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Tetrahedron 60 (2004) 2035–2041
Tetrahedron

Synthesis of β-lactams and β-aminoesters via high intensity ultrasound-promoted Reformatsky reactions☆

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Received 31 October 2003; revised 6 January 2004; accepted 6 January 2004

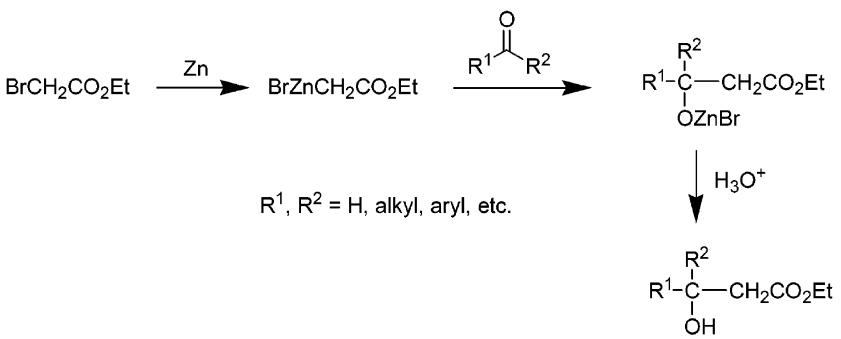
Abstract—Reformatsky reactions of an imine, an α-bromoester, zinc dust and a catalytic amount of iodine in dioxane under high intensity ultrasound (HIU) irradiation from an ultrasonic probe are explored. A series of 16 aldimines with varying electronic demands is evaluated as potential electrophiles for reactions with three α-bromoesters of differing steric demands. This HIU method is successful for both enolizable and non-enolizable imines affording in short reaction times high yields of a β-lactam, the corresponding β-aminoester or a mixture of the two products depending on the identity of the imine and α-bromoester.

1. 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.

The Reformatsky reaction is not limited to aldehydes and ketones as acceptors. Gilman and Speeter[12] first described formation of β-lactams from imines. Functioning as electrophiles in Reformatsky reactions with α-haloesters, imines can provide β-lactams, the corresponding β-aminoesters, or a mixture of the two products (Scheme 2). Kapoor and co-workers[13] report that the relative abundances of these two products are sensitive to the electron-withdrawing nature of the nitrogen atom in the imine. In addition, Dardoize and co-workers[14] found that the relative amounts of β-lactam and β-aminoester to be temperature dependent in ethereal solvents.

In some cases, ultrasonic irradiation can be utilized as an alternative energy source for organic reactions ordinarily accomplished by heating.[15,16] Boudjouk and Han[17] were



Scheme 1. The Reformatsky reaction.

☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tet.2004.01.002

Keywords: Reformatsky reaction; High intensity ultrasound; β-Lactams.
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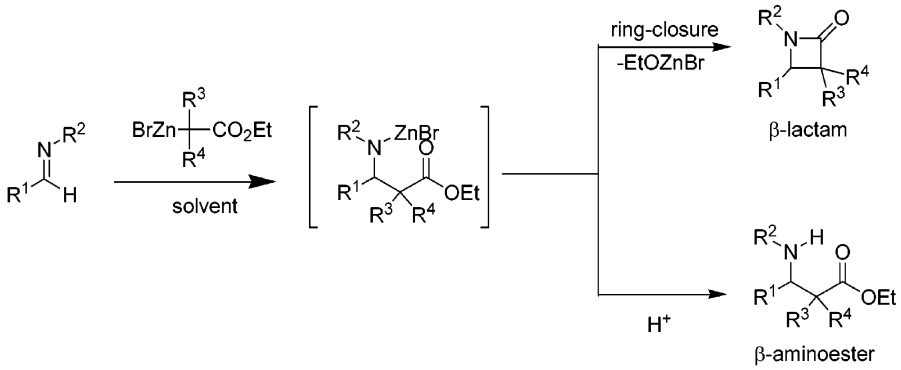
doi:10.1016/j.tet.2004.01.002



Scheme 2. Potential products in the Reformatsky reaction of imines and α-bromoesters.

