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N-(4-METHYLBENZENESULFONYL)- PYRROLIDINES AND PIPERIDINES BY A TANDEM S_N2-MICHAEL ADDITION REACTION

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Abstract. A tandem S_N2-Michael addition sequence has been developed for the preparation of *N*-(4-methylbenzenesulfonyl)- pyrrolidines and piperidines bearing functionalized side chains at C-2.

Introduction. Five- and six-membered nitrogen heterocycles are common structural units in natural products chemistry,[2] and the development of new methods for their synthesis is a continuous effort. Previous work in this laboratory[3] has explored the tandem S_N2-Michael addition reaction of benzylamine with ω-iodo-α,β-unsaturated esters as a route to *N*-benzylpyrrolidine- and *N*-benzylpiperidineacetic esters. The goals of the current project were: (1) to develop a variant of this procedure using *N*-4-methylbenzenesulfonamide as the donor for both steps of the sequence and (2) to evaluate other activating groups on the Michael acceptor moiety.

The use of sulfonamides for the S_N2-Michael sequence is somewhat novel. While there is ample precedent for the alkylation of sulfonamides,[4] less is known about their behavior in the Michael reaction.[5] The fact that carboxamides have been successfully used in conjugate additions[6] suggested that sulfonamides would undergo the desired reaction sequence. The results of our study are reported below.

Results and Discussion. The synthesis of the cyclization substrates is summarized in the Scheme. Starting from 4-chlorobutanol (**1**) or 5-chloropentanol (**2**), Swern oxidation[7,8] followed by Wittig olefination and halide exchange gave the

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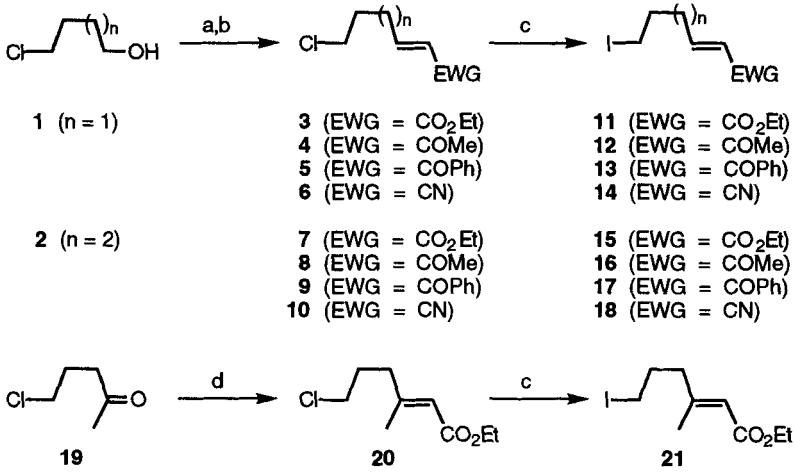
Scheme[a]



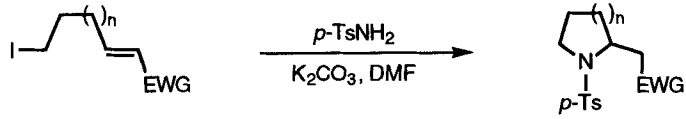
[a]Key: (a) $(COCl)_2$, DMSO, Et_3N, -60 °C; (b) Ph_3P=CH-EWG, PhH, Δ; (c) NaI, acetone, Δ; (d) $(MeO)_2P(O)CH_2CO_2Et$, NaH, DME.

required ω-iodo-α,β-unsaturated carbonyl and nitrile compounds in 55-75% overall yield. One additional substrate (i.e. **21**), hindered at the Michael terminus, was also prepared by a known procedure.[9]

The results of our tandem heterocyclizations are summarized in the Table. Optimum results were obtained by pre-forming the anion of 4-methylbenzenesulfonamide using K_2CO_3 in DMF under anhydrous conditions,[10] then adding the ω-iodo-α,β-unsaturated carbonyl compound or nitrile. All of the cyclizations proceeded in 60-90% yield with the ketones giving the best results. Products were easily purified by chromatography and / or crystallization.

