# Unique Structures Generated by Ugi 3CC Reactions Using Bifunctional Starting Materials Containing Aldehyde and Carboxylic Acid

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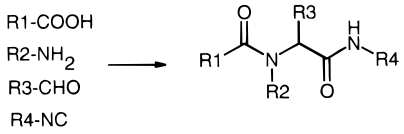
Multiple component condensation (MCC) reactions are well suited for combinatorial library synthesis, due to the fact that products are formed in a single step and diversity can be achieved by simply varying each component.[1] In a Ugi four-component condensation (4CC) reaction,[2] a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in an one-pot manner to afford an N-substituted acyl amino amide (Scheme 1), introducing four independently varying R groups in one reaction.

Although a large diversity can be quickly achieved through the 4CC reaction, the scaffolds that are accessible through the 4CC reaction are limited. Efforts have been made to broaden the scope of structures that are accessible by the 4CC reaction, either through post-condensation transformations or by using bifunctional starting materials. For instance, pyrroles, diketopiperazines, and 1,4-benzodiazepine-2,5-diones were synthesized through post-condensation transformations by using a convertible isocyanide, 1-isocyanocyclohexene.[3] $\beta$-Lactams and piperazine-2-carboxamides were also prepared by post-condensation transformations using functionalized starting materials.[4]

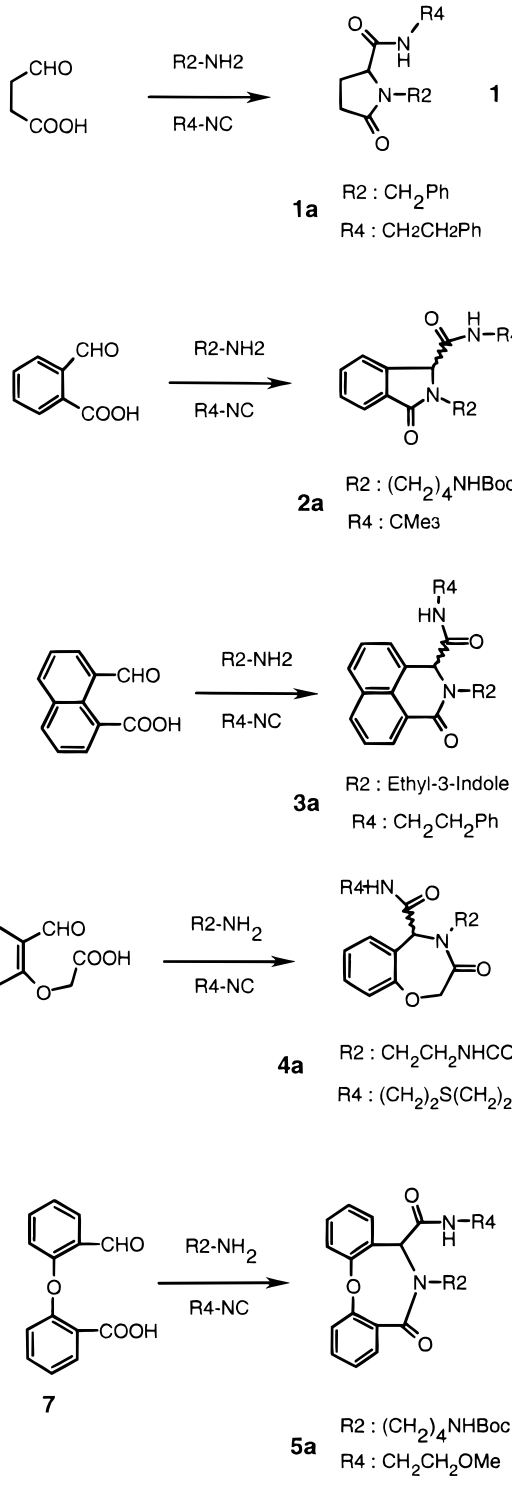
Another strategy to increase scaffold diversity is to use bifunctional starting materials, in which the participating functional groups of two components of the 4CC reaction are present in one structure. Several groups have reported the use of $\beta$-amino acids in a three-component condensation (3CC) reaction to prepare $\beta$-lactams.[2,5] Others reported the synthesis of $\gamma$-lactams by a 3CC reaction using $\omega$-keto acids on solid support.[6]

We have explored the 3CC reactions using bifunctional starting materials that have an aldehyde functional group and a carboxylic acid functional group to prepare various lactam structures. Although the possibilities of using aldehyde−carboxylic acid bifunctional starting materials to prepare lactams were proposed by Ugi,[7] to our knowledge, examples of such reactions have not been

**Scheme 1**




**Scheme 2**

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(1) (a)Balkenhohl, F.; Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, A. D.; Thomas, A. K. *Acc. Chem. Res.* **1996**, *29*, 123−131.

