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One-Step Cyclization: Synthesis of *N*-Heteroalkyl-*N*′-tosylpiperazines

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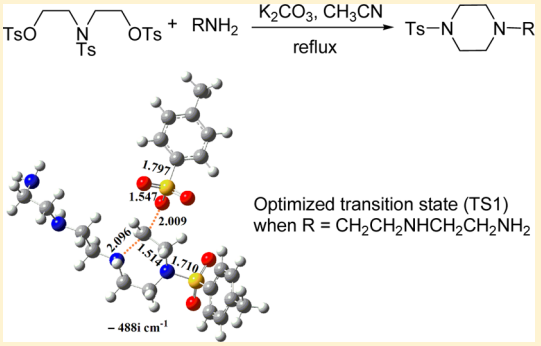
Supporting Information

ABSTRACT: Piperazine derivatives are important intermediates in organic synthesis and useful building blocks in pharmaceutical and fine chemical industries. Currently available synthetic routes for these heterocyclic compounds have limited scope owing to the harsh reaction conditions, low yields, and multistep process. Herein, we reported a practical method for synthesis of alkyl-, alcohol-, amine-, and ester-extended tosylpiperazines under mild conditions with moderate to high yields. This protocol exhibits potential applicability in the synthesis of pharmaceuticals and natural products because of the operational simplicity and the conveniently available reactants. On the basis of the experimental and theoretical results, a plausible mechanism of aliphatic nucleophilic substitution (S_N) in the cyclization has been postulated and evidence for the formation of a six-membered ring has also been confirmed by means of density functional theory (DFT) calculations.



INTRODUCTION

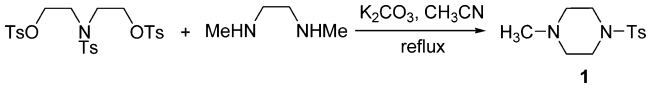
The piperazine scaffold not only is a very useful building block in coordination polymers and fine industrial chemicals,[1,2] but it is also an important pharmacophore found in a large number of biologically active compounds.[3−8] Amine- and alcohol-extended piperazines have considerably extensive applications in the preparation of hardeners of epoxy resins, corrosion inhibitors, insecticides, accelerators for rubber, urethane catalysts, and antioxidants.[9,10] 1-(2-Aminoethyl)piperazine is used as intermedia of nonviral gene delivery vectors.[4] Recently, piperazine derivatives have even been developed as CO_2 capturing materials.[11]

The synthesis of simple 1,4-disubstituted piperazines has received considerable attention, but only a comparatively small number of 1,4-disubstituted piperazines have been prepared by one-step cyclization. In the past decades, amine-extended piperazines were formed as a byproduct of the reaction with ethylene dichloride and ammonia or amines to prepare higher amines in the presence of acid catalysts. This reaction was usually performed at a very high temperature, 300 °C or even higher, and the products were difficult to purify.[12] Another adaptation of the ring closure treatment by hydrochlorides of diethanolamine and aniline in stoichiometric quantities involved heating at about 240 °C for a period of 8 h to provide *N*-monophenylpiperazine.[13,14] Although these methods are one-step cyclizations, their versatility is restricted mainly because of the harsh conditions, including the usage of forced catalysts, high temperatures, and extended reaction times.

A common process for preparing alcohol- and amine-extended piperazines is the coupling of an aliphatic alcohol with an amine reactant, wherein the aliphatic alcohol and/or reactant amine contains a piperazine moiety. Furthermore, it is necessary to use a preferable catalyst containing a Group VB metal oxide, a Group VB metal phosphate, or mixtures thereof.[9] Another reported strategy to synthesize asymmetric piperazine derivatives is selective monoprotection of one nitrogen atom with *tert*-butoxycarbonyl (Boc) in acidic medium, followed by substitution of another unprotected nitrogen and then deprotection to provide the desired products.[15,16] However, this kind of method involves regioselective substitution and deprotection, which usually leads to low yields and is time-consuming because of side reactions during the protection and deprotection of the Boc group, which is not very stable under basic conditions at high temperature. Therefore, because of the limitations of the known methods for diversely substituted piperazines, practical one-step cyclization routes to synthesize *N*-heteroalkyl-*N*′-tosylpiperazines are of particular interest. This kind of tosyl-substituted compound, as well as other sulfonamide piperazine compounds, has exibited potential as an antimalarial drug.[17]

In continuation of our work on the synthesis of 1-methyl-4-tosylpiperazine from *N*,*N*′-dimethylethylenediamine and tosylbis(2-(tosyloxy)ethyl)amine (Scheme 1),[18] we promote the method for using differently substituted amines, even

Scheme 1. Previously Reported Synthesis of 1-Methyl-4-tosylpiperazine



1

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polyamines and amino acid esters, as substrates to synthesize a series of piperazine derivatives. The mechanism of six-membered ring formation is postulated based on the reaction products and detailed computational information.

