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Solid-Phase Synthesis of Substituted 1-Phenyl-2-aminomethyl-benzimidazoles and 1-Phenyl-2-thiomethyl-benzimidazoles

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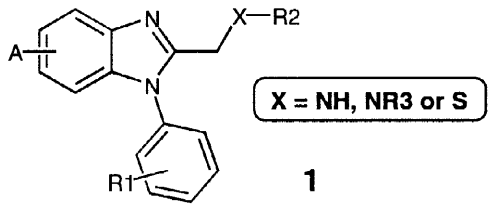
Abstract: A solid-phase route to the title compounds is described. Resin-bound intermediate **2**, derived from 4-fluoro-3-nitrobenzoic acid, was reacted with substituted anilines then reduced with $SnCl_2$/NMP to form *o*-diphenyl diamines **4**. Reaction with bromoacetic anhydride, nucleophilic displacement with amines or thiols in DMSO and subsequent cleavage/cyclization of the resin-bound intermediates **6** with neat TFA gave substituted 1-phenyl-2-aminomethyl-benzimidazoles and 1-phenyl-2-thiomethyl-benzimidazoles **7** in good yield and purity.

Combinatorial chemistry[1-3] has emerged in the last five years as an increasingly powerful tool for accelerating the synthesis and screening of diverse collections of molecules. Solid-phase organic chemistry offers the opportunity of synthesizing molecules via novel routes, which may be difficult or impossible using traditional solution methods. As part of our program of methodology development for library synthesis purposes, we investigated possible routes to the synthesis of benzimidazole libraries.[4-7] In the course of this work, we have developed a novel solid-phase route to the title compounds, which permits the incorporation of diverse sets of amine and mercaptan monomers from a common intermediate.

Substituted 2-amino- and thio-methylbenzimidazoles **1** have proven to be important as drug leads in several drug discovery programs and have relevance as antiarrhythmic and antiviral agents.[8-9]



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The solid-phase synthesis of the title compounds **7** is shown in Scheme 1. Each step illustrated was optimized by cleavage of numerous 1-2 mg samples of the resin-bound intermediates **3-7** under different reaction conditions, enabling the HPLC inspection and MS analysis of the resultant products. In the first step,

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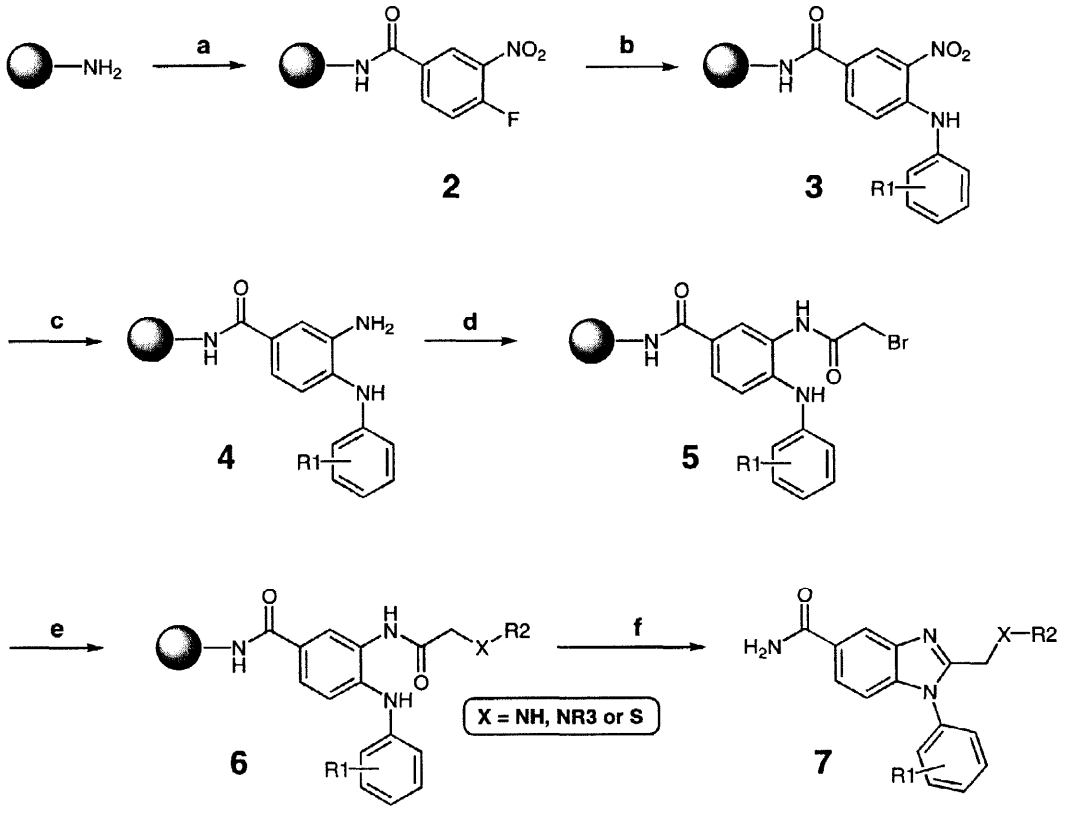
Argogel™-Rink-Fmoc resin was deprotected with 20% piperidine/DMF then coupled with 4-fluoro-3-nitrobenzoic acid, using HATU/DIEA activation, to give the resin-bound fluoro-nitro aryl intermediate **2** in quantitative yield. Nucleophilic aromatic substitution of the fluorine group with several substituted anilines (2M in DMSO, 50°C, 12 h.) gave the *o*-nitro-diphenylamine intermediates **3**. This reaction required the use of a base (DIEA) and elevated temperatures for completion, especially for aniline monomers with deactivating substituents. Reduction of the nitro group was then carried out with the dihydrate of tin(II) chloride in N-methylpyrrolidinone (50°C, 3 h.) to form the *o*-diphenyl diamines **4**. In our hands, the use of this reagent with DMF as solvent (instead of NMP) as previously described[5] led to variable amounts (5-15% by HPLC) of prematurely cyclized 1-phenyl-2(H)-benzimidazole side-products, arising by formyl group transfer from the solvent.[10]



