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Highly Substituted Pyrrolidinones and Pyridones by 4-CR/2-CR Sequence

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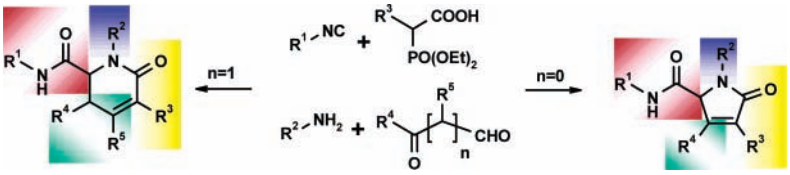
ABSTRACT



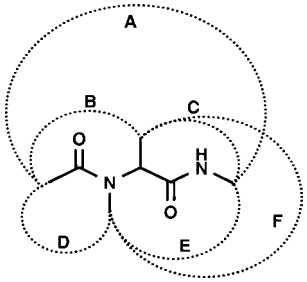
By combining a Ugi four-component reaction of isocyanides, phosphonoacetic acids, primary amines, and glyoxals or alternatively 3-keto aldehydes with a subsequent Wittig ring-closing reaction (using the Horner/Wadsworth/Emmons variant (HWE)), highly substituted 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid amides and 6-oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid amides can be assembled, respectively. The corresponding tandem of a Passerini reaction on 3-keto aldehydes and subsequent Wittig ring closure does not afford the expected six-membered 6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid amides but instead leads to the formation of 4-oxo-pent-2-enoic acid amides via an elimination route.

Heterocycles are among the most important structural classes of chemical substances and are particularly well-represented among natural products and pharmaceuticals. It is estimated that far more then 50% of the published chemical literature concerns heterocyclic structures. One striking structural feature inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in a defined three-dimensional representation, thereby allowing for far less degrees of conformational freedom than the corresponding conceivable acyclic structures. In addition, as a result of the presence of heteroatoms such as O, N, and S, heterocycles often exhibit altered absorption, distribution, metabolism, and excretion properties.

An especially effective and fruitful way to synthesize heterocycles is by isocyanide-based MCR.[1] This strategy relies mostly on the classical Passerini and Ugi reactions. All isocyanide-based MCRs are highly compatible with a range of ancillary functional groups not taking part in the initial MCR. Of particular relevance to heterocycle synthesis is the planned possibility that such functional groups can then be utilized in a secondary reaction to enable ring closure through various methodologies.

Theoretically, the combinations of the functional groups of the classical Ugi reaction utilizing bifunctional educts allow the construction of six topologically different cyclic scaffolds (Scheme 1). Thus, for example, one can distinguish between intramolecular variations wherein two functional

Scheme 1. Intramolecular Isocyanide-Based MCRs, via Bifunctional Starting Materials



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(1) For comprehensive reviews, see: Maccarchini, S.; Torroba, P. *Org. Prep. Proc. Intl.* **1993**, *25*, 141. Dömling, A.; Ugi, I. *Angew. Chem., Intl. Ed.* **2000**, *39*, 3168.

