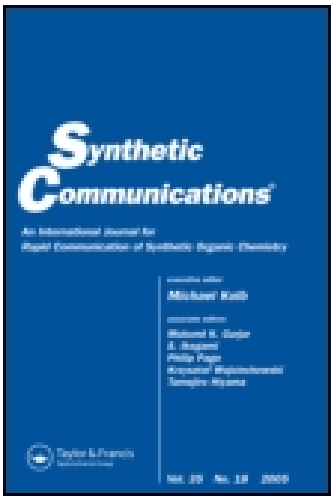

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Water-Mediated Synthesis of Benzazole and Thiourea Motifs by Reacting Naturally Occurring Isothiocyanate with Amines

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WATER-MEDIATED SYNTHESIS OF BENZAZOLE AND THIOUREA MOTIFS BY REACTING NATURALLY OCCURRING ISOTHIOCYANATE WITH AMINES

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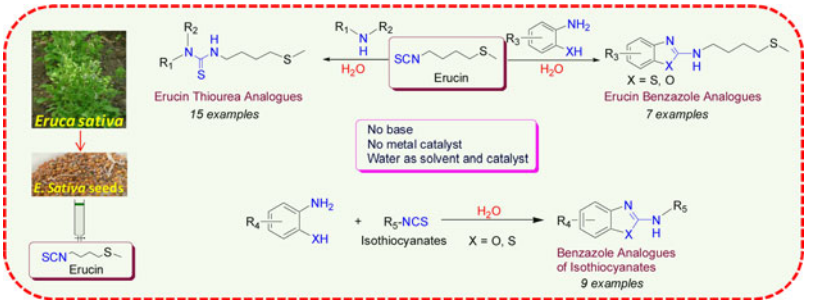
GRAPHICAL ABSTRACT



Abstract *An efficient, green, and facile method has been developed for the synthesis of benzazole and thiourea analogues from naturally occurring erucin in moderate to good yields. The reaction was carried out in water without using any metal catalyst or base. The present method tolerated the various functional groups on aromatic rings and also applicable for other isothiocyanates.*

Keywords Benzazoles; erucin; isothiocyanates; thiourea; water-mediated synthesis

INTRODUCTION

Erucin (4-methylthiobutylisothiocyanate) (Fig. 1), a natural isothiocyanate, is abundantly present in the plant *Eruca sativa* (brassicaceae). This plant is mainly

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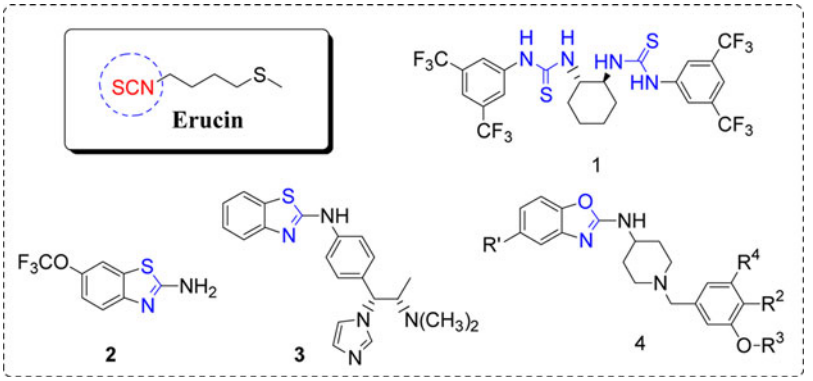


Figure 1. Structures of erucin, bioactive benzazole, and thiourea-bearing molecules.

known for the presence of glucosinolates,[1] which are hydrolyzed by an enzyme myrosinase[2] to give isothiocyanates or nitriles. Extracts of *Eruca sativa* shows various biological activities[3] such as antibacterial, anticancer, antiphlogistic, astringent, diuretic, stimulant, laxative, antacid, and anti-inflammatory activities and also affects blood circulation. Erucin is also known for significant neuroprotective, antioxidant, and anticancer activities.[4,5] Isothiocyanates constitute a significant functional class and are widely applicable as moderately reactive chemoselective electrophiles that are stable toward aqueous reaction conditions.[6]

