Article

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Chemoselective Synthesis of β-Amino Ester or β-Lactam via Sonochemical Reformatsky Reaction

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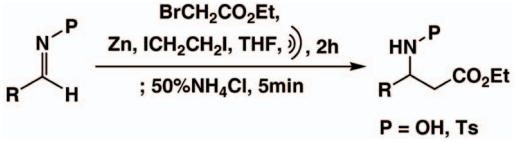
A series of β-amino esters were synthesized by the reaction of *N*-tosyl aldimine or *N*-hydroxy aldimine with bromoacetate by sonochemical Reformatsky reaction. The β-*N*-hydroxyamino ester was obtained and the formed sensitive hydroxylamino functionality was resistant under the reaction condition. The β-lactam also was synthesized by the reaction of *N*-*p*-methoxy aldimine as reacting substrate under this sonochemical Reformatsky reaction condition.

Keywords: Sonochemical Reformatsky reaction; *N*-Hydroxy aldimine; β-*N*-Hydroxyamino ester; β-Lactam.

INTRODUCTION

Since the discovery of the addition of zinc ester enolates to aldehydes by Reformatsky in 1887, this potentially useful β-hydroxyalkanoate synthesis has found wide application in organic synthesis.[1,2] Reformatsky reaction has been recognized as the most useful methods for the formation of carbon–carbon bonds, become a valuable tool in modern organic synthesis, especially the synthesis of β-amino acid[3,4] and β-Lactam.[5,6] The simple and straightforward preparation of β-amino ester or β-lactam is the addition of Reformatsky reagent to an aldimine instead of aldehyde. In generally, a mixture of β-amino ester and β-lactam was generated by the reaction of Reformatsky reagent with aldimine and the complication of the reaction product may manipulate by the introducing patterns of aldimine, solvent or temperature.[7-9] This reaction was sensitive to the nature of the nitrogen substituent of the aldimine and a restraining property of the *N*-*o*-methoxyphenyl imine which lead to sole formation of the β-amino ester was observed and reported.[7] To our knowledge, *N*-hydroxyamino esters could not be generated from the reaction of bromoacetate with *N*-hydroxy aldimine (oxime) by Reformatsky reaction condition because the hydroxyl group was not compatible to zinc enolate.[10] Our laboratory previously developed a simple and an efficient method for the synthesis of β-amino-α,β-unsaturated ester by the addition of bromoacetate to nitrile under a sonochemical Blaise reaction[11] which provide *in situ* activation of zinc[12] without pre-activation of metal before introduction. Thus, we further investigated this sonochemical Barbier-type reaction method for the preparation of β-amino ester by reaction of ethyl bromoacetate with aldimine.[13-16] Herewith, we wish to report the syntheis of β-amino ester by the addition reaction of bromoacetate to *N*-tosyl aldimine and *N*-hydroxy aldimine under sonochemical Reformatsky reraction condition (Scheme I).

Scheme I



RESULTS AND DISCUSSIONS

The feasibility of our approach was first tested by adding ethyl bromoacetate (1.3 mmol) to a mixture of zinc (3.0 mmol), 1,2-diiodoethane (0.5 mmol) and *N*-tosyl aldimine (1.0 mmol) in THF solution (10 mL) and then the reaction mixture was sonicated for 2 hours followed by quenching with water and then the reaction mixture was stirred for 5 minutes (Scheme II). The expected product β-*N*-tosylamino ester was obtained with 57% by using water as reaction quencher. The yield of β-*N*-tosylamino ester was improved to 65% accompanied with β-lactam (5%) when more acidic solution (1 M HCl) was introduced as quencher. The better yield (85%) was obtained when 3.5 equivalent of Zn, 1.0 equivalent of 1,2-diiodoethane and 1.6 equivalent of etehyl bromoacetate were introduced under the reaction condition and then quenched with 50% aqueous NH_4Cl solution. Our previously investigations showed that the reaction mixture of Zn and ICH_2CH_2I in THF became acidic solution (pH ~2) under sonication[16]