(2) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8−21.

(3) (a) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149−1152. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583. (c) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935−8939.

(4) For $\beta$-lactam synthesis, see: Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519−2520. For piperazine-2-carboxamide synthesis, see: Rossen, K.; Sager., J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183−3186.

(5) Pitlik, J.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129−3134.

(6) (a) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359−362. (b) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron*, **1997**, *53*, 6653−6679.

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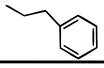
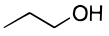
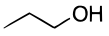
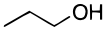
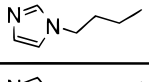
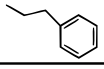
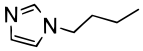
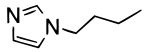
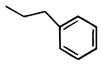
**Table 1. 3CC Reactions. Reactions Were Carried Out at Room Temperature Overnight, and the Yields Were Calculated by the Product Peak Area versus the Total Peak Areas at 215 nm of the HPLC Chromatograms on a C18 Reverse Phase Column**

| Entry | R2 | R4 | Compound, yield | Compound, yield | Compound, yield | Compound, yield | Compound, yield |
|---|---|---|---|---|---|---|---|
| 1 |  |  | 1b, 95% | 2b, 77% | 3b, 57% | 4b, 70% | 5b, 38% |
| 2 |  |  | 1c, 98% | 2c, 96% | 3c, 46% | 4c, 89% | 5c, 42% |
| 3 |  |  | 1d, 98% | 2d, 75% | 3d, 38% | 4d, 91% | 5d, 28% |
| 4 |  |  | 1e, 87% | 2e, 89% | 3e, 60% | 4e, 71% | 5e, 25% |
| 5 |  |  | 1f, 97% | 2f, 75% | 3f, 48% | 4f, 70% | 5f, 35% |
| 6 |  |  | 1g, 90% | 2g, 82% | 3g, 51% | 4g, 81% | 5g, 30% |
| 7 |  |  | 1h, 85% | 2h, 84% | 3h, 55% | 4h, 57% | 5h, 22% |
| 8 |  |  | 1i, 94% | 2i, 92% | 3i, 58% | 4i, 60% | 5i, 19% |
| 9 |  |  | 1j, 92% | 2j, 90% | 3j, 56% | 4j, 63% | 5j, 26% |
| 10 |  |  | 1k, 100% | 2k, 97% | 3k, 62% | 4k, 56% | 5k, 32% |
| 11 |  |  | 1l, 100% | 2l, 100% | 3l, 54% | 4l, 61% | 5l, 29% |
| 12 |  |  | 1m, 100% | 2m, 98% | 3m, 64% | 4m, 81% | 5m, 27% |

reported, possibly due to the limited number of available bifunctional starting materials.[6b] A careful search of the commercially available chemicals turned up quite a few interesting bifunctional molecules that contain both an aldehyde and a carboxylic acid, such as succinic semialdehyde, 2-formylbenzoic acid, 1,8-naphthaldehydic acid, and 2-formylphenoxyacetic acid. Many others can be prepared conveniently.[9] Here, we report the synthesis of heterocyclic structures with unique 5-, 6-, 7-, and 8-membered rings, such as 2-pyrrolidinone-5-carboxamides (**1**), 2-isoindolinone-7-carboxamides (**2**), 1,8-naphtha-$\delta$-lactam (**3**), 1,4-benzoxazepin-3-one-5-carboxamides (**4**), and 1,5-dibenzoxazocin-4-one-6-carboxamides (**5**), through 3CC reactions using appropriate aldehyde−carboxylic acid bifunctional starting materials (Scheme 2).

Starting with succinic semialdehyde, we found that succinic semialdehyde reacted with primary amines and isocyanides to form 2-pyrrolidinone-5-carboxamides (Scheme 2) in high yields. For example, succinic semialdehyde reacted with benzylamine and phenylethyl isocyanide at room temperature overnight to afford compound **1a** in 93% yield. The succinic semialdehyde used in this experiment was in a water solution, indicating that water did not interfere with the reaction. In general, the 3CC reactions of succinic semialdehyde are robust and high yielding. The yields of some of the tested reactions are listed in Table 1.

2-Formylbenzoic acid reacted with primary amines and isocyanides to give 2-isoindolinone-7-carboxamides (Scheme 2). Various amines and isocyanides were incorporated into this structure with moderate to high yields (Table 1). For example, 2-formylbenzoic acid reacted with 4-(*tert*-butoxycarbonylamino)butylamine and *tert*-butyl isocyanide at room temperature overnight to afford **2a** in 87% yield. These reactions of succinic semialdehyde and 2-formylbenzoic acid demonstrated that 5-membered cyclic lactams can be prepared through a 3CC reaction.