On the other hand, the benzazole moiety is a privileged scaffold in numerous bioactive natural products and pharmaceuticals[7] and is also used as a ligand in important organic transformations.[8] These are oftenly used by medicinal chemists for synthesis of drugs[9] such as cytotoxic agents, HIV reverse trancriptase inhibitors, estrogen receptor agonists, orexim-1 receptor antagonists, proton-pump inhibitors, AT1 receptor antagonists, direct thrombin inhibitors, nonsteroidal anti-inflammatory drugs, and sodium channel blockers (Fig. 1). Much attention has been paid to the synthesis of azole derivatives due to their diverse applicability. Similarly, the thiourea backbone also represents a significant structural motif in pharmaceutical agents[10] having antibacterial, antimalarial, antiviral, and antitumor activities, as well as organo-catalytic potential (bis-thiourea).[11] Numerous strategies have been applied earlier for the synthesis of azoles such as via condensation of substituted anilines with isothiocyanates, followed by intramolecular cyclization of the resultant thiourea with transition-metal catalysts (Pd or Cu).[12] Ding et al. synthesized 2-aminobenzothiazole derivatives using copper(I)-catalyzed tendem addition–cyclization reaction in toulene[13] and $FeCl_3$ in water with a phase-transfer catalyst, base (DABCO), and ligand.[14] Li et al. synthesized the same core using FeF_3 or CuBr catalyst.[15] Copper-based catalysts have also been applied for similar transformations in water.[16] Another effective approach for the synthesis of a benzoxazole core is the condensation of 2-aminophenol with either carboxylic acid or aldehyde under high temperature,[17] metal-catalyzed cross coupling,[7b] polymer-supported synthesis under microwave irradiation,[18] transition metal-free, base-mediated synthesis in the presence of dimethylsulfoxide (DMSO),[19] and T_3P-mediated synthesis via dehydrogenation under mild conditions.[20]

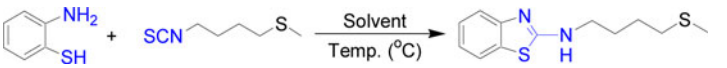
The thiourea core was synthesized by reacting amines with isothiocyanates under solvent or solvent-free conditions and sodium or ammonium thiocyanate in the presence of strong acids [triflouroacetic acid (TFA) or concentrated HCl].[21–23] *N*-Allylthioureas were synthesized from allylic bromide by using the $KSCN/SiO_2$-RNH_2OAc/Al_2O_3 catalytic system.[24] Moreover, to the best of our knowledge direct synthesis of benzazole and thiourea moieties by directly reacting amines with isothiocyanates without using any catalyst or base is not reported. In continuation of our work on the synthesis of azole scaffolds,[25] herein, we describe an environmentally benign approach for the synthesis of benzazole and thiourea scaffolds from a naturally occurring molecule, erucin, by employing water as solvent and catalyst.

RESULTS AND DISCUSSION

Initially, to optimize the best reaction conditions, the reaction of 2-aminothiophenol was carried out with erucin under different conditions (Table 1). The model reaction in ethanol afforded the desired product up to 68% at rt; however, the yield of the reaction was enhanced up to 95% at elevated temperature (Table 1, entries 1–3). The reaction yields were decreased in the mixture of $EtOH/H_2O$ (1:1) even at high temperature (Table 1, entries 4 and 5). Poor yields were observed in cases of isopropanol and toluene at rt (Table 1, entries 6 and 8); however, increase in yields were observed at high temperature (Table 1, entries 7 and 9). To our delight, in the case of water, the increase in reaction temperature up to 120 °C afforded the desired product in excellent yield (95%) in 48 h (Table 1, entry 12).

After optimization of the reaction conditions, the scope of the method was explored for the synthesis of various benzazole- and thiourea-containing analogues of erucin. Different *o*-substituted (-SH, -OH) anilines were tested for the synthesis of benzazole analogues. The reaction of 2-aminothiophenol and 4-chloro-2-aminothiophenol with erucin afforded the corresponding thioazole analogues in 88

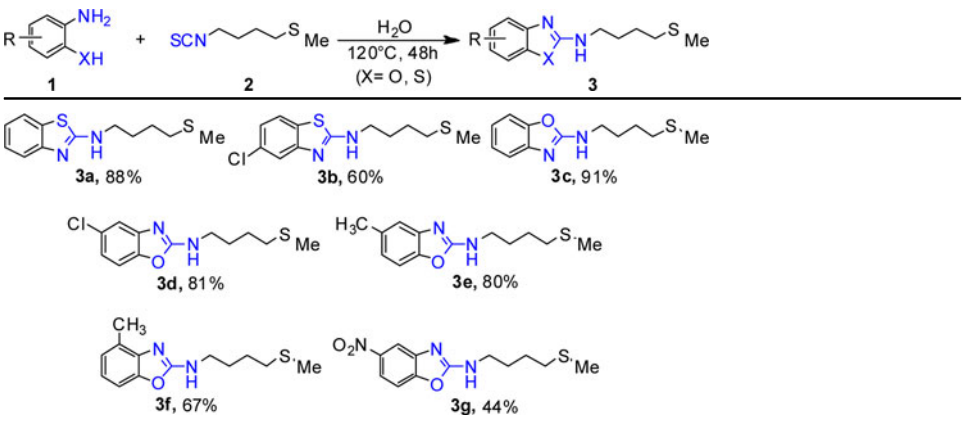
Table 1. Solvent screening for synthesis of benzothiazole analogues of erucin[a]



Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	C_2H_5OH	rt	48	67
2	C_2H_5OH	rt	72	68
3	C_2H_5OH	120	48	90
4	C_2H_5OH/H_2O (1: 1)	rt	48	61
5	C_2H_5OH/H_2O (1: 1)	120	48	75
6	$CH_3CH(OH)CH_3$	rt	48	39
7	$CH_3CH(OH)CH_3$	120	48	72
8	$C_6H_5CH_3$	rt	48	1
9	$C_6H_5CH_3$	120	48	70
10	H_2O	rt	48	19
11	H_2O	120	48	95

[a]Reaction conditions: 2-aminothiophenol (1 mmol), erucin (1 mmol), solvent (5 mL).
[b]GC yields.

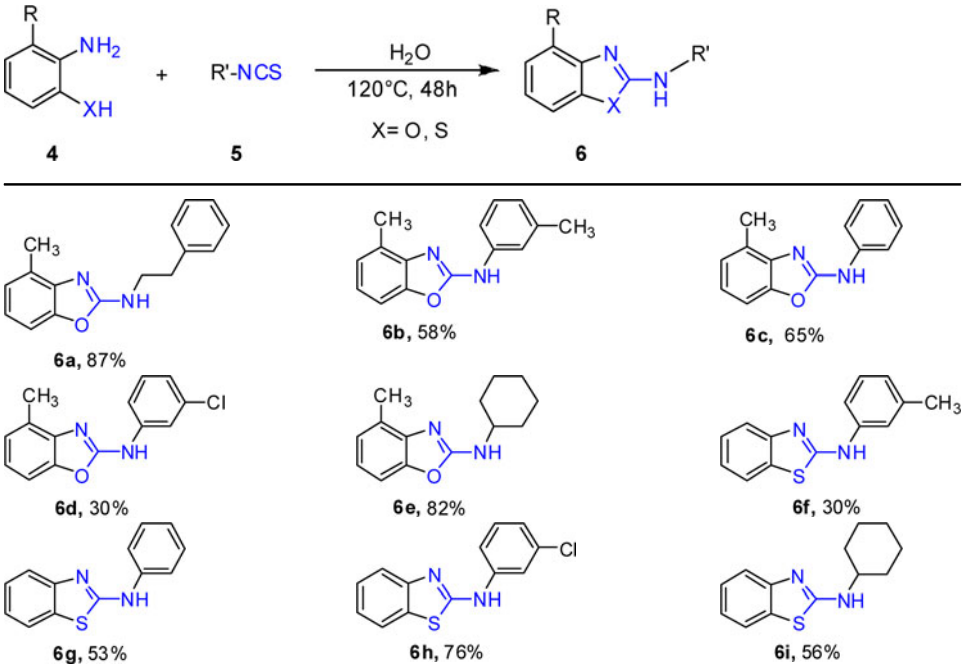
Table 2. Synthesis of benzothiazole and benzoxazole analogues of erucin[a,b]



[a]Reaction conditions: *o*-substituted anilines (1 mmol), erucin (1 mmol), H_2O (5 mL) at 120 °C for 48 h.
[b]Isolated yields.

and 60% yields, respectively (Table 2, entries 3a and 3b). The reactions of substituted aminophenols with erucin were accomplished with moderate to good yields (Table 2, entries 3c–3 g), tolerating -Cl, -Me, and -NO_2 groups. To broaden the scope of the

Table 3. Synthesis of benzazole analogues of different isothiocyanates[a,b]

