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Sulfonylation of 1,4-Diazabicyclo[2.2.2]octane: Charge-Transfer Complex Triggered C–N Bond Cleavage

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A novel charge-transfer complex triggered sulfonylation of 1,4-diazabicyclo[2.2.2]octane (DABCO) with mild reaction conditions has been developed. The formation of a charge-transfer complex between electron-withdrawing (hetero)aryl sulfonyl chloride and DABCO allows the synthesis of *N*-ethylated piperazine sulfonamide in good yields. The reaction has a high functional group tolerance. Spectroscopic studies confirmed the charge-transfer complex formation between sulfonyl chlorides and DABCO, which facilitates the C–N bond cleavage of DABCO.

The *N*-alkylated piperazine is a core structural motif in pharmaceuticals and bioactive natural products and a number of drugs containing this key scaffold that are preclinical and clinical candidates (Figure 1).[1] Importantly, the *N*-alkylated piperazine sulfonamides exhibit diverse pharmacological activities, e.g., MMP-3 inhibition,[2] antimalarial,[3] anti-microbial,[4] anti-cancer,[5] anti-fungal,[6] antibacterial[7] anti-HIV,[8] anti-plasmodial[9] and anticonvulsant[10] etc. Particularly, Sildenafil citrate (Viagra®),[11] Vardenafil (Levitra®)[12] and Mirodenafil[13] are FDA approved drugs for the treatment of male erectile dysfunction and pulmonary arterial hypertension (Scheme 1). Traditional synthetic method toward this structural motif rely upon coupling of sulfonyl chlorides with the appropriate *N*-monoalkyl piperazines which are usually accessed *via* multistep sequences.[14]

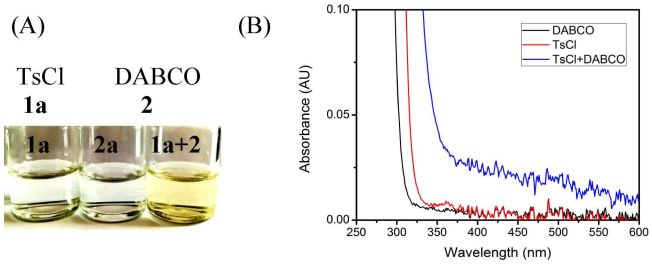
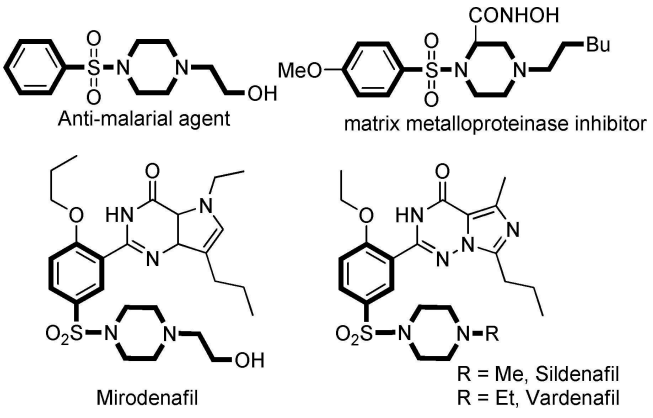


Figure 1. A) Photos of TsCl (**1a**), DABCO (**2**), and **1a** + **2** in MeCN (0.05 M). B) UV/Vis absorption spectra of **1a** (0.05 M), **2** (0.05 M), and their mixture (**1a** + **2**) in MeCN.

1,4-Diazabicyclo[2.2.2]octane (DABCO),[15] a strong nucleophile and a good nucleofugic group in organic synthesis, has been extensively employed as a base or as a catalyst to promote reactions such as the sulfonylation of an alcohol,[16] Morita-Baylis-Hillman reaction,[17] [3 + 3]-cycloaddition,[18] Suzuki-Miyaura cross-coupling,[19] Sonogashira reaction,[20] Stille cross-coupling reaction[21] and Knoevenagel condensation[22] etc. Synthetically, DABCO is a useful building block for the preparation of 1,4-disubstituted piperazines.[14] Pioneered by the work of Ross and Finkelstein,[23] the ring-opening of DABCO,[15,24] prompted by nucleophilic attack on the highly reactive *N*-alkyl quaternary ammonium salts (derived from *in situ* coupling of DABCO with alkyl,[25] aryl[26] and heteroaryl halides,[27] arynes,[28] pyridine *N*-oxides[29] etc.), has been extensively developed for the preparation of 1,4-disubstituted piperazines (Scheme 2).

