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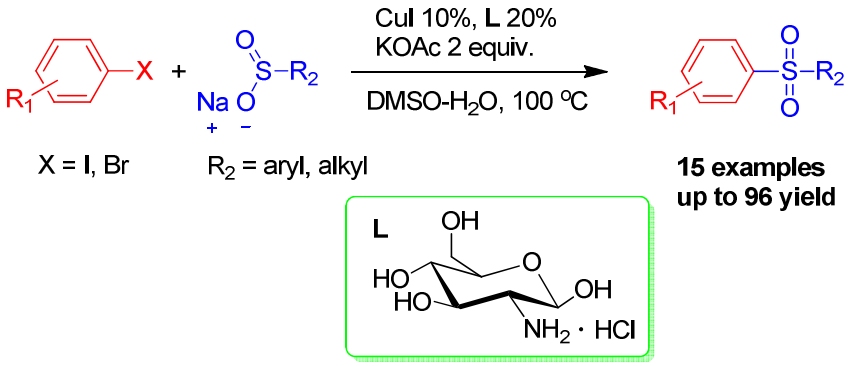

D-glucosamine as a green ligand for copper catalyzed synthesis of aryl sulfones from aryl halides and sodium sulfinates

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D-glucosamine is reported for the first time as a green ligand for copper catalyzed coupling of aryl halides and sodium sulfinates, which provides a simple and extremely efficient new route to unsymmetrical diaryl sulfones. The catalytic reaction proceeded in DMSO-H_2O at 100 °C and gave a variety of aryl sulfones in high yields. The high water solubility of the ligand enables easy catalyst removal. The scope of the method was validated by a single step synthesis of marketed drug Zolimidine, a drug used for peptic ulcers, in 65% yield.

Introduction

The sulfones, as the key structural skeletal framework of many natural products and pharmaceuticals, have attracted considerable interest because of their important biologically active properties.[1] Particularly, aryl sulfones show various pharmacological properties such as anti-tumor activities, anti-inflammatory, anti-fungal, or to inhibit HIV-1 reverse transcriptase.[2] Recently, aryl sulfones scaffolds were incorporated in some commercially available drugs such as Bicalutamide (Casodex) (for the treatment of prostate cancer), Zolimidine (used for the treatment of peptic ulcer), Eletriptan (antimigraine medicine) (Figure 1).

The wide usefulness of compounds containing this skeleton has resulted in the development of synthetic methodologies to construct them and until now various methods have been developed for synthesizing aryl sulfones, such as: (i) a nucleophile substitution reaction of halide with thiol, followed by oxidation of the corresponding sulfide;[3] (ii) Pd- or Cu -catalyzed coupling reactions between sodium sulfinates and aryl halides or aryl boronic acids have been developed as a milder alternative.[4]

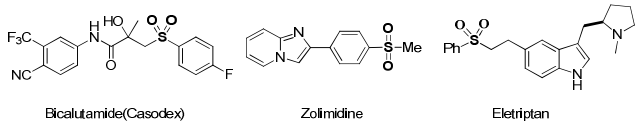

Figure 1. Aryl sulfones-containing drugs.

(iii) sulfonylation of heterocycles with aryl sulfonyl chlorides via metal-catalyzed C-H bonds activation;[5] (v) one-pot synthesis of vinyl sulfones from terminal epoxides and sodium sulfinates.[6] Although a number of modifications on the synthesis of aryl sulfones were developed,[7] the drawbacks are the use of expensive phosphine ligand, harsh reaction conditions, multi-step processes, and low yields in the most of the cases. Meanwhile, to separate the catalyst from the product by a distillation process after the reaction is complicated and may result in the decomposition of the catalyst or formation of by-products. In addition, many methodologies exhibit poor functional group tolerance or generate large quantities of hazardous waste. To resolve this problem, many catalysts have been widely developed,[8] while the rapid assembly and flexible modification of structurally diverse ligand systems by simple synthetic methods are still important for the development of effective catalysts for the widespread applications of coupling reactions.