Scheme 1

(a.) 4-F-3-NO_2benzoic acid, HATU, DIEA, DMF; (b.) $R1C_6H_4$-NH_2, DIEA, DMSO; (c.) $SnCl_2.2H_2O$, NMP; (d.) $(BrCH_2O)_2O$, DMF; (e.) R2-NH_2 (or R2R3-NH or R2-SH), DMSO; (f.) TFA.

The next step was the reaction of resin **4** with an activated form of bromoacetic acid, which was to provide the template for incorporation of the amine and mercaptan diversity elements. Optimal conditions were found using commercially available bromoacetic anhydride (in DMF, 1 h., 10 equiv.), although pre-forming the anhydride with bromoacetic acid and N,N'-diisopropylcarbodiimide (2:1 ratio in DMF) was

almost as good. We assume that the acylation occurs on the primary aniline nitrogen (rather than the de-activated secondary diphenylamine) to give intermediates with the generic structure **5**. No di-acylated products have been observed in the examples studied. Interestingly, when trying to acylate with bromoacetyl bromide/DIEA, we observed formation of the six-membered lactam ring (20% by HPLC) due to internal cyclization of intermediate **5,** along with the expected activated intermediate.

Table 1. Substituted 1-Phenyl-2-methylamino-benzimidazole and -2-methylthio-benzimidazole products

Compound	R1	X-R2	Purity[a] (3 hr) [%]	Purity[a] (16 hr) [%]	Yield[b] [%]
7a	-H	1-pyrrolidyl	55	>95	95
7b	-H	-NHPh	53	>95	82
7c	-H	$-NH(CH_2)_2Ph$	61	>95	88
7d	-H	-SPh	88	>95	71
7e	-H	-S(2-OMe)Ph	>95	>95	74
7f	-H	-S(4-Br)Ph	>95	>95	65
7g	-4-Me	1-pyrrolidyl	65	>95	88
7h	-4-Me	-NHPh	61	>95	75
7I	-4-Me	$-NH(CH_2)_2Ph$	80	>95	91
7j	-4-Me	-SPh	>95	>95	69
7k	-4-Me	-S(2-OMe)Ph	>95	>95	69
7l	-4-Me	-S(4-Br)Ph	>95	>95	67
7m	$-2,4-Me_2$	1-pyrrolidyl	60	>95	89
7n	$-2,4-Me_2$	-NHPh	70	>95	87
7o	$-2,4-Me_2$	$-NH(CH_2)_2Ph$	70	>95	86
7p	$-2,4-Me_2$	-SPh	>95	>95	72
7q	$-2,4-Me_2$	-S(2-OMe)Ph	>95	>95	72
7r	$-2,4-Me_2$	-S(4-Br)Ph	>95	>95	55
7s	-4-F	1-pyrrolidyl	25	80	73
7t	-4-F	-NHPh	17	80	71
7u	-4-F	$-NH(CH_2)_2Ph$	23	85	75
7v	-4-F	-SPh	>95	>95	79
7w	-4-F	-S(2-OMe)Ph	85	>95	75
7x	-4-F	-S(4-Br)Ph	>95	>95	72

[a] Purity based on integral of product peak at 220nm on HPLC; [b] Crude yields based on loading of original starting resin.