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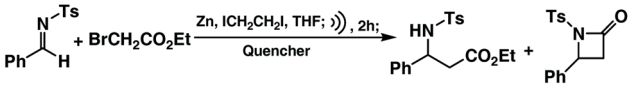
Scheme II Optimization of sonochemical Reformatsky reaction



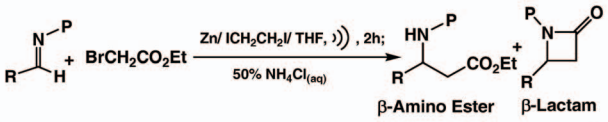
$BrCH_2CO_2Et$	Zn / ICH_2CH_2I	Quencher	β-Amino Ester / β-Lactam
1.3 eq	3.0 / 0.5	H_2O	57% / 0
1.3 eq	3.0 / 0.5	1M HCl	65% / 5%
1.6 eq	3.5 / 1.0	1M HCl	78% / 5%
1.6 eq	3.5 / 1.0	2M HCl	76% / 11%
1.6 eq	3.5 / 1.0	50% NH_4Cl	85% / 3%

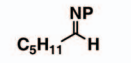
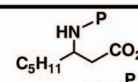
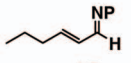
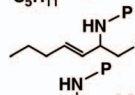
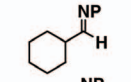
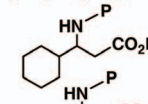
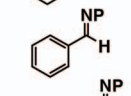
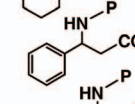
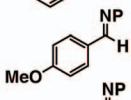
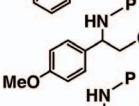
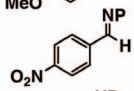
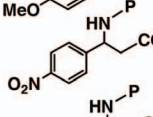
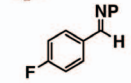
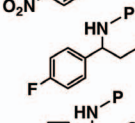
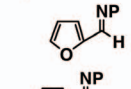
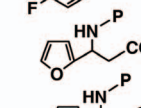
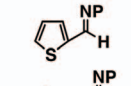
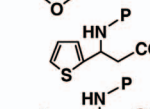
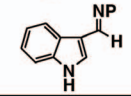
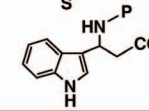
which did not promote the formation of β-lactam by further intramolecular amidation reaction.

N-Hydroxyamino esters have been used as synthetic intermediates and present some applications in organic synthesis.[17-20] In order to afford *N*-hydroxyamino ester, we investigated *N*-hydroxy aldimine under this sonochemical Reformatsky reaction condition. The results showed that the *N*-hydroxyamino ester was obtained as only product when *N*-hydroxy aldimine was used as reacting substrate under the reaction condition (Table 1, entry 4). To understand and expand the scope for synthesis of β-*N*-tosylamino and *N*-hydroxyamino ester by this Reformatsky reaction, a series of *N*-tosyl aldimines and *N*-hydroxy aldimines were prepared and investigated under this sonochemical Reformatsky reraction condition. The results are shown in Table 1, the *N*-hydroxyamino esters were obtained as only product when *N*-hydroxy aldimines were introduced under the reaction condition. While *N*-tosyl aldimine was used as reacting substrate, in most examples, the β-*N*-tosylamino esters were obtained as only product except entries 4, 5 and 7 in Table 1. It is also worthy to know that the formation yield of β-lactam was lower than 3% for these cases. The higher yields of *N*-hydroxyamino esters were obtained when alkyl oximes was used as reacting substrate compared to alkyl *N*-tosylimines (Table 1, entries 1-3). The much higher yields of aryl β-*N*-tosylamino esters were obtained when aryl *N*-tosylimines were used as reacting substrate which compared to aryl oximes (Table 1, entries 4-10).