On the other hand, 1,8-naphthaldehydic acid reacts with an amine and an isocyanide to afford a lactam that has a 6-membered ring (Scheme 2). For instance, 1,8-naphthaldehydic acid reacted with tryptamine and phenylethyl isocyanide to yield **3a** in 84%. Some tested reactions are listed in Table 1 with moderate yields.

2-Formylphenoxyacetic acid reacts with amines and isocyanides to afford 1,4-benzoxazepin-3-one-5-carboxamides that have a 7-membered ring (Scheme 2). Compound **4a** was synthesized in 70% yield by reacting 2-formylphenoxyacetic acid with *N*-acetylethylenediamine and methyl 3-(2′-isocyanoethyl)thiopropionate overnight at room temperature. 2-Formylphenoxyacetic acid reacted with various primary amines and isocyanides to afford products in relatively high yields (Table 1).

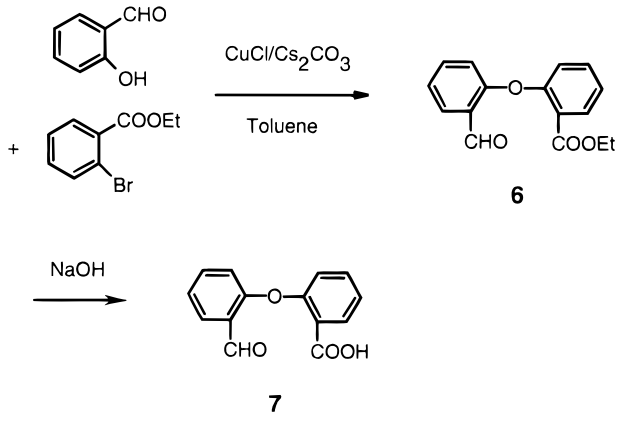
To expand the structure diversity accessible through

(7) Ugi, I.; Achatz, J.; Baumgartner-Rupnik, M.; Danzer, B.; Fleck, C.; Glahsl, G.; Herrmann, R.; Jacob, P.; Kambach, C. *Nat. Prod. Chem.* **1988**, *3*, 107.

(8) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540.

(9) (a) Bleasdale, D. A.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1683−1692. (b) Moody, C. J.; Rahimtoola, K. F. *J Chem. Soc., Perkin Trans. 1* **1990**, 673−679. (c) Gray, N. M.; Dappen, M. S.; Cheng, B. K.; Gordi, A. A.; Biesterfeldt, J. P.; Hood, W. F.; Manahan, J. B. *J. Med. Chem.* **1991**, *34*, 1283−1292. (d) Cook, J. W.; Dickson, G. T.; Jack, J.; Loudon, J. D.; McKeown, J.; MacMillan, J.; Williamson, W. F. *J. Chem. Soc.* **1950**, 139−147.

**Scheme 3**



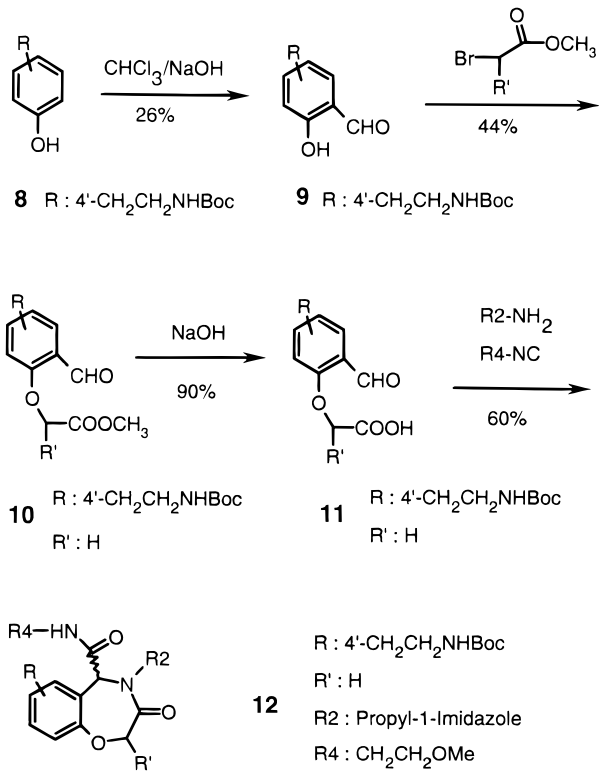

this type of 3CC reactions, 2′-formylphenoxy-2-benzoic acid (**7**) was synthesized and tested in 3CC reactions. As illustrated in Scheme 3, salicylaldehyde and ethyl 2-bromobenzoate were coupled using a reported diaryl ether synthesis procedure[8] to give diaryl ether **6** in 24% yield. Hydrolysis of ester **6** provided 2′-formylphenoxy-2-benzoic acid in nearly quantitative yield. 2′-Formylphenoxy-2-benzoic acid participates in a 3CC reaction to form a heterocyclic structure that has an 8-membered lactam ring (Scheme 2). For instance, **5a** was prepared in 33% yield by reacting 2′-formylphenoxy-2-benzoic acid with 4-(*tert*-butoxycarbonylamino)butylamine and methoxyethyl isocyanide. The yields of the reactions of 2′-formylphenoxy-2-benzoic acid with amines and isocyanides are relatively low, in the range of 20−40% (Table 1), presumably due to the difficulties of forming that 8-membered ring.

