

## A convenient and efficient method for the synthesis of mono- and *N,N*-disubstituted thioureas

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Received 28 April 2005; revised 27 June 2005; accepted 27 June 2005

Available online 14 July 2005

**Abstract**—A convenient method for the synthesis of mono- and *N,N*-disubstituted thioureas by the debenzoylation of *N*-substituted- and *N,N*-disubstituted-*N'*-benzoylthioureas with hydrazine hydrate under solvent-free conditions has been developed. *N*-Substituted-*N'*-benzoylthioureas and hydrazine hydrate were mixed, and stirred at room temperature without a solvent to give the corresponding *N*-substituted thioureas in high yields.

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Thioureas are important compounds as building blocks in the synthesis of heterocycles. For example, thioureas condense with  $\alpha$ -halocarbonyl compounds to afford 2-amino-1,3-thiazoles.<sup>1</sup> Benzothiazoles can be prepared from arylthioureas in the presence of bromine.<sup>2</sup> The use of thioureas to make iminothiazolines,<sup>3</sup> thiohydantoin,<sup>4</sup> 1,3,5-triazines,<sup>5</sup> and 2-amino-oxazolidines<sup>6</sup> was also described recently. Many methods for the synthesis of thioureas have been reported, for example, *N*-substituted thioureas are commonly prepared from the reaction of amines with alkali metal thiocyanates in the presence of a strong acid,<sup>7</sup> aryl isothiocyanates with amines followed by basic hydrolysis,<sup>8</sup> isothiocyanates with ammonia or amines,<sup>9</sup> unsubstituted thioureas with primary alkyl amines at high temperature,<sup>10</sup> primary amines with carbon disulfide in the presence of mercury acetate and aqueous ammonia,<sup>11</sup> and disubstituted cyanamides with hydrogen chloride and LiAlH<sub>4</sub><sup>12</sup> or hydrogen sulfide in the presence of ammonia.<sup>13</sup> Several new methods for the preparation of substituted thioureas have been recently reported.<sup>14</sup> However, these methods have several drawbacks, namely, the need for high reaction temperature, long reaction time, the use of noxious reagents such as hydrogen sulfide and carbon disulfide, and special starting materials. The development of mild, efficient, and environmentally friendly

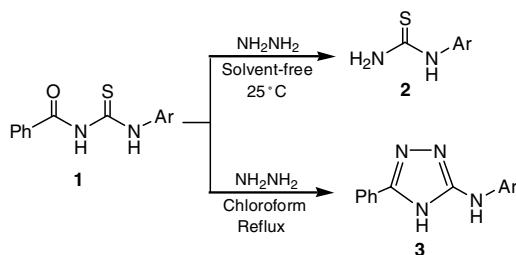
methods is still desired. It has been known that in peptide synthesis involving use of an *N*-protective phthaloyl group, hydrazine is a useful reagent for removal of the protective group.<sup>15</sup> A similar hydrazine cleavage is also employed in the deprotection of the *N*-protective benzoyl group.<sup>16</sup> We found that *N*-aryl-*N'*-benzoylthioureas reacted with hydrazine hydrate under solvent-free conditions to give *N*-arylthioureas in good yields. Similar reactions were carried out in chloroform to afford the corresponding triazoles. We present here a mild and efficient method for the synthesis of mono- and *N,N*-disubstituted thioureas by debenzoylation of *N*-benzoylthioureas with hydrazine hydrate.

Reaction of *N*-aryl-*N'*-benzoylthioureas with hydrazine hydrate was carried out in chloroform or without a solvent. The reactions in chloroform gave the corresponding triazoles in good yields. Under solvent-free conditions, debenzoylation of *N*-aryl-*N'*-benzoylthioureas occurred and the corresponding *N*-arylthioureas were obtained in high yields. For example, *N*-phenyl-*N'*-benzoylthiourea (1 mmol) was allowed to react with hydrazine hydrate (5 mmol) for 3 h in refluxing chloroform to give 3,5-diphenyl-1*H*-1,2,4-triazole in 86% yield. In contrast, the same reaction was carried out at 25 °C for 10 min under solvent-free conditions to afford *N*-phenylthiourea in 95% yield (Scheme 1).

The results obtained are shown in Table 1. In the reaction under solvent-free conditions, the influence of the substituents within the aryl function is less recognizable.

**Keywords:** *N*-Substituted thiourea; Debzoylation; Hydrazine.

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Scheme 1.

Table 1. Synthesis of *N*-arylthiourea **2** and triazoles **3** from *N*-aryl-*N'*-benzoylthiourea

Entry	Ar	Solvent-free <sup>a</sup> Yield <sup>c</sup> of <b>2</b> (%)	Chloroform <sup>b</sup> Yield <sup>c</sup> of <b>3</b> (%)
1		95	86
2		92	77
3		88	35
4		96	31
5		91	64
6		98	82
7		98	67
8		83	87

<sup>a</sup> All reaction were carried out using *N*-aryl-*N'*-benzoylthioureas (1 mmol) and hydrazine hydrate (2 mmol) without a solvent at 25 °C for 10 min.

<sup>b</sup> All reaction were carried out using *N*-aryl-*N'*-benzoylthioureas (1 mmol) and hydrazine hydrate (5 mmol) in chloroform (10 mL) at reflux for 3 h.

<sup>c</sup> Isolated yield.

*p*-Nitrophenylthiourea was obtained in 83% yield (entry 8), whereas hydrolysis of *N*-*p*-nitrophenyl-*N'*-benzoylthiourea with aqueous sodium hydroxide affords *N*-*p*-nitrophenylthiourea in low yield (39–46%).<sup>8b</sup> *N*-Alkyl- and *N,N*-dialkyl-*N'*-benzoylthioureas were also debenzoylated under similar conditions to give the corresponding *N*-alkyl and *N,N*-dialkylthioureas in high yields, respectively. The results obtained are shown in Table 2. The rate of the debenzoylation depends on the length of the alkyl group on the nitrogen in *N*-alkyl-*N'*-benzoylthioureas.

