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Phosphorus Pentasulfide Mediated Conversion of Primary Carbamates into Thiols

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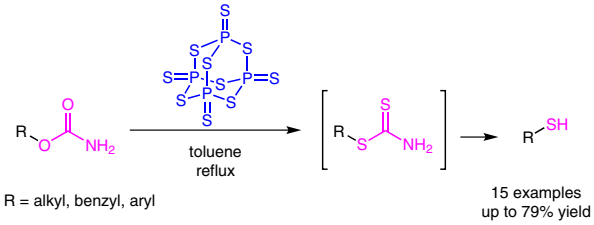

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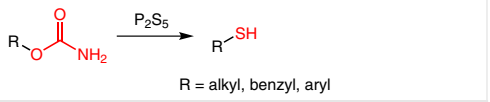
Abstract In this paper, we report a method for the conversion of primary carbamates into thiols in the presence of phosphorus pentasulfide (P_2S_5) in refluxing toluene. Presently, no method exists in the literature for conversion of carbamates into thiols and, to the best of our knowledge, it is the first report for this type of conversion. This method presents an indirect route for the conversion of alcohols into thiols via their carbamate derivatives that may be useful in the total synthesis of compounds containing a thiol functionality.

Key words carbamate, phosphorus pentasulfide, thiocarbamate, dithiocarbamate, thiol

Thiols constitute an important group of sulfur-containing compounds. Thiols have a distinct odor and are often used as gas odorants in industrial applications.[1] They occur naturally as flavouring compounds in several fruits and spices[2] and are found in a variety of enzymes at their active sites.[3] Thiols are produced naturally by the wood-pulping industry, manure and sewer systems,[4] and by the breakdown of sulfur-containing amino acids and lignin.[5] For the laboratory synthesis of thiols, various methods utilizing alcohols, alkyl halides, alkenes as substrate have been reported.[6] However, the immense importance of thiols still leaves scope for further investigations in this area and, in this context, we herein describe a new and efficient method for the preparation of thiols from primary carbamates. During our efforts in thionating the carbamates with P_2S_5, by analogy with the thionation of carbonyl compounds, we found that the reaction, instead of furnishing the desired thiocarbamates, gave the corresponding thiols. An extensive literature survey revealed that no synthetic method has been reported for conversion of carbamates into the corresponding thiols. Phosphorus pentasulfide (P_2S_5), a commercially available reagent, has widely been employed in organic synthesis for numerous applications.[7] The synthetic protocol described in this paper makes use of this reagent to provide an efficient and single-step procedure for the direct conversion of carbamates into thiols (Scheme 1).

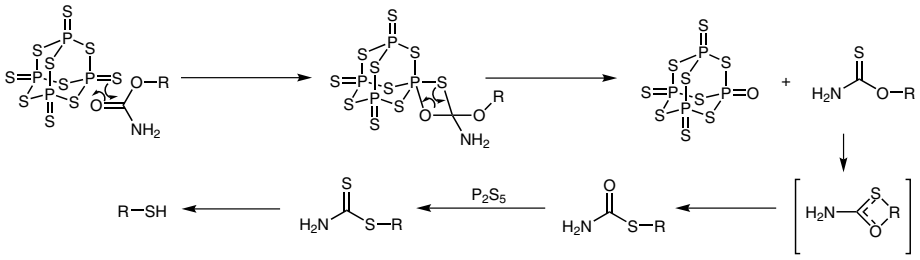


Scheme 1 Conversion of primary carbamate into thiol

Initially, for the reaction optimization, benzyl carbamate (Scheme 1, R = Bn) was chosen as the model substrate and reacted with P_2S_5 in different organic solvents (Table 1). Although, the reaction proceeded in a range of solvents including benzene, toluene, THF, and dichloromethane, the best results in terms of reaction time and yields were obtained in toluene. It was also observed that substoichiometric amounts of reagent and reaction at room temperature resulted in low product yield or incomplete reaction. In fact, an excess of thionating reagent at refluxing temperature was required for reaction completion. Importantly, the re-

