Pergamon

Tetrahedron Letters 43 (2002) 1157–1160

TETRAHEDRON LETTERS

Solid-phase parallel synthesis of substituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts

Achyuta N. Acharya, John M. Ostresh and Richard A. Houghten*

Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, CA 92121, USA

Received 6 November 2001; accepted 6 December 2001

Abstract—The solid-phase synthesis of pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts is described. Following reduction of N^{α} and N^{ε}-diacylated dipeptide derived from resin-bound N^{α}-Fmoc-N^{ε}-Boc-L-lysine, the resulting tetra-amine was selectively *N*-acylated at two positions with a carboxylic acid, with the *N*-acylation most likely occurring at the two internal amines. Treatment of this compound with $POCl_3$ yielded the resin-bound pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salt. The compounds were cleaved from the solid-support and extracted with 95% acetic acid in water.

1. Introduction

The solid-phase synthesis of heterocyclic compounds has gained considerable prominence in recent years. In particular, the synthesis of mixture-based combinatorial libraries, mixtures, and arrays of compounds continues to attract attention because of their potential applications in drug discovery. Dihydroimidazoles are reported to exhibit diverse biological and pharmacological properties. Examples of these include α-receptor stimulation, vasodepressor activity, α-adrenergic inhibition, and sympathomimetic, antihistaminic, histamine-like, and cholinomimetic activity.[1,2] Dihydroimidazoles, such as midaglizole, deriglidole, and efaroxan have been found to be potent antihyperglycemic agents.[3] In a continuation of our efforts to synthesize small molecule heterocyclic compounds from amino acids and peptides, we herein report the solid-phase synthesis of pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts from resin-bound dipeptides.

2. Results and discussion

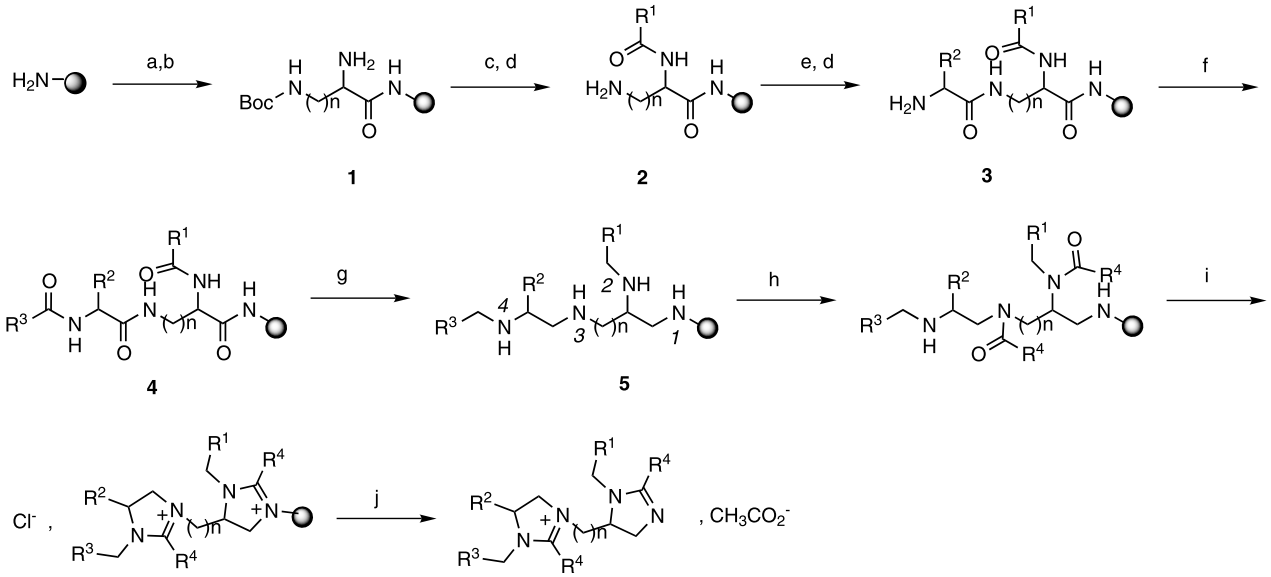
The synthetic strategy for the solid-phase synthesis of pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts is outlined in Scheme 1. N^{α}-Fmoc-N^{ε}-Boc-L-lysine was coupled to *p*-methylbenzhydrylamine (MBHA) resin sealed inside a polypropylene mesh packet,[4] followed by deprotection of the Fmoc group, generating compound **1** having a primary amine.[5] The primary amine was *N*-acylated with a carboxylic acid, followed by deprotection of the Boc group from the side chain to generate compound **2** having a primary amine. Following coupling of a Boc-protected amino acid, the Boc group was deprotected. The primary amine of the resulting resin-bound N^{α}-acylated dipeptide **3** was then *N*-acylated with a carboxylic acid. Completeness of the coupling was monitored by the ninhydrin test.[6] Exhaustive reduction of the resin-bound N^{α} and N^{ε}-diacylated dipeptide **4** with BH_3–THF[7] generated tetra-amine **5** having four secondary amines. *N*-Acylation at the two internal secondary amines was carried out using low concentration of a carboxylic acid in the presence of HBTU and DIEA. Using low concentrations of carboxylic acid (4 equiv. secondary amine versus total 5 equiv. excess of carboxylic acid), *N*-acylation most likely proceeded via the two internal (N2 and N3) secondary amines due to less relative steric hindrance at those secondary amines. Similar reactivity of these secondary amines of resin-bound polyamine was observed in our earlier work.[8] The resin-bound compound **6** was then treated with $POCl_3$[8,9] in dioxane at 110°C to generate compound **7**. This was most likely due to cyclodehydration of the in situ formed imidoyl chloride intermediate[9] to yield the resin-bound pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salt. The compound was cleaved from the solid-support using anhydrous HF[10] and extracted with 95% acetic acid in water to yield **8**.