The charge-transfer complex (CT complex) is formed through partial electronic charge transference between a π-acceptor and a n-donor whereby polarizing and activating the original chemical bond.[30] Sulfonyl chlorides belong to this series of π-acceptors. Previously, we disclosed an interesting charge-transfer complex (CT complex) induced regiospecific C–N bond activation of ethylenediamines whereby aromatic sulfonamides were prepared in high yields.[31] Along the same lines, and in continuation of our interests in the synthesis of sulfur containing compounds,[32] we herein report a CT complex-promoted, catalyst-free synthesis of *N*-ethylated piperazine sulfonamides from reactions



Scheme 1. Representative marketed drugs and drug candidates containing 1-alkyl-4-sulfonylpiperazine core.

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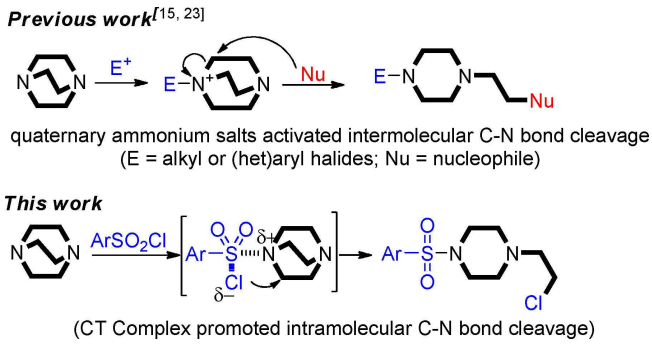
of sulfonyl chlorides and DABCO (Scheme 2). The key feature of this protocol is that C–N bond was activated *via* the *in situ* formed CT complex.

In our initial studies, the reaction of *p*-TsCl (**1a**) and DABCO (**2**) was chosen as a model reaction to optimize the reaction conditions. Reaction temperature plays a key role on this type of reaction. As depicted in table 1, no reaction occurred at room temperature (entry 1). However, the expected product 1-(2-chloroethyl)-4-tosylpiperazine **3a** was formed and was isolated in 38% yield after stirring at 40 °C in MeCN for 24 h (Table 1, entry 2). The best result was obtained after stirring the reaction mixtures at 90 °C for 4 hours (84%, entry 3). Attempts to further enhance the yield of **3a** by adding one equivalent of Lewis acid, e.g., $FeCl_3$, $AlCl_3$ or $ZnCl_2$ or chloride source (n-Bu_4Cl), were failed (entries 4–7). Finally, a solvent screen showed that MeCN was superior to other solvents (Table 1, entries 8–12). The reaction proceeded in moderate yield in ethereal solvents (1,4-dioxane and THF, entries 8 & 9). Reaction employing dichlomethane, chloroform or toluene as a solvent did not improve the yield of **3a** either (Table 1, entries 10–12).

Having established the optimal reaction conditions (Table 1, entries 3), we next studied the scope of sulfonyl chlorides (Table 2). Arylsulfonyl chlorides bearing both electron-donating functional groups (Me, OCF_3 & AcNH), and electron-withdrawing functionalities (F, Br, CF_3 & NO_2) produced the corresponding products (**3b**–**3k**) in good-to-high yields. Steric constraints on the phenyl rings of sulfonyl chlorides plays a role on the yields of sulfonamides. Reaction of 2-(trifluoromethoxy)benzenesulfonyl chloride with DABCO produced **3c** in 73% yield, slightly inferior to its para substituted sibling (**3b**, 77%). Moreover, reaction of the highly sterically hindered 2,4,6-trimethylbenzenesulfonyl chloride with DABCO gave only 42% yield of sulfonamide **3e**.

