HETEROCYCLES, Vol. 101, No. 1, 2020, pp. 363 - 372. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2019, Accepted, 5th August, 2019, Published online, 11th September, 2019
DOI: 10.3987/COM-19-S(F)33

CONSTRUCTION OF QUATERNARY CARBON CENTER BY THE REACTION OF AZA-*o*-QUINONE METHIDE MEDIATED CARBOCATION INTERMEDIATE

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This manuscript is in celebration of Professor Kaoru Fuji's 80th birthday and for his dedication to research and education.

Abstract – Reactions of carbocationic intermediate corresponding to aza-*o*-quinone methide with indoles to construct quaternary carbon center were described. Treatment of *N*-tosylated 2-(2-aminophenyl)propan-2-ol with iron(III) chloride provided tertiary benzylic carbocation intermediate possible to isomerize to the corresponding aza-*o*-quinone methide. The electron-deficient intermediate enabled to undergo nucleophilic attack by indoles, representing the first example of intermolecular formation of quaternary carbon center using aza-*o*-quinone methide mediated carbocation intermediate.

ortho-Quinone methide (*o*-QM), a significantly enhanced electrophile, can be obtained from precursors derived from salicyl alcohols (Figure 1). The precursors can generate *o*-QM by the treatment of acid,[1] fluoride,[2] heating[3] or irradiation of UV light.[4] It is well demonstrated that, once generated, significantly electrophilic *o*-QM enabled a broad range of [4+2] cyclization with alkene dienophiles,[5] other related addition reactions,[6] and also natural product synthesis.[7] Moreover, several groups succeeded in biological use of *o*-QM such as fluorescent labeling of proteins and antibodies[8] and sensor of intracellular β-glucosidase.[9] On the other hand, aza-*o*-quinone methide (aza-*o*-QM), a nitrogen analogue of *o*-QM, was also used in organic synthetic reactions, however aza-*o*-QM have not been studied energetically compared to *o*-QM,[10] so that the synthetic utility of aza-*o*-QM remain unclear. There are a few reports that demonstrate synthetic utility of aza-*o*-QM in the synthesis of tetrahydroquinoline,[11] and indoline spiroamines[12] of potential anticancer communesin F[13] and vincorine[14] (Figure 2). However, all reactions of

aza-*o*-QM reported to date are restricted to the bond forming reaction on primary or secondary carbons, in other words, synthetic approach to obtain quaternary carbon center using aza-*o*-QM remain unexplored. In the course of these studies, we focused on the synthetic application of aza-*o*-QM for quaternary carbon-center formation. Herein, we discuss *N*-tosylated 2-(2-aminophenyl)propan-2-ol as a useful precursor for the generation of aza-*o*-QM which is equivalent to tertiary benzylic carbocation intermediate possible to react with indoles to form diarylmethanes with quaternary carbon centers.

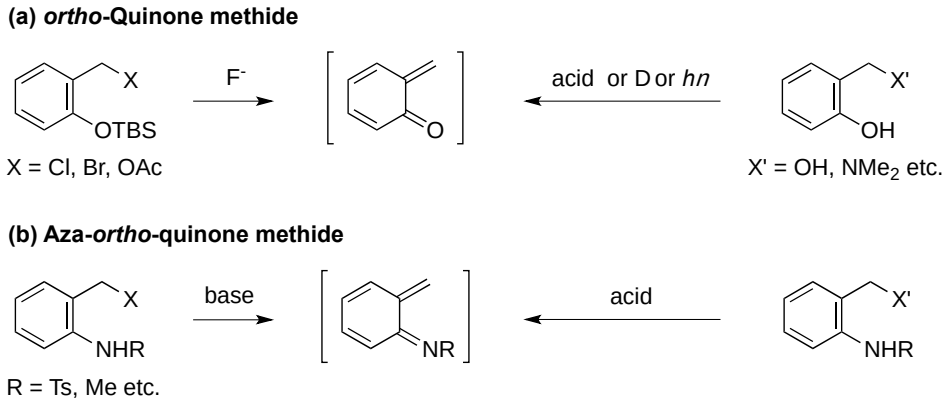


Figure 1. The generation of *ortho*-quinone methide (*o*-QM)