Keywords: solid-phase synthesis; dihydroimidazole.

* Corresponding author. Tel.: 858-455-3803; fax: 858-455-3804; e-mail: rhoughten@tpims.org

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02385-1

Forty control compounds were prepared using 10 carboxylic acids at the first (R^1), third (R^3), and fourth (R^4) positions of diversity and 10 amino acids for the second (R^2) position of diversity. In all cases, complete cyclization was observed by LC-MS and reverse-phase high-pressure liquid chromatography (RP-HPLC). Serine, threonine, aspartic acid, and glutamic acid analogues at the second (R^2) position of diversity yielded side products most likely due to $POCl_3$ mediated dehydration at 110°C. Similarly, amino acids having an extra amine functionality (example ornithine) or generating extra amine functionality after reduction (example



Scheme 1. (a) N^{α}-Fmoc-N^{ε}-Boc-L-lysine (2.5 equiv., 0.05 M, DMF), DIC (2.5 equiv.), HOBt (2.5 equiv.), overnight, rt; (b) 20% piperidine in DMF, 30 min, rt; (c) R^1CO_2H (10 equiv., 0.1 M, DMF), DIC (10 equiv.), HOBt (10 equiv.), overnight, rt; (d) 50% TFA/50% DCM, 30 min, rt; (e) Boc-NHCH(R^2)CO_2H (6 equiv., 0.1 M, DMF), DIC (6 equiv.), HOBt (6 equiv.), 2 h, rt; (f) R^3CO_2H (10 equiv., 0.1 M, DMF), DIC (10 equiv.), HOBt (10 equiv.), overnight, rt; (g) (i) BH_3–THF, 65°C, 72 h; (ii) piperdine, 65°C, 20 h; (h) R^4CO_2H (5 equiv., 0.05 M, DMF), HBTU (5 equiv.), DIEA (10 equiv.), overnight, rt; (i) $POCl_3$ (10 equiv., 0.09 M, dioxane), 110°C, 2.5 h; (j) HF, anisole, 0°C, 7 h. 'n = 4' denotes tether carbon length.

