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Applications of *N*-BOC-Diamines for the Solution Phase Synthesis of Ketopiperazine Libraries Utilizing a Ugi/De-BOC/Cyclization (UDC) Strategy

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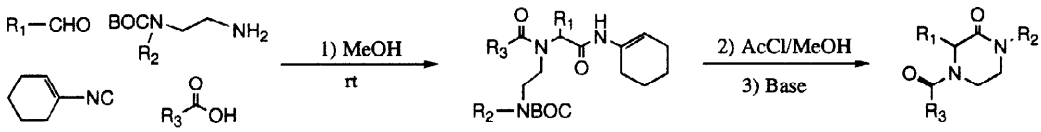
Abstract: This communication reveals a novel application of the 'so-called' convertible isonitrile for the solution phase generation of ketopiperazine libraries. Use of mono N-BOC diamines in the Ugi multi-component reaction (MCR), followed by BOC removal and base treatment (a '3 step, 1-pot procedure') affords ketopiperazines in good yield. The generality of this procedure was further explored revealing novel routes to dihydroquinoxalinones and 1,4-benzodiazepines respectively

The emergence of combinatorial chemistry over the last decade has lead to a renaissance in the study of the multi-component reaction (MCR).[1] Such reactions are powerful tools for producing libraries of compounds containing a common core template, where products are generally formed in a single step displaying functionality from the 3 or more individual reaction components. Efforts in this laboratory are currently focussing on the solution phase synthesis of conformationally constrained Ugi[2] derivatives, specifically employing the so-called Ugi/De-BOC/Cyclization (**UDC**) strategy in a '3 step, 1 pot procedure' recently reported by this group for the preparation of high yielding solution phase libraries of diketopiperazines[3] and 1,4-benzodiazepine-2,5-diones[4] respectively. This paper describes the continuation of this work disclosing the novel synthesis of ketopiperazines[5], Scheme 1, and production of subsequent libraries in a 96-well plate format. Reports of the biological utility of ketopiperazines have appeared in several areas, including applications as antagonists of the platelet glycoprotein IIb-IIIa,[6a] substance P[6b] and as hypocholesteremic agents.[6c]



Scheme 1 : General reaction for Ketopiperazine synthesis

A simplified experimental procedure was followed adding each reagent in order of it's participation in the Ugi reaction mechanism. Equal amounts (0.1 ml) of 0.1 M solutions of the four components were employed generating a theoretical 10 μmol of final ketopiperazine product for 100 % conversion. The 4-component condensation was performed in methanol at room temperature and the solvent evaporated at 65 °C.[7] The deprotection/cyclization steps were performed using a 10 % solution of acetyl chloride in methanol, and a 5%

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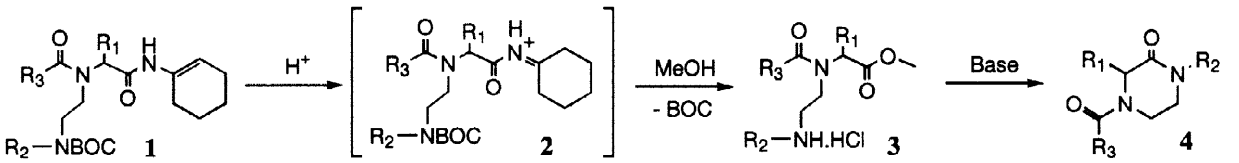
solution of diethylamine in dichloroethane respectively [Note : 10-15 mg of N,N-(diisopropyl)amino-methylpolystyrene (PS-DIEA) is an excellent resin bound alternative to diethylamine]. Solvents were then evaporated at 65 °C. Both area % (A %) yields, determined by lc/ms (UV 220 nm),[8] and isolated yields of specific examples **5**, **6** and **7** are reported in Table 1. A more detailed description of the mechanism of ketopiperazine formation is described in Scheme 2. Specifically, reaction of *N*-mono-BOC diamines and 1-isocyanocyclohexene[9] (the convertible isonitrile) in the Ugi MCR produces the Ugi product with general structure **1**. Subsequent '1 pot' acid catalysed deprotection and conversion to methyl ester **3**, presumably proceeding via the *N*-acyliminium ion intermediate **2**, and base treatment promotes cyclization to the ketopiperazine template **4**, with yields for the overall procedure (4 synthetic steps) ranging from 30 to 97% for the 12 examples reported in this letter. Interestingly, substantial cyclization of the *N*-phenyl diamine to **12**, was observed before base treatment, presumably due to the lower pka of aniline-like amines.



