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Solid phase synthesis of 2-aminobenzothiazoles

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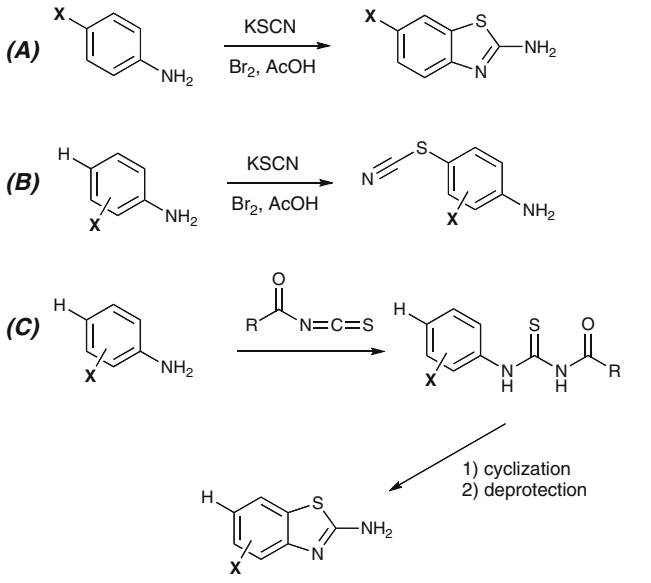
ABSTRACT

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*′-phenylthioureas 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 1A).[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 1B).[8,9] Alternative methods for the syntheses of 4, 5, 6, and 7 substituted 2-aminobenzothiazoles employ phenylthioureas as the synthetic precursors (Scheme 1C). In these cases, heterocycle ring formation can be carried out, albeit non regioselectively, by treating the phenylthioureas with bromine in chloroform[10] 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.

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 iso-



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*).

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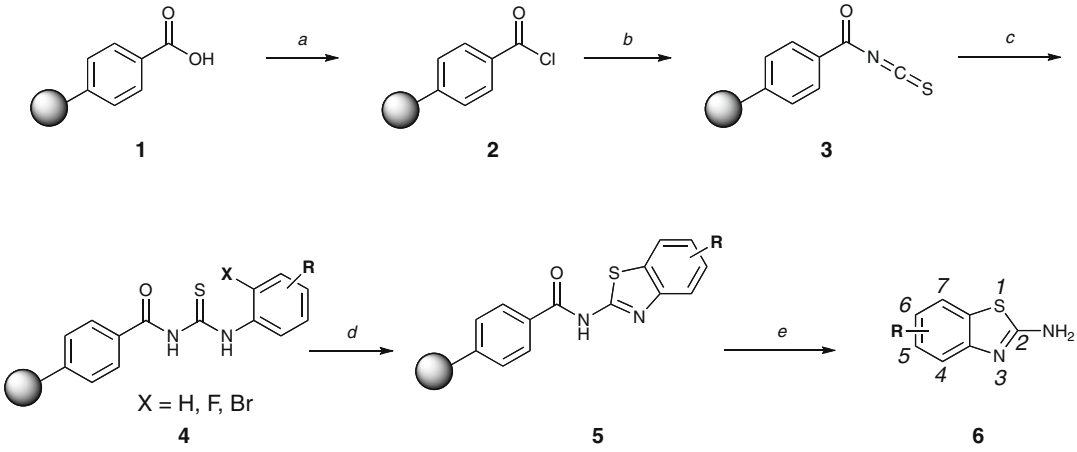


Scheme 2. Reagents and conditions: (a) oxalyl chloride, DCE, rt, 16 h; (b) Bu_4NNCS, DCE/THF, rt, 16 h; (c) aniline, DMF, rt, 16 h; (d) For X = H, *Method A*: Br_2 (6 equiv), acetic acid, rt, 16 h; for X = F, *Method B*: NaH (6 equiv), DMF, rt, 16 h; for X = Br, *Method C*: NaH (10 equiv), DMF, 100 °C, 16 h (e) hydrazine monohydrate, EtOH, 150 °C, MW, 30 min.

thiocyanate band at ~1910 cm^{-1} (Fig. 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 A[14]). 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 (Methods B and C[14]) 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., Fig. 2).

