

A Novel System for the Synthesis of 2-Aminobenzthiazoles using Sodium Dichloroiodate

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Abstract: 2-Aminobenzthiazole is a privileged scaffold with a range of biological activities. However, to date, an efficient protocol for the synthesis of this ring system using aniline as a starting material has been lacking. Herein, for the first time, we describe a highly efficient and mild protocol for the synthesis of 2-aminobenzthiazole using NaCl₂.

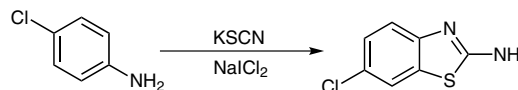
Key words: synthetic methods, oxidative cyclization, sodium dichloroiodate, aniline, aminobenzthiazole

As a privileged scaffold, the benzothiazole core can be found in pharmaceuticals used in the treatment of diabetes,¹ epilepsy,² inflammation,³ amyotrophic lateral sclerosis,⁴ pain,⁵ tuberculosis,⁶ tumor,⁷ and viral infections.⁸

Two common approaches are applied for the construction of 2-substituted benzothiazoles. The first approach uses various oxidants, including Jacobson's and Hugerhoff's methods via oxidative cyclization of thiobenzanilides.⁹ However, using stoichiometric or excess amounts of toxic reagents, such as bromine or metals, is a major drawback of these methods, leading to low functional group tolerance. Synthesis via palladium- or copper-catalyzed cyclization of *ortho*-halobenzo-thioureas,¹⁰ or directly functionalized aromatic C–SH bonds to construct C–S bonds,¹¹ provides an alternative access to benzothiazoles. However, these reactions still require large amounts of catalyst (typically 1–20 mol%) to promote the transformation efficiently. Very recently, the intramolecular nucleophilic aromatic substitution of *o*-halothiobenzanilides (INASOB) promoted by a base was also reported.¹² However, these catalyst-free methods could produce the 2-(alkyl)arylbenzothiazoles only. Thus, there is still a need to develop methods that use less expensive, easily available reagents and starting materials for the construction of this important heterocyclic scaffold.

Sodium dichloroiodate is commercially available as a 50% aqueous solution, and its use has been reported for the iodination of aromatic substrates at 40–70 °C.¹³ More recently, we used this reagent for the transformation of alcohols into aldehydes, and aldehydes into the corresponding nitriles.¹⁴ While working with this reagent, we found that it can be used for regioselective C–S bond-forming reactions and hence could be used for the preparation of

2-aminobenzthiazole. For our preliminary study, 4-chloroaniline was used as a model substrate and we observed that, in the presence of an aqueous solution of sodium dichloroiodate, 4-chloroaniline reacts with potassium thiocyanate to produce 6-chloro-2-aminobenzthiazole (Scheme 1).



Scheme 1 Synthesis of 6-chloro-2-aminobenzthiazole from 4-chloroaniline

The reaction was quite slow at room temperature, but a better isolated yield was obtained between 60–70 °C; further increases in the temperature did not affect the yield or reaction time. Further studies were carried out by using different iodine reagents for this conversion (DIB, DMP, IBX, ICl, I₂, NBS, and NaCl₂) at 70 °C, using a mixture of acetic acid/water (80:20) as a reaction solvent, for more than 24 h. Previous reports on the synthesis of 2-aminobenzthiazole guided us towards the use of acetic acid/water as a reaction medium. However, only NaCl₂ afforded the desired 6-chloro-2-aminobenzthiazole product (Table 1, entry 5).

Table 1 Reaction of 4-Chloroaniline in the Presence of Iodine Reagents^a

Entry	Reagent	Time (h)	Yield (%)
1	iodobenzene diacetate	24	NR
2	<i>o</i> -iodoxybenzoic acid	24	NR
3	iodine monochloride	24	NR
4	sodium dichloroiodate	18	30 ^b
5	iodine	24	NR
6	Dess–Martin periodinane	24	NR
7	<i>N</i> -iodosuccinimide	24	NR

^a Reaction conditions: substrate (1 equiv), potassium thiocyanate (1 equiv), iodine reagent (1 equiv), 70 °C.

^b Isolated yield after silica gel column chromatography.

To optimize the reaction conditions with NaCl₂, a range of solvent systems were tried (Table 2) and a mixture of DMSO–H₂O (90:10) was found to be the most suitable re-

action medium, giving a high reaction rate and an improved yield of the product (Table 2, entry 6).

