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A tandem Petasis–Ugi multi component condensation reaction: solution phase synthesis of six dimensional libraries

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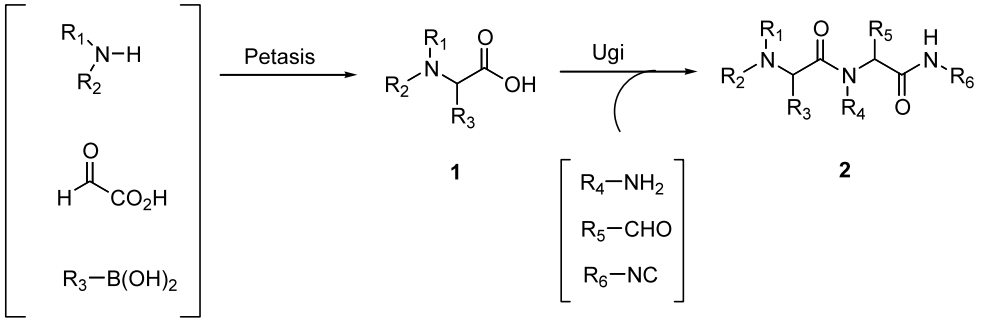
Abstract—Amino acids with three points of diversity generated from the Petasis boronic acid–Mannich reaction can be used as one of the four components of the Ugi condensation to prepare six dimensional libraries of dipeptide amides. © 2002 Published by Elsevier Science Ltd.

The rapid, automated synthesis of molecular diversity to fuel high throughput biological screening for lead generation as well as the synthesis of directed libraries for subsequent lead optimization has evolved into an effective strategy to accelerate drug discovery.[1] Indeed, during the past decade combinatorial chemistry has provided access to greatly expanded chemical collections of drug-like compounds using practical synthetic methods, which proceed in high yields and product purities.[2] Among the most useful methods, which have emerged to meet this synthetic challenge, are the multi component condensations (MCC),[3] due to their ability to efficiently generate large numbers of compounds in one or two synthetic steps. Examples of MCC reactions include the Ugi,[4] Passerini,[5] Biginelli,[6] and the Petasis boronic acid–Mannich reaction.[7] Most of these as well as other MCC have been used to generate combinatorial libraries useful for pharmaceutical discovery.[8]

Following a strategy in which two MCCs are used in tandem can lead to even greater diversity compared with either MCC alone. For example, if ten building blocks are used in a three-component condensation, 1000 distinct compounds are produced, but if a three component and a four-component condensation are used in tandem (producing in effect a six component



Scheme 1. Tandem Petasis–Ugi multi component condensation.

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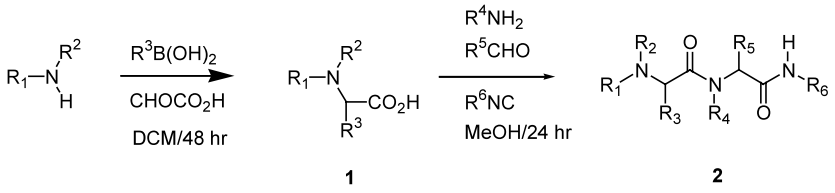
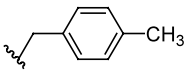
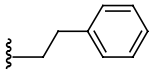
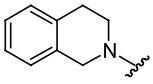
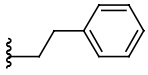
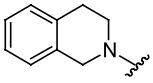
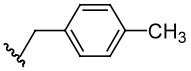
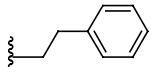
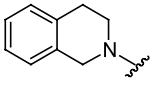
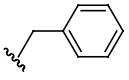
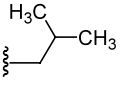
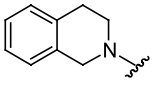
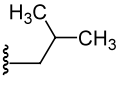
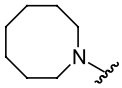
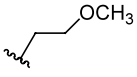
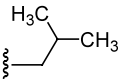
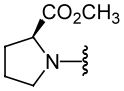
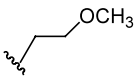
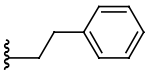
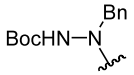
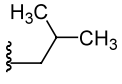
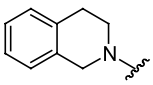
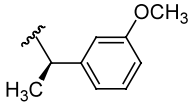
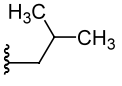
condensation), the number of distinct compounds increases to 1,000,000. In this context, we hypothesized that the Petasis boronic acid–Mannich reaction could be used to prepare carboxylic acids containing three points of diversity, and that these products could in turn be employed as one of the components of the Ugi reaction, subsequently leading to six dimensional libraries (Scheme 1).

