 10 mL of dry acetonitrile, 2.4 g (18.2 mmol) of nitronium tetrafluoroborate and 1.5 g (18.1 mmol) of pyridine, in that order. The resulting stirred solution was allowed to warm to 20 °C over a 0.5-h period. This solution was then transferred via pipet into another flask (under N$_2$) containing 9.0 mmol of **3** in 15 mL of dry acetonitrile.

After this solution was stirred at 20 °C for 1 h, 25 mL of 6 N HCl was added, and the solution was refluxed for 2 h to hydrolyze the phosphoramidate to the nitroaniline derivative. The solution was then neutralized by addition of NaOH and was then extracted with ether. Quantitative separations were done via preparative TLC (vide supra) and products analyzed with the aid of ^{1}H NMR on a Varian XL-200 system.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for summer research fellowships (to S.H.P.) and operating grant funds (to G.W.B.).

Registry No. 3, 1445-38-1; **4**, 58046-12-1; **5**, 7006-95-3; **6**, 83436-57-1; *m*-nitroaniline, 99-09-2; *p*-nitroaniline, 100-01-6; *o*-nitroaniline, 88-74-4.

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[9] Norman, R. O. C.; Rodda, G. K. *J. Chem. Soc. B* **1961**, 3030.

Organic Sonochemistry. Sonic Acceleration of the Reformatsky Reaction

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Received April 1, 1982

The Reformatsky reaction is the most generally applicable procedure for converting aldehydes and ketones to β-hydroxy esters, and, consequently, it has been the subject of extensive synthetic and mechanistic study.[1] Significant improvements in the yields of this reaction have been obtained by using freshly prepared zinc powder,[2] a heated column of zinc dust,[3] and a trimethyl borate–tetrahydrofuran solvent system.[4] Recently we[5] and others[6] have

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0022-3263/82/1947-5030$01.25/0

Table I. Comparison of the Yields and Reaction Times for Reformatsky Reactions

		yield, %; reaction time for $RR'C(OH)CH_2CO_2Et$			
no.	$RR'C{=}O$	sonically accelerated	activated zinc powder[c]	$(MeO)_3B$-THF solvent[d]	conventional method[e,f]
1	$R = C_3H_7$; $R' = H$	90; 5 min[a] 94; 2.5 h[b]	97; 1 h	90; 5 h	69; 12 h
2	$R = C_7H_{15}$; $R' = H$	100; 5 min[a] 100; 2.5 h[b]	78; 1 h		80; 12 h
3	$R = C_6H_5$; $R' = H$	98; 5 min[a] 98; 5 h[b]	98; 1 h	95; 12 h	61; 12 h
4	R = 1-naphthyl; $R' = H$	100; 5 min[a] 98; 2.5 h[b]			
5	R = 2-naphthyl; $R' = H$	100; 5 min[a] 100; 30 min[b]			
6	cyclopentanone	98; 30 min[a] 97; 3 h[b]	97; 1 h	87; 5 h	50; 12 h
7	$R = R' = C_3H_7$	100; 30 min[a] 95; 3 h[b]			
8	$R = C_6H_5$; $R' = CH_3$	90; 30 min[a] 96; 3 h[b]			
9	$R = R' = C_6H_5$	82; 3 h[a]			

[a] Reactions were run at 25–30 °C by using 1:1.2:1.8:0.20 molar ratios of $RR'CO{:}BrCH_2CO_2Et{:}Zn{:}I_2$. [b] Same conditions as in *a* with 1:1.2:3.0:0.84 molar ratios of $RR'CO{:}BrCH_2CO_2Et{:}Zn{:}KI$. [c] Reference 2. [d] Reference 4. [e] Reaction temperature was 80 °C. The activated zinc powder and $(MeO)_3B$–THF modifications were run at 25 °C. The reaction times quoted from ref 1, 2, and 4 are probably not optimized but indicate when the reactions were worked up. [f] Reference 1.

reported significant rate enhancements of chemical reactions carried out in the presence of sonic waves. We are systematically exploring the effects of this phenomenon on chemical reactions, and in this paper we describe the beneficial effects that ultrasonic irradiation has on the Reformatsky reaction.

$$RR'C{=}O + BrCH_2CO_2Et + Zn \rightarrow RR'C(OH)CH_2CO_2Et$$

Our results are summarized in Table I. High yields and very short reaction times are the obvious advantages to this technique. Perhaps more important, however, is the elimination of the need to prepare zinc powder by the active metal reduction of anhydrous zinc chloride.[2,7] Also unnecessary is the use of trimethyl borate.[4]

The optimum reaction conditions call for dioxane solvent, a requirement that surprised us because of its tendency to promote enolization under conventional Reformatsky conditions.[8] In our hands, neither ether nor benzene, common Reformatsky solvents, produced high yields even after several hours of sonication. The reason for this selectivity is not obvious, but it may be related to the liquid strength of the media.[9]

Earlier studies on promoters demonstrated that small quantities of iodine improved the yields of β-hydroxy esters.[1] This was attributed to the suppression of enolization by iodine which reduced protonation of the zinc intermediate. Our observations were similar. In the presence of iodine and sonic waves the reaction times were not only reduced to minutes but the yields were also essentially quantitative. In the absence of iodine the sonicated mixture of zinc, α-bromoethyl acetate, and acetophenone reacted slowly (several hours) and gave no addition product. The recovery of ethyl acetate and acetophenone was quantitative. Potassium iodide was also a very effective additive, producing essentially the same yields as the iodine-promoted reactions but on a slower time scale (30 min to 3 h).