Table 2 Reaction of 4-Chloroaniline in the Presence of Solvents^a

Entry	Solvent	Time (h)	Yield (%) ^b
1	AcOH–H ₂ O	18	30
2	MeCN–H ₂ O	6	40
3	MeOH–H ₂ O	6	NR
4	THF–H ₂ O	5	45
5	CHCl ₃	12	NR
6	DMSO–H ₂ O	4	50

^a Reaction conditions: substrate (1 equiv), potassium thiocyanate (1 equiv), NaCl₂ (1 equiv), 70 °C.

^b Isolated yield after silica gel column chromatography.

To enhance the yield of the product still further, different molar ratios of the reagents were used and it was observed that, for the conversion of one equivalent of 4-chloroaniline into 6-chloro-2-aminobenzthiazole, three equivalents of NaCl₂ and seven equivalents of potassium thiocyanate were found to give the desired product in excellent yield, with reaction being complete within two hours.

To investigate the scope of this reaction, these optimized reaction conditions were used for the synthesis of 2-aminobenzthiazoles from a range of anilines possessing electron-withdrawing and/or electron-donating substituents; the results are summarized in Table 3.^{15,16}

In all cases, excellent yields of the desired product were obtained. Anilines containing both an electron-donating as well as an electron-withdrawing substituent were converted into the corresponding 2-aminobenzthiazole successfully (Table 3, entries 2–15). Under these reaction conditions, esters are unaffected (Table 3, entry 18).

Table 3 Synthesis of 2-Aminobenzthiazoles using NaCl₂^a

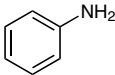
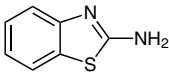
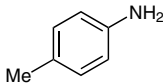
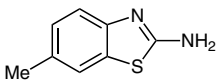
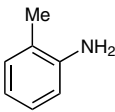
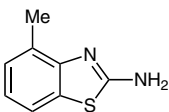
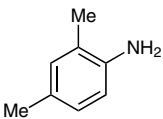
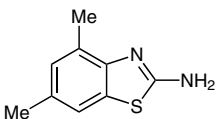
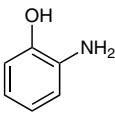
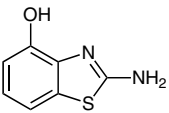
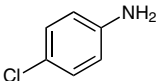
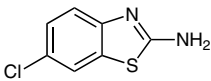
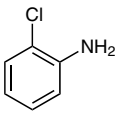
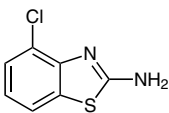
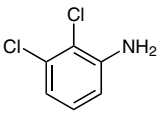
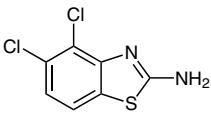
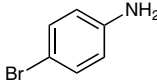
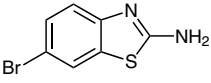
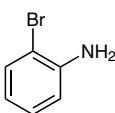
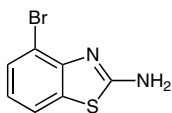
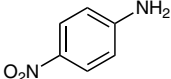
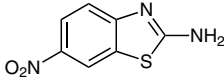
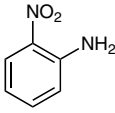
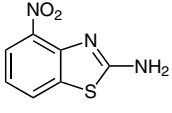
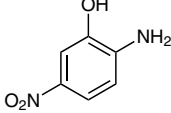
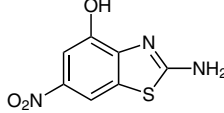
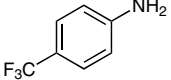
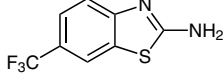
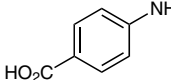
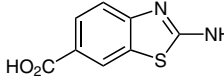
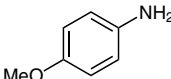
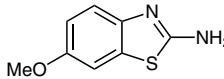
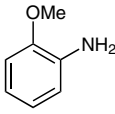
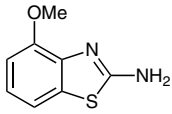
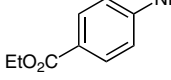
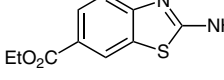
Entry	Aniline	Product	Time (h)	Yield (%) ^b
1			3	87
2			2	97
3			2	91
4			0.5	99
5			2	95
6			2	99
7			0.5	99
8			0.5	98
9			2	99

Table 3 Synthesis of 2-Aminobenzthiazoles using NaCl₂^a (continued)

Entry	Aniline	Product	Time (h)	Yield (%) ^b
10			0.5	97
11			2	99
12			1.5	99
13			5	72
14			2	99
15			10	97
16			3	98
17			4	95
18			6	98

^a Reaction conditions: aniline (1 equiv) potassium thiocyanate (7 equiv), NaCl₂ (3 equiv), 70 °C.

