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Solid-Phase Synthesis of 2-Aminobenzothiazoles

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Abstract

A traceless solid supported protocol for the synthesis of 2-aminobenzothiazoles is described, employing resin-bound acyl-isothiocyanate and a series of anilines. Cyclization of the resulting *N*-acyl, *N'*-phenyl-thioureas generates the 2-aminobenzothiazole scaffold, which can be further elaborated prior to hydrazine-mediated cleavage of the final products from the carboxy-polystyrene resin. A small, focused library of 2-aminobenzothiazoles was prepared.

Libraries of compounds based on diverse heterocyclic scaffolds comprise a key aspect of modern drug discovery. In this context, solid supported synthesis has proved to be a powerful tool leading to a wide-range of heterocyclic compounds.¹ However, to the best of our knowledge, a procedure for the solid phase synthesis of 2-aminobenzothiazoles has not been reported. The 2-aminobenzothiazole scaffold is one of the “privileged” structures in medicinal chemistry.² Indeed, various examples featuring this particular scaffold have been prepared, many exhibiting remarkable biological activities.^{3,4} Given the importance of this particular chemical entity to the field of medicinal chemistry, the development of improved and/or alternative methods for the rapid construction of libraries of derivatives is desirable. Although examples of solid supported synthesis of benzothiazoles have been reported,^{5,6} these methods are not applicable to 2-aminobenzothiazoles. We thus undertook a focused study to adapt previously disclosed methods for solution phase synthesis to the solid phase for this particular class of heterocycles.

The now classical synthesis of 6-substituted 2-aminobenzothiazoles entails treatment of 4-substituted anilines with potassium thiocyanate in the presence of bromine in acetic acid (Scheme 1 A).⁷ This method, however, is not generally applicable as thiocyanation in the para position of anilines is often the predominant reaction when 4-unsubstituted anilines are employed under these or similar oxidation conditions (Scheme 1 B).^{8,9} Alternative methods for the syntheses of 4, 5, 6, and 7 substituted 2-aminobenzothiazoles employ phenylthioureas as the synthetic precursors (Scheme 1 C). In these cases, heterocycle ring formation can be carried out, albeit non regioselectively, by treating the phenylthioureas with bromine in chloroform¹⁰ or acetic acid.¹¹ Alternatively, regiospecific cyclizations can be performed via *S_NAr_i* reactions, employing phenylthioureas obtained from the appropriate ortho-fluoroanilines in the presence of sodium methoxide.¹² We report here adaptation of these reaction conditions onto solid support beginning with resin-bound isothiocyanate.

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The resin-bound isothiocyanate **3** was prepared as previously described in two steps from carboxy-polystyrene (Scheme 2).¹³ Conversion of **3** to the *N*-acyl, *N'*-phenylthioureas of general structure **4** was then readily achieved upon treatment of **3** with the appropriate aniline at room temperature in *N,N*-dimethylformamide.¹⁴ This reaction can be conveniently monitored by infrared spectroscopy following the disappearance of the characteristic isothiocyanate band at $\sim 1910\text{ cm}^{-1}$ (Figure 1). When *X* = H cyclization of **4** to 2-acylaminobenzothiazole **5** was then performed by treatment with six equivalents of bromine in acetic acid (Scheme 2, Method A14). Alternatively, when *X* = F or Br, benzothiazoles obtained (*e.g.*, entries e, and h Table 1), were formed by treatment of the corresponding *N*-acyl, *N'*-phenylthioureas with sodium hydride (Method B & C14) via an S_NAr_i mechanism.

Finally, the desired 2-aminobenzothiazoles of general structure **6** were obtained in good overall yield and >85% purity upon treatment of **5** with 4% hydrazine monohydrate in ethanol (Table 1).¹⁴ Alternative TFA-mediated cleavage conditions were also investigated, however, the optimized hydrazine cleavage conditions proved more reliable, and generally proceeded with little or no trace of contaminants or by-products (*cf.*, Figure 2).

