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Benzyne-Induced Ring Opening Reactions of DABCO: Synthesis of 1,4-Disubstituted Piperazines and Piperidines

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Abstract. The 2-(4-phenylpiperazin-1-yl)ethan-1-amine scaffold is a structurally important motif that occurs frequently in medicinal and pharmaceutical chemistry. Despite the significance of this moiety, general strategies for its synthesis to date have required multistep methods and have been very limited, such as the use of S_NAr-type reactions. Herein, we describe a synthetic methodology employing benzynes, 1,4-diazabicyclo(2.2.2)octane (DABCO), and nitrogen nucleophiles to access these privileged organic compounds. The established protocol proved to be a transition-metal-free, mild reaction that proceeded *via* a quaternary ammonium salt formed from the benzyne and DABCO.

Keywords: Benzyne; Quinuclidine; DABCO; ring opening reaction; nitrogen nucleophiles

The 2-(4-phenylpiperazin-1-yl)ethan-1-amine motif has been widely utilized and plays a structurally vital role in pharmaceutical, agrochemical, and material chemistry, among other fields. In particular, the number of organic compounds containing this backbone that have been synthesized and identified as useful drugs in medicinal chemistry has dramatically increased in recent decades. Among these molecules, flibanserin, developed by Boehringer-Ingelheim, is a medication that was approved by the US Food and Drug Administration (FDA) in 2015 for the treatment of premenopausal woman with hypoactive sexual desire disorder (Figure 1).[1] As well as flibanserin, a variety of drug candidates have been investigated, and were found to possess diverse bioactivities as antifungal agents, dysuria treatment agents, or serotonin and norepinephrine reuptake inhibitors.[2] Owing to the significance of this structural motif, many chemists have been preparing molecules containing this skeleton by conventional methods consisting of at least three steps (Figure 2(a)).[3] However, because of the disadvantages of the multistep procedures in traditional synthetic routes toward the 2-(4-phenylpiperazin-1-yl)ethan-1-amine moiety, a facile and efficient synthetic strategy is still in demand.

Recently, the building of this framework by using an in situ ring-opening reaction[4] of 1,4-diazabicyclo(2.2.2)octane (DABCO) *via* a quaternary ammonium salt has been reported,[4a-4e] including by our group.[4d] In comparison with S_NAr reactions,[5] which require very high temperatures and long reaction times, and which utilize installed electron withdrawing groups on the substrate, these reactions involve new activators, such as pyridine-N-oxide,[4a] 2-bromopyridine,[4c] and aryl(mesityl)iodonium triflate,[4e] for reactions with nucleophilic DABCO. Despite the development of new activators, a reliable method for the synthesis of 1,4-disubstituted piperazines from DABCO is still in demand. Therefore, we decided to further examine the reaction between DABCO and benzynes in the presence of various nitrogen nucleophiles to access 2-(4-phenylpiperazin-1-yl)ethan-1-amine containing compounds.

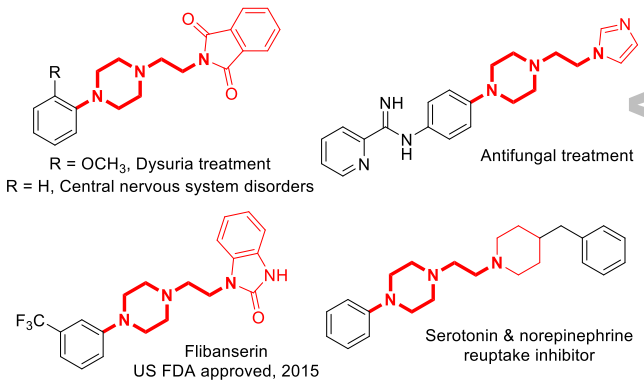

Figure 1. Selected medicines and drug candidates containing the 1,4-disubstituted piperazine backbone.

