J. Org. Chem. **1999,** *64,* 1029−1032 **1029**

Synthesis of Symmetrical *N,N′*-Disubstituted Thioureas and Heterocyclic Thiones from Amines and CS_2 over a ZnO/Al_2O_3 Composite as Heterogeneous and Reusable Catalyst

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Received August 11, 1998

Introduction

The reaction of carbon disulfide with amines has been widely studied in the past few decades. In particular it has been reported that primary amines react with carbon disulfide in pyridine or ethanol giving symmetrical thioureas. The process is catalyzed by different reagents such as sulfur and dimethylchloroformiminium chloride; moreover addition of hydrogen peroxide, iodine, or sodium hydroxide to remove hydrogen sulfide formed in the reaction greatly increases the rate of thiourea formation.[1]

Since the possibility of performing fundamental chemical reactions in the presence of heterogeneous catalysts under solventless conditions to minimize waste production is the subject of active investigation in our group,[2] we reinvestigated the above-described thiourea synthesis by using clay-derived materials as heterogeneous catalysts.

Clay minerals are materials composed of layers of metal or non-metal oxides and hydroxides stacked on top of each other. The ubiquitous cationic clays contain negatively charged sheets neutralized by interlayer cations (Na^+, K^+, Ca^{2+}, etc.).[3] The far less common anionic clays, which were particularly used in this study as catalyst precursors, are rare in nature but relatively simple and inexpensive to prepare in the laboratory. They consist of positively charged metal oxide or hydroxide layers with anions located interstitially.[4]

Results and Discussion

The reaction of aniline **1a** with carbon disulfide **2** to produce *N,N′*-diphenylthiourea **3a** was studied over two heterogeneous catalysts: the commercial acid montmorillonite KSF calcined at 200 °C for 10 h[5] and the basic ZnO/Al_2O_3 composite [Zn-Al HT(500)] prepared in our laboratory from the corresponding hydrotalcite-like hydroxycarbonate (Zn-Al HT) and calcined at 500 °C for 15 h (see Experimental Section).

The catalytic performance of these materials was evaluated in comparison with the uncatalyzed process. A mixture of aniline (0.01 mol, 0.9 g, 0.9 mL), carbon disulfide (0.05 mol, 3.8 g, 3.0 mL), and the heterogeneous catalyst (1.0 g) was reacted in a small autoclave equipped with a stirrer, at 100 °C for 5 h. Figure 1 shows the results in terms of the yield of *N,N′*-diphenylthiourea **3a** through each of the reactions described above as a function of time. Both catalysts enhance the reactivity of the system with respect to the uncatalyzed process. In particular, after 2 h, product **3a** was produced in 83% yield by using the basic catalyst Zn-Al HT(500), in 43% yield with the acid clay KSF, and in only in 17% yield by carrying out the reaction without any catalyst. It should also be noted that both catalysts become rapidly inhibited during the reaction and that the more active deactivates faster. It is reasonable to assume that the reason for the superiority of the Zn-Al HT(500) for achieving catalytic activity is related to the presence of basic oxy and hydroxy groups which can favor the abstraction of H_2S. On the contrary, the acid clay KSF can enhance the electrophilicity of carbon disulfide, but at the same time it can reduce the nucleophilicity of the amine by acid−base interaction.[6]

Moreover, in comparison experiments with calcined zinc and aluminum oxides,[7] product **3a** was obtained in 45% yield and 30% yield, respectively, thus proving a remarkable synergistic effect of both oxides in the mixed material.

Different primary amines were reacted with CS_2 in the presence of the catalyst Zn-Al HT(500) at 100 °C for 2 h. Synthetic results are shown in Table 1. Thioureas **3** were easily recovered by dissolving the final reaction mixture in methanol, removing the catalyst by filtration, and adding water until the precipitation was complete.

