Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5121–5124

TETRAHEDRON LETTERS

Solid-phase synthesis of five-dimensional libraries via a tandem Petasis–Ugi multi-component condensation reaction

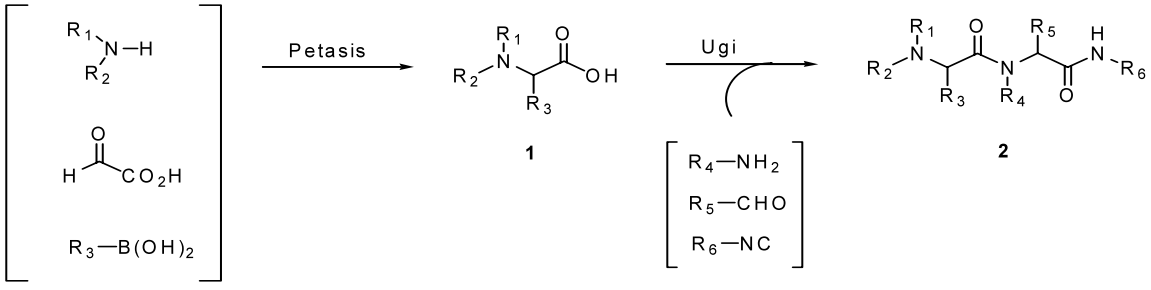
David E. Portlock,[a,*] Dinabandhu Naskar,[b,*] Laura West,[a] Ryszard Ostaszewski[c] and Jack J. Chen[a]

[a]*Combinatorial Chemistry Section, Procter & Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason Montgomery Road, Mason, OH 45040, USA*
[b]*Chembiotek Research International, Block BN, Sector-V, Salt Lake City, Calcutta-700 091, India*
[c]*Warsaw University of Technology, Noakowskiego 3, Warsaw 00-664, Poland*

Received 4 December 2002; revised 25 April 2003; accepted 25 April 2003

Abstract—Five-dimensional libraries of dipeptide amides are readily prepared using a solid-phase tandem Petasis–Ugi multi-component condensation protocol on either a RINK amine or Universal RINK isonitrile resin. The method is practical and can be automated to prepare a large number of compounds useful for high throughput biological screening.

The traditional boundaries of medicinal and organic chemistry have broadened substantially during the past decade in part due to the emergence of solid-phase methods for multi parallel synthesis.[1] Diversity-directed, thematic, and project driven libraries have all been prepared using solid supports, testifying to the utility of this enabling technology to facilitate drug discovery and material science.[2] Similarly, multi-component condensations (MCC) have also changed the landscape of organic and medicinal chemistry due to their ability to efficiently generate large libraries of compounds in one or two synthetic steps.[3] Furthermore, a strategy of using two MCC's in tandem can lead to an exponential increase in diversity compared with either MCC alone.[4] We have recently reported a tandem Petasis–Ugi (Pt–U) MCC in which the Petasis boronic acid–Mannich reaction can be used to prepare carboxylic acids containing three points of diversity.[5] These products can then in turn be employed as one of the components in the Ugi reaction, subsequently leading to six-dimensional libraries (Scheme 1). In our continuing efforts to develop automated methods to prepare large libraries of low molecular weight compounds for drug discovery, we herein report the viability of the tandem Pt–U MCC for solid-support synthesis using examples with both amine (Table 1) and isonitrile (Table 2) resin-based components. Our initial proof-of-concept studies focused on the use of the commercially available Fmoc-protected RINK amine resin, which should provide dipeptide amides **2** (Table 1). The major advantage of this protocol over a classical Ugi MCC, is that the diversity elements on the

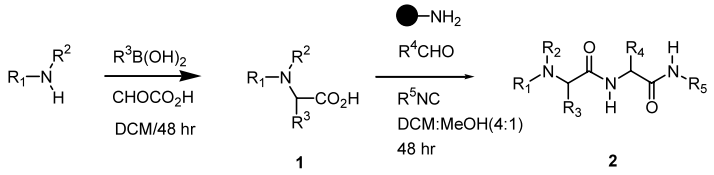


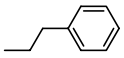
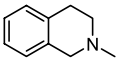
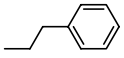
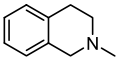
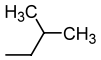
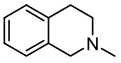
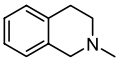
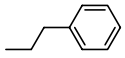
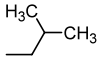
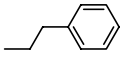
Scheme 1. Tandem Petasis–Ugi multi-component condensation.