The use of 4-methylbenzenesulfonamide in the current reaction offers several advantages. The aromatic moiety facilitates TLC monitoring of the reactions as well as chromatographic purification of the final products. Excess sulfonamide is easily removed during workup by washing with dilute NaOH. Finally, the sulfonamide group imparts stability to the products, allowing them to be easily manipulated and stored. The stability of this functional group is a potential disadvantage with respect to deprotecting the products, but mild dissolving metal conditions have been

Table

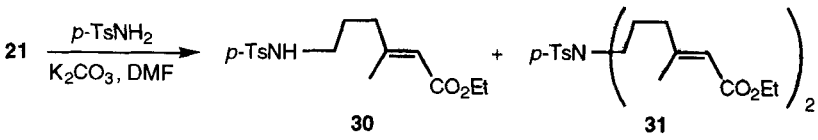


substrate	n	EWG	product	yield (%)
11	1	CO_2Et	**22**	62
12	1	COMe	**23**	91
13	1	COPh	**24**	82
14	1	CN	**25**	66
15	2	CO_2Et	**26**	68
16	2	COMe	**27**	80
17	2	COPh	**28**	81
18	2	CN	**29**	67

been developed for its removal.[11] Additionally, other more easily cleaved sulfonamides are known.[12]

Control experiments were performed to establish the reaction chronology: S_N2-Michael or Michael-S_N2. Competitive S_N2 vs Michael reactions were performed using 4-methylbenzenesulfonamide, iodohexane, and either ethyl (*E*)-2-butenoate, (*E*)-3-penten-2-one, or (*E*)-2-butenenitrile under the standard conditions; each run was monitored for disappearance of the iodide and / or the activated alkene. For the ester and nitrile substrates, only the iodohexane was consumed; for the (*E*)-3-penten-2-one, both the iodide and the enone reacted. Thus, ester and nitrile substrates proceed by an S_N2-Michael process while the ketones could potentially react by both possible mechanisms.

A further experiment was run to assess the importance of steric hindrance on the cyclization process. Since the first step is generally the S_N2 reaction, it was assumed that steric hindrance around the iodide would suppress the reaction. Our earlier work[3] on tandem cyclizations of simple amines and sulfides showed that steric hindrance around the Michael terminus did not impede the cyclization. In the current reaction with the more sterically demanding sulfonamide, however, substitution at the Michael terminus did suppress the ring closure. Thus, reaction of ethyl (*E*)-6-iodo-3-methyl-2-hexenoate (**21**) under standard conditions resulted in mono- and dialkylation of the sulfonamide with no ring closure.



30 31

In summary, we have developed and optimized a procedure for the preparation of C-2 functionalized *N*-(4-methylbenzenesulfonyl)- pyrrolidines and piperidines. The cyclization substrates are easily prepared, the procedure is simple, and the products are obtained in good to excellent yields. The method is limited by its sensitivity to substitution around the iodide and the Michael acceptor. Work is continuing to develop new approaches to heterocycles using tandem reaction processes.

Experimental Section

DMF was vacuum distilled from BaO and stored over 4 Å molecular sieves under N_2. K_2CO_3 (powdered, anhydrous) was dried under vacuum at 110 °C for 24 h and stored under vacuum. (Carboxymethylene)triphenylphosphorane, (acetylmethylene)triphenylphosphorane, (benzoylmethylene)triphenylphosphorane, and (cyanomethylene)triphenylphosphorane were prepared by the literature method.[13] Other commercial reagents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The NH_4Cl (saturated), $NaHCO_3$ (saturated), NaCl (saturated), $Na_2S_2O_3$ (5%), HCl (0.5 M), and NaOH (0.02 M) used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on silica gel GHLF plates (Analtech no. 21521) using UV detection or (2) capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-300 °C. Preparative separations were performed using one of the following methods: (1) crystallization, (2) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015), (3) flash vacuum chromatography[14] on silica gel (Grace, grade 62, 60-200 mesh), or (4) flash chromatography[15] on silica gel (60-200 mesh) mixed with Sylvania no. 2282 UV-active phosphor. Band elution, where appropriate, was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were referenced to polystyrene. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and are referenced to internal Me_4Si. High

resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV; mass spectra (MS, FAB) were obtained in a thioglycerol matrix using Cs at 35 keV.

Representative Procedure for the Swern Oxidation-Wittig Olefination: Ethyl (*E*)-6-Chloro-2-hexenoate (3). A solution of 25.7 g (17.7 mL, 202 mmol) of oxalyl chloride in 200 mL of CH_2Cl_2 was placed in a 1-L four-necked round-bottomed flask equipped with an overhead stirrer, an addition funnel, a thermocouple probe, and a calcium sulfate drying tube. The solution was cooled to -78 °C using a dry ice-acetone bath and a solution of 31.6 g (28.7 mL, 405 mmol) of dimethyl sulfoxide in 50 mL of CH_2Cl_2 was added dropwise during 10 min. The mixture was stirred for 5 min and a solution of 20.0 g (184 mmol) of **1** in 50 mL of CH_2Cl_2 was added dropwise during 10 min. The reaction was stirred for 5 min and 92.2 g (128 mL, 92.0 mmol) of triethylamine was added at a rate which kept the temperature below -50 °C. Once the triethylamine was completely added, the reaction was allowed to slowly warm to rt. The crude reaction mixture was transferred to a separatory funnel containing 200 mL of H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 one additional time and the combined organic layers were washed with 0.5 M HCl, $NaHCO_3$, H_2O, and NaCl, then dried ($MgSO_4$), and concentrated under vacuum. The product was used directly in the next reaction.

