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ONE-POT ARYL-1,4-THIOMORPHOLINE 1,1-DIOXIDE SYNTHESIS VIA DOUBLE 1,4-ADDITION OF IN SITU REDUCED NITROARENES TO DIVINYL SULFONES

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Abstract – One-pot reduction-triggered double aza-Michael type 1,4-addition reactions of various nitroarenes to divinyl sulfones were investigated. In the presence of indium/AcOH in MeOH or in sat. aq NH_4Cl/MeOH, nitroarenes and divinyl sulfones were cyclized to give 1,4-thiomorpholine 1,1-dioxides.

INTRODUCTION

Heterocyclic compounds containing the 1,4-thiomorpholine 1,1-dioxide substructure have appeared in the recent literature as potent antibacterial agents,[1] Aurora-A kinase inhibitors having anti-tumor activity,[2] inhibitors of respiratory syncytial virus (RSV),[3] anti-inflammatory agents,[4] cathepsin S inhibitors,[5] and antimalarial agents.[6] However, only a limited number of synthetic methods for thiomorpholine 1,1-dioxide ring formation are known in the literature.[7] Most of these syntheses utilize the corresponding amines as starting material.[7a-d] In addition to double nucleophilic substitution reactions[7b] or double addition reactions[7a,c,d] of amines, nitro compounds could also be good candidates for the synthesis of thiomorpholine 1,1-dioxides.

During our continuing studies of indium-mediated reductive reactions of nitroarenes,[8] we have found a simple and efficient method for a one-pot reduction-triggered 1,4-addition reaction of various nitroarenes to α,β-unsaturated sulfones to form the corresponding β-(*N*-hydroxylamino)sulfone in good yields,[9] which could potentially be utilized for the synthesis of thiomorpholine 1,1-dioxide derivatives via a double aza-Michael addition to a divinyl sulfone. The reaction is believed to proceed through a radical

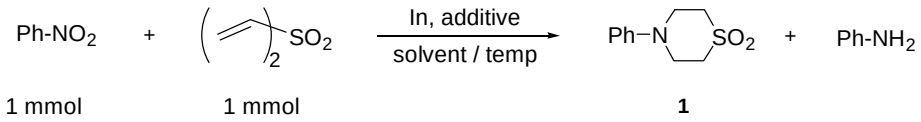
intermediate via single electron transfer (SET).[10] Extension of this reaction to six-membered ring formation, if properly controlled, would be a promising, generally applicable method for the synthesis of thiomorpholine 1,1-dioxides. Herein, we report the one-pot reduction-triggered double 1,4-addition reaction of nitroarenes to divinyl sulfones using indium. Since the use of indium for organic functional group transformations has received increased attention because of environmental issues and the ease of reactions that obviate the need for flammable anhydrous organic solvents and an inert atmosphere,[11] the development of new synthetic methods using indium are noteworthy as green chemistry alternatives.

RESULTS AND DISCUSSION

Reaction conditions that were previously applied to the one-pot reduction-triggered 1,4-addition reaction of nitroarenes to α,β-unsaturated sulfones,[9] i.e., nitrobenzene (1 equiv)/vinyl sulfone (10 equiv)/indium (3 equiv)/iodine (0.8 equiv) in methanol at room temperature, were preliminarily examined with the expectation that 1,4-thiomorpholine 1,1-dioxide ring formation would result from the reaction using a divinyl sulfone (Table 1, entry 1). However, only a low yield of the desired thiomorpholine 1,1-dioxide ring resulted. Thus the reaction conditions were re-investigated to find conditions for ring formation via the double 1,4-addition reaction mediated by indium with several Lewis acid or protic acid additives such as $InCl_3$, I_2, HI, and AcOH in various solvents. Representative control experiments are summarized in Table 1. In the case of I_2 (entries 1, 2), thiomorpholine 1,1-dioxide was obtained in low yield accompanied by aniline (25% (entry 1) and 13% (entry 2)) as the major by-product. In the case of $InCl_3$, reactions proceeded poorly (entry 3, 4). For the reaction in the presence of HI (entry 5), aniline was obtained as the major product (92%) while the desired thiomorpholine 1,1-dioxide was formed as a minor product, which implied that strong acids do not have a positive effect on the cyclization reaction. For the heterocyclization reaction, the relative acidity of the additive seems important.