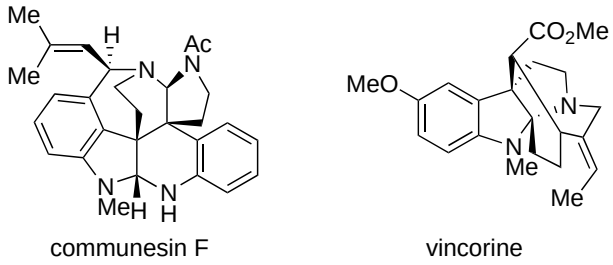
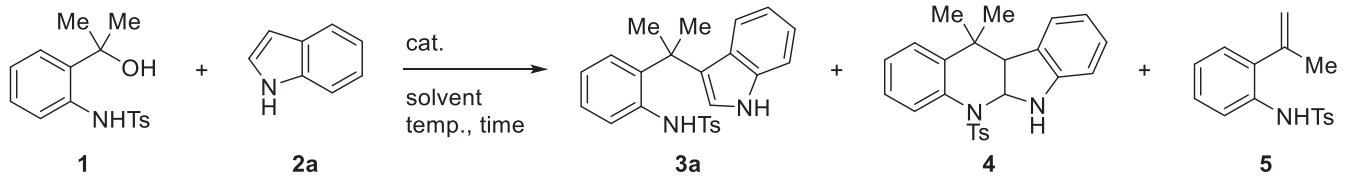


Figure 2. The natural products possessing indoline aminal skeleton

We first examined the reaction of *N*-tosylated 2-(2-aminophenyl)propan-2-ol (**1**), a precursor of aza-*o*-QM generation, with indole **2a** in the presence of several acid catalysts (Table 1). As shown in entries 1 and 2, the reactions did not take place at all in THF solution with a catalytic amount of iron(III) chloride ($FeCl_3$) at room temperature. Solvent exchange to $CHCl_3$ was not effective for the reaction even in refluxing condition (entry 3). These results suggested that higher temperatures would be required to generate aza-*o*-QM or corresponding cation intermediate. As expected, when the reaction was conducted in refluxing 1,2-dichloroethane (DCE), the reaction did proceed to give the coupled product **3a** in 91% yield without concomitant formation of [4+2] cycloadduct **4**, indoline aminal, (entry 4).[15] Additionally,

$Sc(OTf)_3$ catalyzed the reaction as well as $FeCl_3$, to give **3a** in 90% yield in refluxing DCE (entry 6). NMR analysis provided evidence that the C-C bond formation of this reaction occurred exclusively at position 3 of **2a** and regioisomer of **3a** was not observed at all.[15] This is the first example of intermolecular formation of quaternary carbon centers using aza-*o*-QM mediated carbocation intermediate. Other Lewis acid such as $InCl_3$, $Zn(OTf)_2$, $Yb(OTf)_3$ were appeared to be less effective than $FeCl_3$ or $Sc(OTf)_3$ to give the product in poor to moderate yields (entries 7-9). When $Cu(OTf)_2$, $Ni(OTf)_2$ and $Bi(OTf)_3$ were used in the reaction, dehydration of **1** occurred with the formation of styrene derivative **5** in about 30% yield. In contrast, Brønsted acid, methanesulfonic acid (MsOH), apparently did not work well in the reaction, leading to low yield of 10% (entry 13). As a consequence, we found that $FeCl_3$ was optimal catalyst for this reaction because it was a common and cheaper catalyst compared with $Sc(OTf)_3$.

Table 1. The optimization of reaction conditions[a]