The crude aldehyde was dissolved in 300 mL of benzene, 34.8 g (100 mmol) of (carbethoxymethylene)triphenylphosphorane was added and the mixture was heated under reflux for 12 h. The solution was cooled and concentrated under vacuum to afford a tan semisolid mass. The residue was layered on top of a 10-cm x 10-cm plug of silica gel in a sintered glass frit, and 2 L of 15% ether in hexane was poured through under vacuum.[14] Concentration of the eluant gave the crude product as a yellow oil. Purification by flash chromatoagraphy[15] on a 50-cm x 2.5-cm slurry packed silica gel column gave 13.0 g (73.7 mmol, 74%) of **3** as a light yellow oil. The spectral data matched those reported previously.[11]

The following compounds were prepared, on varying scales, using the same procedure. The products were purified by distillation or column chromatography.

(*E*)-7-Chloro-3-hepten-2-one (4): 10.5 g (71.6 mmol, 72%); bp 63-65 °C (3.5 mm Hg); IR (thin film) 1701, 1680, 1630, 1364, 983 cm^{-1}; ^1H NMR δ 6.79 (dt, 1 H, J = 15.9, 6.9 Hz), 6.13 (dt, 1 H, J = 15.9, 1.5 Hz), 3.57 (t, 2 H, J = 6.4 Hz), 2.41 (qd, 2 H, J = 6.7, 1.5 Hz), 2.26 (s, 3 H), 1.96 (quintet, 2 H, J =

6.6 Hz); ^{13}C NMR δ 198.4, 146.0, 132.0, 43.8, 30.6, 29.3, 26.9; HRMS *m/z* Calcd for $C_7H_{11}{}^{35}ClO$: 146.0499. Found: 146.0494.

(*E*)-6-Chloro-1-phenyl-2-hexen-1-one (5): 14.7 g (70.4 mmol, 70%); IR (thin film) 3068, 1672, 1656, 1623, 1604, 1590, 983, 770, 698 cm^{-1}; ^{1}H NMR δ 7.93 (d, 2 H, *J* = 7.1 Hz), 7.55 (t, 1 H, *J* = 7.4 Hz), 7.47 (t, 2 H, *J* = 7.6 Hz), 7.03 (dt, 1 H, *J* = 15.4, 6.6 Hz), 6.91 (d, 1 H, *J* = 15.4 Hz), 3.59 (t, 2 H, *J* = 6.6 Hz), 2.52 (q, 2 H, *J* = 7.0 Hz), 2.01 (quintet, 2 H, *J* = 7.0 Hz); ^{13}C NMR δ 190.6, 147.4, 137.8, 132.8, 128.6 (2), 126.9, 43.9, 30.7, 29.6; HRMS *m/z* Calcd for $C_{12}H_{13}{}^{35}ClO$: 208.0655. Found: 208.0651.

(*E*)-6-Chloro-2-hexenenitrile (6): 6.02 g (46.5 mmol, 62%); bp 61-64 °C (0.5 mm Hg); IR (thin film) 2226, 1637, 975 cm^{-1}; ^{1}H NMR δ 6.71 (dt, 1 H, *J* = 16.3, 7.0 Hz), 5.41 (dt, 1 H, *J* = 16.3, 1.5 Hz), 3.56 (t, 2 H, *J* = 6.3 Hz), 2.43 (qd, 2 H, *J* = 7.2, 1.5 Hz), 1.94 (quintet, 2 H, *J* = 6.3 Hz); ^{13}C NMR δ 153.9, 117.2, 101.1, 43.5, 30.2, 30.1; HRMS *m/z* Calcd for $C_6H_8{}^{35}ClN$: 129.0346. Found: 129.0342.