Although there is precedent for combinations of MCC,[3,9] to our knowledge a tandem Petasis–Ugi MCC reaction (Pt3CC+U4CC = Pt-U6CC) has not been reported.[10] We first examined the practicality of a tandem Pt-U6CC by using commercially available *N*,*N*-dimethylglycine (**1a**, $R_1 = R_2 = CH_3$; $R_3 = H$) as a model Petasis amino acid substrate for the Ugi reaction. In spite of our concerns, that the tertiary amine present in **1a** could retard formation of the protonated imine necessary for the success of the Ugi reaction,[4] the desired product **2a** (Table 1) was obtained in 42% yield after purification. Encouraged by this result, **1b** was subsequently prepared via standard experimental conditions[7] (1 equiv. of each reaction component in DCM, room temperature, 48 h). After removal of DCM, crude **1b** was dissolved in MeOH and treated with the Ugi reaction components. Stirring for 24 h at

Table 1. Tandem Petasis–Ugi multi component condensation reaction



1 **2**

Compd	R^1	R^2	R^3	R^4	R^5	R^6	Yield[a]
2a	CH_3	CH_3	H			2,6-DMP[b]	42%
2b			PMP			2,6-DMP	54%
2c			PMP[c]			2,6-DMP	31%
2d			PMP			2,6-DMP	39%
2e			PMP				30%
2f			PMP			2,6-DMP	73%[d]
2g			PMP			2,6-DMP	32%
2h			PMP			2,6-DMP	39%
2i			PMP			2,6-DMP	40%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, HNMR, and CNMR; [b]2,6-dimethylphenyl; [c]para-methoxyphenyl; [d]1.25 eq. Petasis amino acid, R^4NH_2, and R^5CHO were used.

room temperature, produced the tandem Pt-U6CC product (**2b**) in 54% yield after purification. As expected, the product consisted of a 50:50 mixture of racemic diastereomers (LC-MS). The yield could be improved by using excess of all components relative to the isonitrile; e.g. **2f** was obtained in 73% yield by limiting 2,6-dimethylphenylisonitrile to 0.8 equiv.[11] In this example, the racemic diastereomers (1:1) were separated by preparative RP-HPLC and characterized by H, C NMR, and HRMS. Remarkably, isomer A (t_R = 8.4 min) is a low melting solid (mp 49–50) and exists in $CDCl_3$ as a 1:1 mixture of rotamers, but isomer B (t_R = 9.6 min) is a crystalline solid (mp 144–145) and exists in $CDCl_3$ as a single rotamer. Using an optically active amine for the Petasis boronic acid–Mannich reaction gave **1g** as a 70:30 mixture of diastereomers. Subsequent Ugi condensation provided **2g** in 32% yield and the same isomeric ratio. Hydrazines can also participate in the tandem Pt-U6CC (**2h**), which is consistent with our earlier observations.[10b]

In summary, we have demonstrated that the Petasis boronic acid–Mannich (three-component) condensation can be performed in tandem with the Ugi (four-component) condensation to provide access to six dimensional libraries using practical reaction conditions. This method expands considerably the synthetic versatility of multi-component condensations for the preparation of large, diversity-driven libraries for drug discovery. Application of this methodology to the preparation of low molecular weight heterocyclic scaffolds[10] will be reported in due course.