Thus, AcOH as an additive, a relatively weak acid compared to HI and possibly a better Bronsted-Lowry acid than the Lewis acid $InCl_3$, was tried. In the presence of AcOH, the reaction gave an improved yield of the desired thiomorpholine 1,1-dioxide with a reduced amount of by-products (entry 6). After examining various reaction conditions in the presence of AcOH in MeOH, optimized conditions for the formation of thiomorpholine 1,1-dioxide were found to be nitrobenzene/divinyl sulfone (one equiv)/AcOH (ten equiv)/indium (five equiv) in MeOH at reflux (entry 9). As far as this transformation can be achieved via reduction of nitro group to aniline followed by aza-Michael addition to divinyl sulfone, stepwise addition was also tried; i.e., Nitrobenzene (1 mmol)/AcOH (10 equiv)/indium (5 equiv) in MeOH (10 mL) was refluxed for 9 hours first. Then, divinyl sulfone (1 equiv) was added and stirred for 15 hours at reflux.

Table 1. Indium-mediated reductive double aza-Michael type addition of nitrobenzene to divinyl sulfone under various conditions.



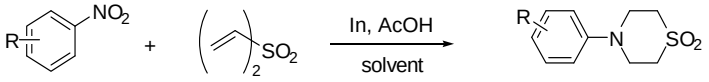
Entry	Molar equiv.		Solvent (mL)/ Temp (^{o}C)	Time (h)	Yield[a](%)	
	In	additive (equiv)			**1**	Anilin e
1	3	I_2 (0.8 eq)	MeOH (3)/reflux	24	24	25
2	3	I_2 (0.8 eq)	toluene (5)/reflux	20	5	13
3[b]	3	$InCl_3$ (0.4)	MeOH (3)/50	48	trace	-
4	4	$InCl_3$ (0.4)	THF/H_2O (5:1)/50	24	14	4
5	5	HI (10 eq)	MeOH (5)/50	6	7	92
6	5	AcOH (10 eq)	MeOH (10)/50	24	44	16
7	3	AcOH (10 eq)	MeOH (10)/reflux	24	52	19
8	5	AcOH (5 eq)	MeOH (10)/reflux	24	50	8
9	5	AcOH (10 eq)	MeOH (10)/reflux	24	63 (55[c])	9
10	5	AcOH (20 eq)	MeOH (10)/reflux	24	53	14
11	2	AcOH (10 eq)	THF (10)/reflux	24	6	4
12	5	AcOH (10 eq)	MeOH/sat-aq. NH_4Cl (6:3)/reflux	24	36	36
13	2	AcOH (10 eq)	MeOH/sat-aq. NH_4Cl (6:3)/reflux	24	64 (62[c])	11
14	1	AcOH (10 eq)	MeOH/sat-aq. NH_4Cl (6:3)/reflux	24	36	-
15	2	-	MeOH/sat-aq. NH_4Cl (6:3)/reflux	24	10	45
16	2	AcOH (10 eq)	MeOH/H_2O (6:3)/reflux	24	50	-

