Research Article

Regioselective Thiocyanation of Aromatic and Heteroaromatic Compounds by Using Boron Sulfonic Acid as a New, Efficient, and Cheap Catalyst in Water

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Highly efficient regioselective thiocyanations of indoles and *N,N*-disubstituted anilines are achieved via a green and simple protocol using boron sulfonic acid (BSA) as a new catalyst and KSCN/H₂O₂ as a mild and environmentally friendly oxidant in aqueous media.

1. Introduction

The electrophilic thiocyanation of aromatics and heteroaromatics is an important carbon-heteroatom bond formation reaction in organic synthesis [1–3]. Thiocyanate is a versatile synthon which can be readily transferred to other functional groups such as sulfide [4–7], aryl nitrile [8], thiocarbamate [9], and thionitrile [10]. Therefore, it is important to find the new and fast methods for synthesis of thiocyanate group containing aromatic systems [11]. In view of the versatility of thiocyanate group in heterocyclic construction [3], it will be important to probe the thiocyanation of aromatic and heteroaromatic compounds. Several methods have been developed for the thiocyanation of arenes by using various reagents under certain conditions [12–21]. Yet, only a limited number of reagents, such as bromine/potassium thiocyanate (only for indoles) [18], *N*-thiocyanatosuccinimide (only for 5-methoxy-2-methylindole and accompanied by two bithiocyanates) [19], ceric ammonium nitrate (CAN) [20], acidic mont K10 clay [21], iodine/methanol, oxone [22], diethyl azodicarboxylate [23], IL-OPPh₂ [24], potassium peroxydisulfate-copper(II) [25], and HCl/H₂O₂ [26] have been applied to the thiocyanation of aromatic and heteroaromatic systems. However, these methodologies suffer from one or more drawbacks such as the low availability or hard

preparation of starting materials [18, 19], the requirement of large excess of strong oxidizing reagents, low yields for some compounds [20], and performances under certain special conditions [21]. Hence, a requirement for developing alternative synthesis routines accessible to the thiocyanation of aromatic and heteroaromatic compounds is in high demand.

There is an increasing interest in the use of environmentally benign reagents and procedures. Aqueous mediated reactions have received considerable attention in organic synthesis due to the environmentally safety reasons. Water is a desirable solvent for chemical reactions because it is safe, nontoxic, environmentally friendly, readily available, and inexpensive compared to organic solvents [27–29]. Therefore, the development of an efficient and convenient thiocyanation synthetic methodology in aqueous medium is an important research area [30, 31].

Boron sulfonic acid (BSA) as acidic catalyst was introduced by Kiasat and Fallah-Mehrjardi and used for the regioselective conversion of epoxides to thiocyanohydrins under solvent-free reaction conditions (Scheme 1) [32].

2. Experimental

2.1. General. Chemicals were purchased from Merck chemical company. IR spectra of the compounds were obtained on

SCHEME 1: Boron sulfonic acid synthesis under nitrogen atmosphere at room temperature.

SCHEME 2: The solvent effect on product yields was investigated using **1a** as a substrate. Both the yields and reaction times listed in Table 1 suggest that water appears to be very favorable for thiocyanations in presence of BSA (as a strong and new catalyst).

a Shimadzu IR-435 spectrometer using a KBr disk. The ^1H NMR spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz in dimethyl sulfoxide ($\text{DMSO}-d_6$) as solvent and tetramethylsilane (TMS) as an internal standard. The progress of reaction was followed with TLC using silica gel SILG/UV 254 and 365 plates. All products are known compounds and were characterized by comparing the IR, ^1H , and ^{13}C NMR spectroscopic data, and their melting points with the literature values. All yields refer to isolated products.

2.1.1. Typical Procedure for 3-Thiocyanato Indole Synthesis. A suspension of indole **1a** (0.117 g, 1 mmol), potassium thiocyanate (0.294 g, 3 mmol), and BSA/ SiO_2 (0.05 g, 5%) in H_2O (7–10 mL) was stirred at room temperature for 5–10 min. After that period H_2O_2 (30%, 0.45 mL) was dropwisely added (2–5 min). The progress of the reaction was monitored by TLC (ethyl acetate: *n*-hexane, 1 : 10). After completion of the reaction, the reaction mixture was extracted with CHCl_3 (3 $\times$ 20 mL), dried with Na_2SO_4 (5 g) for 20 min, filtered, and chloroform removed. Yield 0.167 g (96%); dark brown solid; mp 71–73°C (**1b**) [2, 22, 33]. FT-IR (KBr): ν (cm^{-1}) 2159, 3289; ^1H NMR (FT-300 MHz, CDCl_3): δ (ppm) 8.87 (1H, br s, NH), 7.83 (1H, d, J = 8.8 Hz), 7.46–7.23 (4H, m); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 136.06, 131.22, 127.66, 123.83, 121.87, 118.65, 112.24, and 91.76.

