Pergamon

Tetrahedron Letters 40 (1999) 7633–7636

TETRAHEDRON LETTERS

A solid phase traceless synthesis of benzimidazoles with three combinatorial steps

Jennifer M. Smith and Viktor Krchňák *

SIDDCO, 9040 South Rita Rd, Tucson, AZ 85747, USA

Received 9 July 1999; accepted 9 August 1999

Abstract

A three combinatorial step solid-phase traceless synthesis of benzimidazoles is reported. The aldehyde resin was reductively alkylated by amines, the resin bound secondary amines were reacted with *o*-fluoronitrobenzenes, and the resulting *o*-nitroanilines were reduced by tin chloride. The primary aniline was acylated by acid chlorides. Exposure to acetic acid at elevated temperature cleaved and cyclized the acylated *o*-phenylenediamines to benzimidazoles. © 1999 Published by Elsevier Science Ltd. All rights reserved.

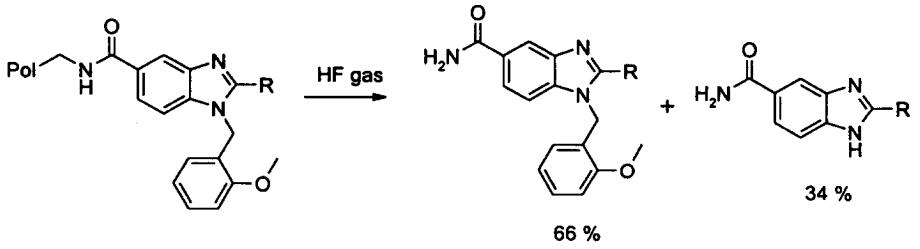
One of the challenges of the solid-phase combinatorial synthesis of heterocyclic compounds is developing chemical routes that provide access to the target compounds without leaving any trace of the linker used for tethering the starting building blocks to the solid support.[1] Numerous chemical schemes were devised that provided the traceless synthesis of heterocyclic compounds.[2] Recent publication of traceless synthesis of benzimidazoles with two combinatorial points[2n] prompted us to report our results concerning the traceless synthesis of benzimidazoles. Our concept of the traceless synthesis of benzimidazoles is based on solid-phase synthesis of a linear precursor and subsequent off resin cyclization.

We observed two side reactions during the synthesis of benzimidazoles from *N*-alkylated resin-bound *o*-phenylenediamines and aldehydes.[3] The first one was dependent on steric rather then electronic effects of substituents on aldehydes and *o*-phenylenediamines and lead to the alkylation of benzimidazoles. The second one occurred during cleavage of the cyclized product from the solid support by gaseous HF. When a benzyl group with an electron donating substituent was present on the nitrogen, the benzyl group was partially cleaved producing a benzimidazole derivative with no substituent on the nitrogen (Scheme 1). We thought that this side reaction could be utilized for the traceless synthesis of benzimidazoles.

To prove the concept, we decided to attach the benzimidazole precursor (*o*-nitroaniline) to the polymer supported *p*-methylbenzhydrylamine (MBHA) linker via the aniline nitrogen atom (Scheme 2). The *p*-methylbenzhydrylamine resin was reacted with *o*-fluoronitrobenzene, the nitro group was reduced by tin chloride, and the *o*-phenylenediamine was cyclized to benzimidazole with an aldehyde.[4] The product was

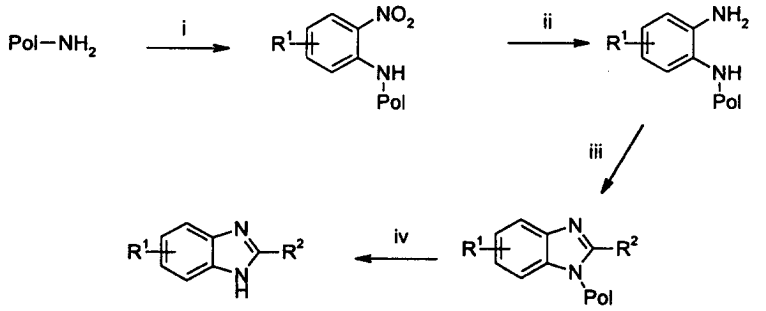
* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01560-9

