

# Straightforward and Highly Efficient Catalyst-Free One-Pot Synthesis of Dithiocarbamates under Solvent-Free Conditions

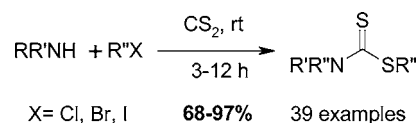
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## ABSTRACT



A highly efficient and simple synthesis of dithiocarbamates is possible based on the one-pot reaction of amines, CS<sub>2</sub>, and alkyl halides without using a catalyst under solvent-free conditions. The mild reaction conditions, high yields, and broad scope of the reaction illustrate the good synthetic utility of this method. The reaction is a highly atom-economic process for production of S-alkyl thiocarbamates and successfully can be used in high quantities in the pharmaceutical or agrochemical industries.

During the last few decades, a central objective in synthetic organic chemistry has been to develop greener and more economically competitive processes for the efficient synthesis of biologically active compounds with potential application in the pharmaceutical or agrochemical industries. In this context, the solventless approach is simple with amazing versatility. It reduces the use of organic solvents and minimizes the formation of other waste. The reactions occur under mild conditions and usually require easier workup procedures and simpler equipment. Moreover, it may allow access to compounds that require harsh reaction conditions under traditional approaches or when the yields are too low to be of practical convenience.<sup>1</sup>

Dithiocarbamates have received considerable attention due to their numerous biological activities<sup>2</sup> and their pivotal role in agriculture<sup>3</sup> and as linkers in solid-phase organic synthesis.<sup>4</sup> They are also used in the rubber industry as vulcani-

sation accelerators<sup>5</sup> and in controlled radical polymerization techniques.<sup>6</sup> Because they have a strong metal binding capacity, they also can act as inhibitors of enzymes and have a

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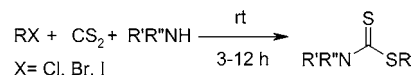
profound effect on biological systems. Dithiocarbamates are also widely used in medicinal chemistry and have found application in the treatment of cancer.<sup>7</sup> Furthermore, dithiocarbamates are versatile classes of ligands with the ability to stabilize transition metals in a wide range of oxidation states.<sup>8</sup>

Dithiocarbamates have a wide range of uses and applications and are produced in great quantities throughout the world. Therefore, the synthesis of this type of molecule has received considerable attention. General methods for their synthesis involve the reaction of an amine with costly and toxic reagents, such as thiophosgene and/or an isothiocyanate.<sup>9</sup> Furthermore, a one-pot reaction of amines with carbonyl sulfide and alkyl halides in organic solvent in the presence of a catalyst also has been developed.<sup>10</sup> However, there are several disadvantages to these methods: many isothiocyanates are hazardous and tedious to prepare and display poor long-term stability with the formation of side products such as urethane in alcoholic media. Such intermediates also require high reaction temperatures, give low or moderate yields of products, and usually entail multistep procedures. Furthermore, these reactions require very toxic reagents and harmful organic solvents such as DMF and DMSO in the presence of a catalyst.

During the course of a study aimed at improving the eco-compatibility of certain organic processes, we evaluated the possibility of performing these organic transformations under solvent-free conditions,<sup>11</sup> so as to develop environmentally benign reactions.<sup>12</sup> Herein, we now describe an efficient, novel, and highly simple procedure for the direct synthesis of thiocarbamates from the one-pot reaction of amines, CS<sub>2</sub>, and alkyl halides, without the use of any catalyst and under solvent-free conditions at room temperature (Scheme 1).

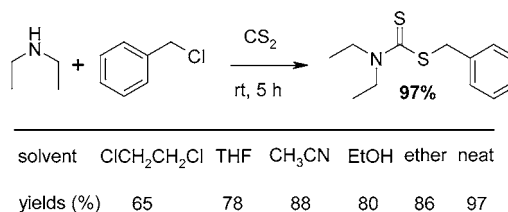
The starting point for our experiments was to optimize the reaction conditions for the large-scale industrial production of *S*-alkyl dithiocarbamates which are used as herbicides, insecticides, and fungicides and produced in large quantities around the world. Thus, after surveying different reaction conditions, it was found that upon simple mixing of diethylamine (6 mmol), CS<sub>2</sub> (6 mmol), and benzyl chloride

**Scheme 1.** One-Pot Synthesis of *S*-Alkyl Dithiocarbamates



(3 mmol) quantitative conversion to *S*-alkyl dithiocarbamate **7** was observed with excellent yields. The reaction was also carried out in organic solvents, such as ClCH<sub>2</sub>CH<sub>2</sub>Cl, THF, diethyl ether, CH<sub>3</sub>CN, and ethanol, for comparison. As shown in Scheme 2, good yields of product were also formed in

**Scheme 2.** Screening of Solvents<sup>a</sup>



<sup>a</sup> Reaction conditions: solvent (4 mL), amine (6 mmol), CS<sub>2</sub> (6 mmol), and benzyl chloride (3 mmol).

organic solvents such as CH<sub>3</sub>CN and THF after 5 h. However, we observed that under solvent-free conditions at room temperature the one-pot reaction proceeded to completion, affording the *S*-alkyl thiocarbamate in excellent yield without the use of any catalyst.

Next, the scope and limitation of this simple process were explored by using a wide range of alkyl halides and amines. A variety of structurally diverse amines and alkyl halides, including chloride, bromide, and iodide, underwent the one-pot reaction smoothly without using any catalyst or solvent to afford the corresponding *S*-alkyl dithiocarbamate derivatives in good to high yields. The results are summarized in Table 1.