RESULTS AND DISCUSSION

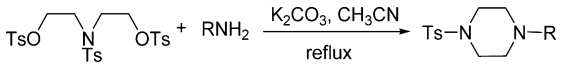
In our studies, tosylbis(2-(tosyloxy)ethyl)amine is chosen as one of starting materials, which can be easily tosylated from cheap chemical diethanolamine. Initially, different diamines possessing two active primary amine groups were used as substrates, coupling with tosylbis(2-(tosyloxy)ethyl)amine in refluxing acetonitrile with potassium carbonate as the base under nitrogen atmosphere, to afford two substituted products, amine-extended piperazines and ditosylpiperazine derivatives (entries 2–5, Table 1). The selectivity for these two kinds of products can be modified by using an optional excess of reactants. Yields of over 90% were achieved when asymmetrically substituted diamines having one active primary amine and one tertiary amine were used (entries 6–8, Table 1). These asymmetrically substituted diamines only have one S_N reaction site that couples with tosylbis(2-(tosyloxy)ethyl)amine to predominantly yield tertiary amine-extended piperazines.

To expand the scope of the substrates, hydroxyl-derived amines were also applied as precursors to couple with tosylbis(2-(tosyloxy)ethyl)amine to furnish two different alcohol-extended piperazines, with yields of 67% and 72%, respectively (entries 9 and 10, Table 1). Importantly, although there are two functional groups (NH_2 and OH) on the structures, only the reactive amine group reacted in this synthetic system, which is the main reason why only one product was observed compared with the substrates containing two active primary amines (entries 9 and 10 vs entries 2–5, Table 1). Kaushik and co-workers have reported an imidazole-catalyzed protocol for monoacylation of 2-(4-tosylpiperazin-1-yl)ethanol in 92% yield.[19] However, the starting material 2-(piperazin-1-yl)ethanol in that reaction is difficult to synthesize whereas, with the present method, 2-(4-tosylpiperazin-1-yl)ethanol **10** was easily obtained by one-step cyclization from two conveniently available reactants, tosylbis(2-(tosyloxy)ethyl)amine and 2-aminoethanol. It was also observed that secondary amine groups in the substrates did not react with tosylbis(2-(tosyloxy)ethyl)amine when primary amine existed (entries 3 and 9, Table 1).

This protocol was further investigated for aromatic amine, which reacted with tosyl-protected diethanolamine to yield *N*-arylpiperazines. But the cyclization of aniline furnished *N*-phenylpiperazine only in a yield of 15% (entry 6, Table 2), and no corresponding product was detected for 4-bromobenzenamine. Pleasingly, 1-benzyl-4-tosylpiperazine was obtained under the same reaction conditions in moderate yield (entry 3, Table 2). Previous researchers have reported the synthesis of 1-benzyl-4-tosylpiperazine by one-pot sulfonamidation from 1-benzylpiperazine.[20] Nevertheless, this compound was obtained via several steps that included protection and deprotection. Similarly, when other alkylamines were applied as starting materials, corresponding *N*-alkylpiperazines were afforded in high yields (entries 1 and 2, Table 2).

Subsequently, to further explore the efficiency and scope of this approach, amino acid esters were utilized. It was found that

