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Increased dipeptoid diversity resulting from post-condensational manipulation of the Ugi reaction products

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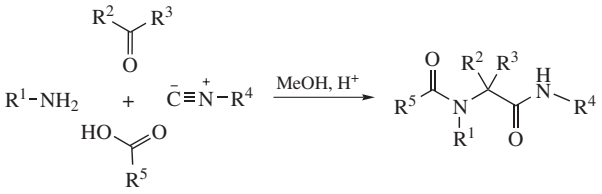
5,6-Dihydropyrazolo[1,5-*a*]pyrazines prepared *via* the Ugi reaction involving pyrazole-3-carboxylic convertible *tert*-butyl isocyanide and subsequent microwave-promoted cyclization, were found to be prone to opening with primary and secondary amines, thereby providing a facile, three-step access to a greater diversity of Ugi-type dipeptoids, some of which cannot be accessed *via* the Ugi reaction itself.

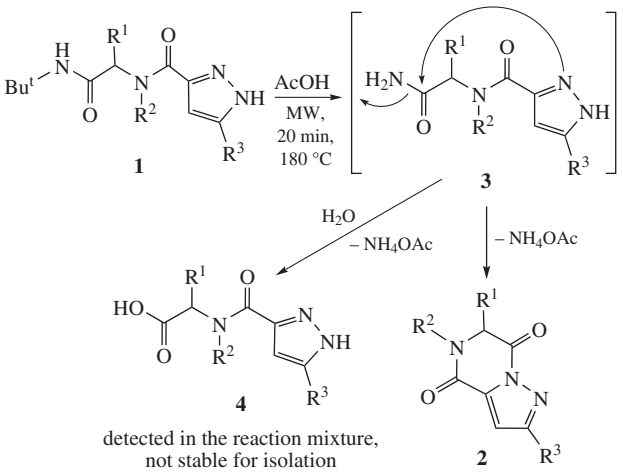
The Ugi reaction (Scheme 1) has undoubtedly occupied a central place both in the toolbox of combinatorial chemistry[1] and in the minds of organic chemists as probably the most prominent multicomponent reaction that can offer access (*via* so-called post-Ugi modifications) to a wide variety of drug-like heterocycles.[2]



Scheme 1

Our group has been actively investigating novel synthetic approaches to medicinally relevant molecular scaffolds,[3] largely stemming from the Ugi reaction itself as well as other isocyanide-based chemistries. Recently, we discovered that products of the Ugi reaction **1** incorporating residues of 1*H*-pyrazole-3-carboxylic acid and *tert*-butylisocyanide can undergo a facile cyclization into the medicinally important 5,6-dihydropyrazolo[1,5-*a*]pyrazines **2** when heated under microwave irradiation in glacial acetic acid (Scheme 2).[4]

Overall, in this two-step sequence (the Ugi reaction + post-Ugi cyclization), *tert*-butyl isocyanide may be regarded as a convertible reagent. We believe the cyclization **1** → **2** may involve generation of the primary amide **3** (on *tert*-butyl elimination) that is more easily cyclized than its *N*-alkyl amide counterparts. This is indirectly confirmed by the presence of the respective carboxylic acid **4** in the reaction mixtures after microwave irradiation (presumably resulting from the hydrolysis of **3** by adventitious water) and may explain lower reactivity of primary and secondary alkyl amides in similar microwave-assisted cyclization.[5]



Scheme 2

While many azole carboxylic acids can be incorporated into dipeptoids similar to **1** *via* the Ugi reaction, many of them fail to participate in microwave-assisted cyclization. Among the azole residues supplied by the carboxylic acid components shown in Figure 1, only 5-methoxylindole moiety participated efficiently in the cyclization onto the terminal *tert*-butyl amide in the respective Ugi reaction products **5** (under higher temperature and upon prolonged exposure to microwave irradiation) to give rise to novel 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones **6** (Scheme 3).[6] Thus, the pyrazole moiety appears to be a unique accessory in the intramolecular ex-isocyanide residue conversion in **1** providing easy access to conformationally restricted peptidomimetics **2**.

