Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1267–1269
Tetrahedron Letters

Solid-phase synthesis of 1,5-substituted 2-(*N*-alkylamino)-imidazolidin-4-ones

Jizhen Li, Zhenfa Zhang and Erkang Fan*

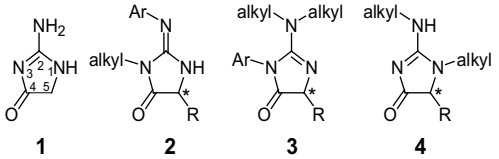
Biomolecular Structure Center, Department of Biochemistry, University of Washington, Seattle, WA 98195, USA

Received 15 September 2003; revised 26 November 2003; accepted 26 November 2003

Abstract—The solid-phase synthesis of 1,5-substituted 2-(*N*-alkylamino)-imidazolidin-4-one from resin-bound amino acid is described. Using a guanidinylating reagent in solution to form the guanidine moiety instead of resin-bound carbodiimide, an *N*-alkyl substitution is introduced specifically onto the 2-amino position. Combined with an alkylation step of the resin-bound amino acid prior to guanidinylation, all desired substitutions of the final products are achieved without racemization at chiral centers. This reaction sequence is also compatible with a variety of protected amino acid side chains.

The rapid synthesis of diverse libraries of small organic molecules for biochemical studies and drug discovery is an active research field.[1,2] Among many classes of small molecule libraries, 2-aminoimidazolin-4-one **1** is a very attractive template for combinatorial synthesis, due to its large number of possible substitution patterns and interesting combination of potential hydrogen bond donors and acceptors on a small five-membered ring system. Even though the solution synthesis of substituted **1** starting from α-amino acids was known in the 1970s and the general synthesis using the aza-Wittig route was reported in the 1980s,[3,4] only recently there have been more reports for parallel synthesis of 2-aminoimidazolin-4-one derivatives in solution[5–9] and on solid support.[10–18]

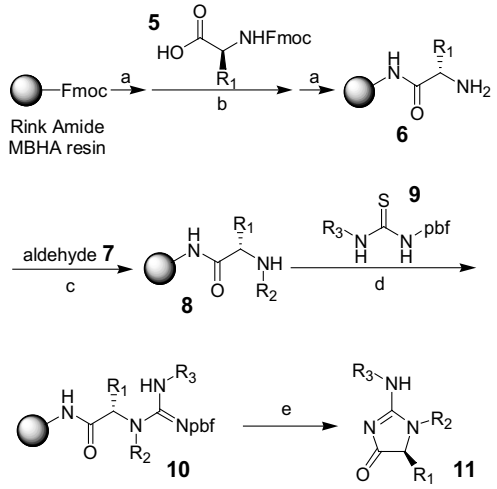
Most pioneering work of the solid-phase procedures demonstrated the clever use of α-amino acids to introduce a chiral substitution at position 5 of **1**. At the same time, on-resin formation of carbodiimide[11–14,16–18] allows for introduction of other substitutions upon the formation of the guanidine moiety before final cyclization. The compounds synthesized usually bear substitutions at the 2-amino, 3- and 5-positions of the parent ring **1**, as shown in **2**. However, this synthetic route has some limitations. First, on-resin carbodiimide formation requires the use of one aromatic substitution in the thiourea or urea precursor. This limits the 2-amino substitution to be aromatic in normal synthesis of **2**. Only in special cases, can one introduce double alkyl substitution at the 2-amino position, as shown in **3**. This changes the hydrogen bonding properties in this class of 2-aminoimidazolin-4-one derivatives as compared to those of **2**.[8,12–14] In addition, further alkylation at position 1 of the parent ring was introduced at the expense of the chiral center at position 5 using the reported method.[17] In this report, we will demonstrate the solid-phase synthesis of derivatives of 2-aminoimidazolin-4-one with well-defined monoalkyl substitutions at the 2-amino position, as shown in **4**. At the same time, alkyl substitution at position 1 is also introduced without loss of the chiral center at position 5 from the original starting amino acid. From a diversity point of view, compound **4** will offer different properties of noncovalent intermolecular interactions than those of **2** or **3**. The synthesis of compound **4** was reported in one alternative route.[15] We would also like to compare our new synthetic method with the alternative method that starts with attachment of a thiourea to solid support.



1 **2** **3** **4**

Keywords: 2-Aminoimidazolidin-4-ones; Solid-phase synthesis.
* Corresponding author. Tel.: +1-206-685-7048; fax: +1-206-685-7002; e-mail: erkang@u.washington.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.127



Scheme 1. Solid-phase synthesis of 1,5-substituted 2-(*N*-alkylamino)-imidazolidin-4-ones **11**. Reagents and conditions: (a) 20% piperidine/DMA; (b) **5** (5 equiv), PyBop (5 equiv), DIPEA (10 equiv), rt, overnight; (c) $NaCNBH_3$ (50 equiv), **7** (50 equiv), trimethyl orthoformate, rt, overnight; (d) **9** (3 equiv), DIPEA (10 equiv), 2-chloro-1-methylpyridinium iodide (3 equiv), rt, 48 h; (e) 94:3:3 trifluoroacetic acid/H_2O/triisopropylsilane, rt, 1 h.

