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C-S bond creation via intramolecular cascade: A new and green method for synthesis of benzothiazoles derivatives

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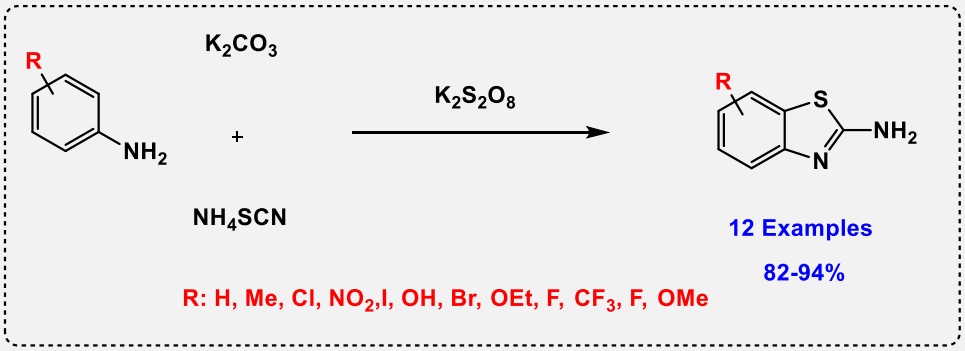
ABSTRACT: A quick and effective approach for synthesizing benzothiazoles using anilines (NH_4SCN, K_2CO_3, and $K_2S_2O_8$) is particularly alluring due to the numerous applications of benzothiazoles as a favored core in the medical and pharmaceutical industries. This work described the practical and efficient method for synthesizing benzothiazole derivatives. This methodology offers an alternate method for synthesizing benzothiazoles while avoiding the usage of dangerous chemical oxidants such bromine, thionyl chloride, iodine, and H_2O_2. In good to outstanding yields, benzothiazoles were produced using the oxidant $K_2S_2O_8$.



KEYWORDS: C-S bond formation, Five-membered heterocycles, Riluzole analogues, Benzothiazole, $K_2S_2O_8$.

■ Introduction

Sulfur and nitrogen, two heteroatoms, make up the primary class of heterocyclic compounds known as benzothiazoles [1–3]. Due to their biological and pharmacological activity, the analogues of benzothiazoles and their derivatives have attracted a lot of study interest, particularly in synthetic, medicinal, and pharmaceutical chemistry [4–6]. They are commonly used in drug development and can be found in bioorganic and medicinal chemistry, such as ethoxzolamide, dithiazanine, idiopathic Parkinson's drug pramipexole [7–9]. Dexpramipexole, lubeluzole, riluzole and other study results published in current scientific literature are a series of examples bioactive molecules containing benzothiazole (**Figure 1**) [4,10–12].

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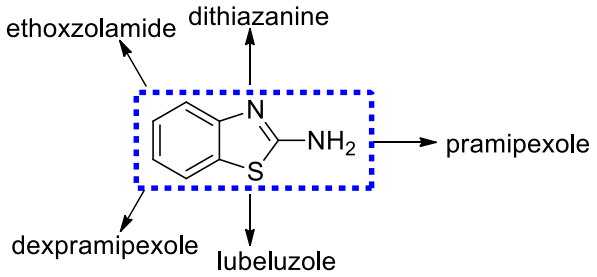
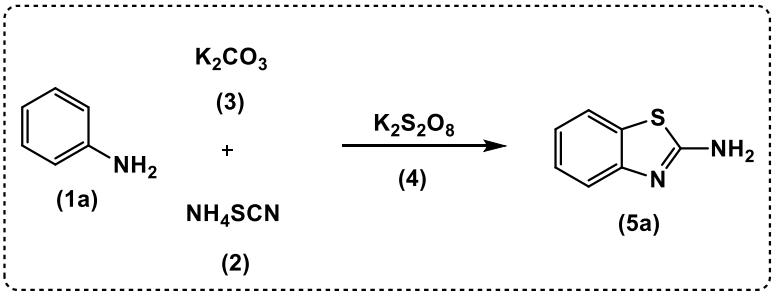


Figure 1. Benzothiazole analogues application in drug discovery.