Scheme 2

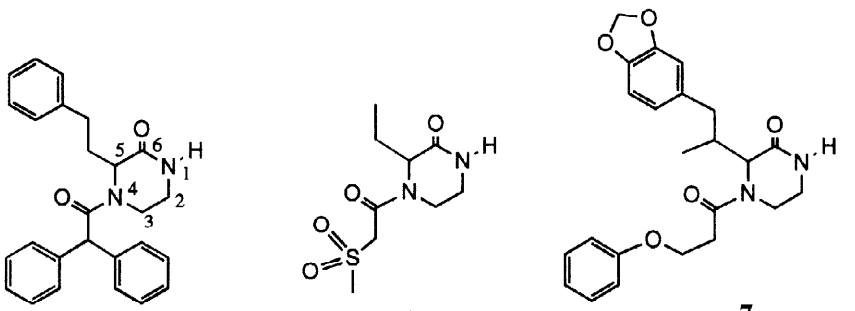


TABLE 1

Entry	4 Isol. %[a]	4 Area %[b]	4 Area %[c]	3 Area %[d]
5	55%	65%	77%	63%
6	75%	81%	97%	60%
7	70%	79%	92%	80%

a Isolated yield of ketopiperazine **4** from 0.3mmol scale reaction. **b** Area % yield of ketopiperazine from 0.3mmol scale reaction. **c** Area % yield of ketopiperazine from 10μmol scale reaction. **d** Area % yield of methyl ester **3** from 10μmol scale reaction.

The reaction is also amenable to scale-up with isolated yields similar to A % yields.[10] For examples **5**, **6** and **7** respectable isolated yields of 55%, 75% and 70% were obtained. **Figures 1** (compound **5**), **2** (compound **6**) and **3** (compound **7**) represent the hplc analysis (UV 220nm) of ketopiperazines prepared in a 10 μmol scale reaction. The major peak in each case corresponds to the ketopiperazine product. The reaction is general for a range of

Figure 1

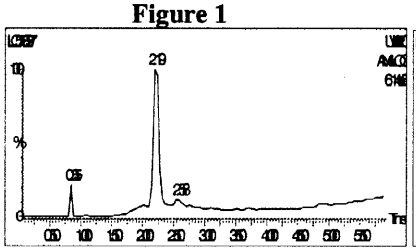


Figure 2

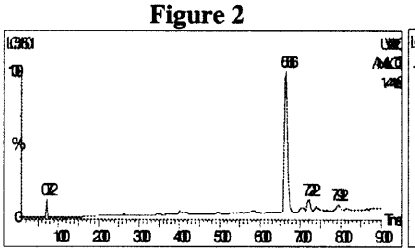
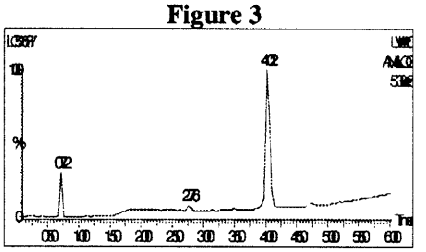
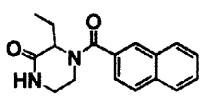


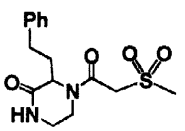
Figure 3



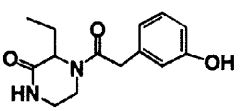
commercially available aldehydes [e.g. aldehydes with attached ester, heteroaryl, aryl, amido, thioalkyl, alkyl & cycloalkyl functionality] and acids [e.g. with attached alkyl, aryl, heteroaryl, acidic and basic functionality]. The lc/ms A % yields taken from one 96-well plate [8 (R_1CHO) x 12 (R_3CO_2H) format] utilising this chemistry are presented below. The *N*-BOC diamines used to exemplify the potential diversity of ketopiperazines at R_2 were synthesised according to a literature procedure by Krapcho et al.[11] Further examples of alternative diamines employed in this methodology show the accessibility of previously unreported dihydroquinoxalinone, **15**, and 1,4-benzodiazepine, **16,** core structures in reasonable yield.