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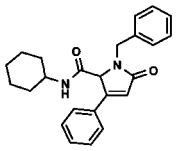
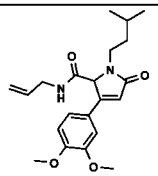
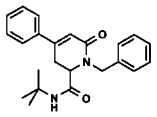
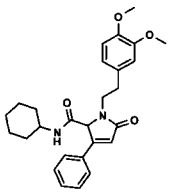
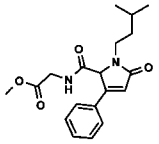
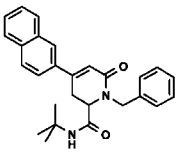
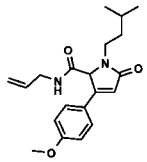
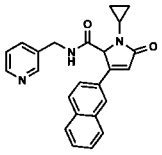
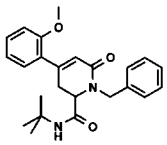
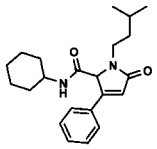
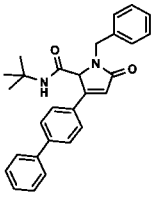
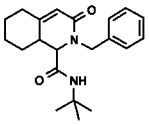
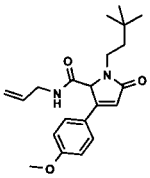
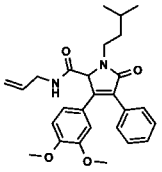
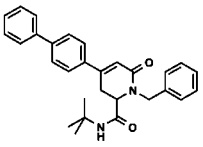
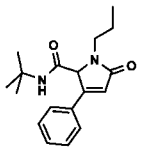
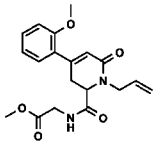
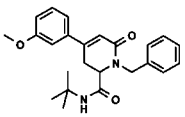
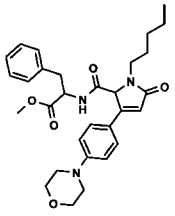
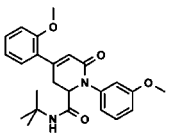
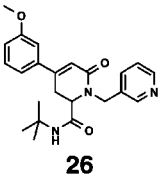
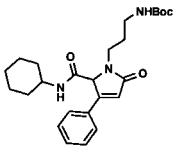
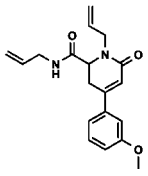
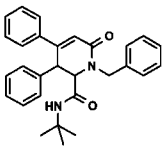
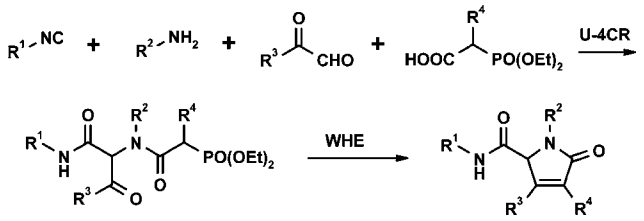
Table 1. Some Produced Substituted 5-Oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid Amides and 6-Oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic Acid Amides[b]

product	yield [%]	product	yield [%]	product	yield [%]
 **5**	24	 **13**	78	 **2**	94
 **6**	34	 **14**	7	 **21**	17
 **7**	18	 **15**	81	 **22**	66
 **8**	16	 **16**	95	 **23**[a]	27
 **9**	76	 **17**	20	 **24**	14
 **10**	25	 **18**	12	 **25**	70
 **11**[a]	23	 **19**	14	 **26**	24
 **12**	26	 **20**	64	 **27**	10

[a] Mixture of diastereomers. [b] Total yields over both steps are given.

Scheme 2. Two-Step Sequence toward Substituted 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylic Acid Amides



groups participating in a MCR are both present in the same molecule versus cases wherein a molecule bears one functional group necessary for the MCR plus a second functional group for a ring-forming reaction. Of these intramolecular possibilities, four have been already realized: cyclic amides, e.g., cyclic hexapeptides **A**, five- to nine-membered (benzo-)-lactams **B**, β-lactams and γ-lactames **D**, and cyclic Schiff bases **F**, whereas amino isocyanide and keto isocyanide derived **C** and **E**, respectively, are still to be explored.[2]

Recently we communicated that glyoxals, phosphono acetic acids, and isocyanides can be utilized to assemble 5-aminoacetylbutenolides in a very versatile and efficient manner by a combination of Passerini and HWE reactions.[3] Herein we want to introduce two more heterocyclic chemotypes, which can be assembled utilizing a Ugi/HWE tandem strategy.