As anticipated, when 3-substituted anilines (*e.g.*, entries c and f, Table 1) were employed, oxidative cyclization conditions (Method A) led to mixtures of two regioisomers (*i.e.*, 5- and 7-substituted 2-aminobenzothiazoles); the relative ratio apparently determined by the steric encumbrance of the substituent in the meta position of the starting aniline. Thus, while 3-bromoaniline furnished a separable 1:1 mixture of 5- and 7-bromo-2-aminobenzothiazoles, under the above reaction conditions, the 3-phenylaniline generated a mixture (95:5) in favor of the 5-substituted-2-amino-benzothiazole (*cf.*, entries c and f, Table 1), which could be readily separated and purified by column chromatography or crystallization. Single crystal X-ray analysis confirmed the structure of **6f** (Figure 3).

Although mixtures of regioisomers are often acceptable in the generation of libraries for HTS, single isomers could be obtained when ring formation was performed via S_NAr_i , as exemplified by entries **e** (Method B) and **h** (Method C); each proceeded regiospecifically to furnish the 7-chloro- and the 5-bromo-2-aminobenzothiazole **6e** and **6h** (Table 1), respectively.

Finally, in order to exemplify the utility of this synthetic protocol for the construction of libraries of 2-aminobenzothiazole derivatives, we evaluated representative resin-bound bromobenzothiazoles **5c** and **5h** as possible starting points for further structural elaboration. Thus, **5c** and **5h** were treated under either Suzuki¹⁵ or Buchwald-Hartwig¹⁶ conditions to yield products of cross-coupling. Representative examples of C–C, and C–N bond forming reactions are summarized in Table 2.

Both cross-coupling reactions were carried out under microwave promoted conditions. For these reactions, 0.05–0.1 mol% of $Pd(PPh_3)_4$ was found to be the preferred catalyst (*cf.*, Table 3).

In summary, we have developed an effective method for the solid supported synthesis of 2-aminobenzothiazoles, with an application to the preparation of a focused library of 2-aminobenzothiazole derivatives.

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14. Experimental procedures and characterization of compounds: **General procedure to prepare derivatives 4**: A mixture of solid phase **3** (theoretical load: 0.96 mmol/g, 200 mg, 0.19 mmol) and aniline (0.48 mmol) in *N,N*-dimethylformamide (1.5 mL) was stirred at room temperature overnight. The solid phase was filtered, washed with *N,N*-dimethylformamide, acetone, and methanol (3×). **General procedures to prepare derivatives 5**: **Method A**: cyclization with bromine. Bromine (150 mg, 0.05 mL, 0.96 mmol) was added to mixture of solid phase **4** (X = H, theoretical load: 0.82 mmol/g, 200 mg, 0.16 mmol) in acetic acid (1.5 mL). The reaction mixture was stirred at room temperature overnight. The solid phase was filtered, washed with water, *N,N*-dimethylformamide and methanol (3×). **Method B**: cyclization with NaH (X = F). NaH (60% wt. oil mineral dispersion, 40 mg, 0.96 mmol) was added to a mixture of solid phase **4** (theoretical load: 0.84 mmol/g, 200 mg, 0.17 mmol) in anhydrous *N,N*-dimethylformamide (1.5 mL). The reaction mixture was stirred at room temperature overnight. Water (0.5 mL) was added, and the solid phase was filtered and washed with water and methanol (×3). **Method C**: cyclization with NaH (X = Br). NaH (60% wt. oil mineral dispersion, 60 mg, 1.54 mmol) was added to a mixture of solid phase **4** (theoretical load: 0.77 mmol/g, 200 mg, 0.15 mmol) in anhydrous *N,N*-dimethylformamide (1 mL). The reaction mixture was heated to 100 °C and stirred overnight. After cooling, water (0.5 mL) was added, and the solid phase was filtered and washed with water and methanol (×3). **Suzuki coupling**. A mixture of solid phase **5c** (theoretical load: 0.82 mmol/g, 200 mg, 0.16 mmol), phenylboronic acid (100 mg, 0.82 mmol), potassium phosphate (170 mg, 0.82 mmol) and tetrakis (triphenylphosphine)palladium (20 mg, 0.1 mol%) in *N,N*-dimethylformamide (1.8 mL) and water (0.2 mL) was heated to 150 °C using microwave irradiation for 30 min. After cooling, the solid phase was filtered, washed with *N,N*-dimethylformamide, dichloromethane and methanol (×3). **Buchwald-Hartwig amination**. A dry microwave vessel was charged with the solid phase **5h** (theoretical load: 0.82 mmol/g, 200 mg, 0.16 mmol), the appropriate amine (0.82 mmol), XPhos (31 mg, 0.07 mmol), tetrakis (triphenylphosphine) palladium (10 mg, 0.05 mol%), and sodium *t*-butoxide (160 mg, 1.64 mmol). Degassed and dry *N,N*-dimethylformamide (2 mL) was added, and the resulting mixture was heated to 150 °C using microwave irradiation for 1 h. After cooling, the solid phase was filtered, washed with *N,N*-dimethylformamide, dichloromethane and methanol (×3). **Cleavage**. Hydrazine monohydrate (80 mg, 0.08 mL, 1.64 mmol) was added to a mixture of the solid phase **5** and ethanol (1.9 mL). The reaction mixture was heated to 150 °C using microwave irradiation for 30 min. After cooling the resin was filtered and washed with ethyl acetate and methanol (×3). The solvent was evaporated and the residue was purified by silica gel column chromatography (using ethyl acetate-*n*-hexane 2:3 as eluent) or by crystallization from the appropriate solvent to give the desired title compound. **2-Amino-4-bromobenzothiazole (6a)**. White solid. Yield: 63%, mp 182–184 °C (from ethanol) (Lit.