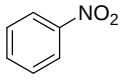
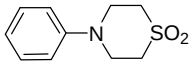
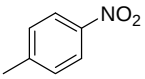
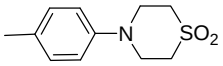
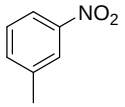
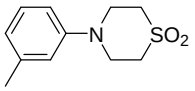
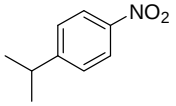
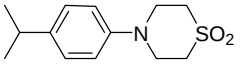
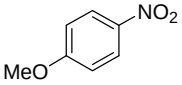
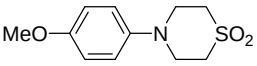
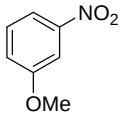
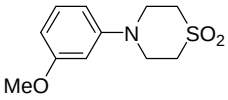
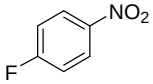
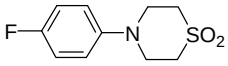
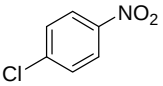
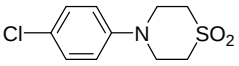
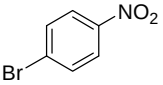
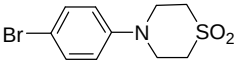
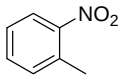
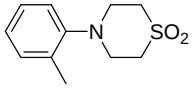
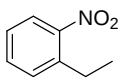
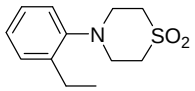
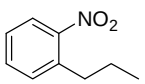
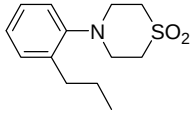
[a]GC yield with an internal standard. [b]Starting substrates mostly recovered. [c]Isolated yield.

However, it produced relatively poor yield of the thiomorpholine 1,1-dioxide (41%) with an increased amount of the aniline product (33%, GC yield) compared to the optimal condition, which implied the formation of aniline did not improve the yield of the desired product. Instead, it lowered the yield of the desired thiomorpholine 1,1-dioxide product. Thus, it is believed that the reductive one-pot transformation of nitronbenzene and divinyl sulfone to thiomorpholine 1,1-dioxide in the presence of AcOH/indium may not be primarily achieved via simple aza-Michael addition of in situ formed aniline to divinyl sulfone similar to our previous result.[9]

Interestingly, reactions in a MeOH/ sat-aq. NH_4Cl co-solvent system also produced thiomorpholine 1,1-dioxide in good yields (entries 12-15) with the best result obtained using two equiv of indium in MeOH/ sat-aq. NH_4Cl (6:3) at reflux (entry 13). Since the reaction conditions for both entries 9 and 13 produced

Table 2. Indium-mediated reductive double aza-Michael type addition of nitroarenes to divinyl sulfone under optimized conditions (Method A: nitroarene (1 mmol)/indium (5 mmol)/AcOH (10 mmol)/divinyl sulfone (1 mmol)/MeOH (10 ml)/24 h/reflux, Method B: nitroarene (1 mmol)/indium (2 mmol)/AcOH (10 mmol)/divinyl sulfone (1 mmol)/ MeOH (6 ml):sat-aq. NH_4Cl (3 ml)/ 24 h/ reflux)



Entry	Substrate	Product		Method	Yield[a](%)
1			**1**	A	55[c](69[b])
2				B	62
3			**2**	A	73[c](82[b])
4				B	64
5			**3**	A	69[c](84[b])
6				B	53
7			**4**	A	57[c](63[b])
8				B	54
9			**5**	A	48[c](59[b])
10				B	35
11			**6**	A	42[c](56[b])
12				B	48
13			**7**	A	47[c](64[b])
14				B	47
15			**8**	A	24[c](47[b])
16				B	35
17			**9**	A	26[c](52[b])
18				B	33
19			**10**	A	20[c,d](30[b])
20				B	37
21			**11**	A	12[c,e](24[b])
22				B	26
23			**12**	A	10[c,f](17[b])
24				B	34

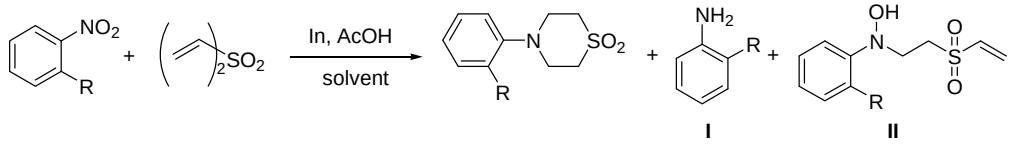
[a] Isolated yield. [b] Conversion yield. [c] Vinyl sulfone (9-50%) was recovered. [d] 17% of aniline was obtained. [e] 27% of aniline was obtained. [f] 14% of aniline was obtained.

