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# MCC/$S_NAr$ methodology. Part 2: Novel three-step solution phase access to libraries of benzodiazepines

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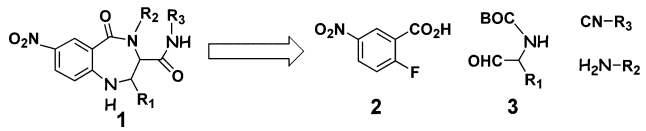
**Abstract**—New developments in the search for novel pharmacological agents over the last decade have focused on the preparation of chemical libraries as sources for new leads for drug discovery. To aid this search a plethora of personal synthesizers and new automation technologies have emerged to help fuel the lead discovery engines of drug discovery organizations. In fact, multi-step solid-phase syntheses of diverse libraries in excess of 10,000 products are now feasible via split and mix techniques. At the same time, a multitude of more efficient, diversity or target oriented solution phase chemical methodologies have appeared in the chemical literature, which have enabled the relatively facile construction of successful lead generation libraries with low FTE input and little capital expenditure. This communication reveals a further application of *N*-BOC-α-aminoaldehydes in the Ugi condensation reaction, followed by a secondary $S_NAr$ cyclization, accessing arrays of biologically relevant benzodiazepines in good yield and overall purity. 

Multi-component reactions (MCR) are widely employed for the rapid assembly of arrays with high molecular diversity.[1] Coupled with a post-condensation modification, their utility is increased even further, giving rise to numerous complex, pharmacologically relevant templates. *N*-BOC-α-aminoaldehydes in particular have proven to be valuable reagents for both the Ugi[2,3] and Passerini[4] condensations enabling secondary reactions to ultimately constrain or improve 'drug-likeness' of the initial flexible peptide-like product. Synthetic applications include novel routes to norstatines,[5] imidazolines,[6] fused 7,5-azepine-tetrazoles[7] and cyclic ureas.[8] Similarly, $S_NAr$ chemistry of polymer bound 4-fluoro-3-nitrobenzoic acid has seen a resurgence of interest and multiple applications in lead discovery circles have been reported, allowing for example the preparation of arrays of dihydroquinoxalinones,[9] benzimidazoles,[10] indoles,[11] benzodiazepines,[12] benzothiazepines[13] and macrocycles,[14] respectively. Thus, it was envisioned that combining the Ugi condensation of *N*-BOC-α-aminoaldehydes with a post-condensation $S_NAr$ cyclization, via use of an internal amino group, would facilitate access to benzodiazepine cores with generic structure **1**, Scheme 1.

Final target molecules contain three initial points of diversity with room for additional functionalization via modification of the nitro group. 2-Fluoro-5-nitrobenzoic acid **2** was selected as the electrophilic component of this reaction and its compatibility with Ugi reaction conditions has been previously shown.[15] Simply mixing **2** with *N*-BOC-α-aminoaldehydes gives the desired condensation product **4** in good yield. The use of aldehydes derived from alanine and phenylalanine are exemplified in this article. Purification is possible at this stage by the use of scavenging resins PS-$TsNHNH_2$ and PS-DIEA which remove excess aldehyde and any unreacted acid.[16] TFA mediated BOC removal and treatment with the proton scavenger PS-morpholine enables cyclization to the benzodiazepine **1**, Scheme 2.

In fact, such a route represents a further example of UDC (Ugi/De-BOC/Cyclize) methodology.[17] Three examples of products isolated as diastereomers and associated yields are shown in Figure 1 and these correlate well with A% (Area%) purities.[18]




**Scheme 1.**

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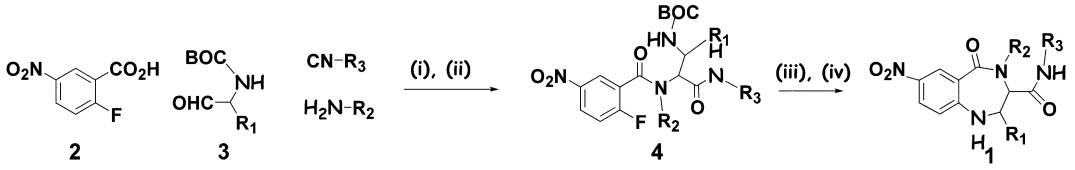


**Scheme 2.** *Reagents and conditions*: (i) *N*-BOC-α-aminoaldehyde (2 equiv.), $R_2NH_2$ (1 equiv.), $R_3NC$ (1 equiv.), **2** (1 equiv.), MeOH, rt, 48 h; (ii) PS-tosylhydrazine (3 equiv.), PS-diisopropylethylamine (3 equiv.), THF:$CH_2Cl_2$ (1:1), 24 h; (iii) 20% TFA/$CH_2Cl_2$, 4 h; (iv) PS-morpholine (3 equiv.), DMF, 36 h.