¹⁷ 183-184 °C). ¹H NMR (DMSO-*d*₆): δ 6.91 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.85 ppm (broad s, 2H). ¹³C NMR (DMSO-*d*₆): δ 110.9, 121.0, 122.5, 129.2, 132.1, 151.3, 167.6 ppm. IR: ν 3450, 3272, 1632, 1530 cm⁻¹. HRMS: calcd for C₇H₅BrN₂S⁺ 228.9401 found 228.9404. **2-Amino-4,7-dichlorobenzothiazole (6b)**. White solid. Yield: 61%, mp 228-230 °C (from ethanol). ¹H NMR (DMSO-*d*₆): δ 7.08 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 8.12 ppm (broad s, 2H). ¹³C NMR (DMSO-*d*₆): δ 120.6, 121.6, 127.9, 129.4, 131.9, 150.5, 167.7 ppm. IR: ν 3399, 3246, 1624, 1556 cm⁻¹. HRMS: calcd for C₇H₅Cl₂N₂S⁺ 218.9551 found 218.9557. **2-Amino-7-bromobenzothiazole (6c)**. White solid. Yield: 35%, mp 189-191 °C (from ethanol) (Lit.¹⁷ 196-197 °C). ¹H NMR (CDCl₃): δ 5.24 (broad s, 2H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.26 (dd, *J* = 1.0 and 7.9 Hz, 1H), 7.48 ppm (dd, *J* = 1.0 and 7.9 Hz, 1H). ¹³C NMR (CDCl₃): δ 114.7, 119.6, 124.5, 125.8, 129.0, 151.5, 166.8 ppm. IR: ν 3402, 3264, 1602 cm⁻¹. HRMS: calcd for C₇H₆BrN₂S⁺ 228.9435 found 228.9432. **2-Amino-6-bromobenzothiazole (6d)**. White solid. Yield: 68%. All data are in agreement with literature.¹⁸ **2-Amino-7-chlorobenzothiazole (6e)**. White solid. Yield: 41%, mp 177-178 °C (from ethanol) (Lit.¹ 169-170 °C). ¹H NMR (CDCl₃): δ 5.32 (broad s, 2H), 7.13 (dd, *J* = 1.0 and 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.44 ppm (dd, *J* = 1.0 and 8.0 Hz, 1H). ¹³C NMR (MeOD): δ 114.4, 119.5, 124.1, 125.2, 128.9, 151.5, 166.8 ppm. IR: ν 3395, 3262, 1633, 1535 cm⁻¹. HRMS: calcd for C₇H₆ClN₂S⁺ 184.9940 found 184.9933. **2-Amino-5-phenylbenzothiazole (6f)**. White solid. Yield: 74% method A, (34% from Suzuki coupling), mp 168-170 °C (from ethanol). ¹H NMR (CD₃OD): δ 7.33-7.37 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.63-7.66 ppm (m, 4H). ¹³C NMR (CD₃OD): δ 118.0, 118.4, 121.1, 121.9, 122.5, 126.7, 127.4, 127.8, 128.1, 128.9, 152.3 ppm. IR: ν 3423, 3230, 1613, 1523 cm⁻¹. HRMS: calcd for C₁₃H₁₁N₂S⁺ 227.0643 found 227.0648. **2-Amino-4,7-dibromobenzothiazole (6g)**. White solid. Yield: 53%, mp 266-267 °C (from ethanol). ¹H NMR (DMSO-*d*₆): δ 7.12 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 8.09 ppm (br s, 2H). ¹³C NMR (DMSO-*d*₆): δ 109.9, 112.1, 124.9, 130.6, 134.0, 151.2, 166.7 ppm. IR: ν 3470, 3177, 1634, 1530 cm⁻¹. HRMS: calcd for C₇H₅Br₂N₂S⁺ 306.8533, found 306.8540. **2-Amino-5-bromobenzothiazole (6h)**. White solid. Yield: 70% using the method C, 38% using method A, mp 195-197 °C (from ethanol) (Lit.¹⁷ 196-198 °C). ¹H NMR (MeOD): δ 7.21 (dd, *J* = 1.8 and 8.3 Hz, 1H), 7.51-7.53 ppm (m, 2H). ¹³C NMR (MeOD): δ 117.4, 118.8, 120.4, 122.6, 128.4, 151.9, 168.2 ppm. IR: ν 3409, 3270, 1642, 1529 cm⁻¹. HRMS: calcd for C₇H₆BrN₂S⁺ 228.9435 found 228.9531. **2-Amino-7-phenylbenzothiazole (7)**. White solid. Yield: 30% from Suzuki coupling, mp 156-158 °C (from ethanol). ¹H NMR (CD₃OD): δ 7.16 (dd, *J* = 2.0 and 7.6 Hz, 1H), 7.36-7.44 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.63-7.65 ppm (m, 2H). ¹³C NMR (CD₃OD): δ 117.8, 121.3, 126.8, 127.9, 128.5, 121.4, 129.5, 135.2, 141.2, 154.2, 167.0 ppm. IR: ν 3451, 3296, 3135, 1621, 1531 cm⁻¹. HRMS: calcd for C₁₃H₁₁N₂S⁺ 227.0643 found 227.0647. **N⁶-(naphthalen-1-yl)benzo[d]thiazole-2,6-diamine (9)**. White solid. Yield: 63%, mp 231-133 °C (from ethanol). ¹H NMR (CD₃OD): δ 6.86 (dd, *J* = 1.1 and 7.9 Hz, 1H), 7.06 (d, *J* = 1.1 Hz, 1H), 7.34-7.54 (m, 9H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.15 ppm (d, *J* = 7.9 Hz, 1H). ¹³C NMR (CD₃OD): δ 105.1, 111.3, 113.6, 119.1, 119.2, 119.8, 120.4, 120.8, 121.0, 123.4, 124.2, 124.3, 126.5, 126.6, 133.6, 151.3, 159.1 ppm. IR: ν 3401, 3348, 3155, 1629, 1605, 1551 cm⁻¹. HRMS: calcd for C₁₇H₁₄N₃S⁺ 292.0908 found 292.0905. **2-amino-5-(4-morpholyl)benzothiazole (8)**. White solid. Yield 40%, mp 213-215 °C (from ethanol). ¹H NMR (DMSO-*d*₆): δ 2.32 (t, *J* = 4.7 Hz, 4H), 3.03 (t, *J* = 4.7 Hz, 4H), 5.98 (dd, *J* = 1.0 and 8.1 Hz, 1H), 6.18 (d, *J* = 1.0 Hz, 1H), 6.61 ppm (d, *J* = 8.1 Hz, 1H). ¹³C NMR (MeOD): δ 48.8, 65.3, 103.9, 110.2, 119.2, 120.6, 149.4, 151.4, 167.9 ppm. IR: ν 3410, 3340, 3170, 1633, 1615, 1545 cm⁻¹. HRMS: calcd for C₁₁H₁₄N₃OS⁺ 236.0858 found 236.0853.