We observed that isocyanides, primary amines, glyoxals, and phospono acetic acids react smoothly under ambient conditions in methanol to provide the corresponding Ugi products. The subsequent HWE reaction, when performed in THF at 0 °C utilizing LiCl and triethylamine as base, results in the formation of the corresponding 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid amides (Scheme 2). Some representative examples are shown in Table 1. During the course of a preliminary investigation of the scope and limitations of this strategy we realized that the use of substituted phosphono acetic acids considerably reduced the yields of the Ugi reaction.

All of the compounds were obviously obtained as racemic mixtures. An X-ray structure analysis of an intermediate Ugi product **1** not surprisingly reveals the α-keto aminoacyl moiety to be present in the enol form (Figure 1).

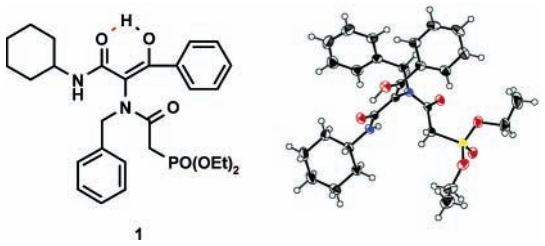
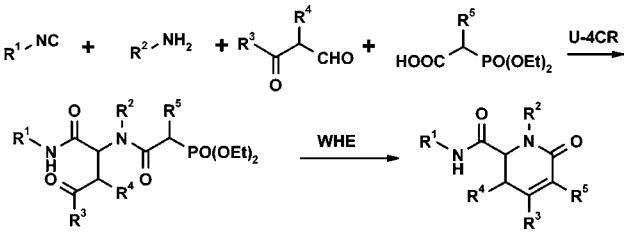


Figure 1.

We also proceeded to demonstrate that isocyanides, primary amines, β-keto aldehydes, and phosphono acetic acids react smoothly at ambient temperature in methanol to afford the corresponding Ugi products and, analogous to the strategy described above, to provide the six-membered substituted 6-oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid amides under HWE conditions (Scheme 3).

Scheme 3. Two-Step Sequence toward Substituted 6-Oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic Acid Amides



Representative examples of this reaction scheme are shown in Table 1. The identity of the products has been proven by spectroscopic means and in one case, **2**, by X-ray structure analysis (Figure 2). Again the reaction is versatile in the starting materials, comprising both aliphatic and aromatic compounds. As with the pyrrolidinones, we noticed that substituted phosphono acetic acids under the present reaction conditions reacted poorly.

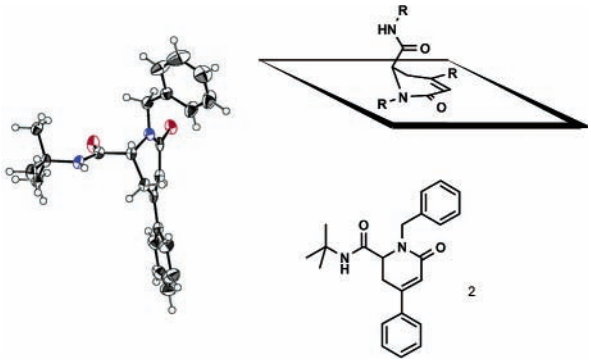
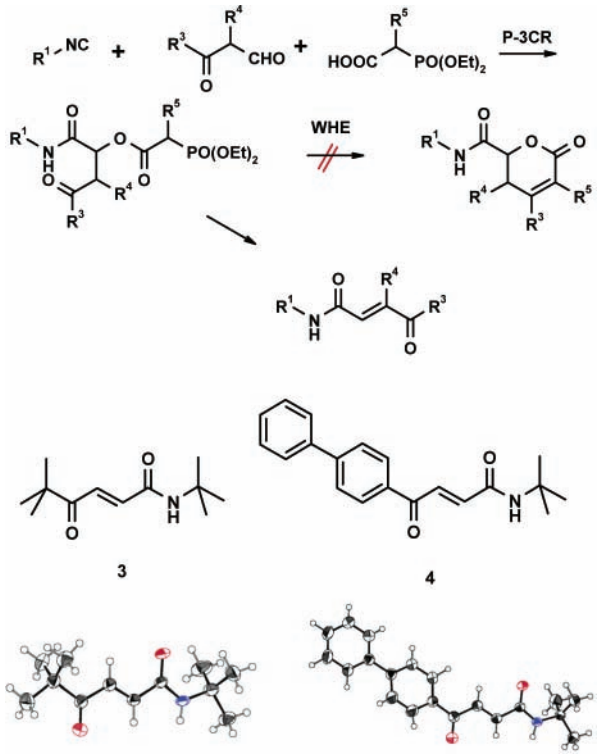


