Synthetic Methods

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Ugi/Aldol Sequence: Expeditious Entry to Several Families of Densely Substituted Nitrogen Heterocycles**

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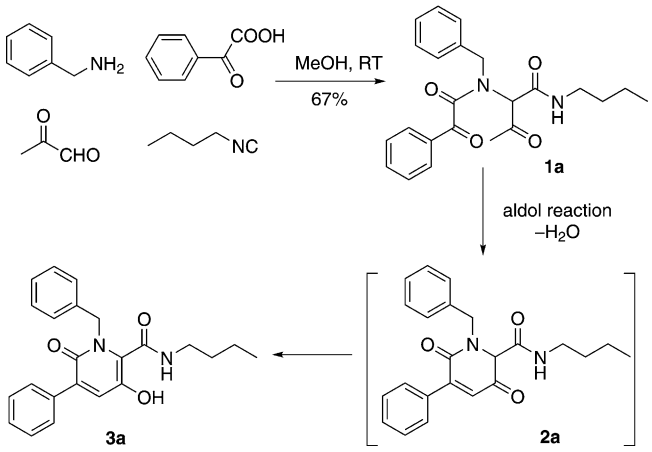
Nitrogen-containing heterocyles represent the vast majority of drugs and biologically relevant molecules. Thus, one of the most investigated areas of present day synthetic organic chemistry is the development of novel and efficient strategies for the assembly of these valuable compounds.[1] In this context, isocyanide-based multicomponent reactions (IMCRs) have met renewed interest[2] because of their unmatched capability to rapidly generate molecular diversity and explore chemical space.[3] In particular, the Ugi reaction (U-4CR) enjoys the lion's share of this methodology growth because of the extreme versatility it displays.[4] As a matter of fact, although this condensation affords a linear peptide backbone, a plethora of strategies are available to rigidify Ugi adducts into more appealing druglike species.[5] To date, Ugi/Diels Alder,[6] Ugi/Buchwald–Hartwig,[7] Ugi/Heck,[8] Ugi/nucleophilic additions/substitutions,[9] and Ugi/ring-closing metathesis[10] pathways constitute the most well-established routes to gain access to a wide variety of cyclic scaffolds, and is in line with the post-condensation modification approach.[2] Recently, more elaborated processes involving extensive manipulations of Ugi products to render natural product-like complex frameworks have also been reported.[11] Within this blossoming and highly diversified arena of research, it is surprising to notice that aldol-type reactions have never been exploited.[12] Indeed, such studies are reported herein and contain examples of four- and five-step, one-pot, post-MCR cascades[13] which creatively generate molecular diversity in exquisite non-obvious ways.

The aldol reaction, first discovered by Wurtz[14] more than one century ago, is still one of the most powerful tools known to create carbon–carbon bonds through the use of easily available starting materials,[15] namely aldehydes and ketones. Given its outstanding importance in the preparation of both top-selling pharmaceuticals[16] and natural products,[17] we were therefore enticed to investigate the possibility to merge the exploratory power of the U-4CR with the potential to convert Ugi products into novel and appealing heterocyclic chemotypes offered by the aldol condensation. To endow the multicomponent reaction (MCR) product with functionalities suitable to participate in an aldol condensation, pyruvic aldehyde and phenylglyoxylic acid were employed, along with benzylamine and *n*-butylisonitrile (Scheme 1). Predictably, this first step proceeded smoothly in methanol under mild reaction conditions overnight to give **1a** in good yield (67%). With this acyclic intermediate bearing ketonic carbonyl groups and an activated methyl in hand, we initiated screening of a panel of solvents and catalysts (Table 1) to achieve the desired aldol-induced cyclization.

Different organic bases were evaluated, as the aldol reaction is most frequently a base-catalyzed transformation proceeding via enolate formation.[15] Interestingly, the targeted modification required microwave irradiation at ele-



Scheme 1. Design of Ugi/aldol sequence.

Table 1: Optimization of the aldol reaction.