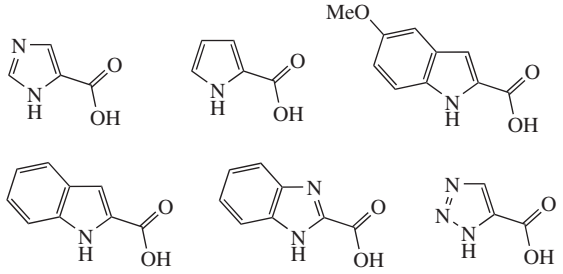
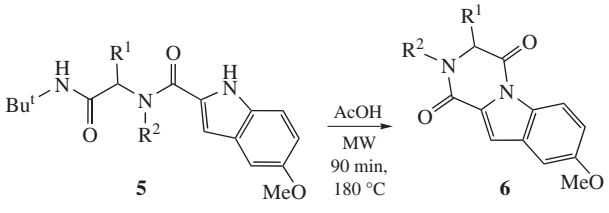
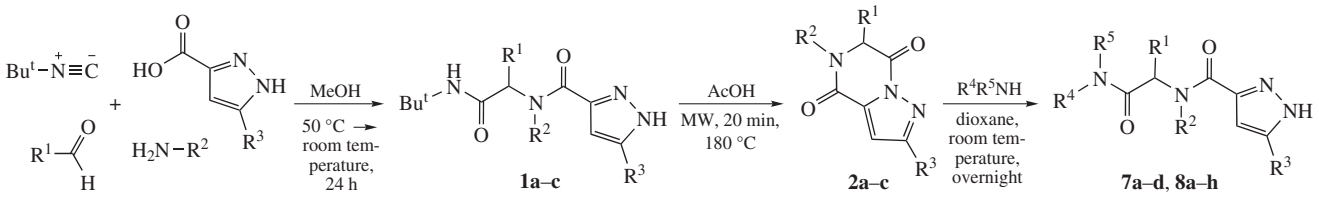


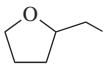
Figure 1 Examples of azole carboxylic acids tried in microwave-assisted cyclization of the respective Ugi reaction products.[5]



Scheme 3



1a–c **2a–c** **7a–d**, **8a–h**

	R^1	R^2	R^3	R^4	R^5	Yield (%)
7a	4-Pr^{i}C$_6$H$_4$	4-MeOC$_6$H$_4$CH$_2$	4-MeC$_6$H$_4$	MeO(CH$_2$)$_2$	H	70
7b	4-Pr^{i}C$_6$H$_4$	4-MeOC$_6$H$_4$CH$_2$	4-MeC$_6$H$_4$	Bn	H	65
7c	Pr^i	4-MeOC$_6$H$_4$CH$_2$	Me		H	69
7d	Pr^i	4-MeOC$_6$H$_4$CH$_2$	Me	Bn	H	70
8a	4-Pr^{i}C$_6$H$_4$	4-MeOC$_6$H$_4$CH$_2$	4-MeC$_6$H$_4$	(CH$_2$)$_2$O(CH$_2$)$_2$		67
8b	4-Pr^{i}C$_6$H$_4$	4-MeOC$_6$H$_4$CH$_2$	4-MeC$_6$H$_4$	(CH$_2$)$_4$		71
8c	4-Pr^{i}C$_6$H$_4$	4-MeOC$_6$H$_4$CH$_2$	4-MeC$_6$H$_4$	(CH$_2$)$_2$N(CO$_2$Et)(CH$_2$)$_2$		68
8d	Pr^i	4-MeOC$_6$H$_4$CH$_2$	Me	(CH$_2$)$_2$O(CH$_2$)$_2$		71
8e	Pr^i	4-MeOC$_6$H$_4$CH$_2$	Me	Me	Et	67
8f	Pr^i	4-MeOC$_6$H$_4$CH$_2$	Me	(CH$_2$)$_2$N(*c*-C$_5$H$_9$)(CH$_2$)$_9$		72
8g	Pr^i	Bn	Cyclopropyl	(CH$_2$)$_2$N(Cy)(CH$_2$)$_9$		68
8h	Pr^i	Bn	Cyclopropyl	(CH$_2$)$_5$		65

