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Straightforward convergent access to 2-arylated polysubstituted benzothiazoles

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Abstract:

A modular access to 2,4 disubstituted benzothiazoles has been achieved though the intermediacy of 4-bromo-2-iodobenzothiazole. The difference in reactivity of both halogens was advantageously exploited to achieve sequential Suzuki-Miyaura cross-coupling giving access to a range of polyaromatic derivatives featuring a central benzothiazole core.

Keywords:

Orthogonal Suzuki-Miyaura cross coupling; benzothiazole; boronic derivatives.

Introduction

The benzothiazole core is considered a privileged fused bicyclic heterocycle in light of its applications in pharmaceutical, agrochemical, and materials chemistry.[1-3] This has driven the development of increasingly efficient methodologies towards the synthesis of functionalised 2-arylated benzothiazole scaffolds.[4-6] More recently, these scaffolds have found applications in organocatalyzed (de)hydrosilylation reactions where they function as carbon-centred Lewis acids in the activation of Si–H σ bonds.[7] Substituted

benzothiazoles are also involved in important applications in organic light-emitting devices (OLEDs).[8-10] Similar to other benzazoles,[11-14] they quite commonly exhibit interesting photochemical properties including processes such as Excited State Intramolecular Proton Transfer (ESIPT).[15, 16] These molecules have also been intensively studied for their dual action potential as metal chelators and as intercalating compounds targeting pathological peptidic aggregates that of interest for imaging various dementias e.g. Alzheimer's Disease.[17, 18]

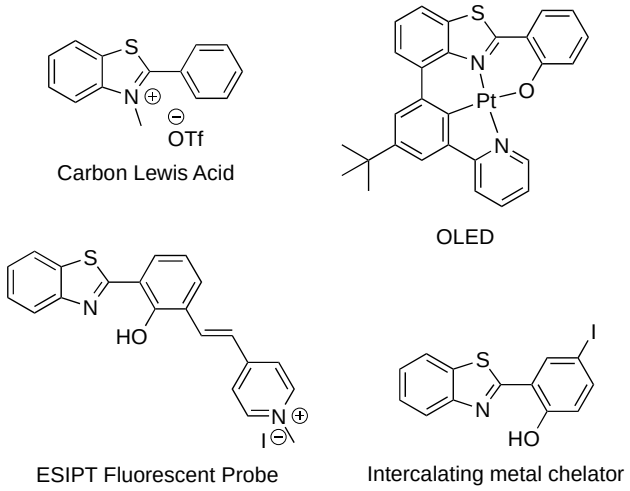


Figure 1: Benzothiazole scaffolds integrated into various applications

Considering that the nitrogen atom of the benzothiazole is key in all the applications mentioned and illustrated above, we focused our attention on modulating its environment by introducing substituents on position 2 and 4 of the benzothiazole core in a convergent fashion. Although numerous strategies have been designed to access substituted benzothiazoles, in nearly all cases, strategies have required non-versatile and non-modular syntheses.[1] One major path relies on the cyclisation of functionalised arylthioamides or arylthioureas. Such starting materials require time-consuming

methods to generate thioamides (or thioureas) prior to cyclisation, most commonly from the corresponding amide with Lawesson's reagent. Alternatively, benzothiazoles can also be accessed by condensing aldehydes with 2-aminothiophenols in the presence of an oxidant (air being the mildest) or reaction with activated esters and/or acid halides. However, drawbacks with these approaches are readily appreciated by considering the poor shelf-life of many aldehydes, the high-reactivity of acid halides, as well as the poor availability of functionalized 2-aminothiophenols, which are themselves air-sensitive and easily decomposed.

