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Efficient and facile synthesis of fused benzimidazole-diazepinones and dibenzimidazole-diazepines *via* a UDC strategy and the hydroamination of an alkyne†

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Two facile approaches have been developed for the synthesis of fused benzimidazole-diazepinones and dibenzimidazole-diazepines based on an Ugi/de-protection/cyclization strategy and the hydroamination of an alkyne. This efficient cascade process afforded the target compounds in good yields via a facile one-pot operation involving the formation of a new C–N bond.

Nitrogen-containing heterocycles are privileged scaffolds that can be found in a wide variety of bioactive pharmaceuticals and agrochemicals.[1] Substituted diazepinone and diazepine compounds are valuable pharmacophores in medicinal chemistry, as exemplified by scaffolds **I**,[2a] **II**,[2b] **III**,[2c] **IV**,[3] **V**[4] and **VI**,[5] which have been reported to show potent antibacterial, antiviral, anticancer, GABA receptor and PARP-1 activities in Figure 1.

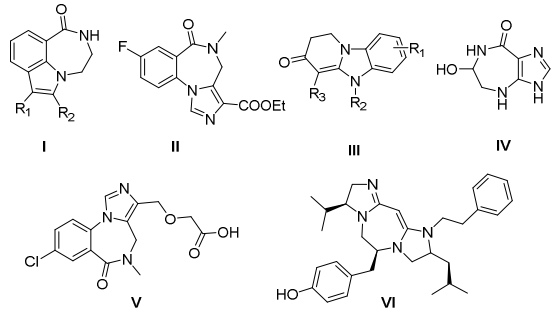
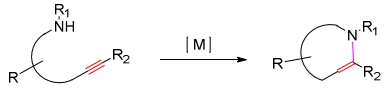


Figure 1 Bioactive diazepinone and diazepine compounds.

The Ugi reaction (U-4CR) is well known as a versatile and highly efficient synthetic tool for the preparation of heterocyclic compounds.[6] Moreover, this multicomponent reaction provides facile access to complex products with high iterative efficiency potential (IEP)[7] for the design of novel drug scaffolds from commercially available starting materials, including primary amines, isonitriles, carboxylic acids and aldehydes or ketones. Notably, the facile post condensation modification of Ugi adducts enriches their structural diversity, and this strategy has been exploited by a plethora of groups in both academic and industrial settings.[8] As part of our ongoing research towards the development of new synthetic methods for the construction of heterocyclic systems, we have used the Ugi reaction to prepare benzodiazepines,[9] benzimidazoles,[10] pyrazoles[11] and quinoxalines,[12] as well as several other systems.[13]



Scheme 1 Transition-metal-catalyzed hydroamination of alkyne.

The C–N bond is one of the most common bonds in organic synthesis, and the development of new methods for the preparation of C–N bonds using commercially available alkynes and amines has attracted considerable interest from numerous researchers (Scheme 1). For instance, metal-catalyzed amination of alkynes to afford a series of nitrogen-containing organic compounds were reported recently.[14-16] However, most of these systems require the presence of a transition-metal catalyst to promote the formation of the C–N bond. Moreover, transition metals are toxic and often expensive material that must be carefully removed from the products, especially during the preparation of pharmaceutical agents for human consumption. With this in mind, we became interested in the development of an environmentally friendly and convenient route for the construction of C–N bonds via the hydroamination of alkynes. It was therefore envisaged that propiolic acid could be reacted with a series of amines to build the corresponding Ugi products, which could be subjected to a hydroamination reaction to give a new C–N bond. Herein, we report the development of an efficient pathway for the formation of two novel scaffolds with some interesting biological activities via an Ugi/de-protection/cyclization (UDC) strategy, followed by the hydroamination of the resulting alkyne.

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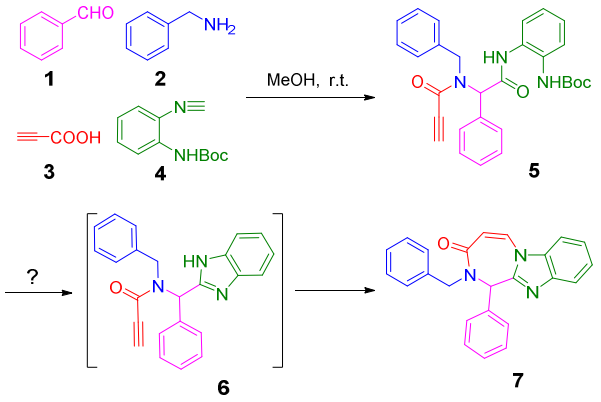
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopy data. See DOI:

We initially stirred a mixture of benzaldehyde (**1**), benzylamine (**2**), propiolic acid (**3**) and *ortho*-*N*-Boc-phenylisonitrile (**4**) in methanol at room temperature overnight (Scheme 2). This reaction provided access to the Ugi adduct **5**, which was isolated as a crude residue, following the removal of the methanol solvent under reduced pressure, and exposed to a series of different addition reaction conditions.



