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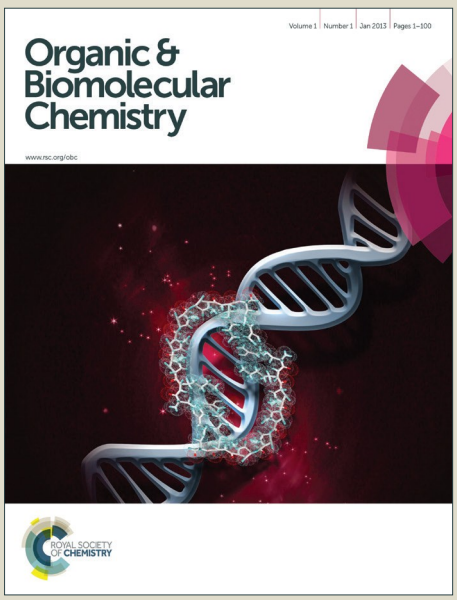

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PAPER

Facile Synthesis of Aza-Spirocyclopropanyl Oxindole by the Reaction of 3-(2-Bromoethyl)-Indole with 2,3-Dimethylimidazole-1-sulfonyl Azide Triflate †

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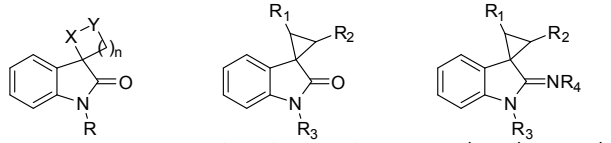
Abstract: 3-(2-bromoethyl)indole reacts with 2,3-dimethylimidazole-1-sulfonyl azide triflate to give an intermediate: N-(2,3-dimethylimidazole)-1-sulfonyl aza-spirocyclopropanyloxindole. This reactive species is captured by alcohol or amine to afford corresponding aza-spiroxindole sulfonate and sulfonamide.

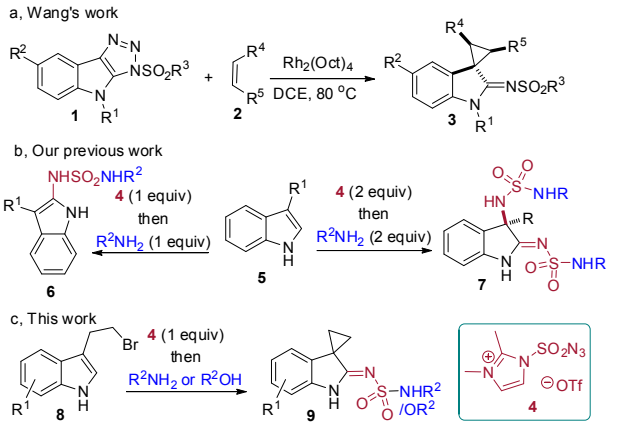
Introduction

Spiroxindole scaffold **I** is a class of privileged framework in the area of pharmaceutical research as a large number of bioactive molecules have been found consisting of this motif, and therefore have captured intensive attention of both synthetic chemists and medicinal chemists.[1] Spirocyclopropanyl oxindoles **II** distinguish themselves from other spiroxindoles by the characteristic fusion of a smallest three-menbered ring with an oxindole ring. These spiroxindoles are not only promising medicinal targets with interesting biological activities,[2] they are also valuable synhtons for other spiroxindoles[3] and accordingly there are many methods developed to access this scaffold.[4] However it's N-analogue, namely aza-spiroxindole **III**, is extremely rare and literature survey finds only one example (Figure 1). 2014 Wang group reported a rhodium catalysed cyclopropanation of alkene **2** with indolyl triazole compound **1** to give **3** (Scheme 1. a).[5]



spiroxindole (**I**) | spirocyclopropanyl oxindole (**II**) | aza-spirocyclopropanyl oxindole (**III**)

Figure 1. Three common ring-opening mechanisms of cyclopropanol



Scheme 1. a, wang's synthesis of aza-spirocycloxindole; b, Reaction of 3-Substituted Indole with 2,3-Dimethylimidazole-1-sulfonyl Azide Triflate and amine; c, Reaction of 3-(2-Bromoethyl)-Indole with 2,3-Dimethylimidazole-1-sulfonyl azide triflate and amine/alcohol.