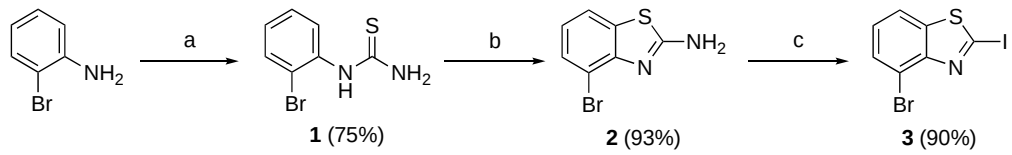
A more facile and highly convergent approach, based on readily-available and stable building blocks, would be to leverage the extensive portfolio of boronic acids to access polysubstituted benzothiazole derivatives through Suzuki-Miyaura cross coupling starting with a suitable 2-iodobenzothioazole as a readily accessed coupling partner. Moreover, taking advantage of the C-2 activated position of the heterocycle might prove sufficiently selective for orthogonal coupling thus providing diversely polysubstituted benzothiazoles in a highly convergent and straightforward fashion. Herein, we present a preliminary report that establishes this strategy as a viable route to polysubsituted benzothiazoles. To test this hypothesis, we envisioned a practical and convergent strategy involving 4-bromo-2-iodobenzothiazole **3** (Scheme **1**) as a key intermediate that would enable regio/chemoselective coupling to deliver a series of C2/C4 arylated benzothiazoles. This strategy is attractive as it is highly modular as it allows for considerable synthetic versatility considering the expansive library of aryl boronic acids and derivatives available, both commercially and synthetically, as suitable coupling partners.[19, 20] Herein, we describe the swift synthesis of versatile intermediate **3**,

substituted with two different halogens that, as part of our design, demonstrates efficient access to the said benzothiazoles via chemoselective and regioselective functionalisation with various aromatic substituents.

Results and Discussion

Synthesis of di-halogenated intermediate

We sought a simple, efficient, and high-yielding synthetic route with an eye to utilizing affordable and common laboratory reagents. Starting from commercially-available 2-bromoaniline, thiourea **1** was obtained following standard protocol.[21, 22] Subsequent Hugershoff cyclization with Br_2 yielded the desired 2-amino-4-bromobenzothiazole (**2**) in excellent yield.[23, 24] One-pot iodination of **2**, under Sandmeyer conditions, provided 4-bromo-2-iodo-benzothiazole (**3**) in excellent yield (Scheme **1**). Key intermediate **3** is obtained in three synthetic steps in 63% global yield without further optimization. This represents a significant improvement over the 5-step approach from the less available 2,3-dibromoaniline as reported in patent literature.[25]