* Corresponding author. E-mail: naskar.d@pg.com; dinabandhu@chembiotek.com

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01119-5

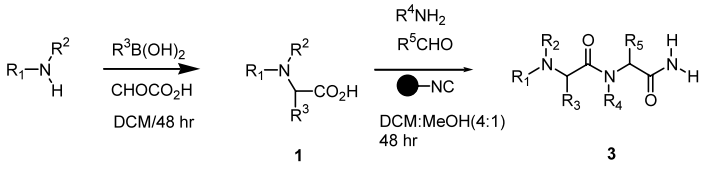
Table 1. Tandem Petasis–Ugi multi-component condensation reaction using a RINK solid-support amine component[6]

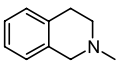
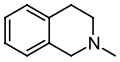
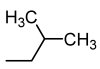
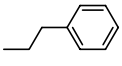
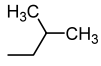
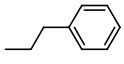
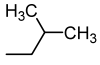


Compd	R^1	R^2	R^3	R^4	R^5	Yield[a]
2a	CH_3	CH_3	H		$-CH_2CO_2Et$	41%
2b			PMP[b]		$-CH_2CO_2Et$	49%
2c			Ph		$-CH_2CO_2Et$	50%
2d			Ph		2,6-DMP[c]	48%
2e			PMP		2,6-DMP	22%
2f			PMP		2,6-DMP	35%
2g			PMP		2,6-DMP	32%

[a] All yields refer to pure, isolated products; All compounds have been characterized by LC-MS, ^1H NMR, ^{13}C NMR. [b]*para*-methoxyphenyl; [c]2, 6-dimethylphenyl.

Table 2. Tandem Petasis–Ugi multi-component condensation reaction using a RINK solid-support isonitrile component[7]



Compd	R^1	R^2	R^3	R^4	R^5	Yield[a]
3a			PMP[b]			36%
3b			PMP			31%
3c			PMP			33%
3d			PMP			72%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, ^1H NMR, and ^{13}C NMR; [b]*para*-methoxyphenyl.

amine terminus are readily controlled with the Petasis MCC. Several examples of this concept were explored and results are summarized in Table 1. In each case the products obtained after cleavage from the resin were purified by column chromatography and the yields were moderate ranging from 22 to 50%. The method is practical and as described in the general procedures, the intermediate Petasis amino acid **1** can be used without purification. Given the large number of commercially available secondary amines, arylboronic acids, and aldehydes, millions of compounds are accessible via this method. As expected, a mixture of diastereomers as obtained in all cases (**2b–g**). Having established the viability of this tandem Pt–U MCC on a RINK amine solid support, we next examined the possibility of using a resin linked isonitrile component.[8] Application of this reagent to the tandem Pt–U reaction (Table 2) successfully provided the expected dipeptide primary amides **3**. Again, the yields are only moderate (31–72%) and a mixture of diasteremers was obtained.

In summary, we have developed a tandem Pt–U MCC reaction sequence using solid-support amine and isonitrile components, which provides dipeptide amides (2 and 3) in moderate yields. Significantly, this tandem MCC strategy is a practical method, which can be automated to provide very large, diverse compound collections for drug discovery.