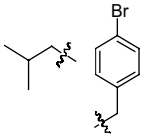
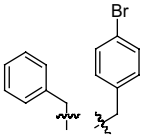
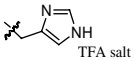
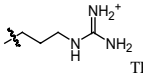
Our synthetic strategy changes the formation of the key guanidine moiety from a resin-bound carbodiimide to a reagent in solution. In doing so, the required aryl substitution for on-resin carbodiimide formation is no longer a limitation for introducing substitution at the 2-amino position. Instead, a large number of guanidinylating methodologies may be employed. In this report, we chose to use 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (pbf) activated thiourea as the guanidinylating reagent.[19] The complete synthetic route is shown in Scheme 1.

First, standard *N*-α-Fmoc protected amino acid **5** was attached to Rink amide MBHA resin. After removal of the Fmoc group, a reductive alkylation procedure[20] with alkyl or aromatic aldehyde **7** introduced the R_2 substitution. The formed secondary amine was subjected to one guanidinylating step to introduce substitution group R_3 by reaction with a pbf activated thiourea **9** in the presence of Mukaiyama reagent (2-chloro-1-methylpyridinium iodide).[19] Finally, the resin-bound product was cleaved in TFA with spontaneous cyclization to give the desired final product **11**. After removal of TFA, the crude mixture was dissolved in water, filtered to remove insoluble components, and then purified by reverse phase HPLC to produce pure **11**.

Following the above procedure, we have tested the synthesis of **11** using six amino acids with very different protected side chains. Together with two aldehydes (one alkyl, one aromatic) and one pbf activated thiourea (*N*-(4-bromobenzyl)-*N*′-(pbf)-thiourea[19]), 10 derivatives of **11** were obtained.[21] The results are listed in Table 1.

The overall isolated yields of the purified product **11** averaged about 30%. These results are comparable to the purified yields of similar compounds.[17] Some reports

Table 1. Results for the synthesis of **11**

Compound	R_1	R_2	R_3	Isolated yields (%)	Observed mass
11a	$-CH_2COOH$			36	382.00 384.00
11b	$-(CH_2)_4NH_3^+$ (TFA salt)			23	395.00 397.00
11c	$-CH_2OH$			32	353.90 355.90
11d	$-(CH_2)_2CONH_2$			32	394.90 396.90
11e	$-CH_2COOH$			30	415.90 417.90
11f	$-(CH_2)_4NH_3^+$ (TFA salt)			35	429.10 431.10
11g	$-CH_2OH$			39	387.90 389.90
11h	$-(CH_2)_2CONH_2$			25	429.00 431.00
11i	 TFA salt			28	437.90 439.90
11j	 TFA salt			32	457.90 459.90

only listed crude yields,[11–15] hence, we cannot directly compare our results with those, which range widely from 20% to 100% in yields and from 60% to 99% in purity.

There are several findings in our results that are worth noting. First, our synthetic route is suitable to a variety of amino acids bearing protected side chains. These cover all of the common protected functional groups in natural amino acids (alcohol, acid, amine, amide, imidazole, and guanidine). Among the large numbers of reported derivatives of 2-aminoimidazolin-4-one synthesized on solid support, only a few examples contain either a protected acid or alcohol (or phenol) group, for which the protections are retained in the final product.[15,18] In contrast, our current results are among the first to show that a synthetic route for substituted 2-aminoimidazolin-4-one is compatible with such a diverse range of protected amino acids.

Secondly, we achieved the introduction of N1 substitution under mild conditions using reductive amination. To the best of our knowledge, the only other solid-phase method that can prepare N1-substituted 2-aminoimidazolin-4-one starting with Fmoc protected amino acids is the method developed by the Houghten group, which utilizes a base promoted alkylation procedure. However, the Houghten procedure produces 1,5-dialkylation that leads to the loss of the chiral properties of the starting amino acids whereas our protocol avoids the racemization of the starting amino acids.

Thirdly, we have observed that the final cyclization upon TFA cleavage of **10** was greatly enhanced by the N1 substitution R_2. During the purification of final

product **11** by HPLC, we did not observe detectable amount of uncyclized product. In contrast, if N1 substitution is absent by omitting the reductive alkylation step in our protocol, the final TFA cleavage will produce a mixture of cyclized and uncyclized products in ~1:1 ratio.

Compared to an alternative synthesis of 1,5-disubstituted 2-alkylaminoimidazolin-4-one by Yang et al. that starts with immobilized isothiourea and utilizes *N*-α-Boc protected amino acids,[15] our method is a good complement in that our starting material uses Fmoc protected amino acids. Because in Fmoc chemistry all side chain protections are acid sensitive and will be concomitantly removed during synthesis using our protocol, we can save extra steps associated with final product deprotection and purification. More importantly, our procedure introduces the N1 substitution during the solid-phase stepwise protocol. In contrast, the Yang method relies on pre-formed N-substituted amino acids to obtain N1 substitution.