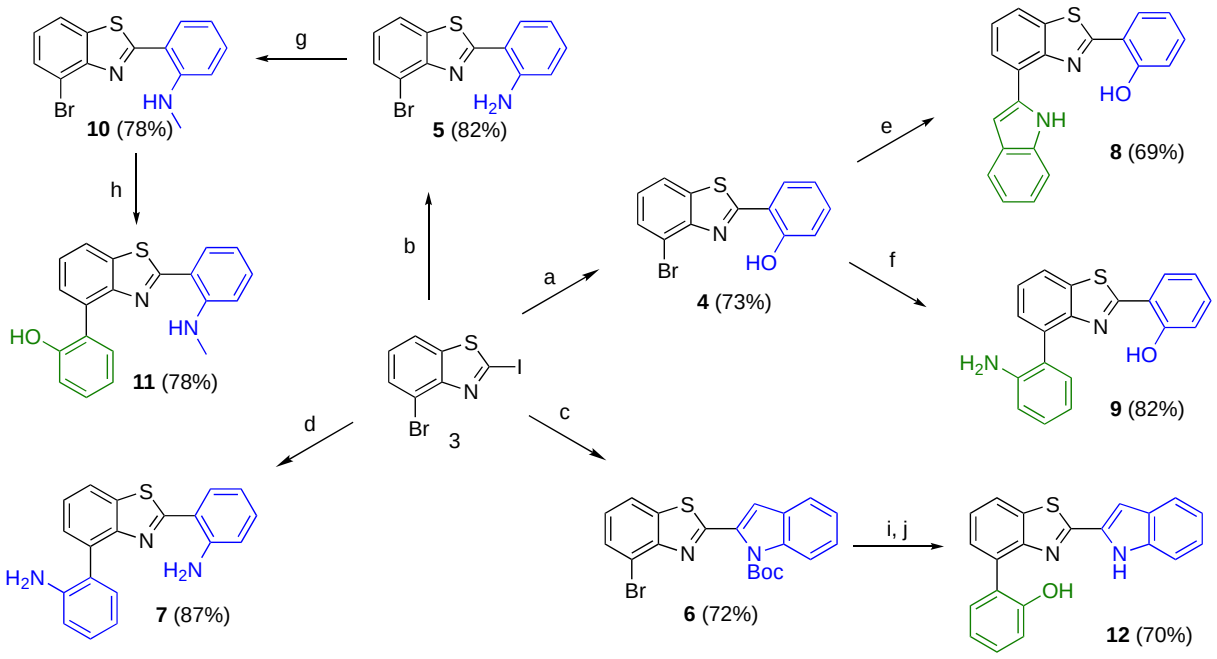
Scheme 1 Synthesis of 4-bromo-2-iodobenzothiazole. **a**, BzCl, NH_4SCN, acetone, reflux, 1 hour. **b**, Br_2, $CHCl_3$, reflux 1.5 hours. **c**, (i) *p*-TsOH·H_2O, MeCN, room temperature, (ii) *t*-BuONO, -5 °C, 30 minutes, (iii) KI, cat. CuI, H_2O, 0 °C then room temperature, 18 h.

Functionalisation of key benzothiazole intermediate

Given the well-established reactivity differences between C(sp^2)-I and C(sp^2)-Br bonds with respect to oxidative addition at a transition metal centre, **3** should submit to

chemoselective and regioselective Suzuki-Miyaura cross-coupling with various aryl boron derivatives (Scheme **2**). Indeed, products of selective mono-arylation of **3** were obtained by initial cross-coupling at C-2, at moderate reaction temperature (90 °C), selective arylation could be achieved while safeguarding the C-Br bond intact for further functionalization (*vide infra*). Notably, 2-hydroxyphenyl-boronic acid, 2-aminophenyl-boronic acid, and *N*-Boc-indole-2-boronic acid could be coupled to **3**, furnishing 2-aryl-4-bromobenzthiazoles **4**, **5** and **6**, respectively in good yields. Notably, if desired, one-pot, double cross-coupling with 2-aminophenylboronic acid was found to be highly efficient, providing the corresponding 2,4-dianiline (**7**) in 87% yield.

To capitalize on the extant C-Br bond, compounds **4**,**6**, and **10** could be further functionalised in step-wise fashion, at C-4, via cross-coupling with various arylboronic acids or trifluoroborates. For example, reaction of **4** with potassium *N*-Boc-indole-2-trifluoroborate, under conditions reported by Molander *et al.*,[26] or with 2-aminophenylboronic acid furnished 2,4-diarylbenzthiazoles **8** and **9**, respectively, in good yields. The aniline in benzothiazole **5** was shown to undergo mono-*N*-methylation, while conserving the C-Br bond,[27] in good yield to provide **10**, which was further cross-coupled with 2-hydroxyphenylboronic acid to furnish 2,4-diarylbenzothiazole **11**. Finally, 4-bromo-2-indolebenzothiazole **6**, after Boc-deprotection of **6** to **6a**, could be coupled with 2-hydroxyphenylboronic acid to provide **12** in high yield.