Along with having a broad range of biological properties, benzothiazole skeleton also has anti-inflammatory, fungicidal, anti-diabetic, analgesic, anti-microbial, antitumor, and anticancer properties [7,13,14]. benzothiazole analogues have been synthesized by various method such as electrosynthesis, hofmann method, jacobsen cyclisation, bromine as catalyst, sulfuric acid as a catalyst, copper- and palladium-catalyzed cyclization, appel's salt, lawesson's reagent, one-pot intramolecular cyclization [15–17]. Moreover, the Br_2 reagent and acetic acid serve as the solvent in the industrial production of benzothiazole. In this paper, we present a novel method for producing benzothiazole in high yields by employing potassium persulfate as an inexpensive and ecologically friendly oxidizing agent in water (**Scheme 1**).



Scheme 1. General approach for synthesis of Benzothiazole analogues.

■ Results and Discussion

As a model reaction in polar solvents such acetonitrile, DMSO, and water at reflux, the reaction of aniline (1), NH_4SCN (**2**), K_2CO_3 (**3**), and $K_2S_2O_8$ (**4**) served as the foundation for our work. The findings demonstrated that, even after a lengthy 6-hour reaction period without a catalyst, no desirable product could be produced at ambient temperature. The isolated yield improved well after 3 hours when the model reaction was carried out at reflux with polar solvents K_2CO_3 (2 eq) and $K_2S_2O_8$ (**Table 1, Entry 2-7**), and the reaction's intended product was separated in 66% (CH_3CN), 81% (DMSO), and 79% CH_3CN isolated yields. (**Table 1, Entry 2-5**).

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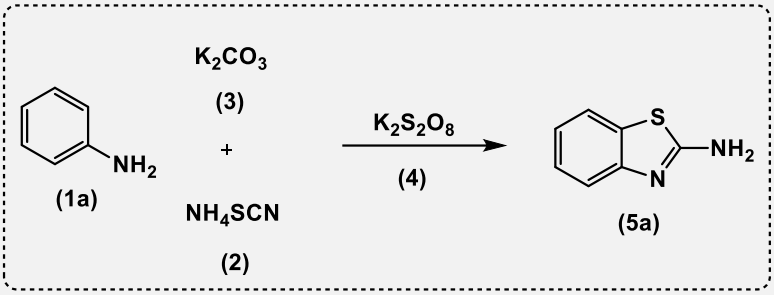
Table 1. Optimization condition reaction [a,b]



Entry	Time (h)	$K_2S_2O_8$ (eq)	Solvent	Temp (°C)	Yield (%) [a]
1	6	-	CH_3CN	r.t	No
2	3	1	CH_3CN	118	38
3	3	2	CH_3CN	118	66
4	3	2	DMSO	100	81
5	3	2	CH_3CN	82	69
6	3	2	H_2O	100	88
7	**1**	**2**	**H_2O**	**100**	**87**
8	0.5	1	H_2O	100	53
9	0.3	1	H_2O	100	44

[a] Isolated yield.
[b] Bold values represent the optimized condition.

So we decided to switch the solvent. In the presence of $K_2S_2O_8$ as an oxidant and K_2CO_3 as a catalyst, a surprisingly high conversion was seen after 1 hour, reflux (yield 87%), when the solvent was changed to water and several solvents were studied for their effects on the reaction. The best solvent for all subsequent processes was determined to be water from an environmental perspective. As a result, $K_2S_2O_8$ and K_2CO_3 were selected as the optimum oxidant and catalyst for the reaction under neat conditions, and the anticipated product **5a** was produced in moderate to good isolated yields in H_2O.

As a result, all derivatives were created using this procedure (83–94%, **Table 2**). Negative effects result from reducing the oxidant quantity, reaction time, or temperature. The isolated yield of the product is negatively impacted by reducing the reaction temperature, reaction time, and oxidant quantity (**Table 1, Entry 1, 2 and 8, 9**).