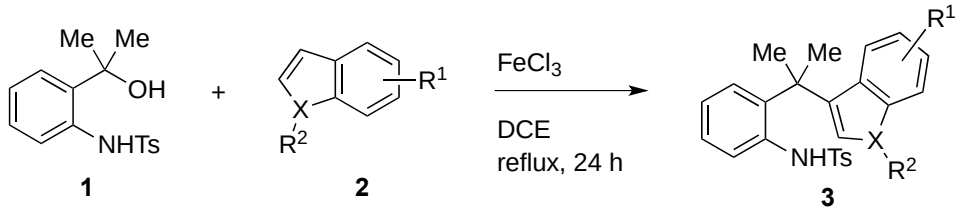


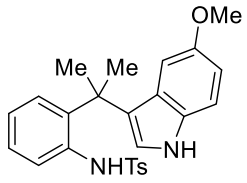
Entry	Cat.	Solvent	Temp. (°C)	Time (h)	Yield of **3a**[b] (%)
1	$FeCl_3$	THF	rt	46	0
2	$FeCl_3$[c]	THF	rt	24	0
3	$FeCl_3$	$CHCl_3$	rt to reflux	51	0
4	$FeCl_3$	DCE	reflux	24	91
5	$Fe(OTf)_3$	DCE	reflux	24	69
6	$Sc(OTf)_3$	DCE	reflux	24	90
7	$InCl_3$	DCE	reflux	24	66
8	$Zn(OTf)_2$	DCE	reflux	24	44
9	$Yb(OTf)_3 \cdot nH_2O$	DCE	reflux	24	28
10[d]	$Cu(OTf)_2$	DCE	reflux	24	31
11[e]	$Ni(OTf)_2$	DCE	reflux	24	45
12[f]	$Bi(OTf)_3 \cdot 4H_2O$	DCE	reflux	24	63
13[g]	MsOH	DCE	reflux	24	10

[a] Reactions were performed with **1** (1.0 eq.), **2a** (1.5 eq.) and acid catalyst (0.1 eq.) in the solvent (0.2 M). [b] Isolated yields. [c] $FeCl_3$ (0.5 eq.) was used. [d] Yield of **5**: 17%. [e] Yield of **5**: 33%. [f] Yield of **5**: 26%. [g] Yield of **5**: 25%.

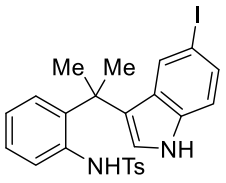
With the optimized condition, the scope of the reaction was examined using several indoles with electron-withdrawing or donating substituent (Table 2). When electron rich 5-methyoxyindole **2b** was employed, the reaction became sluggish and the coupled product **3b** was obtained in low yield. In contrast, electron poor indoles were appeared to be suitable for the reaction. 5-Iodoindole **2c** and 5-methoxycarbonylindole **2d** reacted with **1** to give **3c** and **3d** in good yields, and more electron deficient 5-nitroindole **2e** gave the product quantitatively. When *N*-methylated **2f** and 2-methylindoles **2g** were used, the reaction became slow and some amounts of substrates **2f** and **2g** remained intact. The reaction could occur at different position when 3-methylindole **2h** was used, and regioisomeric **3h** was obtained.[15] We assumed that the interaction between indoles with electron-donating groups and $FeCl_3$ might prevent the formation of aza-*o*-QM from **1**. Unfortunately, less nucleophilic benzofuran **2i** and benzothiophene **2j** compared to indoles were not compatible in this reaction.

Table 2. Scope and limitations of nucleophiles **2**[a,b]

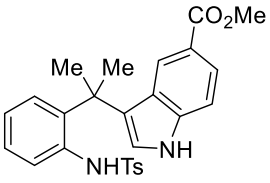




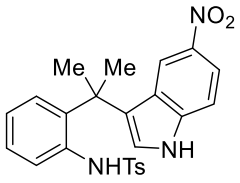
3b
13%



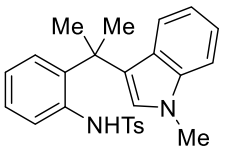
3c
86%



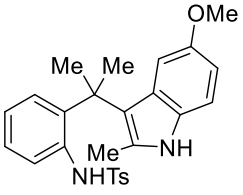
3d
89%



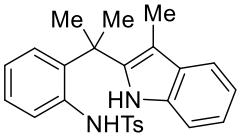
3e
97%



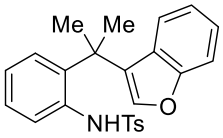
3f
22%



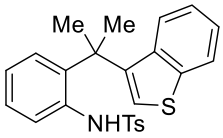
3g
19%



3h
24%



3i
0%



3j
0%

[a] Reactions were performed with **1** (1.0 eq.), **2** (1.5 eq.) and $FeCl_3$ (0.1 eq.) in DCE (0.2 M).