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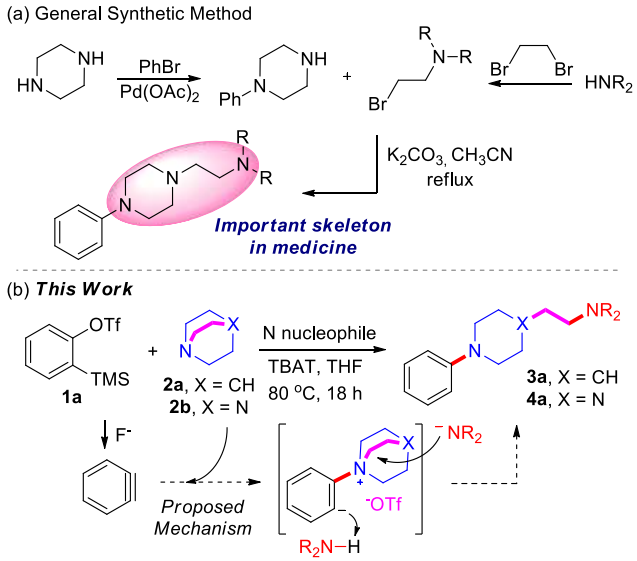
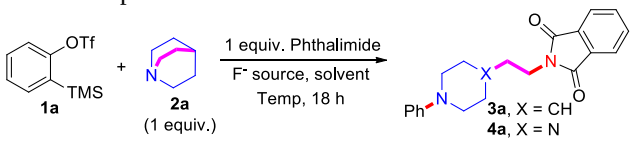


Figure 2. Synthetic strategies for access to 1,4-disubstituted piperazines and piperidines.

On the basis of our previous work,[4d] the reaction of standard benzyne precursor **1a**, quinuclidine **2a**, and phthalimide was performed with CsF in MeCN at 110 °C (Table 1, entry 3). To our pleasure, the expected ring opening reaction of DABCO occurred, and the desired product **3a** was formed in an excellent yield of 90%, as confirmed by 1H NMR spectroscopy. In spite of the high yield, temperatures of 70 and 90 °C were screened to optimize the reaction conditions; however, the reaction at these temperatures led to lower yields

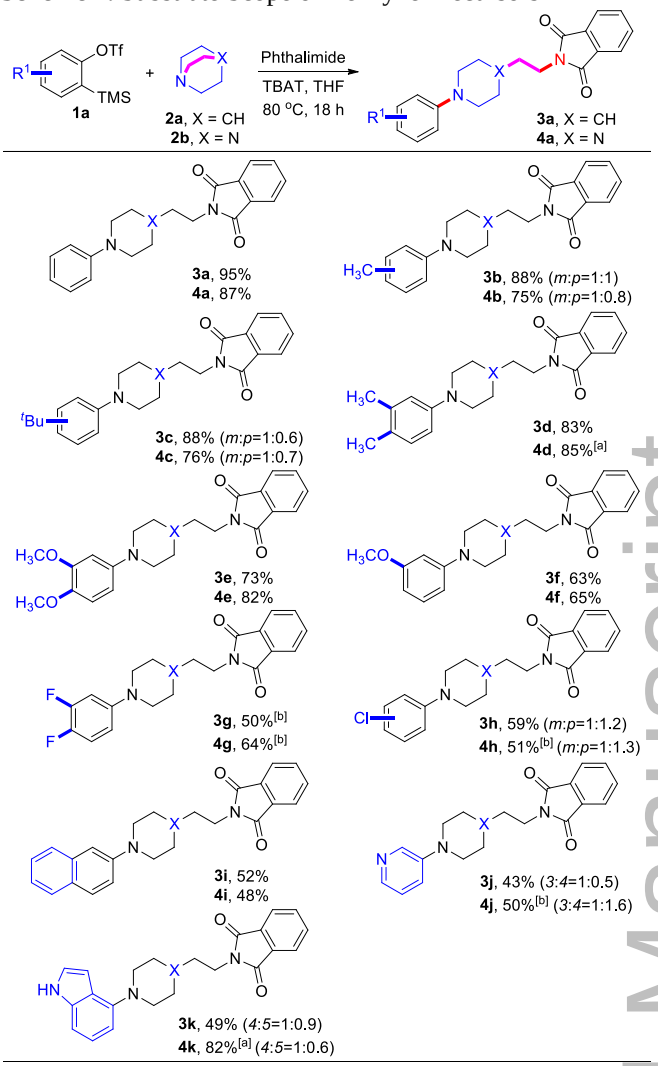
Table 1. Optimization of Reaction Conditions[a]



Entry	F⁻ source / solvent	Temp (°C)	Yield (%)[b]
1	CsF / CH_3CN	70	38%
2	CsF / CH_3CN	90	62%
3	CsF / CH_3CN	110	90%
4	TBAF / THF	80	18%
5	TBAT / THF	60	58%
6	TBAT / THF	80	95%
7	KF, 18-Crown-6 THF	80	74%
8	K_2CO_3, 18-Crown-6 THF	80	64%
9[c]	TBAT / THF	80	70%
10[c,d]	TBAT / THF	80	87%

[a]Reaction conditions: *o*-silyl aryl triflate **1a** (0.1 mmol), quinuclidine **2a** (1 equiv), F⁻ (1.2 equiv), phthalimide (1 equiv), solvent (0.1 M), 18 h.
[b]Isolated yield.
[c]DABCO was used instead of **2a**.
[d]2 equiv DABCO.
Abbreviations: TBAF, tetrabutylammonium fluoride; TBAT, tetrabutylammonium difluorotriphenylsilicate.