Ethyl (*E*)-7-Chloro-2-heptenoate (7): 15.1 g (79.3 mmol, 79%); the spectral data matched those reported previously.[11]

(*E*)-8-Chloro-3-octen-2-one (8): 11.2 g (70.0 mmol, 70%); bp 70-72 °C (3.5 mm Hg); IR (thin film) 1702, 1679, 1630, 1363, 981 cm^{-1}; ^{1}H NMR δ 6.80 (dt, 1 H, *J* = 15.9, 6.9 Hz), 6.10 (dt, 1 H, *J* = 15.9, 1.5 Hz), 3.56 (t, 2 H, *J* = 6.4 Hz), 2.27 (qd, 2 H, *J* = 7.3, 1.5 Hz), 2.25 (s, 3 H), 1.80 (m, 2 H), 1.66 (m, 2 H); ^{13}C NMR δ 198.6, 147.3, 131.6, 44.4, 31.7, 31.4, 26.7, 25.0; HRMS *m/z* Calcd for $C_8H_{13}{}^{35}ClO$: 160.0655. Found: 160.0652.

(*E*)-7-Chloro-1-phenyl-2-hepten-1-one (9): 15.0 g (67.2 mmol, 67%); IR (thin film) 3061, 1672, 1657, 1626, 1608, 1593, 982, 773, 697 cm^{-1}; ^{1}H NMR δ 7.93 (d, 2 H, *J* = 8.0 Hz), 7.57 (m, 1 H), 7.47 (t, 2 H, *J* = 7.6 Hz), 7.07 (dt, 1 H, *J* = 15.5, 6.7 Hz), 6.91 (d, 1 H, *J* = 15.5 Hz), 3.57 (tm, 2 H, *J* = 6.5 Hz), 2.36 (q, 2 H, *J* = 7.4 Hz), 1.84 (m, 2 H), 1.71 (m, 2 H); ^{13}C NMR δ 190.9, 148.8, 137.9, 132.8, 128.6 (2), 126.3, 44.5, 31.8 (2), 25.2; HRMS *m/z* Calcd for $C_{13}H_{15}{}^{35}ClO$: 222.0812. Found: 222.0808.

(*E*)-7-Chloro-2-heptenenitrile (10): 7.02 g (48.9 mmol, 66%); bp 74-76 °C (0.5 mm Hg); IR (thin film) 2226, 1637, 975 cm^{-1}; ^{1}H NMR δ 6.72 (dt, 1 H, *J* = 16.4, 6.9 Hz), 5.37 (dt, 1 H, *J* = 16.4, 1.5 Hz), 3.55 (t, 2 H, *J* = 6.4 Hz), 2.28 (qd, 2 H, *J* = 7.2, 1.5 Hz), 1.78 (m, 2 H), 1.63 (m, 2 H); ^{13}C NMR δ

155.1, 117.4, 100.3, 44.3, 32.3, 31.5, 24.7; HRMS *m/z* Calcd for $C_7H_{10}{}^{35}ClN$: 143.0503. Found: 143.0500.

Ethyl (*E*)-6-Chloro-3-methyl-2-hexenoate (20): This compound was prepared from 5-chloro-2-pentanone (**19**) in 45% purified yield by the method of Cooke and Widener.[11] The spectral data matched those reported.

Representative Procedure for Halide Exchange: Ethyl (*E*)-6-Iodo-2-hexenoate (11). To a solution of 8.83 g (50.0 mmol) of **3** in 400 mL of acetone was added 30.0 g (200 mmol) of NaI. The reaction was heated under reflux for 24 h. The solution was cooled and concentrated under vacuum to afford a brown liquid. The liquid was dissolved in ether and washed with H_2O, $Na_2S_2O_3$, and NaCl, then dried ($MgSO_4$), and concentrated to give 12.4 g (46.1 mmol, 92%) of **11** as a light yellow oil. The spectral data matched those reported previously.[3] The product was used without further purification.

The following compounds were prepared, on varying scales, using the same procedure. Each was used without further purification.

(*E*)-7-Iodo-3-hepten-2-one (12): 15.3 g (64.3 mmol, 99%); IR (thin film) 1703, 1677, 1632, 1366, 978 cm^{-1}; ^1H NMR δ 6.76 (dt, 1 H, *J* = 15.9, 6.9 Hz), 6.14 (dt, 1 H, *J* = 15.9, 1.5 Hz), 3.20 (t, 2 H, *J* = 6.9 Hz), 2.38 (qd, 2 H, *J* = 6.9, 1.5 Hz), 2.26 (s, 3 H), 2.00 (quintet, 2 H, *J* = 7.0 Hz); ^{13}C NMR δ 198.5, 145.6, 132.2, 32.9, 31.3, 27.0, 5.2; MS (FAB) *m/z* 239 (M^++1).