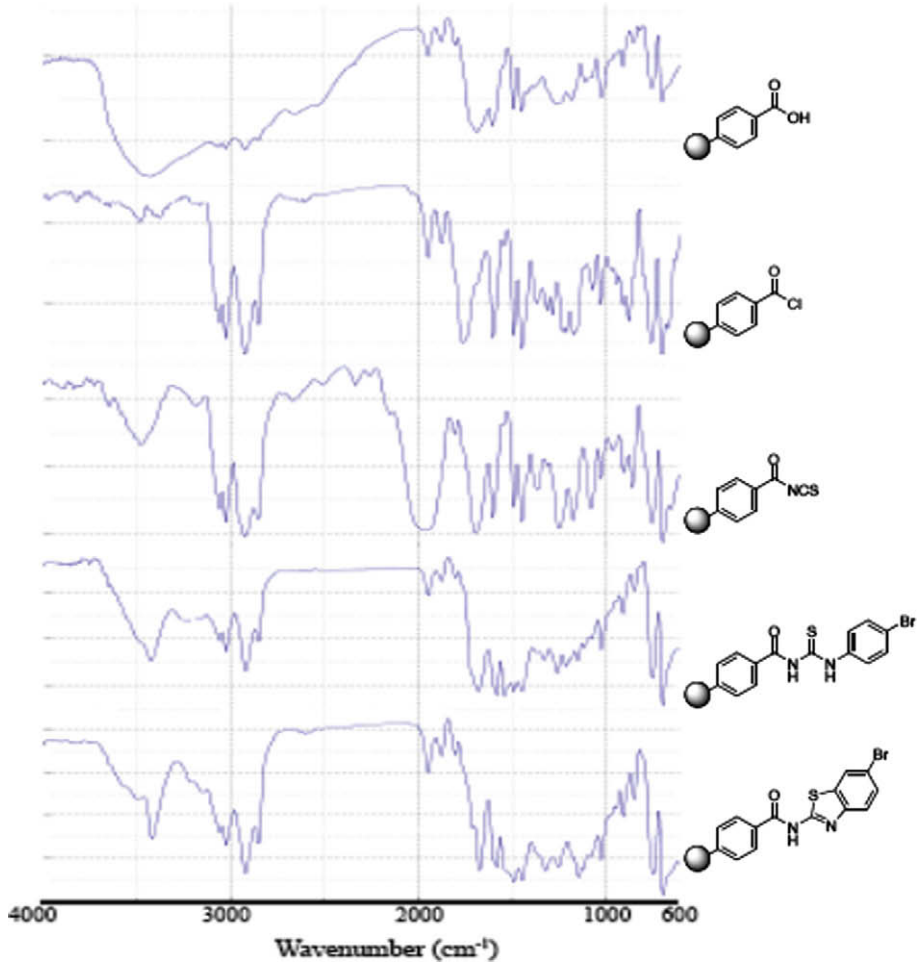


Figure 1. IR spectra.