^b Isolated yield after silica gel column chromatography; structures were confirmed by NMR, IR and comparison of melting points with reported data.

In summary, we have described an efficient protocol for preparing 2-aminobenzthiazole derivatives in excellent yields using NaCl₂ under mild reaction conditions.

Acknowledgment

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References and Notes

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- (15) **General procedure for synthesis of 6-chloro-2-aminobenzothiazole (Table 2, entry 1):** To a stirred solution of 4-chloroaniline (0.1 g, 0.78 mmol) and potassium thiocyanate (0.53 g, 5.5 mmol) in DMSO–H₂O (9:1 mL) was added NaCl₂ (2 M, 0.52 g, 2.3 mmol). The reaction mixture was stirred vigorously at r.t. for 5 min, then the mixture was heated to 70 °C and progress of the reaction was monitored by TLC. The reaction was quenched with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were separated and washed successively with 10% aq Na₂S₂O₄ (2 × 10 mL), 10% aq NaHCO₃ (2 × 15 mL), and finally with H₂O (2 × 20 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. Pure 6-chloro-2-aminobenzothiazole was obtained as a yellow solid after silica gel column chromatography (EtOAc–hexane, 80:20).
- 1,3-Benzothiazol-2-amine (Table 3, entry 1)**
Mp 127–129 °C (Lit.^{16a} 129–130 °C); IR (KBr): 3402, 3266, 3052, 1637, 1525, 1442, 1306, 1102 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.73–7.60 (m, 4 H), 5.70 (s, 2 H). Anal. Calcd for C₇H₆N₂S: C, 55.97; H, 4.03; N, 18.65. Found: C, 55.99; H, 4.04; N, 18.62.
- 6-Methyl-1,3-benzothiazol-2-amine (Table 3, entry 2)**
Mp 132–133 °C (Lit.^{16b} 135–137 °C); IR (KBr): 3373, 3285, 3072, 2934, 1637, 1535, 1458, 1374, 1302, 1107 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.63–7.50 (m, 3 H), 5.49 (s, 2 H), 2.51 (s, 3 H). Anal. Calcd for C₈H₈N₂S: C, 58.51; H, 4.91; N, 17.06. Found: C, 58.47; H, 4.93; N, 17.08.
- 4,5-Dichloro-1,3-benzothiazol-2-amine (Table 3, entry 8)**
Mp 274–277 °C (Lit.^{16c} 275–276 °C); IR (KBr): 3403, 3326, 3221, 1629, 1571, 1460, 1380, 810, 580 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.48–7.36 (m, 2 H), 6.78 (s, 2 H). Anal. Calcd for C₇H₄Cl₂N₂S: C, 38.37; H, 1.84; N, 12.79. Found: C, 38.39; H, 1.85; N, 12.76.
- 6-Nitro-1,3-benzothiazol-2-amine (Table 3, entry 11)**
Mp 245–247 °C (Lit.^{16d} 247–248 °C); IR (KBr): 3452, 3298, 3047, 1652, 1566, 1528, 1494, 1325 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.20–8.12 (m, 3 H), 5.90 (s, 2 H). Anal. Calcd for C₇H₅N₃O₂S: C, 43.07; H, 2.58; N, 21.53. Found: C, 43.02; H, 2.59; N, 21.57.
- 6-(Trifluoromethyl)-1,3-benzothiazol-2-amine (Table 3, entry 14)**
Mp 119–122 °C (Lit.^{16e} 122 °C); IR (KBr): 3461, 3221, 1634, 1600, 1480, 1441, 1340, 1263, 1167, 1128 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.70–7.62 (m, 3 H), 4.32 (s, 2 H).
- 4-Methoxy-1,3-benzothiazol-2-amine (Table 3, entry 17)**
Mp 148–153 °C (Lit.^{16f} 149–151 °C); IR (KBr): 3379, 3283, 3091, 2937, 1636, 1545, 1458, 1333, 1270, 1049 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.37–7.10 (m, 3 H), 5.45–5.10 (br s, 2 H), 3.84 (s, 3 H). Anal. Calcd for C₈H₈N₂OS: C, 53.31; H, 4.47; N, 15.54. Found: C, 53.26; H, 4.48; N, 15.58.
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