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Efficient solution phase synthesis of 2-(*N*-acyl)-aminobenzimidazoles

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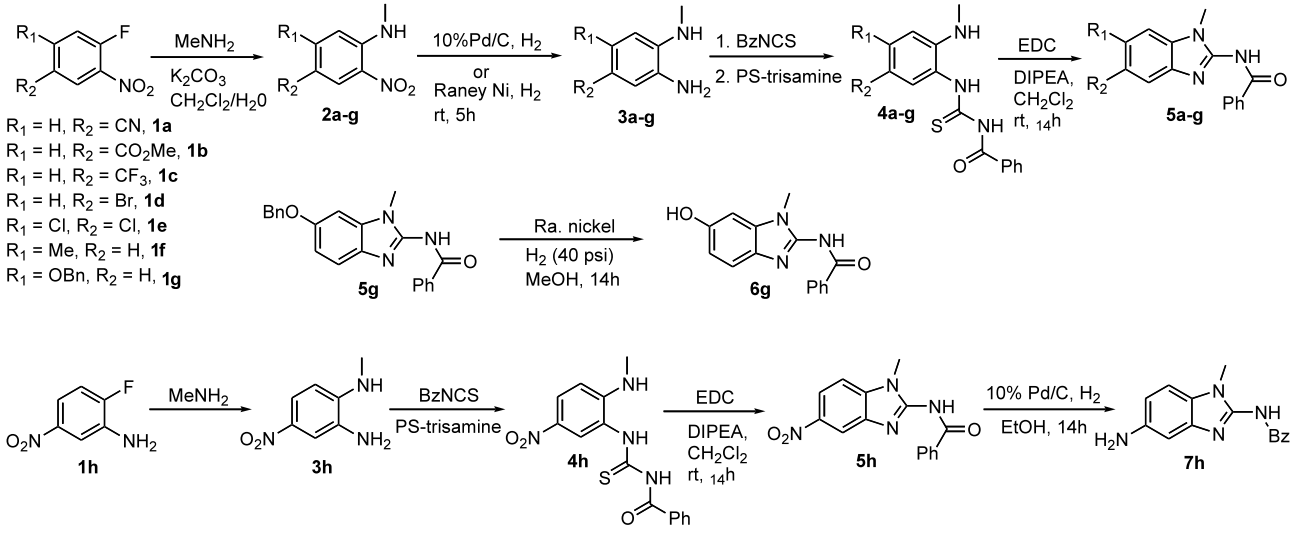
Abstract—An efficient solution phase protocol for the synthesis of 2-(*N*-acyl)-aminobenzimidazoles is reported. The 2-(*N*-acyl)-aminobenzimidazole ring system was assembled using S_NAr reactions, nitro group reduction, acylthiourea formation and cyclization with EDC. The acyl protected 2-aminobenzimidazole derivatives were obtained in high yield and purity without purification of intermediates or final products. This reaction sequence eliminates the use of highly toxic cyanogen bromide, a reagent commonly used to prepare the 2-aminobenzimidazole ring system. © 2002 Elsevier Science Ltd. All rights reserved.

The 2-aminobenzimidazole ring system is an important nucleus for drug discovery and as such represents the core structure of a number of biologically significant molecules.[1,2] For applications in our antibacterial program, we needed access to 2-(*N*-acyl)-aminobenzimidazole derivatives such as **5a**–**e** (Scheme 1).[3] Existing methods for the solution phase synthesis of 2-aminobenzimidazole derivatives typically involve cyclization of an *o*-phenylenediamine using cyanogen bromide or its equivalent to provide the 2-aminobenzimidazole ring system. Subsequent reaction of the 2-amino group with an acid chloride of choice provides the acylated 2-aminobenzimidazole.[1] While these methods work fairly efficiently, the use of cyanogen bromide on a large scale or on a repeated basis was found to be undesirable. Recently, some effort has been expended toward developing efficient solid phase strategies for the preparation of 2-aminobenzimidazole derivatives.[4–8] However, these methods are limiting with respect to the nature of substituents one can introduce on the benzene ring or on the N-1 ring nitrogen. To circumvent these limitations, we decided to explore a solution phase



Scheme 1. Preparation of some representative 2-(*N*-benzoyl)-aminobenzimidazoles.