The last solid-phase step was the displacement of the bromide with a nucleophilic monomer. The structures of the amines and thiols chosen as examples are shown in Table 1. The monomer (2M in DMSO) was reacted with the resin at room temperature for 4 h. to reliably afford intermediates of generic structure **6**. Upon completion of this reaction, the resins were washed and dried in vacuo. The final step was to treat the resin-bound intermediates with trifluoroacetic acid to release the products with a concomitant cyclodehydration to form the benzimidazole products. Several solution methods of forming benzimidazoles from substituted *o*-amide-anilines using acidic conditions have been described.[11-14] Each resin was thus treated with neat trifluoroacetic acid (2 ml per 100 mg resin) for 16 h. After 3 h. of the acidolysis period, a small sample (<5%

total volume) was removed and inspected by HPLC to check on the progress of the cyclodehydration reaction. As shown in Table 1, the benzimidazoles derived from thiol monomers had largely converted to product within this time (entries 7d-f, j-l, p-r and v-x), whereas those derived from amines showed only moderate conversion. Almost all of the samples had formed the desired product (in > 95% HPLC purity) after the 16 h. acidolysis treatment. All of the compounds in Table 1 gave satisfactory MS and NMR spectra.[15]

In summary, we have developed a solid-phase method for synthesis of substituted benzimidazoles from simple monomers. Further work describing methods for synthesizing related compounds from other commercially available monomers will be reported in due course.

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References and Notes

1. Balkenhohl, F.; von dem Bussche-Huennefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288-2337.
2. Thompson, L.A.; Ellman J. A. *Chem. Rev.* **1996**, 555-600.
3. Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-51.
4. Sun, Q.; Yan, B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 361-364.
5. Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201-204.
6. Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Burgess, J. P.; Carroll, F. I. *Tetrahedron Lett.* **1997**, *38*, 5099-5102..
7. Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37*, 4887-4890.
8. Antiarrhythmic, e.g. Ellingboe, J. W.; Spinelli, W.; Winkley, M. W.; Nguyen, T. T.; Parsons, R. W.; Moubarak, I. F.; Kitzen, J. M.; Von Engen, D.; Bagli, J. F. *J. Med. Chem.* **1992**, *35*, 705-716.
9. Antiviral, e.g. (a) Holmes, D. S.; Bethell, R. C.; Cammack, N.; Clemens, I. R.; Kitchin, J.; McMeekin, P.; Mo, C. L.; Orr, D. C.; Patel, B. et al. *J. Med. Chem.* **1993**, *36*, 3129-36. (b) Billich, A.; Aziz, A.; Lehr, P.; Charpiot, B.; Gstach, H.; Scholz, D. *J. Enzyme Inhib.* **1993**, *7*, 213-24.
10. The reaction of dianilines with DMF at elevated temperatures has been used to form such compounds; see, Mataka, S.; Shimojyo, Y.; Hashimoto, I.; Tashiro, M. *Liebigs Ann.* **1995**, 1823-1825.
11. Using $ZnCl_2$/HCl; Goeker, H.; Oelgen, S.; Ertan, R.; Akguen, H.; Oezbey, S.; Kendi, E.; Topcu, G. *J. Heterocycl. Chem.* **1995**, *32*, 1767-73.
12. With polyphosphoric acid; Safronov, A. I.; Traven, V. F. *Zh. Org. Khim.* **1993**, *29*, 1853-1858.
13. Using camphorsulfonic acid; Ogata, M.; Yoshimura, T.; Fujii, H.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 728-730.
14. With acetic acid; Nestor, J. J., Jr.; Horner, B. L.; Ho, T. L.; Jones, G. H.; McRae, G. I.; Vickery, B. H. *J. Med. Chem.* **1984**, *27*, 320-325.
15. e.g. Compound **7a** ^{1}H NMR (400MHz, CD_3SOCD_3) δ 8.35 (1H, s), 8.12 (1H, s), 7.91 (1H, d, J = 8.8 Hz), 7.63-7.72 (5H, m), 7.41 (1H, s), 7.28 (1H, d, J = 8.8 Hz), 4.77 (2H, s), 3.20-3.80 (4H, broad), 1.97 (4H, s); ^{13}C NMR (100MHz, CD_3SOCD_3) δ 167.6, 147.6, 141.0, 137.5, 133.6, 130.1, 129.4, 129.1, 126.7, 123.5, 118.5, 109.9, 54.5, 50.0, 22.9. Mass spectrum (ESI) m/z = 321.3 ($M+H^+$).
Compound **7f** ^{1}H NMR (400MHz, CD_3SOCD_3) δ 8.37 (1H, s), 8.15 (1H, s), 7.94 (1H, d, J = 8.8 Hz), 7.68-7.80 (5H, m), 7.57 (2H, d, J = 8.4 Hz), 7.45 (1H, s), 7.40 (2H, d, J = 8.4 Hz), 7.28 (1H, d, J = 8.8 Hz), 4.56 (2H, s); ^{13}C NMR (100MHz, CD_3SOCD_3) δ 167.6, 151.7, 140.5, 137.6, 134.3, 134.1, 131.6, 130.8, 129.9, 129.1, 128.9, 126.9, 123.2, 119.5, 118.2, 109.7, 29.8. Mass spectrum (ESI) m/z = 439.3 ($M+H^+$).