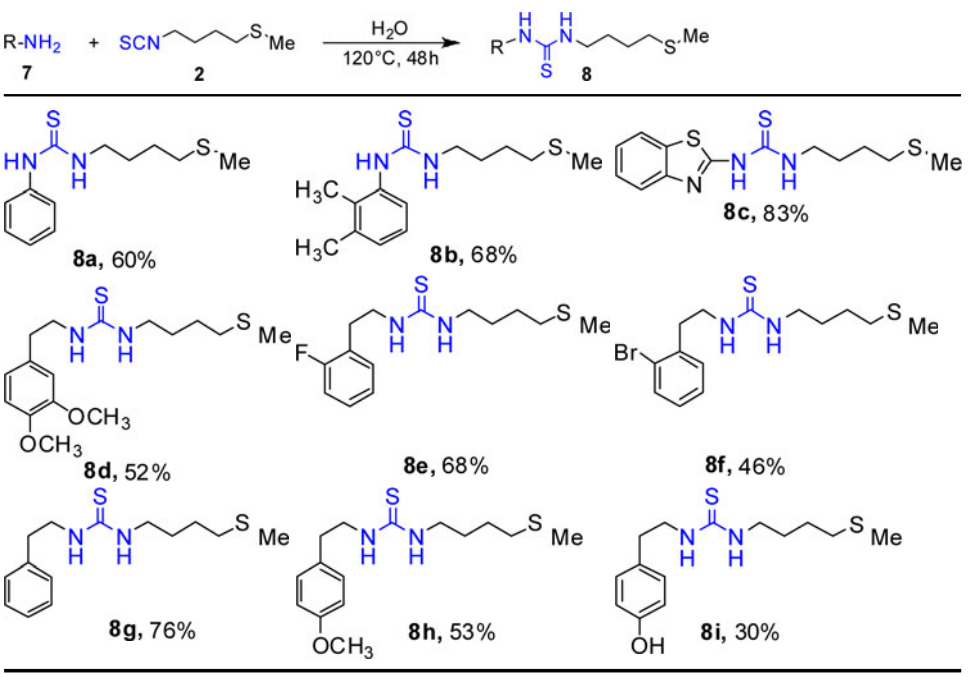


[a]Reaction conditions: *o*-substitutedanilines (1 mmol), isothiocyanates (1 mmol), H_2O (5 mL) at 120 °C for 48 h.
[b]Isolated yields.

method, apart from erucin, reaction with different isothiocyanate was carried out and various benzoxazoles and benzothiazoles were prepared (Table 3). The reaction of 2-amino 3-methyl phenol and 2-aminothiol with m-tollyl isothiocyanate afforded the corrosponding benzazoles in 58 and 30% yields respectively (Table 3, entries 6b and 6f). The reaction of 2-amino 3-methyl phenol and 2-aminothiol with 3-chlorophenyl isothiocyanate afforded corrosponding benzazoles in 30% and 76% yields (Table 3, entries 6d and 6 h). The reaction of 2-amino 3-methyl phenol and 2-aminothiol with phenylisothiocyanate provided moderate yields of 65% and 53% (Table 3, entries 6c and 6 g) while aliphatic substituents afforded the product in moderate to good yields of 82%, 87%, and 56% (Table 3, entries 6a, 6e, and 6i). The reaction of erucin was carried out with different primary amines to prepare the thiourea analogues. Aniline and 2,3-dimethylaniline afforded the desired product in fair yields (Table 4, entries 8a and 8b). The reaction of 2-aminobenzothiazole with erucin afforded the thiourea backbone bearing analogues in good yields (Table 4, entry 8c).

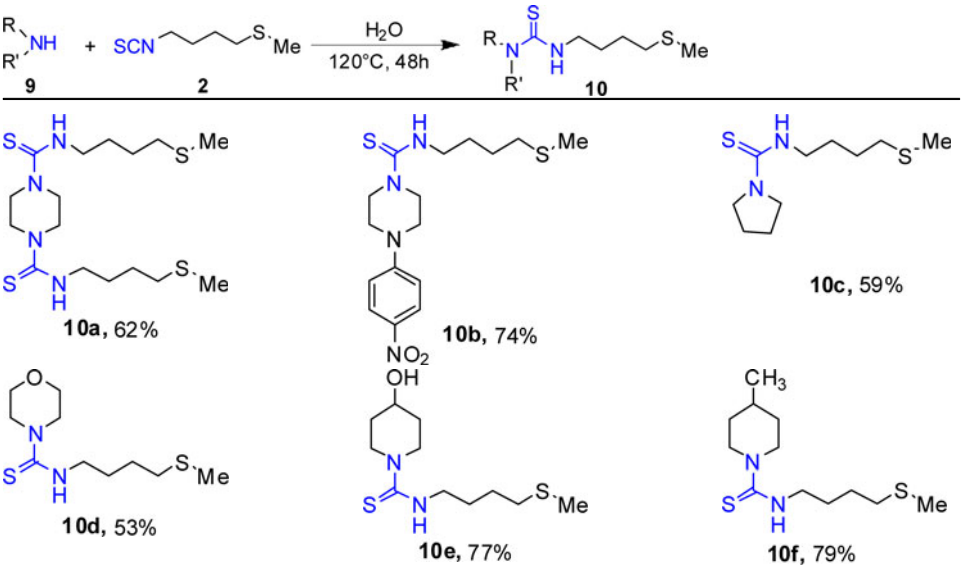
In addition to anilines, the reaction of erucin was also carried out with aliphatic amines. The reaction of various derivatives of phenylethyl amines and benzyl amine afforded the corresponding thiourea analogues tolerating -F, -Br, -OH, and -OMe groups in the aromatic ring (Table 4, entries 8d–8i). The present protocol for the synthesis of thiourea analogues was also applicable to the secondary amines. The reaction of piperazine, 1-(4-nitrophenyl)piperazine, pyrrolidine, morpholine,

