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The Solution Phase Synthesis of Diketopiperazine Libraries via the Ugi Reaction: Novel Application of Armstrong's Convertible Isonitrile.

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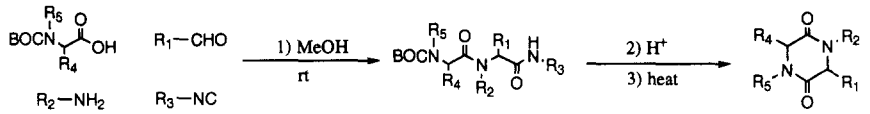
Abstract: This communication describes the generation of high-yielding solution phase diketopiperazine libraries via a '3-step, 1-pot' procedure, employing the Ugi multi-component reaction (MCR), followed by BOC deprotection and cyclization to diketopiperazine (DKP). Exploitation of Armstrong's convertible isonitrile in the Ugi reaction utilising an 'internal nucleophile' approach for diketopiperazine formation is presented.

Solution phase synthesis in combinatorial chemistry represents an attractive method for the rapid generation of large chemical libraries for new lead generation and/or lead optimization.[1] Several groups[2] have reported success in the production of both solution and solid phase libraries using as a starting point the Ugi MCR.[3] Templates generated from exploitation of this versatile 4-component reaction include benzdiazepines,[4] pyrroles,[5] lactams,[6] hydantoins,[3,7] and tetrazoles.[3] Recently, solid phase approaches to DKP library generation via the Ugi reaction[8] and other procedures[9] have appeared, prompting the report herein on a complementary high-yielding solution phase approach.



Scheme 1 : General reaction for DKP synthesis

The general reaction scheme for solution DKP formation is shown above. Equal amounts (0.1ml) of 0.1 M solutions of the four Ugi inputs were used to generate a theoretical 10 μmol of final DKP product in a 96-well plate format. Reagents were transferred into a 96-well plate using a Quadra 96® (Tom-tech) dispensing system. The 4- component condensation step was performed in MeOH at room temperature and the solvent evaporated *in vacuo* at 65 °C.[10] The deprotection/cyclization step was achieved using a 10% solution of TFA in dichloroethane (400 μl/well) at room temperature. The solvent and excess acid were removed via evaporation *in vacuo* at 65 °C.[10] Optimal yields of diketopiperazine were obtained with Ugi products incorporating the so-called 'convertible isonitrile' (cyclohexenyl isonitrile) pioneered by Armstrong et al.[11] These reactions were analyzed by lc/ms giving Area % (A%) yields which corresponded well with scaled up isolated yields of diketopiperazine product. It is

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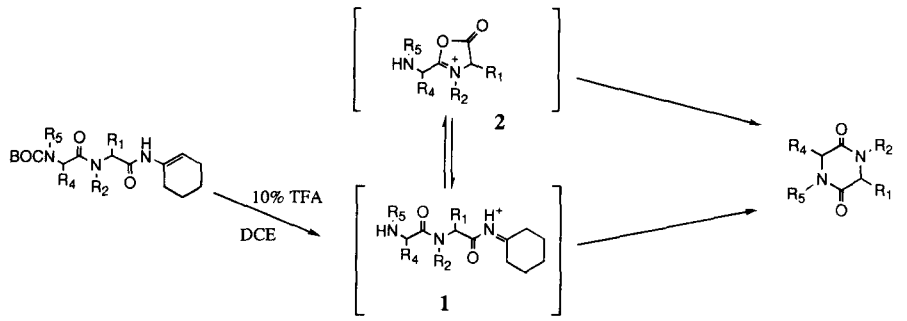
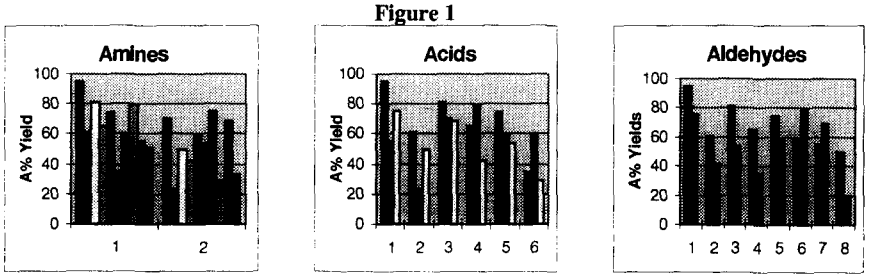
suggested that following removal of the BOC group, cyclization of the newly deprotected amine proceeds via the intermediacy of the N-acyliminium ion, **1**, and/or the corresponding munchnöne, **2**, as suggested by Armstrong in his elegant synthesis of benzodiazepine-2,5-diones.[12]