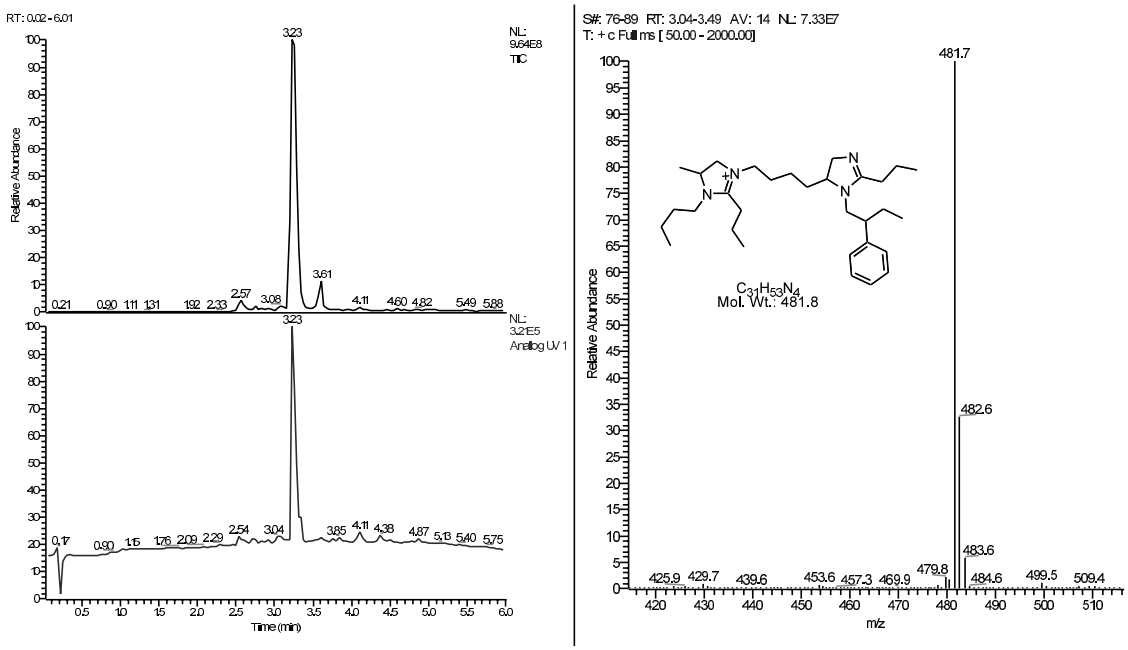


Figure 1. LC-MS of compound **8a** derived from 2-phenylbutyric acid, L-Ala, butyric acid, and butyric acid at the R^1 through R^4 positions, respectively.

Table 1. RP-HPLC purity and masses found for the pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium trifluoroacetates **8**[a]

Product	R^1	R^2	R^3	R^4	MW calcd.	MW found	Purity[b] (%)
8a	$-CH(C_6H_5)C_2H_5$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	481.8 (M^+)	481.7 (M^+)	82
8b	$-CH_2C_5H_4(3\text{-}CH_3)$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	467.8 (M^+)	467.6 (M^+)	83
8c	$-CH_2C_5H_4(3\text{-}CF_3)$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	521.7 (M^+)	521.7 (M^+)	76
8d	$-CH_2C_5H_4(4\text{-}F)$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	471.7 (M^+)	471.7 (M^+)	78
8e	$-CH(CH_3)C_2H_5$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	419.7 (M^+)	419.6 (M^+)	80
8f	$-(CH_2)_2CH_3$	$-CH_2C_6H_5$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	481.8 (M^+)	481.6 (M^+)	74
8g	$-(CH_2)_2CH_3$	$-CH(CH_3)_2$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	433.7 (M^+)	433.6 (M^+)	76
8h	$-(CH_2)_2CH_3$	$-(CH_2)_3CH_3$	$-(CH_2)_2CH_3$	$-CH_2CH_2CH_3$	447.8 (M^+)	447.5 (M^+)	78
8i	$-(CH_2)_2CH_3$	$-CH_3$	$-CH_2C_6H_4(4\text{-}OC_2H_5)$	$-CH_2CH_2CH_3$	497.8 (M^+)	498.1 (M^+)	80
8j	$-(CH_2)_2CH_3$	$-CH_3$	$-C_5H_9$	$-CH_2CH_2CH_3$	431.7 (M^+)	431.7 (M^+)	75
8k	$-(CH_2)_2CH_3$	$-CH_3$	$-(CH_2)_5CH_3$	$-CH_2CH_2CH_3$	447.8 (M^+)	447.6 (M^+)	76
8l	$-(CH_2)_2CH_3$	$-CH_3$	$-C_4H_7$	$-CH_2CH_2CH_3$	417.7 (M^+)	417.5 (M^+)	74
8m	$-(CH_2)_2CH_3$	$-CH_3$	1-Adamantyl	$-CH_2CH_2CH_3$	497.8 (M^+)	497.7 (M^+)	70
8n	$-(CH_2)_2CH_3$	$-CH_3$	$-(CH_2)_2CH_3$	$-(CH_2)_3C_6H_{11}$	570.0 (M^+)	570.2 (M^+)	78
8o	$-(CH_2)_2CH_3$	$-CH_3$	$-(CH_2)_2CH_3$	$-(CH_2)_2CH(CH_3)_2$	461.8 (M^+)	461.6 (M^+)	80
8p	$-(CH_2)_2CH_3$	$-CH_3$	$-(CH_2)_2CH_3$	$-CH_3$	349.6 (M^+)	349.4 (M^+)	82

