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A Mimicry of Primary Amines by Bis-Secondary Diamines as Components in the Ugi Four-Component Reaction**

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In memory of Ivar Ugi

Recent years have witnessed a fast growing interest in multicomponent reactions (MCRs),[1] mainly because of their ability to assemble complicated structures in just a few steps. The Ugi four-component reaction (Ugi 4CR)[2] is one of the cornerstone MCRs and great efforts have been devoted to the exploration of the potential of this transformation.[3] In the archetypal Ugi 4CR, a primary amine, a carbonyl compound, a carboxylic acid, and an isocyanide react in methanol to give α-acylamino amides. Several modifications of the classic Ugi 4CR have been described; these modifications involve the variation of one of the components or the introduction of a linkage between two of them, which leads to interesting potential druglike derivatives of the original α-acylamino amide product.[4]

Although a large number of modifications of the carboxylic acid reactant have been successfully explored (for example, water,[5] alcohol and carbon dioxide,[6] hydrazoic acid[7]), the other components are less well suited to structural changes in view of the accepted mechanism of the Ugi 4CR. Isocyanide is the key reagent of the Ugi 4CR, and the carbonyl compound and the primary amine are required for the formation of the intermediate imine.[8]

Herein we focus our attention on the role of the primary amine (Scheme 1), which reacts first with the carbonyl compound to give an intermediate imine. Protonation by the carboxylic acid moiety to give an iminium ion followed by nucleophilic attack of the isocyanide leads to the formation of a nitrilium ion intermediate, which is subsequently intercepted by the corresponding carboxylate anion.[9] The resulting imino anhydride typically undergoes an irreversible transacylation (Mumm rearrangement)[10] to give the final Ugi 4CR product. The primary amine plays a dual role in this

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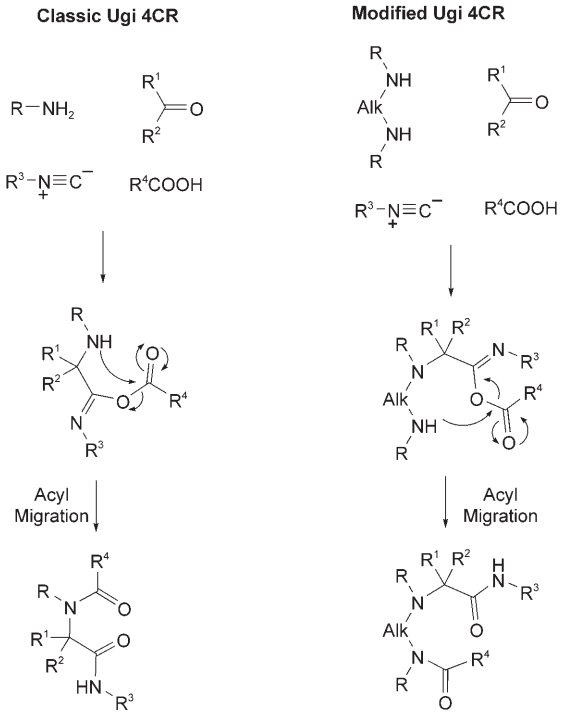


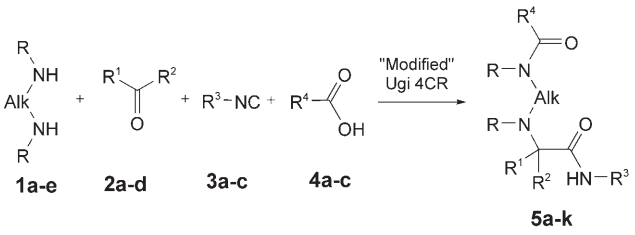
Scheme 1.

mechanism, being simultaneously alkylated, acylated, and losing both hydrogen atoms.

