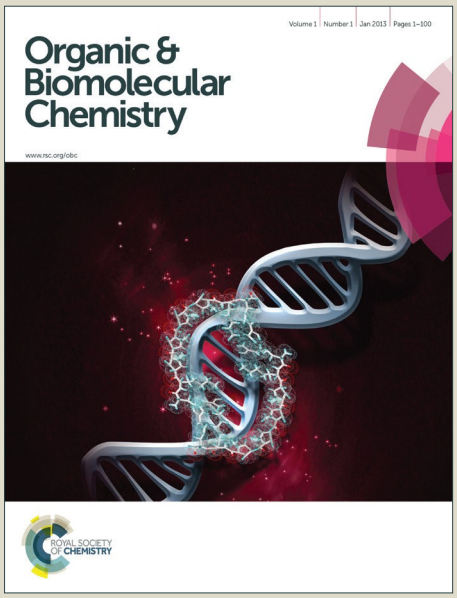
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Ji, Z. Liu, P. Liu and P. Sun, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01208F.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB01208F

Journal Name

ARTICLE

Synthesis of sulfonamides *via* copper-catalyzed oxidative C–N bond cleavage of tertiary amines

Received 00th June 2016,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jing Ji,[‡] Zhenyi Liu,[‡] Ping Liu and Peipei Sun*

A copper-catalyzed coupling reaction of sulfonyl chlorides with tertiary amines *via* the oxidative C–N bond cleavage of tertiary amines was developed. Sulfonamides were synthesized using this strategy in moderate to good yields. The reaction was applicable to various tertiary amines, as well as sulfonyl chlorides.

Introduction

Sulfonamides as elementary structural motifs are widely present in various clinical drugs or agriculturalchemicals (Figure 1).[1] A variety of methods for the construction of S–N bonds provided available routes to obtain sulfonamides. Conventionally, sulfonamides can be synthesized by the nucleophilic substitution of primary or secondary amines to sulfonyl chlorides.[2] Sulfonamides were also readily accessed by combining organometallic reagents, DABCO·$(SO_2)_2$ and amines.[3] Copper-catalyzed or mediated direct S–N bond formation became a prominent strategy for the synthesis of sulfonamides in recent years. For example, the reactions of thiols with amines[4] or formamides[5] furnished corresponding sulfonamides under oxidation conditions. A copper-catalyzed oxidative coupling reaction between sodium sulfinates and secondary amines with O_2 or DMSO as the oxidant was developed.[6] This approach can also be promoted by I_2.[7] In another report, *O*-benzoyl hydroxylamines was employed as the amino sources for this purpose.[8]

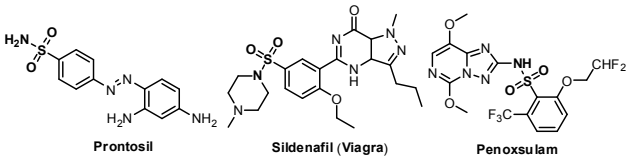


Figure 1 Some pharmaceuticals based on sulfonamides.

Primary or secondary amines were generally used as the coupling partners to construct C–N or N–heteroatom bonds in the synthesis of a variety of amino-containing compounds. As the more stable nitrogen-containing compounds, the application of tertiary amine as amino sources has been aroused much attention in recent years.[9] Through the oxidative C–N bond cleavage, the reaction of tertiary amines with aldehydes catalyzed by $FeCl_2$ gave amides.[10] The quaternary ammonium salt $^nBu_4NI$ could also catalyze this oxidative amidation.[11] The Cu, Ag, Pd or Au-catalyzed reactions of carboxylic acids, esters or anhydrides with tertiary amines furnished amides as well.[12] Other compounds which can be employed as the substrates for the amidation using tertiary amines as the amino sources included benzyl compounds such as benzyl cyanides.[13] In addition, the dialkylamino groups generated by the dealkylation of tertiary amines were used for the amination of benzoxazoles catalyzed by Cu.[14] Though the applications of tertiary amines as the amino sources to form C–N bond were well developed, to construct N–heteroatom bonds using this kind stable nitrogen-containing compounds is still limited.[9] Herein, we wish to report the effective route to synthesize sulfonamides by the coupling of sulfonyl chlorides with tertiary amines *via* the oxidative C–N bond cleavage of tertiary amines.