(*E*)-6-Iodo-1-phenyl-2-hexen-1-one (13): 5.99 g (20.0 mmol, 99%); IR (thin film) 3059, 1673, 1658, 1625, 1610, 1581, 770, 695 cm^{-1}; ^1H NMR δ 7.94 (d, 2 H, *J* = 8.2 Hz), 7.56 (m, 1 H), 7.48 (t, 2 H, *J* = 7.6 Hz), 6.98 (m, 2 H), 3.24 (t, 2 H, *J* = 6.7 Hz), 2.47 (m, 2 H), 2.05 (quintet, 2 H, *J* = 6.9 Hz); ^{13}C NMR δ 190.6, 147.0, 137.8, 132.8, 128.6 (2), 127.0, 33.2, 31.3, 5.5; MS (FAB) *m/z* 301 (M^++1).

(*E*)-6-Iodo-2-hexenenitrile (14): 8.04 g (36.4 mmol, 91%); IR (thin film) 2226, 1637, 975 cm^{-1}; ^1H NMR δ 6.68 (dt, 1 H, *J* = 16.3, 7.0 Hz), 5.43 (dt, 1 H, *J* = 16.3, 1.5 Hz), 3.19 (t, 2 H, *J* = 6.7 Hz), 2.39 (dq, 2 H, *J* = 7.2, 1.5 Hz), 1.97 (quintet, 2 H, *J* = 6.9 Hz); ^{13}C NMR δ 153.5, 117.1, 101.2, 33.7, 30.7, 4.7; MS (FAB) *m/z* 222 (M^++1).

Ethyl (*E*)-7-Iodo-2-heptenoate (15): 7.39 g (26.2 mmol, 93%); the spectral data matched those reported previously.[3]

(*E*)-8-Iodo-3-octen-2-one (16): 17.0 g (67.3 mmol, 99%); IR (thin film) 1704, 1681, 1636, 1365, 979 cm^{-1}; ^1H NMR δ 6.79 (dt, 1 H, *J* = 15.9, 6.9 Hz),

6.10 (br d, 1 H, J = 15.9 Hz), 3.20 (t, 2 H, J = 6.9 Hz), 2.27 (q, 2 H, J = 6.9 Hz), 2.25 (s, 3 H), 1.86 (quintet, 2 H, J = 6.9 Hz), 1.61 (quintet, 2 H, J = 7.0 Hz); ^{13}C NMR δ 198.7, 147.3, 131.7, 32.6, 31.1, 28.7, 26.8, 6.0; MS (FAB) *m/z* 253 (M^++1).

(*E*)-7-Iodo-1-phenyl-2-hepten-1-one (17): 11.0 g (35.0 mmol, 94%); IR (thin film) 3053, 1673, 1658, 1623, 1604, 1589, 773, 697 cm^{-1}; ^{1}H NMR δ 7.94 (d, 2 H, J = 8.2 Hz), 7.56 (m, 1 H), 7.48 (t, 2 H, J = 7.6 Hz), 7.04 (dt, 1 H, J = 15.4, 6.7 Hz), 6.90 (d, 1 H, J = 15.4 Hz), 3.20 (t, 2 H, J = 6.9 Hz), 2.35 (q, 2 H, J = 6.8 Hz), 1.88 (quintet, 2 H, J = 6.9 Hz), 1.65 (quintet, 2 H, J = 7.2 Hz); ^{13}C NMR δ 190.7, 148.7, 137.8, 132.7, 128.6, 128.5, 126.3, 32.6, 31.4, 28.8, 6.1; MS (FAB) *m/z* 315 (M^++1).

(*E*)-7-Iodo-2-heptenenitrile (18): 8.58 g (36.5 mmol, 91%); IR (thin film) 2226, 1637, 967 cm^{-1}; ^{1}H NMR δ 6.71 (dt, 1 H, J = 16.4, 6.9 Hz), 5.36 (br d, 1 H, J = 16.4 Hz), 3.19 (t, 2 H, J = 6.7 Hz), 2.26 (q, 2 H, J = 7.1 Hz), 1.84 (quintet, 2 H, J = 7.1 Hz), 1.59 (quintet, 2 H, J = 7.3 Hz); ^{13}C NMR δ 155.0, 117.4, 100.4, 32.4, 32.0, 28.3, 5.6; MS (FAB) *m/z* 236 (M^++1).

Ethyl (*E*)-6-Iodo-3-methyl-2-hexenoate (21): 10.3 g (36.7 mmol, 92%); IR (thin film) 1718, 1652, 1372 cm^{-1}; ^{1}H NMR δ 5.71 (br s, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 3.17 (t, 2 H, J = 6.9 Hz), 2.26 (br t, 2 H, J = 7.2 Hz), 2.16 (d, 3 H, J = 1.2 Hz), 2.00 (quintet, 2 H, J = 7.0 Hz), 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 166.1, 157.5, 116.7, 59.5, 41.1, 30.7, 18.5, 14.1, 5.3; MS (FAB) *m/z* 283 (M^++1).