first to report that low intensity ultrasound (LIU) from a laboratory cleaning bath greatly improved the rates and yields from Reformatsky reactions of simple aldehydes and ketones with ethyl bromoacetate. However, the zinc dust still had to be 'activated' using the 'Cava' method[18] and the reported conditions called for dried, distilled dioxane as the optimal solvent. Several years later, Bose and co-workers[19] reported a considerable increase in yield, when compared to thermal methods, of β-lactams in LIU-promoted Reformatsky reactions of a series of aryl-substituted imines with methyl bromoacetate in dioxane at room temperature for 4–10 h. However, when this ester component was replaced with methyl α-bromopropionate or methyl α-bromo-β-phenylpropionate, no β-lactam formation was observed although the reactants were consumed. Therefore, the LIU procedure is limited to formation of γ-unsubstituted β-lactams. It is also important to note that the zinc used by Bose and co-workers was 'activated' by washing with nitric acid in order to achieve high yields. When un-activated zinc granules were employed under LIU irradiation, the yields were comparable to those from thermal Reformatsky reactions.

LIU from an ultrasonic cleaner has considerably less power when compared to high intensity ultrasound (HIU) from a direct immersion horn,[20] which can lead to reproducibility problems due to the lower power involved for the former.[21] We have previously reported[22–24] the utility of HIU for Reformatsky reactions of ketones and α-bromoesters and now wish to present the results from our study of HIU-initiated Reformatsky reactions with imines.

2. Results and discussion

2.1. Preparation of imine reactants

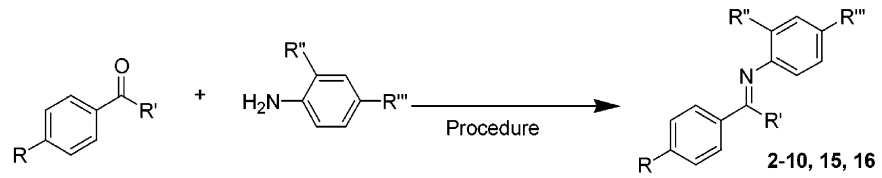
The benzal- or anilino-substituted *N*-benzylideneanilines **2**–**10** and ketone anils **15** and **16** (Table 1) were prepared by adapting two different literature procedures.[25,26] Imines **2**, **3** and **7** were synthesized by Procedure A,[25] which involved stirring the two neat reactants at room temperature. However, for benzaldehyde and *o*-methoxyaniline (entry 8), the reaction was incomplete. Addition of benzene to the neat reactants and refluxing for three days also failed to give complete reaction. Changing to Procedure B,[26] which involved the addition of 5 Å molecular sieves and benzene to the two reactants and stirring at room temperature for 24 h, gave imine **9** in 98% yield. By Procedure B, imines **4**–**6**, **8**–**10**, **15** and **16** were obtained in very high to quantitative yields. Treatment of benzophenone with aniline by Procedure A (entry 12) failed to give the condensation product. Changing to Procedure B produced the corresponding imine in quantitative yield (entry 13). In similar fashion, the imine from acetophenone and aniline was obtained in 98% yield by Procedure B (entry 11).

2.2. HIU Reformatsky reactions

The HIU Reformatsky reactions were conducted in a 20 °C thermostatted cooling bath to control the exothermic reaction and cool the contents from frictional heating produced by direct introduction of HIU irradiation. The reaction flask was partially immersed in the cooling bath during ultrasonication and the in situ temperature rose to 41–42 °C, as determined by a calorimetry experiment. The HIU Reformatsky reactions were performed with unactivated zinc dust, an imine, the α-bromoester, and a catalytic amount of iodine in reagent-grade dioxane with no additional stirring. A series of 16 imines with varying electronic properties was evaluated as potential electrophiles for reactions with three α-bromoesters of differing steric demands.