In summary, we have shown a mild synthetic sequence for 2-aminoimidazolin-4-one derivatives with well-controlled alkyl substitutions. Our protocol is compatible with diverse functional groups commonly found in the starting amino acids, and offers an alternative route that complements other reported methodologies.

Acknowledgements

This work is supported by the National Institutes of Health (GM94655).

References and notes

1. Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600.
2. Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
3. Wegner, M. M.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 3840–3844.
4. Wang, P. C. *Heterocycles* **1985**, *23*, 3041–3042.
5. Ding, M. W.; Tu, H. Y.; Liu, Z. J. *Synth. Commun.* **1997**, *27*, 3657–3662.
6. Ding, M. W.; Xu, Z. F.; Wu, T. J. *Synth. Commun.* **1999**, *29*, 1171–1176.
7. Liepa, A. J.; Wright, D. M. J. *Aust. J. Chem.* **2000**, *53*, 73–76.
8. Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron* **2001**, *57*, 4371–4388.
9. Ding, M. W.; Sun, Y.; Yang, S. J.; Liu, X. P.; Liu, Z. J. *Synth. Commun.* **2003**, *33*, 1651–1658.
10. Fu, M. M.; Fernandez, M.; Smith, M. L.; Flygare, J. A. *Org. Lett.* **1999**, *1*, 1351–1353.
11. Drewry, D. H.; Ghiron, C. *Tetrahedron Lett.* **2000**, *41*, 6989–6992.
12. Li, M.; Wilson, L. J. *Tetrahedron Lett.* **2001**, *42*, 1455–1458.
13. Yu, Y. P.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 521–523.
14. Lange, U. E. W. *Tetrahedron Lett.* **2002**, *43*, 6857–6860.
15. Yang, K. X.; Lou, B. L.; Saneii, H. *Tetrahedron Lett.* **2002**, *43*, 4463–4466.
16. Yu, Y. P.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 3138–3141.
17. Yu, Y. P.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **2002**, *58*, 3349–3353.
18. Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1201–1204.
19. Li, J. Z.; Zhang, G. T.; Zhang, Z. S.; Fan, E. *J. Org. Chem.* **2002**, *68*, 1611–1614.
20. Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720–6722.
21. A representative procedure is given here. Rink amide MBHA resin (0.10 mmol, loading 0.64 mmol/g) was soaked in DMA (9 mL) for 30 min and then was deprotected with 20% piperidine in DMA (9 mL) for 30 min. After washing the resin thoroughly with DMA (9 mL × 3), solutions of DIPEA (10 equiv), Fmoc-L-Asp-(*O*-*tert*-butyl) (5 equiv), and PyBop (5 equiv) in DMA (9 mL) were added to the resin. The reaction mixture was shaken gently overnight to produce resin-supported amino acid. After the Fmoc was removed with 20% piperidine in DMA (9 mL) for 30 min and washing with DMA (9 mL × 3) and dichloromethane (8 mL × 3) separately, the supported **6** was dispensed in trimethyl orthoformate (3 mL), followed by addition of an aldehyde **7** (50 equiv) in trimethyl orthoformate (1 mL) with 1% acetic acid, $NaCNBH_3$ (50 equiv) in trimethyl orthoformate (3 mL) slowly, and then 2 mL more solvent. The alkylation reaction was shaken overnight followed by washing with methanol (9 mL × 3), CH_2Cl_2 (8 mL × 3), and DMA (9 mL × 3). Then the solution of DIPEA (10 equiv) in DMF (3 mL) was added to the resin-supported **8**, followed by the solution of 2-chloro-1-methyl-pyridinium iodide (3 equiv) and *N*-(4-bromobenzyl)-*N*′-(pbf)-thiourea **9** (3 equiv) in DMF (5 mL). The reaction mixture was shaken for 48 h at room temperature. After washing and drying, the resin was cleaved with a mixture of TFA/H_2O/triisopropylsilane (94:3:3, 9 mL) for 1 h. The crude product was washed with hexane (3 mL) to remove TIS and then extracted with water (5 mL), filtered, and purified by HPLC using a C18 column to give the final target product. Using isobutyraldehyde, **11a** was obtained in 36% yield (14.0 mg). ESI-MS (*m*/*z*): 382.00 and 384.00 ($[M+H]^+$ for both Br isotopes). ^1H NMR (CD_3OD, ppm): 7.52–7.55 (d, $J = 8.3$ Hz, 2H), 7.25–7.28 (d, $J = 8.3$ Hz, 2H), 4.57, (s, 2H), 4.48–4.51 (t, $J = 4.2$ Hz, 1H), 2.96–3.44 (m, 4H), 1.98–2.05 (m, 1H), 0.92–0.99 (dd, 6H). Using benzaldehyde, **11e** was obtained in 30% yield (12.5 mg). ESI-MS (*m*/*z*): 415.90 and 417.90 ($[M+H]^+$ for both Br isotopes). ^1H NMR (CD_3OD, ppm): 7.51–7.54 (d, $J = 7.8$ Hz, 2H), 7.25–7.39 (m, 7H), 4.66–4.79 (m, 2H), 4.60 (s, 2H), 4.36 (br, t, 1H), 2.86–2.87 (d, $J = 3.6$ Hz, 2H).