Representative Procedure for the S_N2-Michael Tandem Cyclization: Ethyl 1-(4-Methylbenzenesulfonyl)pyrrolidine-2-acetate (22): To a solution of 0.34 g (2.00 mmol) of 4-methylbenzenesulfonamide in 25 mL of dry DMF was added 0.69 g (5.00 mmol) of powdered, anhydrous K_2CO_3. The reaction was stirred at rt for 1 h at which time 0.54 g (2.00 mmol) of **11** was added in one portion. The reaction was stirred for 24 h, quenched by addition to 50 mL of saturated NH_4Cl, and extracted with ether (2x). The organic extract was washed with 0.02 M NaOH and NaCl, then dried ($MgSO_4$), and concentrated under vacuum. The resulting oil was purified by PTLC eluted with 60% ether in hexane to afford 0.39 g (1.24 mmol, 62%) as a light yellow oil. IR (thin film) 3075, 1736, 1600, 1378, 1338, 1158, 820 cm^{-1}; ^{1}H NMR δ 7.74 (d, 2 H, J = 8.2 Hz), 7.33 (d, 2 H, J = 8.2 Hz), 4.14 (qd, 2 H, J = 7.1, 1.6 Hz), 3.96 (m, 1 H), 3.45 (m, 1 H), 3.11 (m, 1 H), 3.07 (dd, 1 H, J = 16.1, 3.9 Hz), 2.49 (dd, 1 H, J =

16.1, 10.1 Hz), 2.44 (s, 3 H), 1.82-1.51 (complex, 4 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 171.4, 143.6, 134.2, 129.8, 127.6, 60.4, 56.5, 49.1, 41.3, 31.5, 23.6, 21.4, 14.0; HRMS *m/z* Calcd for $C_{15}H_{21}NO_4S$: 311.1191. Found: 311.1189. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.88; H, 6.75. Found: C, 58.05; H, 6.78.

The following compounds were prepared using the same procedure on a 2.00 mmol scale. The products were purified by PTLC eluted with 60% ether in hexane.

1 - (1 - (4- Methylbenzenesulfonyl) -2- pyrrolidinyl) -2- propanone (23): 0.51 g (1.81 mmol, 91%); mp 97-99 °C; IR ($CHCl_3$) 1715, 1599, 1339, 1162, 821 cm^{-1}; ^1H NMR δ 7.72 (d, 2 H, J = 8.1 Hz), 7.33 (d, 2 H, J = 8.1 Hz), 3.92 (m, 1 H), 3.43 (m, 1 H), 3.26 (dd, 1 H, J = 17.9, 3.3 Hz), 3.10 (m, 1 H), 2.68 (dd, 1 H, J = 17.9, 9.6 Hz), 2.44 (s, 3 H), 2.18 (s, 3 H), 1.77 (m, 2 H), 1.49 (m, 2 H); ^{13}C NMR δ 207.4, 143.7, 133.8, 129.8, 127.7, 55.8, 50.6, 49.1, 32.0, 30.4, 23.7, 21.4; HRMS *m/z* Calcd for $C_{14}H_{19}NO_3S$: 281.1086. Found: 281.1082. Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.59; H, 6.71. found: C, 59.74; H, 6.72.

2-(1-(4-Methylbenzenesulfonyl)-2-pyrrolidinyl)-1-phenylethanone (24): 0.56 g (1.63 mmol, 82%); mp 105-107 °C; IR (thin film) 3070, 3034, 1686, 1599, 1369, 1345, 1161, 821 cm^{-1}; ^1H NMR δ 8.01 (d, 2 H, J = 8.2 Hz), 7.74 (d, 2 H, J = 8.2 Hz), 7.60 (t, 1 H, J = 7.6 Hz), 7.40 (t, 2 H, J = 7.6 Hz), 7.33 (d, 2 H, J = 7.8 Hz), 4.13 (m, 1 H), 3.85 (dd, 1 H, J = 17.2, 2.9 Hz), 3.51 (m, 1 H), 3.15 (dd, 1 H, J = 17.2, 10.3 Hz), 3.12 (m, 1 H), 2.43 (s, 3 H), 1.87-1.48 (complex, 4 H); ^{13}C NMR δ 198.7, 143.6, 136.6, 133.8, 133.4, 129.8, 128.7, 128.2, 127.6, 56.6, 49.1, 46.1, 31.7, 23.7, 21.4; HRMS *m/z* Calcd for $C_{19}H_{21}NO_3S$: 343.1242. Found: 343.1239. Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.47; H, 6.12. found: C, 66.69; H, 6.15.

