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The synthesis of aza-β-lactams via tandem Petasis–Ugi multi-component condensation and 1,3-diisopropylcarbodiimide (DIC) condensation reaction

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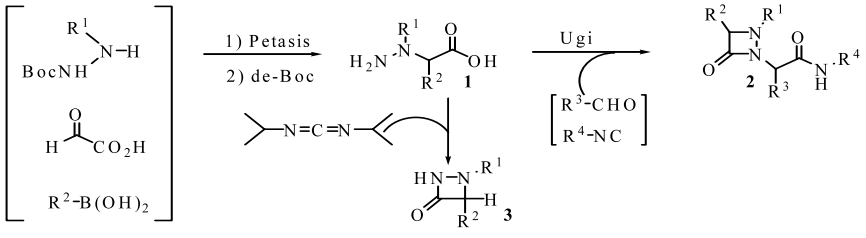
Abstract—The synthetic utility of a tandem Petasis–Ugi multi-component condensation and 1,3-diisopropylcarbodiimide condensation reactions have been employed to efficiently prepare two to four-dimensional libraries of aza-β-lactams.

The development and application of multi-parallel methods for the synthesis of combinatorial libraries has found wide application and success in the pharmaceutical industry.[1,2] Among the most useful methods, which have emerged to generate greatly expanded chemical collections of drug-like compounds, are the multi-component condensations (MCC) due to their ability to efficiently produce large numbers of compounds in one or two synthetic steps.[3] Previous reports from our laboratories and others have demonstrated that multi-component condensations can be used in tandem to increase the potential size of the synthetic array.[4] For example, amino acids with three points of diversity generated by the Petasis Boronic acid–Mannich reaction[5] can be used directly without purification in the Ugi condensation[3], leading to six dimensional libraries of dipeptide amides.[4a] Within this context, we wished to apply this strategy more broadly to the preparation of non-peptide, i.e. drug-like chemical collections, for high throughput biological screening. Herein, we report a novel method for the practical synthesis of aza-β-lactams using a tandem Petasis–Ugi approach and 1,3-diisopropylcarbodiimide condensation reaction.

As a result of our previous endeavors to produce 1-aminohydantoin libraries[6], we had a large number of α-hydrazinocarboxylic acids (**1**) on hand, which were prepared using substituted hydrazines as the amine component in the Petasis Boronic acid–Mannich reaction.[7] It occurred to us that N-substituted-α-hydrazinocarboxylic acids can also be regarded as aza-β-amino acids, and therefore could potentially be used as substrates in the Ugi and DIC condensation to prepare aza-β-lactams (Scheme 1).



Scheme 1. Synthesis of aza-β-lactams via a tandem Petasis–Ugi and DIC condensation approach.

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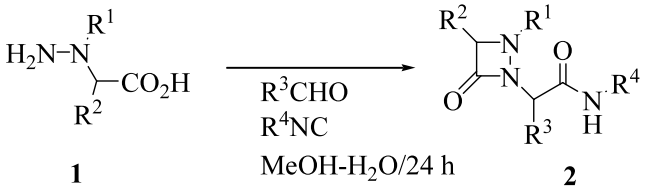
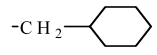
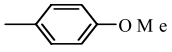
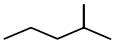
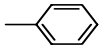
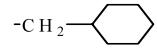
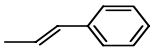
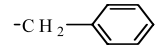
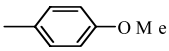
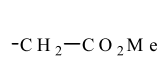
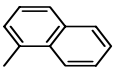
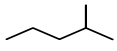
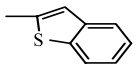
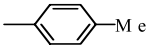
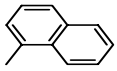
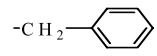
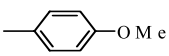
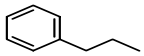
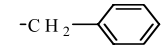
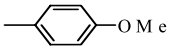
Even though the synthesis of aza-β-lactams has previously received considerable attention[8] due to their potential for antimicrobial and fungicidal activity,[8c,9] the lack of a general synthetic method may have precluded a comprehensive biological evaluation of this interesting structural class of compounds.

In our first experiment, **1a** was generated via a Petasis three component condensation reaction[7] followed by Boc deprotection using 4 M HCl in 1,4-dioxane (Scheme 1 and Table 1). Upon evaporation of the crude reaction mixture, the resulting hydrazine salt was treated directly with one equivalent each of isovaleraldehyde and 2,6-dimethylphenylisocyanide in aqueous methanol. Stirring for 24 h at room temperature, provided **2a** in 53% yield after purification.[10] It should be noted that the reaction does not proceed well without water and that the use of trifluoroacetic acid instead of HCl resulted in variable yields. As expected, the product consisted of a 50:50 mixture of racemic diastereoisomers as demonstrated by LC–MS. Encouraged by this result, **2b–i** were also prepared using these same reaction conditions and afforded 23–79% yield after purification by column chromatography. It is noteworthy that the reactions proceed from the Boc protected hydrazine, glyoxylic acid, and aryl boronic

Table 1. Tandem Petasis–Ugi strategy for the synthesis of aza-β-lactams

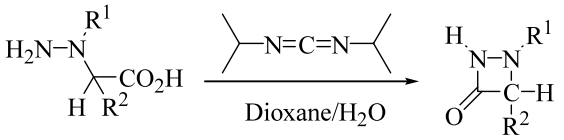


1 **2**

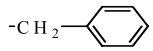
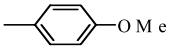
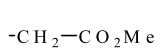
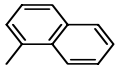
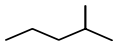
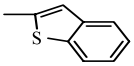
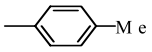
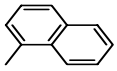
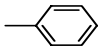
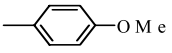
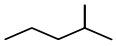
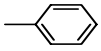
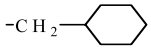
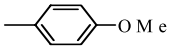
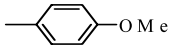
Compound	R^1	R^2	R^3	R^4	Yield[a]
2a				2,6-DMP[b]	53%
2b				2,6-DMP[b]	47%
2c				2,6-DMP[b]	31%
2d				2,6-DMP[b]	74%
2e				2,6-DMP[b]	40%
2f				2,6-DMP[b]	35%
2g				2,6-DMP[b]	23%
2h				$-CH_2CO_2Me$	69%
2i				$-CH_2CO_2Et$	79%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, HNMR, and CNMR; [b]2,6-dimethylphenyl.