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(5) KSF (Fluka) is an acid-activated naturally occurring clay mainly consisting of montmorillonite with the following chemical composition (average values) SiO_2 (54.0%), Al_2O_3 (17.0%), Fe_2O_3 (5.2%), CaO (1.5%), MgO (2.5%), Na_2O (0.4%), and K_2O (1.5%) [information kindly furnished by Süd Chemie AG] and showing the following physicochemical parameters: surface acidity 0.85 mequiv of H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3−TPD): Berteau, P.; Delmon, B. *Catal. Today* **1989**, *5*, 121], surface area 15 ± 10 m^2/g [determined in our laboratory by B.E.T. method: Brunauer, S.; Hemmett, P. H.; Teller, E. *J. Am. Chem. Soc.* **1938**, *60*, 309]. The catalyst was calcined at 200 °C for 10 h to remove the mobile surfacial and interstitial water avoiding the collapse of the laminar structure [Alberti, G.; Costantino, U. Layered Solids and their Intercalation Chemistry. In *Comprehensive Supramolecular Chemistry*; Alberti, G., Bein, T., Eds.; Pergamon: Oxford, 1996; Vol. *7*, pp 1−23].

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(7) Calcined zinc and aluminium oxides were prepared from the corresponding nitrates following the same methodology utilized in the preparation of Zn-Al HT(500) (see ref 4a).

10.1021/jo981629b CCC: $18.00

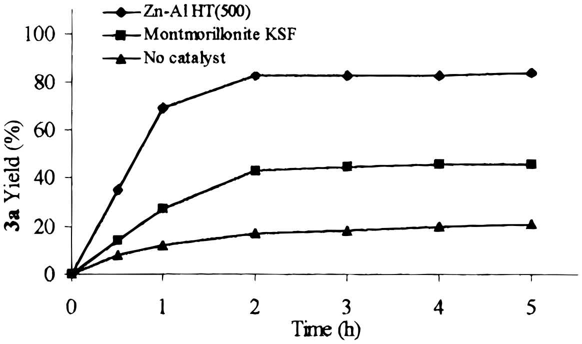
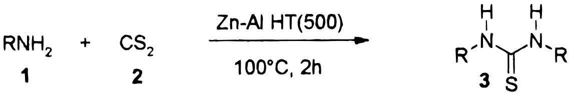


Figure 1.

Table 1. Reaction of Primary Amines with Carbon Disulfide over the Catalyst Zn-Al HT(500)



entry	R	**3** yield [selectivity] (%)
a	C_6H_5	83 [98]
b	$4\text{-}CH_3C_6H_4$	87 [100]
c	$4\text{-}ClC_6H_4$	69 [99]
d	2-pyridyl	57 [92]
e	$C_6H_5CH_2$	98 [100]
f	(*R*)-$C_6H_5(CH_3)CH$	100 [100]
g	C_6H_{11}	91 [97]
h	C_5H_{11}	95 [98]
i	C_8H_{17}	97 [98]
j	$(CH_3)_3C$	100 [100]

Scheme 1

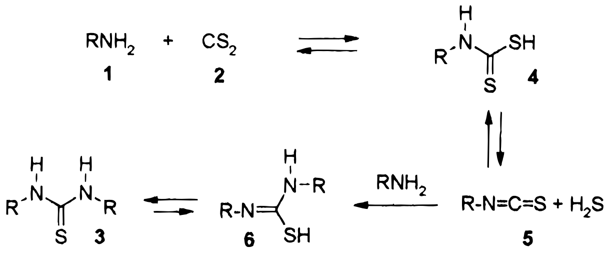
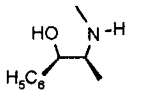
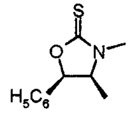
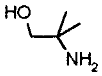
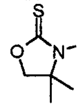
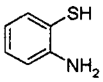
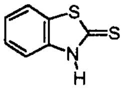
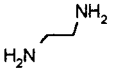
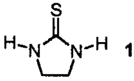


Table 2. Reaction of Amines Bearing an Additional Nucleophilic Group with CS_2 over the Catalyst ZnAl HT(500)

Entry	Amine	Product	Yield [Sel.] (%)
a		 7	98 [98]
b		 8	92 [94]
c		 9	92 [99]
d		 10	100 [100]

The yields of products **3** are affected by the nature of the amine utilized. In fact, as expected for a typical nucleophilic addition, aliphatic amines show higher reactivity than the aromatic ones (compare, for example, Table 1, entries a–d with e–j). Moreover, complete retention of optical activity is observed in the reaction with a chiral amine (Table 1, entry f).