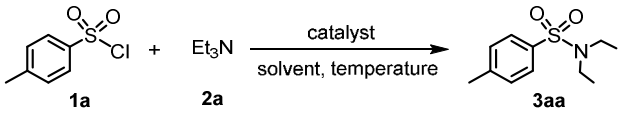
Results and discussion

Initially, we performed the reaction of *p*-toluensulfonyl chloride (**1a**) and triethylamine (**2a**, 2 equiv.) in ethyl acetate at 50 °C under air atmosphere, and no desired product was observed (Table 1, entry 1). Then CuCl was employed as the catalyst for this reaction. To our delight, the sulfonamination product *N,N*-diethyl-*p*-toluensulfonamide (**3aa**) was obtained in 38% yield in the presence of 5 mol% CuCl after 4 h (entry 2). Encouraged by this result, we decided to further optimize the reaction conditions. When the reaction was performed under O_2 atmosphere, a higher yield of 70% could be obtained (entry 3). Next, several other copper catalysts were tested. Among CuBr, CuI, Cu_2O, CuO and $Cu(OAc)_2$, Cu_2O was proved to be the most effective and the reaction gave 75% yield (entries 4–8). Further solvents screening demonstrated that DCE was best suited for this transformation, and a good yield of 83% was obtained (entries 9–14). The low reaction temperature seemed unfavorable to this reaction and a poor yield of 35% was brought at the room temperature (entry 15). However, raising the reaction temperature to 80 °C did not lead to the further improvement of the yield compared with that at 50 °C (entry 16).

College of Chemistry and Materials Science, Nanjing Normal University; Jiangsu Provincial Key Laboratory of Material Cycle Processes and Pollution Control; Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing 210023, China. E-mail: sunpeipei@njnu.edu.cn
[‡]These authors contributed equally.
† Electronic Supplementary Information (ESI) available: Copies of NMR spectra. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6OB01208F

Table 1 Optimization of reaction conditions[a]



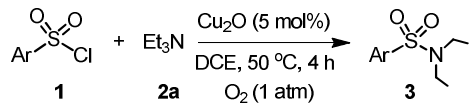
1a 2a 3aa

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1[c]	-	EtOAc	50	0
2[c]	CuCl	EtOAc	50	38
3	CuCl	EtOAc	50	70
4	CuBr	EtOAc	50	59
5	CuI	EtOAc	50	56
6	Cu_2O	EtOAc	50	75
7	CuO	EtOAc	50	72
8	$Cu(OAc)_2$	EtOAc	50	61
9	Cu_2O	Toluene	50	56
10	Cu_2O	CH_3CN	50	76
11	Cu_2O	Dioxane	50	77
12	Cu_2O	DMSO	50	74
13	Cu_2O	DMF	50	13
14	**Cu_2O**	**DCE**	**50**	**83**
15	Cu_2O	DCE	rt.	35
16	Cu_2O	DCE	80	78

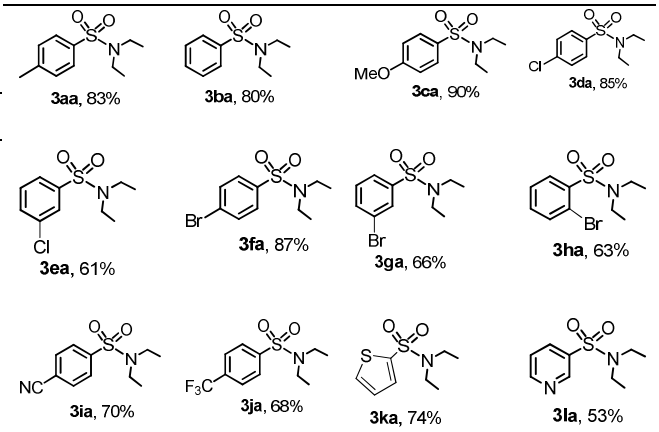
[a]Reaction conditions: Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (5 mol%) and solvent (4 mL) under O_2 (1atm) for 4 h. [b]The yields are isolated one based on **1a**. [c]Under air.