Recently we have disclosed divergent transformations of 3-substituted indole **5** to indole derivatives **6** and **7** through stoichiometric control of reagent 2,3-Dimethylimidazole-1-sulfonyl azide triflate **4** and amine (Scheme 1. b).[6] Here we would like to report an efficient synthesis of aza-spirocloprapanyloxindole **9** from the reaction of 3-(2-bromoethyl)indoles **8** with **4** (Scheme 1. c).

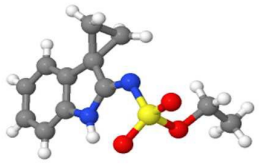


Figure 2. Crystal structure of **9b** (CCDC 1431979)

Results and Discussion

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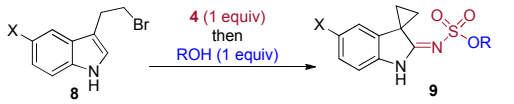
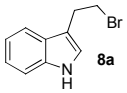
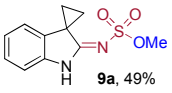
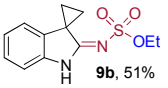
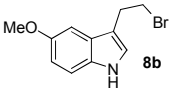
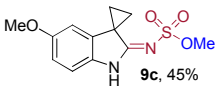
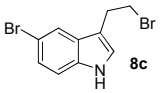
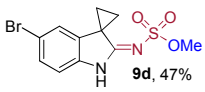
During the course of our study on reaction of indoles with sulfonyl azides, it was found that cyclopropane **9a** was isolated in 49% yield after treatment of 3-(2-bromoethyl)indoles **8a** with **4** in DCE at 40 °C and subsequent quench the reaction with methanol. Similarly, when Ethanol was used in place of methanol, corresponding aza-spiroxindole **9b** was obtained in comparable yield whose structure was established by X-ray crystal diffraction experiment (Figure 2). Substrates **8b** and **8c** with methoxyl and bromide substituents on the indole ring underwent the same reaction to give **9c** and **9d** in analogous yields.

Table 1. Reaction of 3-(2-Bromoethyl)-Indole with 2,3-Dimethylimidazole-1-sulfonyl azide triflate and alcohol[a]



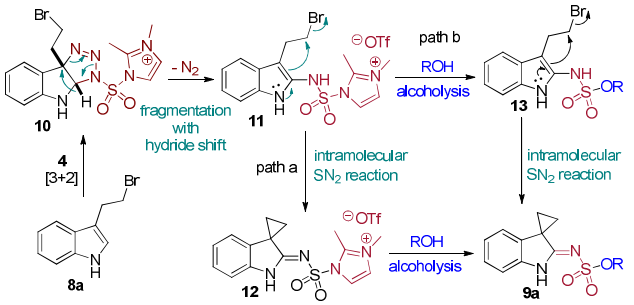
entry	substrate	alcohol	product, yield[b]
1		MeOH	 **9a**, 49%
2	**8a**	EtOH	 **9b**, 51%
3	 **8b**	MeOH	 **9c**, 45%
4	 **8c**	MeOH	 **9d**, 47%

a, Conditions: **8** (0.3-0.7 mmol), **4** (1.0 equiv), DCE (4-8 mL), 40 °C, 20 min then alcohol (1.0 equiv), 30 min; b, isolated yield

Based on previous studies,[6] we reasoned that the initial intermediate produced from the [3 + 2] reaction of **8a** with **4** would be **10** which would fragment with simultaneous 1,2-H shift to afford indolyl sulfuric amide **11.** Upon formation, intermediate **11** would undergo an intramolecular SN_2 reaction cyclizing to spirocyclopropane **12**. Alcoholysis of the imidazolium segment in **12** would then complete the product **9a** (Scheme 2, path a). Alternatively, the transformation of **11** to **9a** could also be achieved via a reversed sequence of SN_2 cyclopropanation and alcoholysis steps (path b).

