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# Solid-phase synthesis of 1,2,5-trisubstituted imidazolidin-4-ones

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ABSTRACT

A general solid-phase synthesis of 1,2,5-trisubstituted imidazolidin-4-ones is described. The key synthetic transformation incorporates a microwave-assisted condensation of an α-amino amide on solid support with an aldehyde in solution to give the corresponding resin-bound imidazolidin-4-one in a simple one-pot procedure.



Imidazolidin-4-ones represent an interesting class of compounds with respect to biological activity.[1,2] Through manipulation of the substituents around the imidazolidin-4-one core, molecules with a variety of biological properties have been discovered. Examples include compounds that exhibit antibacterial activity.[3,4] Imidazolidin-4-ones have also been reported to inhibit binding of VCAM-1 to VLA-4, which are useful in treating inflammation associated with chronic inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, asthma, and inflammatory bowel disease.[5] The structural diversity of substituted imidazolidin-4-ones makes this compound class versatile for drug discovery research and necessitates the development of efficient and versatile syntheses of such molecules.[6,7] Previous work reported by Pospíšil and Potáček describes the formation of 1,2,3-trisubstituted imidazolidin-4-ones under microwave-assisted conditions in a solvent-free system.[8] The work described here extends this methodology to generate a diversified 1,2,5-trisubstituted imidazolidin-4-one system (Fig. 1) on solid phase.

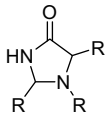
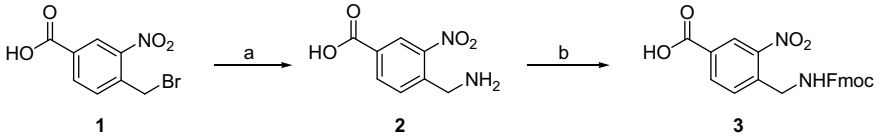


**Figure 1.** 1,2,5-Trisubstituted imidazolidin-4-one.

The aim of this project was to develop a general solid-phase synthesis of imidazolidin-4-ones that allow diverse elements to be incorporated at the N-1, C-2, and C-5 positions. This solid-phase synthesis would subsequently be used to generate parallel and combinatorial 1,2,5-trisubstituted imidazolidin-4-one compound libraries.

A 2-nitrobenzyl-based photo-cleavable linker **3** was selected as the basis for construction of the imidazolidin-4-one system.[9] Amination of 4-(bromomethyl)-3-nitrobenzoic acid (**1**) with ammonia in methanol provides primary amine **2**, which was protected using 9-fluorenylmethyl chloride (Fmoc-Cl) to provide **3** (Scheme 1). This linker allows photo-mediated cleavage of the substituted imidazolidin-4-ones from solid phase, and is compatible with the chemistry required to conduct the synthesis.

Solid-phase synthesis was initiated by acylating aminomethyl-terminated Argogel® (**4**) with *N*-α-*N*-ε-bis-Fmoc-lysine followed by Fmoc deprotection to generate **5** (Scheme 2). This increases the loading capacity of the resin by doubling the number of amino