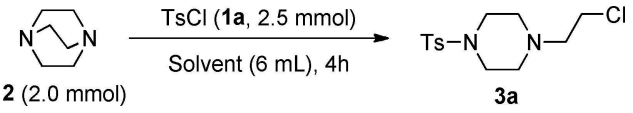
Synthetically important functionalities such as fluoro, bromo, trifluoromethyl, trifluoromethoxyl, amido and nitro were well reserved in sulfonamide products. Heteroaromatic sulfonyl chlorides, *viz.*, 2-thiophenesulfonyl chloride and quinoline-8-sulfonyl chloride, reacted with DABCO smoothly to produce **3l** and **3m** in 76% and 84% isolated yield respectively. The reaction of 2-naphthalenesulfonyl chloride gave rise to **3n** in 73% yield. Furthermore, the applicabilities of aliphatic sulfony chlorides were investigated. Cyclopropylsulfonyl chloride could perform this conversion to give **3o** in 54% yield, albeit other aliphatic sulfonyl chlorides screened, e.g., benzylsulfonyl chlorides, methanesulfonyl chloride, butanesulfonyl chloride and 10-camphorsulfonyl chloride, were all failed to yield the desired sulfonamides products[33] (Table 2, entries 15–18).

In order to verify if a CT complex indeed involved into these reactions, DABCO (**2**) in MeCN was added into a MeCN solution of TsCl (**1a**) at room temperature, the color immediately changed from colorless to yellowish (Figure 1A). The UV – vis absorption spectra of **1a** and **2** were measured separately and combined (Figure 1B). Accordingly, 0.05 M solutions of compounds **1a** and **2** and a mixture of the two



Scheme 2. Nucleophilic ring-opening reactions of DABCO.

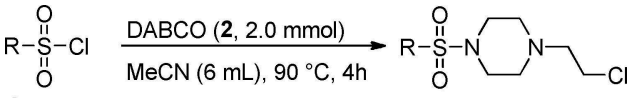
Table 1. Reaction of TsCl with DABCO.[a]



Entry	Solvent	Additive	T [°C]	Yield[b] [%]
1	CH_3CN	–	RT	N.R[c]
2	CH_3CN	–	40	38[c]
3	CH_3CN	–	90	84
4	CH_3CN	$FeCl_3$	90	77
5	CH_3CN	$AlCl_3$	90	74
6	CH_3CN	$ZnCl_2$	90	54
7	CH_3CN	N-Bu_4Cl	90	81
8	1,4-dioxane	–	90	66
9	THF	–	reflux	43
10	CH_2Cl_2	–	reflux	56
11	CH_3Cl	–	reflux	57
12	toluene	–	90	68

[a] TsCl (**1a**, 2.5 mmol) and DABCO (2.0 mmol), designated temperature, 4 h. [b] Isolated yields based on DABCO. [c] 24 h reaction.

Table 2. Reaction of sulfonyl chlorides with DABCO.[a]



Entry	R	Yield [%]
1	4-$CF_3OC_6H_4$	**3b** (77)
2	2-$CF_3OC_6H_4$	**3c** (73)
3	4-$AcNHC_6H_4$	**3d** (74)
4	2,4,6-(i-Pr)$_3C_6H_2$	**3e** (42)
5	C6H5	**3f** (78)
6	4-FC_6H_4	**3g** (68)
7	4-BrC_6H_4	**3h** (79)
8	3,5-$F_2C_6H_3$	**3i** (61)
9	4-$CF_3C_6H_4$	**3j** (67)
10	4-$NO_2C_6H_4$	**3k** (71)
11	2-Thienyl	**3l** (76)
12	8-Quinolyl	**3m** (84)
13	2-Naphthyl	**3n** (73)
14	Cyclopropyl	**3o** (54)
15	Bn	**3p** (N.r.)[c]
16	Me	**3q** (N.r.)
17	n-Bu	**3r** (N.r.)
18	(L)-10-Camphor	**3s** (N.r.)