The investigation began with commercially available *N*-benzylideneaniline (**1**), 1.5 equiv. ethyl bromoacetate, 0.2 equiv. of iodine and 1.8 equiv. of zinc dust in reagent-grade dioxane. The LIU procedure by Bose,[19] which reportedly gave a 70% yield of the corresponding β-lactam **23** was repeated. In our hands, LIU irradiation gave only a very small amount of β-aminoester **17** (2% by GC) together with large amounts of unreacted starting materials. Upon changing from LIU to HIU, complete consumption of the reactants was achieved within 5 min. Results from the initial reactions of *N*-benzylideneaniline (**1**) with ethyl bromoacetate under HIU irradiation are presented in Table 2. For entry 1, the crude product mixture contained a 1:1 mixture of β-aminoester **17** and β-lactam **23**. When a longer reaction time was employed (entry 2), the relative proportion of β-lactam increased. Due to the aforementioned temperature dependence noted by Dardoize and co-workers[14] that influenced the relative amounts of β-lactam and β-aminoester in thermal Reformatsky reactions, the effect of temperature was examined for the HIU-promoted reaction. Lowering of the bath temperature from 20 to 0 °C (entry 3) gave a larger proportion of

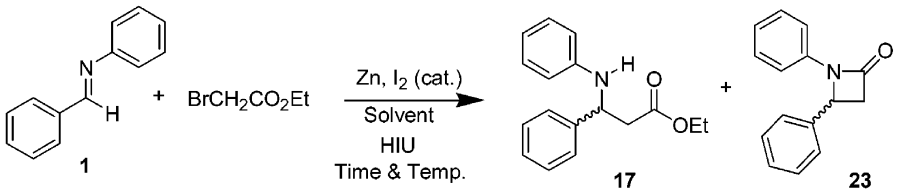
Table 1. Preparation of imines **2**–**10**, **15**, and **16** for Reformatsky reactions



Entry	R	R′	R″	R‴	Prod.[a]	Proc.[b]	Yield[c] (%)
1	Cl	H	H	H	**2**	A	95
2	MeO	H	H	H	**3**	A	96
3	CF_3	H	H	H	**4**	B	98
4	$N(CH_3)_2$	H	H	H	**5**	B	99
5	H	H	H	Cl	**6**	B	97
6	H	H	H	MeO	**7**	A	100
7	H	H	H	CF_3	**8**	B	99
8	H	H	OMe	H	**9**	A	I[d]
9	H	H	OMe	H	**9**	B	98
10	H	H	Et	H	**10**	B	98
11	H	Me	H	H	**15**	B	98
12	H	Ph	H	H	—	A	NR[e]
13	H	Ph	H	H	**16**	B	100

[a] Spectroscopic data are given in Supplementary Material.
[b] Procedure A (*Organic Syntheses*; Wiley: New York, 1941; Coll. Vol. I, p 80); Procedure B (*J. Org. Chem.* **1971**, *36*, 1570).
[c] Isolated yield.
[d] Incomplete reaction as determined by ^{1}H NMR spectroscopy.
[e] No reaction after refluxing in benzene.

Table 2. Reaction of **1** with ethyl bromoacetate



Entry	Time (min)	Temperature (°C)[a]	Solvent	**17/23** ratio[b]
1	5	20	Dioxane	1.0
2	60	20	Dioxane	0.4
3	5	0	Dioxane	5.2
4	60	50	Dioxane	0.2
5	30	20	THF	0.6

[a] Bath temperature.
[b] Ratio determined by GC analysis of the crude reaction product mixture.

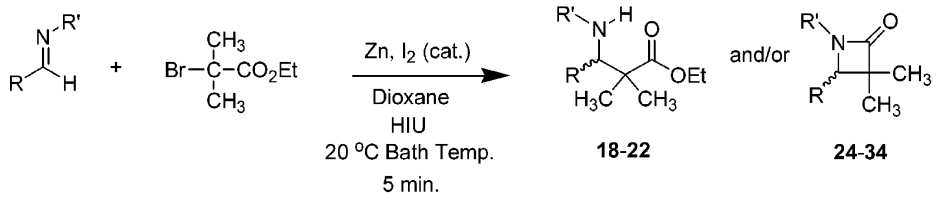
β-aminoester **17** (5.2 times). Entry 4 shows the effect of increasing the bath temperature from 20 to 50 °C with sonication for 60 min. When compared to entry 2, the higher temperature resulted in an enhanced proportion (2 times) of β-lactam **23**. Shankar and co-workers[27] reported that LIU-induced reactions of this type in dioxane gave predominantly the β-aminoester with only traces of β-lactam. Since THF has been used in the synthesis of β-lactams in thermal Reformatsky reactions,[28] it was examined as a solvent for the HIU-promoted reaction resulting in a slightly greater proportion of β-lactam **23** than observed in dioxane (compare entries 2 and 5).

