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Rapid and Green Synthesis of some Benzothiazole-, Benzimidazole- and Benzoxazole-2-thiol Derivatives Using Copper Sulfate in Aqueous Media

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In this study an easy, green, efficient and simple approach is reported for the synthesis of some benzothiazole-, benzimidazole- and benzoxazole-2-thiol derivatives. The proposed approach employs the reaction of corresponding aromatic amine with potassium isopropyl xanthate (Z11) in the presence of copper sulfate ($CuSO_4$) as a catalyst under conventional heating and ultrasonic irradiation. The advantages of this protocol are: using water and glycerol as green solvents, commercially available precursors, simple work-up, an inexpensive catalyst, high yield and short reaction time.

Keywords: Water, Green synthesis, Benzothiazole, Benzimidazole, Benzoxazole, Copper sulfate, Ultrasonic irradiation

INTRODUCTION

Heterocyclic compounds containing oxygen, nitrogen and sulfur atom, show interesting properties which are used in a variety of fields. Benzoxazoles, benzimidazoles, benzothiazole and their derivatives are an important class of this category. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. This compounds show numerous biological activities such as antimicrobial [1], antiviral [2], antifungal [3], antiparasitic, antihistamine [4] anticancer [5], antiulcer [6], antidiabetic and analgesics [7] activities. They have also found application in industry as anti-oxidants, vulkanisation accelerators [8], pesticides, dyes, fluorescent brightening agents, textile auxiliaries and plastics [9].

So far, many synthetic methods have been proposed for the preparation of these compounds by using different types of catalysts and various structural alterations. Reaction of 2-aminothiophenols, 2-aminophenols and 1,2-phenylene-diamines with substituted aldehydes affords the synthesis of 2-substituted corresponding azoles using different catalysts and reaction conditions such as montmorillonite, SiO_2/graphite, microwave/*p*-TsOH, diethyl bromophosphonate/tert-butyl hypochlorite, cerium(IV) ammonium nitrate, H_2O_2/HCl system in ethanol, AcOH/air, microwave/thermal heating [10] and Baker's yeast [11]. Treatment of 2-aminothiophenols, 2-aminophenols and 1,2-phenylene-diamines and substituted aromatic acids in the presence of polyphosphoric acid and formic acid in the presence of acetic anhydride [12] provides a good method to synthesize corresponding azoles in moderate yields. Cyclization of 2-halo (thio) formanilides in the presence of CuI; 1,10-phenanthroline/Cs_2CO_3/manganese tri-acetate, Cs_2CO_3/dioxane, photochemical cyclization induced by chloranil, $Pd(PPh_3)_4/MnO_2$ system under an oxygen atmosphere can give 2-aminobenzothiazoles *via* intramolecular C-S bond formation. Coupling between phenols, thiophenols and aniline and aromatic nitriles in different conditions and various catalysts are other techniques for the synthesis of some azoles [10,13]. Recently several methods have been reported which utilize aniline, substituted aniline and arylthiourea in acid or chloroform with alkali thiocyanate in the presence of oxidizing agent [14]. Previously Deligeorgiev and co-worker reported preparation of different heterocyclic 2-thiones by coupling of 2-aminophenols, 2-aminothio-

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phenols, 1,2-phenylenediamines or 2-amino-3-hydroxy-pyridines with potassium o-ethyldithiocarbonate under MW irradiation at 140-165 °C [15].

All these known synthetic procedures for obtaining thiobenzoxazoles, thiobenzothiazoles and thiobenz-imidazoles from the corresponding 2-aminophenols, 2-aminothiophenols and 1,2-phenylenediamines have some disadvantages such as direct use of toxic carbon disulfide, long reaction times, low yield, high reaction temperatures, heating under an inert atmosphere and laborious procedures for isolation of the products.

According to the twelve principles of green chemistry a green solvent should meet numerous criteria such as low toxicity, non-flammability, non-mutagenicity, non-volatility and widespread availability among others. Moreover, these green solvents have to be cheap and easy to handle and recycle [16].

In this work we have established new methodologies for the green synthesis of some benzothiazole-, benzimidazole- and benzoxazole-2-thiol by the reaction of 2-aminothiophenols, 2-aminophenols and 1,2-phenylene-diamines, respectively with potassium isopropyl xanthate (Z11) in water and glycerol as solvent by heating or under ultrasonic irradiation.

EXPERIMENTAL

Materials

All starting materials and solvents were prepared from Merck and used without further purification.

Equipments

A UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture, was used for sonication. ^{1}H NMR spectra were recorded on a Bruker-Arance AQS 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Infrared spectra were taken with a Shimadzu PU 9716 spectrophotometer, Model 435. All melting points were obtained by Stuart Scientific apparatus.