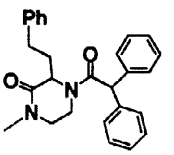
8 77%



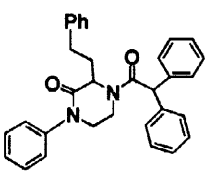
9 77%



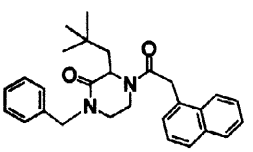
10 69%



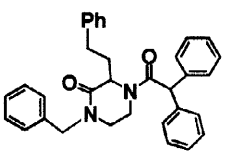
11 83%



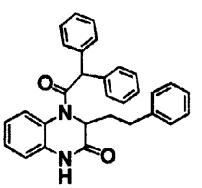
12 70 %



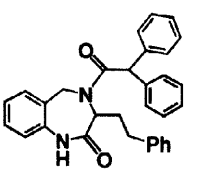
13 80%



14 85%



15 66%



16 30%

In summary, a high yielding solution phase synthesis of ketopiperazines has been reported. The mono *N*-BOC protection strategy and their reaction in the Ugi condensation followed by '1 pot' deprotection and base facilitated cyclization to ketopiperazine is amenable to both scale-up and solution phase library synthesis in a 96-well plate format. The generality of combining *N*-BOC diamines with a UDC strategy was also investigated, allowing novel and efficient syntheses of both dihydroquinoxalinones, **15**, and 1,4-benzodiazepines, **16**,

respectively. The facile production protocol of this approach, coupled with high yields, further enhances the general appeal of this procedure.

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References and Notes

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7. Performed in a SAVANT® evaporator for 2 hours.
8. Lc/ms analysis was performed using a C18 Hypersil BDS 3u 2.1 x 50 mm column (UV 220nm) with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 5 min. HPLC was interfaced with APCI techniques.
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10. Stoichiometric amounts (2 ml) of 0.1 M solutions of the four Ugi components were combined and stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was dried under high vacuum. A 10% solution of AcCl in MeOH (8 ml) was added to the crude material and stirred at room temperature overnight. The solvent was evaporated in vacuo. A 5% solution of diethylamine in dichloroethane was then added to the crude material and the solution shaken overnight at room temperature. The solvent was evaporated in vacuo and crude material pre-absorbed onto flash silica and purified by column chromatography to yield the desired ketopiperazine, **5**, (44 mg, 55%) as a white solid : mp 188-190°C. For major conformer only: $^1H(CDCl_3)$ 7.90 (1H, s, NH), 7.10-7.40 (15H, m, C_6H_5 x 3), 5.60 (1H, s, CHC_6H_5), 4.78- 4.83 (1H, m, $CHCH_2$), 4.05-4.12, 3.31-3.40 (2H, 2x m, CH_2N), 2.98-3.02, 2.80-2.88 (2H, 2x m, CH_2N), 2.50-2.60 (2H, m, $CH_2C_6H_5$), 1.90-2.00, 2.03-2.10 (2H, CH_2). For major conformer only: ^{13}C ($CDCl_3$) 170.2, 168.7, 141.4, 139.8, 128.7, 128.4, 128.3, 126.7, 125.8, 54.5, 53.0, 39.2, 32.9, 31.7. IR (KBr disc) 3260m, 1641s, 1620s (selected peaks only). mspec (APCI) 399 (MH^+), 371. ^1H and ^{13}C assignments have been obtained from ^1H, ^{13}C, DEPT, COSY, HMQC and HMBC experiments. The ^1H and ^{13}C spectra show two sets of resonances throughout the spectrum. Exchange crosspeaks between major and minor forms were observed in a rotating frame Overhauser effect spectroscopy (ROESY). These resonances also show broadening at temperatures above 80°C. These experiments show that the two forms are in slow exchange under the present experimental conditions. HMBC spectrum showed correlation between the methylene protons(H2 and H2') with the carbonyl carbon C6 confirming the ring closure.
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