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Figure 1.
IR spectra.

Figure 2.
LC/MS Analysis of the crude reaction obtained after hydrazine-mediated cleavage (entry f, Table 1); **A**: photodiode array detector; **B**: total ion current; **C**: mass spectrum.

Figure 3.
X-ray crystal structure of compound **6f** (CCDC 753930).

Scheme 1.

Commonly employed methods for the solution phase synthesis of 2-aminobenzothiazoles (**A** and **C**); thiocyanation of 4-unsubstituted anilines upon treatment with potassium thiocyanate in the presence of bromine in acetic acid (**B**).

Scheme 2.

Reagents and Conditions: (a) oxalyl chloride, DCE, rt, 16 h; (b) Bu₄NNCS, DCE/THF, rt, 16 h; (c) aniline, DMF, rt, 16 h; (d) For X = H, *Method A*: Br₂ (6 eq.), acetic acid, rt, 16 h; for X = F, *Method B*: NaH (6 eq.), DMF, rt, 16 h; for X = Br, *Method C*: NaH (10 eq.), DMF, 100 °C, 16 h (e) hydrazine monohydrate, EtOH, 150 °C, MW, 30 min.

Table 1

Representative examples of 2-aminobenzothiazoles prepared.

Entry	Method	Aniline
a	A

Entry	Method	Aniline
b	A
c	A
d	A

Entry	Method	Aniline
e	B
f	A

Entry	Method	Aniline
g	A
h	C

^a Overall yield after purification.

* Approximately a 50:50 mixture of 5- and 7-bromo-2-aminobenzothiazoles;

**
Approximately a 95:5 mixture of 5- and 7-phenyl-2-aminobenzothiazole.

Table 2

Representative examples of cross-coupling reactions.

Conditions	Product
<p>5c* $\xrightarrow[2) \text{ Cleavage}]{1) \text{ Suzuki cross-coupling}}$</p> <p>1) <i>Buchwald-Hartwig amination</i></p> <p>5h $\longrightarrow$</p> <p>2) <i>Cleavage</i></p> <p>1) <i>Buchwald-Hartwig amination</i></p> <p>5h $\longrightarrow$</p> <p>2) <i>Cleavage</i></p>	<p> </p> <p> </p> <p> </p>

* Approximately a 50:50 mixture of 5- and 7-phenyl-2-aminobenzothiazoles (separable).

Table 3

Cross-coupling reaction investigation.

Entry	Conditions	Conversion
<i>Suzuki Coupling (from 5c to 7):</i>		
i	PhB(OH) ₂ , (5.0 eq.), K ₃ PO ₄ (5.0 eq.), Pd(OAc) ₂ (0.1 eq.), DMF-H ₂ O (9:1), MW, 150 °C, 15 min	0%
j	PhB(OH) ₂ , (5.0 eq.), K ₃ PO ₄ (5.0 eq.), Pd(PPh ₃) ₄ (0.1 eq.), DMF-H ₂ O (9:1), MW, 150 °C, 30 min	100%
<i>Buchwald-Hartwig amination (from 5h to 8):</i>		
k	<i>t</i> -BuONa (10 eq.), Morpholine (5 eq.), Pd ₂ dba ₃ (0.05 eq.), BINAP (0.4 eq.), Toluene, 90 °C, 24 h	40%
l	<i>t</i> -BuONa (10 eq.), Morpholine (5 eq.), Pd ₂ dba ₃ (0.05 eq.), XPhos (0.4 eq.), Toluene, 90 °C, 24 h.	50%
m	<i>t</i> -BuONa (10 eq.), Morpholine (5 eq.), Pd ₂ dba ₃ (0.05 eq.), XPhos (0.4 eq.), DMF, 160 °C, MW, 1 h.	50%
n	<i>t</i> -BuONa (10 eq.), Morpholine (5 eq.), Pd(PPh ₃) ₄ (0.05 eq.), XPhos (0.4 eq.), DMF, 160 °C, MW, 1 h	100%

^a Conversion of the starting material by LC-MS analysis after cleavage of the product.