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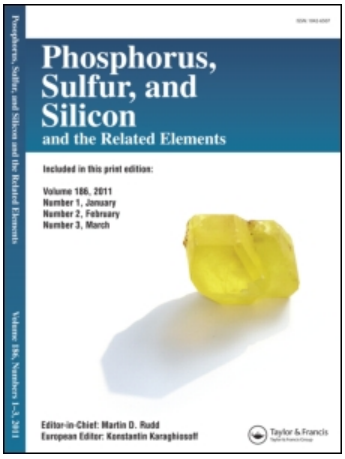

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Basic Alumina-Catalyzed, Solvent-Free Synthesis of Diversified Thioethers

K. Prabakaran[a]; F. Nawaz Khan[ab]
[a] Chemistry Division, School of Science and Humanities, VIT University, Vellore, Tamil Nadu, India [b] Syngene International Limited (Biocon), Banglore, India

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BASIC ALUMINA-CATALYZED, SOLVENT-FREE SYNTHESIS OF DIVERSIFIED THIOETHERS

K. Prabakaran[1,2] and F. Nawaz Khan[1]

[1]*Chemistry Division, School of Science and Humanities, VIT University, Vellore, Tamil Nadu, India*

[2]*Syngene International Limited (Biocon), Banglore, India*

Environmentally and economically benign solvent free syntheses of thioethers are performed by the reaction of benzothiazole thiol with different halides on basic alumina—a simple, cheap, robust catalyst that couples a range of substrates with thiol in excellent yields in a short time. The in vitro antibacterial screening of compounds 3c, e, g, i, j, and k were evaluated against the Gram-positive organism* Staphylococcus aureus *and Gram-negative organisms.* Escherichia coli *and* Proteus mirabilis *by the Agar well diffusion method.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Basic alumina; catalyst; electron-deficient; electron-rich; thioethers

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INTRODUCTION

The formation of carbon–sulfur bonds is considered to be important due to the prevalence of aryl–sulfur bonds in important biological and pharmaceutical materials.[1–3] However, only a few studies have been reported on Pd or Ni catalysis[4–7] or Cu catalysis.[8–11] Recently many methods including 10 mol% CuI, 10 mol% neocuproine, with NaOtBu as the base[12] involving 5 mol% CuI and $HOCH_2CH_2OH$ as ligand,[13] microwave heating [14] using 20 mol% N-methylglycine, 5 mol% CuI, and 2.5 equiv. KOH have been reported.[15] However, the scope is somewhat limited by their use of a strong base and high temperature, and some of these methods suffer from important problems including the use of stoichiometric amounts of the reagents and unpleasant odor substrates, long reaction times, unsatisfactory yields, poor selectivity, and the use of expensive and toxic reagents or catalysts. Fly-ash–supported synthesis of thioether derivatives under microwave irradiation was reported recently.[16] Though satisfying yield of the coupling product is obtained by the above methodologies, no emphasis was given to its high generality or exceptional level of functional group

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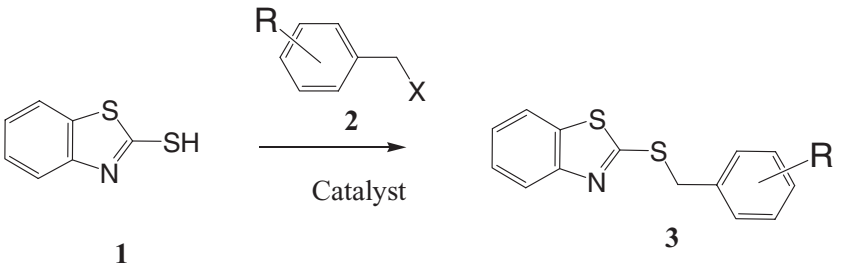
Address correspondence to F. Nawaz Khan, Chemistry Division, School of Science and Humanities, VIT University, Vellore 632 014, Tamil Nadu, India. E-mail: nawaz_f@yahoo.co.in



Scheme 1

toleration. Therefore, it is desirable to find a better alternative method for synthesis of thioethers.

