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De Novo Assembly of Highly Substituted Morpholines and Piperazines

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Supporting Information

ABSTRACT: The morpholine and piperazine with their remarkable physical and biochemical properties are popular heterocycles in organic and medicinal chemistry used in rational property design. However, in the majority of cases these rings are added to an existing molecule in a building block approach thus limiting their substitution pattern and diversity. Here we introduce a versatile de novo synthesis of the morpholine and piperazine rings using multicomponent reaction chemistry. The large scale amenable building blocks can be further substituted at up to four positions, making this a very versatile scaffold synthesis strategy. Our methods thus fulfill the increasing demand for novel building block design and nontraditional scaffolds which previously were not accessible

Morpholine and piperazines are privileged backbones and are abundantly used as substituents or scaffolds in drugs and medicinal chemistry.[1] They can improve pharmacokinetic (PK) properties of molecules, such as water solubility and metabolic stability, while not being essential for direct receptor binding. They can be introduced by two different general strategies. Often they are attached via a building block approach to the receptor binding motif (Figure 1, Imatinib). Less often they are built de novo and used as a central scaffold thus merging major receptor binding features with beneficial PK properties. An elegant de novo assembly of these structures is Bode's SnAP strategy.[2] AMG-8735 is another example of the latter approach; however, it is de novo assembled via an overall lengthy multistep synthesis (~20 steps).[3] In accordance with the above discussion, it shows major improved properties over the piperidine analogue such as higher metabolic stability in hepatocytes, as well as good pharmacokinetic properties. Clearly a de novo approach has many advantages of the sequential approach, including maximal control over the substitution pattern and improved ligand efficiency. However, often the de novo approach is performed via sequential synthesis and can be time and resource costly. In general, poor commercial availability of substituted morpholines/piperazines and a paucity of methods for their preparation can be observed. Therefore, we would like to report an unprecedented, fast, diverse, and useful multicomponent reaction (MCR) for de novo assembly of piperazine and morpolines.[4]

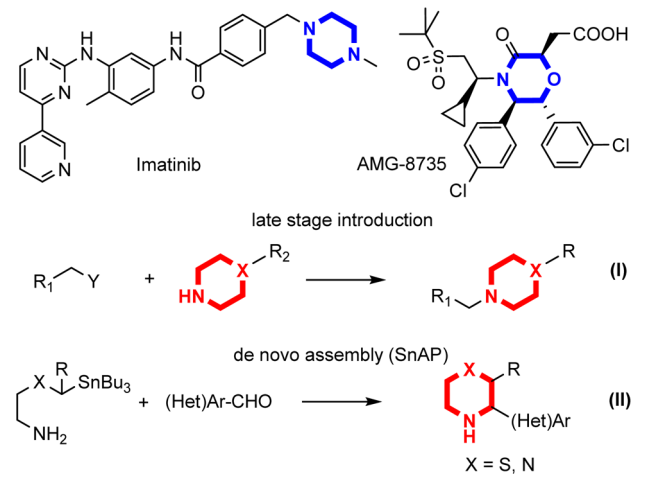

Figure 1. Examples of bioactive compounds with piperazine and morpholine moieties and two complementary synthesis strategies.

In order to allow for the fast and diverse assembly of piperazines and morpholines we envisioned a multicomponent Ugi approach followed by a cyclization by an intramolecular S_N2 reaction. Here we focus on the tetrazole Ugi reaction which in this context delivers a secondary amine moiety as part of the morpholine/piperazine design. Due to the superior functional group compatibility of MCR *in principle*, different designs are possible (Scheme 1): one where the oxo component delivers the nucleofuge and one based on the amine component.

Initially, we envisioned that using an α-halo oxo-component together with an isocyanide, trimethylsilyl azide, and 2-hydroxy or 2-amino or 2-mercaptoethylamine and its derivatives will yield the corresponding Ugi-tetrazole adduct, which under basic