The procedure is efficiently applicable to primary amines, but not to the secondary ones which are quantitatively recovered unchanged. This fact strongly suggests that the dithiocarbamic acid **4** initially formed by nucleophilic attack of the amine to CS_2[8] can be converted into the more electrophilic isothiocyanate **5** (Scheme 1). One equivalent of H_2S is released in this step.Thiourea **3** is thus produced by a rapid addition of a second molecule of amine **1** to **5**.[9] We assume that the basic catalyst can enhance the isothiocyanate production by favoring the abstraction of the NH proton. Supporting evidence for the isothiocyanate intermediacy is suggested by isolation of (±)-1-phenylethyl isothiocyanate in 22% yield in the reaction of (±)-1-phenylethylamine and carbon disulfide at 25 °C for 1 h in the presence of Zn-Al HT(500). Evidently, secondary amines cannot produce the active intermediate **5** and are thus recovered unchanged. However, when amine **1** contains an additional nucleophilic group, a fast intramolecular attack converts intermediate **4** into different heterocyclic thiones in high yield irrespective of the nature of the amino group (see, for example, Table 2, entry a).

Thus, oxazolidine-2-thiones **7**[10] and **8**,[11] 1-mercaptobenzothiazole **9**,[12] and imidazolidine-2-thione **10**[13] were synthesized in high yield and in short reaction time, avoiding use of strong homogeneous acids and bases.

We next studied the reusability of the catalyst in the model reaction with aniline. Thus, methanol was added to the final reaction mixture, and the catalyst was recovered by filtration and further washed with hot methanol to completely remove organic compounds and traces of sulfur which can act as inhibitors.[14] After being dried under vacuum at 120 °C for 2 h, the catalyst was reused. Five cycles were thus repeated without apparent loss of the catalytic activity, with compound **3a** being obtained in 82%, 78%, 75%, 80%, and 78% yield.

Finally, X-ray diffraction (XRD) analysis of the catalyst was performed to check its stability and to recognize possible transformations during the reaction. The XRD analysis, carried out on the Zn-Al HT(500) fresh catalyst, clearly shows the XRD pattern of ZnO (zincite)[15a] as the unique crystalline phase, suggesting that this material

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[8] We did not isolate from our reaction mixtures any dithiocarbamate–amine salts which were previously obtained by carrying out the reaction in acetone or ethanol solution and in the presence of an excess of amine: Foye, W. O.; Speranza, J. P. *Eur. J. Med. Chem.* **1977**, *9*, 177. Bazavova, I. M.; Dubenko, R. G.; Shevchenko, L. I.; Pel'Kis, P. S. *Ukr. Khim. Zh.* **1980**, *46*, 286 (*Chem. Abstr.* **1980**, *93*, 71237p).

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[14] A dramatic drop in the yield of **3a** (~40% yield) was effectively observed by carrying out the model reaction in the presence of sulfur (200 mg).

[15] Powder Diffraction File cards (a) No. 5-0664 and (b) No. 5-0566, JCPDS, International Center for Diffraction Data, Swarthmore, PA.

is a composite system consisting of crystalline grains of zinc oxide in amorphous alumina. After the catalyst runs, two XRD patterns are observed, i.e., that of zincite superimposed by a set of large peaks due to ZnS (sfalerite),[15b] probably produced by the reaction of H_2S with the catalyst. Despite this, the permanence of adequate amounts of zinc oxide allows a high level of catalytic activity at least for five cycles as stated before. One could suppose from these results that after the first run the new catalyst could be a mixture of ZnS and Al_2O_3 or ZnS alone. However, when commercial zinc sulfide [X-ray peak widths (2ϑ) ca. 0.2°] was used as heterogeneous promoter, no catalytic effect was observed (**3a** yield 16%; compound **3a** was obtained in 17% yield without catalyst). On the other hand, an additional experiment with a 4:1 molar ratio mixture of ZnS:basic Al_2O_3 gave product **3a** in 35% yield. A quite similar result (42% yield) was achieved with basic Al_2O_3 alone. From these data we do not exclude the possibility that ZnS could behave as cocatalyst; however, this effect would operate to a significant extent only in the case of the composite system, where ZnS nanocrystallites [X-ray peak widths (2ϑ) ca. 2°] are dispersed in the amorphous alumina.