Table 1. Synthesis of Amine- and Alcohol-Extended Piperazine Derivatives



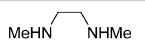
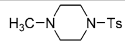
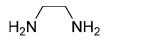
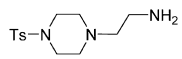
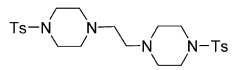
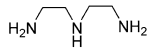
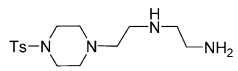
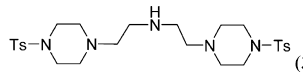
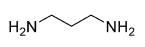
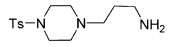
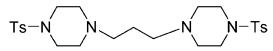
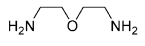
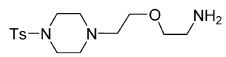
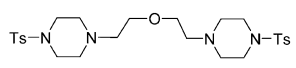
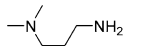
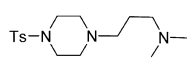
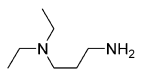
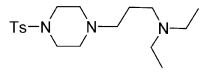
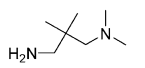
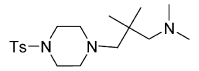
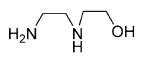
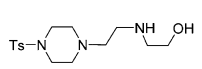
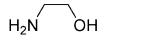
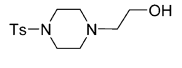
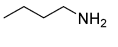
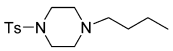
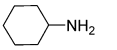
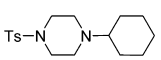
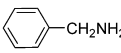
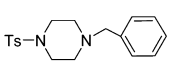
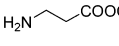
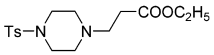
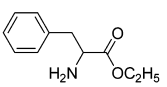
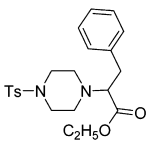
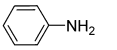
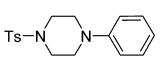
Entry	Substrate	Product		Yield
1			(**1**)	86
2			(**2a**)	70
			(**2b**)	20
3			(**3a**)	72
			(**3b**)	18
4			(**4a**)	72
			(**4b**)	16
5			(**5a**)	71
			(**5b**)	20
6			(**6**)	92
7			(**7**)	90
8			(**8**)	95
9			(**9**)	67
10			(**10**)	72

Table 2. Synthesis of *N*-Alkyl-*N*′-tosylpiperazines and *N*-Aryl-*N*′-tosylpiperazines

Entry	Substrate	Product		Yield
1			(**11**)	71
2			(**12**)	83
3			(**13**)	59
4			(**14**)	61
5			(**15**)	75
6			(**16**)	15

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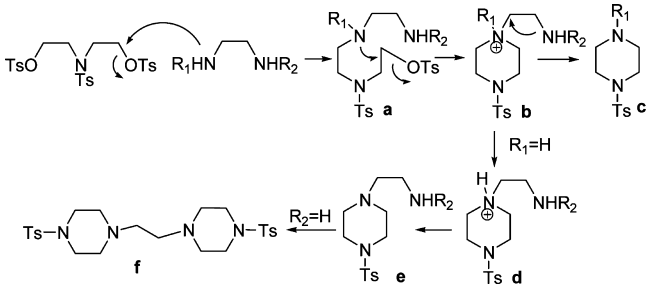
this general one-step cyclization approach was also applicable for the synthesis of tosylpiperazine acid esters, which were achieved in moderate to high yields (entries 4 and 5, Table 2). All of these results indicated that the present protocol is effective for one-step cyclization of *N*-heteroalkyl-*N*′-tosylpiperazines.

To illuminate this interesting reaction, we postulate that there are several substep aliphatic nucleophilic substitutions (S_N) in the cyclization reaction (Scheme 2). After one of the

Scheme 2



amino nitrogen atoms attacks tosylbis(2-(tosyloxy)ethyl)amine to form intermediate **a**, the identical nitrogen atom attacks another carbon, connected to a OTs group, through an intramolecular S_N reaction to give the six-membered ring quaternary ammonium transition compound **b**. When R_1 is methyl or another alkyl group, another nitrogen atom attacks the carbon atom alpha to the quaternary ammonium to give compound **c**. However, when R_1 is hydrogen, quaternary ammonium transition compound **b** converts to amine-extended piperazine **e**. Subsequently, an intermolecular S_N reaction occurs on the nitrogen atom of another terminal amine in compound **e** to give compound **f** in the case of R_2 = H. Evidence for the formation of the six-membered ring was also confirmed on the basis of density functional theory (DFT) calculations (considering *N*,*N*′-dimethylethane-1,2-diamine as the model substrate).

As shown in Table 3, the reaction can proceed via two alternative pathways. One involves the formation of a six-membered ring compound, and the predicted activation energies (TS_1) are about 25.41 and 16.86 kcal/mol in the gas phase and surrounding acetonitrile, respectively. As Figure 1 depicts, the C–N and N–O bond lengths in TS_1 are calculated to be 2.096 and 2.009 Å, respectively. The other pathway is related to the formation of a multiring compound. As Table 3 shows, the activation energies (TS_2) are equal to 29.60 and 20.17 kcal/mol in the gas phase and surrounding acetonitrile,

Table 3. The Relative Energy (RE in kcal/mol) of Nucleophilic Attack Reaction Obtained from the B3LYP/6-31++G(d,p) Method in the Gas Phase and Surrounding Acetonitrile

Six-Membered Ring		
R_1	TS_1	P_1
0.00 (0.00)[a]	25.41 (16.86)	−14.78 (−17.56)
Multiring		
R_2	TS_2	P_2
0.00 (0.00)	29.60 (20.17)	−15.33 (−21.4)

[a]Values in parentheses are obtained from surrounding acetonitrile.