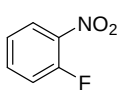
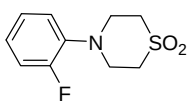
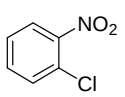
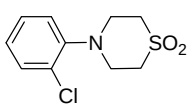
reasonable yields of the cyclic product, we decided to apply both sets of reaction conditions to various arylbenzenes for the synthesis of 4-aryl-1,4-thiomorpholine 1,1-dioxide derivatives as optimal conditions. Thus, both method A (nitrobenzene/divinyl sulfone (1 equiv)/AcOH (10 equiv)/In (5 equiv) in MeOH at reflux) and method B (nitrobenzene/dinvinyl sulfone (1 equiv)/AcOH (10 equiv)/In (2 equiv) in MeOH/sat-aq. NH_4Cl (6:3) at reflux) were examined with various substituted nitroarenes to find the optimal conditions for each substrate, and the results are summarized in Table 2. In general, methods A and B produced 1,4-thiomorpholine 1,1-dioxides in similar yields, but method B seemed to have greater reactivity than method A since the starting divinyl sulfone substrate was always recovered with method A, while no divinyl sulfone was observed with method B.

As shown in Table 2, when *para*- or *meta*-alkyl-substituted nitroarenes were used as the starting substrate, the cyclized thiomorpholine 1,1-dioxide product was obtained as the major product in good yield for both methods A and B (entries 1-8). However, *ortho*-alkyl-substituted nitroarenes exhibited poorer yields of cyclized product (entries 19-24) presumably because of steric hindrance from the ortho-alkyl substituent. Some *para*-heteroatom-substituted nitroarenes (entries 10, 15-18), in which the heteroatom has an electron-donating resonance effect, produced cyclized products in lower yields compared to the *para*-alkyl -substituted nitroarenes.

Interestingly, when ortho-fluoro- or ortho-chloro-substituted nitroarenes were reacted with divinyl sulfone, the major product was the *N*-(2-ethenesulfonylethyl)-*N*-aryl-hydroxylamine instead of the cyclized product (Table 3). Electronegative halogens at the ortho-position of the aromatic ring seemed to retard the second intramolecular nucleophilic attack of nitrogen to the vinyl sulfone group, which may come

Table 3. Indium-mediated reductive double aza-Michael type addition of 2-substituted nitroarenes to divinyl sulfone under the optimized conditions (Refer to Table 2 for Methods A and B)



Entry	Substrate	Cyclized product		Method	Yield[a](%)		
					Cyclized product	I[b]	II[b]
1			**13**	A	5	14	47
2				B	15	18	3
3			**14**	A	0	5	36
4				B	4	5	18

[a] Isolated yield. [b] GC yield with an internal standard.

from the strong inductive effect of the ortho-halogen substituent. More detailed mechanistic studies will be performed in the future.

In conclusion, we have established a new and efficient method for the synthesis of 1,4-thiomorpholine 1,1-dioxides from 2-nitroarene/divinyl sulfone using indium/AcOH under mild conditions. This one-pot cyclization method can be utilized for the introduction of the biologically active 1,4-thiomorpholine 1,1-dioxide moiety starting from a nitro compound.

EXPERIMENTAL

1. General consideration

Most of chemical reagents were purchased from Aldrich and used without further purification in most cases. Solvents were purchased and dried by a standard method. ^{1}H NMR spectra were recorded on 400 MHz Jeol instrument and ^{13}C NMR spectra were recorded on 100 MHz Jeol instrument. Chemical shifts are in ppm from tetramethylsilane (TMS). HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer and GC/MS were recorded on a HP5975 mass spectrometer. IR spectra were recorded on a MB104FTIR (ABB Bomem Inc.). Melting points were determined on an Electrothermal apparatus and are uncorrected. All the major products were isolated by flash column chromatography on silica gel (230 - 400 mesh ATSM, purchased from Merck) with eluents of mixed solvents (ethyl acetate and hexane).