In contrast, when a secondary amine reacts in an Ugi-type reaction, the amine nitrogen atom cannot undergo transacylation. In this case, the isocyanide nitrogen atom usually captures the acyl moiety, to give an α,α′-diacyl amide in a nonnucleophilic solvent.[6a] However, if the stoichiometric amount of the secondary amine is twice that of the other components, the imino anydride intermediate or the α,α′-diacyl amide is promptly attacked by the other secondary amine to give a nearly equimolar mixture of an α-acyl amide and an amide, as was elegantly demonstrated by McFarland.[11]

We were thus prompted to verify whether two secondary amino groups, suitably contained within the same molecule, could take the place of the primary amino group. The "splitting" of the primary amine into two secondary amines could allow the expansion of the skeleton of the MCR product, thus increasing the versatility of the Ugi 4CR and leading to useful new building blocks for the construction of chemical libraries. In detail (Scheme 1), one of the two nitrogen atoms may react with the carbonyl group to afford an iminium ion (in place of the protonated imine), which then interacts with the isocyanide and the carboxylate moiety. The resulting intermediate may undergo a subsequent transacylation in which the acyl moiety migrates to the second nitrogen atom of the diamine (a "remote" Mumm rearrangement), as the first nitrogen atom has already become a tertiary amine and is unable to receive the acyl group.[12]

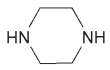
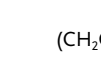
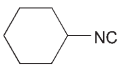
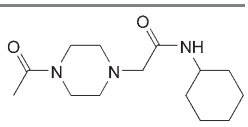
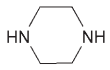
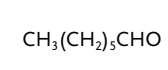
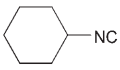
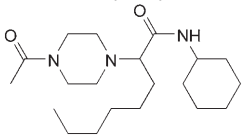
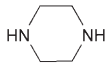
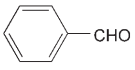
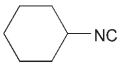
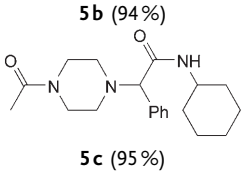
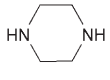
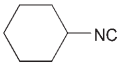
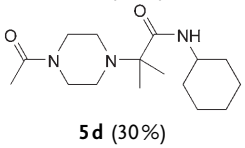
For this reason, we treated piperazine with equimolar amounts of paraformaldehyde, acetic acid, and cyclohexylisocyanide in refluxing methanol. Indeed, we observed a clean transformation, which enabled the isolation, after evaporation and recrystallization or column chromatography, of **5a–k** (Scheme 2).



Scheme 2.

The generality of the N-split Ugi 4CR was then checked by varying the single components. Besides the formaldehyde, alkanals (Table 1, entry 2), aryl aldehydes (Table 1, entry 3), and ketones (Table 1, entry 4) were successfully employed as the carbonyl compound. Good to excellent yields were observed with the exception of the ketone. Steric hindrance could be invoked to justify the modest yield in this case; although the Ugi 4CR is reported to be quite insensitive to steric hindrance,[3] the N-split Ugi 4CR relies on the forma-

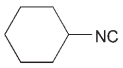
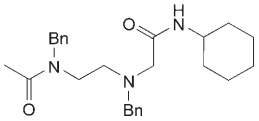
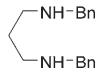
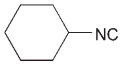
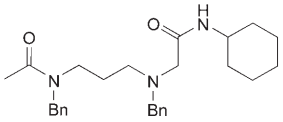
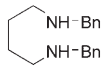
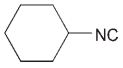
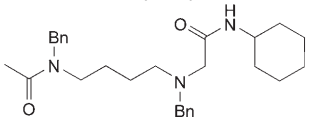
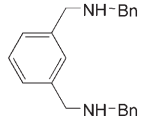
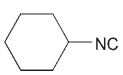
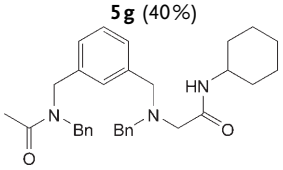
Table 1: Compounds obtained by variation of the carbonyl component.