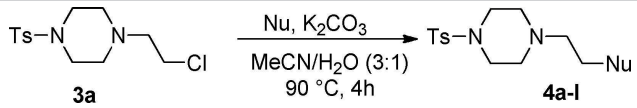
[a] Sulfonyl chloride (**1**, 2.5 mmol) and DABCO (**2**, 2.0 mmol) in MeCN (6 ml), 90 °C, 4 h. [b] Isolated yields based on DABCO. [c] N.r. denotes no reaction.

were prepared in MeCN and analyzed. When mixing **1a** and **2**, a tailing band from 350 to 550 nm appeared, which is attributed to the CT complex arising from charge transfer from **2** to **1a**. Combined with the empirical facts that additional added chloride salts affected neither the yield nor the rate of these reactions (table 1, entry 7), we thus believe that it is the C–T complex rather than a sulfonyl quaternary ammonium salt which is the key active intermediate to facilitate the C–N bond cleavage of DABCO (Scheme 2, this work).

The 1-(2-chloroethyl)-4-tosylpiperazine **3a** contains a 2-chloroethyl group that can be readily modified by reactions with various nucleophiles. Nevertheless, the sulfonamide functionality is susceptible to thiophilic attack,[34] thus it was important to identify both nucleophiles and conditions that would not cleave the S–N bond of sulfonamide group.

A selection of N-, O-, and S-nucleophiles reacted cleanly with **3a** in hot MeCN (ca. 90 °C) to give, predominantly, the desired 1-[(2-(substituted)ethyl]-4-tosylpiperazine **4** products in good to excellent yields (Table 3). MeONa and AcONa were able to react with **3a** to afford **4a** and **4b** in 82% and 78% isolated yields. Similarly, reactions occurred with PhOH and $PhCO_2H$, in the presence of two equivalents of K_2CO_3, to produce **4c** and **4d** proceeded smoothly with similar yields. Also, in the reactions with *N*-methylanilines (Table 3, entries 5–9), significant quantities (10–20% by TLC) of starting material **3a** remained after 8 h or longer reaction time. Increasing the equivalents of both *N*-methylanilines and K_2CO_3 up to 4 equivalents did not improve the yields of product further. Thiophenol and potassium thioacetate reacted quickly with **3a** to yield the desired products in high yields (entries 10 & 11). An exception was sodium phenylsulfinate (Table 3, entry 12), which reacted with the **3a** to give, after 8 h, an inseparable mixture of desired *p*-tolylsulfone **4l** and a *p*-tolylsulfinate isomeric byproduct, derived from O-attack of $PhSO_2Na$ to **3a**.

Table 3. Manipulation on 2-chloroethyl group of **3a**.[a,b]



Entry	Nu	Time [h]	Yield [%]
1	MeONa	4	**4a** (82)[c]
2	AcONa	4	**4b** (78)[c]
3	PhOH	4	**4c** (72)
4	$PhCO_2H$	4	**4d** (75)
5	PhNHMe	8	**4e** (87)
6	*p*-TolNHMe	8	**4f** (80)
7	*m*-TolNHMe	8	**4g** (83)
8	2-FC_6H_4NHMe	12	**4h** (74)
9	3-FC_6H_4NHMe	12	**4i** (72)
10	PhSH	4	**4j** (84)
11	CH_3COSK	4	**4k** (71)[c]
12	$PhSO_2Na$	8	**4l** (76)[c,d]

[a] **3a** (1.0 mmol), Nu (3.0 mmol) and K_2CO_3 (3.0 mmol) in MeCN (3 mL) and H_2O (1.0 mL), 90 °C for 4 h. [b] Isolated yields. [c] Without K_2CO_3. [d] Phenyl sulfone **4l** together with a sulfinate isomeric byproduct was generated.

The success in the functionalization of 2-chloroethyl moiety of 1-(2-chloroethyl)-4-tosylpiperazine inspired us to further explore the possibility of direct conversion of DABCO into N-arylsulfonyl-4-(2-substituted ethyl)piperazines via a one-pot two-step protocol. As shown in Table 4, the reaction of arylsulfonyl chlorides with DABCO gave *N*-arylsulfonyl-4-(2-chloroethyl)piperazines which, without purification, were treated with 3 equiv. of nucleophiles at 90 °C for an additional 4 hours, affording the 4-(2-substituted ethyl) products 5**a**–**n** in acceptable yields.