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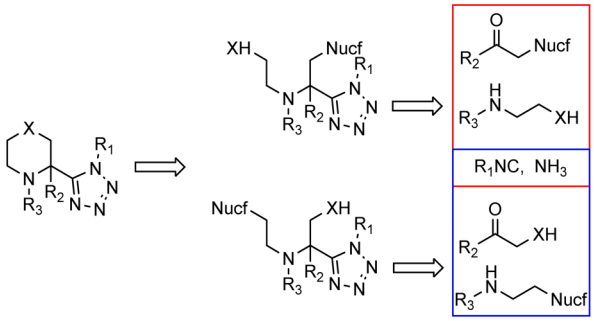
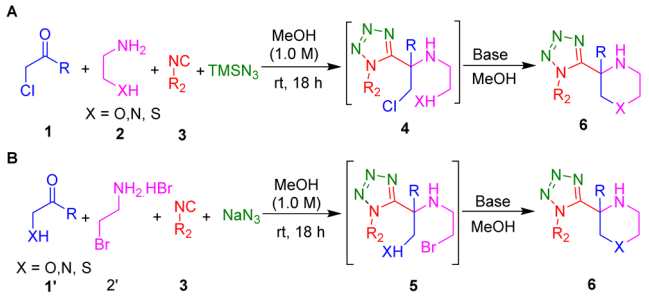
Scheme 1. Retrosynthetic Design of de Novo Assembly of Morpholines and Piperazines by an MCR Approach



conditions should give the corresponding morpholine, piperazine, or thiomorpholine respectively (Scheme 2A).

Scheme 2. MCR Morpholine or Piperazine Synthesis from A α-Halo Oxo-Component and B α-Hydroxy Oxo-Component

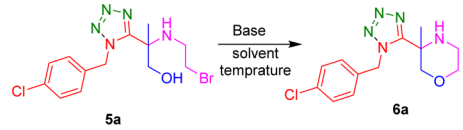


To test this strategy, we decided to use 2-chloroacetaldehyde as an electrophile and *p*-chlorobenzyl isocyanide, trimethylsilyl azide, and ethanolamine as a nucleophile, each 1 equiv, in methanol stirred for 18 h at room temperature (see Scheme 2A). We observed the Ugi-adduct formation (**4**), which was further in situ treated with various bases to give the corresponding morpholine derivative (**6**); however, we only observed trace product formation. Next, we decided to change the electrophile and nucleophile positions from the oxo-component and from the amine component respectively (see Scheme 2B). Unfortunately, in these in situ methods we were unable to isolate the pure products (**6**). However, after isolating the intermediates **4** and **5**, we optimized cyclization conditions with respect to solvents, bases, temperature, and time (Table 1).

We observed that sodium hydride (85% yields) and *tert*-BuOK (79%) in acetonitrile were the optimal base choices for the cyclization. With these optimized conditions, we isolated the intermediate of **4** and **5** and treated with sodium hydride (1.5 eqiuv) in acetonitrile for 1 h at 0 °C to obtain the final cyclized product (**6**). The Ugi adducts **4a** (36%) and **5a** (63%) thus give the morpholine derivative **6a** in 45% and 85% respectively. With these results, we confirmed that the use of an α-hydroxy oxo-component was higher yielding than that of the α-halo oxo-component. Also, we tested various isocyanides in the Ugi reaction followed by the cyclization. In general, we observed good to excellent yields in both reactions (Table 2).

To further simplify the synthesis, we decided to reinvestigate a one-pot Ugi-cyclization procedure. We decided to remove the Ugi solvent methanol after formation of **5a**, followed by addition of NaH in acetonitrile at 0 °C for 1 h. Surprisingly, we obtained the morpholine derivatives (**6a**) in an acceptable 50% yield. To further improve the isolation, we filtered the intermediate (**5a**) through a short silica bed and cyclized using 1.5 equiv of NaH in acetonitrile to give a morpholine derivative (**6a**), now in 68% yield. With these optimized conditions, we tested various isocyanides and hydoxyketones and found in general moderate to good yields of 3,3-disubstituted morpholines (Table 2).

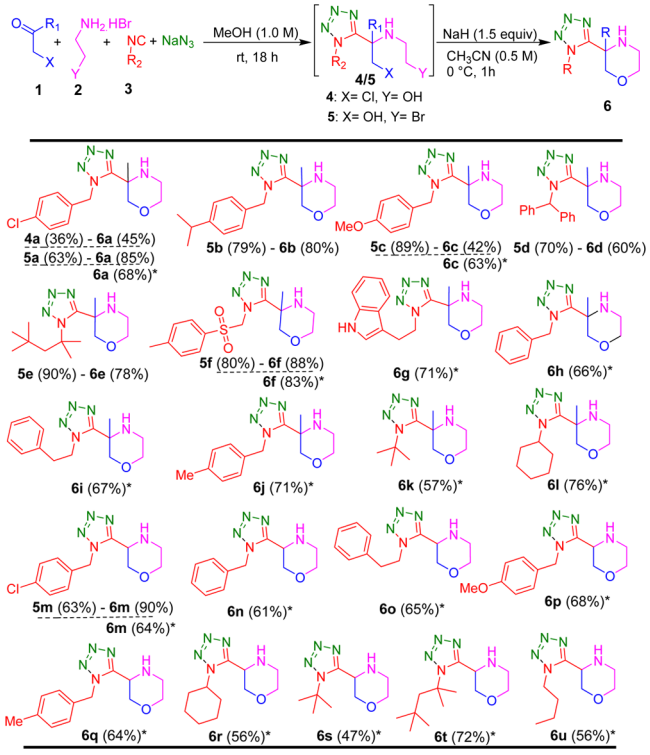
Table 1. Optimization of Cyclization of Ugi-Adduct to Morpholine