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strategy for the synthesis of 2-aminobenzimidazole derivatives such as **5a**–**e**. In this communication, we report an efficient solution phase synthesis of 2-aminobenzimidazole derivatives that does not require the use of cyanogen bromide. Also, unlike reported solid phase syntheses of 2-aminobenzimidazole derivatives, our solution phase approach allows for concurrent introduction of substituents on the aromatic ring as well as on the N-1 ring nitrogen atom.

The synthesis was initiated by S_NAr displacement of fluorine in substituted fluoronitrobenzenes **1a**–**g** using methylamine and K_2CO_3 in a biphasic system (CH_2Cl_2/H_2O) to provide the nitroanilines **2a**–**g** (Scheme 1). It is interesting to note that the S_NAr reaction of methylamine with fluoronitro compounds **1a**–**g** proceeded very cleanly at rt and did not require any forcing conditions or polar solvents such as DMF, DMSO or NMP, which are typically used for solid phase S_NAr displacement reactions.[4–7] As a result, the nitroanilines **2a**–**g** were easily isolated after an aqueous workup in essentially quantitative yield with high purity (>95%), thereby eliminating the need for any purification. Reduction of the nitro group in **2a**–**g** was accomplished using 10% Pd/C or Raney nickel/H_2 gas to yield the corresponding phenylenediamines **3a**–**g**, which were isolated in almost quantitative yields by a simple filtration through celite followed by solvent removal. While 10% Pd/C catalyst worked efficiently for most reductions, it led to complete hydrogenolysis of the Ar–Br bond in **2d** to provide the corresponding dehalogenated phenylenediamine. This problem was not as severe in the case of dichloro analog **2e** where use of 10% Pd/C resulted in dehalogenation to a much smaller degree (<5%). The above problem was easily corrected by using Raney nickel instead of 10% Pd/C. Surprisingly, reduction using Raney nickel was mild enough that the labile benzyl group in **2g** survived the reaction. Treatment of diamines **3a**–**g** with a slight excess of benzoylisothiocyanate (1.1–1.2 equiv.) in CH_2Cl_2, provided the corresponding benzoylthioureas **4a**–**g**. The excess BzNCS in the reaction was scavenged by the addition of a small amount of PS-trisamine resin[9] and the reaction was purified by filtering off the resin. The benzoylthioureas were then cyclized using 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (EDC) to provide the 2-(*N*-benzoyl)-aminobenzimidazoles **5a**–**g**. The presence of an electron withdrawing group (EWG) on the thiourea was critical for efficient cyclization of **4a**–**g** to the corresponding 2-(*N*-benzoyl)-aminobenzimidazole **5a**–**g**. In the absence of an EWG, the cyclization was slow and low yielding, using EDC.[10] The final products **5a**–**g** were isolated in high yield and purity (90–95%) following an aqueous workup and typically did not require any further purification (Table 1). In some cases where the final purities were not >95%, the products were easily purified by trituration with CH_2Cl_2, ether or hexanes. In case of compound **5g**, the benzyl protecting group was cleanly removed using Raney nickel and hydrogen gas (50 psi) to provide benzimidazole **6g** (Scheme 1). The 5-amino substituted benzimidazole **7h** was also prepared as shown in Scheme 1. S_NAr displacement of fluorine in **1h**, followed by sequential treatment with BzNCS, PS-trisamine and EDC provided nitro benzimidazole **5h**. Reduction of the nitro group with 10% Pd/C provided amino benzimidazole **7h** in quantitative yield.[11]