Scheme 2. Transformation of 3 into various 2- and 2,4-disubstituted benzothiazoles. **a**, 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, microwave, 90 °C, 1 hour. **b**, 2-aminophenylboronic acid, $Pd(PPh_3)_4$, XantPhos, Na_2CO_3, 1,4-dioxane/H_2O, microwave, 90 °C, 1 hour. **c**, *N*-Boc-indole-2-boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, 1,4-dioxane/H_2O, microwave, 90 °C, 1 hour. **d**, 2-aminophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, microwave, 120 °C, 5 hours. **e**, potassium *N*-Boc-indole-2-trifluoroborate, $Pd(Oac)_2$, SPhos, Na_2CO_3, EtOH, 85 °C, 5 hours. **f**, 2-aminophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, microwave, 120 °C, 1 hour. **g**, $Re(NH(CH_2CH_2PPh_2)_2)(CO)_3Br$, Cs_2CO_3, MeOH, 140 °C, 5 days. **h**, 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, 120 °C, 18 hours. **i**, TFA/DCM (1:1), room temperature, 2 hours. **j**, 2-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, 120 °C, 1 hour.

Photophysical Properties

Given the increasing interest and application of the absorptive and emissive properties of benzothiazoles, we briefly studied the photophysical properties of these novel benzothiazoles. As a general trend, these benzothiazoles exhibit similar absorption spectra, consisting of large bands in the UV region of the spectrum; they absorb strongly with absorption maxima ranging from 339 to 405 nm that are attributed to characteristic π-π* transitions. However, on closer inspection it becomes evident that the nature of the aromatic group at C-2 determines the absorption profile, while the

substitution at C-4 delivers fine-tuning of the absorption maximum (Figure 2). These compounds were also found to be fluorescent, with broad emission bands ranging from 403 to 519 nm, corresponding to Stoke shifts (Δ_{SS}) varying from 39 to 180 nm. The large Δ_{SS} are only observed for compounds **4, 8** and **9** which feature 2-hydroxylphenyl at C-2, allowing for the possibility of ESIPT which induces significant structural reorganisation in the excited state, accounting for the large Δ_{SS}. In contrast to the relationship observed in absorption, the substituent at C-4 has no effect on emission profiles or maxima.

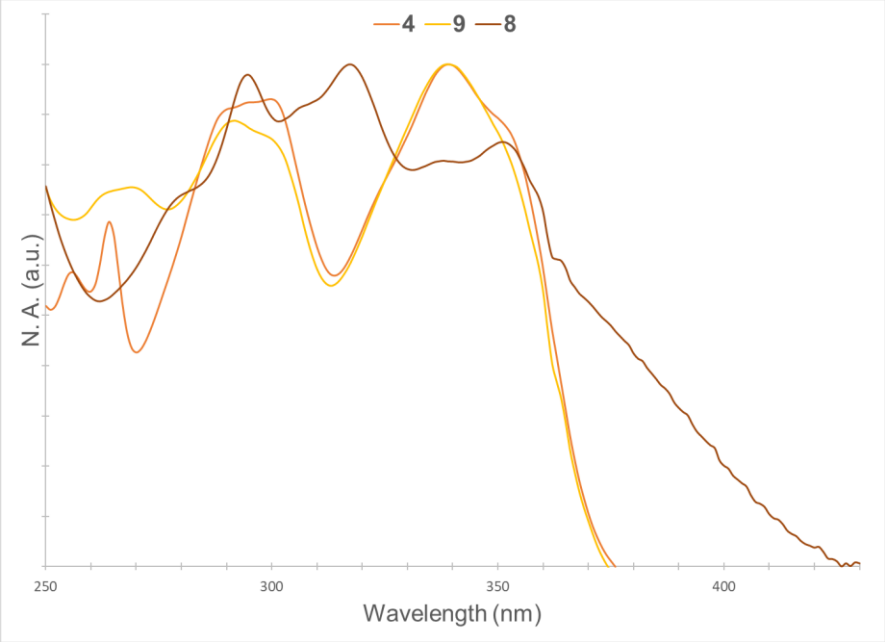


Figure 2: UV Absorption spectra of **4**,**8** and **9**.