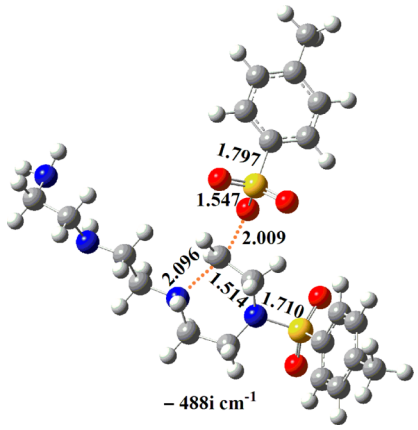


Figure 1. The optimized transition state (TS_1) for nucleophilic attack in the formation of a six-membered ring compound.

respectively. The C–N and N–O bond lengths in TS_2 are computed to be 2.104 and 2.037 Å, respectively (Figure 2). On

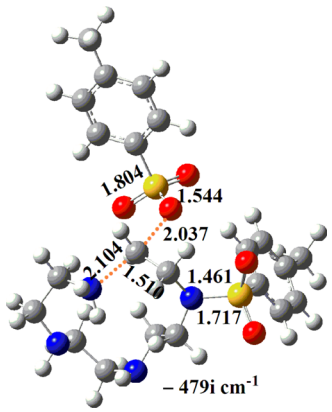


Figure 2. The optimized transition state (TS_2) for the nucleophilic attack reaction in the formation of the multiring compound.

the basis of the present calculations, in contrast to the formation of a multiring compound, the reaction involving the generation of the six-membered ring compound is kinetically more favored. This agrees well with our experimental results that we only obtain the six-membered ring compound during the reaction process.

CONCLUSION

We developed a general and practical one-step protocol for selectively synthesizing alkyl-substituted tosylpiperazines and amine/alcohol-extended tosylpiperazines under mild reaction conditions with moderate to high yields, utilizing different commercially available amines and tosylbis(2-(tosyloxy)ethyl)-amine, which can be easily tosylated from diethanolamine. More advantageously, this method avoided the problem of protection and deprotection for the synthesis of asymmetric piperazine derivatives and exhibited attractive applicability in the synthesis of pharmaceuticals and natural products. Based on the results of experiments and theoretical calculations, a plausible mechanism of aliphatic nucleophilic substitution (S_N) in the cyclization was postulated. The favorable formation of the six-membered ring was also confirmed by means of density functional theory (DFT) calculations.

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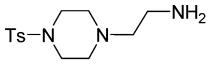
EXPERIMENTAL SECTION

General Methods. Chemicals were commercial reagent grade and used as received without further purification unless otherwise stated. The NMR spectra were recorded in $CDCl_3$ as the internal standards for ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) at room temperature. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. Electrospray ionization mass spectra (ESI-MS) and high-resolution mass spectra (HRMS) were recorded using ESI-mode. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on silica gel detected with UV light (254 nm) or visualized by spraying with phosphomolybdic acid and heating at 200 °C. Silica gel (H, 300–400 mesh) was used for flash chromatography.

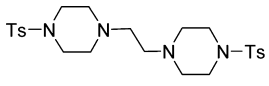
Synthesis of Tosylbis(2-(tosyloxy)ethyl)amine. Diethanolamine (27.5 g, 0.262 mol) was dissolved in distilled CH_2Cl_2 (500 mL) in a three-necked flask. The solution was cooled to 0 °C under a stream of anhydrous N_2, and Et_3N (122 mL, 88.6 g, 0.880 mol) was added. With the temperature maintained at 0 °C, solid TsCl (157 g, 0.823 mol) was added in portions to the vigorously stirred reaction mixture over 5 h. The reaction mixture was then stirred at r.t. overnight. The Et_3N·HCl that had formed was removed by filtration, and the resulting pale yellow filtrate was washed with 1 M aq HCl (3 × 100 mL), followed by H_2O (5 × 200 mL) and sat. aq $NaHCO_3$ (5 × 200 mL). The organic layer was dried with anhydrous Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was recrystallized (EtOH), which gave a white product (120 g, 80%): mp 98–99 °C (lit.[19] 97–99 °C).

General Procedure for the Synthesis of N-Heteroalkyl-N′-tosylpiperazine. Tosylbis(2-(tosyloxy)ethyl)amine (5.83 g, 10.0 mmol), K_2CO_3 (8.00 g, 58.0 mmol), amine (10.0 mmol), and anhydrous MeCN (50 mL) were added to a round-bottom flask. The mixture was heated to reflux under an N_2 atmosphere for 12 h. The mixture was cooled to r.t. and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH–Et_3N as eluent) to give *N*-heteroalkyl-*N′*-tosylpiperazine (see Table 1, Table 2, and Supporting Information).