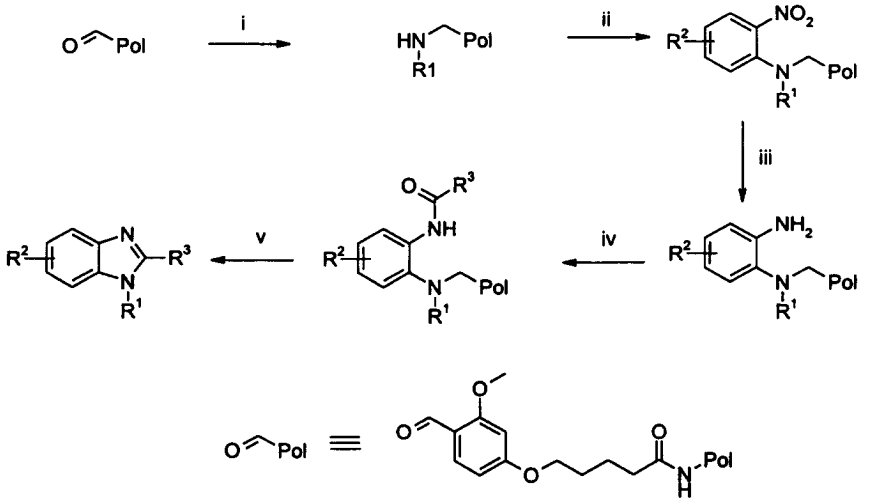


Scheme 1. Cleavage of *N*-benzyl group on benzimidazoles by gaseous HF

cleaved from the resin by gaseous HF. However, this route accessed benzimidazoles with only two points of diversity. We were therefore trying to modify the scheme and include an additional combinatorial step that would provide a synthetic route to benzimidazoles with three points of diversity. After several unsuccessful attempts we succeeded to prepare the target compounds the following way (Scheme 3).



Scheme 2. A synthesis of traceless benzimidazoles with two combinatorial steps. Reagents: (i) *o*-fluoronitrobenzene, DMF, rt, overnight; (ii) $SnCl_2$ in NMP, rt, overnight; (iii) aldehyde in DMF, rt, overnight; (iv) gaseous HF, 2 h



Scheme 3. A traceless synthesis of benzimidazoles with three combinatorial steps. Reagents: (i) amine/$NaBH(AcO)_3$ in DMF/AcOH; (ii) *o*-fluoronitrobenzene, DMSO, rt, overnight; (iii) $SnCl_2$ in NMP, rt, overnight; (iv) acid chloride/DIEA in DCM, rt, overnight; (v) AcOH, 80°C, overnight

The synthesis was developed on (4-(4-formyl-3-methoxyphenoxy)butyryl) resin (Novabiochem, Laufelfingen, Switzerland). The aldehyde resin was reacted with series of amines and formed Schiff base was reduced by $NaBH(AcO)_3$ in 5% AcOH in DMF. We have developed a simple protocol for qualitative

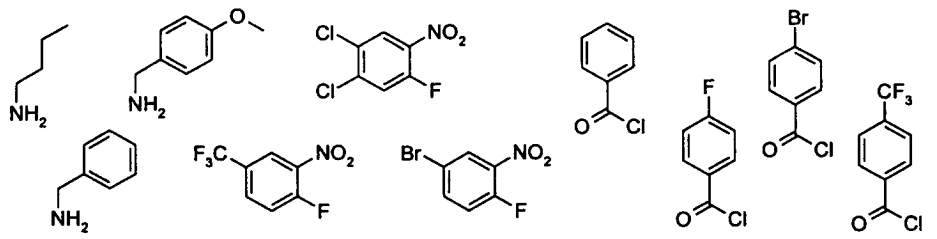


Figure 1. Structure of amines, *o*-fluoronitrobenzenes, and acid chlorides

Table 1
Purity and yield of linkerless benzimidazoles

Entry	R^1	R^2	R^3	Rt (min)	Purity (%)	Yield (%)
1	4-OMe-Bn	4-CF_3	Ph	6.9	82	54
2	4-OMe-Bn	1,2-diCl	4-F-Ph	7.7	94	70
3	Bn	4-CF_3	4-Br-Ph	8.1	88	30
4	Bn	1,2-diCl	4-CF_3-Ph	8.7	91	64
5	n-Bu	4-Br	4-F-Ph	5.8	96	72
6	4-OMe-Bn	4-CF_3	4-Br-Ph	8.0	85	48
7	4-OMe-Bn	1,2-diCl	4-CF_3-Ph	8.6	90	71
8	Bn	4-CF_3	Ph	7.0	90	46
9	Bn	1,2-diCl	4-F-Ph	7.8	96	74
10	n-Bu	4-Br	4-CF_3-Ph	7.4	90	53

and quantitative analytical control of the secondary amine resins.[5] The yield of the reductive amination was over 90% and the purity of Fmoc derivatized amines was excellent. Various *o*-fluoronitrobenzenes were reacted with the secondary amine resin in DMSO yielding tethered *o*-nitroanilines. Overnight reaction at room temperature was found sufficient when using fluoronitrobenzenes containing an electron withdrawing group. The nitro group was reduced by tin chloride in NMP and the aniline was acylated by acid chlorides in DCM. When the acylated intermediate was exposed to TFA a mixture of acylated *o*-phenylenediamine and target benzimidazole was isolated. The benzimidazole was obtained as the major peak consistently. When the mixture in acetic acid was exposed to 80°C overnight, the acylated *o*-phenylenediamine cyclized quantitatively to the benzimidazole. To shorten the two step procedure of cleavage and cyclization, we exposed the resin-bound intermediates to AcOH at elevated temperature overnight. The target benzimidazoles do not carry any memory of the linker, the third nitrogen valence used to attach the intermediate to the resin was utilized in the subsequent cyclization step.