2. General procedure for indium-mediated aza-Michael type double addition reactions of 2-nitroarenes to divinyl sulfones

2.1. Method A

Nitrobenzene derivative (1 mmol) was added to a mixture of indium powder (574 mg, 5.0 mmol), acetic acid (0.566 mL, 10 mmol) in MeOH (5 mL), and then vinyl sulfone (1 mmol) in MeOH (5 mL) was added. The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, it was diluted with CH_2Cl_2 (30 mL), filtered through Celite, poured into sat-aq $NaHCO_3$ solution (30 mL), and then extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 15/85) through a silica gel column to give the corresponding 4-phenylthiomorpholine 1,1-dioxide derivative.

2.2. Method B

Nitrobenzene derivative (1 mmol) was added to a mixture of indium powder (230 mg, 2.0 mmol) and acetic acid (0.566 mL, 10mmol) in MeOH (3 mL), and then vinyl sulfone (1 mmol) in MeOH (3 mL) and saturated aq. NH_4Cl (3 mL) was added. The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, it was diluted with Et_2O (30 mL), filtered through Celite,

poured into 10% aqueous $NaHCO_3$ solution (30 mL), and then extracted with Et_2O (30 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with EtOAc/hexane (v/v = 15/85) through a silica gel column to give the corresponding 4-phenylthiomorpholine 1,1-dioxide derivatives.

4-Phenylthiomorpholine 1,1-dioxide (1) solid; mp 131.5-133.8 °C; TLC (40% EtOAc/hexane) R_f 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 2H), 6.91-6.96 (m, 3H), 3.85 (t, J = 5.4 Hz, 4H), 3.11 (t, J = 5.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.58, 129.74, 120.58, 116.33, 50.49, 47.63; IR (KBr) 3007, 2977, 2931, 2921, 1590, 1575, 1499, 1377, 1301 cm^{-1}; GC-MS m/z (rel. intensity) 211 (M^+, 100), 145 (88), 104 (90), 91 (30), 77 (67).

4-(4-Methylphenyl)thiomorpholine 1,1-dioxide (2) Solid; mp 142.8-144.8 °C; TLC (40% EtOAc/hexane) R_f 0.41; ^{1}H MNR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.79 (t, J = 5.4 Hz, 4H), 3.11 (t, J = 5.4 Hz, 4H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.64, 130.64, 130.22, 116.83, 50.57, 48.19, 20.40; IR (KBr) 3032, 2977, 2928, 1609, 1511, 1382, 1311 cm^{-1}; GC-MS m/z (rel. intensity) 225 (M^+, 100), 159 (53), 118 (56), 91 (38); HRMS (EI) calcd. for $C_{11}H_{15}NO_2S$ 225.0823, found 225.0824.

4-(3-Methylphenyl)thiomorpholine 1,1-dioxide (3) Solid; mp 99.5-103.3 °C; TLC (40% EtOAc/hexane) R_f 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.0, 8.0 Hz, 1H), 6.71-6.77 (m, 3H), 3.84 (t, J = 5.0 Hz, 4H), 3.10 (t, J = 5.0 Hz, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.62, 139.59, 129.56, 121.72, 117.13, 113.41, 50.53, 47.66, 21.73; IR (KBr) 3034, 2987, 2933, 2839, 1606, 1580, 1385, 1314 cm^{-1}; GC-MS m/z (rel. intensity) 225 (M^+, 100), 159 (65), 118 (63), 91 (46); HRMS (EI) calcd. for $C_{11}H_{15}NO_2S$ 225.0823, found 225.0821.

4-(4-Isopropylphenyl)thiomorpholine 1,1-dioxide (4) Solid; mp 129.0-132.4 °C; TLC (40% EtOAc/hexane) R_f 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.81 (t, J = 5.0 Hz, 4H), 3.12 (t, J = 5.0 Hz, 4H), 2.86 (sep, J = 6.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.79, 141.67, 127.57, 116.72, 50.60, 48.09, 33.16, 24.03; IR (KBr) 3002, 2958, 2936, 2841, 1610, 1512, 1383, 1321 cm^{-1}; GC-MS m/z (rel. intensity) 253 (M^+, 43), 238 (100); HRMS (EI) calcd. for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1137.