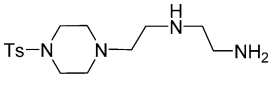
2a

1-(2′-Aminoethyl)-4-tosylpiperazine (2a). **2a** was obtained as a pale-yellow liquid in 70% yield (1.98 g). IR (KBr, cm^{-1}): 3356, 2948, 2816, 1596, 1454, 1349, 1164, 950, 733. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 6.4 Hz, 2 H), 7.31 (d, J = 6.4 Hz, 2 H), 3.00 (br, 4 H), 2.72 (t, J = 6.0 Hz, 2 H), 2.51 (br, 4 H), 2.43–2.42 (m, 5 H), 2.13 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 132.1, 129.4, 127.6, 60.0, 52.2, 46.0, 38.4, 21.5. LRMS (ESI): m/z = 284 ([M + H]$^+$). HRMS (ESI): calcd for $C_{13}H_{22}N_3O_2S$ ([M + H]$^+$); 284.1433; found: 284.1423.



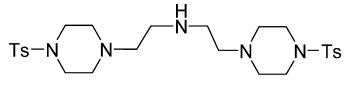
2b

1-Tosyl-4-(2-(4-tosylpiperazin-1-yl)ethyl)piperazine (2b). **2b** was obtained as a white solid in 20% yield (1.01 g): mp 253.3–253.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 4 H), 7.28 (d, J = 8.0 Hz, 4 H), 2.96 (br, 8 H), 2.51–2.49 (m, 8 H), 2.41 (s, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 132.0, 129.5, 127.7, 55.3, 52.6, 46.0, 21.6. LRMS (ESI): m/z = 507 ([M + H]$^+$).



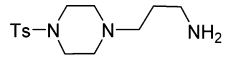
3a

***N*^{1}-(2-(4-Tosylpiperazin-1-yl)ethyl)ethane-1,2-diamine (3a).** **3a** was obtained as a light yellow oil in 72% yield (2.34 g). IR (KBr, cm^{-1}): 3429, 3138, 2853, 1629, 1400, 1163, 952, 731. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 3.01 (br, 4 H), 2.77 (t, J = 6.0 Hz, 2 H), 2.67–2.63 (m, 4 H), 2.53–2.50 (m, 4 H), 2.49–2.47 (m, 5 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 132.4, 129.5, 127.7, 57.2, 52.3, 51.7, 46.1, 46.0, 41.1, 21.6. LRMS (ESI): m/z = 327 ([M + H]$^+$). HRMS (ESI): calcd for $C_{15}H_{27}N_4O_2S$ ([M + H]$^+$): 327.1855; found: 327.1856.



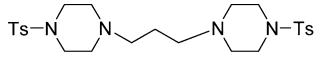
3b

Bis(2–4-tosypiperazin-1-yl)ethyl)amine (3b). **3b** was obtained as a white solid in 18% yield (0.81 g): mp 50.3–51.2 °C. IR (KBr, cm^{-1}): 3429, 3133, 2924, 2853, 1629, 1455, 1400, 1164, 951, 731. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.0 Hz, 4 H), 7.30 (d, J = 8.0 Hz, 4 H), 2.96 (br, 8 H), 2.67 (t, J = 6.4 Hz, 4 H), 2.48–2.45 (m, 12 H), 2.43 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 132.2, 129.5, 127.6, 56.6, 52.2, 46.0, 21.6. LRMS (ESI): m/z = 550.0 ([M + H]$^+$). HRMS (ESI): calcd for $C_{26}H_{40}N_5O_4S_2$ ([M + H]$^+$): 550.2522; found: 550.2536.



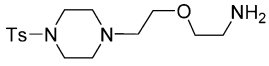
4a

3-(4-Tosylpiperazin-1-yl)propan-1-amine (4a). **4a** was obtained as a yellow oil in 72% yield (2.14 g). IR (KBr, cm^{-1}): 2966, 2810, 1598, 1455, 1351, 1166, 949, 813, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 3.00 (br, 4 H), 2.69 (t, J = 6.8 Hz, 2 H), 2.52–2.49 (m, 4 H), 2.42 (s, 3 H), 2.38 (t, J = 6.8 Hz, 2 H), 1.61–1.54 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 129.4, 127.6, 94.2, 55.8, 52.2, 46.0, 40.4, 29.9, 21.5. LRMS (ESI): m/z = 298 ([M + H]$^+$).



