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# Efficient synthesis of 1,4-disubstituted polyfunctional piperazines via a sequential one-pot Ugi/nucleophilic addition five-component reaction

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This Letter is dedicated to Professor Mansour Abedini on the occasion of his 70th birthday

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ABSTRACT

Polyfunctional 1,4-disubstituted piperazines were successfully synthesized stereoselectively via a one-pot, five-component Ugi/nucleophilic addition reaction sequence. Regio- and stereo-selective addition of piperazine to an activated alkyne under catalyst-free conditions and high yields of products are advantages of this method.

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The synthesis of new biologically active molecules is important in the development of improved and innovative drugs. Finding a suitable route with fewer reaction steps for the synthesis of pharmaceutical scaffolds is very interesting. The piperazine ring is found in a number of biologically active compounds, including several marketed drugs,[1] and is considered to be a privileged structure in drug discovery.[2] Due to the broad pharmacological interest in piperazine derivatives, their synthesis has been of widespread interest.[3] For example, *N*-arylpiperazines are key structural elements of a variety of biologically active compounds. In neuroscience in particular, they are often found in ligands for serotonin (5-hydroxytryptamine, 5-HT) and dopamine receptors, and monoamine transporters.[4] Research on 1,4-disubstituted piperazines as potent 7-transmembrane guanine nucleotide-binding regulatory protein receptor antagonists has gained significant interest,[5] and various methods have been developed for the synthesis of this group of compounds.[6,7] Drawbacks of these methods include harsh thermal conditions, long reaction times, modest yields, the use of expensive reagents, and in some cases, multi-step reactions. Therefore, further development of synthetic methods in order to produce a variety of these templates remains an important task.

Combinatorial chemistry is widely used in pharmaceutical research as a powerful approach for the synthesis of active pharmaceutical ingredients.[8] In this field, multicomponent condensation reactions based on isocyanides have been utilized efficiently in conjunction with combinatorial chemistry to prepare polyfunctional compounds in short reaction sequences.[9] Functionalized starting materials have been used as partners in Ugi reactions, therefore various carboxylic acids, amines, isocyanides, and benzaldehyde derivatives were selected as reactants for our one-pot reaction. Carboxylic acids which contain an acetylenic functional group and which have a low p$K_a$ were selected for this multicomponent reaction. As part of a program aimed at developing multicomponent synthetic routes to biologically active heterocyclic scaffolds,[10] we were interested in preparing a diverse set of polyfunctional 1,4-disubstituted piperazines using Ugi four-component condensation (Ugi-4CC) reaction conditions. Thus one-pot, five-component reactions of primary amines **1**, aldehydes **2**, propargylic acid (**3**), isocyanides **4**, and piperazine **5** leading to the regio- and stereo-selective formation of polyfunctional 1,4-disubstituted piperazines are described (Scheme 1). The reaction could precede via formation of an N-substituted-2-alkynamide **I** (Scheme 2) as an intermediate which contains an active triple bond suitable for further nucleophilic addition reactions.

The results are summarized in Table 1.