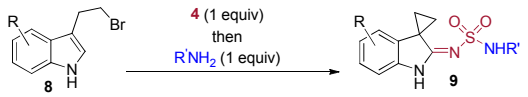
According to the above mechanism discussion, we reasoned that more nucleophilic amine would be effective as well to capture the sulfuric intermediate. Indeed, when benzyl amine was introduced to the reaction mixture of **8a** and **4**, aza-spirocyclopropanyl oxindole **9e** was obtained in excellent yield (Table 2, entry 5). Other primary amines such as n-butylamine, Phenethylamine and even bulky *t*-butylamine were all good reagents to give corresponding indolinidenesulfuric diamide **9e**-**9h** in high yields (Table 2 entry 6-8). 6-Bromination on the indole ring resulted in a ~10% reduce in yields (entries 9-10). Comparable result was obtained with 8-chlorated substrates.

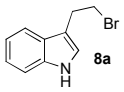
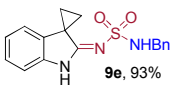
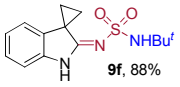
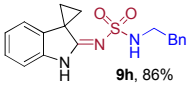
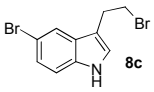
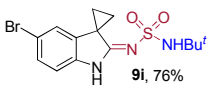
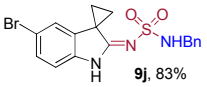
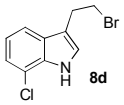
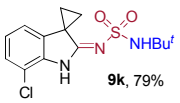
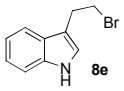
N-methylated substrate **8d** was also good substrate for this reaction albeit affording slightly lower yields (entries 12-13).



Scheme 2. Possible reaction pathways

Table 2. Reaction of 3-(2-Bromoethyl)-Indole with 2,3-Dimethylimidazole-1-sulfonyl azide triflate and amine[a]



entry	substrate	amine	product, yield[b]
5	 **8a**	$BnNH_2$	 **9e**, 93%
6	**8a**	*t*-$BuNH_2$	 **9f**, 88%
7	**8a**	*n*-$BuNH_2$	 **9g**, 92%
8	**8a**		 **9h**, 86%
9	 **8c**	*t*-$BuNH_2$	 **9i**, 76%
10	**8c**	$BnNH_2$	 **9j**, 83%
11	 **8d**	*t*-$BuNH_2$	 **9k**, 79%
12	 **8e**	*n*-$BuNH_2$	 **9l**, 71%
13	**8e**	*t*-$BuNH_2$	 **9m**, 63%

a, Conditions: 8 (0.3-0.7 mmol), 4 (1.0 equiv), DCE (4-8 mL), 40 °C, 20 min then amine (1.0 equiv), 30 min; b, isolated yield

In order to distinguish the operating pathway, the reaction mixture of **8a** with **4** was submitted to NMR experiments. A prominent signal appeared at 1.7 ppm indicating the existence of cyclopropanyl ring and a strong broad peak around 5.25 ppm was attribute to the N-H. These observations support that the reaction proceed through cyclopropanyl intermediate **11** (Scheme 2, path a).

Conclusions

In summary, an interesting cyclopropantion reaction is devised providing a facile access to aza-spirocyclopropanyloxindole derivatives. 3-(2-bromoethyl)indoles react with 2,3-Dimethylimidazole-1-sulfonyl azide triflate to produce an intermediate, N-(2,3-Dimethylimidazole)-1-sulfonyl aza-spirocyclopropanyloxindole. Harvesting this reactive species by addition of alcohol or amine afford corresponding aza-spiroxindole sulfonate and sulphonamide, providing an efficient method to conjugate the indole moiety with alcohols and amines.