Scheme 1. Substrate Scope of Benzyne Precursors



[a] DABCO **2b** (1 equiv) was used.
[b]110 °C.

of 38% and 62% (entries 1 and 2). To achieve a lower-temperature reaction, other fluoride reagents, namely TBAF and TBAT, were used at 80 °C, with **3a** being isolated in 18% and 95% yields, respectively (entries 4 and 6). Furthermore, among the tested temperatures, the reaction at 80 °C provided the best yield (entries 5 and 6). The reaction utilizing benzyne-triggered reagents, such as a combination of KF or K_2CO_3 with 18-crown-6, produced **3a** in 74% and 61%, respectively (entries 7 and 8). Surprisingly, when the reaction employing DABCO instead of quinuclidine was attempted, the desired product **4a** was obtained in a good yield of 70% (entry 9). Finally, if 2 equivalents of DABCO were utilized, the reaction generated **4a**[4e] in 87% yield (entry 10).

With the optimized reaction conditions in hand, we next explored the scope of the aryne precursors (Scheme 1). As well as **3a** and **4a** from the standard substrates, the corresponding products **3b**, **4b**,[3d,6] **3c**, and **4c** were prepared in good-to-high yields (75-88%). All the regioisomers derived from methyl- or *tert*-butyl-substituted substrates were separated by column

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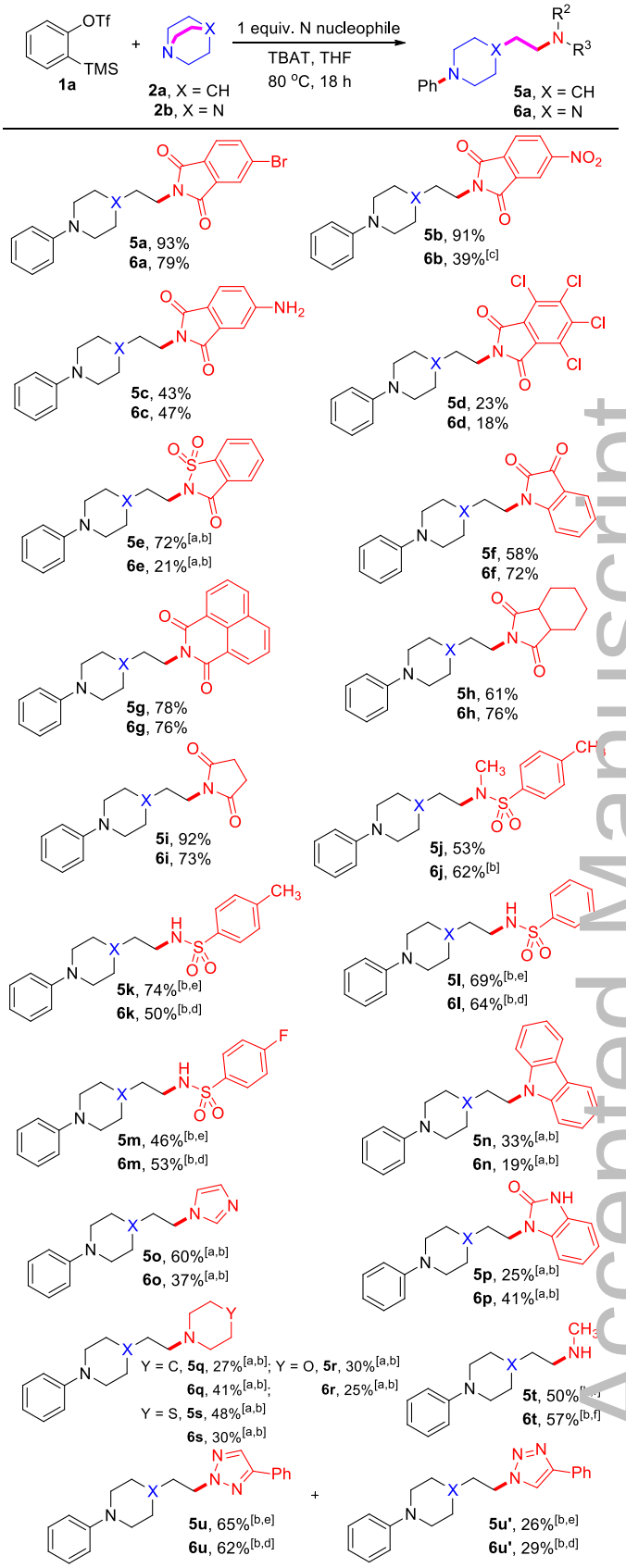
chromatography, and their structures were analyzed based on NMR, IR, and mass spectra. Similarly, dimethyl-, dimethoxy-, and methoxy-substituted benzyne precursors generated the desired products (**3d-3f** and **4d-4f**[3f]) as single regioisomers in moderate to excellent yields (63-85%). The reactions with halogen substituted 2-(trimethylsilyl)phenyl triflates led to the formation of **3g**, **4g**, **3h**, and **4h**[3f] in yields of 50%, 64%, 59%, and 51%, respectively. The reactions with polyaromatic compounds proceeded to afford **3i** and **4i** in moderate yields of 52% and 48%. Other reactions of heteroaromatic substrates such as 3,4-pyridyne or indolyne precursors produced **3j**, **4j**,[3f] **3k**, and **4k** as a mixture of regioisomers, which were isolated completely in combined yields of 43%, 50%, 49%, and 82%, respectively, and the structures were confirmed by NMR spectroscopy.