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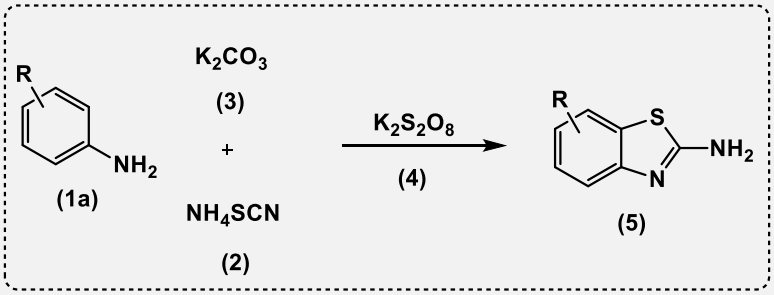
Table 2. Synthesis of benzothiazoles derivatives



Entry	R	m.p ^{Lit} (°C)	m.p (°C)	Yield %
5a	H	168-171 [18]	169-172	86
5b	Me	134-136 [19]	131-134	90
5c	Cl	196-198 [20]	194-197	94
5d	NO_2	199-201 [21]	196-199	83
5e	OMe	164-166 [22]	197-201	92
5f	Br	214-216 [23]	212-215	94
5g	OEt	162-165 [24]	159-163	89
5h	I	206-208 [25]	208-211	88
5i	OH	263-265 [26]	264-267	85
5j	F	183-184 [27]	180-183	91
5k	$PhCH_2O$	135 [22]	132-135	84
5l	CF_3	113-115 [20]	111-114	82

The potential method for the synthesis of riluzole analogues **5(a-l)** is provided in **Scheme 2** and indicates that SO_4^{-}. plays a greater role in the reaction mechanism, in accordance with related research for the oxidation reactions by $K_2S_2O_8$. When aniline **1(a)** and NH_4SCN **2** combine in water by an addition reaction, 1-(4-(trifluoromethoxy)phenyl)thiourea is the result **(a)**. After that, 1-(4 trifluoromethoxy)phenyl)thiourea **(a)** was activated in the presence of K_2CO_3 to produce N-(4-trifluoromethoxyphenyl)carbamimidothioic acid **(b)**. When $K_2S_2O_8$ was applied, the reaction continued with radical routh and the intermediate **(c)** underwent intramolecular electrophilic cyclization to produce the product **5(a).** following proton transfer. In actuality, the compounds were produced by a series of intramolecular cyclization reactions. No additional product reaction was noticed.

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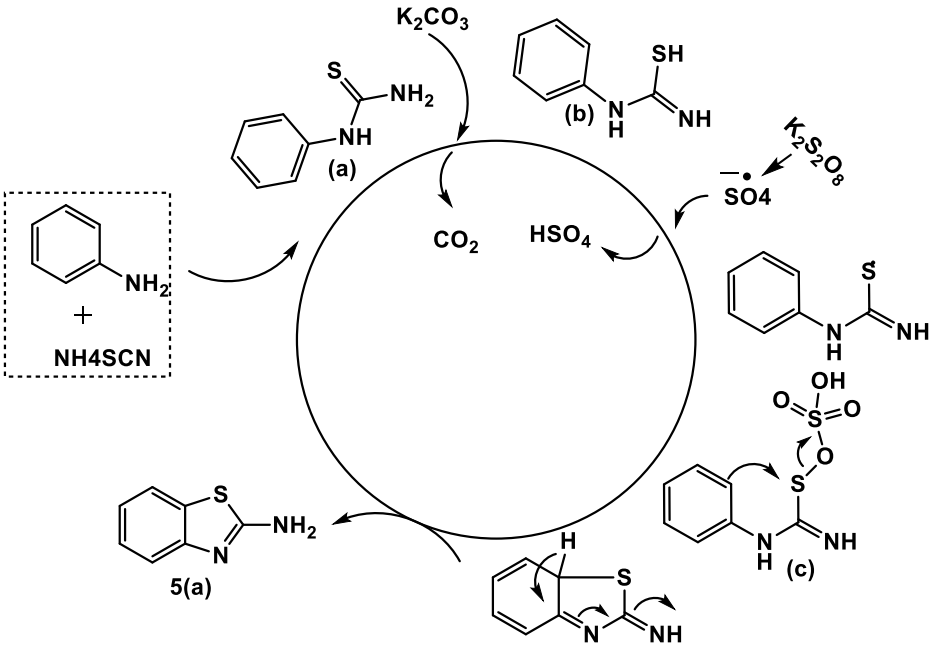
Encouraged by this success, we continued the NH_4SCN **2** and K_2CO_3 (**3)** reaction with a variety of additional anilines **1(b-l)** under comparable circumstances (**Table 2**) (**Scheme 2**). Encouraged by this achievement, we thought that this strategy might be expanded for the reaction of KSCN (**2)** and K_2CO_3 (**3)** with a variety of different anilines **1(b-l)**, in order to create a simpler, more effective, and more dependable technique for the synthesis of benzothiazoles derivatives **5(a-l)**. After screening the solvents, it was noted that employing H_2O as a solvent under ideal reaction circumstances led to high conversion rates (**Table 2, Entry 7**).