[b] Isolated yields.

We achieved the reaction of **1** with indoles catalyzed by $FeCl_3$ or $Sc(OTf)_3$, leading to form diarylmethane with quaternary carbon centers. The reaction occurred with high regioselectivity at position

3 of indoles in favor of somewhat electron deficient indoles. This is the first example of forming quaternary carbon centers using aza-*o*-QM or corresponding carbocation intermediate. The reaction mechanism is unclear to date but detailed mechanistic study to realize wide scope of reaction substrate including electron rich indoles and other heterocyclic compounds is underway.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Jasco FT/IR-410 spectrometer and were reported in wavenumbers (cm^{-1}). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on JNM-GX400 spectrometers; Chemical shifts of ^1H NMR were reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ^{13}C NMR were reported in ppm from the center line of a triplet at 77.16 ppm for deuteriochloroform. All data were reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometer.

Tetrahydrofuran (THF) was distilled over benzophenone ketyl sodium just before use. All commercially available materials were used as received without further purification. All experiments were carried out under argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

***N*-(2-(1-Hydroxy-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (1)**[16]

To a solution of *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide (2.23 g, 7.7 mmol) in THF (61 mL) was added MeMgBr (3.0 M solution in Et_2O, 5.65 mL, 16.9 mmol) dropwise at 0 °C over 20 min. After stirred for 22.5 h, the solution was heated to reflux for 3.5 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (40 mL) at 0 °C and extracted with AcOEt. The organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The title product (**1**) was purified by column chromatography (hexane:AcOEt = 2:1) and was obtained in 83% yield (1.96 g).

A yellow solid; IR (KBr) 3518, 3172, 2983, 2941, 1167 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.51 (6H, s), 2.36 (3H, s), 2.56 (1H, s), 6.92-7.00 (1H, m), 7.09-7.19 (2H, m), 7.22 (2H, d, *J* = 8.4 Hz), 7.52-7.58 (1H, m), 7.74 (2H, d, *J* = 8.4 Hz), 9.81 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 21.6, 30.9, 75.4, 119.9, 123.5, 126.1, 127.3, 128.3, 129.7, 134.6, 136.4, 137.3, 143.7; HRMS (EI) Calcd. for $C_{16}H_{19}NO_3S$: 305.1086 (M^+), Found: 305.1086.

General procedure for reaction of 1 with indole 2. $FeCl_3$ (0.02 mmol, 0.1 eq.) was added to a solution of **1** (0.2 mmol) and **2** (0.3 mmol, 1.5 eq.) in DCE (1.0 mL, 0.2 M) at room temperature under an Ar atmosphere, and the mixture was heated to reflux for 24 h. After cooling to rt, the reaction mixture was diluted with $CHCl_3$ (3.0 mL), quenched by the addition of sat. aq. $NaHCO_3$ (20 mL), and extracted with

$CHCl_3$. The organic layer was washed with brine (20 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt) to afford **3**.

***N*-(2-(1-(1*H*-Indol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3a): 3a** was purified by column chromatography (hexane:AcOEt = 3:1) and was obtained in 91% yield (73.9 mg).

A yellow solid; IR (KBr) 3432, 3216, 2982, 1335, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.78 (6H, s), 2.25 (3H, s), 6.72-6.87 (6H, m), 7.04-7.14 (3H, m), 7.16-7.24 (1H, m), 7.33-7.37 (1H, m), 7.37-7.43 (1H, m), 7.59-7.67 (2H, m), 8.51 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 21.6, 29.4, 37.7, 111.9, 117.1, 119.8, 120.57, 120.64, 122.9, 123.3, 123.5, 125.3, 126.5, 127.0, 127.6, 129.5, 134.9, 136.1, 136.4, 137.6, 143.3; HRMS (EI) Calcd. for $C_{24}H_{24}N_2O_2S$: 404.1558 (M^+), Found: 404.1560.

***N*-(2-(1-(1*H*-5-Methoxyindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3b): 3b** was purified by column chromatography (hexane:AcOEt = 4:1) and was obtained in 13% yield (11.7 mg).