A previous report showed that β-lactam was formed as the only product with one-step process when *N*-*p*-methoxy imine was used as reacting substrate by using activated zinc granules and dioxane as solvent under ultrasound.[21] Thus, we further investigated the reaction of *N*-*p*-methoxy imine under this sonochemical reaction condition (Scheme III). The experimental results showed that β-*N*-*p*-methoxyamino ester was generated as the major product when H_2O and 50% NH_4Cl were used as quencher under the reaction condition. The β-lactam with 96% yield could be obtained as the sole product when quenching with more acidic solution (2M HCl) to the reaction mixture under this sono-

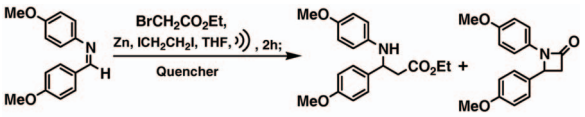
Table 1. Synthesis of β-*N*-tosylamino and β-*N*-hydroxyamino esters



Entry	Imine	P	Product	Yield[a](A.E./Lactam)
1		Ts OH		65% / 0% 72% / 0%
2		Ts OH		73% / 0% 80% / 0%
3		Ts OH		-------[b] 70% / 0%
4		Ts OH		85% / 3% 76% / 0%
5		Ts OH		90% / 2% 63% / 0%
6		Ts OH		81% / 0% 47% / 0%
7		Ts OH		89% / 3% 64% / 0%
8		Ts OH		81% / 0% 49% / 0%
9		Ts OH		76% / 0% 32% / 0%
10		Ts OH		-------[b] 36% / 0%

(a) The yields were dertermined after chromatographic purification.
(b) The aldimine was not prepared and investigated.

Scheme III Optimization of *N*-methoxy imine as reacting substrate



Quencher	Yield[a] β-Amino Ester / β-Lactam
H_2O	86% / 11%
50% NH_4Cl	72% / 17%
1M HCl	12% / 79%
2M HCl	0% / 96%

(a) The yields were dertermined after chromatographic purification.

chemical reaction condition. The β-lactam was successfully synthesized by using *N*-*p*-methoxy aldimine as reacting substrate and quenched with 2 M HCl solution under this sonochemical Reformatsky reaction condition.

Our experimental results showed that chemoselectivity of this sonochemical Reformatsky reraction which rely on the introduction of *N*-substituted aldimine patterns. The consequently intramolecular amidation was completed when *N*-*p*-methoxy aldimine was used as reacting substrate under the reaction condition without further introducing amidating agent.

As a conclusion, we demonstrate here an efficient method for the synthesis of β-*N*-tosylamino esters from extensively applied *N*-tosyl aldimines via sonochemical Reformatsky reaction. *N*-Hydroxy aldimine (oxime) as reacting substrate leads to the formation of β-*N*-hydroxyamino ester as sole product under this sonochemical reaction condition. The β-*N*-hydroxyamino ester was afforded by Reformatsky reaction of *N*-hydroxy aldimine as reacting substrate without protection of reactive hydroxyl functionality

EXPERIMENTAL

General: All reagents were purchased from Aldrich and Riedel-deHaen and all were used directly without further purification. The ^{1}H NMR (proton nuclear magnetic resonance) spectra were recorded at 300 MHz (Bruker-AC300P) with deuteriochloroform ($CDCl_3$, Aldrich 99.8 atom% D) as the solvent and the internal standard. The ^{13}C NMR (carbon nuclear magnetic resonance) spectra were recorded at 75.5 MHz (Bruker-AC300P) with $CDCl_3$ as the solvent and the internal standard. Chemical shifts are reported in parts per million and resonance patterns are reported with the notations of either s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constant (*J*) are reported in hertz (Hz).