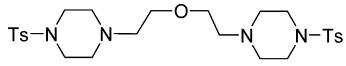
4b

1-Tosyl-4-(3-(4-tosylpiperazin-1-yl)propyl)piperazine (4b). **4b** was obtained as a white solid in 16% yield (0.83 g): mp 169.1–169.7 °C. IR (KBr, cm^{-1}): 3410, 3101, 3062, 2954, 2812, 1597, 1454, 1348, 1169, 1163, 1092, 947, 822, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.0 Hz, 4 H), 7.28 (d, J = 8.0 Hz, 4 H), 2.97 (br, 8 H), 2.47–2.44 (m, 8 H), 2.42 (s, 6 H), 2.28 (t, J = 7.2 Hz, 4 H), 1.62 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 131.9, 129.3, 127.6, 55.8, 52.1, 45.9, 24.1, 21.5. LRMS (ESI): m/z = 521 ([M + H]$^+$). HRMS (ESI): calcd for $C_{25}H_{37}N_4O_4S_2$ ([M + H]$^+$): 521.2256; found: 521.2227.



5a

2-(2-(4-Tosylpiperazin-1-yl)ethoxy)ethanamine (5a). **5a** was obtained as a light yellow liquid in 71% yield (2.32 g). IR (KBr, cm^{-1}): 3375, 3134, 2921, 2856, 1597, 1456, 1348, 1167, 953, 734. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 3.51 (t, J = 5.6 Hz, 2 H),3.44 (t, J = 5.2 Hz, 2 H), 3.01 (br, 4 H), 2.84 (t, J = 5.6 Hz, 2 H), 2.58–2.55 (m, 6 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 129.4, 127.7, 94.2, 72.3, 68.3, 57.4, 52.5, 45.9, 41.2, 21.6. LRMS (ESI): m/z = 328 ([M + H]$^+$). HRMS (ESI): calcd for $C_{15}H_{26}N_3O_3S$ ([M + H]$^+$): 328.1695; found: 328.1688.



5b

1-(2-(2-(4-Tosylpiperazin-1-yl)ethoxy)ethyl)-4-tosylpiperazine (5b). **5b** was obtained as a white solid in 20% yield (1.10 g): mp 140.2–141.2 °C. IR (KBr, cm^{-1}): 3130, 2933, 2808, 1597, 1451, 1388, 1343, 1163, 1109, 950, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 4 H), 7.30 (d, J = 8.4 Hz, 4 H), 3.45 (t, J = 6.0 Hz, 4 H), 2.98 (br, 8 H), 2.55–2.50 (m, 12 H), 2.42 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 131.9, 129.4, 127.7, 68.5, 57.1, 52.6, 45.9, 21.6. LRMS (ESI): m/z = 551 ([M + H]$^+$). HRMS (ESI): calcd for $C_{26}H_{39}N_4O_5S_2$ ([M + H]$^+$): 551.2362; found: 551.2367.

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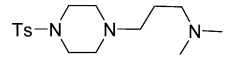
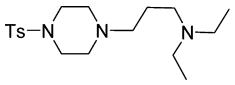


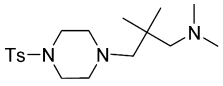
6

***N,N*-Dimethyl-3-(4-tosylpiperazin-1-yl)propan-1-amine (6).** **6** was obtained as a yellow solid in 92% yield (2.99 g): mp 66−68 °C. IR (KBr, cm^{-1}): 2948, 2816, 1596, 1454, 1349, 1164, 950, 815, 733. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 3.00 (br, 4 H), 2.52−2.49 (m, 4 H), 2.42 (s, 3 H), 2.35 (t, J = 7.6 Hz, 2 H), 2.23 (t, J = 7.6 Hz, 2 H), 2.18 (s, 6 H), 1.62−1.55 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 132.0, 129.4, 127.7, 57.6, 56.1, 52.2, 46.0, 45.4, 29.7, 25.1. LRMS (ESI): m/z = 326 ($[M + H]^+$). HRMS (ESI): calcd for $C_{16}H_{28}N_3O_2S$ ($[M + H]^+$): 326.1902; found: 326.1885.



