Indium-Mediated Facile Preparation of 2-(Heterocyclic thio)-1-(2,3,4-trimethoxyphenyl)ethanone in Aqueous Media

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An environmentally benign and efficient process for the preparation of 1-(2,3,4-trimethoxyphenyl)-2-substituted heterocyclic thio ethanone derivatives was achieved by the reactions of mercapto compounds with 2-bromo-1-(2,3,4-trimethoxyphenyl)ethanone in water mediated by indium in very high yields. Antifungal activities of the compounds were examined and moderate activity was obtained.

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Introduction.

Among the antifungal agents, albondazole, *i.e.* carrying both azole and thioether residues, became of interest for its effectiveness against pathogenic fungi and viruses. Since then, a number of thioether compounds were synthesized and found to be fungicidal, virucidal, and herbicidal [1-15]. In those works, especially among diaryl thioethers, it is noteworthy that the activity increased when one of the aryl residues was a heteroaryl group. Encouraged by the successful results obtained from these works, we prepared a series of 6-chloro-3-pyridylmethyl heterocyclic thioether derivatives, in which one of the aryl residues was replaced with pyridinyl in a bioisosteric approach, and significant virucidal activity against Tobacco Mosaic Virus (TMV) were obtained [16]. In this study, with pyrogallic acid as the lead compound, a series of new1-(2,3,4-trimethoxyphenyl)ethanone heterocyclic thioether derivatives were designed and synthesized and their antifungal activities were tested.

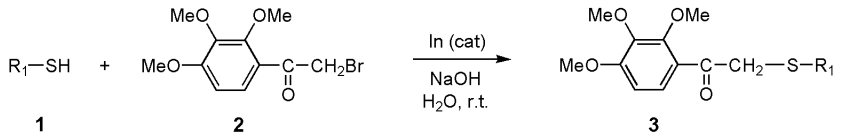
Thioether synthesis had been classically conducted in the presence of strong base and reflux conditions. However, under strongly basic hot conditions, the amount of byproduct, formed through C–Cl hydrolyzation, increased. In this paper, indium was used to promote thioether synthesis in aqueous media at room temperature and high yields were observed which was inferred due to the catalytic effect of indium. An indium mediated aqueous organic reaction had been attractive due to its excellent catalytic activity in water [17-21].

Results and Discussion.

In our experiments we found that the reactions of 2-mercaptobenzothiazole (**1a**), 2-mercapto benzimidazole (**1b**), 2-mercaptopyrimidine (**1c**), 2-mercapto-4,6-dimethylpyrimidine (**1d**), and 2-mercapto-5- methyl-1,3,4-thiadiazole (**1e**) with 2-bromo-1-(2,3,4-trimethoxyphenyl)-ethanone (**2**) [22] could proceed very well under the same conditions to afford thioether product **3** in very high yields (Scheme 1).

Indium, tin, zinc, and tetrabutylammonium bromide were used as catalysts, and 1% mole equiv was used for the reaction to proceed to completion. Reactions of various mercapto compounds **1a-e** (2mmole) with **2** in 20 mL of water catalyzed by 0.02 mmole indium, tin, zinc or tetrabutylammonium bromide are listed in Table 1. It can be seen from Table 1 that the yields were very high under the given reaction conditions for entries 1-5. 2-Mercaptobenzimidazole (**1b**) reacted with 2-bromo-1-(2,3,4-trimethoxyphenyl)ethanone (**2**) in the presence of indium in water at ambient temperature for 1, 2 and 3h produced **3b** in 62%, 79% and 86% yields respectively. The high yield may be due to indium weakening the C-Br bond thus making it easier for the bromine atom to leave. When the thioether synthesis was mediated by indium in water, the reaction went smoothly at room temperature for 4 hr, whereas when zinc, tin, or tetrabutylammonium bromide were tested, relatively low conversion of the starting material **1b** was observed at room temperature (entries 9-11). Very low yield was observed when no indium was used as

Scheme 1



1 **2** **3**

1a: R_1= benzothiazol-2-yl
1b: R_1= benzimidazol-2-yl
1c: R_1= pyrimidin-2-yl
1d: R_1=4,6-dimethylpyrimidin-2-yl
1e: R_1=5-methyl-1,3,4-thiadiazol-2-yl

Thioether synthetic reaction of **1a-1e** and acetophenone **2** in water catalyzed by indium.

catalyst at room temperature for 1 hr in entry 12 while with time prolonged to 12 hr the yield is enhanced to 68% (entry 14). When the reactions were heated, by-product was evidently increased because 2-bromo-1-(2,3,4-trimethoxyphenyl)ethanone (**2**) was sensitive to heat and base medium. The by-product was the hydroxyl ketone, 2-hydroxyl-1-(2,3,4-trimethoxyphenyl)ethanone (**4**), which was traced by silica gel TLC and separated by column chromatography and confirmed through elemental analysis, EIMS and ^{1}H NMR. Hence it was inferred that the C-Br bond of reactant **2** was hydrolyzed.