Carbohydrates are one of the most naturally abundant bioorganic molecules which have been widely used in organic synthesis.[9] They represent excellent tools as chiral auxiliaries, reagents, organocatalysts and ligands for asymmetric synthesis,[10] as carbohydrates can be easily functionalized to provide efficient catalysts, which are applicable in a large number of catalytic asymmetric reactions.[11] Some monosaccharide molecules have generated significant attention for their green and essential roles in transition metal catalyzed reactions.[12] However, their effect is still unclear. To this purpose and continuing our longstanding interest in developing novel C-S bond-forming reactions for the efficient construction of hetero-cyclic frameworks,[13] we embarked on the development of C-S bond formation under mild condition. Herein, we describe an efficient catalytic system for the cross-coupling of a wide range of aryl halides with sodium benzenesulfonates using D-Glucosamine as a green ligand.

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Results and discussion

First, 4-iodoanisole (**1a**) and sodium benzensulfinate (**2a**) was chosen as a model and screened a series of ligands under the conditions of 10 mol% CuI, 20 mol% ligand, K_2CO_3 as the base and DMSO-H_2O(1:1) mixture as the solvent at 100 ℃ for 24 h. In the very first reaction, D-glucose **L1** was used as ligand and this condition gave the desired product in 31% yield. This encouraged us to continue the screening using other monosaccharide molecules as ligands(Figure 2). Out of all the ligands screened, D-glucosamine **L5** provided 55% as the maximum yield of the product. Surprisingly, it was found that monosaccharide-based ligands gave a better result than several conventional ligands such as 2-aminopyridine(**L9**), 1,2-phenylene diamine(**L10**) L-proline(**L11**), ethane-1, 2-diamine (**L12**), 1,10-phenathroline (**L13**), which are very well known in the literature of coupling chemistry.

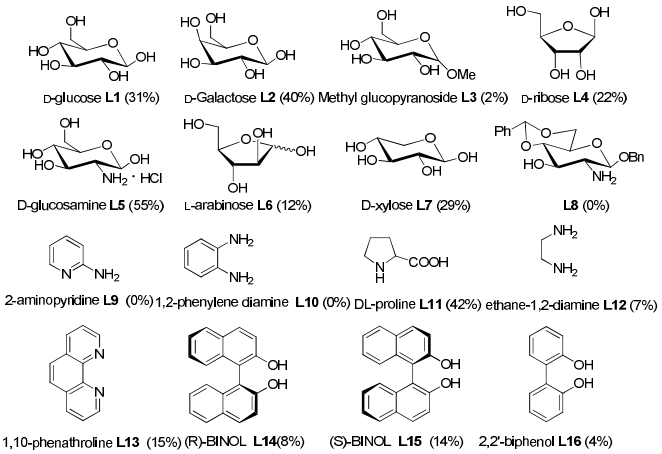
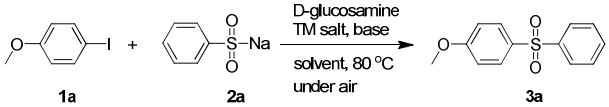


Figure 2. Optimization and comparison of reactivity between mono-saccharide ligands and conventional ligands in aryl sulfones synthesis.

Next, several organic solvent/H_2O (1 :1) mixtures, bases, catalyst loading and temperatures were screened for this reaction. Further experimentations revealed that this C-S cross-coupling reaction was effective in polar aprotic organic solvent/H_2O (1 :1) mixtures such as DMSO and DMF (Table 1, entries 1 and 2). In stark contrast, the coupling reaction proceeded less efficiently in nonpolar solvent such as 1,4-dioxane and toluene(Table 1, entries 3 and 4). While trying the reaction using only water as solvent, no product was obtained. Notably, the reactions through use of strong bases, including Na_2CO_3, Cs_2CO_3, KOH, and NaOH, occurred with low reaction conversions (Table 1, entries 6, 7, 10, 11). The reaction with KOAc as the base resulted in the formation of **3a** in 93% yield (Table 1, entry 8). While checking the minimum requirement of catalyst loading for the best performance of the reaction, it has been found that 10 mol% of CuI and 20 mol% of **L5** is the optimal catalyst requirement. On either decreasing the catalyst loading, the yield of the product got affected. For example, when 10 mol% of **L5** was used, only 78% yield was achieved. When the reaction was performed at 80 °C, the reaction was found to be inefficient (Table 1, entry 12).