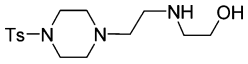
7

***N,N*-Diethyl-3-(4-tosylpiperazin-1-yl)propan-1-amine (7).** **7** was obtained as a light yellow oil in 90% yield (3.18 g). IR (KBr, cm^{-1}): 2966, 2810, 1598, 1455, 1351, 1166, 949, 813, 732. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 3.00 (br, 4 H), 2.52−2.44 (m, 8 H), 2.42 (s, 3 H), 2.39−2.31 (m, 4 H), 1.60−1.53 (m, 2 H), 0.98 (t, J = 7.0 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 132.0, 129.3, 127.6, 56.3, 52.2, 50.6, 46.8, 46.0, 24.5, 21.5, 11.7. LRMS (ESI): m/z = 354 ($[M + H]^+$). HRMS (ESI): calcd for $C_{18}H_{32}N_3O_2S$ ($[M + H]^+$): 354.2215; found: 354.2211.



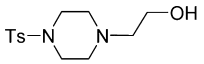
8

***N,N*,2,2-Tetramethyl-3-(4-tosylpiperazin-1-yl)propan-1-amine (8).** **8** was obtained as a light yellow solid in 95% yield (3.35 g): mp 84−86 °C. IR (KBr, cm^{-1}): 2948, 2816, 1596, 1454, 1349, 1164, 950, 733. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 2.96 (br, 4 H), 2.59−2.57 (m, 4 H), 2.44 (s, 3 H), 2.21 (s, 6 H), 2.14 (s, 2 H), 2.01 (s, 2 H), 0.78 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 132.5, 129.4, 127.6, 68.8, 66.3, 54.7, 48.8, 46.4, 38.1, 24.4, 21.6. LRMS (ESI): m/z = 354 ($[M + H]^+$). HRMS (ESI): calcd for $C_{18}H_{32}N_3O_2S$ [M^+ + H]: 354.2215; found: 354.2207.



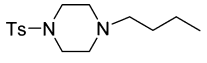
9

2-(2-(4-Tosylpiperazin-1-yl)ethylamino)ethanol (9). **9** was obtained as a yellow solid in 67% yield (2.19 g): mp 67−68 °C. IR (KBr, cm^{-1}): 3158, 2922, 2845, 1596, 1454, 1341, 1163, 1058, 946, 812, 731. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.4 Hz, 2 H), 7.30 (d, J = 8.4 Hz, 2 H), 3.57 (t, J = 4.8 Hz, 2 H), 3.00 (br, 4 H), 2.73−2.66 (m, 4 H), 2.53−2.46 (m, 6 H), 2.43 (s, 3 H), 2.22 (br, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 129.5, 127.7, 94.3, 60.8, 57.2, 52.3, 50.9, 46.0, 45.6, 21.5. LRMS (ESI): m/z = 328.0 ($[M + H]^+$). HRMS (ESI): calcd for $C_{15}H_{26}N_3O_3S$ ($[M + H]^+$): 328.1695; found: 328.1687.



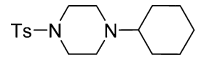
10

2-(4-Tosylpiperazin-1-yl)ethanol (10). **10** was obtained as a white solid in 72% yield (2.05 g): mp 131−132 °C. IR (KBr, cm^{-1}): 3411, 2912, 2809, 2766, 1451, 1338, 1163, 1092, 1055, 949, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 3.56 (t, J = 5.6 Hz, 2 H), 3.01 (br, 4 H), 2.59−2.57 (m, 4 H), 3.53 (t, J = 5.6 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 132.2, 129.5, 127.6, 58.9, 57.8, 52.0, 46.1, 21.6. LRMS (ESI): m/z = 285 ($[M + H]^+$).



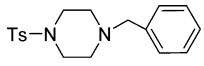
11

Butyl-4-tosylpiperazine (11). **11** was obtained as a white solid in 71% yield (2.10 g): mp 79−80 °C. IR (KBr, cm^{-1}): 3050, 2925, 2850, 2809, 2746, 1596, 1447, 1352, 1174, 941, 810, 729. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 3.00 (bt, 4 H), 2.50 (t, J = 4.8 Hz, 4 H), 2.42 (s, 3 H), 2.30 (t, J = 7.6 Hz, 2 H), 1.43−1.35 (m, 2 H), 1.31−1.22 (m, 2 H), 0.87 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 132.2, 129.3, 127.6, 57.8, 52.2, 46.0, 28.8, 21.4, 20.4, 13.7. LRMS (ESI): m/z = 297 ($[M + H]^+$).