With the optimized reaction conditions in hand, we then investigated the reaction of various arylsulfonyl chlorides (**1**) with triethylamine (**2a**) (Table 2). Arylsulfonyl chlorides with various substituents on benzene rings were tested. The results showed that for the substrates whether with electron donating groups such as methyl, methoxyl, or with electron-withdrawing groups such as halo, cyano, trifluoromethyl, the reaction could proceed smoothly and give the corresponding sulfonamidation products in moderate to good yields (**3aa–3ja**). In addition, a heterocyclic derivatives thiophene-2-sulfonyl chloride **2k** and pyridine-3-sulfonyl chloride **2l** were also applied to this reaction and the corresponding sulfonamides (**3ka**, **3la**) were obtained in 74% and 53% yields respectively.

Table 2 Reaction of arylsulfonyl chlorides with triethylamine[a]



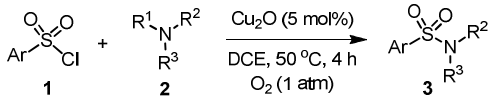
1 2a 3



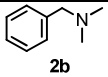
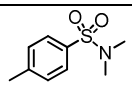
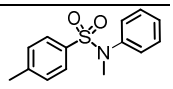
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Cu_2O (5 mol%), DCE (4.0 mL) in a sealed tube at 50 °C for 4 h. All yields are isolated ones.

Next, a series of tertiary amines were then tested except trimethylamine (Table 3). For the asymmetrical tertiary amines we used, the obvious selectivity of C–N bond cleavage could be observed. Using *p*-toluensulfonyl chloride as the coupling partner, when *N,N*-dimethylbenzylamine was used, the benzyl was removed and a *N,N*-dimethyl-*p*-toluensulfonamide (**3ab**) was generated. Some *N,N*-dialkylarylamines were then employed as the amino sources. In these cases the C–N bonds between alkyl and amino group were selectively broken and the *N*-alkyl-*N*-arylsulfonamides (**3ac-3ag**) were obtained, which was obviously due to the more stability of the C–N bond between aryl and amino group. Interestingly, for the reaction of 1-alkylpiperidine, the cleavage of C–N bond took place on the methyl or ethyl, and arylsulfonylpiperidines (**3ah**, **3ch**) were produced, which might also be because of the special stability of the six-membered ring of piperidine. Similar result was found when 4-methylmorpholine (**2j**) was used as the amino source (**3aj**).

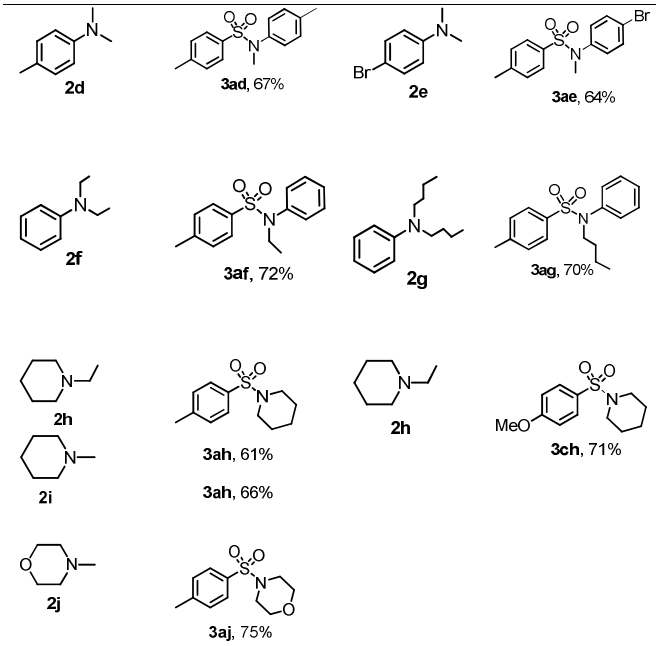
Table 3 The reaction of sulfonyl chlorides with various tertiary amines[a]