Experimental section

General experimental methods

NMR spectra were recorded using Bruker AV-300 / AV-400 spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on an agilent 6230 spectrometer and were obtained by peak matching. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator and/or by exposure to phosphormolybdic acid/cerium (IV) sulfate/ ninhydrine followed by brief heating with a heat gun. Liquid chromatography (flash chromatography) was performed on 200-300 Å mesh silica gel (SiO2).

General experimental procedure for the reaction of 8 with 4 and alcohol/amine

4 (0.5 mmol) was added to a mixture of **8** (0.5 mmol) in 1,2-DCE (8 mL) at 40 ^{o}C, and the reaction was stirred for 20 min at 40 oC. RNH_2 or ROH (0.5 mmol) was added, and the reaction was stirred for 30 min at 40 ^{o}C. The reaction was concentrated, the residue was purified by flash column chromatography eluting with hexanes/EtOAc to give **9**.

9a. Following the general procedure, **8a** (70 mg, 0.31 mmol), **4** (110 mg, 0.31 mmol) and MeOH (10 mg, 0.31 mmol) were converted into **9a** (39 mg, 49%): White solid. m.p 166-167 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.29 – 7.25 (m, 1H), 7.14-7.10 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 1.96-1.93 (m, 2H), 1.80-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.3, 131.3, 127.3, 123.8, 118.6, 111.3, 56.9, 30.8, 23.1; HRMS (ESI) *m/z* Calcd for $C_{11}H_{13}N_2O_3S^+$ $[M + H]^+$ 253.0631, found 253.0620.

9b. Following the general procedure, **8a** (111 mg, 0.50 mmol), **4** (176 mg, 0.50 mmol) and EtOH (23 mg, 0.50 mmol) were converted into **9b** (68 mg, 51%): White solid. m.p 171-172 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.28 – 7.24 (m, 1H), 7.15 – 7.09 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.94 – 1.91 (m, 2H), 1.78 – 1.75 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 140.4, 131.3, 127.3, 123.7, 118.5, 111.3, 67.3, 30.7, 22.9, 14.8; HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}N_2O_3S^+$ $[M + H]^+$ 267.0790, found 267.0779.

9c. Following the general procedure, **8b** (95 mg, 0.38 mmol), **4** (132 mg, 0.38 mmol) and MeOH (12 mg, 0.38 mmol) were converted into **9c** (46 mg, 43%): White solid. m.p 151-152 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.80 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 1.97 – 1.93 (m, 2H), 1.77 – 1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.9, 133.8, 132.9, 112.0, 111.9, 105.4, 56.8, 55.8, 31.1, 23.1; HRMS (ESI) *m/z* Calcd for $C_{12}H_{14}N_2NaO_4S^+$ $[M + Na]^+$ 305.0566, found 305.0560.

9d. Following the general procedure, **8c** (199 mg, 0.66 mmol), **4** (232 mg, 0.66 mmol) and MeOH (21 mg, 0.66 mmol) were converted into **9d** (80 mg, 37%): Yellow oil. ^{1}H NMR (300 MHz, DMSO) δ 11.65 (s, 1H), 7.45 (d, *J* = 9.5 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 1H), 3.75 (s, 3H), 2.00 (d, *J* = 4.0 Hz, 2H), 1.74 (d, *J* = 3.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 171.7, 141.2, 134.6, 130.1, 122.9, 116.0, 114.5, 57.1, 31.3, 23.6; HRMS (ESI) *m/z* Calcd for $C_{11}H_{12}BrN_2O_3S^+$ $[M + H]^+$ 330.9752, found 330.9752.