The use of sodium hydroxide as the base in the reaction was superior to sodium carbonate or potassium carbonate for the preparation of thioether **3** because little yield was obtained in the latter case. For example, the reaction of **1a** with **2** in the presence of 2 mmol of sodium carbonate and potassium carbonate afforded 47% and 51 % of **3a**, respectively. Potassium hydroxide can also be used as base in the above reaction and behaves similarly to sodium hydroxide under our reaction conditions.

Fungicidal activities against *Exserobilum turcicum* (*E.t.*), *Botrytis cinerea* (*B.c.*), and *Sclerotinia sclerciorurs* (*S.s.*) were evaluated *in vivo* at a concentration of 500 mg/L by a preventives foliar application in a green house. The test results are shown in Table 2 from which it can be seen that compounds **3a**, **3b**, and **3e** have moderate inhibitory activities against *E.t., B.c.* and *S.s.*

Conclusion.

By using indium as the catalyst, the thioether synthesis was found to proceed smoothly in aqueous media at room temperature. The current method presents a very attractive and appealing synthetic process for thioether acetophenone because of the following advantage: (1) very high yield and (2) the use of water as the reaction medium.

Preliminary bioassay suggested that these compounds have moderate fungicidal activity against *E.t., B.c.* and *S.s.* For example, the extent of inhibition for compounds **3a** and **3b** against *S.s.* (*in vivo*) were 71-72% at a concentration of 500mg/L.

EXPERIMENTAL

The reagents and solvents were all analytical reagents or chemically pure and were obtained from Shanghai Reagent Company. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. Infrared spectra were recorded on a Bruker VECTOR22 spectrometer. The ^{1}H NMR spectra were recorded on a Varian INOVA 400 (400 MHz) Pulse Fourier-transform NMR spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Spliting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were acquired on an HP5988A spectrometer using the EI method. Elemental analyses were performed on a Vario III CHN analyzer. Analytical TLC and column chromatography were performed on silica gel GF254. Column chromatographic purification was carried out using silica gel.

General Procedure for the Preparation of **3**.

A mixture of **1** (2 mmole) and **2** (2 mmole) in 20 mL of water were stirred vigorously at room temperature for 10 minutes. Then 3 mL sodium hydroxide solution (2.6%, w/w) was added. With stirring 2.3 mg indium was added. The reaction was followed and monitored by TLC (petroleum ether:ethyl acetate = 1:3 by volume). After the reaction was completed (4 h), the solid was collected by filtration and washed with sodium carbonate (5%, w/w) and water until neutral. The crude solid was purified by column chromatography using acetone/petroleum ether as eluent to give the target compound **3a**. The product was air dried to give 712 mg (95%) of **3a**. The yields of **3** are listed in Table 1.

2-(Benzothiazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**3a**).

This compound has mp 121–122 °C; IR: 2932, 2838, 1645, 1585, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-8.01 (d, 1H, benzothiazole, *J*=7.6 Hz), 7.77-7.79 (d, 1H, benzothiazole, *J*=7.6 Hz), 7.53-7.55 (d, 1H, phenyl, *J*=8.8 Hz), 7.42-7.46 (t, 1H, benzothiazole, *J*=7.6 Hz), 7.33-7.77 (t, 1H, benzothiazole, *J*=7.6 Hz), 6.94-6.98(d, 1H, phenyl, *J*=8.8 Hz), 4.99 (s, 2H, CH_2), 3.79-4.00 (3s, 9H, $3CH_3O$); EIMS: m/z 375(M^+, 6.2).

Anal. Calcd. for $C_{18}H_{17}NO_4S_2$: C, 57.58; H, 4.56; N, 3.73. Found: C, 57.61; H, 4.75; N 3.92.

2-(Benzimidazol-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**3b**).

This compound has mp 118–119 °C; IR: 2942, 2842, 1656, 1585, 1098 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.80-7.82 (d, 1H, benzimidazole, *J*=7.6 Hz), 7.74-7.76(d, 1H, benzimidazole, *J*=7.6 Hz), 7.63-7.65(d, 1H, phenyl, *J*=8.8 Hz), 7.37-7.41 (t, 1H, benzimidazole, *J*=7.6 Hz), 7.27-7.30 (d, 1H, benzimidazole, *J*=7.6 Hz), 7.26 (s, 1H, NH), 6.74-6.76 (d, 1H, phenyl, *J*=8.8 Hz), 4.90 (s, 2H, CH_2), 3.90-4.11 (3s, 9H, $3CH_3O$); EIMS: m/z 358(M^+, 7.2).