Entry	Cat.	Equiv	Solvent	Conditions	Yield [%][a]
1	DIPEA	2.0	DMSO	150°C, 10 min	5
2	DIPA	2.0	DMSO	150°C, 10 min	55
3	TEA	2.0	DMSO	150°C, 10 min	55
4	DIPA	2.0	DMF	150°C, 10 min	60
5	DIPA	2.0	DMF	160°C, 20 min	88
6	DIPA	2.0	THF	160°C, 20 min	55
7	DIPA	2.0	DCE	160°C, 20 min	9
8		10% TFA/DCE		150°C, 10 min	14
9		10% TFA/DCE		160°C, 20 min	30

[a] Yield of isolated product. DCE = 1,2-dichloroethane, DMF = *N*,*N*′-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

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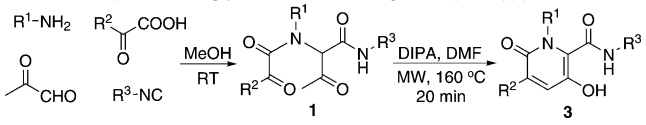
vated temperatures ($\geq 150\,^{\circ}C$), but was nevertheless feasible in a straightforward and satisfactorily clean way. Of note, after the nucleophilic attack and dehydration leading to the α,β-unsaturated compound **2a**, which was never isolated, further isomerization afforded 5-hydroxypyridine-2-one **3a**. Triethylamine (TEA) and *N*,*N*-diisopropylamine (DIPA) proved to be equally effective (Table 1, entries 2 and 3), whereas use of *N*,*N*-diisopropylethylamine (DIPEA) under the same reaction conditions in DMSO afforded only a negligible amount (5%) of the title product (entry 1). Variation of the solvent showed that DMF (entries 4 and 5) was beneficial for the desired conversion, especially when irradiating at 160 °C for 20 minutes. Conversely, decreasing the polarity of the medium by employing DCE (entry 7) resulted in a dramatic drop of the yield. Since the aldol condensation is also known to be feasible through acid-promoted enol formation, a 10% TFA/DCE solution was employed as both the solvent and the catalyst (entries 8 and 9), but was found to have remarkably less efficacy compared to DIPA in DMF.

After optimizing the second step of the sequence, we exposed different building blocks to our protocol to both determine its generality and to prepare a small collection of compounds **3** (Table 2). While the carbonyl input was always represented by pyruvic aldehyde, two different arylglyoxylic

Table 2: Scope of the Ugi/aldol route leading to 5-hydroxypyridin-2-ones.

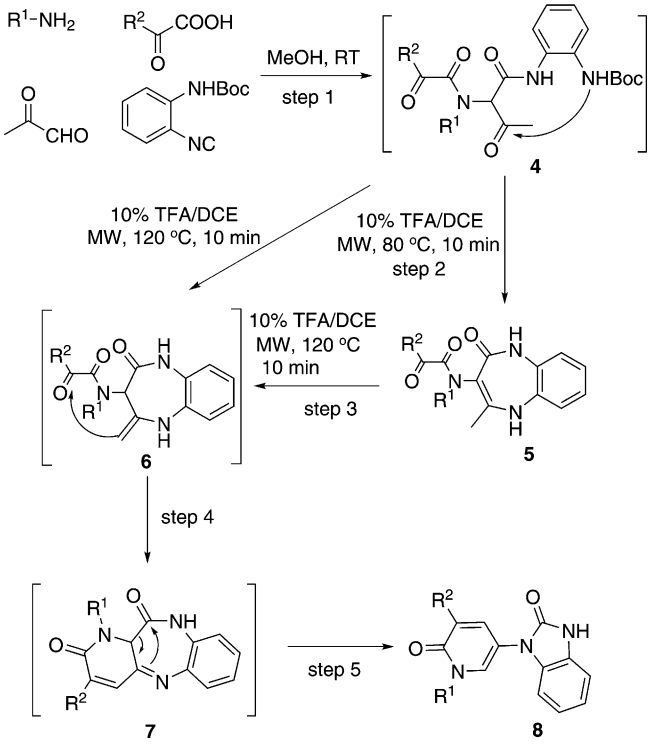


Entry	R^1	R^2	R^3	Yield [%][a]	
1	Bn	Ph	*n*Bu	**1a**: 67	**3a**: 88
2	phenethyl	Ph	*n*Bu	**1b**: 55	**3b**: 91
3	*i*Bu	2-thienyl	Bn	**1c**: 53	**3c**: 88
4	Ph	2-thienyl	Bn	**1d**: 48	**3d**: 90
5	Ph	2-thienyl	*n*Bu	**1e**: 58	**3e**: 85
6	phenethyl	2-thienyl	*c*Pent	**1f**: 47	**3f**: 87
7	2-$ClC_6H_4CH_2$	2-thienyl	*c*Pent	**1g**: 51	**3g**: 84
8	Bn	2-thienyl	*c*Pent	**1h**: 53	**3h**: 86