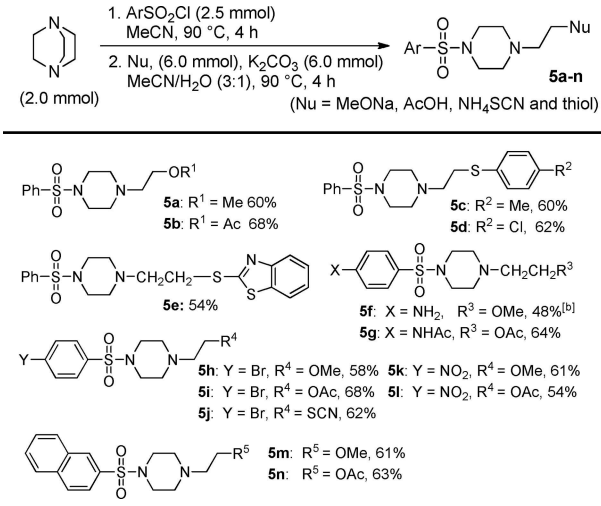
In summary, we have demonstrated that the charge transfer complex induced reactions of sulfonyl chlorides with DABCO could afford the corresponding 1-(2-chloroethyl)-4-arylsulfonyl piperazines in good yields under mild reaction conditions. The 2-chloroethyl moiety of these 1-(2-chloroethyl)-4-tosylpiperazines could be further manipulated by a variety of nucleophiles into 1-(2-substituted ethyl)-4-tosylpiperazines. Beside its wide functional group tolerance, this transformation showed potential applications in organic syntheses, especially in the synthesis of bioactive *N*-ethylated piperazine sulfonamides.

Experimental Section

General

All reactions were performed in Schlenk tubes under argon. MeCN was distilled from phosphorous pentoxide prior to use. ^1H (400 or 600 MHz), ^{13}C (101 or 151 MHz) spectra were recorded in $CDCl_3$ solutions. Flash chromatography was performed on silica gel (300–400 mesh).

Table 4. One-pot two-step synthesis of 1-(2-substitued ethyl)-4-sulfonylpiperazines.[a]



[a] Isolated yields based on DABCO. [b] AcNH in **3d** was decomposed by MeONa to NH_2.

Reactions of Sulfonyl Chlorides with DABCO

To a dry 10 mL Schlenk-tube equipped with a stirring bar, DABCO **2** (2.0 mmol) in 3 mL of MeCN was added. After the solution was heated to 90 °C, sulfonyl chloride **1** (2.5 mmol) in MeCM (3.0 mL) were added and the reaction mixtures were heated and stirred under air for 4 hours. 1-(2-chloroethyl)-4-arylsulfonylpiperazines were obtained after usual workup and purification on silica gel column chromatography.

Manipulations on the 2-Chloroethyl Moiety of 1-(2-chloroethyl)-4-Tosylpiperazine 3 a

To a dry 10 mL Schlenk-tube equipped with a stirring bar, 1-(2-chloroethyl)-4-tosylpiperazine **3 a** (1.0 mmol), K_2CO_3 (3.0 mmol), MeCN (4 mL), H_2O (1.0 mL) and the corresponding nucleophile (3.0 mmol) were added and the reaction mixtures were then heated to 90 °C for 4 hours. The desired 1-(2-substituted ethyl)-4-arylsulfonylpiperazines were obtained after usual workup and purification by silica gel column chromatography.

Direct Conversion of DABCO into *N*-Arylsulfonyl-4-(2-substituted ethyl)piperazines

To the reaction mixtures obtained from reaction of sulfonyl chloride **1** (2.5 mmol) and DABCO (2.0 mmol) in MeCM (6.0 mL), nucleophile Nu (6.0 mmol), water (2 mL) and K_2CO_3 (6.0 mmol) were added and the reaction mixtures were heated and stirred under air for another 4 hours. 1-(2-substituted ethyl)-4-arylsulfonylpiperazines were obtained after usual workup and purification by silica gel column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: charge-transfer complex · sulfonyl chloride · DABCO · Sulfonamides · piperazine

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