In continuation of our interests on C–C bond formation and organosulfur compounds,[17–23] in this article we describe C–S bond formation in the synthesis of thioethers by simple, economical, and environmentally benign procedures, by avoiding volatile and toxic organic solvents (Scheme 1, Tables I–III) in the presence of Montmorillonite K10 catalyst or other inorganic catalysts such as basic alumina, bentonite, etc. (Table II). The reactions carried out utilizing Montmorillonite K10 clay gave low yield. However, the reaction took less time in the presence of basic alumina. The optimization of catalyst amount was also performed (Table III). The reusability of the catalyst in synthesis has also been explored (Table S1, available online in the Supplemental Materials). The antimicrobial activities of compounds have been evaluated for a range of bacterial species (Table S2, Supplemental Materials). From the data, it is obvious that the reaction proceeds very smoothly in a simple, clean, and easier protocol. Also the formation of disulfide, a common side reaction in thiol chemistry, is very much suppressed.

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RESULTS AND DISCUSSION

As a part of our research, synthesis of thioether (**3a**) from benzothiazole (**1**) and 1-(chloromethyl)-4-chlorobenzene (**2a**) was performed in the presence of Montmorillonite K-10, silica gel, and basic alumina catalysts, the results of which (Table II) indicated the formation of thioether in high yields exclusively in basic alumina catalyst. The essence of the basic alumina catalyst can be understood from following facts: When benzothiazole thiol (**1**) was treated with basic alumina under conventional heating in the presence of 1-(chloromethyl)-4-chlorobenzene (**2a**), the product **3a** was obtained in quantitative yield (entry 5, Table II), and that the same reaction when performed without basic alumina catalyst, the product **3a** was obtained in much lower yield in 2 h (entry 1, Table III). The optimization of the reaction with different amounts of basic alumina was carried out, and the results show at 0.14 g, yield was good (Table III). Diversified thioethers have been synthesized (Scheme 1) and are summarized (Tables I–III).

Reusability of Catalyst

The reusability of the catalyst was explored by checking the successive runs of reactions on recycled catalyst, i.e., catalyst recovered by filtration from the reaction mixture,

Table I Synthesis of thioethers by solvent-free, basic alumina catalysis[a]

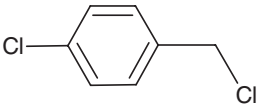
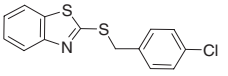
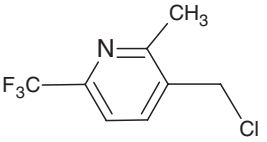
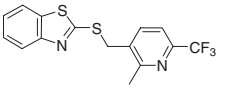
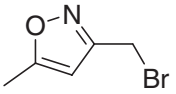
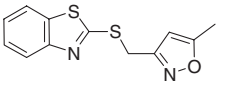
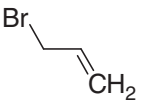
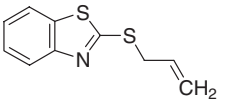
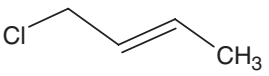
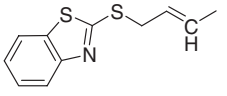
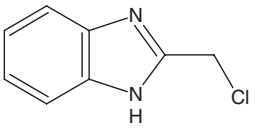
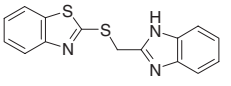
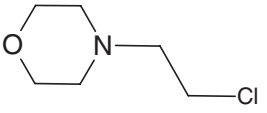
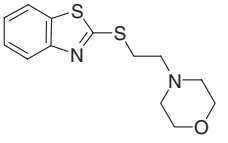
		Heating at 50°C under solvent-free conditions		
Sl. No	Reactant **2**	Time taken (h)	Product, **3a–j**	Yield[c]%
1	 **2a**	0.5	 **3a**	86.2
2	 **2b**	0.5	 **3b**	60.6
3	 **2c**	0.5	 **3c**	97.8
4	 **2d**	0.5	 **3d**	91.5
5[b]	 **2e**	0.5	 **3e**	75.8
6[b]	 **2f**	1	 **3f**	86.8
7[b]	 **2g**	overnight	 **3g**	91.6

