A new and efficient synthesis of 2-aminobenzothiazoles derivatives from *o*-nitroaniline

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A novel synthesis of 2-aminobenzothiazoles from a transition-metal-free reaction between aryl isothiocyanates and *o*-nitroaniline in the presence of K_2CO_3 is reported. The newly developed method is an efficient and cost-effective approach to synthesise 2-aminobenzothiazoles.

Keywords: 2-aminobenzothiazoles, aryl isothiocyanates, *o*-nitroaniline, new precursor

2-Aminobenzothiazole derivatives have attracted considerable attention due to their promising biological applications in drug discovery and development for the treatments of epilepsy,[1] tuberculosis,[2] inflammation,[3] diabetes,[4] viral infection,[5] tumours[6] and allergies.[7] Riluzole[8] (**A**) is used to treat amyotrophic lateral sclerosis and R116010 (**B**) exhibits anti-tumour activity[9] (Fig. 1).

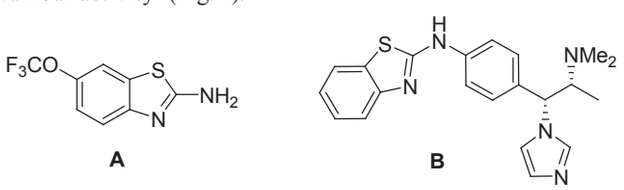


Fig. 1 Chemical structures of Riluzole (**A**) and R116010 (**B**).

Historically, 2-aminobenzothiazole derivatives were prepared by using different catalysts or agents. Hoffmann[10] first reported the formation of 2-anilinobenzothiazole from the reaction of 2-aminothiophenol and phenyl isothiocyanate. Some groups have synthesised aminobenzothiazoles by cyclisations of substituted anilines with the help of potassium and ammonium thiocyanates[11–15] in the presence of bromine as catalyst. Phenylthiourea derivatives have also been employed for the synthesis of these important compounds.[16–18] Transition metal-catalysed (Pd or Cu) intramolecular cyclisation of (2-halophenyl) thioureas is a powerful strategy for construction of the 2-aminobenzothiazole core.[19–21] Recently, copper(I)-catalysed tandem addition–cyclisation reactions of 2-iodoanilines with isothiocyanates in toluene have been described.[22] A green, alternative tandem approach based on the $FeCl_3$-catalysed reaction of 2-iodoaniline with isothiocyanates in water has been reported.[23] Another investigation has been carried out using DDQ to promote C–S bond formation under transition-metal-, ligand- and base-free conditions.[24] Direct functionalisation of aromatic C–H bonds to construct C–S bonds, provided another access to benzothiazoles.[25] A simple protocol for the arylation process of different aromatic heterocycles including benzotriazoles without any transition-metal catalyst, involving the use of an excess of potassium hydroxide in dimethyl sulfoxide, has been reported.[26] Therefore, a variety of effective strategies have been developed for the synthesis of these compounds. Although the above methods for the synthesis of 2-aminobenzothiazole derivatives have advantages, many of these procedures have some disadvantages including low yields, various uses of reagents, high cost catalysts, high temperatures for completion of the reaction as well as prolonged reaction times. On the other hand, much attention has been paid to the use of 2-haloanilines and 2-aminothiophenols as precursors that provide another limitation for these methods. As part of our continuing efforts for the expeditious synthesis of biologically relevant heterocyclic compounds[27] and by taking advantage of recent experience in the use of nitroarenes in coupling reactions,[28,29] we now report our recent efforts towards the synthesis of diverse 2-aminobenzothiazoles *via* tandem addition–cyclisation reactions of *o*-nitroaniline (as a new precursor) with aryl isothiocyanates in DMSO. This transformation proceeded smoothly under mild conditions in the presence of K_2CO_3 and the corresponding products were generated in good to excellent yields (Scheme 1).

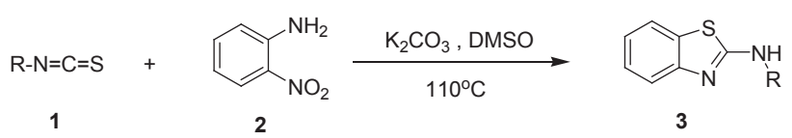
Results and discussion

To optimise the reaction conditions, the *in situ* generated thiourea, obtained by treating phenyl isothiocyanate **1a** (1 equiv.) with *o*-nitroanilinine **2** (1 equiv.), followed by the addition of base and solvent with heating for 5 h, afforded the product 2-aminobenzothiazole **3a**, as depicted in Table 1**.** It was found that the highest yields were obtained using K_2CO_3 (2 equiv.) as base and DMSO as solvent at 110 °C (entry 4).