For example, *N*-butyl-*N'*-benzoylthiourea disappeared within 20 min (entry 1) whereas *N*-hexyl- and *N*-decyl-

Table 2. Synthesis of *N*-alkyl- and *N,N*-disubstituted thioureas from *N*-substituted-*N'*-benzoylthioureas<sup>a</sup>

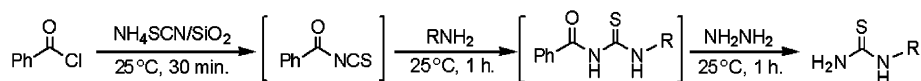
Entry	R <sup>1</sup>	R <sup>2</sup>	Time (min)	Yield <sup>b</sup> of <b>5</b> (%)
1	Butyl	H	20	99
2	<i>iso</i> -Butyl	H	10	92
3	<i>sec</i> -Butyl	H	30	98
4	<i>tert</i> -Butyl	H	20	99
5	Hexyl	H	180	100
6	Decyl	H	180	100
7	Allyl	H	10	97
8	Benzyl	H	10	97
9	Et	Et	10	89
10	Methyl	Butyl	10	93
11	Methyl	Phenyl	10	98
12	Propyl	Phenyl	10	96
13	Butyl	Butyl	10	75

<sup>a</sup> A mixture of *N*-alkyl-*N'*-benzoylthiourea (1 mmol) and hydrazine (3 mmol) was stirred at 25 °C under solvent-free conditions.

<sup>b</sup> Isolated yield.

*N'*-benzoylthiourea were observed after 120 min. Increasing the reaction time to 180 min, these benzoylthioureas disappeared and *N*-hexyl- and *N*-decylthiourea were obtained quantitatively (entries 5 and 6). *N*-Allyl- and *N*-benzyl-*N'*-benzoylthiourea easily reacted with hydrazine hydrate and the reactions were completed within 10 min at 25 °C to give *N*-allyl and *N*-benzylthiourea in high yields, respectively. *N,N*-Dialkyl-*N'*-benzoylthioureas also reacted under similar conditions to give the corresponding *N,N*-dialkylthioureas in high yields. For instance, *N,N*-diethyl-*N'*-benzoylthiourea gave *N,N*-diethylthiourea in 89% yield (entry 9). It has been reported that *N,N*-diethyl-*N'*-benzoylthiourea is transamidated with alkyl amines to give the corresponding *N*-alkyl-*N'*-benzoylthioureas.<sup>17</sup> However, in our method, transamidation did not occur. *N*-Substituted-*N'*-aryl and *N'*-acylthioureas also reacted with hydrazine hydrate as well as *N*-substituted-*N'*-benzoylthioureas to afford *N*-substituted thioureas.

We carried out one-pot synthesis of *N*-substituted thioureas under solvent-free conditions as follows (Scheme 2). First, benzoyl isothiocyanate is formed by the reaction of benzoyl chloride with silica gel supported ammonium thiocyanate (NH<sub>4</sub>SCN/SiO<sub>2</sub>). Second, the benzoyl isothiocyanate reacts with an amine to afford the *N*-substituted-*N'*-benzoylthiourea. Third, the *N*-substituted thiourea is formed by debenzoylation of the *N*-substituted-*N'*-benzoylthiourea with hydrazine hydrate. For example, benzoyl chloride (1 mmol) and NH<sub>4</sub>SCN/SiO<sub>2</sub><sup>18</sup> (2 mmol) were mixed and stirred at 25 °C for 30 min, and then aniline (2 mmol) was added



Scheme 2.

to the reaction mixture and stirred for 1 h. Finally, hydrazine hydrate (10 mmol) was added and the resulting mixture was stirred for 1 h. The products were extracted with 1,2-dichloroethane followed by isolation of *N*-phenylthiourea (84%) by flash column chromatography. *N*-Benzylthiourea was obtained in 85% yield by this method.

In conclusion, we have developed a mild, simple, and efficient method for the synthesis of mono- and *N,N*-disubstituted thioureas by debenzoylation of *N*-substituted- and *N,N*-disubstituted-*N'*-benzoylthioureas with hydrazine hydrate under solvent-free conditions. The starting materials, *N*-substituted-*N'*-benzoylthioureas, can be easily prepared in one-pot from benzoyl chloride,  $\text{NH}_4\text{SCN}/\text{SiO}_2$  and an amine.<sup>19</sup>

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- Silica gel-supported ammonium thiocyanate was prepared as follows. Silica gel (18.48 g) was added to a solution of ammonium thiocyanate (20 mmol 1.52 g) in dry acetonitrile (50 mL), and the mixture was stirred at room temperature for 30 min. The acetonitrile was removed under reduced pressure. The resulting reagent was dried in vacuo (15 mmHg) at room temperature for 3 h.
- Typical procedure for *N*-substituted-*N'*-benzoylthioureas: To a slurry of  $\text{NH}_4\text{SCN}/\text{SiO}_2$  (20 mmol, 20 g) in 1,2-dichloroethane (100 mL) was added benzoyl chloride (10 mmol). The mixture was stirred at 25 °C for 2 h, and then an amine (20 mmol) was added to it and stirred for an additional 1 h. The reaction mixture was filtered to remove the supported reagent, and the filtrate was washed with 5% HCl, brine, and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure to leave the crude product, which was purified by recrystallization (methanol).