9e. Following the general procedure, **8a** (140 mg, 0.63 mmol), **4** (221 mg, 0.63 mmol) and $BnNH_2$ (12 mg, 0.63 mmol) were converted into **9e** (192 mg, 93%): White solid. m.p 146-147 ^{o}C. ^{1}H NMR (300 MHz, DMSO) δ 10.98 (s, 1H), 7.44 (t, *J* = 6.6 Hz, 1H), 7.33 – 7.30 (m, 3H), 7.27 – 7.18 (m, 4H), 7.04 – 7.01 (m, 2H), 4.09 (d, *J* = 6.5 Hz, 2H), 1.70 – 1.67 (m, 2H), 1.45 – 1.41 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 169.1, 142.4, 138.9, 131.5, 128.7, 128.3, 127.8, 127.5, 127.1, 123.1, 119.5, 112.2, 111.7, 46.9, 30.3, 22.2; HRMS (ESI) *m/z* Calcd for $C_{17}H_{18}N_3O_2S^+$ $[M + H]^+$ 328.1114, found 328.1113.

9f. Following the general procedure, **8a** (78 mg, 0.35 mmol), **4** (123 mg, 0.35 mmol) and $^{t}BuNH_2$ (26 mg, 0.35 mmol) were converted into **9f** (90 mg, 88%): White solid. m.p 152-153 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.23 (dd, *J* = 11.9, 4.5 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 4.76 (s, 1H), 1.88 – 1.84 (m, 2H), 1.69 – 1.65 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 141.1, 131.2, 127.1, 123.0, 118.3, 111.1, 53.9, 30.2, 30.0, 21.9; HRMS (ESI) *m/z* Calcd for $C_{14}H_{20}N_3O_2S^+$ $[M + H]^+$ 294.1271, found 294.1271.

9g. Following the general procedure, **8a** (78 mg, 0.35 mmol), **4** (123 mg, 0.35 mmol) and $^{n}BuNH_2$ (26 mg, 0.35 mmol) were converted into **9g** (94 mg, 92%): White solid. m.p 159-160 ^{o}C. ^{1}H NMR (300 MHz, DMSO) δ 10.95 (s, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.09 – 6.98 (m, 2H), 6.79 (t, *J* = 6.1 Hz, 1H), 2.84 (dd, *J* = 13.3, 6.8 Hz, 2H), 1.78 (dd, *J* = 7.8, 3.8 Hz, 2H), 1.56 (dd, *J* = 7.7, 3.6 Hz, 2H), 1.46 – 1.36 (m, 2H), 1.31 – 1.23 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 169.0, 142.4, 131.4, 127.3, 122.9, 119.4, 111.9, 43.0, 31.4, 30.3, 22.1, 19.9, 14.1; HRMS (ESI) *m/z* Calcd for $C_{14}H_{20}N_3O_2S^+$ $[M + H]^+$ 294.1276, found 294.1277.

9h. Following the general procedure, **8a** (78 mg, 0.35 mmol), **4** (123 mg, 0.35 mmol) and Phenethylamine (43 mg, 0.35 mmol) were converted into **9h** (103 mg, 86%): White solid. m.p 175-176 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.21 – 7.08 (m, 6H), 7.04 – 6.98 (m, 2H), 6.81 (d, *J* = 7.4 Hz, 1H), 4.46 (t, *J* = 6.4 Hz, 1H), 3.26 (q, *J* = 6.9 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 1.79 – 1.75 (m, 2H), 1.64 – 1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 140.8, 138.1, 131.2, 128.8, 128.7, 127.2, 126.7, 123.3, 118.4, 111.1, 44.8, 35.6, 30.3, 22.7; HRMS (ESI) *m/z* Calcd for $C_{18}H_{20}N_3O_2S^+$ $[M + H]^+$ 342.1276, found 342.1280.