Scheme 4

We proceeded to study the chemical behaviour of 5,6-dihydropyrazolo[1,5-*a*]pyrazines **2** and found them to be prone to alkaline hydrolysis at elevated temperatures. Indeed, refluxing a solution of any of **2** in dioxane in the presence of 2 equiv. of aqueous KOH led to its complete conversion into the corresponding salt of carboxylic acid **4** (according to LC-MS analysis). However, despite numerous attempts, we were unable to isolate and purify any of the acids **4** (presumably, due to facile decarboxylation).

Compounds **2** can be regarded as internal pyrazolides of the carboxylic acids **4** and therefore it is unsurprising that they are reactive toward nucleophiles.[7] We therefore turned our attention to the potential of opening **2** with various amines (rather than hydroxyl anion) that would provide access to a greater variety of Ugi-type dipeptoids with terminal amide diversity resulting from generally much more available primary amines (compared to the variety of isocyanides) (Scheme 4).

The representative 5,6-dihydropyrazolo[1,5-*a*]pyrazines **2a–c** were prepared in good isolated yields *via* the microwave-assisted cyclization of the Ugi adducts **1a–c** (without isolation of the latter), as described previously.[4] Subsequent overnight treatment of **2a–c** with 2 equiv. of a primary or a secondary amine in dioxane at room temperature gave cleanly the expected secondary (**7a–d**) or tertiary (**8a–h**) amides in uniformly good yields (Scheme 4).[†] Notably, no similar ring opening was observed for the 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones **6**, even on prolonged exposure to primary and secondary amines at dioxane reflux temperatures. This seems unsurprising in view of the greater stability (*e.g.*, toward hydrolysis) of *N*-acyl indoles compared to *N*-acyl pyrazoles.[8]

In summary, we have developed an efficient access to Ugi-type dipeptoids containing a greater diversity of terminal secondary amides as well as hitherto undescribed tertiary amide analogs thereof. This novel protocol stems from our previously disclosed methodology of microwave- assisted cyclization of pyrazole-containing Ugi reaction products and significantly expands the chemical space of dipeptoids rapidly and efficiently accessible by the multicomponent approach.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.01.016.

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[†] *General procedure for the preparation of compounds* **7** and **8**. Compound **2** (0.5 mmol) synthesized as described previously,[4] was dissolved in dioxane (2 ml) and treated with an amine (0.6 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the target amide **7** (**8**) was isolated by column chromatography on silica gel using an appropriate gradient of methanol in dichloromethane as eluent.

For **8a**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 13.37 (s, 1H), 7.65 (d, 2H, *J* 7.7 Hz), 7.27 (d, 2H, *J* 7.7 Hz), 7.04–7.19 (m, 4H), 6.93 (m, 1H), 6.76 and 6.58 (AB qd, 4H, *J* 8.3 Hz), 5.09 (s, 1H), 4.42 (s, 1H), 3.65 (s, 3H), 3.09–3.57 (m, 8H), 2.84 (m, 1H), 2.35 (s, 3H), 1.17 (d, 6H, *J* 6.9 Hz), 1.07 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 Hz) δ: 167.2, 167.0, 163.9, 157.4, 154.5, 151.6, 148.3, 139.2, 137.1, 131.3, 130.9, 130.2, 129.6, 129.4, 128.7, 127.8, 126.5, 126.0, 125.4, 125.2, 112.8, 66.1, 65.5, 54.9, 33.2, 23.9, 23.7, 20.9. Found (%): C, 72.24; H, 6.83; N, 9.92. Calc. for $C_{34}H_{38}N_4O_4$ (%): C, 72.06; H, 6.76; N, 9.89.

For characteristics of compounds **7a–d** and **8b–h**, see Online Supplementary Materials.