Conclusions

In conclusion we have shown that the ZnO/Al_2O_3 composite [Zn-Al HT(500)], easily prepared in the laboratory, can afford an efficient and reusable catalyst in the synthesis of symmetric *N,N′*-disubstituted thioureas from primary amines and carbon disulfide. This procedure can also be applicable to the synthesis of different heterocyclic thiones by using amines bearing additional nucleophilic groups.

The use of this heterogeneous catalyst makes product isolation easier, gives a clean reaction, and is of course advantageous in an economical and environmental sense. A possible drawback of the present methodology is represented by the production of H_2S. However, removal of this hazardous compound from reaction mixtures represents a general and previously solved problem.[16]

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Mass spectra were obtained in EI mode at 70 eV. Microanalyses were carried out by the Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università di Parma, Italy. TLC analyses were performed on Merck 60 PF_{254} silica gel plates using mixtures of hexane−ethyl acetate (25−35%). XRD spectra were obtained on a Philips PW 1050 instrument using the Cu−Kα radiation. All the reagents were of commercial quality from freshly opened containers.

Synthesis of Zn-Al HT(500).[4a] NaOH (1.75 mol, 70.0 g), Na_2CO_3 (0.47 mol, 50.0 g), and distilled water (500 mL) were introduced in a 2-L flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer. Then a solution of $Zn(NO_3)_2\cdot 6H_2O$ (0.50 mol, 148.7 g) and $Al(NO_3)_3\cdot 9H_2O$ (0.25 mol, 93.8 g) in distilled water (300 mL) was added dropwise at room temperature during 5 h under vigorous stirring. Following the addition which results in a heavy slurry, the flask content was heated at 65 ± 5 °C for about 18 h with continuous vigorous stirring. The slurry was then cooled to room temperature, filtered, and washed until the sodium content in the resulting solid was below 0.1% (dry basis). The solid was then dried under vacuum at 125 °C for 18 h, giving a white powder. The X-ray powder pattern of this material corresponds to that of a mixture of ZnO and Zn-Al HT. This material was calcined at 500 °C for 15 h, giving a catalyst with a surface area of 124 ± 6 m^2/g [determined in our laboratory by B.E.T. method: see ref 5] and with the following chemical composition (average values): Zn (33.70%), Al (7.63%).

Synthesis of *N,N′*-Disubstituted Thioureas 3. General Procedure. The selected amine (0.01 mol), Zn-Al HT(500) (1.0 g), and CS_2 (3 mL) were heated at 100 °C in a small autoclave under vigorous stirring. After 2 h the reaction mixture was cooled to room temperature and the excess of carbon disulfide removed under reduced pressure. Hot methanol (50 mL) was added, and the catalyst was removed by filtration and washed with hot methanol (50 mL). After cooling to room temperature, the *N,N′*-disubstituted thiourea was precipitated by adding distilled water (250 mL). The product was isolated by Buchner filtration and recrystallized from methanol.

