A New and Facile Route for the Synthesis of Thiocarbamates from Aniline, Carbon Monoxide, and Thiols Mediated by Selenium

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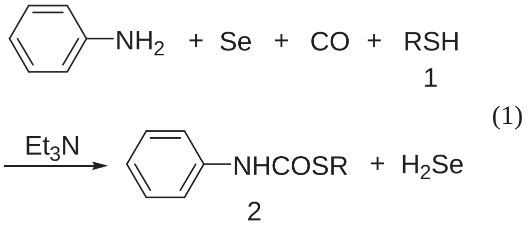
(Received January 21, 2005; CL-050096)

A new and facile route for the synthesis of thiocarbamates was reported. Mediated by selenium, aniline reacts very readily with carbon monoxide and thiols in the presence of triethylamine, to afford the corresponding thiocarbamates mostly in moderate to excellent yields under mild reaction conditions. Selenium can be easily recovered and recycled.

Thiocarbamates have received considerable attention owing to their importance in medicine as bactericides[1] and antivirus;[2] in biology as bioregulators[3] and enzyme inhibitors;[4] and in agriculture as pesticides[5] and herbicides.[6] Various methods are known in the literature for the synthesis of thiocarbamates. Most frequently used approaches include; (1) the reaction of amine with carbon monoxide and element sulfur, followed by alkylation with alkyl halides;[6c,6e,7] however, this method suffers from drawbacks such as multistep approaches, voluminous solvent required; (2) Intramolecular rearrangements of various derivatives; however, these methods are extremely limited in starting materials;[8] (3) Addition of thiols to isocyanates; deleterious, expensive and less readily available isocyanates and catalysts are limitations associated with these methods;[6d,9] (4) Oxidative coupling of aryl thiols with amines and carbon monoxide; but this method usually requires complex and expensive catalysts.[10] In addition, thiocarbamates synthesis has also been accomplished by selenium-catalyzed carbonylation of amine and disulfide.[11] Cyclic thiocarbamates can be obtained from the reaction of amino thiols with carbon monoxide in the presence of selenium.[12]

A recent report disclosed the synthesis of thiocarbamates by a two-step approach making use of trichloroacetyl chloride, thiols, and amines.[13] Although this method proceeds in high yields, it posed the following problem: incorporating moisture-sensitive reaction which need cautious operations and applying significant excess of trichloroacetyl chloride and amines.



$$H_2Se + 1/2\ O_2 \longrightarrow Se + H_2O \quad (2)$$

Herein, we describe a new and facile one-pot approach to thiocarbamates. Mediated by stoichiometric selenium, aniline reacts very readily with thiols in the presence of triethylamine at ambient temperature under atmospheric pressure of carbon monoxide, to afford the corresponding thiocarbamates and hydrogen selenide (Eq 1). Selenium can be easily recovered by oxidizing hydrogen selenide in the open air (Eq 2) and can be recycled.

In order to find the optimal experimental conditions, the reaction of aniline with propanethiol was examined. All reagents were used directly without further purification. In the absence of selenium or triethylamine, the reaction couldn't proceed at all. Other bases commonly used such as organic bases pyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and inorganic bases sodium acetate, sodium hydroxide and potassium hydroxide did not work (Table 1, Entries 2–6). The reaction was conducted at ambient temperature, for the higher the temperature, the more the side-product diphenylurea (Table 1, Entries 7–9). The reaction proceeded well without solvent, reaching completion within 10 h. The desired product phenylthiocarbamic acid *S*-propyl ester was obtained in high yield in addition to a little side-product diphenylurea. Selenium can be easily recovered from the reaction mixture by simple filtration after its precipitation. The product was purified either by column chromatography or by recrystallization from light petroleum ether.[14]

To demonstrate the scope and efficiency of the present method, a variety of thiols were tested under the optimal conditions and the results were summarized in Table 2. As shown in Table 2, the reaction is amenable to a range of thiols. For straight chain thiols, the reaction proceeded well to give the corresponding thiocarbamates in high yields (Entries 1, 2, 4, 6, 7). Phenylthiocarbamic acid *S*-benzyl ester (**2i**) was obtained in excellent yields (Entry 9). Steric factors seemed to explain the lower yields of thiocarbamates with branch components (Entries 3,