1-(4-Methylbenzenesulfonyl)pyrrolidine-2-acetonitrile (25): 0.35 g (1.32 mmol, 66%); IR (thin film) 2251, 1599, 1383, 1330, 1167, 818 cm^{-1}; ^1H NMR δ 7.73 (d, 2 H, J = 8.2 Hz), 7.36 (d, 2 H, J = 8.2 Hz), 3.81 (m, 1 H), 3.50 (m, 1 H), 3.17 (m, 1 H), 2.89 (dd, 1 H, J = 16.8, 3.8 Hz), 2.82 (dd, 1 H, J = 16.8, 7.7 Hz), 2.45 (s, 3 H), 2.00-1.85 (complex, 3 H), 1.59 (m, 1 H); ^{13}C NMR δ 144.2, 133.8, 130.0, 127.6, 117.5, 55.9, 49.5, 31.1, 25.2, 23.8, 21.4; HRMS *m/z* Calcd for $C_{13}H_{16}N_2O_2S$: 264.0933. Found: 264.0929. Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.09; H, 6.06. Found: C, 59.31; H, 6.09.

Ethyl 1-(4-Methylbenzenesulfonyl)piperidine-2-acetate (26): 0.44 g (1.36 mmol, 68%); IR (thin film) 3040, 1736, 1599, 1383, 1333, 1160, 814 cm^{-1}; ^1H NMR δ 7.72 (d, 2 H, J = 8.2 Hz), 7.29 (d, 2 H, J = 8.2 Hz), 4.53 (m, 1 H), 4.10 (qd, 2 H, J = 7.1, 2.0 Hz), 3.80 (dm, 1 H, J = 14.0 Hz), 2.94 (td, 1 H, J = 12.6, 2.3 Hz), 2.62 (dd, 1 H, J = 15.0, 9.2 Hz), 2.48 (dd, 1 H, J = 15.0, 5.8 Hz), 2.42 (s, 3 H), 1.57-1.23 (complex, 6 H), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 170.9, 143.1, 138.2, 129.7, 127.0, 60.6, 49.5, 40.8, 34.9, 27.5, 24.4, 21.3, 18.1, 13.9; HRMS *m/z* Calcd for $C_{16}H_{23}NO_4S$: 325.1348. Found: 325.1344. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.08; H, 7.08. Found: C, 59.33; H, 7.14.

1-(1-(4-Methylbenzenesulfonyl)-2-piperidinyl)-2-propanone (27): 0.48 g (1.62 mmol, 80%); IR (thin film) 1714, 1599, 1340, 1160, 821 cm^{-1}; ^1H NMR δ 7.71 (d, 2 H, J = 8.1 Hz), 7.30 (d, 2 H, J = 8.1 Hz), 4.52 (m, 1 H), 3.79 (dm, 1 H, J = 15.1 Hz), 2.94 (td, 1 H, J = 12.8, 2.2 Hz), 2.82 (dd, 1 H, J = 16.1, 9.2 Hz), 2.60 (dd, 1 H, J = 16.1, 4.7 Hz), 2.42 (s, 3 H), 2.13 (s, 3 H), 1.55-1.21 (complex, 6 H); ^{13}C NMR δ 206.3, 143.3, 138.1, 129.8, 127.1, 48.6, 43.8, 41.1, 30.2, 27.6, 24.4, 21.4, 18.2; HRMS *m/z* Calcd for $C_{15}H_{21}NO_3S$: 295.1240. Found: 295.1239. Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 61.02; H, 7.12. Found: C, 60.90; H, 7.08.

2-(1-(4-Methylbenzenesulfonyl)-2-piperidinyl)-1-phenylethanone (28): 0.58 g (1.62 mmol, 81%); mp 130-132 °C; IR (thin film) 3070, 3034, 1686, 1599, 1369, 1345, 1161, 821 cm^{-1}; ^1H NMR δ 7.91 (d, 2 H, J = 8.3 Hz), 7.70 (d, 2 H, J = 8.3 Hz), 7.58 (t, 1 H, J= 7.7 Hz), 7.46 (t, 2 H, J = 7.7 Hz), 7.25 (d, 2 H, J = 7.8 Hz), 4.68 (dm, 1 H, J = 10.1 Hz), 3.86 (dm, 1 H, J = 13.7 Hz), 3.33 (dd, 1 H, J = 15.9, 10.1 Hz), 3.13 (dd, 1 H, J = 15.9, 3.8 Hz), 3.05 (td, 1 H, J = 13.7, 2.6 Hz), 2.38 (s, 3 H), 1.64-1.25 (complex, 6 H); ^{13}C NMR δ 197.8, 143.2, 138.1, 136.6, 133.4, 129.8, 128.7, 128.2, 127.1, 49.3, 41.3, 38.8, 27.4, 24.7 21.4, 18.2; HRMS *m/z* Calcd for $C_{20}H_{23}NO_3S$: 357.1399. Found: 357.1395. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.23; H, 6.44. Found: C, 67.45; H, 6.46.