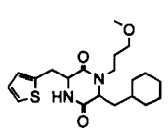
Scheme 2

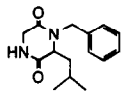
Complete disappearance of the initial Ugi condensation product is observed in every example. Lc/ms A% yields[13] for the 3-step conversion for a range of examples taken from a 96-well plate are shown in the three bar graphs below, Figure 1. The 96-well plate was produced in a 2 (RNH_2) x 6 (RCO_2H) x 8 (RCHO) x 1 (RNC) format with the numbers on the x-axis corresponding to a particular component. For example lc/ms A% yields of 3 wells, containing acid 4 as an initial Ugi component, are represented by 3 bars. Similarly 10 wells, represented by 10 bars were analysed for the final DKP product containing amine 2.

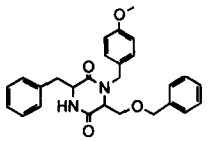
Figure 1



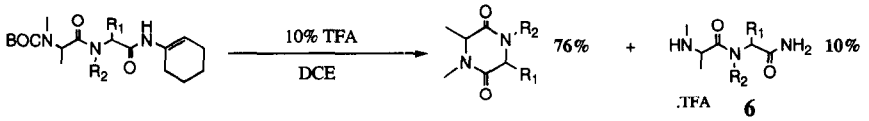
The reaction is general for both a range of commercially available aldehydes [e.g., aldehydes with attached ester, heteroaryl, aryl, amido, thioalkyl, alkyl & cycloalkyl functionality], primary amines [e.g., with attached hydrogen (i.e. NH_3), alkyl, aryl, heteroaryl, acidic and basic functionality] and *N*-BOC-α-amino acids (see Table 1). Area % yields of DKP ranged from 20% to 95% and resembled very closely yields of their corresponding Ugi precursors. The requirements for high yielding Ugi reactions have been previously reported.[3] Three specific examples, **3**, **4** and **5**, are presented along with yields.


3 : 78%


4 : 65%

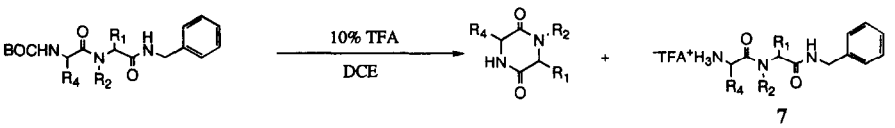

5 : 43%

A fourth point of diversity may be added to the reaction product by using *N*-substituted *N*-BOC α-amino acid inputs. This is exemplified by the high yielding conversion of an *N*-methylated α-amino acid as shown in Scheme 3.[14] The carboxamide side product **6** is presumably formed by hydrolysis of the intermediate *N*-acyliminium ion **1** produced on enamide protonation. Such by-products have been reported before for Ugi reactions employing the convertible isonitrile.[4,15]



Scheme 3

In an attempt to find an alternative and commercially available reagent to cyclohexenyl isonitrile, a series of isonitriles were investigated for their ability to form DKP's under similar reaction conditions. In general, a propensity for DKP formation was observed for benzyl isocyanide, *n*-butyl isocyanide and diethyl isocyanomethyl phosphonate whereas the more sterically hindered isonitriles, namely cyclohexyl, isopropyl or 1,1,3,3-tetramethylbutyl isocyanides showed only trace amounts of the desired DKP. Results for benzyl isocyanide, Scheme 4, are shown in Table 1 in combination with seven different *N*-BOC-α-amino acids.



Scheme 4

N-BOC-AMINO ACID	Ugi A% Yield	A% Yield of DKP	A% Yield of 7
Glycine	92%	20%	63%
L-Alanine	92%	18%	63%
2,2-Dimethylglycine	86%	51%	0%
L-Phenylalanine	79%	36%	30%
L-2-Phenylglycine	72%	14%	53%
L-Proline	90%	0%	64%
2,2-Cyclopropaneglycine[16]	75%	50%	0%

Table 1

In each case the Ugi reaction proceeded in good yield (72 - 92%).[14] Most promising DKP conversions were generally observed for the two di-substituted glycine derivatives (≥ 50%). Interestingly in both cases no uncyclized deprotected amine was detected. No diketopiperazine formation was observed with proline. The

remaining amino acids gave DKP yields from 14 to 36%. For each example the mass balance was accounted for by the yield of deprotected amine **7**. It remains to be seen if conditions can be developed to provide improved alternatives to cyclohexenyl isonitrile.

In summary, the present investigation reveals a novel application of the Ugi reaction and the so-called 'convertible isonitrile' for the generation of solution phase diketopiperazine libraries. The relative simplicity of solution phase production protocols over solid phase, and the generally good yields, make this a highly attractive procedure.

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