A Representative Procedure for Synthesis of β-*N*-hydroxyamino ester: Ethyl bromoacetate (1.6 mmol) was added to a solution of zinc (3.5 mmol), 1,2-diiodoethane (1.0 mmol) and *N*-hydroxy aldimine (1.0 mmol) in anhydrous THF (10 mL) and the reaction mixture was sonicated in a commercial ultrasonic cleaning bath[22] (Elma-T490DH, 50 *k*Hz) for two hours at around 43 ^{o}C. After the sonication, an aqueous 50% NH_4Cl (8.0 mL) was added and stirred for 5 to 30 minutes. The reaction mixture was extracted with ethyl acetate (10 mL ×3) and the combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluent. **Ethyl-3-tosylaminooctanoate (Table 1, Entry 1):** ^{1}H-NMR: δ 0.90 (3H, t, *J* = 7.3 Hz), 1.13-1.24 (7H, m), 1.32-1.48 (4H, m), 2.34 (3H, s), 2.68 (1H, dd, *J* = 15.1, 4.0 Hz), 2.76 (1H, dd, *J* = 15.1, 5.1 Hz), 3.11-3.20 (1H, m), 3.97 (2H, q, *J* = 7.3 Hz), 5.09 (1H, NH, d, *J* = 7.2 Hz), 7.13 (2H, d, *J* = 6.7 Hz), 7.68 (2H, d, *J* = 6.7 Hz). ^{13}C-NMR: δ 13.8, 14.0, 22.9, 24.6, 26.7, 27.2, 38.1, 53.6, 59.9, 125.4, 135.7, 136.3, 142.1, 169.7. **Ethyl-3-hydroxyaminooctanoate (Table 1, Entry 1):** ^{1}H-NMR: δ 0.89 (3H, t, *J* = 7.1), 1.13-1.24 (7H, m), 1.32-1.49 (4H, m), 2.72 (1H, dd, *J* = 14.7, 4.2 Hz), 2.80 (1H, dd, *J* = 14.7, 5.3 Hz), 4.17 (2H, q, *J* = 7.1 Hz), 7.41 (1H, NH, br). ^{13}C-NMR: δ 13.8, 14.1, 25.1, 25.8, 26.8, 27.4, 39.9, 55.8, 70.1, 170.1. **Ethyl-3-tosylamino-4-octenoate (Table 1, Entry 2):** ^{1}H-NMR: δ 0.87 (3H, t, *J* = 7.4), 1.09-1.58 (5H, m), 2.10 (2H, dt, *J* = 5.8, 6.4 Hz), 2.31-2.53 (5H, m), 3.81-3.87 (1H, m), 4.04 (2H, t, *J* = 7.4 Hz), 5.02 (1H, NH, d, *J* = 7.1 Hz), 6.48 (1H, dt, *J* = 15.1, 5.4 Hz), 7.18 (2H, d, *J* = 6.8 Hz), 7.41 (1H, dd, *J* = 15.1, 5.8 Hz), 7.70 (2H, d, *J* = 6.8 Hz). ^{13}C-NMR: δ 14.4, 23.0, 24.9, 35.2, 40.3, 59.5, 60.3, 125.3, 135.6, 136.2, 142.3, 169.7. **Ethyl-3-hydroxyamino-4-octenoate (Table 1, Entry 2):** ^{1}H-NMR: δ 0.90 (3H, t, *J* = 7.0), 1.25-1.51 (5H, m), 2.19 (1H, m), 2.35-2.61 (3H, m), 3.97-4.02 (1H, m), 4.17 (2H, q, *J* = 7.0 Hz), 6.69 (1H, dd, *J* = 14.8, 5.7 Hz), 7.32 (1H, NH, br), 7.42 (1H, dt, *J* = 14.8, 6.1 Hz). ^{113}C-NMR: δ 14.9, 25.9, 36.1, 45.9, 62.2, 70.7, 123.1, 132.3, 170.3. **Ethyl-3-hydroxyamino-3-cyclohexylpropionate (Table 1, Entry 3):** ^{1}H-NMR: δ 1.06-1.45 (9H, m), 1.51-1.80 (4H, m), 1.95 (1H, m), 2.51-2.69 (2H, m), 3.39-3.47 (1H, m), 4.14 (2H, q, *J* = 7.1 Hz), 7.11 (1H, NH, br). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.5, 22.8, 23.1, 29.8, 46.0, 56.7, 70.2, 170.8. **Ethyl-3-tosylamino-3-phenylpropionate (Table 1, Entry 4):** ^{1}H-NMR: δ 1.13 (3H, t, *J* = 7.2 Hz), 2.37 (3H, s), 2.73 (1H, dd, *J* = 15.8, 5.9 Hz), 2.83 (1H, dd, *J* = 15.8, 6.4 Hz), 4.01 (2H, q, *J* = 7.2 Hz), 4.73 (1H, q, *J* = 6.6 Hz), 5.65 (1H, NH, d, *J* = 7.6 Hz), 7.09-7.23 (7H, m), 7.61 (2H, d, *J* = 6.8 Hz). ^{13}C-NMR: δ 13.9, 21.4, 41.4, 54.4, 60.8, 126.4, 127.0, 127.6, 128.4, 129.3, 137.5, 139.3, 143.1, 170.5. HRMS: *m/z* 348.1271 (2.2, M+1) (calcd. for $C_{18}H_{21}NO_4S$, M+1, 348.1270). MS: *m/z* 348 (2.2), 262 (42), 261 (73), 260 (base), 194 (12), 191 (90), 177 (16), 164 (13), 157 (21), 156 (27), 146 (44), 139 (20), 135 (15), 118 (10), 106 (12), 105 (24), 104 (73), 103 (25), 92 (30), 91 (72), 77 (18), 65 (24). **Ethyl-3-hydroxyamino-3-phenylpropionate (Table 1, Entry 4):** ^{1}H-NMR: δ 1.26 (3H, t, *J* = 7.0 Hz), 2.70 (1H, dd, *J* = 16.1, 5.0 Hz), 2.78 (1H, dd, *J* = 16.1, 6.4 Hz), 4.19 (2H, q, *J* = 7.0 Hz), 5.14 (1H, dd, *J* = 8.5, 5.0 Hz), 7.27-7.45 (6H, m). ^{13}C-NMR: δ 14.1, 43.3, 60.9, 70.3, 125.7, 128.4, 142.5, 150.3, 172.4. **Ethyl-3-(toluene-4-sulfonylamino)-3-(4-methoxyphenyl)-propionate (Table 1, Entry 5):** ^{1}H-NMR: δ 1.13 (3H, t, *J* = 7.3 Hz), 2.38 (3H, s), 2.68 (1H, dd,