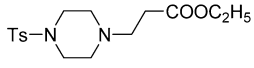
12

1-Cyclohexyl-4-tosylpiperazine (12). **12** was obtained as a white solid in 83% yield (2.67 g): mp 113−116 °C. IR (KBr, cm^{-1}): 3050, 2925, 2850, 2809, 2746, 1596, 1447, 1352, 1174, 1060, 941, 810, 729. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 2.98 (br, 4 H), 2.63 (t, J = 4.8 Hz, 4 H), 2.41 (s, 3 H), 2.25−2.19 (m, 1 H), 1.78−1.74 (m, 4 H), 1.62−1.59 (m, 1 H),1.25−1.03 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 132.1, 129.3, 127.6, 63.2, 48.1, 46.5, 28.9, 26.2, 25.8, 21.5. LRMS (ESI): m/z = 323 ($[M + H]^+$).



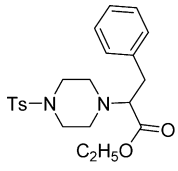
13

1-Benzyl-4-tosylpiperazine (13). **13** was obtained as a light yellow solid in 59% yield (1.95 g): mp 119−120 °C. IR (KBr, cm^{-1}): 3113, 3024, 2938, 2907, 2848, 2821, 1592, 1449, 1396, 1341, 1162, 938, 814, 741. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 2 H), 7.30−7.20 (m, 7 H), 3.46 (s, 2 H), 3.00 (br, 4 H), 2.50 (t, J = 4.8 Hz, 4 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 137.3,132.3, 129.5, 128.9, 128.1, 127.7, 127.1, 62.6, 52.1, 46.1, 21.6. LRMS (ESI): m/z = 331 ($[M + H]^+$).



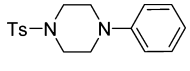
14

Ethyl 3-(4-Tosylpiperazin-1-yl)propanoate (14). **14** was obtained as a white solid in 61% yield (2.07 g): mp 82−83 °C. IR (KBr, cm^{-1}): 2966, 2910, 2819, 1722, 1596, 1459, 1393, 1347, 1159, 936, 813, 737. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 4.08 (q, J = 6.8 Hz, 2 H), 2.99 (br, 4 H), 2.67 (t, J = 6.8 Hz, 2 H), 2.53 (t, J = 4.8 Hz, 4 H), 2.42 (s, 3 H), 2.41−2.39 (m, 2 H), 1.21 (t, J = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 155.6, 143.4, 129.4, 127.6, 60.4, 53.1, 51.9, 45.9, 32.3, 21.5, 14.2. LRMS (ESI): m/z = 341 ($[M + H]^+$).



15

Ethyl 3-Phenyl-2-(4-tosylpiperazin-1-yl)propanoate (15). **15** was obtained as a white solid in 75% yield (3.12 g): mp 126−128 °C. IR (KBr, cm^{-1}): 3029, 2977, 2899, 2838, 1726, 1450, 1398, 1331, 1249, 1161, 946, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.23−7.14 (m, 3 H), 7.12−7.09 (m, 2 H), 4.07−4.00 (m, 2 H), 3.88 (q, J = 5.2 Hz, 1 H), 3.04−2.98 (m, 5 H), 2.86−2.76 (m, 3 H), 2.72−2.66 (m, 2 H), 2.43 (s, 3 H), 1.12 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 155.6, 143.4, 137.4, 129.4, 128.9, 128.2, 127.7, 126.3, 69.2, 60.4, 48.9, 46.4, 35.6, 21.6, 14.4. LRMS (ESI): m/z = 417 ($[M + H]^+$), 439 ($[M + Na]^+$). HRMS (ESI): calcd for $C_{22}H_{29}N_2O_4S$ ($[M + H]^+$): 417.1848; found: 417.1827.



16

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1-Phenyl-4-tosylpiperazine (16). **16** was obtained as a white solid in 15% yield (0.23 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 7.25−7.21 (m, 2 H), 6.89−6.84 (m, 3 H), 3.23 (t, J = 4.4 Hz, 4 H), 3.14 (t, J = 4.4 Hz, 4 H), 2.43 (s, 3 H). LRMS (ESI): m/z = 317 ([M + H]$^+$).

Computational Methods. In the present studies, all geometries of reaction species were calculated by means of B3LYP/6-31++G(d,p) method,[21−23] and frequency calculations were also employed to confirm the structures as minimum points in energy and achieve the relevant zero point energy (ZPE) in the gaseous phase. For each transition state, intrinsic reaction coordinate (IRC) calculations were performed to guarantee its correct connection to the designated local minima. Solvation energies were added as single-point calculations using the conductor-like solvation model CPCM[24,25] at the B3LYP/6-31++G (d, p) level based on the gas-phase structures. In this model, a cavity around the system is surrounded by a polarizable dielectric continuum. In addition, a dielectric constant of 36.64 is used to model the surrounding acetonitrile.

■ ASSOCIATED CONTENT

Supporting Information

Computational detail and copies of spectra for the products **2**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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