Entry	Diamine	Carbonyl compound	Isocyanide	Carboxylic acid	Product (yield)
1					
	1a	**2a**	**3a**	**4a**	**5a** (75%)
2					
	1a	**2b**	**3a**	**4a**	**5b** (94%)
3					
	1a	**2c**	**3a**	**4a**	**5c** (95%)
4					
	1a	**2d**	**3a**	**4a**	**5d** (30%)

tion of a crowded, fully alkylated intermediate iminium ion (versus the less encumbered iminium ion derived from the protonation of an imine).

Table 2 reports the products obtained from the variation of the secondary diamine. As well as piperazine, *N*,*N*′-diaryl ethylenediamine **1b** (Table 2, entry 1), propanediamine **1c** (Table 2, entry 2), butanediamine **1d** (Table 2, entry 3), and *m*-xylylenediamine **1e** (Table 2, entry 4) were successfully subjected to the N-split Ugi 4CR protocol. As shown, although the desired conversion always takes place, the yields vary widely within the range 35–95%, with the best result being obtained with *N*,*N*′-dibenzyl-1,3-propanediamine. The length and the conformational mobility of the linking moiety connecting the two secondary amines evidently play a crucial role in the "remote" Mumm rearrangement step, although a precise rationalization cannot be given at this stage. The remarkable 56% yield for the reaction of *N*,*N*′-dibenzyl-1,3-xylylenediamine is quite unexpected, as the putative "remote" Mumm rearramgement involves an 11-membered metacyclophane. Preliminary data from molecular modeling studies of the tetrahedral intermediate in the formation of **5h** (MMFF, Spartan Package)[13] shows the absence of significant strain in the macrocyclic structure; similar 11-membered metacyclophanes are known to be stable.[14]

Table 2: Compounds obtained by variation of the secondary diamine.[a]

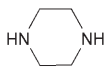
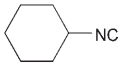
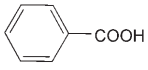
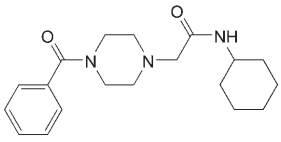
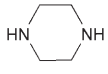
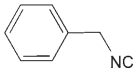
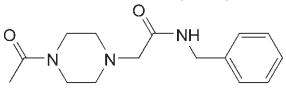
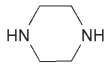
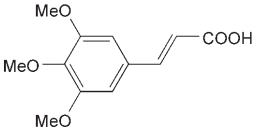
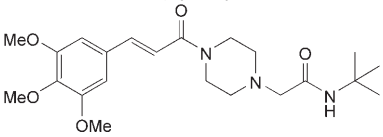
Entry	Diamine	Carbonyl compound	Isocyanide	Carboxylic acid	Product (yield)
1					
	1b	**2a**	**3a**	**4a**	**5e** (35%)
2					
	1c	**2a**	**3a**	**4a**	**5f** (95%)
3					
	1d	**2a**	**3a**	**4a**	**5g** (40%)
4					
	1e	**2a**	**3a**	**4a**	**5h** (56%)

[a] Bn = benzyl.

Modification of the isocyanide and the carboxylic acid were similarly performed, and the results are listed in Table 3. As with the parent Ugi 4CR, structural modification of one or both components does not affect either the progress or the yield of the corresponding reactions, which are still characterized by good overall efficiency.

Furthermore, Table 3 (entry 3) exemplifies the extraordinary synthetic power of this transformation: the product **5k** is a known vasodilator and is usually synthesized in four steps starting from piperazine.[15] The N-split Ugi 4CR allows its one-pot preparation in higher yield from commercially available compounds and avoids the time- and chemical-consuming

Table 3: Compounds obtained by variation of carboxylic acid and isocyanide.