J = 15.1, 6.2 Hz), 2.80 (1H, dd, *J* = 15.1, 6.6 Hz), 3.74 (3H, s), 4.01 (2H, q, *J* = 7.3 Hz), 4.67 (1H, dd, *J* = 7.3, 6.6 Hz), 5.61 (1H, NH, d, *J* = 7.3 Hz), 6.70 (2H, d, *J* = 8.7 Hz), 7.01 (2H, d, *J* = 8.7 Hz), 7.17 (2H, d, *J* = 8.4 Hz), 7.59 (2H, d, *J* = 8.4 Hz). ^{13}C-NMR: δ 14.2, 21.4, 42.4, 57.1, 62.6, 66.0, 118.9, 126.3, 128.8, 129.1, 129.4, 137.5, 139.3, 159.2, 177.1. HRMS: *m/z* 377.1314 (1.7) (calcd. for $C_{19}H_{23}NO_5S$, 377.1297). MS: *m/z* 377 (1.7), 291 (12), 290 (66), 223 (17), 222 (base), 161 (13), 155 (40), 137 (27), 135 (26), 134 (57), 133 (12), 91 (55), 77 (12), 65 (13). **Ethyl-3-hydroxyamino-3-(4-methoxyphenyl)propionate (Table 1, Entry 5):** ^{1}H-NMR: δ 1.26 (3H, t, *J* = 7.2), 2.74 (1H, dd, *J* = 15.2, 4.9 Hz), 2.83 (1H, dd, *J* = 15.2, 5.8 Hz), 3.75 (3H, s), 4.17 (2H, q, *J* = 7.2 Hz), 5.01 (1H, m), 6.84 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.41 (1H, NH, br). ^{13}C-NMR: δ 14.6, 45.9, 62.3, 66.4, 73.0, 119.3, 128.6, 130.2, 144.9, 162.1, 177.9. **Ethyl-3-tosylamino-3-(4-nitrophenyl)propionate (Table 1, Entry 6):** ^{1}H-NMR: δ 1.23 (3H, t, *J* = 7.4 Hz), 2.39 (3H, s), 2.73 (1H, dd, *J* = 15.2, 5.9 Hz), 2.82 (1H, dd, *J* = 15.2, 6.5 Hz), 4.27 (2H, q, *J* = 7.4 Hz), 5.06 (1H, dd, *J* = 7.2, 6.5 Hz), 5.98 (1H, NH, d, *J* = 7.2 Hz), 7.32 (2H, d, *J* = 8.3 Hz), 7.76 (2H, d, *J* = 8.7 Hz), 7.91 (2H, d, *J* = 8.3 Hz), 8.24 (2H, d, *J* = 8.7 Hz). ^{13}C-NMR: δ 14.0, 21.5, 41.9, 55.9, 61.0, 123.8, 126.2, 127.9, 129.4, 138.1, 142.2, 144.2, 158.2, 173.7. **Ethyl-3-hydroxyamino-3-(4-nitrophenyl)propionate (Table 1, Entry 6):** ^{1}H-NMR: δ 1.30 (3H, t, *J* = 7.0 Hz), 2.39 (3H, s), 2.78 (1H, dd, *J* = 15.0, 5.1 Hz), 2.82 (1H, dd, *J* = 15.0, 6.0 Hz), 4.23 (2H, q, *J* = 7.0 Hz), 5.42 (1H, dd, *J* = 8.2, 6.0 Hz), 7.74 (1H, d, *J* = 8.7 Hz), 8.02 (1H, NH, br), 8.23 (2H, d, *J* = 8.7 Hz). ^{13}C-NMR: δ 14.1, 46.4, 61.9, 72.0, 123.7, 129.1, 145.0, 161.8, 177.2. **Ethyl-3-tosylamino-3-(4-fluorophenyl)propionate (Table 1, Entry 7):** ^{1}H-NMR: δ 1.07 (3H, t, *J* = 7.1 Hz), 2.31 (3H, s), 2.65 (1H, dd, *J* = 15.3, 4.9 Hz), 2.73 (1H, dd, *J* = 15.3, 5.5 Hz), 3.96 (2H, q, *J* = 7.1 Hz), 4.73 (1H, dd, *J* = 8.0, 5.5 Hz), 6.25 (1H, NH, d, *J* = 8.0 Hz), 6.77 (2H, dd, *J* = 16.2, 8.7 Hz), 7.02-7.24 (4H, br), 7.53 (2H, d, *J* = 8.3Hz). ^{13}C-NMR: δ 14.1, 21.9, 42.7, 56.0, 62.2, 117.8, 126.1, 128.4, 129.6, 136.9, 140.0, 159.9, 