4-(4-Methoxyphenyl)thiomorpholine 1,1-dioxide (5) Solid; mp 146.0-148.1 °C; TLC (40% EtOAc/hexane) R_f 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90-6.93 (m, 2H), 6.85-6.88 (m, 2H), 3.78 (s, 3H), 3.68 (t, J = 5.2 Hz, 4H), 3.14 (t, J = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.84, 142.73, 119.42, 114.82, 55.54, 51.02, 49.50; IR (KBr) 3076, 3043, 2979, 1961, 2925, 2831, 1610, 1513, 1380, 1308 cm^{-1}; GC-MS m/z (rel. intensity) 241 (M^+, 100), 226 (30), 175 (23), 134 (41); HRMS (EI) calcd. for $C_{11}H_{15}NO_3S$ 241.0773, found 241.0771.

4-(3-Methoxylphenyl)thiomorpholine 1,1-dioxide (6) Solid; mp 72.9-76.2 °C; TLC (40% EtOAc/hexane) R_f 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 8.1, 8.1 Hz, 1H), 6.44-6.53 (m, 3H), 3.85 (t, J = 5.0 Hz, 4H), 3.80 (s, 3H), 3.09 (t, J = 5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.99, 148.75, 130.55, 108.76, 105.10, 103.13, 55.27, 50.44, 47.46; IR (KBr) 3099, 3076, 3022, 2993, 2943, 2921, 2891, 1610, 1506, 1362, 1303 cm^{-1}; GC-MS m/z (rel. intensity) 241 (M^+, 100), 175 (65), 134 (40); HRMS (EI) calcd. for $C_{11}H_{15}NO_3S$ 241.0773, found 241.0774.

4-(4-Fluorophenyl)thiomorpholine 1,1-dioxide (7) Solid; mp 126.1-123.9 °C; TLC (40% EtOAc/hexane) R_f 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97-7.04 (m, 2H), 6.88-6.93 (m, 2H) 3.73 (t, J = 5.4 Hz, 4H), 3.13 (t, J = 5.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.06, 156.66, 145.04, 145.02, 119.05, 118.98, 116.29, 116.06, 50.85, 49.05; IR (KBr) 3075, 3052, 3001, 2935, 2909, 2861, 1599, 1513, 1370, 1306 cm^{-1}; GC-MS m/z (rel. intensity) 229 (M^+, 82), 163 (74), 122 (100), 109 (33), 95 (53); HRMS (EI) calcd. for $C_{10}H_{12}FNO_2S$ 229.0573, found 229.0572.

4-(4-Chlorophenyl)thiomorpholine 1,1-dioxide (8) Solid; mp 162.4-164.1 °C; TLC (40% EtOAc/hexane) R_f 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 3.81 (t, J = 5.0 Hz, 4H) 3.12 (t, J = 5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.44, 129.63, 126.07, 117.81, 50.52, 47.91; IR (KBr) 3088, 3059, 3038, 2987, 2939, 2841, 1592, 1491, 1378, 1309 cm^{-1}; GC-MS m/z (rel. intensity) 245 (M^+, 100), 179 (79), 138 (79), 111 (39), 75 (18); HRMS (EI) calcd. for $C_{10}H_{12}ClNO_2S$ 245.0277, found 245.0280.

4-(4-Bromophenyl)thiomorpholine 1,1-dioxide (9) Solid, mp 199.0-201.6 °C; TLC (40% EtOAc/hexane) R_f 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 3.82 (t, J = 4.9 Hz, 4H), 3.10 (t, J = 4.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.80, 132.57, 118.10, 113.27, 50.47, 47.73; IR (KBr) 3082, 3060, 2993, 2934, 2938, 1650, 1587, 1491, 1380, 1313 cm^{-1}; GC-MS m/z (rel. intensity) 291 (M+1, 100), 223 (81), 184 (74), 155 (34), 117 (40); HRMS (EI) calcd. for

$C_{10}H_{12}BrNO_2S$ 288.9772, found 288.9776.