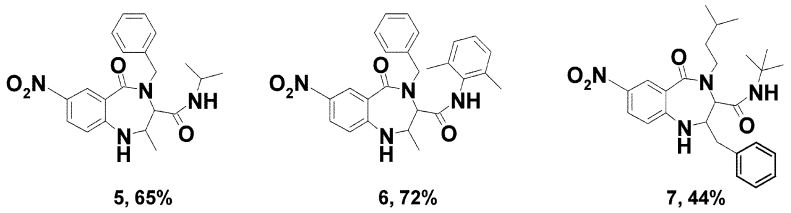
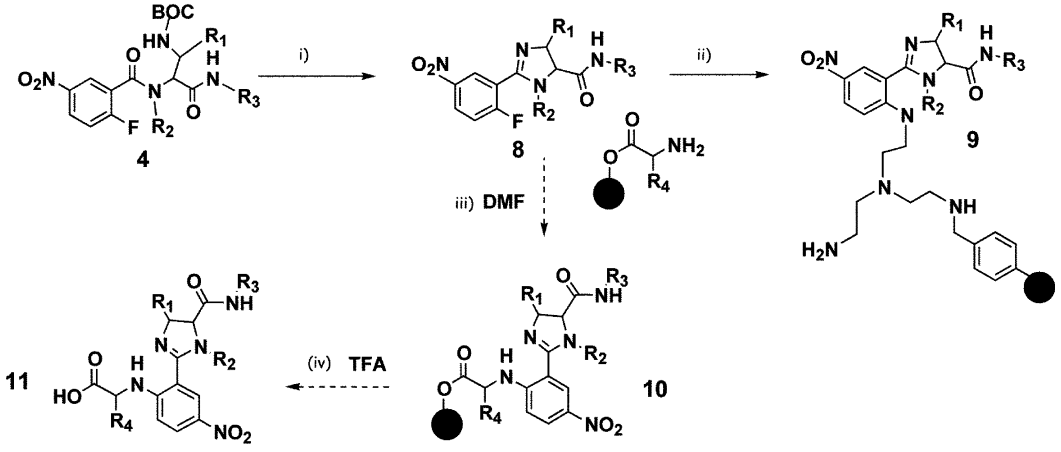


**Figure 1.**

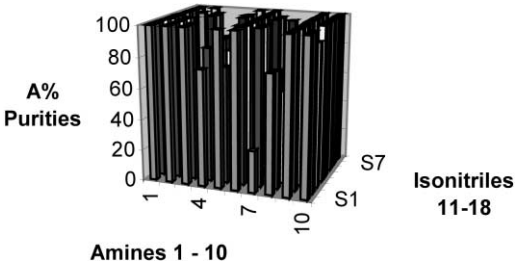


**Scheme 3.** *Reagents and conditions*: (i) **4**, TFA, dichloromethane, 24 h; (ii) PS-trisamine, THF:DCE, 1:1; (iii) Wang bound α-amino acid, DMF, PS-DIEA; (iv) 20% TFA/$CH_2Cl_2$, 4 h.

Interestingly, a major side product was detected after BOC removal. Analysis of the product revealed a competing acid-catalyzed cyclization to give imidazolines **8** as shown in Scheme 3. An identical approach for the preparation of imidazoline libraries has been previously reported.[6] The amount of imidazoline formed during this reaction was substantially minimized by evaporation of the TFA/DCM solvent at low temperature. Any subsequently formed side product was then easily removed by scavenging with PS-trisamine to give the immobilized product **9**. Resin capture of **8** with Wang bound α-amino acids to potentially give **10** and subsequent deprotection giving **11** is currently under investigation.

Encouraged with the initial isolated yields of BDP **1** the protocol was adapted to 96-well plate production status.[19] An 80 member array of benzodiazepines was thus successfully prepared in a Whatman plate, dispensing and filtering operations being performed by a Quadra96 (Tom-tech) and Rapid Plate 96 (Zymark). The following selection of reagents were utilized in a 1 (aldehyde)×1 (acid)×8 (isonitriles)×10 (amines) array. Tables 1–3 represent: (a) final A% purities of BDP **1** after PS-trisamine scavenging. (b) A% purities of BDP **1** directly prior to tris-amine scavenging. (c) A% purities of observed imidazoline side product prior to removal.