Table 1. The influence of base and temperature on the carbonylation of aniline to thiocarbamates[a]

Entry	Base	Temp.	Yield[b]/%
1	None	Ambient Temp.	0
2	Pyridine	Ambient Temp.	0
3	DBU	Ambient Temp.	0
4	NaOAc	Ambient Temp.	0
5	NaOH	Ambient Temp.	0
6	KOH	Ambient Temp.	0
7	Et$_3$N	Ambient Temp.	86(6)[c]
8	Et$_3$N	30 °C	77(15)[c]
9	Et$_3$N	70 °C	36(57)[c]

[a]Reaction conditions: aniline, 5 mmol; propanethiol, 5 mmol; Se, 5 mmol; base, 10 mmol; 10 h; atmospheric pressure of carbon monoxide. [b]Isolated yield. [c]Diphenylurea.

Table 2. Isolated yields of thiocarbamate using aniline as one of the reactants[a]

Entry	Thiol	R	Product	Yield/%
1	**1a**	Ethyl	**2a**	86
2	**1b**	Propyl	**2b**	86
3	**1c**	Isopropyl	**2c**	64
4	**1d**	Butyl	**2d**	83
5	**1e**	*tert*-Butyl	**2e**	17
6	**1f**	Pentyl	**2f**	83
7	**1g**	Hexyl	**2g**	83
8	**1h**	Cyclohexyl	**2h**	74
9[b]	**1i**	Benzyl	**2i**	90
10	**1j**	Phenyl	**2**	31
11[c]	**1k**	4-Chlorophenyl	**2k**	22
12	**1l**	4-Methylphenyl	**2l**	40
13	**1m**	4-Methoxyphenyl	**2m**	53

[a]Reaction conditions: aniline, 5 mmol; thiol, 5 mmol; Se, 5 mmol; Et$_3$N, 10 mmol; 10 h; ambient temperature; atmospheric pressure of carbon monoxide. [b]8 h. [c]2 mL acetone.

5, 8). When aryl thiols were used instead of alkyl thiols in the reactions, poor yields were obtained (Entries 10–13). This is mostly due to the weak nucleophilicity of aryl thiols. Electric effect of aryl thiols seemed to affect the reaction observably. The aryl thiol bearing electron-donating group is more reactive than that with electron-withdrawing group, resulting in the higher product yield of the former (Entry 13, **1m**) than the latter (Entry 11, **1k**).

Recycling of selenium was carried out by filtration of catalyst from the crude reaction mixture followed by drying it. Using the reaction of aniline with propanethiol as an example, the reusability of the catalyst was tested and the product yield only dropped from 86 to 78% after five recycles.

In summary, we have developed a new and facile one-pot approach to thiocarbamates. Using straight or less hindered alkyl thiols as thiol reactant, this reaction can proceed well with aniline to thiocarbamates in high yields. Simple starting materials, cheap and recyclable selenium, one-pot synthesis, mild reaction conditions, simple operation of the reaction, and simple purification of the products make the present method very significant from the view point of application.

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14 Typical experimental procedure is as follows (Table 2, Entry 2): To a 500-mL three-neck round-bottom flask, selenium (5 mmol), aniline (5 mmol), propanethiol (5 mmol), and triethylamine (10 mmol) were added. The reactor was sealed, and then vacuumized. Then carbon monoxide was introduced to it. The reactor was then connectted with atmospheric pressure of carbon monoxide. The reaction proceeded at ambient temperature with stirring. After 10 h, the apparatus was placed in the open air. The crude product was then dissolved in THF and stirred for another 30 min to precipitate selenium. Selenium was then recovered by filtration. The filtrate was concentrated. The pure phenylthiocarbamic acid *S*-propyl ester (2b) was obtained either by column chromatography (silica gel, chloroform/petroleum ether, 2/1) in 86% yield or by recrystallization from light petroleum ether in 73% yield as colorless needles. mp: 83–84 °C (lit.[15] mp: 84 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42–7.07 (m,6H), 2.95 (t, $J = 8.0$ Hz, 2H), 1.68 (sextet, $J = 8.0$ Hz, 2H), 0.99 (t, $J = 8.0$ Hz, 3H).

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Published on the web (Advance View) March 19, 2005; DOI 10.1246/cl.2005.606