Unsuccessful in our attempts to obtain solely the β-lactam or β-aminoester product from ethyl bromoacetate, the more hindered DL-ethyl α-bromopropionate was tested. This ester provided 3.8 times as much β-aminoester as β-lactam.

The even more hindered ester ethyl α-bromoisobutyrate was then evaluated in reaction with **1** and afforded a 94% isolated yield of β-lactam **24** after 5 min of HIU irradiation. In light of this result, ethyl α-bromoisobutyrate was selected as the α-bromoester component for a series of HIU-initiated Reformatsky reactions designed to probe the importance of electronic effects of substituents in the imine component.

To determine the influence of substituents on the benzal- or anilino-ring of *N*-benzylideneaniline (**1**) upon β-lactam formation, a series of imines was examined (Table 3). Substituents of *p*-Cl, *p*-OMe, *p*-CF_3 and *p*-NMe_2 on the benzal ring (entries 2–5) and *p*-Cl, *p*-OMe, *p*-CF_3, *o*-OMe and *o*-Et on the anilino ring (entries 6–10) were chosen. These substituents provide electron-donating (OMe and NMe_2), weakly electron-withdrawing (Cl), and strongly electron-withdrawing (CF_3) groups. With *p*-Cl, *p*-OMe, or

Table 3. β-Lactams/β-aminoesters (AE) prepared via HIU Reformatsky reactions



Entry	R	R′	Prod (s).	Yield (%)[a]	
				β-AE	β-Lactam
1	Ph	Ph	**24**	0	94
2	*p*-ClC_6H_4	Ph	**25**	0	72
3	*p*-$MeOC_6H_4$	Ph	**26**	0	86
4	*p*-$CF_3C_6H_4$	Ph	**27**	0	79
5	*p*-$Me_2NC_6H_4$	Ph	**28**	0	72
6[b]	Ph	*p*-ClC_6H_4	**18**,**29**	1.0	4.5
7	Ph	*p*-$MeOC_6H_4$	**30**	0	79
8	Ph	*p*-$CF_3C_6H_4$	**19**	82	0
9	Ph	*o*-$MeOC_6H_4$	**20**	92	0
10	Ph	*o*-EtC_6H_4	**31**	0	82
11[b]	Ph	Me	**21**,**32**	1.0	10
12	Ph	*t*-Bu	**33**	0	93
13	Ph	Bn	**34**	0	92
14	Ph	$SO_2C_6H_4$	**22**	98	0

[a] Isolated yield.
[b] Ratio determined by GC analysis of the crude product mixture.

p-CF_3 or *p*-NMe_2 on the benzal-ring (entries 2–5), only the corresponding β-lactams **25**–**28** were isolated in 72–86% yields after 5 min of HIU irradiation. However, when the analogous substituents were present on the anilino-ring, a substituent effect was observed. For entry 7, the *p*-OMe substituent gave only β-lactam **30** in 79% yield. With *p*-Cl (entry 6), a mixture of β-aminoester **18** and β-lactam **29** was produced. GC and ^{1}H NMR analysis of the crude product after workup revealed 4.5 times as much β-lactam as β-aminoester. With *p*-CF_3 (entry 8), only β-aminoester **19** was produced in 82% yield. This substituent effect can be explained by consideration of the mechanism (Scheme 2) and the electronic properties of the substituent. A lack of sensitivity to substituents on the benzal-ring arises from their inability to affect the nucleophilicity of the nitrogen atom. However, when these substituents are present on the anilino-ring, they have a direct inductive effect on the nitrogen atom, and, therefore, can influence ring closure to the β-lactam. For electron-donating *p*-OMe, ring-closure to form β-lactam **30** is favored. Weakly electron-withdrawing *p*-Cl reduces the nucleophilicity of the nitrogen atom, thereby decreasing the amount of β-lactam **29** formed. Strongly electron-withdrawing *p*-CF_3 markedly diminishes the nucleophilicity of the nitrogen atom, which eliminates the ring-closure reaction altogether with β-aminoester **19** as the sole product.