***N,N′*-Diphenylthiourea (3a)**: yield 0.95 g (83%), white solid; mp 152−3 °C (lit.[17] mp 152 °C).

***N,N′*-Bis[4-methylphenyl]thiourea (3b)**: yield 1.12 g (87%), white solid; mp 173−5 °C (lit.[17] mp 174−5 °C).

***N,N′*-Bis[4-chlorophenyl]thiourea (3c)**: yield 1.03 g (69%), white solid; mp 166−7 °C (lit.[17] mp 167 °C).

***N,N′*-Bis[2-pyridyl]thiourea (3d)**: yield 0.66 g (57%), white solid; mp 152−3 °C (lit.[18] mp 152−4 °C).

***N,N′*-Dibenzylthiourea (3e)**: yield 1.26 g (98%), white solid; mp 145−7 °C (lit.[19] mp 146−8 °C).

(*R,R*)-*N,N′*-Bis[α-methylbenzyl]thiourea (3f): yield 1.42 g (100%), pale gray solid; mp 200−1 °C (lit.[20] mp 202−3 °C); $[\alpha]^{25}_D = -104.2$ [$c = 1.3$; $CHCl_3$] (lit.[20] $[\alpha]^{25}_D = -105.4$ [$c = 1.3$; $CHCl_3$]).

***N,N′*-Dicyclohexylthiourea (3g)**: yield 1.09 g (91%), white solid; mp 179−80 °C (lit.[21] mp 180−2 °C).

***N,N′*-Dipentylthiourea (3h)**: yield 1.03 g (95%), white solid; mp 56−8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8−1.0 (6 H, m), 1.2−1.5 (8 H, m), 1.5−1.7 (4 H, m), 3.4 (4 H, br s), 5.8 (2 H, br s); IR (KBr) 3220, 1560 cm^{-1}; MS m/z (M^+) 216 (3), 183 (4), 127 (6), 43 (100). Anal. Calcd for $C_{11}H_{24}N_2S$: C, 61.1; H, 11.2; N, 13.0. Found: C, 61.3; H, 11.1; N, 12.9).

***N,N′*-Dioctylthiourea (3i)**: yield 1.46 g (97%), white solid; mp 55−6 °C (lit.[22] mp 53−55 °C).

***N,N′*-Di-*tert*-butylthiourea (3j)**: yield 0.94 g (100%), white solid; mp 129−31 °C (lit.[23] mp 131−2 °C).

(±)-1-Phenylethyl isothiocyanate (5): yield 0.36 g (22%), pale yellow oil; bp 131−134 °C/20 mmHg (lit.[24] bp 133−134 °C/20 mmHg).

Synthesis of Heterocyclic Thiones 7, 8, 9, and 10. General Procedure. The selected amine (0.01 mol), Zn-Al HT-(500) (1.0 g), and CS_2 (3 mL) were heated at 100 °C in a small autoclave under vigorous stirring. After 2 h the reaction mixture was cooled to room temperature and the excess of carbon disulfide removed under reduced pressure. The crude was chromatographed on silica gel column with hexane−ethyl acetate mixtures (20−30%) to give the products.

(4*S*,5*R*)-3,4-Dimethyl-5-phenyloxazolidine-2-thione (7): yield 2.03 g (98%), white solid; mp 49−50 °C (lit.[10] mp 48−9 °C); $[\alpha]^{25}_D = -214$ [$c = 1.3$; MeOH] (lit.[10] $[\alpha]^{25}_D = -216$ [$c = 1.3$; MeOH]).

3,4-Dimethyloxazolidine-2-thione (8): yield 1.21 g (92%), white solid; mp 121−2 °C (lit.[11] mp 123 °C).

1-Mercaptobenzothiazole (9): yield 1.54 g (92%), white solid; mp 176−7 °C (lit.[12] mp 177 °C).

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Imidazolidine-2-thione (10): yield 1.02 g (100%), white solid; mp 195−6 °C (lit.[25] mp 195−7 °C).

Acknowledgment. The authors are grateful to Prof. Angelo Vaccari (Dipartimento di Chimica Industriale e dei Materiali, Università di Bologna, Italy) for helpful discussions. The authors acknowledge the support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, the Consiglio Nazionale delle Ricerche (CNR), Italy and the Universities of Parma and Camerino (MC) (National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni"). The facilities of the Centro Interdipartimentale Misure (CIM) [NMR and mass instruments] and of the Centro di Studio per la Strutturistica Diffrattometrica del CNR [XRD] were used. Thanks are due to Mr Pier Antonio Bonaldi for technical collaboration.

JO981629B

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