1 2 3

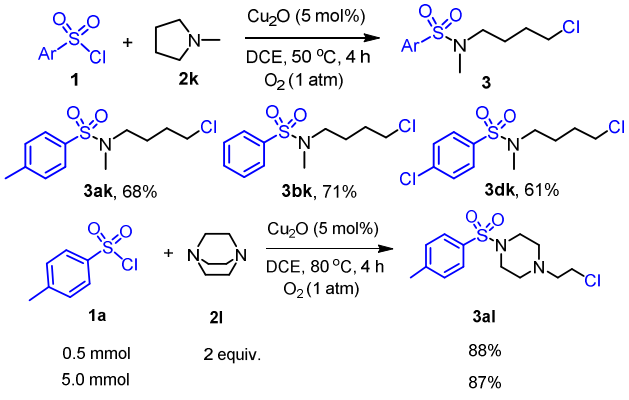
Substrates (**2**)	Products (**3**)	Substrates (**2**)	Products (**3**)
			
2b	**3ab**, 62%	**2c**	**3ac**, 79%

View Article Online
DOI: 10.1039/C6OB01208F



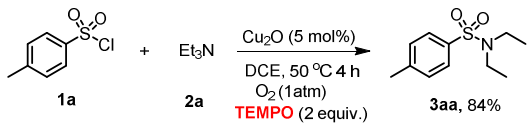
[a]Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), Cu_2O (5 mol%), DCE (4.0 mL) in a sealed tube at 50 °C for 4 h. All yields are isolated ones.

Unexpectedly, if the five-membered nitrogen containing heterocyclic compound 1-methylpyrrolidine (**2k**) was used, the chlorinated ring-opening sulfonamides were generated (**3ak**, **3bk**, **3dk**) (Scheme 1). Similar chlorinated product (**3al**) was also obtained from 1,4-diazabicyclo[2.2.2]octane (**2l**). In addition, under the established reaction condition, 1.32 g (yield 87%) of 1-(2-chloroethyl)-4-tosylpiperazine (**3al**) was obtained when 5.0 mmol *p*-toluensulfonyl chloride was used, which revealed that the yield was not evidently influenced when the reaction took place in a gram scale.



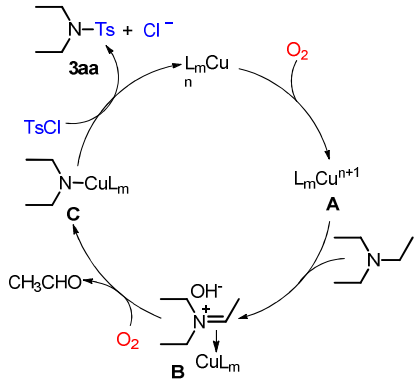
Scheme 1 Synthesis of chlorinated ring-opening sulfonamides.

When 2.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added, the reaction was not evidently affected, which indicated that the transformation might not be a radical process (Scheme 2).



Scheme 2 Control experiment.

Although the exact mechanism for this reaction is not clear, based on our above results and the related reports, a plausible mechanism for the present process can be proposed as shown in scheme 3. Firstly, the high-valent copper salt (**A**) was formed by the oxidation of oxygen.[5,13a,14] Then tertiary amine was oxidized by copper salt (**A**) to give iminium ion **B** *via* the one-electron oxidation of nitrogen. From the hydrolysis of **B** activated by hydroxyl ion and the elimination of aldehyde, a cupric ammine intermediate **C** was generated. The intermediate **C** further reacted with sulfonyl chloride to afford the final product sulfonamide and regenerate Cu catalyst. From some cyclic tertiary amines such as **2k** and **2l**, the chlorinated products were obtained. The mechanism for this transformation is waiting to be studied.



Scheme 3 Proposed reaction mechanism.

Conclusions

In summary, we developed a convenient method for the synthesis of sulfonamides by the copper-catalyzed C–N bond selective cleavage of tertiary amines and S–N bond formation. The reaction was applicable to various tertiary amines, as well as arylsulfonyl chlorides. The mild reaction conditions and convenient operation provided possibility to apply this methodology in the synthesis of multifarious sulfonamides and the related compounds.

Experimental section

General considerations

All reactions were run in a sealed tube with a Teflon lined cap under O_2 (1 atm) atmosphere. Chemicals were commercially available and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometers in $CDCl_3$ [using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00 ppm; for ^{13}C, δ = 77.00 ppm) as internal

View Article Online
DOI: 10.1039/C6OB01208F

standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were obtained with a Waters Q-TOF mass spectrometer. Melting points are uncorrected.