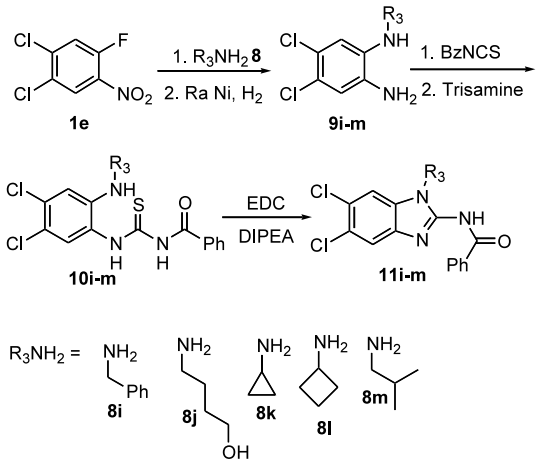
A variety of other amines may be substituted in place of methylamine, as shown in Scheme 2. The S_NAr reaction of **1e** with amines **8i**–**m** proceeded smoothly to provide the corresponding nitroanilines, which were reduced using Raney nickel and H_2 gas at atm. pressure to provide the corresponding *o*-phenylenediamines **9i**–**m**. Reaction with BzNCS followed by removal of excess BzNCS using trisamine resin provided the benzoylthioureas **10i**–**m**. As described above, cyclization to the corresponding 2-aminobenzimidazoles **11i**–**m** was accomplished using EDC (Table 1, Scheme 2).

The use of another acylisothiocyanate was examined (Scheme 3). FmocNCS (1 equiv.) was reacted with phenylenediamine **3e** (1 equiv.) to provide the Fmoc-thiourea **12e**. Cyclization with EDC provided the Fmoc

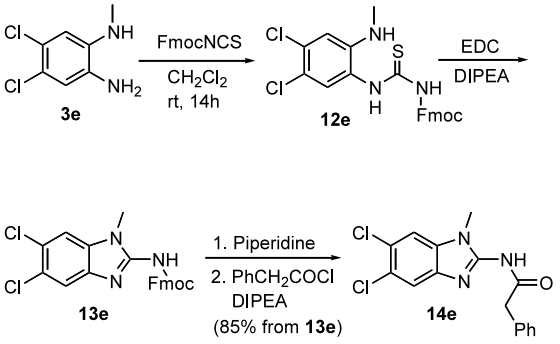
Table 1. Solution phase synthesis of 2-(*N*-benzoyl)-aminobenzimidazoles

Compound[a]	R_1	R_2	R_3	Method[b]	Yield[c] (%)
5a	H	CN	CH_3	A	90
5b	H	CO_2Me	CH_3	A	89
5c	H	CF_3	CH_3	A	86
5d	H	Br	CH_3	B	95
5e	Cl	Cl	CH_3	B	95
5f	Me	H	CH_3	B	82
5g	OBn	H	CH_3	B	91
5h	H	NO_2	CH_3	C	90
11i	Cl	Cl	$PhCH_2$	B	91
11j	Cl	Cl	$(CH_2)_4OH$	B	88
11k	Cl	Cl	Cyclopropyl	B	94
11l	Cl	Cl	Cyclobutyl	B	82
11m	Cl	Cl	Isobutyl	B	80

[a] All new compounds showed satisfactory analytical data.[14]
[b] Ref. [11].
[c] Overall yield of products obtained after four steps.



Scheme 2. Synthesis of 2-aminobenzimidazoles using different amines.



Scheme 3. Preparation of 2-(*N*-acyl)-aminobenzimidazoles.

protected 2-aminobenzimidazole **13e** in high yield (98% over four steps). To further expand on the utility of the method, 2-(*N*-Fmoc)-aminobenzimidazole **13e** was deprotected using piperidine in DMF[12,13] and the free 2-amino group was acylated, using phenylacetylchloride to provide **14e** (85% over two steps). Since a variety of acid chlorides are commercially available, this method should allow for easy incorporation of further diversity at the 2-amino position of the benzimidazole ring system. The use of FmocNCS also provides additional versatility to the synthesis for solid phase applications, given the ease of deprotection of the Fmoc group on solid support.

