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Ultrasound-assisted synthesis of substituted 2-aminobenzimidazoles, 2-aminobenzoxazoles, and related heterocycles

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ABSTRACT

A sonochemical method for the synthesis of 2-aminobenzimidazoles and 2-aminobenzoxazoles, as well as chiral aminooxazolines and a chiral substituted quinazolin-5-one is reported. Using the Ph_3P–I_2 system in the presence of triethylamine as a desulfurization agent, monothioureas prepared in situ from the reaction of bis-nucleophiles with isothiocyanates underwent rapid cyclization to afford a variety of *N*-heterocyclic compounds in good to excellent yields under mild conditions.

Introduction

2-Aminobenzimidazoles and 2-aminobenzoxazoles are important pharmacophores in medicinal chemistry. Both natural products and synthetic molecules possessing these heterocyclic scaffolds have been shown to exhibit useful pharmacological and biological properties such as antimicrobial, antiallergic, immunosuppressive, and antiviral activities.[1–4] For example, ageladine A (**I**), a marine natural product, was reported as a promising antimetastatic agent.[5,6] Compound **II** was identified as a novel class of orally active antimalarial agent,[7] while compound **III** is a potent p38α MAP kinase inhibitor for the treatment of inflammatory disease.[8] Compound **IV** acts as a potent A_{2B} adenosine receptor antagonist which may be useful for the treatment of diabetes, asthma, and chronic obstructive pulmonary disease.[9] Finally, suvorexant (**V**) has recently been approved as a therapeutic drug for insomnia[10,11] (Fig. 1).

Currently, there are several approaches for the synthesis of these heterocyclic systems. One of the most convenient routes involves the cyclodesulfurization of the preformed monothioureas, derived from bis-nucleophiles such as *o*-phenylenediamine or aminophenol derivatives. Some examples of desulfurization agents include HgO,[12] polymer-supported carbodiimide,[13] TsCl/NaOH,[14] $LiOH/H_2O_2$,[15] hypervalent iodine(III),[16] 1,1′-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT),[17] and BOP reagent.[18] However, these methods are associated with one or more limitations such as being expensive or using highly toxic reagents, requiring long reaction times or harsh reaction conditions, and having low chemoselectivity and yields.

Ultrasound has proven to be a powerful process intensification tool for organic synthesis, presumably due to the acoustic cavitation phenomenon.[19] Compared to conventional stirring, reactions under ultrasonic irradiation have been reported to proceed with shortened times, improved yields, and selectivity.[20–22] Although a number of ultrasound-promoted heterocyclization reactions toward five- or six-membered rings have been developed,[23–26] surprisingly, the synthesis of 2-aminobenzimidazoles and related heterocycles has not been reported under ultrasonic irradiation.

Triphenylphosphine (Ph_3P) is a readily available and inexpensive reagent which has been used in combination with several halogenated additives as effective dehydrating agents.[27] Recently, we reported that the combination of Ph_3P and I_2 could be used to promote the guanylation of thioureas, presumably through the formation of a carbodiimide intermediate.[28] To the best of our knowledge, this reagent system has never been used in cyclodesulfurization reactions where all reactive species are presented in one-pot. Herein, we report a facile and effective sonochemical method for the synthesis of substituted 2-aminobenzimidazoles and 2-aminobenzoxazoles, as well as other

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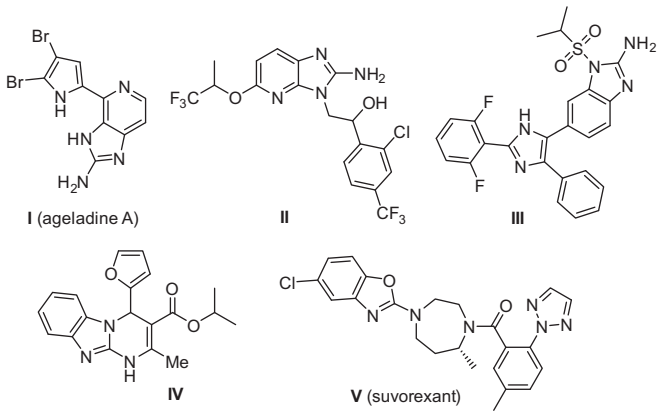


Figure 1. Representative examples of bioactive molecules containing the 2-aminobenzimidazole and 2-aminobenzoxazole moieties.

related heterocyclics through the Ph_3P–I_2 reagent system promoted cyclodesulfurization of monothiourea intermediates.

Results and discussion

Our investigation began with the ultrasonic-assisted cyclodesulfurization of monothiourea **VI**, generated in situ from the reaction of *o*-phenylenediamine with phenylisothiocyanate. The effect of both the halogen additive and type of base was evaluated. Typically, the reaction was carried out by mixing Ph_3P (1.5 equiv) and the additive (1.5 equiv) in dichloromethane at 0 °C. The preformed thiourea (1.0 equiv) was then added, followed by base (3.0 equiv). The reaction mixture was then sonicated in an ultrasonic bath at ambient temperature for a further 10 min before product isolation.