At last, several Cu, Pd or Ag salts such as CuBr, $Cu(OAc)_2$, $Pd(OAc)_2$ and AgOAc were screened for this coupling reaction. No C-S coupling product was obtained when the reaction was carried out without ligand **L5** (Table 1, entry 14). This result clearly shows that ligand **L5** is necessary for the best performance of the coupling reaction. It was found that CuI gave the best result and Cu salts generally showed better reactivity than Pd and Ag salts (Table 1, entries 15-20).

After optimizing all parameters such as ligand, solvent, base, catalyst loading, temperature and metal-salt, we initiated our investigation into the scope of the D-glucosamine **L5** catalyzed coupling of aryl halides and sodium benzenesulfonate and the results are summarized in Table 2. Many valuable functional groups such as hydroxyl-, carbonyl-, chloro-, and trifluoromethyl groups were well tolerated. Substrates containing either an electron donating (Table 2, entries 1 and 2) or withdrawing group (Table 2, entries 3-6) at the *para*-position showed similar reactivity to the parent **3a**. Furthermore, substituents at *meta*-, or

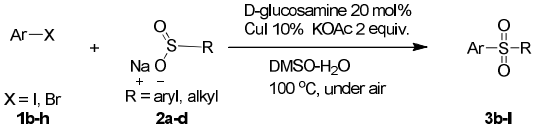


Entry	TM salt	Solvent/ H_2O(1:1)	Base	Temp. [°C]	Yield (%)[b]
1	CuI	DMSO	K_2CO_3	100	55
2	CuI	DMF	K_2CO_3	100	50
3	CuI	Toluene	K_2CO_3	100	6
4	CuI	1,4-dioxane	K_2CO_3	100	trace
5	CuI	H_2O	K_2CO_3	100	trace
6	CuI	DMSO	Na_2CO_3	100	23
7	CuI	DMSO	Cs_2CO_3	100	20
8	**CuI**	**DMSO**	**KOAc**	**100**	**93** (78)[c]
9	CuI	DMSO	K_3PO_4	100	17
10	CuI	DMSO	KOH	100	trace
11	CuI	DMSO	NaOH	100	trace
12	CuI	DMSO	KOAc	80	30
13	CuI	DMSO	KOAc	110	93
14	None	DMSO	KOAc	110	0
15	CuBr	DMSO	KOAc	100	25
16	$CuBr_2$	DMSO	KOAc	100	71
17	$Cu(OAc)_2$	DMSO	KOAc	100	75
18	$Cu(OTf)_2$	DMSO	KOAc	100	33
19	$Pd(OAc)_2$	DMSO	KOAc	120	12
20	AgOAc	DMSO	KOAc	110	trace

[a] Reaction conditions: CuI (0.1 mmol), D-glucosamine **L5** (0.2 mmol), 4-iodoanisole **1a** (1 mmol), sodium benzenesulfonate **2a** (1.2 mmol), base (2.0 mmol), Solvent : H_2O (4 mL 1:1), 100 °C under air. [b] Isolated yield, [c] 10 mol% of D-glucosamine **L5** was used.

Table 1 Optimization of Reaction Conditions.[a]

Table 2. Reaction between aryl halides and sodium sulfinates[a]