In summary, an efficient procedure for the synthesis of 2-(*N*-acyl)-aminobenzimidazoles is reported. The procedure features the use of an acylisothiocyanate and EDC to effect ring closure of substituted *o*-phenylenediamines to the corresponding 2-(*N*-acyl)-aminobenzimidazoles. The procedure eliminates the use of highly toxic cyanogen bromide, a reagent commonly used to prepare the 2-aminobenzimidazole ring system. Barring aqueous workups and filtrations, no purification of the intermediates and final products is required. This procedure complements existing solid and solution phase strategies for the preparation of the medicinally important benzimidazole ring system.

Acknowledgements

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8. Refs. 4, 5 and 7 describe efficient cyclization of *N*-arylthioureas to 2-(*N*-aryl)-aminobenzimidazoles on solid support, using DCC or DIC. A limitation of this methodology is that the *N*-aryl group cannot be manipulated to provide either unsubstituted 2-aminobenzimidazoles or 2-(*N*-acyl)-aminobenzimidazoles.
9. PS-trisamine resin was purchased from Argonaut Technologies Inc.
10. For cyclization of unactivated thioureas to 2-aminobenzimidazole derivatives in solution using iodomethane or mercury salts, see Ref. 1.
11. **Method A**: $MeNH_2$ (40% solution in H_2O, 1 mL) was carefully added to a suspension of 5-cyano-2-fluoronitro benzene **1a** (1 mmol, 0.166 g) and K_2CO_3 (2 mmol, 0.276 g) in CH_2Cl_2 (1 mL) and the resulting biphasic solution was stirred at rt for 14 h. The reaction was diluted with H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to provide nitroaniline **2a**, which was then hydrogenated using 10% Pd/C (25 mg) in EtOH (10 mL) for 6 h at rt. The reaction was filtered through celite and the filter bed was thoroughly washed with EtOH. The resulting solution was concentrated to provide diamine **3a** which was dissolved in CH_2Cl_2 (2 mL) and the reaction was cooled in an ice bath. Benzoylisothiocyanate (1.1 mmol, 0.163 mL) was added to the above solution and the reaction was stirred at rt for 14 h. Trisamine resin (25 mg, loading 1.4 mmol/g) was then added and the reaction stirred for additional 3 h. The reaction was then filtered and concentrated to provide crude benzoylthiourea **4a** which was dissolved in CH_2Cl_2 (2 mL). DIPEA (5 mmol, 0.78 mL) and EDC (1.5 mmol, 0.287 g) were sequentially added to the reaction which was stirred for 14 h at rt. The reaction was diluted with EtOAc and the organic phase was washed with 5% HCl, satd Na_2CO_3, brine, dried ($MgSO_4$) and concentrated to provide benzimidazole **5a** as a white solid (0.246 g, 90% over four steps). **Method B**: This method was identical to Method A, except that Raney nickel (catalytic) was used

in place of 10% Pd/C for nitro group reduction. **Method C**: This method was identical to Method A, except that **1h** (1 mmol) was heated with $MeNH_2$ (2 mL) in a sealed tube at 100°C and sequentially treated with BzNCS (1.1 equiv.), PS-Trisamine (25 mg) followed by ring closure with EDC (1.5 mmol) and DIPEA (5 mmol).