9i. Following the general procedure, **8c** (144 mg, 0.48 mmol), **4** (168 mg, 0.48 mmol) and ^{t}BuNH$_2$ (35 mg, 0.48 mmol) were converted into **9i** (135 mg, 76%): White solid. m.p 194-195 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.31 (s, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 1.84 (s, 2H), 1.56 (s, 2H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 167.4, 141.8, 134.2, 129.9, 122.7, 114.9, 113.5, 53.0, 30.3, 30.1, 22.2; HRMS (ESI) *m/z* Calcd for $C_{14}H_{19}BrN_3O_2S^+$ $[M + H]^+$ 372.0376, found 372.0368.

9j. Following the general procedure, **8c** (144 mg, 0.48 mmol), **4** (168 mg, 0.48 mmol) and BnNH$_2$ (52 mg, 0.48 mmol) were converted into **9j** (161 mg, 83%): White solid. m.p 188-189 °C. ^{1}H NMR (300 MHz, DMSO) δ 10.79 (s, 1H), 7.49 (s, 1H), 7.39 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.30 – 6.98 (m, 7H), 4.08 (s, 2H), 1.76 (d, *J* = 4.0 Hz, 2H), 1.42 (d, *J* = 3.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 168.7, 141.9, 138.9, 134.3, 129.9, 128.5, 128.1, 127.4, 122.5, 115.0, 113.8, 46.9, 30.4, 22.8; HRMS (ESI) *m/z* Calcd for $C_{17}H_{17}BrN_3O_2S^+$ $[M + H]^+$ 406.0219, found 406.0208.

9k. Following the general procedure, **8d** (159 mg, 0.67 mmol), **4** (236 mg, 0.67 mmol) and ^{t}BuNH$_2$ (49 mg, 0.67 mmol) were converted into **9k** (146 mg, 71%): White solid. m.p 157-158 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.27 (t, *J* = 6.9 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.67 (s, 1H), 3.41 (s, 3H), 2.59 (s, 2H), 1.71 (s, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 167.5, 142.6, 133.0, 127.3, 123.2, 118.5, 109.6, 53.1, 30.2, 30.0, 29.8, 22.3; HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}N_3O_2S^+$ $[M + H]^+$ 308.1427, found 308.1429.

9l. Following the general procedure, **8d** (154 mg, 0.65 mmol), **4** (228 mg, 0.65 mmol) and ^{n}BuNH$_2$ (48 mg, 0.65 mmol) were converted into **9l** (126 mg, 63%): White solid. m.p 153-154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 7.09 (td, *J* = 7.6, 0.8 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.0 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 1H), 3.51 (s, 3H), 3.19 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.73 (q, *J* = 4.3 Hz, 2H), 1.70 (q, *J* = 4.4 Hz, 2H), 1.61 (t, *J* = 7.6 Hz, 2H), 1.48 – 1.36 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 142.6, 132.90, 127.3, 123.4, 118.5, 109.8, 43.7, 42.3, 31.3, 29.9, 22.2, 20.0, 14.1; HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}N_3O_2S^+$ $[M + H]^+$ 308.1433, found 308.1432.

9m. Following the general procedure, **8e** (230 mg, 0.89 mmol), **4** (314 mg, 0.89 mmol) and ^{t}BuNH$_2$ (66 mg, 0.89 mmol) were converted into **9m** (230 mg, 79%): White solid. m.p 197-198 °C. ^{1}H NMR (300 MHz, DMSO) δ 10.96 (s, 1H), 7.32 (s, 1H), 7.07 (s, 2H), 6.74 (s, 1H), 1.79 (s, 2H), 1.57 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, DMSO) δ 167.7, 143.8, 131.5, 130.4, 122.5, 120.9, 111.8, 53.0, 30.1, 30.0, 21.9; HRMS (ESI) *m/z* Calcd for $C_{14}H_{19}ClN_3O_2S^+$ $[M + H]^+$ 328.0881, found 328.0871.

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