[a] The crude yields (by weight) obtained were 60–75% in all cases with respect to the initial loading of the resin at 1.10 meq/g.
[b] Crude purity determined from the relative peak areas (%) of HPLC chromatograms with monitoring at 214 nm.

glutamine, asparagine) were excluded at the second R^2 position of diversity due to undesired *N*-acylation (in step h, Scheme 1). One representative LC-MS of compound **8a** is presented as Fig. 1. The final compounds were obtained in moderate yield and good purity. Sixteen randomly selected individual control compounds are presented in Table 1. The lower than expected yield is attributed to the premature acidolytic cleavage of both starting material and product by HCl formed during $POCl_3$ treatment.[11] Thus, anhydrous conditions were maintained to minimize premature cleavage.

3. Conclusion

The synthesis of pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts from resin-bound *N*-diacylated dipeptides is presented. Due to the high purity of the final products, this approach can be extended to prepare a combinatorial library of thousands of compounds.

Acknowledgements

A.N.A. thanks the Department of Industries, Govt. of Orissa, India for sanction of study leave. This work was funded by National Cancer Institute Grant No. CA 78040 (Houghten).

References

1. Gilman, A. G.; Goodman, L. S. In *The Pharmacological Basis of Therapeutics*; 10th ed.; Macmillan & Co.: New York, 2001; Chapter 10, pp. 215–268.
2. Greenhill, J. V.; Lue, P. *Progress in Medicinal Chemistry*; Elseiver Science: New York, 1993; p. 203.
3. Bihan, G. L.; Rondu, F.; Pele, A.-T.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola, B.-L.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem* **1999**, *42*, 1587.
4. Houghten, R. A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.
5. *Typical procedure for the individual synthesis of pentasubstituted dihydroimidazolylbutyl dihydroimidazol-3-ium salts*. A polypropylene mesh packet consisting of 100 mg of MBHA resin was sealed. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% *N*,*N*′-diisopropylethylamine (DIEA) in DCM and washed with DCM. Polypropylene bottles were used for all reactions. All the amino acids used had L-configurations. (1) *Preparation of the resin-bound* N^{α} and N^{ε}*-diacylated dipeptide derived from* N^{α}*-Fmoc-*N^{ε}*-Boc-Lysine* (Scheme 1). N^{α}-Fmoc-N^{ε}-Boc-L-lysine (2.5 equiv., 0.05 M, overnight) in DMF was coupled to MBHA resin using DIC and HOBt (2.5 equiv. each) at room temperature. The coupling was monitored by the ninhydrin test. Following washes with DMF (four times), the N^{α}-Fmoc group was deprotected using 20% piperidine in DMF for 30 min and washes with DMF (four times) and DCM (three times). The resulting primary amine was *N*-acylated with a carboxylic acid (10 equiv., 0.1 M, overnight) in DMF in the presence of DIC (10 equiv.) and HOBt (10 equiv.), followed by washes with DMF (four times) and DCM (three times). The N^{ε}-Boc group was deprotected using 50% trifluoroacetic acid in DCM for 30 min, followed by neutralization with 5% DIEA in DCM. A Boc-amino acid (6 equiv., 0.1 M) in DMF was coupled in the presence of DIC (6 equiv.) and HOBt (6 equiv.) for 2 h, followed by deprotection of the Boc group and neutralization was performed as described above. The resulting primary amine was *N*-acylated with