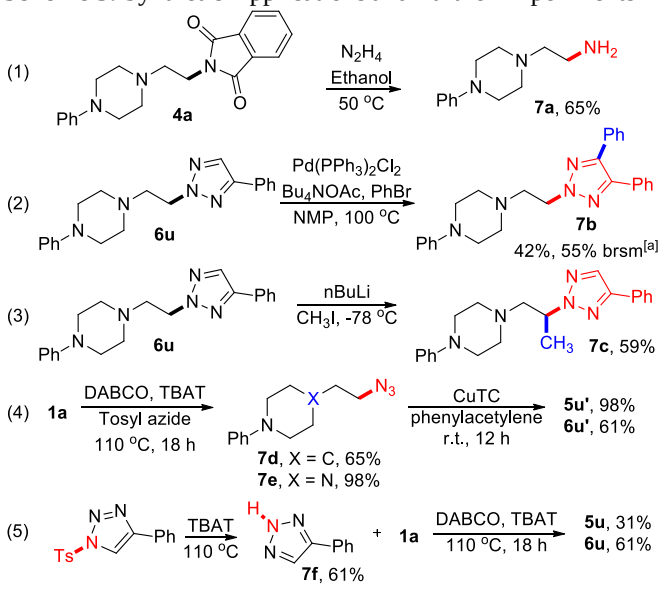
In order to further examine the scope of the nitrogen nucleophiles that could be used in the reaction, a variety of amines were treated with standard benzyne under the optimal conditions (Scheme 2). Phthalimides with bromo, nitro, or amine groups attached at the 4-position were suitable coupling partners to deliver the corresponding products **5a-5c** and **6a-6c** in moderate to excellent yields (39-93%). Tetrachlorophthalimide reacted to form the desired products **5d** and **6d** in slightly lower yields of 23% and 18%, respectively. Saccharin, isatin, 1,8-naphthalimide, and *N*,4-dimethylbenzenesulfonamide were tolerated and yielded the adducts **5e-5g**, **5j**, **6f-6g**,[8] and **6j**[4e] in good yields (53-78%), whereas product **6e**[7] was obtained in 21% yield at 110 °C. The reactions of hexahydro-*1H*-isoindole-1,3(*2H*)-dione and succinimide, without an aromatic ring, gave rise to the expected products **5h**, **5i, 6h** and **6i**[9] in high yields (61-92%). In the case of isocyanates, the targeted products **5k-5m** and **6k**[10]**-6m**[10] were obtained with yields of 46-74% after elimination of the carbonyl moiety on the nucleophiles by using around 3 equivalents of TBAT at 110 °C. Interestingly, by utilizing carbazole, imidazole, and 2-hydroxybenzimidazole as nucleophiles, the desired products **5n-5p**, **6n**, **6o**,[4e] and **6p**,[11] which was considered an important skeleton, were synthesized at 110 °C in moderate yields. In addition, piperidine, morpholine, and thiomorpholine, without the electron-withdrawing group that stabilizes the nitrogen nucleophile, were converted into **5q-5s** and **6q**[10]**-6s**[10] in moderate yields (25-48%). The reaction with 10 equivalents of methyl amine, which is