175.4. MS: *m/z* 279 (10), 278 (55), 211 (13), 210 (base), 164 (19), 155(70), 122 (42), 121(12), 91 (83), 65(13). **Ethyl-3-hydroxyamino-3-(4-fluorophenyl)propionate (Table 1, Entry 7):** ^{1}H-NMR: δ 1.26 (3H, t, *J* = 7.3 Hz), 2.65 (1H, dd, *J* = 15.3, 5.3 Hz), 2.85 (1H, dd, *J* = 15.3, 6.4 Hz), 4.13 (2H, q, *J* = 7.3 Hz), 5.30 (1H, dd, *J* = 8.1, 6.4 Hz), 7.07 (2H, m), 7.56 (2H, m), 7.92 (1H, NH, br). ^{13}C-NMR: δ 14.8, 46.8, 61.9, 72.1, 124.1, 126.4, 130.2, 146.0, 177.9. HRMS: *m/z* 227.0949 (6.2) (calcd. for $C_{11}H_{14}FNO_3$, 227.0958). MS: *m/z* 227 (6.2), 210 (24), 195 (21), 181 (19), 179 (36), 153 (51), 149 (53), 140 (20), 139 (28), 125 (49), 124 (92), 123 (base), 122 (80), 121 (36), 111 (21), 109 (67), 101 (23), 97 (27), 96 (29), 95 (63), 75 (28), 71 (34). **Ethyl-3-tosylamino-3-furan-2-yl-propionate (Table 1, Entry 8):** ^{1}H-NMR: δ 1.23 (3H, t, *J* = 6.9 Hz), 2.40 (3H, s), 2.79 (1H, dd, *J* = 15.1, 5.8 Hz), 2.88 (1H, dd, *J* = 15.1, 6.3 Hz), 4.14 (2H, q, *J* = 6.9 Hz), 4.77-4.86 (1H, m), 5.58 (1H, NH, d, *J* = 8.7 Hz), 6.01 (1H, d, *J* = 3.3 Hz), 6.15 (1H, d, *J* = 3.0 Hz), 7.17-7.25 (3H, m), 7.67 (1H, d, *J* = 8.1 Hz). ^{13}C-NMR: δ 13.9, 21.6, 41.2, 54.1, 60.9, 107.1, 117.5, 126.6, 129.4, 137.3, 138.9, 141.3, 158.8, 175.1. MS: *m/z* 250 (19), 182 (base), 171 (24), 155 (43), 91 (77), 65 (11). **Ethyl-3-hydroxyamino-3-furan-2-yl-propionate (Table 1, Entry 8):** ^{1}H-NMR: δ 1.26 (3H, t, *J* = 6.6 Hz), 2.79 (1H, dd, *J* = 15.0, 5.5 Hz), 2.86 (1H, dd, *J* = 15.0, 6.5 Hz), 4.22 (2H, q, *J* = 6.6 Hz), 4.90-4.99 (1H, m), 6.46 (1H, d, *J* = 2.1 Hz), 6.62 (1H, d, *J* = 3.3 Hz), 7.12 (1H, d, *J* = 2.1 Hz), 7.32 (1H, NH, br). ^{13}C-NMR: δ 14.4, 40.4, 59.9, 71.9, 109.8, 117.1, 143.9, 162.1, 176.0. HRMS: *m/z* 199.0827 (2.1) (calcd. for $C_9H_{13}NO_4$, 199.0845). MS: *m/z* 199 (2.1), 181 (9), 175 (9), 167 (23), 165 (10), 149 (13), 125 (12), 121 (28), 120 (14), 111 (base), 108 (10), 101 (12), 97 (32), 95 (82), 94 (21), 81 (10), 71 (10). **Ethyl-3-tosylamino-3-thiophen-2-yl-propionate (Table 1, Entry 9):** ^{1}H-NMR δ 1.18 (3H, t, *J* = 7.3 Hz), 2.37 (3H, s), 2.79 (1H, dd, *J* = 14.5, 5.3 Hz), 2.85 (1H, dd, *J* = 14.5, 6.1 Hz), 4.01 (2H, q, *J* = 7.3 Hz), 4.95 (1H, ddd, *J* = 8.5, 6.1, 5.3 Hz), 5.73 (1H, NH, d, *J* = 8.5 Hz), 6.75-6.82 (2H, m), 7.10 (1H, d, *J* = 1.5 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 7.69 (1H, d, *J* = 8.4 