Chinese Chemical Letters Vol. 15, No. 10, pp 1140-1142, 2004
http://www.imm.ac.cn/journal/ccl.html

Indium-mediated Facile Synthesis of (6-Chloropyridine-3-yl)methyl Heterocyclic Thioether Derivatives in Aqueous Media

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Abstract: A series of substituted (6-chloropyridine-3-yl)methyl heterocyclic thioether derivatives were prepared by indium mediating in water. The preliminary biological tests showed that compound **3d** exhibited good antiviral activity.

Keywords: Thioether, green synthesis, antiviral activity, indium.

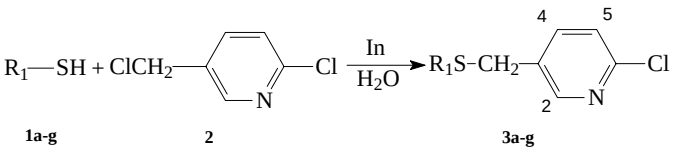
During these years, a great variety of thioether compounds with heterocycle have been synthesized due to their broad-spectrum biological activities such as fungicidal, insecticidal, herbicidal and plant-growth regulative activities. Their dosage and mammalian toxicity are very low[1-3]. In this paper, a series of pyridyl substituted thioethers were prepared with metal catalyst in water. All of them are new compounds and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The preliminary biological tests showed that some of them exhibit good antiviral activities.

Experimental

The products **3a-g** were prepared as described in **Scheme 1**, the key reactant **1a-g** were prepared according to literature[4-8].

General procedure for preparation of compounds **3a-g: 1a-g** (6 mmol) was added in water (25 mL), sodium hydroxide(250 mg) was added. The mixture was stirred at room temperature for 3 hrs, then 2-chloro-5-chloromethylpyridine (1.00 g, 6 mmol) and 0.5 mg

Scheme 1



1a-g **2** **3a-g**

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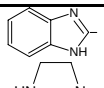
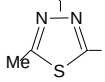
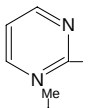
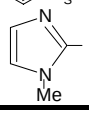
Table 1 Physical data of compounds **3a-g**

Compd.	R_1	Yield (%)	m.p. (°C) *	Elemental analysis (%, Calcd.) **		
				C	H	N
3a		94.3	168-170	56.56 (56.41)	3.98 (3.71)	15.25 (15.23)
3b		92.7	122-123	47.27 (47.30)	4.43 (4.47)	18.19 (18.20)
3c		91.6	70-71	50.57 (50.62)	3.38 (3.39)	17.66 (17.62)
3d		78.0	91-92	50.57 (50.62)	3.38 (3.39)	17.66 (17.62)
3e		90.1	98-99	54.15 (54.10)	4.73 (4.65)	15.63 (15.60)
3f		87.6	78-79	53.25 (53.30)	3.01 (3.00)	9.51 (9.60)
3g		88.9	67-68	50.07 (50.08)	4.16 (4.17)	17.55 (17.57)

* Melting points were determined on a XT-4 melting point apparatus, the thermometer was uncorrected.

**Elemental analysis were performed on a Elementar Vario-III elemental analyzer instrument.

Table 2 The reaction conditions for preparation of compounds **3a-g**.

Entry	Metal	Reaction temperature	Phase transferred catalyst	Yield (%)
1	indium	room temp.	/	94.3
2	zinc	room temp	*n*-Bu_4Br	24.6
3	zinc	56°C	*n*-Bu_4Br	64.3
4	tin	room temp	*n*-Bu_4Br	27.8
5	tin	56°C	*n*-Bu_4Br	66.7

indium were added slowly. The reaction mixture was stirred at room temperature, after 7 hrs the mixture was filtrated. The solid was washed with sodium hydroxide (10%, w/w), and washed with water to pH 7. Recrystallization from petroleum ether-toluene gave the desired product **3a-g**.

Results and Discussion

When the etherification was mediated by indium in water, the reaction went smoothly at room temperature without any promoter, when use of zinc or tin phase-transferred catalysts heat was usually required. (Reactant **1a** was tested and the results shown in **Table 2**). Indium mediated organic reactions in aqueous medium had been so attractive that several research papers were published during the past several years together with several reviews[9-11]. With this method compound **3a-g** could be synthesized in high yields, which could then be purified easily by recrystallization[12]. An organic co-solvent is not

necessary either. In the absence of indium and water, the reaction was much slower and the yield of the product was decreased, when the reaction mixture was heated in DMF or acetonitrile in the presence of K_2CO_3 and triethylamine. In this condition the by-products were produced because 2-chloro-5-chloromethylpyridine was sensitive to the basic aqueous medium and heating.