Scheme 2. Possible mechanism for the synthesis of benzothiazoles derivatives.

The structure of products **5a** was characterized by IR, ^{1}HNMR, ^{13}CNMR, CHN and Mass spectroscopy. IR spectrum of **5a** exhibits bands due to amine group at 3325 and 3043 cm^{-1} in the structure. The ^{1}HNMR spectrum of **5a** shows two singlet signal for the NH_2 (δ_H 4.63 ppm) and aromatic ring (δ_H 7.32 ppm), a doublet signal for the aromatic ring (δ_H 7.24-7.29 ppm), singlet signal aromatic ring (δ_H 7.59 ppm). ^{13}CNMR spectrum of **5a** showed 7 distinct signals. All compounds **5(a-g)** derivatives were well-known and established by IR, ^{1}HNMR, ^{13}CNMR spectroscopy [18-33].

The findings of a comparison between the current procedure's effectiveness and greener aspect and the literature are displayed in **Table 3**. Using green oxidants and solvents under mild reaction conditions, this approach improves halogenation yields and streamlines the procedure.

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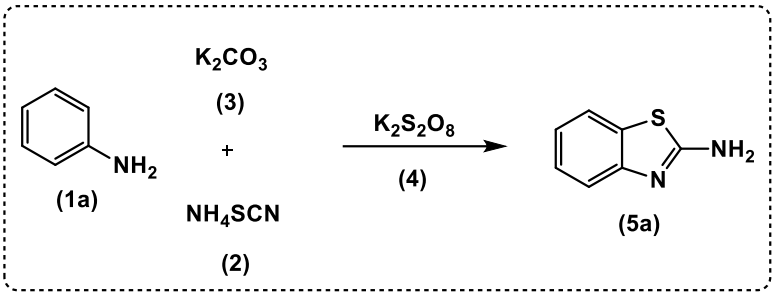
Table 3. comparisons of reported reactions for the synthesis of benzothiazole analogues in the literature



Entry	Reagent	Time (h)	Yield (%)	Solvent	Ref
1	Br_2	12	80	Acetic acid	[18]
2	$NaICl_2$	3	87	DMSO	[28]
3	$SOCl_2$	4	95	-	[29]
4	H_2O_2+I_2	24	94	CH_3CN	[30]
5	tris(2,2'-bipyridyl)ruthenium dichloride	10	90	CH_3CN	[31]
6	Pt, e	6	87	CH_3OH	[32]
7	Fe, e	4	85	DMSO	[33]
8	**$K_2S_2O_8$**	**1**	**89**	**H_2O**	**This work**

■ Summary and Outlook

The creation and synthesis of a number of benzothiazoles derivatives **5(a-g)** is summarised. By the aniline **1** and NH_4SCN **2** reaction, we successfully devised a mild, eco-friendly, and highly effective approach for the synthesis of fused heterocycles including a variety of benzothiazoles derivatives **5(a-g).** Our research describes a fairly straightforward reaction that is carried out under benign conditions with $K_2S_2O_8$ and K_2CO_3 acting as a safe, affordable, and readily accessible catalyst. Without the use of column chromatography, all compounds were simply worked up (filtered) and produced in good to exceptional yields.

■ Experimental

All reagents and solvents are commercially available and were purchased and used without further purification. Melting points were obtained in open capillary tubes on an electro-thermal 9200 apparatus. IR spectra were recorded in KBr pellets on a shimadzu IR 470 spectrophotometer. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were determined on a bruker 400 DRX avance instrument. elemental analyses for C, H and N were performed using a heraus CHN rapid analyzer.

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General Procedure for the preparation of compounds 5(a-g).

A mixture of aniline **1** (1mmol), NH_4SCN **2** (1mmol), K_2CO_3 **3** (1mmol) and $K_2S_2O_8$ **4** (2 mmol) in H_2O (6 mL) was heated at reflux for 1 h and the reaction progress was monitored by TLC (Ethyl acetate: n-Hexane, 2:1), after completion of the reaction, mixture was filtered off, washed with water and recrystallized in EtOH to afford the pure product **5**.

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