References

1. 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) Edwards, P. J.; Morrell, A. I. *Curr. Opin. Drug Discov. Devel.* **2002**, *5*, 594; (c) Dolle, R. E. *J. Combi. Chem.* **2002**, *4*, 369.
2. For reviews, see: (a) Golebiowski, A.; Klopfenstein, S. R.; Portlock, D. E. *Curr. Opin. Chem. Biol.* **2001**, *5*, 273 and references cited therein; (b) Wennemers, H. *Combin. Chem. HTS* **2001**, *4*, 273; (c) Dagani, R. *Chem. Eng. News* **2001**, 27 Aug, 59.
3. (a) Domling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306; (b) Ugi, I.; Heck, S. *Combin. Chem. HTS* **2001**, *4*, 1; (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (d) Bienayme, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
4. (a) Constabel, F.; Ugi, I. *Tetrahedron* **2001**, *57*, 5785; (b) Lee, D. L.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709; (c) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168 and references cited therein.
5. The concept of a tandem Petasis–Ugi multi-component condensation has been disclosed by us previously, see: (a) CHI's Seventh Annual High Throughput Organic Synthesis Symposium, '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; (c) Portlock, D. E.; Ostaszewski, R.; Naskar, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603.
6. *General procedure for the tandem Petasis–Ugi multi-component condensation reaction using a RINK amine component* (Table 1): To a stirred mixture of glyoxylic acid monohydrate (0.582 g, 6.32 mmol) in CH_2Cl_2 (33 mL) was added heptamethyleneimine (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 CH_2Cl_2 was removed under reduced pressure. To an oven-dried solid-phase reaction vessel was added Fmoc protected RINK resin (1.08 g, 0.76 mmol, ACT, 0.7 mmol/g, 100–200 mesh) and treated with 25% piperidine/DMF (15 mL, 2×15 min). After this time, the resin was drained and washed with DMF (3×5 mL), MeOH (3×5 mL), CH_2Cl_2 (3×5 mL). The resin was dried under vacuum for 20–30 min. To this reaction vessel was added CH_2Cl_2/MeOH (30 mL, 4:1) followed by 3-phenylpropionaldehyde (0.671 g, 5 mmol), **1g** (1.39 g, 5 mmol) and then 2,6-dimethylphenylisocyanide (0.656 g, 5 mmol). The reaction vessel was agitated for 24 h. After this time, the resin was drained and washed with DMF (3×5 mL), MeOH (3×5 mL), DCM (3×5 mL). The product were now cleaved from the resin with 40%TFA/DCM/0.5%TIPS (2×15 mL, 2×15 min each) and finally washed with DCM (2×15 mL). The combined solutions were removed and dried under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc:hexanes) to give 0.130 g (32%) of **2g** as a 50:50 mixture of racemic diastereomers. Analytical HPLC: Polaris C18 column (4.6×250 mm, 3 μm particle size), mobile phase 0.1% aqueous phosphoric acid/CH_3CN linear gradient over 30 min, 1 mL/min, two peaks detected by ELS and UV at 215 nm, $t_R = 13.03$ and 13.09 min. **2g**: $R_f = 0.28$ (4% MeOH:CH_2Cl_2); white solid, mp 86–87°C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.18$–1.83 (m, 19H), 1.88 (s, 6H), 2.20 (s, 6H), 2.21–2.48 (m, 6H), 2.61–2.86 (m, 5H), 3.15–3.23 (m, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 4.12 (t, 1H), 4.61 (t, 1H), 5.32 (s, 1H), 5.41 (s, 1H), 6.55 (d, 2H), 6.70 (d, 2H), 6.79 (d, 2H), 6.96 (d, 2H), 6.98–7.39 (m, 14H), 7.49 (d, 2H), 8.62 (br., 1H), 10.03 (br., 1H), 10.20 (br., 1H), 10.64 (br., 1H); ^{13}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 (11C), 44.34, 50.7, 54.0, 55.9, 57.7, 59.1, 70.3, 70.5 (8C), 115.8, 120.1, 127.9, 128.7, 131.8, 133.7, 135.5, 162.1 (8C), 169.6, 170.4 (2C); LCMS (ELSD): 542 ($M+H^+$); HRMS: 542.335742 [calcd for $C_{34}H_{43}N_3O_3$ 542.338268 $(M+H)^+$].
7. *General procedure for the tandem Petasis–Ugi multi-component condensation reaction using a RINK isonitrile component* (Table 2): To a solution of amino acid **1a** (0.194 g, 0.7 mmol) in methanol was added isobutyl amine (0.0512 g, 0.7 mmol) followed by the addition of phenylacetaldehyde (0.094 g, 0.7 mmol). To this mixture was added 4 ml of tetrahydrofuran, the resulting mixture was then pipetted onto dry RINK isonitrile resin (0.200 g, 0.14 mmol). This mixture was then allowed to react for 12–16 h, after this time the resin was drained and washed with DMF, methanol, CH_2Cl_2. The product was removed from the resin by cleaving with a stock solution of 15% trifluoroacetic acid, 0.5% triisopropylsilane, in CH_2Cl_2 for 15 min. The cleavage mixture was evaporated to dryness then purified by preparative thin layer chromatography (silica gel, 30% hexanes:EtOAc). **3a**:

$R_f = 0.28$ (4% MeOH:DCM); white solid, mp 86–87°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$–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); ^{13}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 (11C), 44.34, 50.7, 54.0, 55.9, 57.7, 59.1, 70.3, 70.5 (8C), 115.8, 120.1, 127.9, 128.7, 131.8, 133.7, 135.5, 162.1 (8C), 169.6, 170.4 (2C); LCMS (FIA/ESI): 500 ($M+H^+$); HRMS: 500.289502 [calcd for $C_{31}H_{37}N_3O_3$ 500.291317 $(M+H)^+$].

8. (a) Chen, J. J.; Golebiowski, A.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett*. **2002**, *43*, 4083; (b) Chen, J. J.; Golebiowski, A.; McClenagham, J.; Klopfenstein, S. R. *Tetrahedron Lett*. **2001**, *42*, 2269.