



Highly efficient and catalyst-free synthesis of unsymmetrical thioureas under solvent-free conditions

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ABSTRACT

A highly efficient and simple synthesis of unsymmetrical thioureas is reported based on the reaction of readily synthesized dithiocarbamates with amines, without using any catalyst under solvent-free conditions. The short reaction time, high yields, and solvent-free conditions are advantages of this method. We did not observe the formation of any symmetric disubstituted thiourea, under these reaction conditions.

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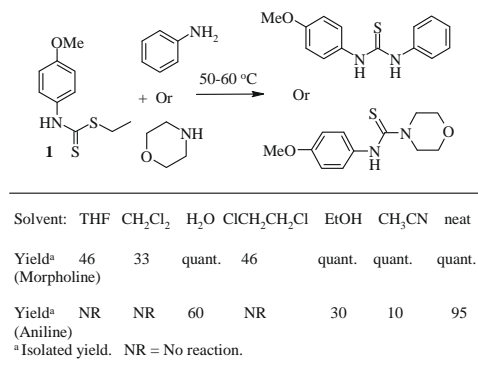
With increasing global environmental concerns, the design of 'solvent-free' green processes has gained significant attention from synthetic organic chemists.¹ As a result, many reactions are designed to proceed cleanly and efficiently in the solid state or under solvent-free conditions.² Less chemical pollution, lower cost, and an easier workup procedure are the main reasons for the recent increase in the popularity of solvent-free reactions.

Thioureas have attracted much attention by virtue of their bioactivities as pharmaceuticals and pesticides. Various thiourea derivatives and their metal complexes exhibit analgesic,³ anti-inflammatory,⁴ antimicrobial,⁵ anticancer,⁶ and antifungal activities.⁷ Moreover, thioureas are important as building blocks in the synthesis of heterocycles. For example, thiourea condenses with 2-halocarbonyl compounds to afford 2-aminothiazoles.⁸ Benzothiazoles can be prepared from arylthioureas in the presence of bromine.⁹ The use of thioureas to make iminothiazolines,¹⁰ thiohydantoin, ¹¹ 1,3,5-triazines,¹² and 2-amino-oxazolidines¹³ has been described. Also, the use of thiourea as an organocatalyst has been described.¹⁴ A great variety of procedures have been reported for the preparation of substituted thioureas. The procedures having widest use, which are also of practical interest for industrial synthesis, can be collected into three groups: (i) reaction of primary amines mainly with thiophosgene or its less toxic and less hazardous substitutes;¹⁵ (ii) reaction of primary or secondary amines with isothiocyanates¹⁶ (isothiocyanates are prepared mainly from thiophosgene in an organic solvent); and (iii) reaction of primary amines with carbon disulfide in the presence of mercury acetate and reaction of unsubstituted thioureas with primary alkylamines at high temperature in aqueous ammonia,¹⁷ which gave the symmetrical thioureas.¹⁸ Recently, several other new methods for the preparation of substituted thioureas have been reported.¹⁹ For

example, Yin et al. reported an efficient method for the synthesis of disubstituted thioureas via the reaction of *N,N*-di-Boc-substituted thiourea with alkyl or aryl amines in the presence of NaH as base.²⁰ However, many reported methods suffer from drawbacks and limitations related to harsh reaction conditions such as high reaction temperature, long reaction times, the use of a strong acid or base, and toxic reagents such as thiophosgene and hydrogen sulfide. Therefore, the development of mild, efficient, and environmentally benign methods for the synthesis of novel thioureas is of great importance in the search for bioactive molecules as well as in synthetic chemistry. Thus, we report here a novel, mild, catalyst-free, and green procedure for the synthesis of unsymmetrical thioureas using dithiocarbamates and various amines under solvent-free conditions.

In previous work, we reported a one-pot and simple method for the synthesis of dithiocarbamates from an amine, CS₂, and different nucleophile acceptors, such as alkyl halides, activated olefins, and epoxides, under solvent-free or aqueous conditions (Scheme 1).²¹ Encouraged by the work of Artuso and co-workers which utilized dimethyl dithiocarbonate for the synthesis of substituted ureas in water,²² we focused our attention on the synthesis of unsymmetrical thioureas from easily prepared dithiocarbamates and different amines under solvent-free conditions. After synthesizing the starting dithio-carbamates,^{21a-c} we optimized the reaction conditions by changing the temperature, solvent, and equivalents of amine for the reaction of **1** with aniline and morpholine as model reactions. We screened the reaction in solvents including H₂O, ethanol, CH₂Cl₂, THF, ClCH₂CH₂Cl, and CH₃CN. As shown in Scheme 1, the reaction of morpholine with **1** gave moderate to excellent yields in various organic solvents, but aniline gave only poor to moderate yields in these organic solvents. However, under solvent-free conditions, the reaction of the dithiocarbamate with various aromatic and aliphatic amines proceeded to completion, affording unsymmetrical thioureas in excellent yields without the use of any

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Scheme 1. Screening of solvents.

catalyst. Our studies showed that the reactions were complete at 50–60 °C in most cases. The reaction of **1** was also carried out with different equivalents of aniline and morpholine. We found that about 1.1 equiv of amine was sufficient to achieve complete conversion of the dithiocarbamate to a thiourea.