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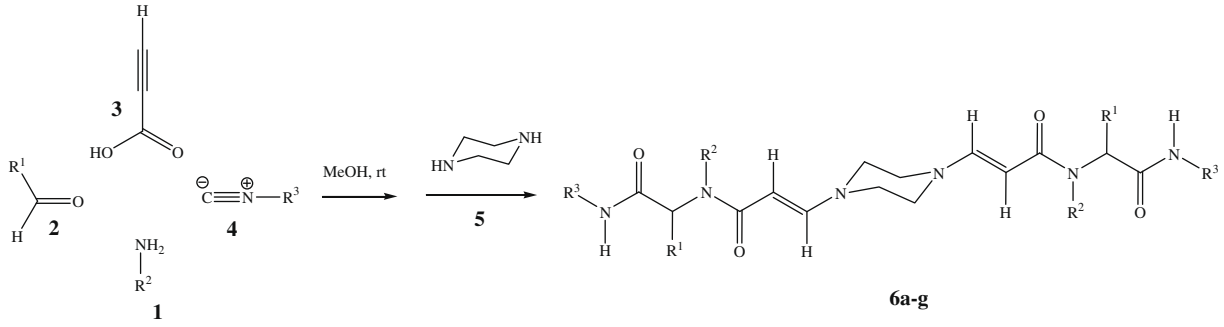
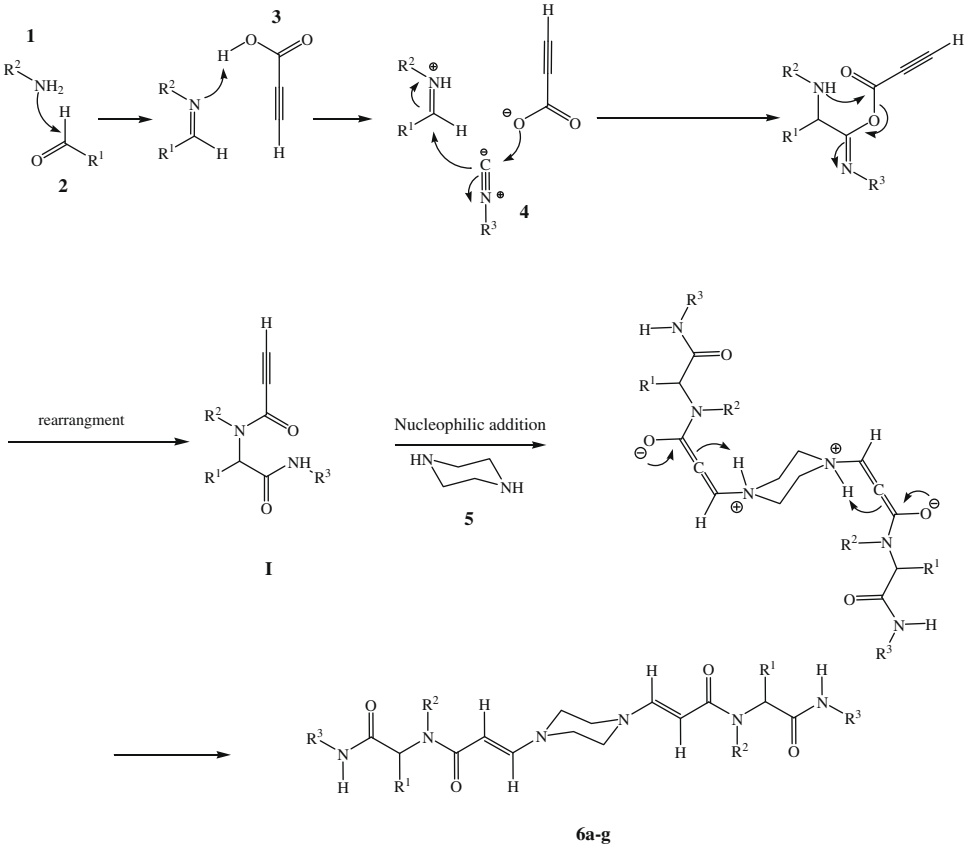



**Scheme 1.** Stereoselective synthesis of 1,4-disubstituted piperazines via a sequential one-pot Ugi/nucleophilic addition five-component reaction.




**Scheme 2.** The proposed mechanism for the stereoselective synthesis of functionalized 1,4-disubstituted piperazine derivatives **6a**–**g** via sequential Ugi/nucleophilic addition.

**Table 1**
Synthesis of polyfunctionalized 1,4-disubstituted piperazine derivatives via a five-component reaction

| Product | $R^1$ | $R^2$ | $R^3$ | Yield[a] (%) |
|---|---|---|---|---|
| **6a** | Ph | Ph | Cyclohexyl | 90 |
| **6b** | Ph | 4-$BrC_6H_4$ | *t*-Bu | 94 |
| **6c** | 4-$BrC_6H_4$ | Allyl | *t*-Bu | 93 |
| **6d** | 4-$BrC_6H_4$ | Ph | *t*-Bu | 95 |
| **6e** | 4-$BrC_6H_4$ | 4-$BrC_6H_4$ | *t*-Bu | 97 |
| **6f** | 4-$ClC_6H_4$ | 4-$BrC_6H_4$ | *t*-Bu | 95 |
| **6g** | 2-Thienyl | Ph | Cyclohexyl | 88 |

[a] Isolated yield.

The starting materials were added according to the known Ugi sequence addition. A proposed mechanism for the synthesis of functionalized enaminones **6a**–**g** is shown in Scheme 2. The Ugi intermediate **I** contains functional groups which are suitable for further reactions. In all cases, the Ugi products, with an active triple bond, have high affinity toward nucleophilic addition, and the reaction could proceed without any catalyst or separation of intermediate **I**. Following formation of **I**, piperazine **5** was added which reacted with the activated triple bond yielding enaminones **6a**–**g** as the sole products. To explore the scope and limitations of this reaction, the procedure was extended to various benzaldehyde derivatives. In all cases, enaminones **6** were isolated as the *E*-isomers.

The *E* stereochemistry for compounds **6a**–**g** was assigned by $^1H$ NMR spectroscopy with the characteristic peaks at 4.15–4.32 ppm and 7.18–7.34 ppm for the vinylic protons having *J* values of 12.7–14.0 Hz. This stereoselectivity can be explained according to the proposed mechanism shown in Scheme 2. The isolated products were characterized unambiguously on the basis of spectroscopic

data. The high resolution mass spectra of the products displayed the requisite molecular ion peaks.