2.1.2. Preparation of Boron Sulfonic Acid (BSA) [26, 32]. A 50 mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged in the flask and chlorosulfonic acid (8.74 g, ca. 5 mL, 75 mmol in 5 mL CH_2Cl_2) was added dropwise over a period of 1 h at room temperature under N_2 gas. HCl evolved immediately. After completion of the addition, the mixture was shaken for

85 min, while the residual HCl was eliminated by suction. The mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid (^1H NMR spectrum of BSA in acetone- d_6 showed absorption at 12.22 ppm) and then 14.4 g SiO_2 was added and mixed. Finally, dried and a grayish solid material was obtained in 95.6% yield (21.6 g).

3. Results and Discussion

The thiocyanation was investigated at various conditions. In the absence of BSA, reaction was not accomplished, but in the presence of 5% BSA (0.05 g BSA equal 0.15 mmol H^+) the reaction took place with best result. We have found that BSA is active as a catalyst towards the thiocyanation of aromatic and heteroaromatic compounds using H_2O_2 as an oxidant (Scheme 2). To identify optimal conditions for the synthesis of aryl thiocyanates, we began with an investigation of the conversion of indole into the corresponding indole thiocyanate using BSA/ H_2O_2 /KSCN in water as a model reaction (Scheme 2).

The stoichiometry of the reactants was also varied. A ratio of 1 : 4 : 3 (indole : H_2O_2 : KSCN) was found to be the most suitable, and decreasing the amount of H_2O_2 or potassium thiocyanate increased the reaction time and lowered the yield.

The scope of this reaction was further examined using various arenes under optimized conditions (Table 2).

As shown in Table 2, indole and electron-rich indoles gave the desired products in excellent yields (Table 2, entries 1–3). Also, electron-deficient indoles such as 5-bromoindole reacted with potassium thiocyanate and BSA/ H_2O_2 to afford the corresponding 5-bromo-3-thiocyanatoindole in good yield, but required longer reaction time (Table 2, entry 4). This observation can be attributed to the lower electron density of such substrates. The lower yield is probably attributed to the steric hindrance of 2-substituted indole (Table 2, entry 3). The addition was highly regioselective

SCHEME 3: The proposed mechanism for the thiocyanation of indoles and *N,N*-dialkylanilines.TABLE 1: Solvent effects on the thiocyanation of **1a**.

Solvent	Time (h, min) ^a	Yield (%) ^b
Water	00:05	98
Acetonitrile	01:20	80
Tetrahydrofuran	02:00	73
Dichloromethane	08:00	70
Carbon tetrachloride	12:00	47
Ethanol	00:30	89

^a The reaction time.^b Isolated yield of the products after column chromatography.

occurring at the 3-position of the indole ring [25]. Various *N,N*-disubstituted aromatic amines were converted into the respective 4-thiocyanato amines in high to excellent overall yields (Table 2, entries 5–10). The reactions were clean and the products were obtained with high-*para*-selectivity (Table 2, entries 9, 10). However, in the case of *para*-substituted amine, *ortho*-thiocyanation did not occur (Table 2, entry 14).

When indoline was used as a substrate, the reaction was not complete (Table 2, entry 11). The same result was shown for 1,2,3,4-tetrahydroquinoline (Table 2, entry 12) and 1-phenylpiperazine (Table 2, entry 13). On the other hand, *N,N*-4-trimethylaniline, *o*-methylaniline, anisole, pyrrole, acetanilide, imidazole, pyrazine, and pyrrole-3-carbaldehyde

(Table 2, entries 14–21) did not react with potassium thiocyanate and BSA/H₂O₂ to afford the corresponding derivatives.

In comparison with other reported methods using other reagents which require refluxing conditions, the assistance of ultrasonic irradiation, toxic solvent, or oxidant, this method works under milder and greener reaction conditions.

The proposed reaction mechanism is shown in Scheme 3. In the first step, H₂O₂ reacts with BSA(H⁺) to presumably in situ form hydrogen peroxonium ion (H₃O₂⁺) [34]. We have shown that the counter ion of an acid did not have any role in the course of the reaction and H₂SO₄ acts the same as HCl. Subsequently, reaction of hydrogen peroxonium ion with SCN[−] generates HOSCN, which is in the presence of H⁺ able to produce thiocyanium ion ⁺SCN³⁵ and H₂O. In the last step of the reaction electrophilic substitution of thiocyanium ion ⁺SCN with indole will generate the corresponding indole thiocyanate.

4. Conclusions

We have developed an efficient, simple, and green thiocyanation of aromatic and heteroaromatic compounds using BSA/H₂O₂/KSCN in water as solvent, which takes place with high regioselectivity. This procedure offers advantages such as simple workup, short reaction time, low cost of reagents, mild reaction conditions, and clean formation of the desired products in high yields.

TABLE 2: Substrate scope in the thiocyanation reaction of arenes using KSCN/BSA/H₂O₂ [26].

Entry	Substrate (a)	Product (b)	Time (min)	Yield %
1			5	98
2			15	89
3			13	82
4			25	94
5			10	98
6			40	80
7			30	78
8			10	97

TABLE 2: Continued.

Entry	Substrate (a)	Product (b)	Time (min)	Yield %
9			14	95
10			10	92
11			80	55 ^a
12			70	60 ^a
13			60	45 ^a
14
15
16
17
18
19
20
21

^a This reactions were not complete (determined by TLC).

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