References

1. For reviews, see: (a) Golebiowski, A.; Klopfenstein, S. R.; Portlock, D. E. *Curr. Opin. Chem. Biol.* **2001**, *5*, 273; (b) Schreiber, S. L. *Science* **2000**, *287*, 1964; (c) *Modern Drug Discovery*, 1999, *July/August*, whole issue; (d) Dolle, R. E. *Mol. Diversity* **1998**, *3*, 199.
2. For leading references, see: (a) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, 2002; Vols. 1 and 2; (b) Sucholeiki, I. *High-Throughput Synthesis. Principles and Practices*; Marcel Dekker: New York, 2001; (c) Czarnik, A. W. *Solid-Phase Organic Synthesis*; Wiley Interscience: New York, 2001; Vol. 1.
3. (a) Ugi, I.; Heck, S. *Combi. Chem. HTS* **2001**, *4*, 1; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
4. (a) Ugi, I.; Domling, A.; Werner, B. *J. Heterocyclic Chem.* **2000**, *37*, 647; (b) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021 and references cited therein.
5. For example, see: (a) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943; (b) Beck, K.; Magnin-Lachaux, M.; Herdtweck, E.; Domling, A. *Org. Lett.* **2001**, *3*, 2875.
6. Kappe, C. O. *Accts. Chem. Res.* **2000**, *33*, 879 and references cited therein.
7. (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463; (b) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545.
8. Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Tetrahedron Organic Chemistry Series, Pergamon: New York, 1998; Chapters 1 and 4.
9. (a) Constabel, F.; Ugi, I. *Tetrahedron* **2001**, *57*, 5785; (b) Domling, A.; Herdtweck, E.; Ugi, I. *Acta Chem. Scand.* **1998**, *52*, 107.
10. The concept of a tandem Petasis–Ugi multi-component condensation has been disclosed by us previously, see: (a) CHIs Seventh Annual High Throughput Organic Synthesis Symposium, Portlock, D. E. 'Synthesis of Thematic Libraries for a Platform Target-Based Approach to Drug Discovery', 13–15 Feb 2002, San Diego, CA; (b) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845.
11. **General procedure**: To a stirred mixture of glyoxylic acid monohydrate (0.582 g, 6.32 mmol) in CH_2Cl_2 (33 mL) was added heptamethylenimine (0.715 g, 6.32 mmol) followed by 4-methoxyphenylboronic acid (0.96 g, 6.32 mmol). The resulting mixture was stirred at ambient temperature for 48 h and after this time, the solvent was removed under reduced pressure. The crude product **1f** was dissolved in MeOH (9 mL) and to this solution was added 2-methoxyethylamine (0.475 g, 6.32 mmol) and isovaleraldehyde (0.544 g, 6.32 mmol). This solution was allowed to stir at ambient temperature for 10 min and then 2,6-dimethylphenylisocyanide (0.328 g, 5.0 mmol) was added. The resulting mixture was stirred at ambient temperature for 24 h and after this time, the MeOH was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 40% EtOAc:hexanes) to give 2.021 g (73%) of **2f** as a 1:1 mixture of racemic diastereomers, which were separated by preparative HPLC (Inertsil ODS3, 8 microns, 5.0×25 cm, mobile phase 65% MeOH, 35% H_2O, 0.1% TFA, flow rate 50 mL/min; t_R = 8.4 min (**isomer A**) and t_R = 9.6 min (**isomer B**). **2f (A)**: R_f = 0.62 (50% EtOAc:hexanes); white solid, mp 49–50°C (uncorrected); H NMR ($CDCl_3$, 300 MHz): δ = 0.38–2.05 (m, 13H), 0.72–0.78 and 0.97–0.99 (rotamers 1 and 2, 2m, 6H), 2.05 and 2.22 (rotamers 1 and 2, 2s, 6H), 3.01–4.18 (m, 8H), 3.33 and 3.43 (rotamers 1 and 2, 2s, 3H), 3.81 and 3.88 (rotamers 1 and 2, 2s, 3H), 4.60–4.80 (m, 1H), 5.96 (s, 1H), 6.94–7.96 (m, 8H); C NMR ($CDCl_3$, 75 MHz): 18.6, 21.7, 22.7, 23.1, 23.8, 24.0, 24.4, 24.6, 25.1, 25.2, 25.5, 25.6, 26.3, 37.9, 39.2, 43.2, 52.6, 55.6, 55.8, 55.9, 58.2, 59.1, 59.5, 69.3, 69.9, 71.6, 115.8, 120.0, 120.7, 127.4, 127.7, 128.4, 128.5, 131.9, 133.8, 134.3, 135.5, 162.1, 165.72, 166.43; LCMS (ELSD): 552 ($M+H^+$); HRMS: 552.378545 [calcd for $C_{33}H_{49}N_3O_4$ 552.380133 $(M+H)^+$]. **2f (B)**: R_f = 0.76 (50% EtOAc:hexanes); white solid, mp 144–145°C (uncorrected); H NMR ($CDCl_3$, 300 MHz): δ = 0.88–0.92 (m, 6H), 1.2–2.1 (m, 13H), 2.2 (s, 6H), 3.0–3.7 (m, 8H), 3.3 (s, 3H), 3.8 (s, 3H), 5.02 (t, 1H), 5.9 (s, 1H), 7.0 (d, 2H), 7.0–7.1 (m, 3H), 7.59 (d, 2H), 8.3 (s, 1H); C NMR ($CDCl_3$, 75 MHz): 18.4, 18.6, 21.5, 22.5, 23.1, 23.6, 24.4, 24.8, 25.3, 25.7, 37.8, 44.34, 50.7, 54.0, 55.9, 57.7, 59.1, 70.3, 70.5, 115.8, 120.1, 127.9, 128.7, 131.8, 133.7, 135.5, 162.1, 169.6, 170.4; LCMS (ELSD): 552 ($M+H^+$); HRMS: 552.377520 [calcd for $C_{33}H_{49}N_3O_4$ 552.380133 $(M+H)^+$].