Using this novel approach, all five starting materials were mixed in one-pot within short intervals to maximize bond formation for complexity generation and diversification. Addition of the fifth component (piperazine) took place one hour after mixing the other four starting materials which led to the formation of a precipitate. It would appear that addition of piperazine accelerates the rate of reaction and the final products were obtained in high yields within 2–3 h. Completion of an Ugi-4MCR usually takes 1–2 days. The triple bond in the N-substituted-2-alkynamide intermediate has high reactivity toward addition of nucleophiles, and is the reason behind the change in equilibrium to form the final product.

X-ray crystallographic data of similar analogues confirmed the *cisoid* structures for the enaminones.[10b] It is conceivable that the initial event is formation of the Ugi product (an N-substituted 2-alkynamide) which has efficient capacity for nucleophilic addition of piperazine to the activated alkyne moiety to produce products **6a**–**g**. In all cases, 1:1 mixtures of diastereoisomers were formed.

In conclusion, we have established an efficient method for the stereoselective synthesis of polyfunctional 1,4-disubstituted piperazines in high yields, via a one-pot, five-component reaction under mild conditions. The reaction scope is broad, permitting the use of four points of diversity in the starting materials. Due to the well-recognized utility of piperazines, many libraries of compounds can be prepared using this method as structural scaffolds for further diversification.

*General procedure for the synthesis of enaminones* **6a**–**g**. Primary amine **1** (1 mmol) was added to a solution of aldehyde **2** (1 mmol) in methanol (5 mL), and the reaction mixture was stirred at room temperature for 1 h. Then, propargylic acid (**3**) (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanide **4** (1 mmol). The resulting solution was stirred for 1 h at rt. Next, piperazine (**5**) (0.5 mmol) was added. The reaction was monitored by TLC (*n*-hexane–EtOAc, 1:2) and was complete after 2–3 h. The solvent was removed under reduced pressure and the resulting crude oil was crystallized from a mixture of EtOAc–*n*-hexane.

(2*E*,2′*E*)-3,3′-(Piperazine-1,4-diyl)-bis{*N*-(4-bromophenyl)-*N*-[2-(*tert*-butylamino)-2-oxo-1-phenylethyl]acrylamide}(**6b**). Mp 272–274 °C; IR (KBr, $cm^{-1}$): 3280, 2963, 1679, 1648, 1567; $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 1.21$ (s, 18H, *t*-Bu), 2.96 (br s, 8H, $CH_2N$), 4.18 (d, 2H, $J = 13.4$ Hz, =CH), 6.13 (s, 2H, CH), 6.99–7.15 (m, 14H, $H_{Ar}$), 7.22 (d, 2H, $J = 13.4$ Hz, =CHN), 7.26 (d, 4H, $J = 8.2$ Hz, $H_{Ar}$), 7.66 (br s, 2H, NH); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta = 28.4$, 47.1, 50.1, 63.0, 87.1, 119.6, 127.2, 127.7, 129.7, 130.8, 133.3, 136.6, 140.0, 150.0, 167.2, 169.6; HR-MS (ESI) calcd for $C_{46}H_{53}Br_2N_6O_4$ $[M+H]^+$ 911.24914, found 911.24896; calcd for $C_{46}H_{52}Br_2N_6O_4Na$ $[M+Na]^+$ 933.23106, found 933.23090.

(2*E*,2′*E*)-3,3′-(Piperazine-1,4-diyl)-bis{*N*-(4-bromophenyl)-*N*-[2-(*tert*-butylamino)-1-(4-chlorophenyl)-2-oxoethyl]acrylamide} (**6f**). Mp = 278–280 °C; IR (KBr, $cm^{-1}$): 3316, 2978, 1678, 1658, 1567; $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 1.20$ (s, 18H, *t*-Bu), 2.96 (br s, 8H, $CH_2N$), 4.17 (d, 2H, $J = 14.0$ Hz, =CH), 6.12 (s, 2H, CH), 7.01 (d, 4H, $J = 8.5$ Hz, $H_{Ar}$), 7.07 (br s, 4H, $H_{Ar}$), 7.19 (d, 4H, $J = 8.5$ Hz, $H_{Ar}$), 7.23 (d, 2H, $J = 14.0$ Hz, =CHN), 7.32 (d, 4H, $J = 8.3$ Hz, $H_{Ar}$), 7.70 (br s, 2H, NH); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta = 28.3$, 50.2, 62.2, 86.8, 119.9, 127.8, 131.0, 131.5, 131.9, 133.3, 135.7, 139.9, 150.1, 167.2, 169.3, HR-MS (ESI) calcd for $C_{46}H_{51}Br_2Cl_2N_6O_4$ $[M+H]^+$ 979.17108, found 979.17101; calcd for $C_{46}H_{50}Br_2Cl_2N_6O_4Na$ $[M+Na]^+$ 1001.15302, found 1001.15296.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.054.

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