Anal. Calcd. for $C_{18}H_{18}N_2O_4S$ (358.4): C 60.32, H 5.06, N 7.82, found C 60.37, H 5.04, N 7.60.

2-(Pyrimidin-2-ylthio)-1-(2,3,4-trimethoxyphenyl)ethanone (**3c**).

This compound has mp 99–100 °C; IR: 2941, 2838, 1660, 1591, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46-8.48 (d, 2H, pyrimidine, *J*=4.8 Hz), 7.56-7.58 (d, 1H, phenyl, *J*=8.8 Hz), 6.94-6.96 (t, 1H, pyrimidine, *J*=4.8 Hz), 6.72-6.74 (d, 1H, phenyl, *J*=8.8 Hz), 4.64 (s, 2H, CH_2), 3.89-4.07 (3s, 9H, $3CH_3O$); EIMS: m/z 320 (M^+, 6.1).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$ (320.4): C, 56.24; H, 5.03; N 8.74. Found: C, 56.11; H, 4.86; N 8.70.

2-(4,6-Dimethylpyrimidin-2-ylthiol)-1-(2,3,4-trimethoxyphenyl)ethanone (**3d**).

This compound has mp 112–113 °C; IR: 2940, 2842, 1656, 1585, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.55 (d, 1H, phenyl, *J*=8.8 Hz), 6.71-6.73 (d, 1H, phenyl, *J*=8.8 Hz), 6.66 (s, 1H, pyrimidine), 4.60 (s, 2H, CH_2), 3.89-4.06 (3s, 9H, $3CH_3O$); EIMS: m/z 348(M^+, 4.2).

Anal. Calcd. for $C_{17}H_{20}N_2O_4S$ (348.4) C 58.60, H 5.79, N 8.04, found C 58.61, H 5.75, N 8.19.

2-(5-Methyl-1,3,4-thiadiazol-2-ylthiol)-1-(2,3,4-trimethoxyphenyl)ethanone (**3e**).

This compound has mp 101−102 °C; IR: 2940, 2842, 1667, 1585, 1096 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.63-7.66 (d, 1H, phenyl, *J*=8.8 Hz), 6.73-6.75 (d, 1H, phenyl, *J*=8.8 Hz), 4.89 (s, 2H, CH_2), 3.88-4.08 (3s, 9H, $3CH_3O$); EIMS: m/z 340(M^+, 4.2).

Anal. Calcd. for $C_{14}H_{16}N_2O_4S_2$ (340.4): C, 49.39; H, 4.74; N 8.23. Found: C, 49.25; H, 4.85; N, 8.48.

2-Hydroxyl-1-(2,3,4-trimethoxyphenyl)ethanone(**4**).

The reaction condition is the same as the general procedure except the mixture was heated to 50 °C. The crude crystal was isolated by column chromatography using acetone/petroleum ether as eluent to give **3a** (74.3%) and **4**(19.2%) with physical and spectral data of **4** as follows: mp 76-78 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.74 (s, 1H, OH), 3.84-3.97 (3s, 9H, 3'MeO-), 4.67 (s, 2H, $-CH_2$), 6.70-6.72 (d, 1H, Ar-H, J=8 Hz), 7.58-7.60 (d, 1H, Ar-H, J=8 Hz); EIMS: m/z 226(M^+, 17.4).

Anal. Calcd. for $C_{11}H_{14}O_5$ (226.2): C, 58.40; H, 6.24. Found: C, 58.25; H 6.46.

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Table 1

Various Reaction Conditions of **1a-e** with **2** [a]

Entry	Thiol	Catalyst	Reaction time (h)	Product	Yield (%)
1	**1a**	indium	4	**3a**	95
2	**1b**	indium	4	**3b**	92
3	**1c**	indium	4	**3c**	93
4	**1d**	indium	4	**3d**	94
5	**1e**	indium	4	**3e**	89
6	**1b**	indium	1	**3b**	62
7	**1b**	indium	2	**3b**	79
8	**1b**	indium	3	**3b**	86
9	**1b**	zinc	4	**3b**	77
10	**1b**	tetrabutylammonium bromide	4	**3b**	80
11	**1b**	tin	4	**3b**	84
12	**1b**	-	1	**3b**	52
13	**1b**	-	4	**3b**	58
14	**1b**	-	12	**3b**	68

[a] The solvent was H_2O in all the entries and all reactions were conducted at room temperature.

Table 2

Fungicidal Activities of Compounds **3a-e**

Compd.	Inhibition rate (%)				
	3a	**3b**	**3c**	**3d**	**3e**
E.t.	49	59	0	0	61
B.c.	62	61	10	20	49
S.s.	71	72	5	19	54

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