An *o*-OMe substituent on the anilino ring has been shown by Adrian and co-worker[29] to give preferentially β-aminoesters with a variety of imines and methyl bromoacetate in dichloromethane at room temperature in a 'silent' reaction. The preference for β-aminoester isolation was attributed to 'an inductive effect arising from close proximity of the *o*-OMe substituent to the nitrogen–zinc bond, thus reducing its nucleophilic character.' In the present study, the *o*-OMe substituent on the anilino ring under HIU irradiation with ethyl α-bromoisobutyrate gave the corresponding β-aminoester **20** in 92% yield (entry 9). To probe the influence of steric effects in the production of β-aminoester **20**, another reaction was performed in which *o*-OMe was replaced by *o*-Et (entry 10). In this case, β-lactam **31** was produced in 82% yield, which reveals that steric effects are not solely responsible for formation of the β-aminoester, since Et and OMe substituents are similar in size.

Entries 11–14 demonstrate that the HIU method is not limited to *N*-aryl imines. Enolizable imines (entries 11 and 13) are also compatible with this HIU method. *N*-benzylidenemethylamine gave a 10:1 favoring of β-lactam **32** over β-aminoester **21** (entry 11). Hindered aliphatic *N*-benzylidene-*t*-butylamine yielded 93% of β-lactam **33** after 5 min of HIU irradiation (entry 12). *N*-Benzylidenebenzylamine gave a 92% yield of β-lactam **34** (entry 13). When *N*-benzylidenebenzenesulfonamide was used as the imine component (entry 14), only β-aminoester **22** was isolated in 98% yield. This results from electron-withdrawal by the sulfonyl group thereby reducing the nitrogen atom nucleophilicity and eliminating the ring closure reaction.

To probe the scope of these HIU-promoted Reformatsky reactions further, two ketimines were examined as potential electrophiles. Acetophenone anil (**15**) failed to react with the simplest ester, ethyl bromoacetate, in 5 min of HIU irradiation with recovery of unreacted imine, acetophenone and aniline (from hydrolysis during workup). Benzophenone anil (**16**) gave no reaction with either ethyl bromoacetate after 5 or 60 min of HIU irradiation or ethyl α-bromoisobutyrate after 5 min of HIU irradiation with recovery of unreacted imine. Therefore, ketone anils are judged to be too hindered to react under these HIU

conditions. Benzophenone anil has been reported to be an ineffective electrophile with lithium enolates as well.[30]

In further effort to define the scope of the HIU-promoted Reformatsky-type reaction, two cyclic α-bromoesters were examined. *N*-Benzylideneaniline (**1**) was reacted with commercially available methyl α-bromocyclohexanecarboxylate for both 5 and 60 min and ethyl α-bromocyclobutanecarboxylate for 5 min under HIU irradiation in attempts to form spiro-lactams. However, neither of these cyclic α-bromoesters reacted and only unreacted starting materials were recovered. Thus, cyclic α-bromoesters are found to be unreactive under these HIU reaction conditions. Bergbreiter and Newcomb[30] report that the thermal reaction between the lithium enolate of ethyl cyclohexanecarboxylate and *N*-benzylideneaniline gave a good yield of the corresponding spirolactam.

3. Conclusions

HIU-induced Reformatsky reactions of various imines and α-bromoesters have been examined. The HIU-induced reactions of aldimines with ethyl α-bromoisobutyrate afford good yields of either a β-aminoester or β-lactam, in most cases depending on the identity of the imine, in short reaction times. The HIU procedure was successful for both enolizable and non-enolizable imines. Only when the reactants become bulky did the HIU method fail. It was not necessary to 'activate' the zinc and reagent-grade dioxane was used as the solvent. These factors, as well minimal purification of the crude products, make this HIU method attractive for performing Reformatsky reactions.