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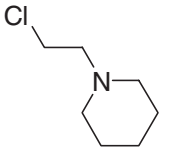
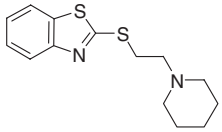
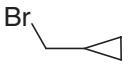
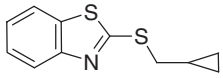
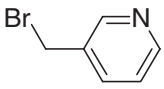
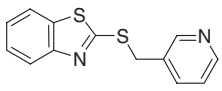
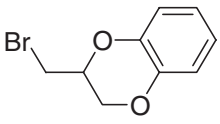
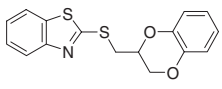
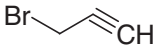
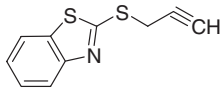
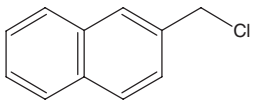
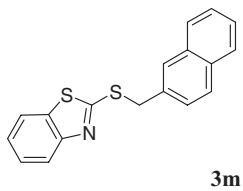
Table I Synthesis of thioethers by solvent-free, basic alumina catalysis[a] *(Continued)*

		Heating at 50 °C under solvent-free conditions		
Sl. No	Reactant **2**	Time taken (h)	Product, **3a–j**	Yield[c]%
8[b]	 **2h**	2	 **3h**	86.6
9[b]	 **2i**	1	 **3i**	88.3
10[b]	 **2j**	overnight	 **3j**	32.4
11	 **2k**	1	 **3k**	76.2
12	 **2l**	0.5	 **3l**	95.2
13	 **2m**	0.5	 **3m**	94.5

[a] **1** = 1 equiv, **2** = 1.2 equiv, catalyst = 0.14 g.
[b] All products were characterized by ^{1}H NMR and IR spectroscopic data.
[c] **3** in isolated yields after column chromatography.

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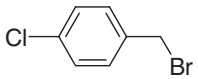
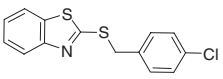
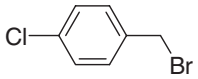
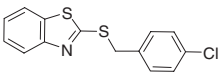
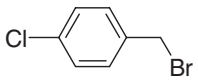
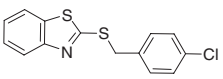
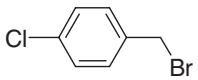
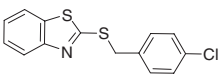
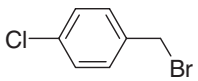
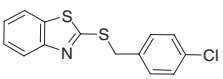
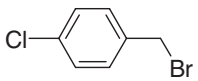
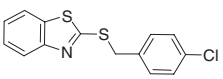
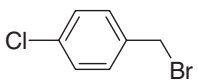
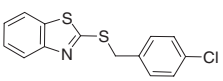
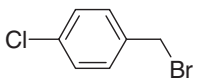
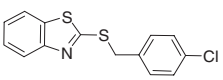
washed with ethyl acetate, and dried. Then it was utilized in a second run of reaction process. It was noticed that subsequent experiments gave almost similar yields, (Table S2) and the catalyst is not leached.

Table II Selection of catalyst[a]

Sl.No.	Catalyst used	Refluxing at 50°C solvent-free conditions		
		Amount of Catalyst used (mg)	Time (h)	Product **3a**
1	Silica Gel, 60–120	100	4	Nil
2	Bentonite	100	4	Nil
3	Montmorillonite KSF	100	4	Nil
4	Montmorillonite K10	100	4	23.1
5	Ammonium chloride/ H_2O	100	24	36.8
6	Bu_4NBr	100	4	41.2
7	Acidic alumina	100	4	Nil
8	Basic alumina	100	0.5	77.4

[a]Benzothiazole thiol **1** (1 equiv) and 1-(chloromethyl)-4-chlorobenzene- **2a** (1.2 equiv).

Table III Optimization of catalyst concentration in the synthesis of 2-(4-chlorobenzylthio)benzo[d]thiazole[a]

Sl.No.	Halide, R R X	Refluxing at 50°C solvent free conditions			
		Basic alumina G	Time (h)	Product **3a** (R)	Yield[b] (%)
1		None	2		Nil
2		0.02	1		30.5
3		0.04	1		43.6
4		0.06	1		65.6
5		0.08	0.5		72.7
6		0.1	0.5		77.4
7		0.12	0.5		81.7
8		0.14	0.5		86.2

[a]**1** = 1 equiv, **2a** = 1.2 equiv.
[b]**3a** in isolated yield.