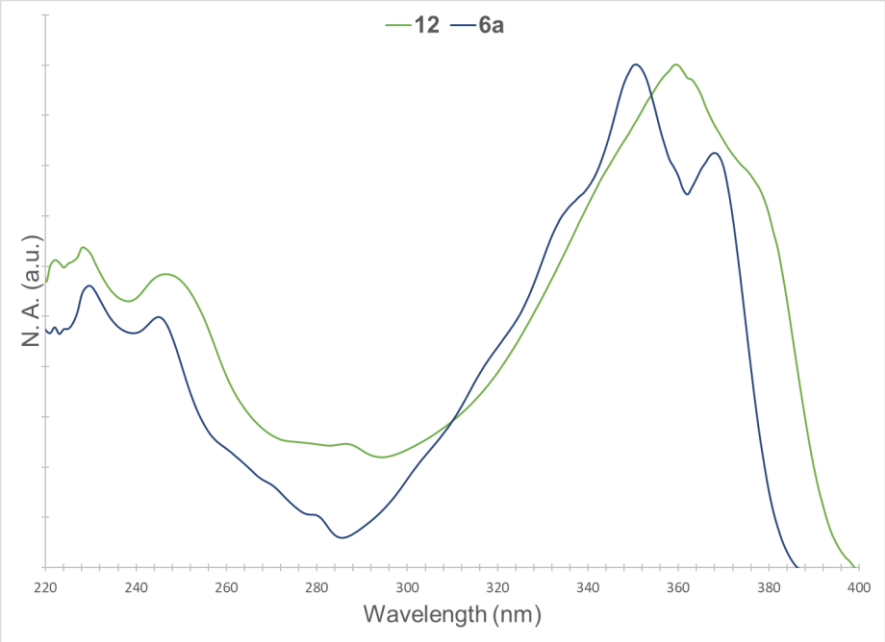


Figure 2: UV Absorption spectra of **12** and **6a**.

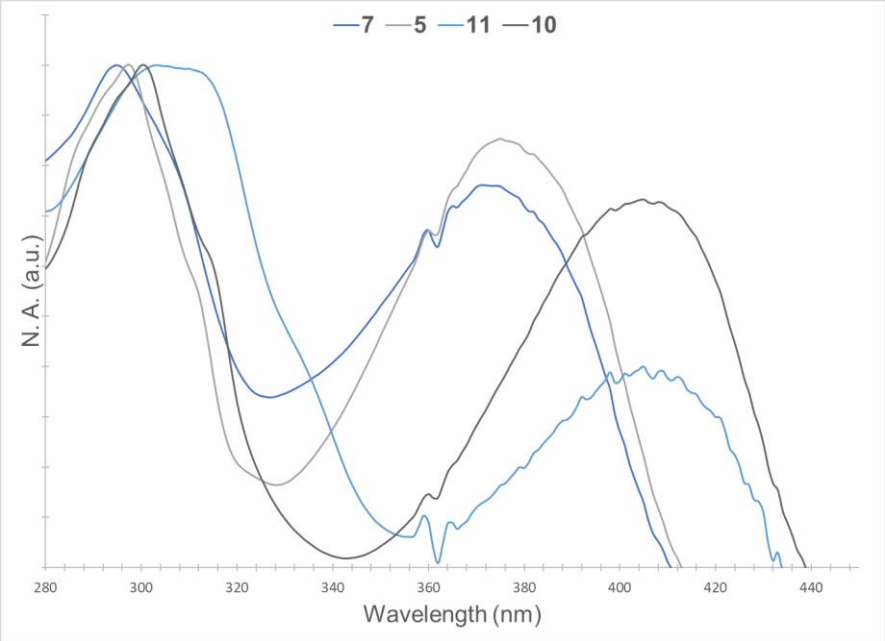


Figure 2: UV Absorption spectra of **5**, **7**, **10** and **11**.