Hz). ^{13}C-NMR: δ 14.1, 21.8, 41.2, 56.5, 60.7, 124.7, 125.4, 126.0, 126.9, 130.0, 137.4, 139.9, 143.2, 174.7. MS: *m/z* 266 (33), 199 (12), 198 (base), 155 (31), 152 (11), 110 (19), 91 (42). **Ethyl-3-hydroxyamino-3-thiophen-2-yl-propionate (Table 1, Entry 9):** ^{1}H-NMR: δ 1.28 (3H, t, *J* = 7.3 Hz), 2.79 (1H, dd, *J* = 15.1, 5.4 Hz), 2.85 (1H, dd, *J* = 15.1, 6.6 Hz), 4.18 (2H, q, *J* = 7.3 Hz), 5.45 (1H, ddd, *J* = 8.4, 6.6, 5.4 Hz), 6.84 (1H, d, *J* = 1.6 Hz), 7.11 (1H, d, *J* = 1.8 Hz), 7.41 (1H, d, *J* = 1.6 Hz), 7.65 (1H, NH, br). ^{13}C-NMR: δ 14.4, 42.5, 61.5, 71.9, 125.1, 126.7, 127.7, 143.5, 175.9. HRMS: *m/z* 215.0609 (4.5) (calcd. for $C_9H_{13}NO_3S$, 215.0616). MS: *m/z* 215 (4.5), 198 (5), 137 (10), 127 (68), 113 (12), 112 (13), 111 (base), 110 (15), 109 (11), 97 (13), 84 (17), 83 (15), 57 (10). **Ethyl-3-hydroxyamino-3-indol-3-yl-propionate (Table 1, Entry 10):** ^{1}H-NMR: δ 1.23 (3H, t, *J* = 6.5 Hz), 2.78 (1H, dd, *J* = 15.1, 5.5 Hz), 2.90 (1H, dd, *J* = 15.1, 6.8 Hz), 4.23 (2H, q, *J* = 6.5 Hz), 5.48-5.56 (1H, m), 7.20 (1H, m), 7.31 (1H, ArNH, br), 7.55 (1H, *J* = 6.4 Hz), 7.68 (1H, d, *J* = 6.4 Hz), 7.73-7.83 (2H, m), 8.18 (1H, NH, br). ^{13}C-NMR: δ 13.8, 41.3, 60.8, 71.0, 113.8, 114.6, 120.8, 123.4, 123.7, 125.6, 132.9, 139.8, 175.2. **Ethyl-3-(4-methoxy-phenyl)-3-(4-methoxy-phenylamino)-propionate (Scheme III):** ^{1}H-NMR: δ 1.18 (1H, t, *J* = 7.2 Hz), 2.76 (2H, d, *J* = 6.9 Hz), 3.70 (3H, s), 3.77 (3H, s), 4.13 (2H, q, *J* = 7.2 Hz), 4.71 (1H, t, *J* = 6.9 Hz), 6.54 (2H, d, *J* = 12.3 Hz), 6.69 (2H, d, *J* = 10.2 Hz), 6.85 (2H, d, *J* = 10.2 Hz), 7.27 (2H, d, *J* = 12.3 Hz). ^{13}C-NMR: δ 14.1, 42.4, 56.1, 62.6, 64.5, 65.8, 118.9, 128.1, 128.8,

129.1, 129.4, 138.6, 155.6, 159.2, 176.1. **1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (Scheme III):** ^{1}H-NMR: δ 2.92 (1H, dd, *J* = 15.3, 2.1 Hz), 3.52 (1H, dd, *J* = 15.3, 4.8 Hz), 3.74 (3H, s), 3.81 (3H, s), 4.93 (1H, dd, *J* = 4.8, 2.1 Hz), 6.78 (2H, d, *J* = 9.1 Hz), 6.91 (2H, d, *J* = 6.3 Hz), 7.23 (2H, d, *J* = 9.1 Hz), 7.29 (2H, d, *J* = 6.3 Hz). ^{13}C-NMR: δ 45.6, 52.3, 53.8, 53.9, 112.6, 112.9, 116.5, 125.6, 128.5, 129.8, 154.2, 158.0, 162.5.

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22. The bath should be filled with water containing some 3-5% detergent. In our laboratory, we used Decon 90 which permits much more even cavitation in bath water.