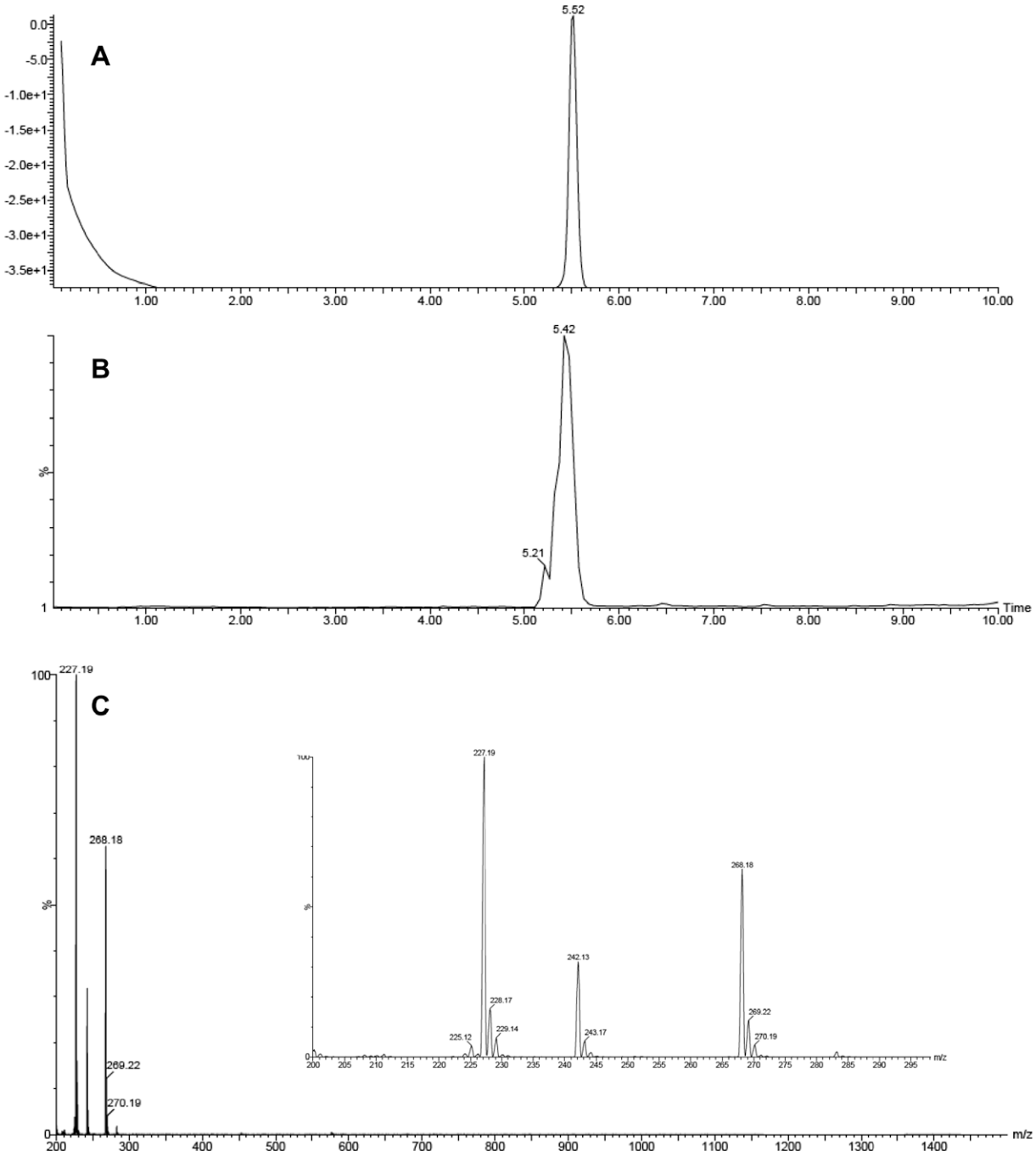


Figure 2. LC/MS analysis of the crude reaction obtained after hydrazine-mediated cleavage (Table 1, entry f); A: photodiode array detector; B: total ion current; C: mass spectrum.

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** (Fig. 3).

Although mixtures of regioisomers are often acceptable in the generation of libraries for HTS, single isomers could be obtained

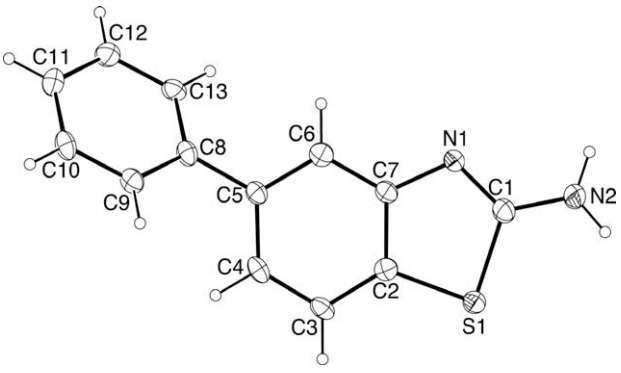
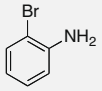
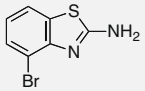
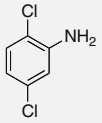
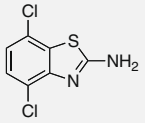
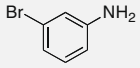
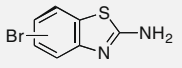
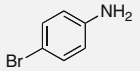
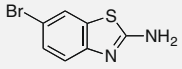
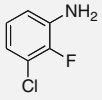
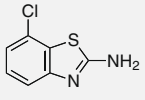
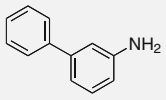
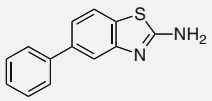
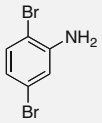
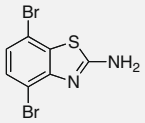
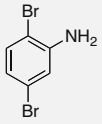
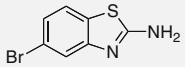


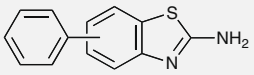
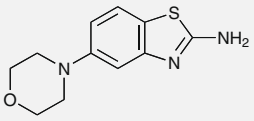
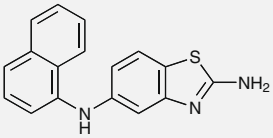
Figure 3. X-ray crystal structure of compound **6f** (CCDC 753930).

Table 1
Representative examples of 2-aminobenzothiazoles prepared

Entry	Method	Aniline	Product **6**	Yield[a] (%)
a	A			63
b	A			61
c	A			73[*]
d	A			68
e	B			41
f	A			74[**]
g	A			53
h	C			70

[a] Overall yield after purification.
[*] Approximately a 50:50 mixture of 5- and 7-bromo-2-aminobenzo-thiazoles.
[**] Approximately a 95:5 mixture of 5- and 7-phenyl-2-aminobenzothiazole.