base	equiv	temp; time	solvent	% yield of **6a**[a]
Et_3N	2	23 °C, 18 h	CH_2Cl_2	–
Et_3N	2	23 °C, 5 h	CH_3CN	–
DIPEA	2	23 °C, 18 h	CH_3CN	–
DBU	2	0–23 °C, 18 h	CH_3CN	–
K_2CO_3	2	23 °C, 18 h	CH_3CN	–
K_2CO_3	2	23 °C, 18 h	CH_3CN	27
KOH	2	23 °C, 18 h	CH_3CN	72
NaOMe	1.	0–23 °C, 18 h	CH_3CN	51
t-BuOK	3	0–23 °C, 1 h	CH_3CN	79
NaH	**1.5**	**0 °C, 1 h**	**CH_3CN**	**85**
NaH	2	0–23 °C, 5 h	CH_3CN	30

[a]Isolated yields.

Table 2. MCR for the Ugi-Adduct 4 and 5 and Synthesis of Morpholines 6 Derivatives[a,b,c]



[a]Yields of isolated, analytically pure compounds after chromatography are given. [b]The reactions were performed on 1.0 mmol scale using amine (1.0 equiv), aldehyde/ketone (1.0 equiv), isocyanide (1.0 equiv), and NaN_3 (1.0 equiv) in MeOH (1.0 M); cyclization reaction was performed in CH_3CN using NaH (1.5 equiv) at 0 °C to rt for 1 h. [c]One-pot overall isolated yield.

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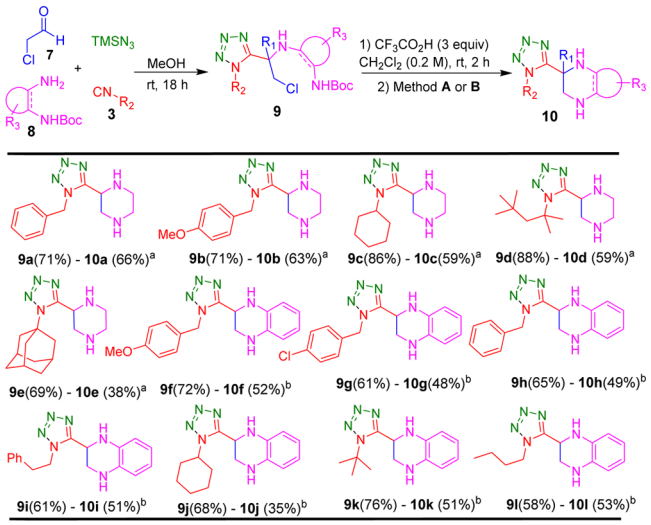
Next, we tested the synthesis of piperazine derivatives first using unsubstituted ethylene diamine. Isolation issues (high water solubility of the Ugi product) and several side products led us to use monoboc-protected ethylene diamine (**8**) instead (Table 3). For example, monoboc-protected ethylenediamine

Table 3. MCR for the Ugi-Adduct of 9 for Piperazine and Tetrahydroquinoxalines 10 Synthesis[a,b,c]

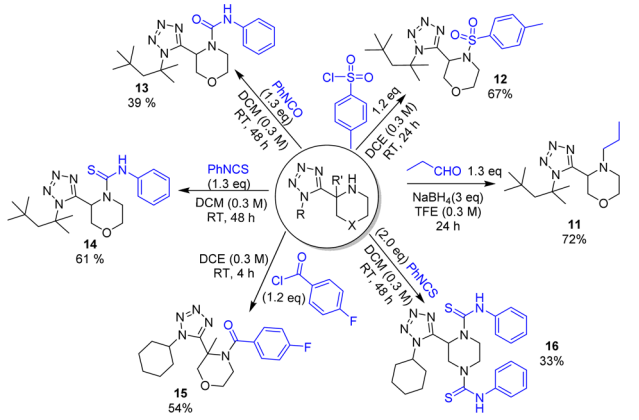


[a]Method **A**: cyclization reaction was performed in CH_3CN using *t*BuOK (3.0 equiv) at 60 °C. [b]Method **B**: cyclization reaction was performed in CH_3CN using NaH (1.5 equiv) at 0 °C to rt for 1 h. [c]Yields of isolated, analytically pure compounds after chromatography are given. The reactions were performed on 1.0 mmol scale using monobocprotected amine (**8**, 1.0 equiv), *α*-halo aldehyde/ketone (1.0 equiv), isocyanides (1.0 equiv), and $TMSN_3$ (1.0 equiv) in MeOH (1.0 M); Boc-deprotection was performed in CH_2Cl_2 with TFA at rt.