Next, the scope and limitations of this process were explored by using a wide range of amines. Structurally diverse amines including primary and secondary aliphatic amines, primary aromatic amines, and ammonia underwent the reaction without using any catalyst or solvent to afford the corresponding unsymmetrical thiourea. Also, the reaction was carried out with four different *S*-alkyl dithiocarbamates. The results are summarized in Table 1.

As shown in Table 1, the reaction of dithiocarbamates derived from primary aliphatic and aromatic amines gave substituted thioureas with excellent yields. However, reaction with dithiocarbamates based on a secondary amine was not possible. Thioureas containing adamantyl groups were synthesized in excellent yields. Also, optically active thioureas were synthesized by the reaction of a chiral amine with dithiocarbamates or of amines with a chiral dithiocarbamate.

The reaction of 1,3-propanediamine with dithiocarbamates **1** and **3** gave the corresponding bis-thioureas **5** and **6** in quantitative yields as shown in Scheme 2.

We also compared the reactivities of primary and secondary aliphatic amines with a dithiocarbamate as outlined in Scheme 3. We found that pyrrolidine reacted with dithiocarbamate **1** in the presence of butylamine to give an unsymmetrical thiourea in more than 95% yield, but butylamine gave less than 5% of the corresponding unsymmetrical thiourea.

Generally, the solvent-free reaction is experimentally simple and proceeded well without any catalyst, and generated virtually no byproducts. All the reactions performed here involved stirring homogenous liquids, due to the low melting point of the *S*-alkyl dithiocarbamates. As the reaction proceeded, the mixture solidified as the product formed. As the reactions are run under neat and catalyst-free conditions, no side products form in the reaction mixture (apart from entries 28 and 29, Table 1), and in some cases, the pure thioureas were isolated by simple extraction. Usually, washing the solidified mixture with 2 M HCl and filtration of the solids gave the pure unsymmetrical thiourea. All compounds gave satisfactory NMR spectra (see Supplementary data).

In conclusion, we have developed an efficient method for the synthesis of unsymmetrical thioureas from readily synthesized *S*-alkyl dithiocarbamates and amines. Importantly, no symmetrical disubstituted thioureas were formed under these reaction conditions. This method represents a simple procedure involving mild reaction conditions, and has general applicability. It avoids hazardous organic solvents and toxic catalysts and typically provides nearly quantitative yields of products.

Table 1

Synthesis of unsymmetrical thioureas from dithiocarbamates and amines under solvent-free conditions^a

Entry	Dithiocarbamate	Amine	Yield ^c (%)
1		a	95
2		b	Quant.
3		c	Quant.
4		d	Quant.
5		e	89
6		f	95
7		g	92
8		h	Quant.
9		j	Quant.
10		k	Quant.
11		a	90
12		b	76
13		d	85
14		f	90
15		h	64
16		a	Quant.
17		b	60
18		c	50
19		d	90
20		e	Quant.
21		f	95
22		h	80
23		i ^d	Quant.
24		j	Quant.
25		a	Quant.
26		c	Quant.
27		d	Quant.
28		g ^e	85
29		i ^e	70

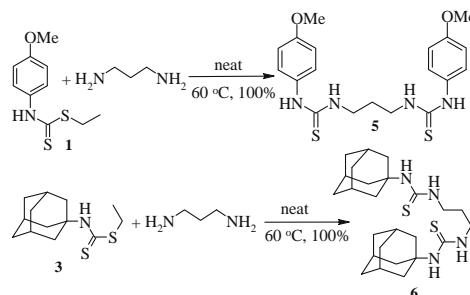
^b 1.0 mL of a 25% aqueous solution of ammonia was used in the reaction.

^a Reaction conditions: dithiocarbamate (5 mmol), amine (7 mmol), 60 °C, 4 h.

^c Isolated yields.

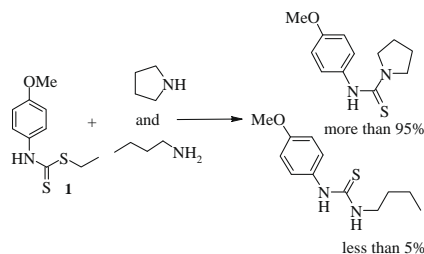
^d Reaction performed at 90 °C.

^e 10% of isothiocyanate was also obtained.



Scheme 2. Reaction of a diamine with dithiocarbamates.

General procedure for the synthesis of unsymmetrical thioureas: To a test tube equipped with a magnetic stirrer bar, dithiocarbamate (5 mmol) and amine (7 mmol) were added. The reaction mixture was warmed to 60 °C with vigorous stirring. The progress of the reaction was checked by TLC (silica gel; ethyl acetate/petroleum ether 1:5). In most cases, the reaction mixture solidified when



Scheme 3. Comparing the reactivity of primary and secondary aliphatic amines toward a dithiocarbamate.

the reaction was complete. After completion, 5 mL of 2 M HCl was added to remove excess amine, and filtration of the slurry gave the unsymmetrical thiourea. In most cases, pure unsymmetrical thiourea was obtained without any further purification. If needed, purification was achieved by washing the solids with hot petroleum ether or by column chromatography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.10.063](https://doi.org/10.1016/j.tetlet.2008.10.063).

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