4. Experimental

Zinc dust (Fisher, 99.9%) was used directly unless otherwise noted. THF was distilled from sodium-benzophenone ketyl radical. Iodine crystals were used as obtained from a commercial source (Mallickrodt). Dioxane (EM Science) was used without drying. The imines and α-bromoesters were utilized as obtained from commercial sources or prepared by published procedures[25,26] and were utilized without purification. All compounds gave satisfactory physical and spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded at 499.7 or 300.1 and 125.7 MHz, respectively) in $CDCl_3$ with TMS as internal standard. HIU was provided by an ultrasonic processor probe system (20 kHz, 600 W, 13 mm tip diameter at a power level of 7) from Sonics and Materials, Inc. (Newton, CT) that was modified in-house for insertion into a custom-designed and -fabricated, four-armed, 25-mL, glass sonochemical reaction vessel. During irradiation, the reaction vessel was cooled in a 20 °C circulating temperature bath. LIU (Low Intensity Ultrasound) was produced with a Branson Model 2510 ultrasonic laboratory cleaner (117 V, 100 W, 40 kHz). GC analyses was performed on a HP-1 19091Z-413E 30 m×0.32 mm×0.25 μm 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).

4.1. General procedure for Reformatsky reactions under HIU irradiation

The 25-mL, 4-armed sonochemical reaction vessel flask was capped with rubber septa and flushed with nitrogen for several minutes. Then zinc dust (1.18 g, 18 mmol) and iodine (0.50 g, 2.0 mmol) were added. Half of the dioxane (12.5 mL) solvent was added and nitrogen was bubbled through the mixture. The imine (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 100 mL of 2% hydrochloric acid 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 ($MgSO_4$) 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–hexane (1:1/v:v) as eluent and, if necessary, Kugelrohr evaporation of the remaining volatile impurities under high vacuum (0.3 Torr) to give the product.

4.1.1. 3,3-Dimethyl-1,4-diphenyl-2-azetidinone (24). The title compound was prepared in 94% yield after chromatography and recrystallization from methanol; white solid; mp 145–148 °C (lit. mp 147.5–148.5 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.52 (s, 3H), 4.80 (s, 1H), 6.99–7.08 (m, 1H), 7.16–7.22 (m, 2H), 7.22–7.27 (m, 2H), 7.28–7.40 (m, 5H); ^{13}C NMR δ 17.9, 22.7, 55.3, 66.4, 117.2, 123.6, 126.5, 127.9, 128.6, 128.9, 135.5, 137.8, 171.4. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.38; H, 6.54; N, 5.60.

4.1.2. 4-(4-Chlorophenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (25). The title compound was obtained in 72% yield after chromatography, flash Kugelrohr distillation up to 124 °C and recrystallization from hexanes; peach solid; mp 87–89 °C (lit. mp 91–92.5 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.50 (s, 3H), 4.78 (s, 1H), 6.90–7.09 (m, 1H), 7.09–7.18 (m, 2H), 7.18–7.26 (m, 2H), 7.26–7.37 (m, 4H); ^{13}C NMR δ 17.8, 22.5, 55.3, 66.5, 116.9, 123.6, 127.8, 128.7, 128.9, 133.6, 134.0, 137.4, 170.9. Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.79; H, 5.70; N, 4.93.

4.1.3. 4-(4-Methoxyphenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (26). The title compound was realized in 86% yield after chromatography, flash Kugelrohr distillation up to 144 °C and recrystallization from hexanes; white solid; mp 88–90 °C (lit. mp 87–89 °C);[30] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.50 (s, 3H), 3.78 (s, 3H), 4.75 (s,

1H), 6.83–6.93 (m, 2H), 6.96–7.07 (m, 1H), 7.07–7.16 (m, 2H), 7.19–7.29 (m, 2H), 7.29–7.36 (m, 2H); ^{13}C NMR δ 17.9, 22.7, 55.1, 55.3, 66.1, 114.0, 117.2, 123.5, 127.3, 127.7, 128.9, 137.8, 159.3, 171.5. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.14; H, 6.86; N, 5.06.