General Procedure for Preparation of Compounds

Condition (i). To a solution of potassium isopropyl xanthate (1.5 mmol) in water (5 ml) was added $CuSO_4$ (10 mol%) followed by 2-aminophenols or 2-aminothiophenol or 1,2-phenylenediamines (1 mmol). The mixture was stirred at 90 °C for an appropriate time according to Table 4. The progress of the reaction was monitored by TLC (eluent: n-hexane/EtOAc, 3:1). After completion of the reaction, the mixture was cooled to the room temperature and acidified with HCl solution and was cooled in ice-water. The precipitate was filtered, washed with a little cold water, and recrystallized from 95% ethanol to afford the pure corresponding compound.

Condition (ii). To a solution of potassium isopropyl xanthate (1.5 mmol) in water (5 ml) was added $CuSO_4$ (10 mol%) followed by 2-aminophenols or 2-aminothiophenol or 1,2-phenylenediamines (1 mmol). The reaction mixture was irradiated at room temperature with ultrasound for an appropriate time according to Table 4. The progress of the reaction was monitored by TLC (eluent: n-hexane/EtOAc, 3:1). After completion of the reaction, the mixture was cooled to the room temperature and acidified with HCl solution and was cooled in ice-water. The precipitate was filtered, washed with a little cold water, and recrystallized from 95% ethanol to afford the pure corresponding compound. TLC monitored all reactions and all yields refer to isolated ones. All products have been described previously and fully characterized by NMR, IR and melting point by comparison with the reported literature data.

Selected experimental data for benzoxazole-2-thiol (Table 4, entry 1) Yield = 94%, M.P.: 190-192 °C; IR (KBr) = 3320 (NH), 1619 (C=C), 12790, 1131 (C=S) cm^{-1}, ^{1}H NMR (DMSO-d_6): δ (ppm) = 8.55 (d, 1H, ArH), 7.8 (t, 1H, ArH), 7.3 (d, 1H, ArH), 7.2 (t, 1H, ArH), 5.1 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ (ppm) = 174.6, 156.9, 148.5, 145.3, 137, 2 122.4, 121.2, 113.7.

RESULT AND DISCUSSION

The reaction conditions were optimized using reaction of 2-aminophenol with potassium isopropyl xanthate as an example. In the first instance, the impact of catalyst loading on the yield of the product was evaluated. It was observed that 10 mol% of copper sulfate gives the optimum yield (Table 1).

Next, we investigated the effect of solvent on the synthesis of benzoxazole-2-thiol. Among three solvents

Table 1. Screening of $CuSO_4$ for Benzoxazole-2-thiol Synthesis[a]

Entry	$CuSO_4$ (mol%)	Yield (%)
1	5	65
2	**10**	**85**
3	15	85
4	20	80

[a]Reaction conditions: 2-aminophenol (1.0 mmol), potassium isopropyl xanthate (1.5 mmol), H_2O (5.0 ml), 90 °C, 4 h.

Table 2. Effect of Solvent and Temperature on the Synthesis of Benzoxazole-2-thiol[a]

Entry	Solvent	Time (min)	Yield (%)
1	THF	250	Trace
2	Glycerol	220	80
3	Glycerol[b]	600	50
4	**H_2O**	**240**	**85**
5	H_2O[b]	600	42

[a]Reaction conditions: 2-aminophenol (1.0 mmol), potassium isopropyl xanthate (1.5 mmol), $CuSO_4$ (10 mol%), Solvent (5.0 ml), 90 °C, 4 h. [b]at r.t.

Table 3. Effect of Catalysts on the Synthesis of Benzoxazole-2-thiol[a]

Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	$NiSO_4$	50	8	50
2	$NiSO_4$	90	8	67
3	$NiSO_4$	110	8	67
4	CuI	90	7	55
5	CuBr	90	7	53
6	$MgSO_4$	90	5	81
7	$CuSO_4$	50	7	65
8	**$CuSO_4$**	**90**	**4**	**85**
9	TiHMS.Pd	90	6	70
10	$PbSO_4$	90	6	70

[a]Reaction conditions: 2-aminophenol (1.0 mmol), potassium isopropyl xanthate (1.5 mmol), catalyst (10 mol%), H_2O (5.0 ml).