A white amorphous; IR (KBr) 3365, 3216, 2978, 1336, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.76 (6H, s), 2.28 (3H, s), 3.31 (3H, s), 6.05 (1H, d, J = 2.0 Hz), 6.81 (2H, d, J = 8.0 Hz), 6.84-6.92 (1H, m), 6.89 (2H, d, J = 8.0 Hz), 7.03-7.12 (2H, m), 7.13-7.17 (1H, m), 7.31 (1H, d, J = 9.2 Hz) 7.33-7.37 (1H, m), 7.54 (1H, br s), 7.58-7.66 (1H, m), 8.32 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 21.6, 29.4, 37.6, 55.3, 102.0, 112.5, 113.4, 117.2, 121.2, 122.9, 123.3, 125.7, 126.4, 127.1, 127.6, 129.5, 131.6, 134.8, 136.0, 136.5, 143.3, 153.9; HRMS (EI) Calcd. for $C_{25}H_{26}N_2O_3S$: 434.1664 (M^+), Found: 434.1672.

***N*-(2-(1-(1*H*-5-Iodoindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3c): 3c** was purified by column chromatography (hexane:AcOEt = 3:1) and was obtained in 86% yield (91.2 mg).

A brown amorphous; IR (KBr) 3387, 3239, 2971, 1334, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.72 (6H, s), 2.32 (3H, s), 6.81 (2H, d, J = 7.6 Hz), 6.91 (2H, d, J = 7.6 Hz), 6.96 (1H, s), 7.06-7.18 (3H, m), 7.13-7.17 (1H, m), 7.21 (1H, d, J = 7.2 Hz) 7.39-7.48 (2H, m), 7.58 (1H, d, J = 7.6 Hz), 8.69 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 21.7, 29.6, 37.5, 83.7, 113.9, 117.1, 121.5, 122.9, 123.6, 126.5, 127.0, 127.8, 127.9, 129.3, 129.7, 131.2, 134.1, 135.5, 136.1, 136.6, 143.7; HRMS (EI) Calcd. for $C_{24}H_{23}IN_2O_2S$: 530.0525 (M^+), Found: 530.0529.

***N*-(2-(1-(1*H*-5-Methoxycarbonylindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3d): 3d** was purified by column chromatography (hexane:AcOEt = 3:1) and was obtained in 89% yield (82.6 mg).

A white amorphous; IR (KBr) 3360, 3235, 2973, 1690, 1616, 1337, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.77 (6H, s), 2.24 (3H, s), 3.76 (3H, s), 6.84 (2H, d, J = 8.8 Hz), 6.87 (2H, d, J = 8.8 Hz), 7.09-7.16 (2H, m), 7.17-7.23 (1H, m), 7.35-7.43 (3H, m) 7.46 (1H, s), 7.63-7.70 (1H, m), 7.89 (1H, d, J = 8.8 Hz), 8.89 (1H, d, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.5, 29.7, 37.7, 51.9, 111.6, 117.6, 121.9, 122.0, 123.5, 123.8,

124.1, 124.9, 125.1, 126.6, 126.9, 127.9, 129.5, 134.6, 135.8, 136.0, 140.2, 143.5, 167.7; HRMS (EI) Calcd. for $C_{26}H_{26}N_2O_4S$: 462.1613 (M^+), Found: 462.1617.

***N*-(2-(1-(1*H*-5-Nitroindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3e): 3e** was purified by column chromatography (hexane:AcOEt = 3:1) and was obtained in 97% yield (87.0 mg).

A pale yellow solid; IR (KBr) 3353, 3287, 2969, 1334, 1164 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6 1drop) δ: 1.77 (6H, s), 2.25 (3H, s), 6.87 (2H, d, *J* = 8.4 Hz), 6.93 (2H, d, *J* = 8.4 Hz), 7.13-7.21 (3H, m), 7.24-7.30 (1H, m), 7.49 (1H, d, *J* = 8.8 Hz), 7.51-7.58 (2H, m), 7.63-7.69 (1H, m), 8.04-8.10 (1H, m), 10.41 (1H, br s); ^{13}C NMR ($CDCl_3$ + DMSO-d_6 1drop) δ: 21.4, 29.7, 37.6, 112.0, 117.5, 117.8, 118.1, 123.9, 124.1, 124.5, 125.9, 126.5, 126.7, 128.1, 129.3, 134.2, 135.8, 135.9, 140.7, 141.4, 143.7; HRMS (EI) Calcd. for $C_{24}H_{23}N_3O_4S$: 449.1409 (M^+), Found: 449.1411.