**Scheme 1.** Reagents and conditions: (a) $NH_3$, MeOH, 25 °C; (b) Fmoc-Cl, $Na_2CO_3$, THF, $H_2O$, 25 °C.

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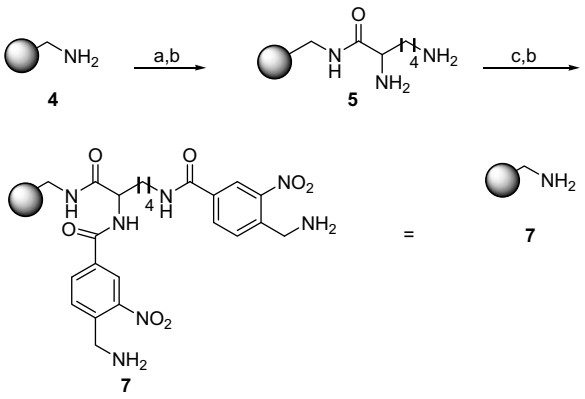
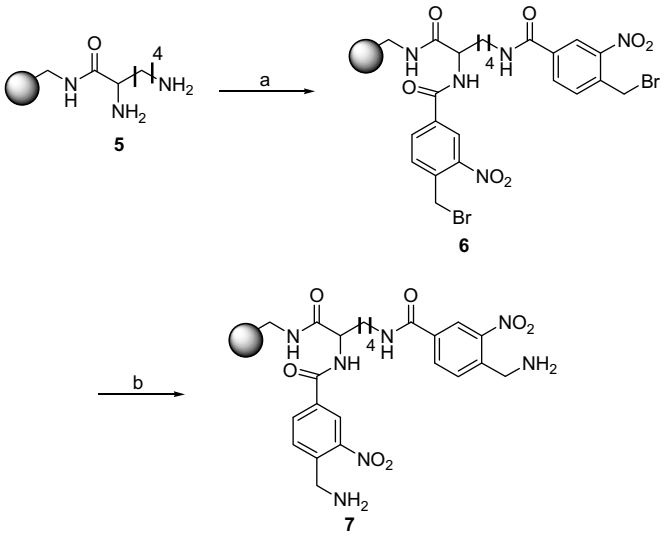


**Scheme 2.** Reagents and conditions: (a) *N*-α-*N*-ε-bis-Fmoc-Lys, HOBt monohydrate, DIC, $CH_2Cl_2$, DMF, 25 °C; (b) piperidine, DMF, 25 °C; (c) **3**, HOBt monohydrate, DIC, $CH_2Cl_2$, DMF, 25 °C.



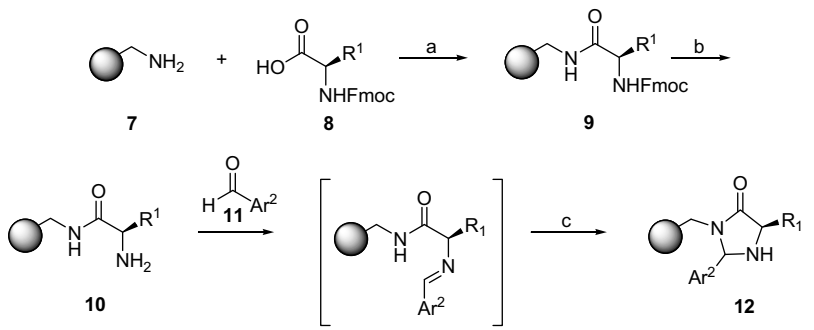
**Scheme 3.** Reagents and conditions: (a) **1**, HOBt monohydrate, DIC, $CH_2Cl_2$, DMF, 25 °C; (b) 7 M $NH_3$ in MeOH, THF, 25 °C.

groups for further functionalization. The double-loaded resin was subsequently acylated with **3** followed by Fmoc deprotection to provide resin-bound primary amine **7**.

Formation of **7** can be achieved more directly through coupling of **1** with **5** to provide **6** (Scheme 3). This is followed by amination with ammonia to give **7**. However, this solid-phase amination results in significantly diminished yields due to cross-linking of the generated primary amine with unreacted benzyl bromide.

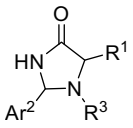
Acylation of **7** with an Fmoc-protected α-amino acid **8** provided **9**, which was then Fmoc deprotected to provide resin-bound α-amino amide **10** (Scheme 4). A range of α-amino acids **8** were successfully employed (Table 1). Glutamic acid, serine, and diaminopropionic acid incorporated acid-labile protecting groups on their side chains. Reaction of **10** with 1.0 M aromatic aldehyde **11** under microwave-assisted conditions at 180 °C resulted in efficient conversion to the diastereomeric imidazolidin-4-one **12**.[10] This reaction is very rapid, going to completion in 10 min. The $R^1$ substituent derived from the amino acid significantly influences the cyclization. When $R^1$ is not hydrogen, the reaction occurs readily with clean conversion. However, when $R^1$ is hydrogen, a less facile cyclization occurs with formation of significant side products. One possible explanation for this observation may be the ease of generation of the required reactive conformation for cyclization of the putative imine intermediate. The energy required to adopt this conformation from the extended non-reactive conformation may be less when there is an $R^1$ substituent. Employing the microwave conditions, imidazolidin-4-one **12** formation was successfully achieved with a set of electronically diverse aromatic aldehydes **11** (Table 1).