**Table 1.**



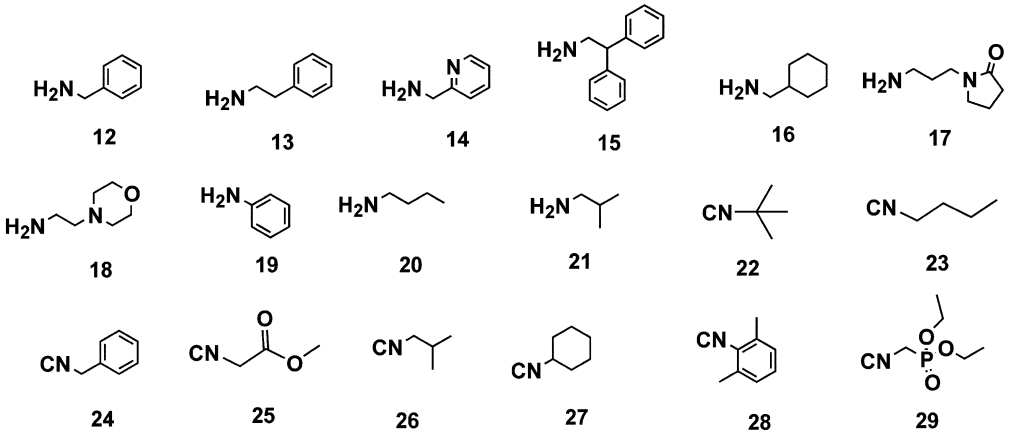



**Table 2.**

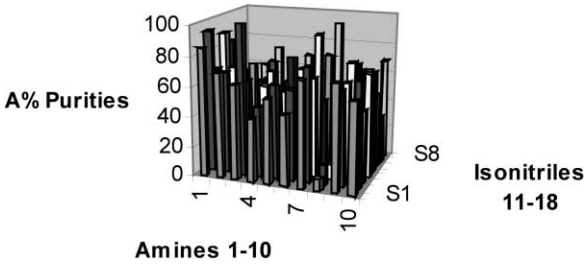
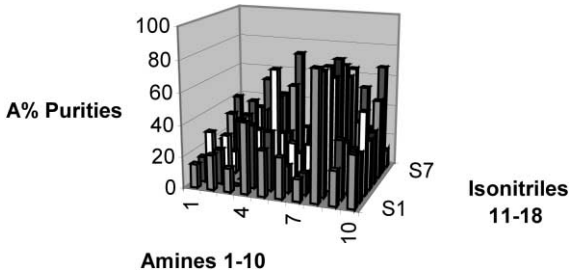



**Table 3.**




Impressively, post-scavenging purities of BDP **1** averaged 93% (as judged by LC/MS, UV215 nm).[20] Pre-scavenging, the relative ratio of BDP **1** to imidazoline was 2:1. The majority of reagent inputs behaved similarly; however, it was evident that imidazoline formation was favored with the use of aniline (Av. A% 72%).

In conclusion, this communication has revealed a new utility for post-condensation transformations of the Ugi product involving $S_NAr$ methodology, enabling facile and rapid access to high purity arrays of benzodiazepines. Current studies are now focusing on potentially higher yielding solid-phase approaches to this methodology, coupled with nitro group reduction and functionalization.

## Acknowledgements

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## References

1. For two reviews, see: (a) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *3*, 366; (b) Domling, A. *Combinatorial Chemistry & High Throughput Screening* **1998**, *1*, 1.
2. (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8; (b) Ugi, I.; Steinbruckner, C. *Chem. Ber.* **1961**, *94*, 734; (c) Ugi, I.; Domling, A.; Horl, W. *Endeavor* **1994**, *18*, 115.
3. Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
4. (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126; (b) Gokel, G.; Ludke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; p. 145.
5. (a) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769; (b) Semple, J. E.; Rowley, D. C.; Brunck, T. K.; Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 315; (c) Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985; (d) Jones, W.; Tadesse, S.; Chenera, B.; Viswanadhan, V.; Hulme, C. A. C. S. 223rd, American Chemical Society Meeting & Exposition, April 2002, New Orleans; (e) Nixey, T.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 6833.
6. Hulme, C.; Ma, L.; Romano, J.; Morrissette, M. *Tetrahedron Lett.* **1999**, *40*, 7925.
7. Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681.
8. Hulme, C.; Ma, L.; Romano, J.; Morton, G.; Tang, S.-Y.; Cherrier, M.-P.; Choi, S.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883.
9. Morales, G. A.; Corbett, J. W.; Degrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172.
10. (a) Phillips, G. B.; Wei, G.-P. *Tetrahedron Lett.* **1996**, *37*, 4887; (b) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185.
11. Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799.
12. Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060.
13. Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 2219.
14. Kiselyov, A. S.; Smith, L.; Tempest, P. *Tetrahedron* **1999**, *55*, 14813.
15. (a) Tempest, P.; Ma, V.; Kelly, M.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959; (b) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079.
16. Purchased from Argonaut® technologies.