4-(2-Methylphenyl)thiomorpholine 1,1-dioxide (10) Solid; mp 141.0-143.5 °C; TLC (40% EtOAc/hexane) R_f 0.47; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.22 (m, 2H), 7.04-7.08 (m, 2H), 3.42 (t, J = 5.2 Hz, 4H), 3.21 (t, J = 5.2 Hz, 4H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.12, 132.61, 131.30, 126.90, 124.82, 120.30, 52.57, 50.57, 17.74; IR (KBr) 3059, 3025, 2982, 2959, 2933, 2849, 2835, 1593, 1579, 1495, 1377, 1308 cm^{-1}; GC-MS m/z (rel. intensity) 225 (M^+, 100), 159 (30), 144 (80), 131 (25), 118 (94), 91 (39); HRMS (EI) calcd. for $C_{11}H_{15}NO_2S$ 225.0823, found 225.0819.

4-(2-Ethylphenyl)thiomorpholine 1,1-dioxide (11) Solid; mp 118.6-120.8 °C; TLC (40% EtOAc/hexane) R_f 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.25 (m, 4H), 3.41 (t, J = 5.2 Hz, 4H), 3.21 (t, J = 5.2 Hz, 4H), 2.70 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.79, 139.09, 129.29, 126.81, 125.58, 121.11, 52.63, 51.33, 23.75, 14.81; IR (KBr) 3061, 3031, 2978, 2964, 2924, 2864, 2847, 1597, 1496, 1386, 1336, 1302 cm^{-1}; GC-MS m/z (rel. intensity) 239 (M^+, 73), 158 (37), 132 (100), 118 (31); HRMS (EI) calcd. for $C_{12}H_{17}NO_2S$ 239.0980, found 239.0982.

4-(2-Propylphenyl)thiomorpholine 1,1-dioxide (12) Solid; mp 83.2-85.4 °C; TLC (40% EtOAc/hexane) R_f 0.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.24 (m, 4H), 3.40 (t, J = 5.1 Hz, 4H), 3.20 (t, J = 5.1 Hz, 4H), 2.63 (t, J = 7.7 Hz, 2H), 1.60-1.69 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.03, 137.79, 130.08, 126.85, 125.53, 121.29, 52.65, 51.40, 33.01, 23.88, 14.27; IR (KBr) 3072, 2982, 2965, 2930, 2854, 1597, 1493, 1386, 1310 cm^{-1}; GC-MS m/z (rel. intensity) 253 (M^+, 100), 172 (22), 146 (60), 132 (89), 118 (40); HRMS (EI) calcd. for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1132.

4-(2-Fluorophenyl)thiomorpholine 1,1-dioxide (13) Solid; mp 133.3-136.0 °C; TLC (40% EtOAc/hexane) R_f 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-7.11 (m, 4H), 3.62 (t, J = 5.1 Hz, 4H), 3.21 (t, J = 5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.82, 154.37, 138.40, 138.31, 124.68, 124.64, 124.28, 124.20, 120.61, 116.62, 116.43, 52.00, 49.47, 49.44; IR (KBr) 3074, 2986, 2936, 2844, 1605, 1500, 1379, 1349, 1313 cm^{-1}; GC-MS m/z (rel. intensity) 229 (M^+, 62), 163 (78), 122 (100), 109 (23), 95 (32); HRMS (EI) calcd. for $C_{10}H_{12}FNO_2S$ 229.0573, found 229.0569.

4-(2-Chlorophenyl)thiomorpholine 1,1-dioxide (14) Solid; mp 129.0-132.4 °C; TLC (40% EtOAc/hexane) R_f 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.9, 1.4 Hz, 1H), 7.23-7.28 (m, 1H),

7.05-7.10 (m, 2H), 3.55 (t, J = 5.2 Hz, 4H), 3.25 (t, J = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.91, 130.73, 129.10, 127.80, 125.24, 121.60, 52.39, 50.01; IR (KBr) 3075, 3050, 3020, 2977, 2959, 2922, 2835, 1616, 1579, 1510, 1470, 1379, 1310 cm^{-1}; GC-MS m/z (rel. intensity) 245 (M^+, 53), 179 (100), 138 (100), 111 (36), 75 (22) ; HRMS (EI) calcd. for $C_{10}H_{12}ClNO_2S$ 245.0722, found 245.0279.

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