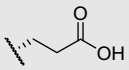
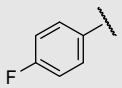
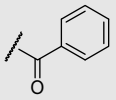
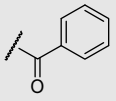
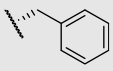
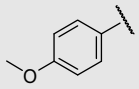
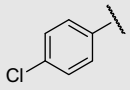
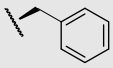
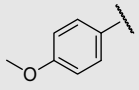
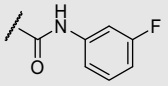
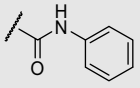
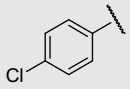
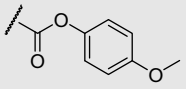
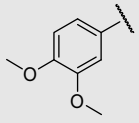
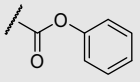
The imidazolidin-4-one **12** was further functionalized via N-derivatization (Scheme 5). Initial experiments identified differing levels of reactivity for the two imidazolidinone diastereomers. Under mild acylation conditions, for example, using benzoic acid and DIC, only the cis-diastereomer is acylated. When more forcing N-derivatization conditions are applied, for example, using benzoic acid and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), both diastereomers are benzoylated. Also, only the cis-diastereomer reacts with less reactive electrophiles such as sulfonyl chlorides. The higher reactivity of the cis-diastereomer is likely due to the fact that one face of the five-membered ring is not subject to steric hindrance by either the 2- or the 5-substituent. For the trans-diastereomer, the approach of the electrophile to either face of the five-membered ring is sterically hindered by one of these substituents. This hypothesis is supported by the fact that the exact nature of the $R^1$ and $Ar^2$ substituents also affects the N-derivatization, which is more facile with smaller $R^1$ and $Ar^2$ groups. The cis- and trans-stereochemistry was determined by NOE and $^1H$ NMR experiments. Also, in the cis-diastereomer, the $R^1$ and $Ar^2$ groups have restricted rotation due to steric interaction, and hence exhibit rotamers in the $^1H$ NMR spectrum. Using a combination of relatively reactive electrophiles and/or forcing conditions, complete N-derivatization of both the cis- and the less reactive trans-diastereomers of **12** was achieved. Successful amide **13** formation was performed with both benzoic acid and acetic anhydride, urea **14** formation with both phenyl isocyanate and 3-fluorophenyl iso-



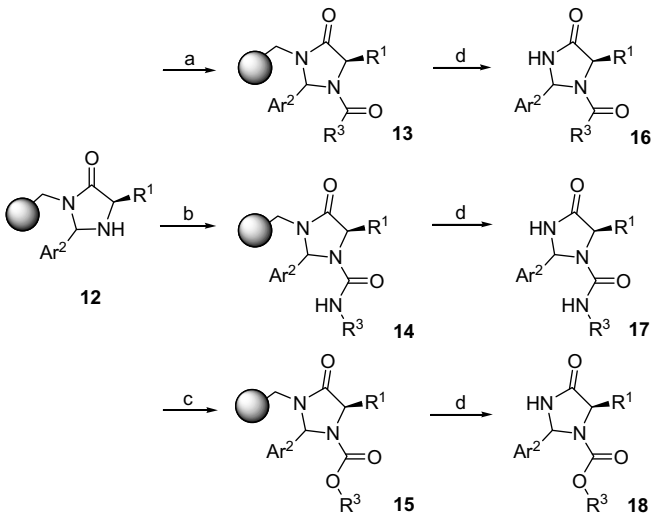
**Scheme 4.** Reagents and conditions: (a) HOBt monohydrate, DIC, $CH_2Cl_2$, DMF, 25 °C; (b) piperidine, DMF, 25 °C; (c) DMF, microwave, 180 °C.