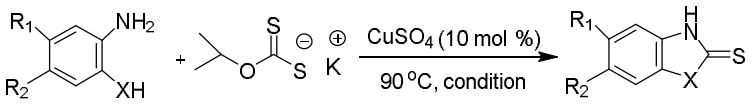
tested, water yielded the best results, glycerol gave a good yield of the products and solvent such as THF was ineffective (Table 2). The reaction conducted at room temperature gave moderate yields but proceeded smoothly at 90 °C similar to the results obtained at 100 °C as shown in Table 2. The role of water as the reaction medium and its mechanism is still unclear. Recently, it has been reported [17] that some organic molecules can react on the surface of water. High reaction rates has been the subject of most of these studies, particularly when at least one component involved in this reaction bore a polar group, enabling some degree of solubility. The significant enhancement in reaction rate has been attributed to hydrophobic packing, solvent polarity, hydration and hydrogen bonding [18-19].

The reaction was then screened with several metal catalysts for the synthesis of benzoxazole-2-thiol; the results are summarized in Table 3. The combination of $CuSO_4$ in water at 90 °C provided the best results (Table 3, entry 8). However, the reaction with $CuSO_4$ at room temperature and 50 °C required longer reaction time and gave the product in moderate yield (65%, Table 3, entry 7). While reactions with other metal salts, such as $NiSO_4$, $MgSO_4$, $PbSO_4$, CuI and CuBr required longer reaction time to produce significant amounts of benzoxazole-2-thiol.

The yields were highly dependent upon the reaction temperature, solvent and the catalyst. The optimum reaction conditions for the synthesis of benzoxazole-2-thiol were found to be: $CuSO_4$ (10 mol%), at 90 °C with glycerol or water (5.0 ml) as the solvent.

In order to explore the scope of this novel transformation, we examined the cyclization reaction of a variety of substituted 2-aminophenols, 2-aminothiophenol and 1,2-phenylenediamines with potassium isopropyl xanthate in water or glycerol under directed ultrasound

Table 4. Synthesis of some Benzothiazole-, Benzimidazole- and Benzoxazole-2-thiol



Entry	X	R_1	R_2	Solvent	Heating conditions		Ultrasonic irradiation		M.p. (°C)
					Time (min)	Yield (%)	Time (min)	Yield (%)	
1	O	H	H	Glycerol	240	85	40	94	190-192 [20]
2	O	Cl	H	Glycerol	210	78	70	89	220-222 [21]
3	O	Me	H	Glycerol	200	94	20	95	207-208 [22]
4	O	H	Me	Glycerol	180	94	35	95	207-208 [22]
5	S	H	H	Glycerol	150	85	70	91	171-170 [20]
6	NH	Me	H	Glycerol	150	78	45	86	288-290 [23]
7	O	H	H	Water	240	85	75	89	190-192 [20]
8	O	Cl	H	Water	405	76	90	85	220-223 [21]
9	O	Me	H	Water	305	90	50	90	207-208 [22]
10	O	H	Me	Water	285	90	80	91	207-208 [22]
11	S	H	H	Water	360	81	90	89	170-173 [20]
12	NH	Me	H	Water	420	80	90	89	289-291 [23]

irradiation or heating at 90 °C (Table 4). In general, all reactions were very clean, and the products were obtained in high yields under the optimized conditions.

The effect of ultrasound on different reactions has been widely studied during the last two decades [24-26]. The application of ultrasound to chemical reactions can cause an increase in the yields of reactions and in some cases the ratio of products formed. When ultrasound passes through a liquid medium, the most important effect is the generation of many cavities. This leads to high temperatures and high pressure within the cavities during their collapse. Ultrasonic irradiation can also be used to influence selectivity and yields of reactions. Therefore, we decided to investigate the effect of ultrasonic irradiation on the synthesis of benzoxazole-2-thiol catalyzed by $CuSO_4$. In this manner 2-aminophenols was mixed with potassium isopropyl xanthate in the presence of $CuSO_4$ and was exposed to ultrasonic irradiation and benzoxazole-2-thiol was obtained in high yield (94%) in 40 min. Reaction of a variety of substituted 2-aminophenols, 2-aminothiophenol and 1,2-phenylenediamines with potassium isopropyl xanthate in water or glycerol, in the presence of $CuSO_4$ and under ultrasonic irradiation, afforded corresponding benzothiazole-, benzimidazole- and benzoxazole-2-thiol, respectively in 86-94% yield (Table 4).

CONCLUSIONS

In conclusion, we have explored a green rout, simple practical, and efficient catalytic procedure for the synthesis of some substituted benzothiazole-, benzimidazole- and benzoxazole-2-thiol in water or glycerol as a green solvent. The method offers several noteworthy advantages including good yields of products, easy work-up, in combination with stability, non-toxicity, easy preparation and cheapness of the catalyst. On the other hand, ultrasonic irradiation increased the catalytic activity and caused higher product yields in a short reaction time.

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