General experimental procedures

A mixture of 4-methylbenzenesulfonyl chloride **1a** (0.5 mmol), Et_3N **2a** (1.0 mmol), Cu_2O (5 mol%) and DCE (2.0 mL) was sealed in a 25 mL tube with a Teflon lined cap under oxygen atmosphere. The tube was then placed in an oil bath, stirred and heated at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (25 mL × 3). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified over a column of silica gel (eluent: hexane/ethyl acetate = 10 : 1) to afford the desired product **3aa**.

***N,N*-Diethyl-4-methylbenzenesulfonamide** (**3aa**).[8] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.70 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.23 (q, J = 7.2 Hz, 4H), 2.43 (s, 3H) 1.13 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 142.9, 137.4, 129.6, 127.0, 42.0, 21.6, 14.1.

***N,N*-Diethylbenzenesulfonamide** (**3ba**).[8] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83–7.80 (m, 2H), 7.57–7.53 (m, 1H), 7.52–7.47 (m, 2H), 3.26 (q, J = 7.2 Hz, 4H), 1.12 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 140.4, 132.2, 129.0, 126.9, 42.0, 14.1.

***N,N*-Diethyl-4-methoxybenzenesulfonamide** (**3ca**).[15] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.75–7.72 (m, 2H), 6.98–6.94 (m, 2H), 3.86 (s, 3H), 3.21 (q, J = 7.2 Hz, 4H), 1.12 (t, J = 7.2 Hz 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 162.6, 132.1, 129.0, 114.1, 55.6, 41.9, 14.1.

4-Chloro-*N,N*-diethylbenzenesulfonamide (**3da**).[16] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.77–7.74 (m, 2H), 7.49–7.46 (m, 2H), 3.25 (q, J = 7.2 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 139.0, 138.7, 129.3, 128.4, 42.0, 14.1.

3-Chloro-*N,N*-diethylbenzenesulfonamide (**3ea**).[15] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.81 (s, 1H), 7.72–7.69 (m, 1H), 7.55–7.53 (m, 1H), 7.48–7.44 (m, 1H), 3.27 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 142.2, 135.2, 132.4, 130.3, 127.0, 125.0, 42.2, 14.2.

4-Bromo-*N,N*-diethylbenzenesulfonamide (**3fa**).[17] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.70–7.63 (m, 4H), 3.25 (q, J = 7.2 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 139.6, 132.3, 128.5, 127.1, 42.1, 14.1.

3-Bromo-*N,N*-diethylbenzenesulfonamide (**3ga**).[18] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.97 (s, 1H), 7.77–7.74 (m, 1H), 7.70–7.68 (m, 1H), 7.41–7.37 (m, 1H), 3.27 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 142.4, 135.3, 130.6, 129.9, 125.5, 123.0, 42.2, 14.2.

2-Bromo-*N,N*-diethylbenzenesulfonamide (**3ha**).[19] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.15–8.13 (m, 1H), 7.75–7.72 (m, 1H), 7.46–7.42 (m, 1H), 7.40–7.36 (m, 1H), 3.40 (q, J = 7.2 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 139.8, 135.6, 133.3, 132.1, 127.4, 120.4, 41.2, 13.7.

4-Cyano-*N,N*-diethylbenzenesulfonamide (**3ia**).[17] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.95–7.93 (m, 2H), 7.83–7.81 (m, 2H), 3.29 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 144.9, 132.9, 127.5, 117.4, 116.0, 42.1, 14.1.

***N,N*-Diethyl-4-(trifluoromethyl)benzenesulfonamide** (**3ja**).[20] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.96 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 3.29 (q, J = 7.2 Hz, 4H), 1.16 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 144.1, 134.0 (q, J = 32.9 Hz), 127.4, 126.2 (q, J = 3.6 Hz), 123.3 (q, J = 271.1 Hz), 42.1, 14.2.