Scheme 2 Synthetic routes to fused benzimidazole-diazepinones **7**.

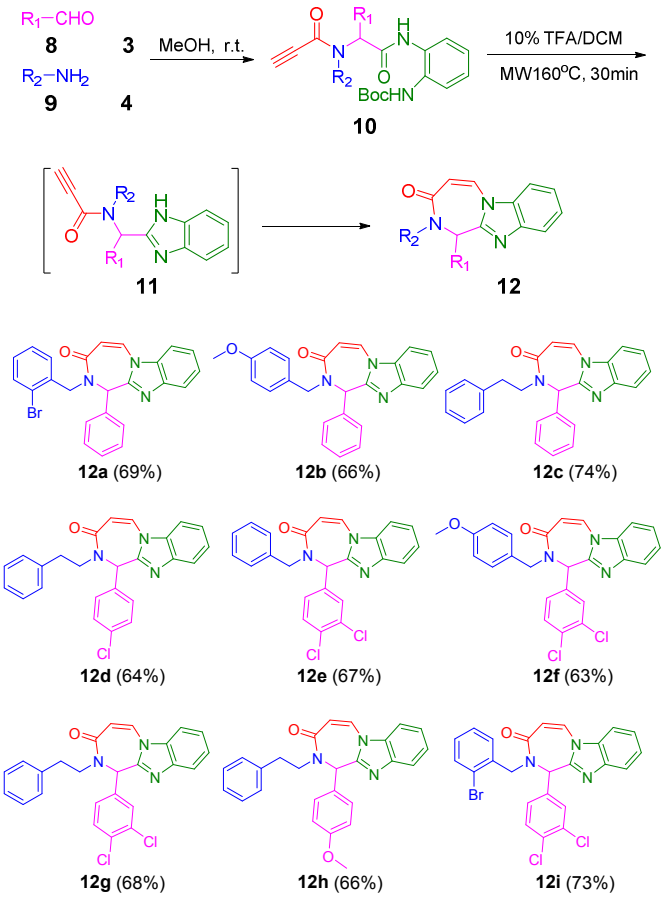
Table 1 Optimization of the conditions for the synthesis of the fused benzimidazole-diazepinones **7**.

Entry	Conditions	Equiv.	Temp. (°C)	Time (min.)	Yield (%)[a]
1	Na_2CO_3	2.0	MW150	10	27
2	K_2CO_3	2.0	MW150	10	31
3	NaOH	2.0	MW150	10	32
4	KOH	2.0	MW150	10	14
5	TEA	2.0	MW150	10	trace
6	DIPEA	2.0	MW150	10	39
7	DIPA	2.0	MW150	10	17
8	10% TFA/DCE		MW150	10	61
9	5% HCl/AcOH		MW150	10	52
10	10% TFA/DCE		MW160	10	68
11	10% TFA/DCE		MW160	20	74
12	**10% TFA/DCE**		**MW160**	**30**	**82**
13	10% TFA/DCE		MW170	10	65
14	10% TFA/DCE		MW170	20	52
15	10% TFA/DCE		MW180	10	30

[a]Yield of target compound **7** in one-pot operation. MW = microwave.

Based on the results of our previous research,[17] we investigated the effects of several different inorganic and organic bases on the outcome of this reaction (Table 1). Unfortunately, all of the bases tested in the current study afforded very low yields of the desired fused benzimidazole-diazepinone **7** when the reaction was heated under microwave irradiation conditions at 150 °C for 10 min (Table 1, entry 1–7). For example, only a trace amount of the desired product was obtained when triethylamine (TEA) was used as base (Table 1, entry 5). Notably, the yield of **7** increased when the crude Ugi product was heated under microwave irradiation conditions in an acidic solution (Table 1, entry 8–12). Based on these results, we considered several different acidic systems, and the results showed that heating the Ugi product in a 10% TFA/DCE solution at 160 °C under microwave irradiation for 30 min afforded the cyclized product **7** in 82% yield over two steps (Table 1, entry 12). The peak of intermediate compound **6** could be found from LC/MS data at low temperature. Surprisingly, increasing the temperature of the microwave irradiation process from 160 to 180 °C led to a pronounced decrease in the yield of the desired product (Table 1, entries 12, 13 and 15). Furthermore, extending the reaction time under microwave irradiation conditions at 170 °C in 10% TFA/DCE did not promote the cyclization step (Table 1, entry 14).