The generality of the present method was also extended to amine components. Primary, allylic, benzylic, hindered, and unhindered secondary and tertiary alkyl primary amines were used in this protocol with excellent results. However, aromatic amines did not participate in the reaction. The reactions were completed after 3–12 h affording 68–97% yields. Commercially available alkyl halides and amines were used under the same reaction conditions for both reactive and unreactive alkyl halides and amines. Thus, a diverse set of synthetically useful dithiocarbamate products can potentially be prepared in one step by this method.

Generally, the solvent-free reaction is experimentally simple, proceeds well without any catalyst, and generates virtually no byproducts. Equally important is the wide scope, high selectivity, and nearly quantitative yields of this transformation, which collectively allow significant structural diversity to be incorporated into the products, many of which could not be obtained via the older procedures. Furthermore, all the reactions performed here involved stirred homogeneous liquids. As the reaction proceeds, the mixture solidifies

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**Table 1.** One-Pot Synthesis of *S*-Alkyl Dithiocarbamates without a Catalyst under Solvent-Free Conditions<sup>a</sup>

RX + CS <sub>2</sub> + R'R''NH $\xrightarrow{rt}$ R'R''N=C(S)SR 1-39									
entry	amine	halide	product	yield (%)	entry	amine	halide	product	yield (%)
1		Ph-CH <sub>2</sub> -Cl	<b>1</b>	95	21	Ph-NH <sub>2</sub>	CH <sub>3</sub> -I	<b>21</b>	82
2			<b>2</b>	95	22		Ph-CH <sub>2</sub> -Cl	<b>22</b>	76
3		CH <sub>2</sub> =CH-Cl	<b>3</b>	76	23		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -Br	<b>23</b>	75
4		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -Br	<b>4</b>	94	24		CH <sub>3</sub> -I	<b>24</b>	80
5		CH <sub>3</sub> -I	<b>5</b>	97	25	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	Ph-CH <sub>2</sub> -Cl	<b>25</b>	82
6		CH <sub>3</sub> -I	<b>6</b>	97	26	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -Br	<b>26</b>	78
7	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	Ph-CH <sub>2</sub> -Cl	<b>7</b>	97	27	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	CH <sub>3</sub> -I	<b>27</b>	80
8			<b>8</b>	90	28		Ph-CH <sub>2</sub> -Cl	<b>28</b>	97
9	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	CH <sub>2</sub> =CH-Cl	<b>9</b>	74	29			<b>29</b>	92
10	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -Br	<b>10</b>	92	30		CH <sub>2</sub> =CH-Cl	<b>30</b>	76
11			<b>11</b>	76	31		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -Br	<b>31</b>	86
12	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	CH <sub>3</sub> -I	<b>12</b>	98	32			<b>32</b>	78
13	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	CH <sub>3</sub> -I	<b>13</b>	98	33		CH <sub>3</sub> -I	<b>33</b>	97
14		Ph-CH <sub>2</sub> -Cl	<b>14</b>	82	34		CH <sub>3</sub> -I	<b>34</b>	97
15		CH <sub>3</sub> -I	<b>15</b>	86	35		Br-CH <sub>2</sub> -C(=O)OMe	<b>35</b>	80
16		Ph-CH <sub>2</sub> -Cl	<b>16</b>	80	36		CH <sub>2</sub> =CH-Cl	<b>36</b>	68
17		CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -Br	<b>17</b>	78	37		Br-CH <sub>2</sub> -C(=O)OMe	<b>37</b>	76
18		CH <sub>3</sub> -I	<b>18</b>	82	38		CH <sub>2</sub> =CH-Cl	<b>38</b>	70
19	Ph-CH <sub>2</sub> -NH <sub>2</sub>	Ph-CH <sub>2</sub> -Cl	<b>19</b>	78	39		Br-CH <sub>2</sub> -C(=O)OMe	<b>39</b>	82
20	Ph-CH <sub>2</sub> -NH <sub>2</sub>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> -Br	<b>20</b>	80					

<sup>a</sup> Reaction conditions: For a detailed experimental operation, see Supporting Information. Amine (6 mmol), CS<sub>2</sub> (6 mmol), alkyl halide (3 mmol), rt. Isolated yields are based on the alkyl halide.

as the product is formed. Because the reactions are run neat and there are no side products in some cases, the pure products are isolated by simple extraction. All compounds gave satisfactory NMR spectra (see Supporting Information).

In conclusion, we have developed the most practical and reliable procedure currently available for the synthesis of a wide range of *S*-alkyl dithiocarbamates by using inexpensive and readily available starting materials in one pot. This method represents a simple and green procedure, uses mild reaction conditions, and has general applicability. It avoids hazardous organic solvents and toxic catalysts and gives nearly quantitative yields without any byproducts in most cases. In addition, this procedure can be performed on a multigram scale under operationally simple and environmentally safe conditions which could potentially prove useful

for the large-scale industrial production of certain herbicides and other commercial dithiocarbamate drugs. Our procedure also opens a new route for the assembly of complex products from simple starting materials with potential applications in combinatorial chemistry. Further exploitation of this methodology is currently underway in our laboratories.

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**Supporting Information Available:** General experimental details and spectral data (<sup>1</sup>H and <sup>13</sup>C NMR) of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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