1-(4-Methylbenzenesulfonyl)piperidine-2-acetonitrile (29): 0.37 g (1.34 mmol, 67%); mp 118-120 °C; IR (thin film) 2252, 1599, 1384, 1333, 1167, 821 cm^{-1}; ^1H NMR δ 7.72 (d, 2 H, J = 8.2 Hz), 7.32 (d, 2 H, J = 8.2 Hz), 4.38 (m, 1 H), 3.77 (dm, 1 H, J = 14.0 Hz), 2.91 (ddd, 1 H, J = 14.0, 12.5, 2.8 Hz), 2.73 (dd, 1 H, J = 16.8, 9.9 Hz), 2.56 (ddd, 1 H, J = 16.8, 5.5, 0.5 Hz),

2.44 (s, 3 H), 1.85 (dm, 1 H, J = 12.5 Hz), 1.66-1.31 (complex, 5 H); ^{13}C NMR δ 143.8, 130.0, 129.8, 127.1, 117.3, 49.2, 40.6, 26.7, 24.0, 21.4, 18.7, 17.8; HRMS *m/z* Calcd for $C_{14}H_{18}N_2O_2S$: 278.1090. Found: 278.1086. Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.43; H, 6.47. Found: C, 60.56; H, 6.51.

Ethyl (*E*)-6-(4-Methylbenzenesulfonyl)amido-3-methyl-2-hexenoate (30): 0.28 g (0.88 mmol, 44%); IR (thin film) 3280, 3058, 1712, 1650, 1600, 1334, 1155, 821 cm^{-1}; ^1H NMR δ 7.75 (d, 2 H, J = 8.2 Hz), 7.32 (d, 2 H, J = 8.2 Hz), 5.58 (q, 1 H, J = 1.2 Hz), 4.65 (br s, 1 H), 4.13 (q, 2 H, J = 7.1 Hz), 2.94 (q, 2 H, J = 6.8 Hz), 2.43 (s, 3 H), 2.12 (t, 2 H, J = 6.8 Hz), 2.08 (d, 3 H, J = 1.2 Hz), 1.64 (quintet, 2 H, J = 7.0 Hz), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 166.7, 158.2, 143.6, 137.0, 129.8, 127.1, 116.3, 59.5, 42.6, 37.5, 27.3, 21.4, 18.5, 14.2; HRMS *m/z* Calcd for $C_{16}H_{23}NO_4S$: 325.1348. Found: 325.1343. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.07; H, 7.08. Found: 59.22; H, 7.11.

***N,N*-Bis ((*E*)-5- ethoxycarbonyl-4- methyl-4- pentenyl)-4- methylbenzenesulfonamide (31)**: 0.18 g (0.40 mmol, 20%); IR (thin film) 3065, 1714, 1655, 1602, 1346, 1158, 812 cm^{-1}; ^1H NMR δ 7.67 (d, 2 H, J = 8.2 Hz), 7.30 (d, 2 H, J = 8.2 Hz), 5.64 (q, 2 H, J = 1.2 Hz), 4.15 (q, 4 H, J = 7.1 Hz), 3.09 (t, 4 H, J = 7.5 Hz), 2.43 (s, 3 H), 2.13 (d, 6 H, J = 1.2 Hz), 2.13 (t, 4 H, J = 7.5 Hz), 1.70 (quintet, 4 H, J = 7.5 Hz), 1.28 (t, 6 H, J = 7.1 Hz); ^{13}C NMR δ 166.7, 158.3, 143.4, 136.7, 129.8, 127.2, 116.2, 59.5, 48.0, 37.7, 26.4, 21.4, 18.6, 14.2; HRMS *m/z* Calcd for $C_{25}H_{37}NO_6S$: 479.2341. Found: 479.2337. Anal. Calcd for $C_{25}H_{37}NO_6S$: C, 62.63; H, 7.72. Found: C, 62.45; H, 7.74.

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