4.1.4. 3,3-Dimethyl-1-phenyl-4-(4-trifluoromethylphenyl)-2-azetidinone (27). The title compound was prepared in 79% yield after chromatography, flash Kugelrohr distillation up to 130 °C, and recrystallization from hexanes; white solid; mp 91–94 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3H), 1.55 (s, 3H), 4.87 (s, 1H), 7.01–7.14 (m, 1H), 7.20–7.31 (m, 4H), 7.34 (d, J=7.9 Hz, 2H), 7.62 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 17.9, 22.7, 55.7, 65.8, 117.0, 123.9, 125.64, 125.66, 125.69, 125.73, 126.9, 137.5, 139.8, 170.9. Anal. Calcd for $C_{18}H_{16}F_3NO$: C, 67.70; H, 5.05; N, 4.39. Found: C, 67.93; H, 5.03; N, 4.39.

4.1.5. 4-(4-Dimethylaminophenyl)-3,3-dimethyl-1-phenyl-2-azetidinone (28). The title compound was obtained in 72% yield after chromatography and recrystallization from hexanes; white solid; mp 139–141 °C (lit. mp 141–142 °C);[28] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.47 (s, 3H), 2.92 (s, 6H), 4.71 (s, 1H), 6.67 (d, J=8.7 Hz, 2H), 6.95–7.03 (m, 1H), 7.05 (d, J=8.5 Hz, 2H), 7.14–7.28 (m, 2H), 7.28–7.41 (m, 2H); ^{13}C NMR δ17.8, 22.6, 40.2, 55.2, 66.3, 112.1, 117.2, 122.4, 123.3, 127.4, 128.8, 137.9, 150.0, 171.8. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.82; H, 7.56; N, 9.60.

4.1.6. 1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenyl-2-azetidinone (30). The title compound was realized in 79% yield after chromatography and recrystallization from dichloromethane–hexanes; light purple solid; mp 140–144 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1748 cm^{-1}; ^{1}H NMR^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.51 (s, 3H), 3.74 (s, 3H), 4.77 (s, 1H), 6.72–6.85 (m, 2H), 7.13–7.23 (m, 2H), 7.23–7.29 (m, 2H), 7.29–7.39 (m, 3H); ^{13}C NMR δ 17.9, 22.7, 55.31, 55.33, 66.5, 114.2, 118.4, 126.5, 127.9, 128.6, 131.4, 135.6, 155.8, 170.8. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.08; H, 6.71; N, 5.00.

4.1.7. Ethyl 2,2-Dimethyl-3-phenyl-3-(4-trifluoromethylphenylamino)propionate (19). The title compound was prepared in 82% yield after chromatography, flash Kugelrohr distillation up to 135 °C, and recrystallization from hexanes; yellow solid; mp 52–54 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3405, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.11–1.20 (m, 6H), 1.30 (s, 3H), 4.06–4.19 (m, 2H), 4.46 (d, J=7.6 Hz, 1H), 5.32 (d, J=7.4 Hz, N–H), 6.50 (d, J=8.7 Hz, 2H), 7.15–7.35 (m, 7H); ^{13}C NMR δ 14.0, 20.7, 24.8, 46.6, 61.0, 64.2, 112.4, 126.34, 126.37, 126.40, 126.43, 127.7, 128.1, 128.2, 138.5, 149.4, 176.4. Anal. Calcd for $C_{20}H_{22}F_3NO_2$: C, 65.74; H, 6.07; N, 3.83. Found: C, 65.53; H, 6.12; N, 3.82.

4.1.8. Ethyl 3-(2-methoxyphenylamino)-2,2-dimethyl-3-phenylpropionate (20). The title compound was obtained in 92% yield after chromatography, flash Kugelrohr distillation up to 132 °C and recrystallization from hexanes; light yellow solid; mp 63–64 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3429, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09–1.21 (m, 6H), 1.25 (s, 3H), 3.84 (s, 3H), 4.02–4.19 (m, 2H), 4.55 (d, J=7.6 Hz, 1H), 5.36 (d, J=7.4 Hz, N–H), 6.25–6.36 (m, 1H), 6.48–6.58 (m, 1H), 6.58–6.67 (m, 1H), 6.67–6.73 (m, 1H), 7.11–7.21 (m, 1H), 7.21–7.34 (m, 4H); ^{13}C NMR δ 13.9, 20.5, 24.2, 46.9, 55.5, 60.7, 64.0, 109.2, 110.6, 116.1, 120.9, 127.2, 127.8, 128.3, 136.9, 139.4, 146.7, 176.3. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.58; H, 7.72; N, 4.35.