17. For a review of UDC methodology, see: Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
18. LC/MS analysis was performed using a C18 Hypersil BDS 3μ 2.1×50 mm column with a mobile phase of 0.1% TFA in $CH_3CN/H_2O$, gradient from 10% $CH_3CN$ to 100% over 15 min. HPLC was interfaced with APCI techniques.
19. For full experimental details of MCR production protocols, see: Hulme, C.; Bienayme, H.; Nixey, T.; Chenera, B.; Jones, W. J.; Tempest, P.; Smith, A. Library Generation via Post Condensation Modifications of Isocyanide Based Multi-Component Reactions, *Methods Enzymol.* **2003**, in press.
20. The following procedure was followed for the preparation of examples **5** and **6** shown below: A mixture of (1-methyl-2-oxo-ethyl)-carbamic acid tert-butyl ester (1.0 M, 2 mL in MeOH), benzyl amine (0.5 M, 2 mL in MeOH), isonitrile (0.5 M, 2 mL in MeOH) and 2-fluoro, 5-nitro benzoic acid (0.5 M, 2 mL in MeOH) were stirred at room temperature for 48 h. The reaction mixture was dried, re-dissolved in 1:1 DCM:THF and 5 equiv. of PS-$TsNHNH_2$ and PS-DIEA were added and gently shaken for 18 h. The reaction was filtered and the solvent evaporated. A 20% TFA/DCM solution (10 mL) was added and the resulting mixture was stirred for 2 h before evaporated at room temperature. The resulting yellow oil was dissolved in DMF and 5 equiv. of PS-DIEA was added and the reaction mixture shaken for 14 h. PS-Trisamine (5 equiv.) was added and gently shaken for 14 h to remove any dihydroimidazole side products. The reaction was filtered and the solvent evaporated in vacuo. The crude oil purified by Gilson chromatography to yield **5**, (246 mg, 61%, 2:1 ratio of diastereomers as judged by $^1$H NMR) and **6**, (242 mg, 53%, 3:1 ratio of diastereomers as judged by $^1$H NMR), respectively, as yellow solids. Experimental data for two examples: **5**: $^1$H NMR (DMSO-$D_6$): $\delta$ 8.94 (1H, m), 8.41–7.91 (2H, m), 7.60–7.28 (6H, m), 6.85–6.64 (2H, m), 4.97–4.85 (1H, m), 4.62–4.48 (1H, m), 4.26–4.14 (1.5H, m), 3.67 (1H, m), 3.48 (0.5H, m), 1.40 (2H, d, $J$=6.8 Hz), 0.92 (2H, d, $J$=6.6 Hz), 0.87 (1H, d, $J$=6.5 Hz), 0.81 (1H, $J$=6.5 Hz), 0.74 (1H, $J$=6.5 Hz), 0.62 (2H, d, $J$=6.6 Hz). $^{13}$C NMR (DMSO-$D_6$): $\delta$ 167.2, 166.8, 166.6, 165.7, 151.7, 150.6, 137.9, 137.4, 136.3, 136.1, 132.3, 129.7, 128.9, 128.8, 128.0, 127.8, 126.5, 126.1, 118.1, 117.8, 117.2, 116.0, 66.4, 65.0, 55.3, 54.2, 54.0, 50.8, 22.4, 22.2, 22.1, 20.5, 17.5. Calcd for $C_{21}H_{24}N_4O_4$: M=396, found: (M+1)+=397. **6**: $^1$H NMR (DMSO-$D_6$): $\delta$ 9.18 (1H, s), 8.98 (1H, d, $J$=3.0 Hz), 8.12 (1H, d, $J$=2 Hz), 7.96 (1H, dd, $J$=9.5, 3.0 Hz), 7.46 (2H, m), 7.36 (3H, m), 7.00–6.71 (4H, m), 5.23 (1H, d, $J$=15 Hz), 4.60–4.42 (2H, m), 3.56 (1H, m), 1.54 (8H, m), 0.96 (1H, d, $J$=6.8 Hz). $^{13}$C NMR (DMSO-$D_6$): $\delta$ 167.4, 166.9, 166.3, 165.9, 151.6,150.3, 137.7, 137.2, 136.5, 136.2, 135.9, 135.8, 135.2, 132.6, 132.5, 129.8, 129.0, 128.9, 128.0, 127.9, 127.1, 126.5, 126.3, 118.3, 118.0, 117.1, 66.7, 65.0, 55.5, 55.4, 54.5, 54.4, 50.8, 20.8, 18.3, 18.2, 17.8. Calcd for $C_{26}H_{26}N_4O_4$: M=458, found: (M+1)+=459.