Preliminary bioassay suggests that these compounds have good antiviral activity against TMV. For example, the inhibitory rate of compound **3d** to TMV (*in vitro*) was 68.2% at 4.0 mg/L.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China (Grant No.20162001) and the Foundation for University Prominent Teacher by Ministry of Education.

References and Notes

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12. IR spectra were recorded on a Shimadzu IRPrestiage-21 spectrometer. NMR spectra were measured on a Varian INOVA 400MHz FT-NMR spectrometer in DMSO-d_6 (with exception of **3c** in $CHCl_3$) with TMS as internal standard. IR(ν/cm^{-1}, KBr): **3a:** 1459, 1586; **3b:** 1459, 1574; **3c:** 1460, 1584; **3d:** 1457, 1561; **3e:** 1460, 1584; **3f:** 1562.8, 1584.9; ^{1}H NMR(δ/ppm, all in DMSO-d_6 with exception of **3c** in $CDCl_3$, H-2, H-4, H-5 refer to pyridine hydrogen atoms which illustrated in **Scheme 1**): **3a**: 12.61 (s, 1H, NH), 8.49 (s, 1H, H-2), 7.91-7.93 (d, 1H, J=7.6Hz, H-4), 7.41-7.43 (d, 1H, J=8.4Hz, H-5), 7.36-7.54 (m, 2H, benzoimidazole), 7.11-7.11 (m, 2H, benzoimidazole), 4.56 (s, 2H, CH_2); **3b:** 8.39-8.40 (d, 1H, J=2.4Hz, H-2), 7.85-7.88 (dd, 1H, J=8.4, 2.4Hz, H-4), 7.43-7.45 (d, 1H, J=8.4Hz, H-5), 6.64 (s, 1H, NH), 4.23 (s, 2H, CH_2), 3.46 (s, 4H, $2CH_2$); **3c:** 8.43 (s, 1H, H-2), 7.78-7.80 (d, 1H, J=7.6Hz, H-4), 7.26-7.28 (d, 1H, J=8.4Hz, H-5), 4.49 (s, 2H, CH_2), 2.72 (s, 3H, CH_3); **3d:** 8.63 (s, 2H, pyrimidine), 8.47 (s, 1H, H-2), 7.89-7.91 (d, 1H, J=6.8Hz, H-4), 7.42-7.43 (d, 1H, J=7.6Hz, H-5), 7.22 (s, 1H, pyrimidine), 4.38 (s, 2H, CH_2); **3e:** 8.47-8.47 (d, 1H, J=2.4Hz, H-2), 7.88-7.91 (dd, 1H, J=8.4, 2.4Hz, H-4), 7.41- 7.43 (d, 1H, J=8.0Hz, H-5), 6.94 (s, 1H, pyrimidine), 4.33 (s, 2H, CH_2), 2.33 (s, 6H, $2CH_3$); **3f:** 8.54 (s, 1H, H-2), 7.97 (s, 2H, benzothiazole), 7.87 (s, 1H, H-4), 7.45 (s, 2H, benzothiazole), 7.34 (s, 1H, H-5), 4.65 (s, 2H, CH_2); **3g:** 8.18-7.82(m, 3H, pyridine) , 7.76-7.10(m, 2H, imidazole), 4.17(s, 2H, CH_2), 3.38(s, 3H, CH_3); **^{13}CNMR**: **3a:** 149.91, 148.99, 148.93, 143.54, 140.03, 135.48, 133.90, 124.03, 1231.80, 121.23, 117.50, 110.42, 31.32; **3b:** 162.2, 149.9, 148.8, 140.1, 134.5, 123.4, 30.2; **3c:** 165.6, 163.4, 150.6, 149.9, 139.6, 131.6, 124.1, 33.85, 15.6; **3d:** 169.9, 157.9, 150.0, 148.8, 140.1, 133.95, 124.08, 117.6, 30.4; **3e:** 167.1, 166.6, 150.1, 148.6, 140.2, 134.3, 123.9, 116.2, 30.3, 23.2; **3f:** 165.26, 152.4, 150.2, 149.2, 140.3, 134.7, 132.8, 126.4, 124.6, 124.1, 121.8, 121.2, 32.7.

Received 14 July, 2003