Table 2
Representative examples of cross-coupling reactions

	Conditions	Product	Yield
5c[*]	1) *Suzuki cross-coupling* 2) *Cleavage*	 **7**	34% of 5-Phenyl 30% of 7-Phenyl
5h	1) *Buchwald-Hartwig amination* 2) Cleavage	 **8**	40%
5h	1) *Buchwald-Hartwig amination* 2) Cleavage	 **9**	52%

[*] Approximately a 50:50 mixture of 5- and 7-phenyl-2-aminobenzo-thiazoles (separable).

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.

Table 3
Cross-coupling reaction investigation

Entry	Conditions	Conversion[a] (%)
	*Suzuki coupling (from **5c** to **7**):*	
i	$PhB(OH)_2$, (5.0 equiv), K_3PO_4 (5.0 equiv), $Pd(OAc)_2$ (0.1 equiv), DMF–H_2O (9:1), MW, 150 °C, 15 min	0
j	$PhB(OH)_2$, (5.0 equiv), K_3PO_4 (5.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), DMF–H_2O (9:1), MW, 150 °C, 30 min	100
	*Buchwald–Hartwig amination (from **5h** to **8**):*	
k	*t*-BuONa (10 equiv), morpholine (5 equiv), Pd_2dba_3 (0.05 equiv), BINAP (0.4 equiv), toluene, 90 °C, 24 h	40
l	*t*-BuONa (10 equiv), morpholine (5 equiv), Pd_2dba_3 (0.05 equiv), XPhos (0.4 equiv), toluene, 90 °C, 24 h.	50
m	*t*-BuONa (10 equiv), morpholine (5 equiv), Pd_2dba_3 (0.05 equiv), XPhos (0.4 equiv), DMF, 160 °C, MW, 1 h.	50
n	*t*-BuONa (10 equiv), morpholine (5 equiv), $Pd(PPh_3)_4$ (0.05 equiv), XPhos (0.4 equiv), DMF, 160 °C, MW, 1 h	100

[a]Conversion of the starting material by LC–MS analysis after cleavage of the product.

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 bromobenzo thiazoles **5c** and **5h** as possible starting points for further structural elaboration. Thus, **5c** and **5h** were treated under either Suzuki[15] or Buchwald–Hartwig[16] 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-aminobenzo-thiazoles, with an application to the preparation of a focused library of 2-aminobenzothiazole derivatives.

Acknowledgment

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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 (triphenylphos phine)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). ^{1}H 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 (br s, 2H). ^{13}C 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 $C_7H_6BrN_2S^+$ 228.9401 found 228.9404.*2-Amino-4,7-dichlorobenzothiazole* (**6b**): White solid. Yield: 61%, mp 228–230 °C (from ethanol). ^{1}H NMR (DMSO-d_6): δ 7.08 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 8.12 ppm (br s, 2H). ^{13}C 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 $C_7H_5Cl_2N_2S^+$ 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). ^{1}H NMR ($CDCl_3$): δ 5.24 (br 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). ^{13}C NMR ($CDCl_3$): 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 $C_7H_6BrN_2S^+$ 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). ^{1}H NMR ($CDCl_3$): δ 5.32 (br d 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). ^{13}C 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 $C_7H_6ClN_2S^+$ 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). ^{1}H NMR (CD_3OD): δ 7.33–7.37 (m, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.63–7.66 ppm (m, 4H). ^{13}C NMR (CD_3OD): 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 $C_{13}H_{11}N_2S^+$ 227.0643 found 227.0648.*2-Amino-4,7-dibromobenzothiazole* (**6g**): White solid. Yield: 53%, mp 266–267 °C (from ethanol). ^{1}H 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). ^{13}C 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 $C_7H_5Br_2N_2S^+$ 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). ^{1}H NMR (MeOD): δ 7.21 (dd, J = 1.8 and 8.3 Hz, 1H), 7.51–7.53 ppm (m, 2H). ^{13}C 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 $C_7H_6BrN_2S^+$ 228.9435 found 228.9531.*2-Amino-7-phenylbenzothiazole* (**7**): White solid. Yield: 30% from Suzuki coupling, mp 156–158 °C (from ethanol). ^{1}H NMR (CD_3OD): 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). ^{13}C NMR (CD_3OD): 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 $C_{13}H_{11}N_2S^+$ 227.0643 found 227.0647.*N*^{6}*-(Naphthalen-1-yl)benzo[d]thiazole-2,6-diamine* (**9**): White solid. Yield: 63%, mp 231–133 °C (from ethanol). ^{1}H NMR (CD_3OD): 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). ^{13}C NMR (CD_3OD): 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 $C_{17}H_{14}N_3S^+$ 292.0908 found 292.0905.*2-Amino-5-(4-morpholyl)benzothiazole* (**8**): White solid. Yield 40%, mp 213–215 °C (from ethanol). ^{1}H 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). ^{13}C 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 $C_{11}H_{14}N_3OS^+$ 236.0858 found 236.0853.

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