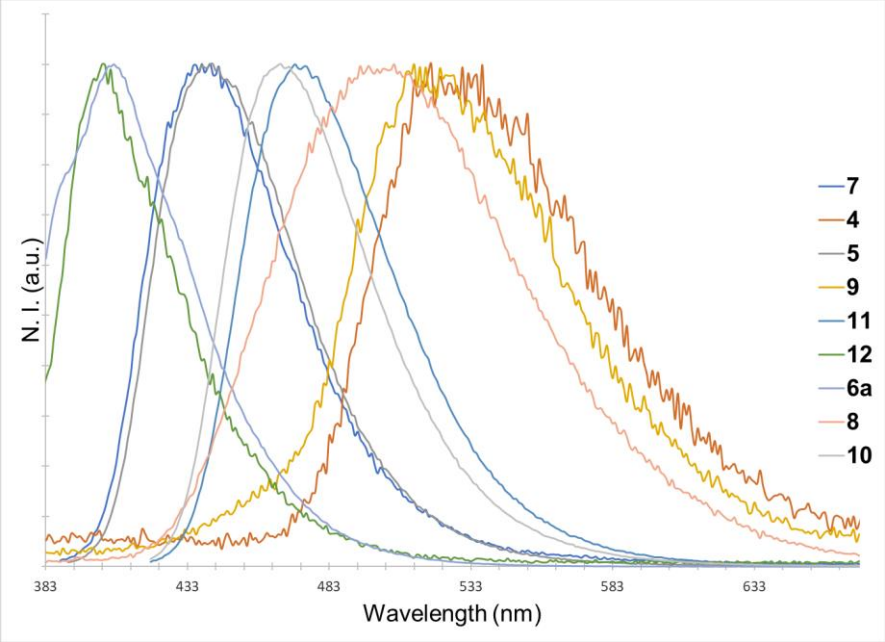


Figure 2: Fluorescence spectra of **4**, **5**, **6a**, **7**, **8**, **9**, **10**, **11** and **12**.

Table 1 Photophysical properties of compounds 4-12

Compound	λ_{abs} (nm)	log ε (M^{-1} cm^{-1})	λ_{em} (nm)	Δ_{ss} (nm - cm^{-1})
4	339	4.1	519	180 - 10231
5	376	4.0	442	66 -3971
6a	368	4.4	407	39 - 2604
7	373	4.0	438	65 - 3979
8	351	4.1	506	155 - 8727
9	339	4.2	513	174- 10005
10	405	4.1	466	61- 3232
11	405	3.6	471	66 - 3460
12	360	4.5	403	43 - 2964

Conclusion

In conclusion, here we have demonstrated the facile synthesis of a wide variety of 2-aryl-4-bromo and 2,4-diarylbenzothiazole derivatives via selective Suzuki-Miyaura cross-coupling with key benzothiazole intermediate **3**. This scaffold has proven versatile, allowing selective structural elaboration firstly at the C-2 position, in high yields, followed by functionalisation at the C-4 position; the scaffold can also be di-functionalised in one-pot at both the C-2 and C-4 positions. This strategy gives rapid access to a diverse family of benzothiazoles with tuneable photophysical properties. Although our synthesis is somewhat limited in scope, we have demonstrated that this reaction manifold is readily amenable to preparing a large number of tricyclic compounds starting with (hetero)arylboronic acids. Hence, in this preliminary report, we acknowledge this methodology serves as a proof of concept for its expansion towards the functionalisation of other positions on the benzothiazole core in a similar fashion. It is readily anticipated more densely functionalized bromoanilines will readily submit to this reaction scheme. The novel benzothiazoles derivatives reported here accessible through **3**, or derivatives thereof, are further anticipated to be of interest for photophysical studies in both solution and the solid-state, as well as their investigation as Lewis acid catalysts and as chelators for various metal cations. Studies towards these goals are currently underway.

Supporting Information

Supporting information including extensive experimental details and compounds characterizations (IR, ^{1}H and ^{13}C NMR, HRMS) are provided.

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