reacted with 2-chloroacetaldehyde, benzyl isocyanide, and trimethylsilyl azide in methanol furnishing the Ugi-tetrazole adduct **9a** in a good 71% isolated yield within 12 h. The isolated Ugi-adduct **9a** was treated with 3 equiv of trifluoroacetic acid (TFA) in dichloromethane at room temperature for 2 h furnishing the TFA salt of the amine. After removal of the solvent, cyclization was accomplished with *t*BuOK (3 equiv) in acetonitrile at 60 °C for 1 h, yielding piperazine derivative **10a** in 66% overall yield. Different substituted isocyanides in general gave derivatives (**10**) in good yields (Table-3, **10b**−**10e**) including super bulky adamantane isocyanide (**10e**, 38%). Next, we explored the use of *o*-phenylenediamine for the synthesis of 2-substituted tetrahydroquinoxaline. Analogously, the monoboc-protected *o*-phenylenediamine reacted to affod the Ugi tetrazole product **9f** (72% yield), which after deprotection and base (NaH) induced cyclization yields the quinoxaline **10f** (52%). Moreover, other isocyanides such as benzylisocyanide, 4-chlorobenzyl isocyanide, and linear and branched aliphatic isocyanides also reacted with monoboc-protected *o*-phenylenediamine, chloroacetaldehyde, and trimethylsilyl azide affording **10g**−**10l** in good yields (Table 3).

Furthermore, to underscore the usefulness of the produced scaffolds we showcase some further transformations of the secondary amine of morpholines and piperazines via reductive amination (**11**, 72%), sulfonation (**12**, 72%), acylation (**15**, 54%), and urea (**13**, 39%) and thiourea (**14**, **16**, 61%, 33%) formation (Scheme 3).

Scheme 3. Further Functionalization of Morpholines and Piperazines



Several crystal structures also have been obtained and support the proposed structures of the scaffolds (Figure 2).

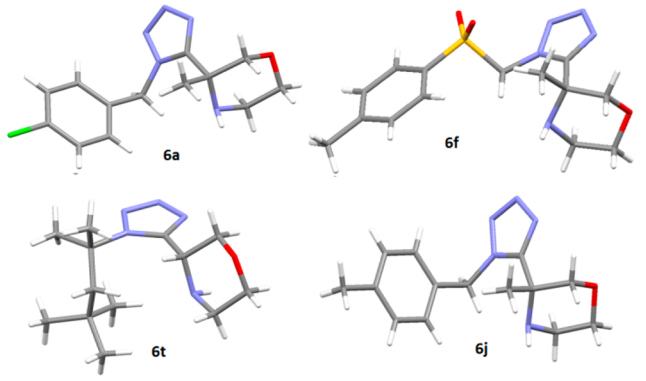


Figure 2. Crystal structures of **6a**, **6f**, **6j**, and **6t** were confirmed by X-ray analysis.

Morpholines and piperazines are among the 25 most frequent nitrogen heterocycles in U.S. FDA approved drugs.[5] From a medicinal chemistry design standpoint of view, morpholines and piperazines are outstanding since they combine three-dimensionality with superior PK properties. "Escape from flatland", i.e. saturation, correlates well with solubility, an experimental physical property important to success in the drug discovery setting.[6] Based on the excellent scaffold properties these scaffolds are now part of the screening decks of the European Lead Factory (ELF).[7−12] In summary, we have identified a novel method for the synthesis of substituted N-unprotected piperazines, morpholines, and tetrahydroquinoxalines. This robust and operationally simple two-step, air- and moisture-tolerant procedure is a valuable addition to MCR chemistry and expands its unique scaffold diversity. Work is ongoing to identify valuable biological targets for our compound libraries and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03807.

General experimental procedures, compound characterization data, ^1H and ^{13}C spectra of all compounds (PDF)
Crystallographic data for **6a** (CIF)

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Crystallographic data for **6f** (CIF)
Crystallographic data for **6j** (CIF)
Crystallographic data for **6t** (CIF)

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Notes

The authors declare no competing financial interest.

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