Entry	Diamine	Carbonyl compound	Isocyanide	Carboxylic acid	Product (yield)
1					
	1a	**2a**	**3a**	**4b**	**5i** (80%)
2					
	1a	**2a**	**3b**	**4a**	**5j** (95%)
3					
	1a	**2a**	**3c**	**4c**	**5k** (77%)

steps needed to discriminate the chemically equivalent nitrogen atoms of the diamine.[16] Additional advantages for the large-scale application of this protocol are its high atom economy (always approaching unity) and environmentally friendly nature (the only by-product is one water molecule per product molecule).[17]

In summary, we have described herein a novel and efficient multicomponent reaction that allows extension of the conventional Ugi 4CR product backbone and provides a new way to create molecular diversity. We have only scraped the surface of its potential in synthetic and medicinal chemistry within the text. Additional work is in progress to elucidate in detail the applicability and limitations of this new weapon in the synthetic chemist's arsenal.

Experimental Section

Typical procedure: Carbonyl compound **2a–d** (1 equiv), carboxylic acid **4a–c** (1 equiv), and isocyanide **3a–c** (1 equiv) were added sequentially to a solution of diamine **1a–e** (1 equiv) in methanol (0.5 M) at room temperature. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography or by recrystallization.

Physical data for selected compounds (all data correspond to the main rotamer): **5a**: white powder; m.p. 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) : $\delta = 6.92$ (brs, 1H), 3.80 (m, 1H), 3.64 (brs, 2H), 3.49 (brs, 2H), 3.02 (s, 2H), 2.53 (brs, 4H), 2.08 (s, 3H), 1.95–1.12 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C): $\delta = 168.8$, 168.2, 61.4, 53.2, 52.9, 47.3, 46.1, 41.3, 32.8, 25.3, 24.5, 20.9 ppm; MS (ESI): *m/z* (%) 268 (100) $[M+H]^+$. **5d**: yellowish powder; m.p. 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta = 7.04$ (brd, 1H), 3.63 (m, 1H), 3.51 (brs, 2H), 3.38 (brs, 2H), 2.29 (brs, 4H), 2.00 (s, 3H), 1.75–1.08 (m, 10H), 1.08 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C): $\delta =$ 175.3, 169.2, 63.5, 47.5, 47.1, 46.9, 46.4, 42.1, 33.1, 25.6, 24.6, 21.0, 20.6 ppm; MS (ESI): *m/z* (%) 296 (100) $[M+H]^+$. **5f**: pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta = 7.23$–7.15 (m, 10H), 6.78 (brd, 1H), 4.37 (s, 2H), 3.61 (m, 1H), 3.48 (s, 2H), 3.29 (t, $J = 7.4$ Hz, 2H), 2.93 (s, 2H), 2.39 (t, $J = 6.8$ Hz, 2H), 2.00 (s, 3H), 1.95–0.99 ppm (m, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C): $\delta = 170.9$, 170.0, 137.0, 136.8, 128.8, 128.4, 128.3, 128.2, 127.4, 125.9, 59.6, 58.1, 52.5, 52.1, 47.5, 44.1, 32.9, 26.4, 25.3, 24.7, 21.6 ppm; MS (ESI): *m/z* (%) 436 (100) $[M+H]^+$. **5i**: pale yellow solid; m.p. 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta = 7.34$ (brs 5H), 6.85 (brd, 1H), 3.74 (m, 1H), 3.57 (brs, 4H), 2.96 (s, 2H), 2.48 (brs, 4H), 1.81–1.11 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C): $\delta = 170.4$, 168.2, 135.7, 129.8, 128.5, 127.0, 61.6, 53.4 (×2), 47.5, 33.1, 25.6, 24.7 ppm; MS (ESI): *m/z* (%) 330 (100) $[M+H]^+$. **5k**: white solid; m.p. 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): $\delta = 7.56$ (d, $J = 15.4$ Hz, 1H), 6.90 (brs, 1H), 6.70 (s, 2H), 6.68 (d, $J = 15.4$ Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 3.72 (brs, 4H), 2.97 (s, 2H), 2.59 (brs, 4H), 1.35 ppm (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50 °C): $\delta = 165.6$ (×2), 153.6, 143.3, 140.3, 130.8, 116.1, 105.6, 62.2, 60.9, 56.5, 53.3 (×2), 50.8, 28.9 ppm; MS (ESI): *m/z* (%) 420 (100) $[M+H]^+$.

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