a carboxylic acid in the same manner as described above. (2) *Exhaustive reduction of amide groups of the N^{α} and N^{ε}-diacylated dipeptide by BH_3–THF*. Exhaustive reduction of the N^{α} and N^{ε}-diacylated dipeptide was carried out in 50 mL glass conical tubes under nitrogen. The resin packet (0.11 meq resin) was added to each tube, followed by addition of boric acid (12 equiv.) and trimethyl borate (12 equiv.). Borane–THF complex (1 M, 40 equiv.) was added slowly. After cessation of hydrogen evolution, the capped tubes were heated at 65°C for 72 h, followed by decantation of the reaction solution and quenching with methanol (MeOH). The resin was washed with DMF and MeOH (four times), followed by treatment with piperidine at 65°C for 20 h to disproportionate the borane complexes. Following decantation of the piperidine–borane solution, the resin packet was washed with DMF (four times), DCM (four times) and MeOH (two times) and dried. (3) *Selective N-acylation at two internal secondary amine of the tetra-amine*. Following neutralization, *N*-acylation was performed with a carboxylic acid (5 equiv., 0.06 M, overnight) in DMF in the presence of HBTU (5 equiv.) and DIEA (10 equiv.). The resin was washed with DMF (four times), DCM (two times), IPA (two times), and DCM (three times). (4) *Cyclization on treatment with $POCl_3$*: The cyclization of the *N*-diacylated compound was carried out in 50 mL conical tubes under nitrogen. To each tube was added the resin packet, $POCl_3$ (10 equiv., 0.09 M), and anhydrous dioxane. The capped tubes were heated at 110°C for 2.5 h followed by decantation of the reaction solution. The resin was washed with dioxane (two times), DMF, MeOH (four times each), DCM (two times), IPA (two times) and DCM (four times). The resin was cleaved by anhydrous HF in the presence of anisole at 0°C for 7 h and the cleaved product was extracted with 95% acetic acid in H_2O and lyophilized. The compound was purified by preparative high-pressure liquid chromatography (HPLC) and characterized by LC-MS and ^{1}H NMR spectroscopy. **(5*S*)-1-Butyl-5-methyl-3-{4-[1-(2-phenylbutyl)-2-propyl-4,5-dihydro-1H-imidazol-5-yl] butyl}-2-propyl-4,5-dihydro-1H-imidazol-3-ium trifluoroacetate (8a)**: MS (APCI) m/z 481.7 (M^+), ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.71–0.77 (m, 6H), 0.90–1.01 (m, 4H), 1.08–1.11 (m, 6H), 1.26–1.29 (m, 8H), 1.48–1.61 (m, 9H), 1.71–1.75 (m, 3H), 2.15–2.19 (m, 1H), 2.57–2.61 (m, 1H), 2.78–2.82 (m, 1H), 2.88–2.91 (m, 1H), 3.31–3.57 (m, 2H), 3.72–3.75 (m, 3H), 3.92–3.96 (m, 1H), 4.23–4.24 (m, 1H), 4.38–4.40 (m, 1H), 7.26–7.35 (m, 5H), 9.76 (s, 1H), 10.05 (s, 1H).

6. Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.
7. Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622.
8. Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 612.
9. (a) Fodor, G.; Nagubandi, S. *Tetrahedron*. **1980**, *36*, 1279; (b) Bohle, E.; Egg, H.; Gollner, B.; Jussel, C. *Sci. Pharm*. **1989**, *57*, 333; (c) Gauthier, J. A.; Jirkovsky, I. US Patent No. 4379926, **1983**.
10. Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Peptide Prot. Res.* **1986**, *27*, 673.
11. Huheey, J. E. *Inorganic Chemistry*; Harper and Row: New York, 1983; p. 289.