Pergamon

Tetrahedron Letters 41 (2000) 5419–5421

TETRAHEDRON LETTERS

Solid-phase synthesis of substituted 2-aminomethylbenzimidazoles

John P. Kilburn,[a,b,*] Jesper Lau[a] and Raymond C. F. Jones[b,†]

[a]*Novo Nordisk A/S, Novo Nordisk Park, DK 2760 Maaleov, Denmark*
[b]*Chemistry Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK*

Received 12 April 2000; accepted 23 May 2000

Abstract

Resin-bound 4-fluoro-3-nitrobenzoic acid is converted by reaction with a range of amines and reduction, to substituted 1,2-diaminobenzenes, whose reaction with activated amino acids followed by acid-catalyzed cyclisation gave resin-bound benzimidazoles; Fmoc-deprotection, acylation and TFA-mediated cleavage gave substituted 2-aminomethylbenzimidazoles via a new solid support strategy. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: solid-phase synthesis; benzimidazole; combinatorial chemistry.

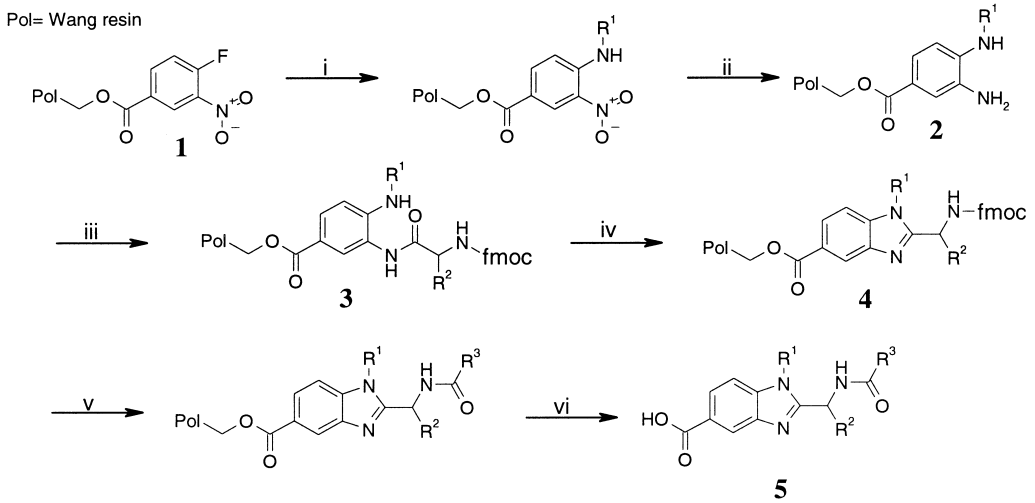
Combinatorial chemistry has over the past decade made impressive advances in the generation of small molecule libraries;[1] these advances, taken together with high throughput screening, have given the medicinal chemist an invaluable tool in drug discovery.[2] Solid-phase organic chemistry, whilst sometimes limited, enables the chemist to rapidly survey many reactions that would be otherwise difficult, laborious and expensive via traditional solution methods. An example of such a reaction is the formation of substituted benzimidazoles from 1,2-diaminobenzenes and carboxylic acids. There are to date a number of solid-phase strategies reported for the synthesis of benzimidazoles,[3] the most attractive with regard to high purity and yield involves the reaction of aldehydes with resin bound 1,2-diaminobenzenes.[4] The availability of aldehydes, which contain other functional groups, is limited, and thus restricts the molecular diversity of the scaffold. Reports of the solid-phase synthesis of benzimidazole libraries from 1,2-diaminobenzenes and carboxylic acids have the key cyclisation step as the last cleavage step.[5] This limits the chemistry which could otherwise be undertaken if the benzimidazole moiety had been formed on the resin.

* Corresponding author. Fax: +45 44 66 34 50; e-mail: jpk@novo.dk
† Present address: Department of Chemistry, Loughborough University, Loughborough LE11 3TU, UK.