Table 1 Optimisation of the reaction conditions for the preparation of **3a**

Entry	Solvent	Base	T/°C	Yield/%[a]
1	–	K_2CO_3 (2 equiv.)	110	–
2	DMSO	K_2CO_3 (1 equiv.)	110	62
3	DMSO	K_2CO_3 (2 equiv.)	80	70
4	DMSO	K_2CO_3 (2 equiv.)	110	82
5	DMSO	KOH (1 equiv.)	110	45
6	DMSO	KOH (2 equiv.)	110	55
7	DMF	KOH (2 equiv.)	110	55
8	DMF	K_2CO_3 (2 equiv.)	110	43

[a]Isolated yield



1 **2** **3**

Scheme 1

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Using the optimised conditions, the scope and generality of this transformation were examined by using various phenyl isothiocyanates and the corresponding results are listed in Table 2.

Table 2 Synthesis of 2-aminobenzothiazoles **3**

3	R	Yield/%	M.p./°C	Lit. m.p./°C
a	C_6H_5	82	157–159	158–160[30]
b	4-MeC_6H_4	80	179–180	178–179[30]
c	4-$MeOC_6H_4$	75	154–155	153–155[30]
d	4-ClC_6H_4	82	208–209	208–209[30]
e	3,5-$(CF_3)_2C_6H_3$	79	151–153	150–153[31]
f	*t*-Bu	80	90–94	91–95[31]
g	4-FC_6H_4	78	213–214	216–217[30]
h	2,4-$(CH_3)_2C_6H_3$	80	134–137	135–136[32]

Conclusion

In conclusion we have developed a simple and efficient tandem reaction for the synthesis of 2-aminobenzothiazoles from isothiocyanates and *o*-nitroaniline under basic conditions in DMSO without the presence of expensive catalysts or ligands. Of particular importance, the requirement for an *ortho*-halo and *ortho*-thio-substituted precursor for synthesising of 2-aminobenzothiazoles could be eliminated by this procedure.

Experimental

All chemicals used in this work were purchased from Merck and Aldrich companies. All the reactions were checked by TLC using silica-coated plates. The products obtained by the new procedure were identified by comparison of their melting points and spectral data with those of authentic samples. IR spectra were recorded on a Jasco IR-680 spectrophotometer. NMR spectra were obtained for solutions in DMSO-d_6 on a Bruker Avance AQS spectrometer (^{1}H, 500 MHz; ^{13}C 100 MHz).

Synthesis of 2-aminobenzothiazoles **3a–h;** *general procedure*

A mixture of the appropriate isothiocyanate **1** (2 mmol) and *o*-nitroaniline **2** (2 mmol) was stirred at room temperature for 30 min. The reaction between the isothiocyanate and o-nitroaniline was conducted in the absence of solvent. After completion of the reaction (monitored by TLC), potassium carbonate (4 mmol) and dimethyl sulfoxide (3 mL) were added to reaction mixture and it was heated 110 °C for 5 h. The reaction mixture was cooled to room temperature Water (3 mL) was then added and the mixture was extracted with EtOAc (3 × 6 mL). The organic layers were dried with anhydrous $MgSO_4$ and under vacuum. The residue was purified by column chromatography using EtOAc-*n*-hexane(4:1) as eluent.

2-Anilinobenzothiazole (**3a**): White solid, m.p. 157–159 °C (lit. 158–160 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09–7.17 (m, 2H), 7.25 (t, J=7.5 Hz, 1H), 7.40 (t, J=8.1 Hz, 2H), 7.50 (app. d, $J_{app.}$=8.0 Hz, 2H), 7.55 (app. d, $J_{app.}$=7.9 Hz, 1H), 7.60 (app. d, $J_{app.}$=7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.1, 119.3, 120.4, 121.5, 123.1, 125.1, 128.8, 129.1, 138.9, 150.2, 164.

2-(4-Methylanilino)benzothiazole (**3b**): White solid, m.p. 179–180 °C (lit. 178–179 °C); 1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.12 (d, J=8.0 Hz, 1H, *p*-tolyl), 7.21 (d, J=7.8 Hz, 2H, *p*-tolyl), 7.30 (t, J=7.8 Hz, 1H, *p*-tolyl), 7.32 (app. d, $J_{app.}$=8.1 Hz, 2H), 7.45 (app. d, $J_{app.}$=7.5 Hz, 1H), 7.60 (app. d, $J_{app.}$=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 119.1, 120.8, 121.1, 121.9, 125.4, 129.3, 129.9, 134.1, 137.1, 151.2, 165.5.

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