**Table 1**
1,2,5-Trisubstituted imidazolidin-4-ones synthesized on solid phase



| Compound | $R^1$ | $Ar^2$ | $R^3$ | pmol per bead[a] | Yield[b] (%) | Purity[c] (%) |
|---|---|---|---|---|---|---|
| **16a** |  |  |  | 274 | 12 | 80 |
| **16b** |  |  |  | 930 | 38 | 84 |
| **16c** |  |  |  | 465 | 19 | 94 |
| **16d** |  |  |  | 596 | 25 | 87 |
| **17a** |  |  |  | 800 | 33 | 90 |
| **17b** |  |  |  | 529 | 22 | 82 |
| **18a** |  |  |  | 678 | 28 | 88 |
| **18b** |  |  |  | 572 | 24 | 88 |

[a] Based on comparison with an analytical reference.
[b] Based on average loading per bead.
[c] Based on HPLC analysis at 220 nm.



**Scheme 5.** Reagents and conditions: (a) 0.25 M benzoic acid, BOPCl, DIEA, $CH_2Cl_2$, or neat acetic anhydride, 25 °C; (b) 0.25 M isocyanate, $CH_2Cl_2$, 25 °C; (c) 0.25 M chloroformate, DIEA, $CH_2Cl_2$, 25 °C; (d) TFA/$H_2O$/isopropanol (3:20:80), *hv* (265–325 nm wavelength), 50 °C.

cyanate, and carbamate **15** formation with both phenyl chloroformate and 4-methoxyphenyl chloroformate.

All final products were generated on resin as a pair of diastereomers with a ratio of approximately 1:1. The compounds incorporating acid-labile protecting groups were deprotected with TFA. Release of the 1,2,5-trisubstituted imidazolidin-4-ones **16**–**18** from the solid support was achieved by photolysis (Scheme 5).

To determine the yield in the photolysis, the combined eluent from 20 beads of each compound was quantitatively analyzed versus an analytically pure sample of the corresponding imidazolidin-4-one. Released compound yields range from 12% to 38% over eight steps (Table 1). The purity level of the crude substituted imidazolidin-4-one is exceptionally high. This is exemplified in Figure 2, which shows the HPLC profile at 220 nm of the purified analytical standard of **16d** in comparison to the crude bead eluent.[11]

In conclusion, a general solid-phase synthesis of 1,2,5-trisubstituted imidazolidin-4-ones has been developed. The synthesis performs well with a wide range of $R^1$, $Ar^2$, and $R^3$ components, and provides a high level of purity. This route provides an effective and efficient method for the construction of both parallel and combinatorial 1,2,5-trisubstituted imidazolidin-4-one libraries.