***N,N*-diethylthiophene-2-sulfonamide** (**3ka**).[21] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.56 (d, J = 4.4 Hz, 2H), 7.10 (t, J = 4.4 Hz 1H), 3.27 (q, J = 7.2 Hz, 4H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 140.9, 131.3, 131.1, 127.2, 42.6, 14.2.

***N,N*-Diethylpyridine-3-sulfonamide (3la)**. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.05 (s, 1H), 8.80 (d, J = 4.0 Hz, 1H), 8.12 (dd, J = 8.0, 1.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 3.30 (q, J = 7.2 Hz, 4H), 1.18 (t, J = 7.2 Hz 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 152.8, 147.8, 137.2, 134.6, 123.7, 42.1, 14.2; HRMS-ESI (m/z): calcd for $C_9H_{14}N_2O_2SNa$ $[M + Na]^+$ 237.0669, found 237.0672.

***N,N,*4-Trimethylbenzenesulfonamide** (**3ab**).[5] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.68 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 2.71 (s, 6H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.5, 132.5, 129.6, 127.8, 38.0, 21.5.

***N*,4-Dimethyl-*N*-phenylbenzenesulfonamide** (**3ac**).[7b] White solid. Mp: 87-89 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.45–7.42 (m, 2H), 7.33–7.24 (m, 5H), 7.12–7.10 (m, 2H), 3.18 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.6, 141.6, 133.5, 129.4, 128.8, 127.9, 127.3, 126.6. 38.1, 21.6.

***N*,4-Dimethyl-*N*-(*p*-tolyl)benzenesulfonamide** (**3ad**).[22] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.47–7.44 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.00–6.97 (m, 2H), 3.15 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.4, 139.0, 137.2, 133.6, 129.5, 129.3, 128.0, 126.5, 38.2, 21.6, 21.0.

***N*-(4-Bromophenyl)-*N*,4-dimethylbenzenesulfonamide** (**3ae**).[7b] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.45–7.42 (m, 4H), 7.27 (d, J = 8.4 Hz, 2H), 6.99 (dd, J = 6.8, 2.4 Hz, 2H), 3.14 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.8, 140.7, 133.1, 132.0, 129.5, 128.1, 127.9, 120.9, 37.9, 21.6.

***N*-Ethyl-4-methyl-*N*-phenylbenzenesulfonamide** (**3af**):[23] Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.52–7.49 (m, 2H), 7.35–7.25 (m, 5H), 7.08–7.05 (m, 2H), 3.62 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.3, 138.9, 135.5, 130.9, 129.4, 129.0, 127.8, 127.7, 45.5, 21.5, 14.0.

***N*-Butyl-4-methyl-*N*-phenylbenzenesulfonamide** (**3ag**).[24] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7,48 (dd, J = 6.4, 1.6 Hz, 2H), 7.35–7.29 (m,3H), 7.25 (d, J = 7.6 Hz, 2H), 7.07–7.05 (m, 2H), 3.54 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.40–1.34 (m, 4H), 0.87 (t, J = 6.8 Hz 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.2, 139.2, 135.3, 130.9, 129.3, 128.9, 128.8, 127.7, 50.2, 30.2, 21.5, 19.6, 13.6.

1-Tosylpiperidine (**3ah**).[25] Yellow soild. Mp: 71-79 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.65 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.98 (t, J = 5.6 Hz, 4H), 2.45 (s, 3H), 1.68–1.62 (m, 4H), 1.45–1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.3, 133.3, 129.5, 127.7, 46.9, 25.2, 23.5, 21.5.

1-((4-Methoxyphenyl)sulfonyl)piperidine (**3ch**).[26] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.70 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 3,89 (s, 3H), 2.97 (t, J = 5.6 Hz, 4H), 1.68–1.62 (m, 4H), 1.45–1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 162.8, 129.8, 127.9,114.1, 55.6, 46.9, 25.2, 23.5.

View Article Online
DOI: 10.1039/C6OB01208F

4-Tosylmorpholine (3aj).[6] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7,65 (d, J = 8.0 Hz, 2H), 7,36 (d, J = 8.0 Hz, 2H), 3.75 (t, J = 4.8 Hz 4H), 2.99 (t, J = 4.8 Hz 4H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 144.0, 132.0, 129.8, 127.9, 66.1, 46.0, 21.6.