Table 4. Synthesis of thiourea analogues of erucin by reaction with primary amines[a,b]



[a]Reaction conditions: amines (1 mmol), erucin (1 mmol), H_2O (5 mL) at 120 °C for 48 h.
[b]Isolated yields.

Table 5. Synthesis of thiourea analogues of erucin by reaction with secondary amines[a,b]



[a]Reaction conditions: amines (1 mmol), erucin (1 mmol), H_2O (5 mL) at 120 °C for 48 h.
[b]Isolated yields.

4-hydroxypiperidine, and 4-methylpiperidine with erucin gave the corresponding thiourea analogues in moderate to good yields (Table 5, entries 10a–10f). In the case of piperazine, double functionalized product was obtained (Table 5, entry 10a). The thiourea and urea analogues of piperazine have been reported as highly potent antiglycating agents.[26]

Furthermore, the biological evaluation of erucin as well as its analogues for the anticancer potential is under progress in our laboratory.

The mechanism of water-catalyzed azole synthesis is well established.[27] Water acts as a dual activation catalyst for the synthesis of benzazoles via electrophilic as well as nucleophilic activation steps from aldehydes and *o*-substituted anilines. On the basis of earlier reports,[17,26] it has been postulated that the nucleophilic attack of amine group on the isothiocyanate moiety of erucin results in the formation of

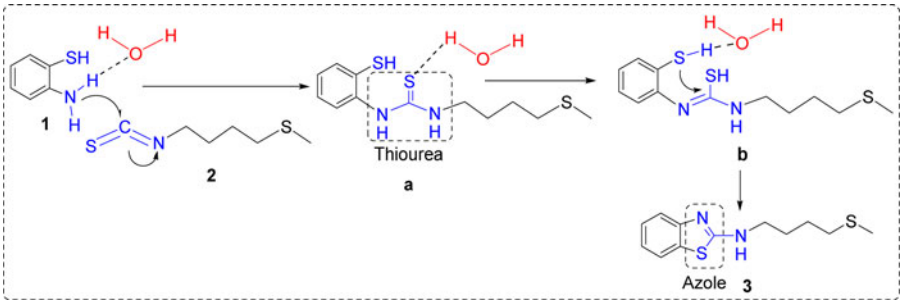


Figure 2. Plausible reaction pathway.

thiourea derivative (a). The ambifilic activation of thiol and thiocarbonyl groups of thiourea derivative (a) by water leads to its cyclization via intermediate (b) for the formation of azole scaffolds (Fig. 2).

CONCLUSION

A new, green, metal-free method has been developed for the synthesis of various benzazoles (benzothiazole and benzoxazole) and thiourea analogues of an abundantly available natural molecule, erucin, in water. The present protocol tolerated the various sensitive functional groups and was also applicable to other isothiocyanate compounds instead of erucin. The present work provides diverse azoles and thiourea-backbone-bearing molecules, which constitute effective pharmacophores in modern drug discovery.

EXPERIMENTAL

General Experimental Procedure for the Synthesis of Benzazole Analogues of Isothiocyanates

The stirred suspension of isothiocyanates (1 mmol) and *o*-substituted anilines (1 mmol) in H_2O (5 mL) was refluxed at 120 °C for 48 h. After completion, the reaction mixture was extracted with ethyl acetate, filtered, passed through anhydrous Na_2SO_4, and dried under vacuum. The crude product was purified by column chromatography over silica gel (60–120 mesh) with an appropriate mixture of *n*-hexane and ethyl acetate.

General Experimental Procedure for the Synthesis of Thiourea Analogues of Erucin

The stirred suspension of erucin (1 mmol) and amines (1 mmol) in H_2O (5 mL) was refluxed at 120 °C for 48 h. After completion, the reaction mixture was extracted with ethyl acetate, filtered, passed through anhydrous Na_2SO_4, and dried under vacuum. The crude product was purified by column chromatography over silica gel (60–120 mesh) with an appropriate mixture of *n*-hexane and ethyl acetate.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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