4.1.9. 1-(2-Ethylphenyl)-3,3-dimethyl-4-phenyl-2-azetidinone (31). The title compound was prepared in 82% yield after chromatography and recrystallization from hexanes; white solid; mp 104–105 °C; IR (deposit from CH_2Cl_2 on a NaCl plate) 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.28 (t, J=7.6 Hz, 3H), 1.53 (s, 3H), 2.73–2.90 (m, 2H), 5.04 (s, 1H), 7.07–7.13 (m, 2H), 7.14–7.19 (m, 2H), 7.19–7.24 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR δ 14.0, 18.3, 22.5, 24.9, 54.5, 68.1, 122.5, 126.1, 126.2, 126.5, 127.7, 128.4, 129.3, 134.1, 136.1, 137.2, 171.9. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.76; H, 7.58; N, 5.03.

4.1.10. 1-*tert*-Butyl-3,3-dimethyl-4-phenyl-2-azetidinone (33). The title compound was realized in 93% yield after chromatography and recrystallization from hexanes; light yellow solid; mp 81–83 °C (lit. mp 85.5–87 °C);[29] IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3H), 1.31 (s, 9H), 1.35 (s, 3H), 4.34 (s, 1H), 7.20–7.32 (m, 3H), 7.32–7.41 (m, 2H); ^{13}C NMR δ17.3, 22.6, 53.3, 53.7, 66.1, 123.5, 126.8, 127.6, 128.1, 138.6, 174.6. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.86; H, 9.22; N, 6.11.

4.1.11. 1-Benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (34). The title compound was prepared in 92% yield after chromatography, flash Kugelrohr distillation up to 140 °C and hexanes wash; colorless oil; IR (neat) 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (s, 3H), 1.35 (s, 3H), 4.42 (dd, J=14.9, 14.9 Hz, 2H), 4.10–4.20 (s, 1H), 7.08–7.19 (m, 4H), 7.22–7.33 (m, 4H), 7.33–7.41 (m, 2H); ^{13}C NMR δ 17.6, 22.2, 44.0, 56.0, 65.7, 126.7, 127.5, 127.8, 128.3, 128.5, 128.6, 135.7, 135.9, 174.0. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.20; H, 7.15; N, 5.23.

4.1.12. Ethyl 3-benzenesulfonylamino-2,2-dimethyl-3-phenylpropionate (22). The title compound was obtained in 98% yield after chromatography and recrystallization from ethyl acetate–hexanes; white solid; mp 128–130 °C; IR (deposit from CH_2Cl_2 solution onto a NaCl plate) 3269, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.19 (t, J=7.2 Hz, 3H), 1.28 (s, 3H), 4.08 (q, J=7.1 Hz, 2H), 4.45 (d, J=9.9 Hz, 1H), 6.45 (d, J=9.8 Hz, NH), 6.81–6.96 (m, 2H), 6.96–7.09 (m, 3H), 7.10–7.22 (m, 2H), 7.25–7.36 (m, 1H), 7.44–7.63 (m, 2H); ^{13}C NMR δ 13.9, 22.1, 24.3, 46.9, 61.0, 64.6, 126.7, 127.3, 127.7, 127.9, 128.3, 131.7, 136.7, 140.4, 175.9. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.28; H, 6.49; N, 3.94.

4.2. 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 mmol) were added to the flask. Half of the dioxane (12.5 mL) solvent was added. The imine (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 thermostatted. At the end of the reaction, 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 100 mL of 2% hydrochloric acid and the rinsings were added to the separatory funnel. The 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, which was analyzed by ^1H NMR spectroscopy and GC.

Acknowledgements

This research was supported by a grant from the PG Research Foundation. We thank NSF for Grant CHE-9808436 that was used to purchase the Varian Unity INOVA NMR spectrometer. R.R.M. was a Welch Summer Student Program participant.

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