Figure 2.

(2) Isocyano carboxylic acids as educts, e.g.: (a) Gockel, G.; Lüdke, Ugi, I. In *Isonitrile Chemistry*; Ugi, I. Ed.; Academic Press: New York, 1971; p 159. Bossio, R.; Marcaccini, S.; Paoli, P.; Pepino, R. *Synthesis* **1994**, 672. Formyl(keto)carboxylic acids as educts, e.g.: (b) Gross, H.; Gloede, J.; Keitel, I.; Kunath, D. *J. Prakt. Chem.* **1968**, *37*, 192. Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591. β-Amino acids and peptides as educts, e.g.: (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810. Failli, A.; Immer, H.; Götz, M. *Can. J. Chem.* **1979**, *57*, 3257. Cyclic Schiff bases, e.g.: (d) Dömling, A.; Ugi, I. *Angew. Chem., Intl. Ed. Engl.* **1993**, *32*, 563. Dömling, A.; Ugi, I. Herdtweck, E. *Acta Chem. Scand.* **1998** *52*, 107. Unprotected isocyano amines with a primary or secondary amine are mostly unstable, but see, e.g., *p*-isocyano aniline: (f) New, R. G. A.; Sutton, L. S. *J. Chem. Soc.* **1932**, 1415. Kim, M.; Euler, W. B.; Rosen, W. *J. Org. Chem.* **1997**, *62*, 3766. Protected isocyano amines are known and very useful compounds, e.g., in PNA synthesis: (g) Dömling, A. *Nucleosides Nucleotides* **1998**, *17*, 1667.

(3) Beck, B.; Magnin-Lachaux, M.; Herdtweck E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875.

Scheme 4



In analogy to the above-described MCR/HWE strategy leading to the synthesis of pyridones, we were interested in further investigating the feasibility of formation of the corresponding oxo-counterparts, namely, 6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid amides (Scheme 4). Surprisingly, even though the Passerini intermediate could be detected in almost all reactions, the expected cyclized product arising from the HWE reaction was not obtained. Thus, we argued that under the basic reaction conditions an elimination reaction leading toward the highly conjugated 4-keto acrylic acid amides must be occurring. This hypothesis was proven by X-ray structure analysis of two crystalline products, **3** and **4** (Scheme 4).

In conclusion, we report here the first convergent assembly of five- and six-membered 5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid amides and 6-oxo-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid amides, respectively. The unoptimized overall yields for the two reaction steps are mostly below 50%. From the standpoint of array synthesis, the strategy described here has high potential utility. The needed starting materials are broadly commercially available or are easily synthesized.[4] The chemistry is easily adaptable to a 96-well plate synthesis format. In our hands, the quality of the products resulting from a filtration procedure through a 96-well filtration plate is mostly very high (>90% purity by NMR). As an added advantage, in many cases the products crystallize straight out of ethyl acetate.

Acknowledgment. This work is dedicated to Kris Venkat on the occasion of his 57th birthday.

Supporting Information Available: General procedure for the reactions and ^{1}H and ^{13}C NMR, X-ray, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035787N

(4) A versatile source of isocyanides: www.priaton.de