[a] Yield of isolated product. MW = microwave.

acids, three isonitriles, and five aromatic and aliphatic amines were evaluated. The Ugi MCR furnished the dipeptide-like products **1** in fair to good yields ranging from 47 to 67% after the well-established method of stirring in a mild chemical environment.[18] Acyclic precursors were subsequently purified by column chromatography and treated with DIPA in DMF under microwave-promoted heating to produce the 5-hydroxypyridin-2-ones **3** in excellent yields. Gratifyingly, the synthetic route proved to be robust and tolerated a variety of different substituents. Moreover, the aldol step could be performed in a very clean manner, and intermolecular aldol condensations were not observed.

Having developed this novel methodology for the diversification of the Ugi backbone and displaying general applicability and providing a 2-pyridone heterocyclic core in two concise straightforward steps, our next goal was to further build the complexity of final products and gain access to more elaborated molecular scaffolds. As a consequence, studies were directed at an additional transformation capable of assembling a nitrogen-containing ring (Scheme 2).



Scheme 2. Synthetic route leading to hybrid pyridinone-3-yl-benzimidazol-2-ones **8**. Boc = *tert*-butoxycarbonyl.

Benzodiazepines possess a wide spectrum of biological activities[19] which goes well beyond their classical applications as sedatives and anxiolytics. With our expertise in the field of benzodiazepine synthesis,[20] it seemed natural to attempt embedding such a valuable scaffold into the Ugi/aldol products. According to our synthetic plan (Scheme 2), replacement of the commercially available isonitriles with *ortho*-*N*-Boc-phenylisonitrile, bearing an additional masked amino group,[21] would allow an anticipated domino process which included two post-MCR modifications in one pot. Thus, attack of the anilinic amine onto the pyruvaldehyde-derived carbonyl group in the presence of 10% TFA/DCE was intended to form the intermediate **6**, thus paving the way to a subsequent acid-promoted aldol reaction (imine aldol[22] in this case) and rendering the unprecedented tricyclic species **7**. To our surprise, microwave irradiation at 120 °C generated a different product and X-ray structural analysis[23] unambiguously determined the structure to be the pyridinone-3-yl-benzimidazol-2-one chemotype **8**. This phenomenon was unanticipated, although over 30 years ago strong thermal conditions were reported to trigger benzodiazepines to undergo benzimidazol-2-one rearrangements.[24] Upon experimenting with lower temperatures (80 °C) the expected proposed kinetic product **5h** was obtained in an almost quantitative amount (see Table 3, entry 8). Excitingly, the

unprecedented bis(heterocycle) **8** was of great interest and its preparation was equivalent to a cascade sequence of four distinct transformations occurring after the initial Ugi condensation.

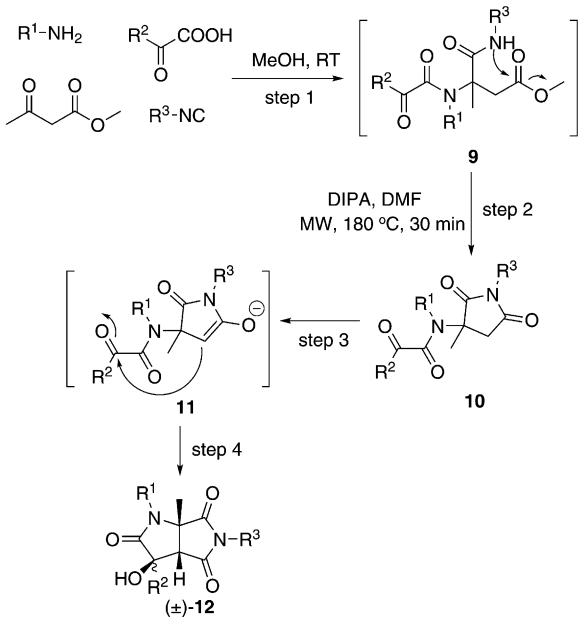
A small collection of compounds having the generic structure **8** was thus prepared by means of the five-step, one-pot protocol. After completion of the Ugi reaction, solvent was evaporated in vacuo and the crude reaction mixture was directly exposed to acidic thermal rearrangement conditions, thus providing the bis(heterocycle)s **8** (Table 3, entries 1–7). Remarkably, excellent yields (47 to 58%) over five steps were obtained and only one final chromatography step was required.