With the optimized reaction conditions in hand, we proceeded to investigate the scope of this reaction using a variety of different starting materials, which resulted in the preparation of a small collection of generic compounds **12**. Four different benzaldehydes and four different amines were subjected to the one-pot UDC strategy to give the corresponding fused benzimidazole-diazepinones **12** in good yields over two steps (63–74%), following the purification of the products by column chromatography (Scheme 3). Thus the new UDC strategy allowed for the successful connection of two ring systems, as well as the formation of a new fused benzimidazole-diazepinone scaffold with high skeletal diversity.

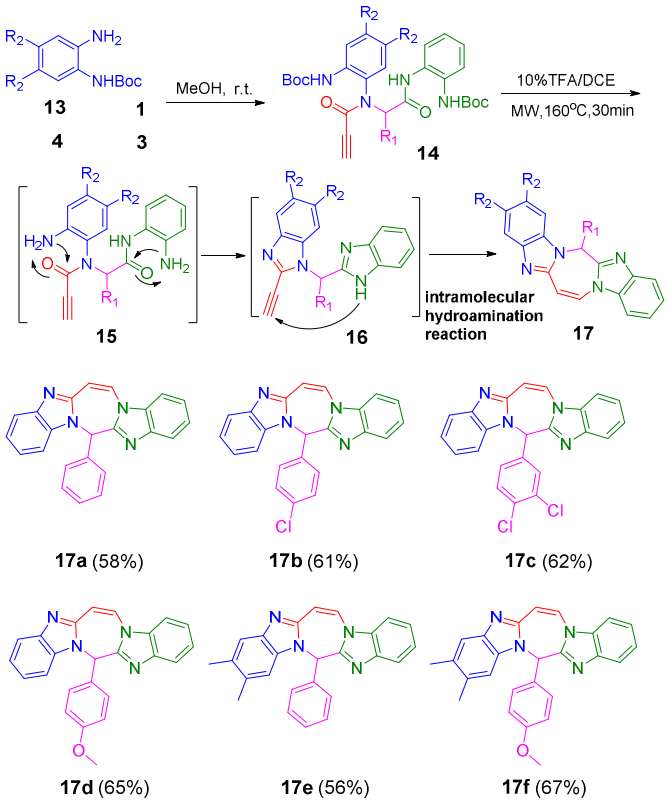


Scheme 3 Synthetic route and isolated yields (%) for the fused benzimidazole-diazepinones **12**.

Benzimidazoles are core structures in medicinal chemistry.[18] With this in mind, we became interested in the possibility of using this U-4CR for the conversion of the Ugi products into unusual polyheterocyclic chemotypes. Herein, we describe the development of a robust method for the introduction of a second benzimidazole unit into these structures to afford *bis*-benzimidazoles of general structure **16**. In this way, the UDC cascade method provided facile access to several interesting tri-heterocyclic scaffolds. In contrast to the other method described above for the formation of the fused benzimidazole-diazepinones, we used *N*-Boc-1,2-phenylenediamine (**13**) as the amine substrate instead of a simple amine or aniline. The

synthetic route used for the preparation of the dibenzimidazole-diazepine is shown in Scheme 4.

The Ugi adduct **14** resulting from this reaction was subsequently subjected to the UDC reaction conditions described above to give the corresponding *bis*-benzimidazole **17a**. Pleasingly, the desired product was obtained in a satisfactory yield of 58%. With the optimization reaction conditions in hand, we explored the scope of this cascade reaction using a variety of benzaldehydes and isonitriles, which resulted in the formation of a small collection of compounds **17** with yields ranging from 56 to 67%.



Scheme 4 Synthetic routes and isolated yield (%) of fused dibenzimidazole-diazepines **17**.

In summary, we have developed a metal-free synthetic tool for the formation of new C–N bonds based on an Ugi four-component reaction using propiolic acid, amines, isonitriles and benzaldehydes as starting materials. Under the optimized reaction conditions, we succeeded in the construction of a small collection of novel fused benzimidazole-diazepinones and dibenzimidazole-diazepines using a cascade process. This UDC strategy therefore represents a powerful protocol that could be used in medicinal chemistry for designing drug-like compounds.

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Graphical abstract

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Microwave assistant synthesis of fused benzimidazole-diazepinones and dibenzimidazole-diazepines using a one-pot procedure.