According to Table 1, using I_2 as the additive in the presence of triethylamine gave the best result compared to those using *N*-bromosuccinimide (NBS) or bromine (Br_2) (Entries 1–3). Changing the base to imidazole led to lower product yield due to incomplete conversion of the formed carbodiimide intermediate (Entry 4). The reaction in the presence of *N*,*N*′-dimethylaminopyridine (DMAP) and 1,8-diazabicycloundec-7-ene (DBU) only gave the product in trace amount (Entries 5–6). In these reactions, most of the starting thiourea was unreacted, indicating that these bases were ineffective or led to decomposition of the formed reactive species. The benefit of ultrasound was further confirmed by the low conversion of the reaction mediated by the Ph_3P–I_2/Et_3N system under traditional stirring where the formed thiourea and corresponding carbodiimide intermediate still remained (Entry 7).

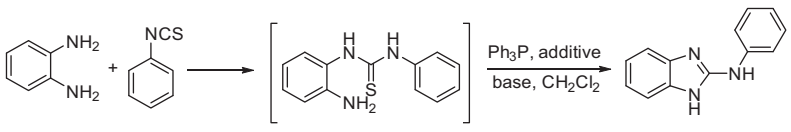
With the optimized reaction conditions in hand, a series of substituted 2-aminobenzimidazoles were synthesized from phenylenediamines and isothiocyanates (Table 2). The reaction of *o*-phenylenediamine with aryl isothiocyanates proceeded rapidly, especially when the isothiocyanates contained an electron withdrawing group (Entries 1–4). Slightly longer reaction times were required when an electron donating group was presented at the *para*-position of the phenyl isothiocyanate (Entry 6) or when using the relatively sterically hindered 1-napthylisothiocyanate (Entry 7). Apart from aryl isothiocyanates, the reaction conditions were also applicable to alkyl isothiocyanates where benzyl isothiocyanate reacted smoothly to afford the corresponding product in good yield (Entry 8). Other diamine derivatives were also viable substrates under the applied conditions (Entries 9–14), although the electron-deficient dibromo-substituted substrate (Entry 14) reacted less favorably, providing lower yields of the corresponding aminobenzimidazole.

The chemistry could be extended to other related bis-nucleophiles such as the reaction of 2-aminophenol with isothiocyanates which produced substituted 2-aminobenzoxazole derivatives in reasonable yields (Entries 15–18). Due to the lower nucleophilicity of the OH group compared to the $-NH_2$ group, extended reaction times were required for reaction completion. Nevertheless, it is noteworthy that, under our developed conditions, the reaction between 2-aminophenol and 1-napthylisothiocyanate proceeded with high chemoselectivity to provide the expected *N*-(naphthalen-1-yl)benzo[*d*]oxazol-2-amine in good yield, whereas the reaction mediated by 1,1′-(ethane-1,2-diyl) dipyridinium bistribromide gave the 2-(naphtho[1,2-*d*]thiazol-2-ylamino)phenol as the major product.[17]

Encouraged by these results, the scope of the reaction was further extended to chiral bis-nucleophiles. Using (1*S*,2*R*)-1-amino-2-indanol as the nucleophilic substrate, the reaction with aryl isothiocyanates proceeded rapidly to provide a series of chiral aminooxazoline derivatives in good to excellent yields (Scheme 1). Notably, no side-products such as those derived from activation of the hydroxyl group were observed. The substituted aminooxazolines are potentially useful as chiral auxiliary ligands for asymmetric processes.[29–32]

It should be noted that, based on ^1H NMR spectroscopic analysis of compound **3b** as a representative molecule, the product was obtained as a single diastereomer with retention of configuration of the chiral centers. The signal of H-8a (Fig. 2) appears as a doublet of doublet of doublets at δ_H 5.39 ppm with coupling constants

Table 1
Optimization of the reaction conditions[a]



Entry	Additive	Base	Method	Yield (%)
1	NBS	Et_3N	))), 10 min	53
2	Br_2	Et_3N	))), 10 min	48
3	I_2	Et_3N	))), 10 min	90
4	I_2	Imidazole	))), 10 min	75
5	I_2	DMAP	))), 10 min	Trace
6	I_2	DBU	))), 10 min	Trace
7	I_2	Et_3N	Stirring, 10 min	Trace

[a] Reaction conditions: *o*-phenylenediamine (0.41 mmol), phenylisothiocyanate (0.41 mmol), Ph_3P (0.62 mmol), additive (0.62 mmol), base (1.23 mmol), CH_2Cl_2 (2 mL), 0 °C–rt.