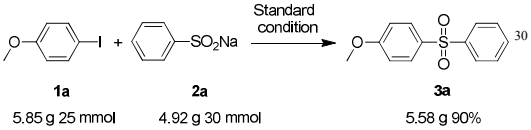
Entry	Ar	X	R	Yield(%)[b]
1	Ar = *p*-Me-C_6H_4	I	Ph	94(**3b**)
2	Ar = *p*-HO-C_6H_4	I	Ph	90(**3c**)
3	Ar = *p*-Cl-C_6H_4	I	Ph	86(**3d**)
4	Ar = *p*-NO_2-C_6H_4	I	Ph	88(**3e**)
5	Ar = *p*-CF_3-C_6H_4	I	Ph	92(**3f**)
6	Ar = *p*-CH_3CO-C_6H_4	I	Ph	75(**3g**)
7	Ar = *m*-NO_2-C_6H_4	I	Ph	87(**3h**)
8	Ar = *o*-Me-C_6H_4	I	Ph	76(**3i**)
9	Ar = *o*-Me*C*OO-C_6H_4	I	Ph	92(**3j**)
10	Ar = Ph	I	Ph	96(**3k**)
11	Ar = Ph	Br	Ph	72(**3k**)
12	Ar = Ph	I	*p*-Me-C_6H_4	95(**3b**)
13	Ar = Ph	I	*p*-Cl-C_6H_4	80(**3d**)
14	Ar = Ph	I	Me	97(**3l**)

[a] Reaction conditions: CuI (0.1 mmol), D-glucosamine (0.2 mmol), **1b-h** (1 mmol), **2a-d** (1.2 mmol), KOAc (2.0 mmol), DMSO: H_2O (4 mL 1:1), 100 °C under air. [b] isolated yield. [c] 120℃, 48 h.

ortho-positions of the benzene ring do not affect the efficiency of this transformation (76-92%, Table 2, entries 7-9).

We also found that the aryl bromides worked well in our reaction condition although higher reaction temperature and longer reaction time were required in comparison with aryl iodides (Table 2, entry 11). Both aryl sulfinates and alkyl sulfinates afforded sulfones in excellent yields (Table 2, entries 12-14). It seemed that the reactivity was influenced by the nucleophilic ability of sulfinates. In addition, we found sulfinates with electron-donating group on the benzene ring performed better than those with electron-withdrawing group (entry12 vs entry13).

To test the feasibility of a large-scale reaction, the reaction of 4-iodoanisole (**1a**) (25 mmol) and sodium benzenesulfinate (**2a**) (30 mmol) was investigated. The reaction could afford 5.58 g of **3a** in 90 % yield after recrystallization (Scheme 1). Therefore, this protocol could be used as a practical method to synthesize the precursors of some important bioactive molecules. Next the recyclability of catalyst was subsequently tested. After completion of the reaction under the optimal conditions reaction, taking advantage of the good solubility of products and the insolubility of catalyst in solvent, so a simple filtration was sufficient to separate the catalyst solution from the products. The recyclability of the catalyst was then studied in the C-S coupling reaction and the results are shown in Table 3. In the recycling experiment, the separated catalyst was recharged with fresh substrate for the next run under the same reaction conditions. The results show that good yield can be obtained after second cycle(Table 3, run 2) and the reaction yield continue to decrease for the next cycle. We speculated that the good solubility of ligand in water is the main cause of yield decrease and additional work aimed at improving the recyclability of the ligand will be continued.



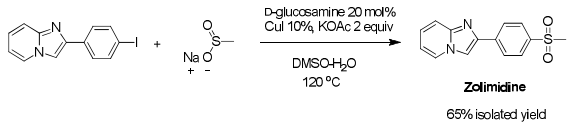
Scheme 1. Large-scale reaction: **1a** (25 mmol), **2a** (30 mmol), DMSO-H_2O (1:1, 100 mL), KOAc (50 mmol), 100 °C, 24 h. Isolated yield after recrystallization.

Table 3. Catalyst recycling for C-S coupling reaction.

Run	1	2	3	4	5
Yield（%）	93	85	77	70	65

Reaction conditions: see Table 1, Entry 8. The catalyst was recovered by simple filtration after reaction.

With this methodology in hand, we turned our attention to the synthesis of Zolimidine,[14] a drug used for peptic ulcers, in a single step (Scheme 2). When 2-(4-iodophenyl)imidazo[1,2-a]pyridine (1.0 mmol) was treated with sodium methanesulfinate (1.2 mmol) in the presence of 10 mol% of CuI and 20 mol% of D-glucosamine in DMSO-H_2O at 120 °C for 24 h, Zolimidine was isolated in 65% yield.



Scheme 2. One-step synthesis of Zolimidine.