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Antibacterial Study

The in vitro antibacterial screening of compounds **3c**, **e**, **g**, **i**, **j** and **k** was evaluated against the selected Gram-positive organism *Staphylococcus aureus* and Gram-negative organisms *Escherichia coli* and *Proteus mirabilis* by Agar well diffusion method, and is presented in the Supplemental Materials (available online).

CONCLUSION

A mild procedure has been found for the coupling reactions of different halides with thiols using basic alumina as catalyst. The salient features of this method are high generality, exceptional level of functional group toleration, satisfying yield of the coupling product, and environmentally and economically benign conditions.

EXPERIMENTAL

All reactions were carried out in resealable tubes, under a high-purity nitrogen atmosphere. Flash-column chromatography was performed using neutral alumina. Melting points were taken in open capillary tubes. IR spectra in KBr pellets were recorded on Nucon Infrared spectrophotometer. Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer.

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General Procedure of the Coupling Reaction

To thiol (**1**) (1.0 equiv.), halides (**2**) (1.2 equiv) were added at room temperature under nitrogen, and then the catalyst was added, the mixture was heated to 50°C, and stirred at the same temperature until completion of reaction, monitored by TLC. The mixture was extracted several times (3 × 20 mL) with DCM or EtOAc. The combined organic layers were concentrated. Purification of the residue to the thioether (**3**) was performed by flash chromatography on neutral alumina (petroleum ether/ethyl acetate).

2-(4-Chlorobenzylthio)benzo[d]thiazole (3a)

Thiol (**1**) (0.15 g, 0.897 mmol), 1-(chloromethyl)-4-chlorobenzene (**2a**) (0.173 g, 1.0762 mmol), and basic alumina (140 mg) were taken in a 50-mL RB flask, refluxed at 50°C for 30 min, and stirred at the same temperature for 1 h. Reaction was monitored by TLC, and after completion of the reaction, was worked up as above to give crude product 2-(4-chlorobenzylthio)benzo[d]thiazole (**3a**), which was purified by column chromatography using neutral alumina and pet ether:ethyl acetate as eluent (Compound **3a**, Table I).

A similar procedure was followed to obtain the other thioether derivatives **3** from different halides **2** (Scheme 1, Table I). Products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and GCMS spectral techniques, and known compounds have been compared with reports in the literature.

Analytical Data

Data of a few compounds **3a**,**b** that have not been reported earlier are given in the following sections. The data of other compounds **3d–m** are given as a supporting document, which is available online in the Supplemental Materials.

2-(4-Chlorobenzylthio)benzo[d]thiazole (3a). Yield 86.2%, Yellow solid, mp 114 °C**,** IR (KBr pellets, ν cm^{-1}) 3058, 2926, 1584, 1491, 1456, 1426, 1309, 1094, 1004, 830, 753, 499. ^{1}H NMR (400 MHz, $CDCl_3$) 7.92–7.89 (d, J = 8.08 Hz, 1H), 7.77–7.75 (d, J = 8.0Hz, 1H), 7.46–7.39 (m, 3H), 7.34–7.28 (m, 3H), 4.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 153.01, 135.34, 134.97, 133.59, 130.49, 126.13, 124.42, 121.57, 121.05, 36.86; LC-MS m/z 292.1 (M^+); $C_{14}H_{10}NS_2Cl$, Mol. Wt.: 291.1.23,.

2-((6-(Trifluoromethyl)-2-methylpyridin-3-yl)methylthio)benzo[d]thiazole (3b). Yield 60.6%, Colorless liquid, IR (KBr pellets, ν cm^{-1}) 3064, 2924, 1589, 1460, 1428, 1405, 1260, 1181, 1139, 1116, 1018, 997, 759. ^{1}H NMR (400 MHz, $CDCl_3$) 7.97–7.95 (d, J = 7.88 Hz, 1H), 7.92–7.90 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 4 Hz, 1H), 7.48–7.43 (m, 2H), 7.35–7.33 (t, J = 7.12 Hz, 1H), 4.67 (s, 2H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.65, 158.39, 152.85, 138.58, 138.07, 135.43, 133.70, 126.24, 121.63, 121.16, 118.09, 118.07, 42.67, 34.08, 22.42; LC-MS m/z 341.1 (M^+); $C_{15}H_{11}F_3N_2S_2$, Mol. Wt.: 340.

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