Table 3: Scope of the Ugi/aldol-based cascade involving *ortho-N*-Boc-phenylisonitrile.[a]

Entry	R^1	R^2	Yield [%][b]	
1	phenethyl	Ph	–	**8a**: 53
2	methoxyethyl	Ph	–	**8b**: 58
3	phenethyl	2-thienyl	–	**8c**: 52
4	Ph	*i*Bu	–	**8d**: 55
5	2,6-$Cl_2C_6H_3CH_2$	Ph	–	**8e**: 52
5	2-furyl	2-furyl	–	**8f**: 47
7	Ph	2-thienyl	–	**8g**: 56
8	3-BrC_6H_4	4-$FC_6H_4CH_2$	**5h**: 95[c]	**8h**: 88[d]

[a] Reaction conditions: see Scheme 2. [b] Overall yield of isolated product. [c] Yield of product isolated from the Ugi product **4h**. [d] Yield of product isolated from **5h**.

Encouraged by the above results, which demonstrated high versatility of the new methodology, we envisaged a second strategy exploiting a sequential domino nucleophilic attack/aldol condensation. In this case, pyruvic aldehyde was replaced by methyl acetoacetate as the source of the activated methylene. Intrigued by the possibility of targeting the highly unusual bicyclic five-membered rings **12**, we postulated a tandem approach entailing nucleophilic substitution onto the ester moiety and a subsequent aldol step (Scheme 3). Once the MCR step was completed, methanol was removed and the crude **9** was subjected to irradiation under basic conditions to directly afford the final products (±)-**12**. Notably, the 180°C temperature was essential to drive the process to completion, and when milder reaction conditions were attempted (120°C, 20 min) the unique pyrrolidine dione **10a** (R^1 = Bn, R^2 = 2-thienyl, R^3 = *n*Bu) predominated (66% yield). Use of a panel of amines, isonitriles, and arylglyoxylic acids allowed the preparation of a small collection of richly and diversely substituted bicyclic chemotypes (**12**; Table 4) in very good yields over four steps. Notably, to the best of our knowledge this represents the first route into this class of tricarbonylic molecules, and the few reported strategies leading to similar scaffolds[25] are much less straightforward and diversity-enabling. To our delight, NMR spectra and HPLC-/MS traces invariably showed a single set of signals or single peak respectively, thereby suggesting that one diastereoisomer was predominat. The stereochemistry was finally resolved by X-ray crystallography,[26] and a *cis* relationship



Scheme 3. The domino process leading to compounds **12**.

Table 4: Scope of the domino process leading to compounds **12**.[a]

Entry	R^1	R^2	R^3	Yield [%][b]
1	Bn	2-thienyl	*n*Bu	**12a**: 56
2	Bn	2-thienyl	Bn	**12b**: 53
3	3,4-$(OMe)_2C_6H_3CH_2$	Ph	*n*Bu	**12c**: 48
4	*i*Bu	Ph	*n*Bu	**12d**: 52
5	2-furyl	2-thienyl	Bn	**12e**: 52
6	phenethyl	2-thienyl	Bn	**12f**: 55
7	2-$ClC_6H_4CH_2$	2-furyl	*c*Hex	**12g**: 50
8	2,6-$Cl_2C_6H_3CH_2$	2-furyl	Bn	**12h**: 54

[a] Reaction conditions: see Scheme 3. [b] Yield of isolated product.

between the hydroxy, hydrogen and methyl groups on the bicyclic junction was confirmed. This enticing finding was not completely surprising as fused five-membered ring bicyclic species are in fact well-known to be preferentially assembled in the *cis* form, and high diastereoselectivity during formation of such polycyclic systems through similar nucleophilic mechanisms is not unprecedented.[27] A crystal structure in the form of two hydrogen-bonded enantiomeric units of **12a** confirmed the product structure. Separation of the two optical isomers was performed by analytical HPLC using a chiral stationary phase,[28] and the ease of the method paves the way to the possibility of recovering optically pure **12** upon running the separation on a preparative scale.

In summary, we have developed a novel and first-in-class MCR-based methodology, which exploits post-Ugi aldol condensations to gain access to unique and densely substituted heterocycles. During further elaboration, final products were accessed through a series of unprecedented one-pot cascade reactions, thus assembling scaffolds of high complexity in non-obvious, yet operationally friendly ways. Subsequent efforts will be aimed at the application of these strategies toward the total synthesis of natural products.

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