***N*-(4-Chlorobutyl)-N,4-dimethylbenzenesulfonamide** (**3ak**). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.67 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 2.71 (s, 3H), 2.44 (s, 3H), 1.90–1.83 (m, 2H), 1.74–1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.4, 134.3, 129.7, 127.4, 49.1, 44.5, 34.5, 29.2, 24.5, 21.5; HRMS-ESI (m/z): calcd for $C_{12}H_{18}ClNO_2SNa$ $[M + Na]^+$ 298.0640, found 298.0880.

***N*-(4-Chlorobutyl)-*N*-methylbenzenesulfonamide** (**3bk**). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.80–7.78 (m, 2H), 7.59–7.52 (m, 3H), 3.61 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 2.74 (s, 3H), 1.90–1.83 (m, 2H), 1.73–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 137.4, 132.6, 129.1, 127.3, 49.1, 44.5, 34.5, 29.1, 24.5; HRMS-ESI (m/z): calcd for $C_{11}H_{16}ClNO_2SNa$ $[M + Na]^+$ 284.0483, found 284.0493.

4-Chloro-*N*-(4-chlorobutyl)-*N*-methylbenzenesulfonamide (**3dk**). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.73 (dd, J = 6.4, 2.0 Hz, 2H), 7.52 (dd, J = 6.4, 2.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 2.74 (s, 3H), 1.90–1.83 (m, 2H), 1.76–1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 139.2, 136.0, 129.4, 128.7, 49.1, 44.4, 34.5, 29.1, 24.5; HRMS-ESI (m/z): calcd for $C_{11}H_{16}Cl_2NO_2S$ $[M + H]^+$ 296.0273, found 296.0278.

1-(2-Chloroethyl)-4-tosylpiperazine (**3al**).[27] White soild. Mp: 125-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.63 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.52 (t, J = 6.4 Hz, 2H), 3.04 (t, J = 4.8 Hz, 4H), 2.72 (t, J = 6.4 Hz, 2H), 2.60 (t, J = 4.8 Hz, 4H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 143.8, 132.3, 129.7, 127.9, 59.2, 52.1, 45.9, 40.8, 21.5.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Project 21272117, 21502097, 21420102002), the Natural Science Foundation of the Education Department of Jiangsu province (15KJB150015), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. The authors also thank Mr. Hailong Liu for the determination of HRMS.

Notes and references

1 (a) J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel, and K. Seibert, *J. Med. Chem.*, 2000**,** **43**, 775; (b) A. Scozzafava, T. Owa, A. Mastrolorezo and C. T. Supuran, *Curr. Med. Chem.*, 2003, **10**, 925; (c) A. Natarajan, Y. Guo, F. Harbinski, Y. H. Fan, H. Chen, L. Luus, J. Diercks, H. Aktas, M. Chorev and J. A. Halperin, *J. Med. Chem*., 2004, **47**, 4979.

2 (a) K. K. Andersen, in *Comprehensive Organic Chemistry*. Ed. D. N. Jones, Pergamon Press, Oxford, 1979, vol. 3; (b) M. Harmata, P. Zheng, C. Huang, M. G. Gomes, W. Ying, K.-O. Ranyanil, G. Balan and N. L. Calkins, *J. Org. Chem.*, 2007, **72**, 683.

3 (a) H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson and M. C. Willis, *Org. Lett*., 2011, **13**, 4876; (b) C. Waldmann, O. Schober, G. Haufe and K. Kopka, *Org. Lett*., 2013, **15**, 2954; (c) A. S. Deeming, C. J. Russell and M. C. Willis, *Angew. Chem., Int. Ed*., 2015, **54**, 1168.

4 N. Taniguchi, *Eur. J. Org. Chem.*, 2010, 2670.

5 X. Huang, J. Wang, Z. Ni, S. Wang and Y. Pan, *Chem. Commun.*, 2014, **50**, 4582.

6 X. Tang, L. Huang, C. Qi, X. Wu, W. Wu and H. Jiang, *Chem. Commun.*, 2013, **49**, 6102.

7 (a) K. Yang, M. Ke, Y. Lin and Q. Song, *Green Chem.*, 2015, **17**, 1395; (b) X. Pan, J. Gao, J. Liu, J. Lai, H. Jiang and G. Yuan, *Green Chem.*, 2015, **17**, 1400.