Scheme 2. Substrate Scope of Various Nucleophiles



[a]N nucleophile (2 equiv) was used.
[b]110 °C.
[c]DABCO **2b** (1 equiv) was used.
[d]TBAT (3 equiv) was used.
[e]TBAT (3.6 equiv) was used.
[f]N nucleophile (10 equiv) was used.

Scheme 3. Synthetic Applications and Further Experiments



[a]Abbreviations: brsm, based on recovered starting material.

volatile, gave **5t**[10] and **6t**[12] in 50% and 57%, respectively. In the case of 4-phenyl-1-tosyl-*1H*-1,2,3-triazole, the anticipated products **5u**, **5u'**, **6u**, and **6u'**[13] were produced in combined yields of 91% and 91%.

Next, further experiments such as C-H activation, alkylation, and deprotection were performed to prove the synthetic usefulness and applications of this methodology (Scheme 3). Deprotection reaction of the phthalimide proceeded well to give primary amine **7a**[3h] in 65% yield (Scheme 3, (1)). In comparison with the traditional method, this synthetic route provided a facile and efficient shortcut to access to 2-(4-phenylpiperazin-1-yl)ethan-1-amine. C-H activation at the C5 atom in **6u** by treatment with a Pd catalyst system yielded **7b** (55% yield brsm, 42% conversion, Scheme 3, (2)). In addition, unexpectedly, an alkylation reaction with *n*-BuLi and MeI led to the formation of **7c** in 59% yield (Scheme 3, (3)).

For the conversion of various structures, we focused on the potentiality of the azide nucleophile (Scheme 3, (4)). Reactions with tosyl azide proceeded to afford **7e**,[4e,13,14] and **7d**; this was followed by a click reaction to generate **5u'** and **6u'** in 98% and 61% yields, respectively. Based on these results, tosyl azide was not only a suitable nucleophile for transformation into diverse scaffolds but it was also tolerated under these reaction conditions. In particular, with regard to detosylation of tosyl azide, 4-phenyl-1-tosyl-*1H*-1,2,3-triazole reacted with TBAT to form adduct **7f** in 61% yield (Scheme 3, (5)). A ring-opening reaction was performed with **7f** to identify major products **5u** and **6u** (Scheme 2); **5u** and **6u** were isolated in yields of 31% and 61%, respectively.

In conclusion, we have developed a new practical method for the synthesis of 2-(4-phenylpiperazin-1-yl)ethan-1-amine derivatives, which have attracted attention for their bioactivities. This work demonstrates that the reactions involved are general and simple single step that provide a breakthrough approach to this framework. A variety of arynes and nucleophilic amines with or without electron-withdrawing groups are tolerated under these mild conditions. Remarkably, in some cases, the nucleophilic amines are generated by elimination of a tosyl or carbonyl group triggered by fluoride. Thus, these experimental results indicate that not only are numerous amines appropriate coupling partners, but that they also provide transformation opportunities in synthetic applications. To expand the structures and discover potential drugs, further investigations are currently in progress.

Experimental Section

General Procedure for Ring Opening Reaction of DABCO

A mixture of neat 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 0.1 mmol), 1-azabicyclo[2.2.2]octane (**2a**, 0.1 mmol), and TBAT (0.12 mmol) in THF (0.1 M) was stirred for 30 min at room temperature. Phthalimide (0.1 mmol) was added after checked the TLC and the reaction mixture was heated at 80 °C for 18 h. The reaction mixture was filtered and the residue was purified by column chromatography (silica gel hexane/ethyl acetate).

Acknowledgements

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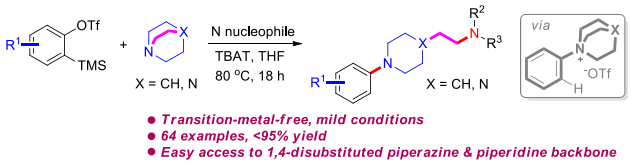

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