12. Piperidine (33 μL, 0.34 mmol) was added to a solution of **13e** (30 mg, 0.068 mmol) in DMF (0.3 mL). The reaction was stirred at rt for 14 h after which it was loaded onto a short plug of silica gel. The plug was eluted with 50% EtOAc/hexanes followed by 10%MeOH/1%NH_4OH/CH_2Cl_2. The CH_2Cl_2 fractions were collected, concentrated and the resulting solid was redissolved in CH_2Cl_2 (0.5 mL) and DIPEA (50 μL). The reaction was cooled in an ice bath and $PhCH_2COCl$ (0.08 mmol, 11 μL) was added. The reaction was stirred for 14 h at rt after which it was diluted with CH_2Cl_2 and the organic layer was washed with dil. HCl, brine, dried ($MgSO_4$) and concentrated to yield **14e** (85% over two steps).
13. Other methods for deprotection of the Fmoc group in **13e** were also examined. We found that the Fmoc group could be successfully deprotected using PS-trisamine resin. Unfortunately we were never able to completely scavenge the dibenzofulvene from the reaction using PS-trisamine resin under a variety of conditions. We also attempted to replace the FmocNCS with CbzNCS to allow for cleaner deprotection. However, CbzNCS is not commercially available and its synthesis was complicated due to the formation of side products.
14. Analytical data for some 2-(*N*-benzoyll)-aminobenzimidazoles. **5a**: ^{1}H NMR (400 MHz, DMSO-d_3): δ 12.93 (s, br, 1H), 8.25 (d, 2H, $J=6.8$), 7.79 (s, 1H), 7.67–7.46 (m, 5H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_3): δ 183.4, 162.9, 147.1, 143.0, 140.8, 138.6, 138.4, 137.5, 136.5, 128.9, 124.5, 120.0, 113.5, 38.1. HRMS calcd for $C_{16}H_{12}N_4O$: 277.1084, observed: 277.1085. **5b**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.9 (s, br, 1H), 8.25 (d, 2H, $J=6.8$), 8.1 (s, 1H), 7.87 (d, 1H, $J=6.8$), 7.55–7.45 (m, 5H), 3.85 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_3): δ 183.2, 175.7, 162.9, 147.3, 143.2, 140.7, 138.3, 137.5, 136.4, 133.6, 133.1, 122.2, 118.8, 61.6, 38.0. HRMS calcd for $C_{17}H_{15}N_3O_3$: 310.1186, observed: 310.1190. **5c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.59 (s, br, 1H), 8.36 (d, 2H, $J=6.8$), 7.55–7.44 (m, 5H), 7.31 (d, 1H, $J=7.6$), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 159.2, 141.7, 136.9, 135.9, 133.5, 132.5, 132.3, 129.8, 127.1, 124.7, 113.2, 112.7, 32.8. HRMS calcd for $C_{16}H_{12}F_3N_3O$: 320.1005, observed: 320.1013. **5d**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.79 (s, br, 1H), 8.24 (d, 2H, $J=6.8$), 7.66 (s, 1H), 7.52–7.38 (m, 5H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.1, 162.2, 147.4, 140.7, 139.7, 138.9, 138.2, 137.4, 136.8, 134.6, 123.7, 120.8, 37.9. HRMS calcd for $C_{15}H_{12}BrN_3O$: 330.0236; observed: 330.0236. **5e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.41 (s, br, 1H), 8.32 (d, 2H, $J=6.8$), 7.51–7.26 (m, 6H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 154.6, 137.3, 131.6, 129.8, 129.2, 128.0, 127.9, 127.1, 126.9, 112.5, 110.4, 28.5. HRMS calcd for $C_{15}H_{11}Cl_2N_3O$: 320.0352, observed: 320.0343. **11m**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.42 (s. br, 1H), 8.31 (d, 2H, $J=6.8$), 7.55–7.31 (m, 5H), 4.01 (d, 2H, $J=7.6$), 2.37 (m, 1H), 1.035 (d, 6H, $J=6.8$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 154.9, 137.5, 131.6, 129.6, 129.2, 128.0, 27.7, 126.9, 126.7, 112.4, 110.9, 60.5, 49.9, 28.1, 20.3. HRMS calcd for $C_{18}H_{17}Cl_2N_3O$: 362.0821, observed: 362.0827.