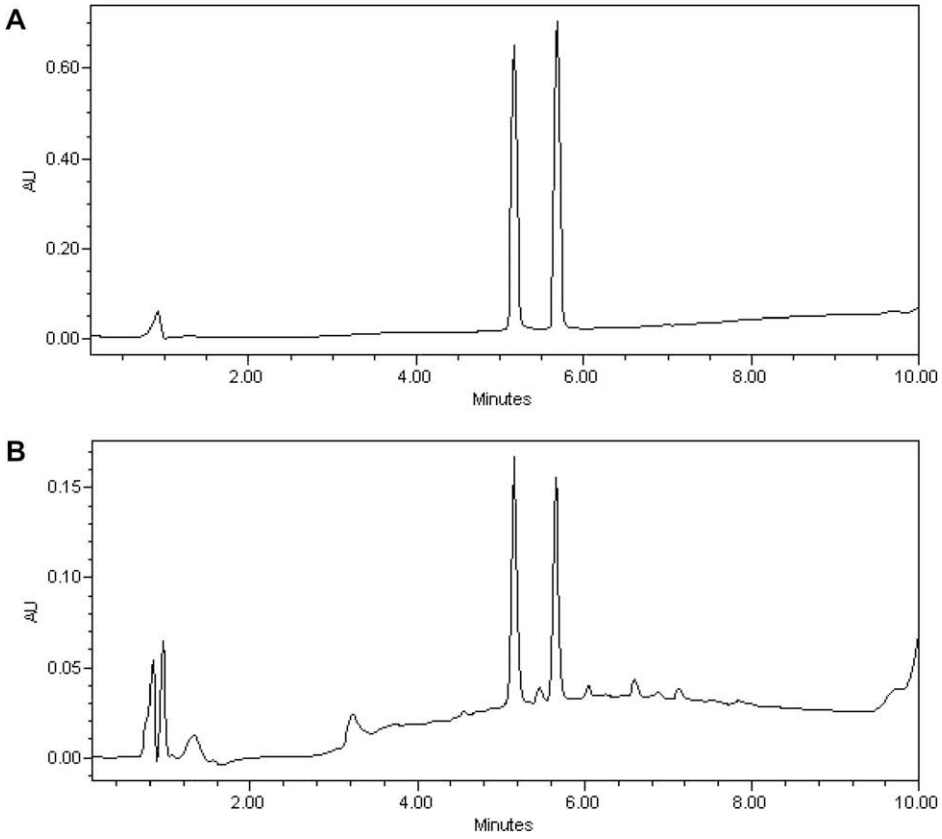



**Figure 2.** (A) HPLC profile of the standard of **16d** at 220 nm. (B) HPLC profile of the crude bead eluent of **16d** at 220 nm.

## References and notes


1. Lyssikatos, J. P.; Yang, B. V. U.S. Patent 6,194,438, 2001.
2. Gauthier, M. P.; Michaux, C.; Rolin, S.; Vastersaegher, C.; de Leval, X.; Julemont, F.; Pochet, L.; Masereel, B. *Bioorg. Med. Chem.* **2006**, *14*, 918–927.
3. Gomes, P.; Araujo, M. J.; Rodrigues, M.; Vale, N.; Azevedo, Z.; Iley, J.; Chambel, P.; Morais, J.; Moreira, R. *Tetrahedron* **2004**, *60*, 5551–5562.
4. Araujo, M. J.; Bom, J.; Capela, R.; Casimiro, C.; Chambel, P.; Gomes, P.; Iley, J.; Lopes, F.; Morais, J.; Moreira, R.; De Oliveira, E.; Do Rosario, V.; Vale, N. *J. Med. Chem.* **2005**, *48*, 888–892.
5. Hull, K. G.; Sidduri, A.; Tilley, J. PCT Int. Appl. WO0048994, 2000.
6. Blass, B. E.; Coburn, K.; Fairweather, N.; Fluxe, A.; Hodson, S.; Jackson, C.; Janusz, J.; Lee, W.; Ridgeway, J.; White, R.; Wu, S. *Tetrahedron Lett.* **2006**, *47*, 7497–7499.
7. Houghten, R. A.; Ostresh, J. M.; Yu, Y. *Tetrahedron* **2002**, *58*, 3349–3353.
8. Pospíšil, J.; Potáček, M. *Heterocycles* **2004**, *63*, 1165–1173.
9. Nestler, H. P.; Bartlett, P. A.; Still, W. C. *J. Org. Chem.* **1994**, *59*, 4723–4724.
10. Microwave reactions were performed using a Emrys™ Optimizer at 180 °C for 10 min.
11. Analytical HPLC analysis was conducted using a PDA-linked Waters Millenium 2290 and Phenomenex columbus 5u 100 × 2 mm C18 column.