Based on the results of experimnets and literatures,[4] a plausible mechanism for the green and practical method to construct aryl sulfones is illustrated in **Figure** 3. Initially, under alkaline conditions CuI electrophilic attack at the 1-OH and 2-NH_2 of the D-glucosamine afforded intermediate(**A**), a subsequent oxidative addition process results in formation of intermediate (**B**), nucleophilic displacement of halogen to give an intermediate (**C**) by reductive elimination with the regeneration of the intermediate (**A**) and provided the target product.

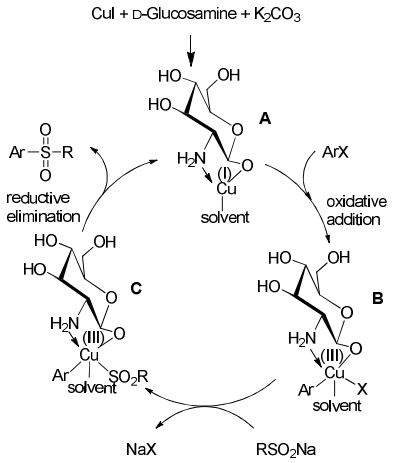


Figure 3. A plausible mechanism.

Conclusions

To the best of our knowledge, this is the first example of using D-glucosamine as a green ligand for copper catalyzed coupling of aryl halides and sodium sulfinates. The methodology can tolerate many important functional groups, including those containing ether, ester, and nitro groups, and we anticipate that it will find wide applicability due to its simple operating procedure. By using this protocol, the marketed drug zolimidine (antiulcer) could be easily synthesized in a concise route. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our laboratory.

Experimental section

General information

The starting materials were commercially available and were used without further purification except solvents. The products were isolated by column chromatography on silica gel (200-300 mesh) using petroleum ether (60-90°C) and ethyl acetate. Melting points were determined on an X-5 Data microscopic melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature with $CDCl_3$ or DMSO-d_6 as solvent unless otherwise noted and tetramethylsilane (TMS) as the internal standard. ^{1}H NMR data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet and br = broad), coupling constant (*J* values, Hz). ^{13}C NMR data were reported in terms of chemical shift (δ ppm). Mass spectra (EI-MS) were acquired on an Agilent 5975 spectrometer. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates.

General procedure for CuI-catalyzed coupling of aryl halides and sodium sulfinates.

A mixture of aryl halide (1 mmol), sodium benzenesulfonate (1.2 mmol), copper iodide (0.1 mmol), D-glucosamine(0.2 mmol), and 4 mL of DMSO-H_2O (1:1) in a sealed tube was heated to 100 °C under air. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. After drying with anhydrous $MgSO_4$ overnight, the liquid was analyzed by GC-MS. The residue was concentrated under reduced pressure to afford the desired product without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, which are consistent with those reported in the literature.[3-4]

General procedure for the catalyst recycling experiment.

To check if the catalyst is recyclable, the C-S coupling reaction was repeated five times with the same catalyst sample, which was recovered after each reaction.After completion of the reaction under the optimal conditions reaction, a simple filtration was sufficient to separate the catalyst solution from the products when the reaction was cool down. The catalyst was washed with ethyl acetate twice and was dried for 6 h at 75 °C. Then the separated catalyst was recharged with fresh substrate for the next run under the same reaction conditions.

Selected spectral data of the products

1-(4-Methoxyphenylsulfonyl)benzene 3a. white solid; m.p.: 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.79 (m,4H), 7.46-7.41 (m, 3H), 6.90-6.88 (m, 2H), 3.77 (s,3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 141.3, 131.8, 128.9, 128.2, 126.3, 113.5, 54.6. GC-MS (EI) [M]+: m/z calcd. for C13H12O3S: 248.0, found: 248.

1-(*p*-Tolylsulfonyl)benzene 3b. white solid; m.p.: 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.77-7.75 (m, 2H), 7.48-7.40 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 140.9, 137.5, 131.9, 128.9, 128.2, 126.6, 126.4, 20.5. GC-MS (EI) [M]+: m/z calcd. for C13H12O2S: 232.0, found: 232.