While it seems clear that iodine and potassium iodide aid the reaction by suppressing enolization, the increased rates at which zinc reacts with the bromo ester suggest that these promoters are also activating the zinc surface.[10] In the absence of sonic waves, iodine-promoted reactions gave modest yields of β-hydroxy esters in 24 h when the molar ratios listed in the Table were used. Very high yields of the β-hydroxy ester were obtained after several hours with simply stirring at room temperature when large excesses of zinc and iodine were used. With KI, stirring alone led to no product.

The stoichiometry of the small-scale reactions listed in Table I is not optimized. Very likely the same results could be achieved with less iodine than the 1:0.2 carbonyl compound/iodine molar ratio employed. On the larger scale reaction, for example, only a 38.5:1 ratio was needed to give complete reaction in <5 min (Experimental Section).

Experimental Section

The ketones and aldehydes and ethyl bromoacetate were used as obtained from commercial sources when the purity was ≥97% as indicated by ^1H NMR. Lower purity reagents were distilled or recrystallized to ≥97% purity. Dioxane was stirred over KOH, distilled from sodium, and stored over molecular sieves. Zinc dust was activated by the method of Cava.[11] Iodine and potassium iodide were used as obtained from commercial sources. The sonicator was a Branson Model 220 ultrasound laboratory cleaner (117 V, 150 W, 50/60 Hz). Proton magnetic resonance spectra were obtained on a Varian Model EM 390. Infrared spectra were obtained from a Perkin-Elmer Model 137.

General Procedure for Small-Scale Reactions. In a typical experiment, a dry nitrogen filled, 100-mL, single-necked,

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(7) It is pertinent to mention here that very reactive metal powders (M = Zn, Cr, Ni, Mg) are readily produced at room temperature if the reduction of the metal halide by lithium is done in the presence of sonic waves: Boudjouk, P.; Ohrbohm, W. H.; Han, B.-H.; Thompson, D., unpublished results.

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round-bottomed flask was charged with 10 mL of dioxane, 5 mmol of the carbonyl compound, 6 mmol of α-bromoethyl acetate, 9 mmol of zinc dust, and 1 mmol of iodine. The flask was then partially submerged in the sonicator in a place that produced the greatest agitation of the reaction mixture. The reaction conditions for potassium iodide aided reactions were similar except that relatively larger quantities of zinc (15 mmol) and promoter (4.2 mmol of KI) were used. The progress of the reaction, i.e., disappearance of carbonyl substrate, was monitored by ^{1}H NMR.

Product isolation was straightforward. The crude product was poured into an ice–water mixture (100 mL) which was extracted with methylene chloride (2 × 200 mL) followed by separation and drying of the organic fraction. Removal of the volatiles by flash evaporation and high vacuum ($\sim$0.1 torr) gave the desired β-hydroxy ester. Each product was characterized by IR, NMR, and mass spectroscopy. These spectra were compared to those of authentic samples. Yields in the table are based on quantities of isolated product with >95% purity by NMR.

Larger Scale Reformatsky Reaction Using *n*-Butanal and Ethyl Bromoacetate. An oven-dried, nitrogen-filled, 250-mL, single-necked, round-bottomed flask was charged with 25 mL of dioxane, 5.4 g (75 mmol) of butanal, 15 g (90 mmol) of ethyl bromoacetate, and 8.5 g (130 mmol) of zinc dust. The flask was immersed to the solvent level in the sonicator, and iodine was added to the slurry until it became exothermic. This required about 0.5 g ($\sim$2 mmol) of I_2. The progress of the reaction was monitored by following the disappearance of the aldehyde proton (triplet, δ 9.8) by ^{1}H NMR. The absorption was gone in <5 min.

The product mixture was poured slowly into an ether–ice slurry with stirring, and 1 g of KI was added to remove I_2 from the organic layer. This was extracted with ether (2 × 200 mL), and the combined extracts were dried over $CaCl_2$. Removal of the volatiles by flash evaporation followed by vacuum distillation gave 10.9 g (91%) of ethyl 3-hydroxyhexanoate [bp 75 °C (0.1 torr)] which was identified by ^{1}H NMR and mass spectroscopy.

Acknowledgment. We thank the Air Force Office of Scientific Research for financial support through Grant No. 80-0239.