8 H. Zhu, Y. Shen, Q. Deng and T. Tu, *Chem. Commun.*, 2015, **51**, 16573.

9 K. Ouyang, W. Hao, W. X. Zhang and Z. Xi, *Chem. Rev*., 2015, **115**, 12045.

10 Y. Li, F. Jia, and Z. Li, *Chem. Eur. J*., 2013, **19**, 82.

11 S. Wang, J. Wang, R. Guo, G. Wang, S. Y. Chen and X. Q. Yu, *Tetrahedron Lett*., 2013, **54**, 6233.

12 (a) B. Xiong, L. Zhu, X. Feng, J. Lei, T. Chen, Y. Zhou, L. B. Han, C. T. Au and S. F. Yin, *Eur. J. Org. Chem.*, 2014, 4244; (b) X. Zhang, W. Yang and L. Wang, *Org. Biomol. Chem*., 2013, **11**, 3649; (c) Y. S. Bao, B. Zhaorigetu, B. Agula, M. Baiyin and M. Jia, *J. Org. Chem*., 2014, **79**, 803; (d) Y. S. Bao, M. Baiyin, B. Agula, M. Jia and B. Zhaorigetu, *J. Org. Chem*., 2014, **79**, 6715; (e) H.-C. Cheng, W.-J. Hou, Z.-W. Li, M.-Y. Liu and B.-T. Guan, *Chem. Commun.,* 2015, **51**, 17596.

13 X. Chen, T. Chen, Q. Li, Y. Zhou, L. B. Han and S. F. Yin, *Chem. Eur. J*., 2014, **20**, 12234.

14 S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett*., 2011, **13**, 522.

15 C. Schneider, E. Broda and V. Snieckus, *Org. Lett*., 2011, **13**, 3588.

16 W. Li, M. Beller and X. Wu, *Chem. Commun*., 2014, **50**, 9513.

17 R. Pandya, T. Murashima, L. Tedeschi and A. G. M. Barrett, *J. Org. Chem*., 2003, **68**, 8274.

18 S. Crosignani, A. Pretre, C. Jorand-Lebrun, G. Fraboulet, J. Seenisamy, J. K. Augustine, M. Missotten, Y. Humbert, C. Cleva, N. Abla, Hamina Daff, O. Schott, M. Schneider, F. Burgat-Charvillon, D. Rivron, I. Hamernig, J. F. Arrighi, M. Gaudet, S. C. Zimmerli, P. Juillard and Z. Johnson, *J. Med. Chem.,* 2011, **54**, 7299.

19 C. B. Bheeter, R. Jin, J. K. Bera, P. H. Dixneuf and H. Doucet, *Adv. Synth. Catal*., 2014, **356**, 119.

20 I. Pena, E. J. Cocinero, C. Cabezas, A. Lesarri, S. Mata, P. Ecija, A. M. Daly, A. Cimas, C. Bermffldez, F. J. Basterretxea, S. Blanco, J. A. Fernandez, J. C. Lopez, F. Castano and J. L. Alonso, *Angew. Chem*., 2013, **52**, 11840.

21 D. W. Slocum and P. L. Giere, *J. Org. Chem.*, 1973, **28**, 4189.

22 D. M. T. Chan, K. L. Monaco, R. Wang and M. P. Winters, *Tetrahedron Lett*., 1998, **39**, 2933.

23 A. L. Reznichenko and K. C. Hultzsch, *J. Am. Chem. Soc*., 2012, **134**, 3300.

24 X. Geng, S. Mao, L. Chen, J. Yu, J. Han, J. Hua and L. Wang, *Tetrahedron Lett*., 2014, **55**, 3856.

25 N. B. Palakurthy and B. Mandal, *Tetrahedron Lett*., 2011, **52**, 7132.

26 A. Shavnya, S. B. Coffey, A. C. Smith and V. Mascitt, *Org. Lett*., 2013, **15**, 6226.

27 H. Jens, H. Siegfried, K. Rainer, S. Michaela and W. Hermann, *Synthesis*, 1997, 1443.