0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)00871-6

Prompted by an ongoing interest in aminoalkylimidazole systems,[6] we have developed and report herein a new strategy for the closure of the benzimidazole ring whilst attached to the resin.

Optimisation of each of the following steps was monitored by cleavage of small portions of the resins, which were analysed using HPLC and MS methods. Commercial Wang resin[7] was first loaded with 4-fluoro-3-nitrobenzoic acid using a standard diisopropyl carbodiimide (DIC)/DMAP coupling procedure.[8] A range of amines could then be incorporated via nucleophilic aromatic substitution with the resin-bound 4-fluoro-3-nitrobenzoate in DMF. The nitro-group was reduced using tin(II) chloride dihydrate in *N*-methylpyrrolidone (NMP) to afford the substituted 1,2-diaminobenzenes **2** (Scheme 1).



Scheme 1. *Reagents*: (i) R^1NH_2, DMSO, 20°C, 16 h; (ii) $SnCl_2{\cdot}2H_2O$, NMP, 20°C, 16 h; (iii) $FmocNHCHR^2CO_2H$, PyBroP/DIPEA, NMP, 20°C, 16 h; (iv) AcOH, 90°C, 16 h; (v) piperidine:NMP (1:4 v/v), 20°C, 20 min; then R^3COOH, DIC/HOBt/DIPEA, DCP:NMP (1:1 v/v), 20°C, 16 h; (vi) TFA:CH_2Cl_2 (1:1 v/v), 20°C, 1 h

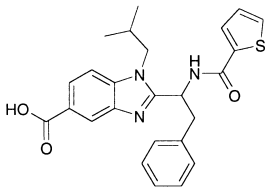
Acylation of the resin bound primary aniline **2** was accomplished using bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBroP)/DIPEA coupling no diacylation was observed. The symmetric anhydride method with DIC gave products of diminished yield and purity.[9]

The next step was the acid-catalysed cyclisation of resin bound amide **3**. This was achieved by treatment of the resin with glacial acetic acid at 90°C. The Wang resin was stable under these conditions although temperatures higher than this caused degradation of the resin. The ensuing Fmoc-protected resin **4** was deprotected with piperidine in NMP to afford the resin-bound 2-aminomethylbenzimidazole moiety. This could then be acylated with a range of acids using the DIC/HOBt/DIPEA coupling procedure[10] in 1,2-dichloropropane (DCP)/NMP to give the resin-bound 2-acylaminomethylbenzimidazoles **5** (Table 1). Cleavage of the final products was obtained by treatment of the resin with TFA/DCM for 1 h.

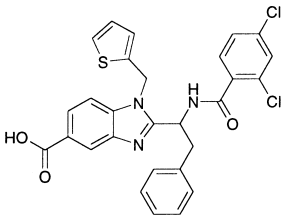
Deprotection of acylated aniline **3** with piperidine/NMP, followed by treatment with benzoic acid (PyBroP/DIPEA, NMP, 16 h, 20°C) yielded 56% of a double acylated product, in which the secondary aniline had also been acylated. This illustrates the importance of closing the benzimidazole ring before other similar reactions can be performed.

In summary, we have demonstrated a new solid-phase strategy for the synthesis of substituted 2-aminomethylbenzimidazoles **5**, with the benzimidazole moiety being formed whilst resin-bound. The 2-aminomethylbenzimidazoles were prepared in eight steps and 36–86% overall yields.