4-(Benzenesulfonyl)phenol 3c. brown solid; m.p.: 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (br s, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 7.56-7.47 (m, 3H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 131.8, 129.1, 128.1, 126.2, 115.0. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_3S$: 234.0, found: 234.

1-(4-Chlorophenylsulfonyl)benzene 3d. white solid; m.p.: 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.88 (m, 4H), 7.60-7.46 (m, 5H).^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 140.0, 139.8, 133.4, 129.6, 129.4, 129.1, 127.6. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9ClO_2S$: 252.0, found: 252.

1-(4-Nitrophenylsulfonyl)benzene 3e. yellow solid; m.p.: 143-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36-8.34 (m, 2H), 8.15-8.13 (m, 2H), 7.99-7.97 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 147.3, 140.0, 134.1, 129.7, 128.9, 128.0, 124.5. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9NO_4S$: 263.0, found: 263.

1-(Trifluoromethyl)-4-(phenylsulfonyl)benzene 3f. white solid; m.p.: 90-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 6.8 Hz, 2H), 8.99-7.98 (m, 2H), 7.78 (d, *J* = 6.8 Hz, 2H), 7.64-7.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 140.6, 133.7, 129.5, 128.2, 127.9, 126.4, 126.4, 126.3. GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_9F_3O_2S$: 286.0, found: 286.

1-(4-(Phenylsulfonyl)phenyl)ethanone 3g. white solid; m.p.: 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (m,4H), 7.97 (m, 2H), 7.61 (m, 1H), 7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 145.4, 140.7, 140.3, 133.6, 130.9, 129.4, 129.0, 128.0, 127.8, 115.3, 26.8. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}O_3S$: 260.0, found: 260.

3-Nitrol-(phenylsulfonyl)benzene 3h. yellow solid; m.p.: 163-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36-8.24 (m, 2H), 8.15-8.13 (m, 2H), 7.99-7.97 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.55 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 142.9, 139.0, 133.0, 132.0, 129.7, 128.7, 126.9, 126.6, 121.9. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_9NO_4S$: 263.0, found: 263.

1-Methyl-2-(phenylsulfonyl)benzene 3i. white solid; m.p.: 73-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 0.8,

0.8Hz, 1H), 7.90 (m, 2H), 7.61-7.49 (m, 4H), 7.44 -7.41(m, 1H), 7.25 (d, J = 6 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 138.9, 138.0, 133.5, 132.9, 132.6, 129.4, 129.0, 127.6, 126.4, 20.1. GC-MS (EI) [M]+: m/z calcd. for $C_{13}H_{12}O_2S$: 232.0, found: 232.

Methyl 2-(phenylsulfonyl)benzoate 3j. white solid; m.p.: 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (m, 1H), 7.98 (m, 2H), 7.65-7.52 (m, 6H), 3.94 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 141.4, 138.9, 133.4, 133.3, 133.2, 130.9, 130.2, 129.2, 129.0, 127.8, 53.1. GC-MS (EI) [M]+: m/z calcd. for $C_{14}H_{12}O_4S$: 276.0, found: 276.

1-(Phenylsulfonyl)benzene 3k. white solid; m.p.: 122-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.96 (m, 4H), 7.59-7.50 (m, 6H) .^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 133.1, 129.2, 127.6. GC-MS (EI) [M]+: m/z calcd. for $C_{12}H_{10}O_2S$: 218.0, found: 218.

4-(Methanesulfonyl)benzene 3l. white solid; m.p.: 90-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.64-7.62 (m, 1H), 7.57-7.54 (m, 2H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 133.6, 129.3, 127.2, 44.4. GC-MS (EI) [M]+: m/z calcd. for $C_7H_8O_2S$: 156.0, found: 156.

Zolimidine. yellowish white solid ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.15 (m, 3H), 8.03-7.97 (m, 3H), 7.73 (d, J = 9.2 Hz, 1H), 7.31-7.29 (m, 1H), 6.89 (t, J = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 142.6, 139.6, 127.9, 126.7, 126.3, 126.0, 117.4, 113.5, 109.8, 44.5. GC-MS (EI) [M]+: m/z calcd. For $C_{14}H_{12}N_2O_2S$: 272.0, found: 272.

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