***N*-(2-(1-(1-Methylindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3f): 3f** was purified by column chromatography (hexane:AcOEt = 4:1) and was obtained in 22% yield (18.1 mg).

A pale orange solid; IR (KBr) 3208, 3053, 2971, 1325, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.77 (6H, s), 2.25 (3H, s), 3.87 (3H, s), 6.71-6.87 (6H, m), 7.02-7.12 (3H, m), 7.21-7.28 (2H, m), 7.37 (1H, d, *J* = 8.8 Hz), 7.57 (1H, br s), 7.59-7.65 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 21.5, 29.6, 33.1, 37.6, 109.8, 117.2, 119.4, 120.8, 122.0, 122.5, 123.2, 125.2, 125.8, 126.4, 126.9, 127.5, 129.4, 135.0, 136.2, 136.4, 138.4, 143.1; HRMS (EI) Calcd. for $C_{25}H_{26}N_2O_2S$: 418.1715 (M^+), Found: 418.1714.

***N*-(2-(1-(5-Methoxy-2-methylindol-3-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3g): 3g** was purified by recrystallization (hexane: $CHCl_3$ = 4:1) and was obtained in 19% yield (17.3 mg).

Colorless crystals; IR (KBr) 3398, 3169, 2974, 2939, 1329, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.79 (6H, s), 2.28 (3H, s), 2.60 (3H, s), 3.30 (3H, s), 6.06-6.11 (1H, m), 6.74 (1H, d, *J* = 9.2 Hz), 6.89 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 7.03-7.18 (4H, m), 7.54-7.70 (2H, m), 8.00 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 15.2, 21.6, 29.6, 39.2, 55.4, 102.6, 111.2, 111.9, 115.0, 117.7, 123.4, 125.6, 127.1, 127.3, 127.7, 129.5, 130.7, 131.7, 136.32, 136.34, 137.2, 143.3, 153.7; HRMS (EI) Calcd. for $C_{26}H_{28}N_2O_3S$: 448.1821 (M^+), Found: 448.1827.

***N*-(2-(1-(3-Methylindol-2-yl)-1-methylethyl)phenyl)-4-methylbenzenesulfonamide (3h): 3h** was purified by column chromatography (hexane:AcOEt = 9:1 to 4:1) and was obtained in 24% yield (19.7 mg).

A yellow oil; IR (KBr) 3413, 3373, 3276, 2975, 1333, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.78 (6H, s), 1.96 (3H, s), 2.32 (3H, s), 6.62 (1H, s), 7.03 (2H, d, *J* = 7.6 Hz), 7.06-7.24 (6H, m), 7.29 (1H, d, *J* = 8.0 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.51 (2H, t, *J* = 7.6 Hz), 7.85 (1H, br s); ^{13}C NMR ($CDCl_3$) δ: 9.21, 21.6, 28.5, 39.2, 108.2, 111.1, 118.6, 119.0, 120.0, 122.6, 124.0, 126.0, 127.3, 128.0, 129.5, 130.0, 135.0, 135.99, 136.05, 136.9, 137.5, 143.6; HRMS (EI) Calcd. for $C_{25}H_{26}N_2O_2S$: 418.1715 (M^+), Found: 418.1710.

***N*-(2-(1-Methylethenyl)phenyl)-4-methylbenzenesulfonamide (5):** A yellow oil; IR (KBr) 3279, 2973, 2920, 2854, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.69 (3H, s), 2.36 (3H, s), 4.68 (1H, s), 5.26 (1H, q, J = 1.2 Hz), 6.98-7.08 (3H, m), 7.17-7.25 (3H, m), 7.58-7.67 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 21.6, 24.6, 117.3, 120.6, 124.5, 127.3, 128.1, 128.2, 129.7, 132.9, 134.8, 136.4, 142.2, 144.0; HRMS Calcd. for $C_{16}H_{17}NO_2S$: 287.0980 (M^+), Found: 287.0988.

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