Besides those bifunctional reagents that are commercially available, a variety of them can be synthesized conveniently. For instance, the synthesis of 2-formylphenylacetic acid,[9a] 3-formylindole-2-carboxylic acid,[9b] 2-formylindole-3-acetic acid,[9c] 2′-formyldiphenyl-2-carboxylic acid[9d] have been reported. In our laboratory, 2-formylphenoxyacetic acid derivatives were prepared (Scheme 4) using substituted phenols. As shown in Scheme 4, phenols were converted to salicylaldehyde derivatives by the Reimer−Tiemann reaction.[10] Alkylation of the salicylaldehyde derivatives followed by saponification yielded bifunctional compound **11**, which then reacted with primary amines and isocyanides to form substituted 1,4-benzoxazepin-3-one-5-carboxamides (**12**). In structure **12**, four independent R groups were introduced through a series of reactions, thus allowing rapid achievement of diversity.

In conclusion, by using bifunctional starting materials that have aldehyde and carboxylic acid functional groups in a 3CC reaction, unique lactam structures were prepared. These new structures broaden the scaffolds that are accessible through Ugi reactions, and many of them may represent interesting pharmacophores. Furthermore, these 3CC reactions are amenable to solution-phase as well as solid-phase combinatorial library synthesis, thus allowing rapid synthesis of relevant small molecule libraries.

(10) (a) Wynberg, H.; Meijer, E. W. *Org. React.* **1982**, *28*, 2. (b) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553−1555.

**Scheme 4**




## Experimental Section

$^1$H NMR spectra were recorded using 60 or 200 MHz NMR spectrometers. Chemical shifts were referenced with TMS as the internal standard. HPLC was run on a 0.4 × 10 cm C18 column with 0.1% TFA water as buffer A and acetonitrile as buffer B.

**Synthesis of Compound 2a.** To 2.0 g (13.3 mmol) of 2-formylbenzoic acid in 10 mL of methanol was added 2.5 g (13.3 mmol) of 4-(*tert*-butoxycarbonylamino)butylamine and 1.4 mL (13.3 mmol) of *tert*-butyl isocyanide. The resulting solution was stirred at room temperature overnight. TLC showed that the reaction was complete after the incubation. Volatile solvent was then removed in vacuo. The remaining residue was purified by flash chromatography eluted with 1:1 hexane/ethyl acetate to afford 4.6 g (87%) of the purified product. FAB-MS: found $[M + H]^+ = 404$, calcd $[M + H]^+ = 404$. $^1$H NMR ($CDCl_3$): $\delta$ 7.67 (m, 4H), 5.85 (s, 1H), 4.95 (s, 1H), 3.20 (m, 4H), 1.58 (m, 4H), 1.43 (s, 9H), 1.29 (s, 9H).

**Synthesis of Compound 4a**. To 0.5 g (2.78 mmol) of 2-formylphenoxyacetic acid in 5.0 mL of DMSO were added 0.28 g (2.78 mmol) of *N*-acetylethylenediamine in 5.0 mL of methanol and 0.52 g (2.78 mmol) of ethyl 3-(2′-isocyanoethyl)thiopropionate. The reaction solution was stirred at room temperature overnight followed by removal of the volatile organic solvent in vacuo. Then 20 mL of water was added to the remaining solution, and the solution was extracted with 20 mL of ethyl acetate 5 times until no reaction product was left in the water layer. The combined extract was dried with sodium sulfate and concentrated. Compound **4a** was then purified on a silica flash column eluted with 10:1 ethyl acetate/methanol to obtain 0.85 g (yield is 70%). FAB-MS: found $[M + H]^+ = 452$, calcd $[M + H]^+ = 452$. $^1$H NMR ($CDCl_3$): $\delta$ 7.31 (m, 4H), 6.60 (t, 1H), 4.96−4.00 (m, 3H), 3.60 (s, 3H), 3.54−3.36 (m, 6H), 2.61 (m, 6H), 1.90 (s, 3H).

**Supporting Information Available:** Synthetic procedures and $^1$H NMR, IR, and MS spectra of phenylethyl isocyanide, methoxyethyl isocyanide, methyl 3-(2′-isocyanoethyl)thiopropionate, compound **1**, **3**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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