Table 2. 1,3-Diisopropylcarbodiimide condensation reaction



1 **3**

Compound	R^1	R^2	Time (h)	Yield[a]
3a			0.50	64%
3b			0.50	62%
3c			0.66	61%
3d			0.66	62%
3e			0.50	29%
3f			0.50	27%
3g			0.50	36%
3h	—H		0.50	0%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, ^{1}HNMR, and ^{13}CNMR.

acid all in one pot without purification until the final product (**2**) is isolated.

We first examined the reaction with 1,3-diisopropylcarbodiimide and hydrazine carboxylic acid salt (**1a**, R_1 = benzyl, R^2 = methoxy phenyl) (Scheme 1, Table 2) which afforded the desired product within half an hour which was purified by column chromatography to provide **3a** in 64% yield.[11] Encouraged by this result, **3b**–**g** were synthesized in 27–62% yield after purification by column chromatography. However, when R^1 = H, R^2 = methoxyphenyl (**3h**), this reaction failed to give any desired product (LC–MS).

It is noteworthy that the reactions proceed from the Boc protected hydrazine, glyoxylic acid, and aryl boronic acid all in one pot without purification until the final product (**3**) is isolated.

In conclusion, we have demonstrated that a tandem Petasis–Ugi multi-component condensation strategy and 1,3-diisopropylcarbodiimide condensation reaction can be used to prepare aza-β-lactams containing two to four elements of diversity. Although the yields are only moderate, the methods provide rapid entry into this interesting structural class of molecules.

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10. **General procedure**: The α-hydrazinocarboxylic acid (Boc protected **1d**) (115 mg, 0.297 mmol) was stirred with 4 M HCl in 1,4-dioxane (2 mL) for 3 h at ambient temperature. The solvent was removed and the residue was co-evaporated with dicholoromethane, toluene and dried under reduced pressure. This hydrazino salt (**1d**) was then treated with isovaleraldehyde (26 mg, 0.297 mmol) and 2,6-dimethylphenylisocyanide (39 mg, 0.297 mmol) in $MeOH/H_2O$(2 mL, 8:2) and allowed to stir for 24 h at ambient temperature. After this time, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography using silica gel and EtOAc/hexanes as eluent to afford (107 mg, 74%) the expected compound (**2d**) as a viscous oil: $R_f = 0.37$ (30% EtOAc:hexanes); Analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron 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, $t_R = 19.04$ and 19.07 min; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.02$ (d, 3H), 1.07 (d, 3H), 1.97–2.08 (m, 2H); 2.19 (s, 6H), 2.21–2.29 (m, 1H), 3.67 (s, 3H), 4.05–4.10 (m, 2H), 4.49 (d, 1H), 4.89 (s, 1H), 6.65 (d, 2H), 7.01–7.18 (m, 6H), 7.17–7.45 (m, 4H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 18.73, 21.93, 23.13, 25.36, 38.64, 55.46, 60.71, 64.59, 80.33, 114.19, 127.49, 128.41, 128.61, 128.90, 129.00, 129.15, 129.79, 129.99, 135.23, 135.42, 159.89, 168.01, 169.15; LCMS (ELSD): 486 ($M+H^+$); HRMS: 486.277271 [Calcd for $C_{30}H_{35}N_3O_3$ 486.275667 $(M+H)^+$].
11. **General procedure**: 1,3-Diisopropylcarbidiimide condensation reaction: The hydrazino carboxylic acid (115 mg, 0.297 mmol) was treated with 4.0 M HCl in 1,4-dioxane (2 mL) for 3 h at ambient temperature. The solvent was removed and the residue was co-evaporated with toluene, dichloromethane and dried under reduced pressure. To a solution of hydrazino salt in dioxane/water (2 mL, 8:2) at 0–5°C was added 1,3-diisoproylcarbodiimide (DIC) (75 mg, 0.594 mmol, 2 equiv.) dropwise. This reaction was allowed to stir for 0.5 h at this temperature. The reaction mixture was filtered off and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography using silica gel and EA/hexane as eluent (40% EA/hexane) to afford the expected compound **3a** (51 mg, 64%) as a viscous oil; $R_f = 0.57$, 50% EtOAc:hexane; ^1H NMR ($CDCl_3$, 300 MHz): $\delta =$ 3.81 (s, 3H), 3.96 (d, 1H), 4.10 (d, 1H); 4.92 (s, 1H), 6.92 (d, 2H), 7.34 (d, 2H), 7.35–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): 55.69, 65.98, 82.21, 114.58, 125.48, 128.41, 129.01, 129.12, 129.46, 136.97, 160.19, 169.71; LCMS (ELSD): 269 ($M+H^+$); HRMS: 269.129539 [Calcd for $C_{16}H_{16}N_2O_2$ 269.129003 $(M+H)^+$].