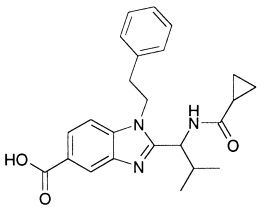
Table 1
Listing of benzimidazoles **5** synthesised, with purity as assessed by integration of ELS peak areas; the figure in parenthesis refers to crude yield calculated from the original loading of the Wang resin



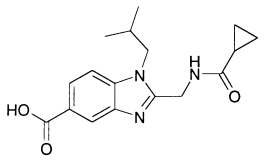
5a: 80(63)



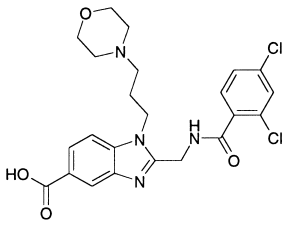
5b: 70(51)[11]



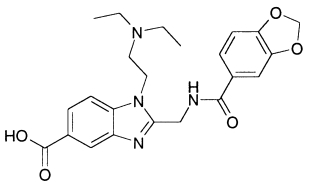
5c: 81(64)



5d: 84(86)



5e: 99(36)



5g: 96(49)

References

1. (a) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643–5678. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554. (d) Thompson, L. A.; Ellman, J. A. *Chem. Rev*. **1996**, *96*, 555–600. (e) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 17–42. (f) Balkenhohl, F.; Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2288–2337.
2. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, P. A.; Gallop, M. A. *J. Med. Chem*. **1994**, *37*, 1385–1401.
3. (a) Huang, W.; Scarborough, R. M. *Tetrahedron Lett*. **1999**, *40*, 2665–2668. (b) Smith, J. M.; Gard, J.; Cummings, W.; Kanizasi, A.; Krchňák, V. *J. Combi. Chem*. **1999**, *1*, 368–370. (c) Yeh, C.; Sun, C. *Synlett* **1999**, *6*, 810–812. (d) Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett*. **1998**, *39*, 201–204. (e) Phillips, G. B.; Wei, G. P. *Tetrahedron Lett*. **1996**, *37*, 4887–4890.
4. (a) Smith, J. M.; Krchňák, V. *Tetrahedron Lett*. **1999**, *40*, 7633–7636. (b) Blettner, C. G.; König, W. A.; Rühter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, *3*, 307–310. (c) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett*. **1999**, *40*, 6185–6188. (d) Sun, Q.; Yan, B. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 361–364. (d) Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett*. **1998**, *39*, 6655–6658.
5. Tumelty, D.; Schwarz, M. K.; Needels, M. C. *Tetrahedron Lett*. **1998**, *39*, 7467–7470.
6. Jones, R. C. F.; Gilbert, I. H.; Rees D. C.; Crockett, A. K. *Tetrahedron*, **1995**, *51*, 6315–6336.
7. Wang resin (*p*-benzyloxybenzyl alcohol resin) was purchased from Novabiochem, Laufelfingen, Switzerland.
8. Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett*. **1998**, *39*, 6655–6658
9. Neustadt, B. R.; Smith, E. M.; Nechuta, T.; Zhang, Y. *Tetrahedron Lett*. **1998**, *39*, 5317–5320
10. R^3COOH (10 equiv.), HOBt (10 equiv.), DIC (10 equiv.), DIEA (10 equiv.), NMP:DCP (1:1 v/v), 16 h, 20°C.
11. NMR data for **compound 5b**; dH [400MHz; $(CD_3)_2SO$] 12.79 (1H, s, OH), 9.42 (1H, d, J = 8.6 Hz, NH), 8.26 (1H, s, Ar-H), 7.90 (1H, d, J = 8.6 Hz, Ar-H), 7.72 (1H, d, J = 8.6 Hz, Ar-H), 7.61 (1H, d, J = 2.0 Hz, Ar-H), 7.45 (1H, d, J = 6.6 Hz, thienyl-H), 7.42 (1H, d, J = 6.6 Hz, Ar-H), 7.28–7.24 (5H, m, Ar-H), 7.08 (1H, d, J = 5.09 Hz, Ar-H), 7.06 (1H, d, J = 3.05 Hz, thienyl-H), 6.97 (1H, dd, J = 5.0, 3.5 Hz, theinyl-H), 5.85 (2H, s, NCH_2), 5.77 (1H, m, $CHCH_2$, 3.40 (2H, d, J = 7.6 Hz, CH_2CH).