A small set of compounds was synthesized in a combinatorial fashion on manually operated Domino Blocks[6] using building blocks shown in Fig. 1. The purity of the products was analyzed by HPLC and ranged from 82 to 96% (Table 1), average being over 90%.[7] The correct molecular weight was confirmed by mass spectrometry (PE-Sciex API III+ with an articulated ion spray sample inlet system). Structure was confirmed by NMR spectra.[8]

In summary, we developed a new and straightforward solid-phase traceless synthesis of benzimidazoles with three combinatorial steps. The reaction conditions are amendable to a synthesis of large combinatorial libraries and the purity of final product is excellent.

References

1. Rather than using a relative term 'traceless linker' we prefer to use the terminology traceless synthesis. For example, the Wang linker may leave a trace (carboxyl group) on a heterocyclic compound, however, it is suitable for the linkerless

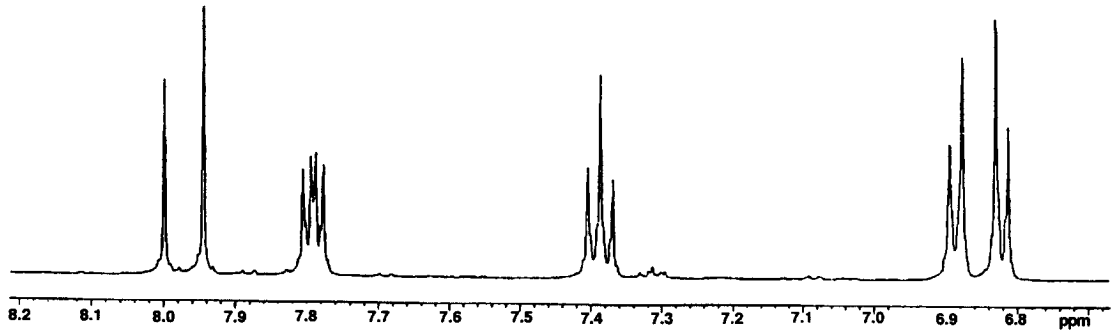


Figure 2. An aromatic region of the NMR spectrum of compound **2**

synthesis of peptides since the carboxyl group is an inherent part of peptides. On the other hand the silicon linker leaves a trace, the benzene ring, if the benzene moiety is not a part of the target compound.

2. (a) Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483–1486. (b) Lorsbach, B. K.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1996**, *61*, 8716–8717. (c) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 211–214. (d) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885–2893. (e) Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 6102–6103. (f) Kroll, F. E. K.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573–8576. (g) Jin, S.; Holub, D. P.; Wustrow, D. J. *Tetrahedron Lett.* **1998**, *39*, 3651–3654. (h) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800–2801. (i) Millington, C. R.; Quarrell, R.; Lowe, G. *Tetrahedron Lett.* **1998**, *39*, 7201–7204. (j) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317–8320. (k) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* **1998**, *63*, 9204–9211. (l) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244–2250. (m) Cobb, J. M.; Fiorini, M. T.; Goddard, C. R.; Theoclitou, M.-E.; Abell, C. *Tetrahedron Lett.* **1999**, *40*, 1045–1048. (n) Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668.
3. Smith, J.; Krokhina, G.; Gard, J.; Kaniszai, A.; Krchňák, V., submitted for publication
4. The reaction of *o*-phenylenediamine with aldehyde yields benzimidazoline, which is prone to oxidation to benzimidazole. We never detected this primary product.
5. Pre-weighted sample of the secondary amine resin was treated with 0.5 M Fmoc-Cl and 0.5 M DIEA in DCM for 1 h. After washing the resin with DCM and DMF, the Fmoc group was cleaved by 10 min treatment with 50% piperidine in DMF. The resin was washed with DMF, all washes were collected, the absorbance at 302 nm was measured, and the Fmoc release was quantified. Another sample of Fmoc-Cl treated secondary amine resin was cleaved by TFA for 1 h, TFA was evaporated, sample dissolved in MeOH and the purity evaluated by analytical HPLC.
6. Krchňák, V.; Padera, V. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3261–3264.
7. Analytical gradient HPLC profile was run on a ProC18 4.6×50 mm analytical column (YMC, Wilmington, NC), gradient 0–70% of ACN in 7 min. The purity was estimated based on analytical traces at 280 nm.
8. All compounds listed in Table 1 provided expected NMR spectra (500 MHz, DMSO-d_6). One example is shown in Fig. 2.