Registry No. 1, 123-72-8; 2, 124-13-0; 3, 100-52-7; 4, 66-77-3; 5, 66-99-9; 6, 120-92-3; 7, 123-19-3; 8, 98-86-2; 9, 119-61-9; $C_3H_7CH(OH)CH_2CO_2Et$, 2305-25-1; $C_7H_{15}CH(OH)CH_2CO_2Et$, 6071-25-6; $C_6H_5CH(OH)CH_2CO_2Et$, 5764-85-2; 1-$C_{10}H_7CH(OH)CH_2CO_2Et$, 83463-90-5; 2-$C_{10}H_7CH(OH)CH_2CO_2Et$, 83463-91-6; $C_3H_7(C_3H_7)C(OH)CH_2CO_2Et$, 10297-62-8; $C_6H_5(CH_3)C(OH)CH_2CO_2Et$, 2293-60-9; $C_6H_5(C_6H_5)C(OH)CH_2CO_2Et$, 894-18-8; $BrCH_2CO_2Et$, 105-36-2; I_2, 7553-56-2; 1-[(ethoxycarbonyl)methyl]-1-cyclopentanol, 3197-76-0.

Mechanistic Diversity in the Acetamidomercuration of Substituted Cyclohexenes[1]

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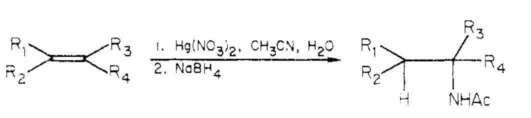
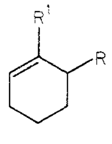
Received May 4, 1982

Reaction between an alkene and a mercury(II) salt in the presence of acetonitrile, followed by reductive cleavage of the intermediate organomercurial, constitutes a synthetic procedure for overall addition of the elements of acetamide to the carbon–carbon double bond (eq 1).[2]

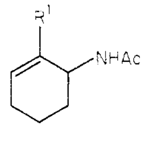


(1)

However, unlike its better-known counterpart, the oxymercuration–demercuration of alkenes,[3] the sequence represented by eq 1 has not been applied to a very wide range of structural types. In fact, studies to date have been limited mainly to monosubstituted ethylenes, cyclohexene, and cyclopentene, although Brown and Kurek[2] reported failure to obtain the expected product from 2-methyl-1-pentene (the product was not identified), and Delpech and Khuong-Huu[4] reported formation of a series of allylic amides from a steroidal ethylidenecyclopentane. We recently had occasion to attempt the acetamidomercuration–demercuration of several substituted cyclohexenes (**1a–d**) and observed a variety of reactions in addition to that embodied above as eq 1. Although we plan no further work in this area, we wish to call our results to the attention of others who may have interest in this reaction.



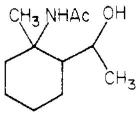
1a, $R^1 = C_6H_5$; $R = CH(OH)CH_3$
b, $R^1 = C_6H_5$; $R = H$
c, $R^1 = CH_3$; $R = CH(OH)CH_3$
d, $R^1 = CH_3$; $R = H$



2, $R = C_6H_5$
3, $R = CH_3$

Lithium aluminum hydride reduction of 6-acetyl-1-phenylcyclohexene[5] afforded 6-(1-hydroxyethyl)-1-phenylcyclohexene (**1a**), the respective diastereomers of which could be separated cleanly by medium-pressure liquid chromatography (MPLC)[6] over silica gel. Reduction of 6-acetyl-1-methylcyclohexene[5] afforded the corresponding alcohol (**1c**), the diastereomers of which were not separable in this case by either TLC or MPLC. Reaction of either diastereomer of **1a** under standard acetamidomercuration conditions, that is, mercuric nitrate in wet acetonitrile at room temperature for 0.5–24 h,[2] afforded the allylic amide **2** in 80% isolated yield. 1-Phenylcyclohexene (**1b**) also afforded **2**, in 70% yield, under the same conditions. In addition to the carbon–carbon bond cleavage observed with **1a**, these reactions are notable for the ease with which reaction takes place, given the inertness of **1a** (our observation) and **1b**[3] toward oxymercuration, and the surprising mildness with which allylic oxidation of **1b** takes place, in view of the considerably more vigorous conditions required to effect allylic oxidation of alkenes by using mercuric acetate in acetic acid.[7]

The similarity in reaction products from **1a** and **1b** does not carry over to their methyl analogues **1c** and **1d**. 1-Methylcyclohexene (**1d**) does undergo allylic oxidation to amide **3** in 80% yield, but **1c** is converted to a pair of products consisting of the expected product (**4**, 52%) and the allylic amide **5** (37%). **1c** is also converted to diol **6** (>80%) under the usual[3] oxymercuration conditions. Both



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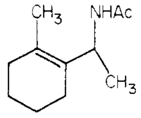

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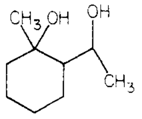

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(1) Financial support was supplied by the National Science Foundation (Grant No. CHE 79-04907).

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