Table 1 Effect of Reaction Medium and Reagents on Conversion of Benzyl Carbamate into Benzyl Thiol

Entry	Solvent	Reagent	Time (h)	Yield (%)
1	THF	P_2S_5	2.5	35
2	CH_2Cl_2	P_2S_5	2.5	30
3	benzene	P_2S_5	3.0	45
4	toluene	P_2S_5	3.0	75
5	toluene	Lawesson's reagent	4.0	–
6	toluene	$PSCl_3$	4.0	–



Scheme 2 Plausible mechanism for reaction between carbamate and P_2S_5

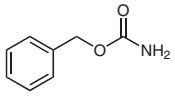
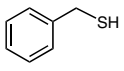
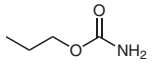
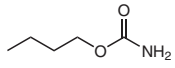
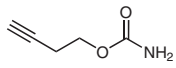
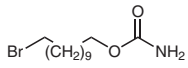
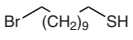
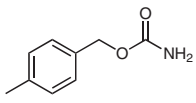
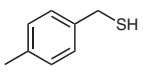
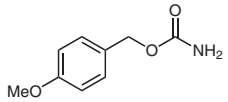
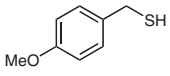
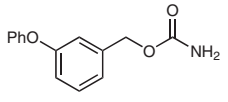
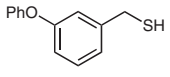
action gave the thiol as the major product with no disulfide formation. Interestingly, no reaction of the carbamate was observed with other thionating agents such Lawesson's reagent and $PSCl_3$ and, in those cases, starting material was recovered.

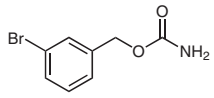
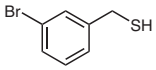
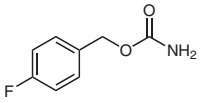
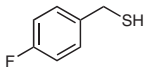
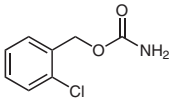
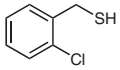
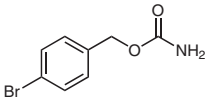
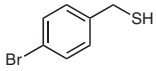
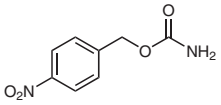
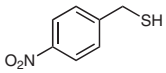
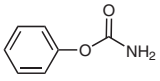
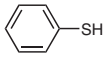
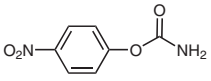
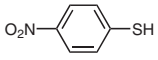
To study the scope and limitations of this conversion, a variety of carbamates (Scheme 2, Table 2) were treated with P_2S_5 in refluxing toluene to yield the corresponding thiols in good to moderate yields. The results indicate that the reaction rates were more susceptible to substituent effect in comparison to the product yields. Simple short-chain carbamates reacted rapidly to give the corresponding thiols. Increasing the alkyl chain length decreased both rate and yield of the reaction (Table 2, entries 2 vs. 5), presumably due to steric effects. In comparison to the alkyl substrates, the benzyl derivative reacted sluggishly possibly due to steric hindrance by the benzene ring and this was further evident by the longer reaction time required by 3-phenoxybenzyl carbamate (Table 2, entry 8). In the case of benzyl carbamates, the presence of electron-donating groups such as methyl and methoxy groups on the phenyl ring (Table 2, entries 6 and 7) caused reaction-rate acceleration while electron-withdrawing halogen substituents diminished the rate of reaction. Aryl carbamates were also suitable substrates and gave the corresponding thiols in good yields.

A possible mechanism for reaction between carbamate and P_2S_5 is proposed to involve initial thionation of the carbamate carbonyl group to give the corresponding *O*-thiocarbamate that subsequently undergoes Newman–Kwart rearrangement to the corresponding *S*-thiocarbamate.[8] Further thionation of the latter with P_2S_5 gives a dithiocarbamate derivative[9] that, in the presence of acid, decomposes to give the corresponding thiol. To support the intermediacy of the *S*-thiocarbamate in the reaction, benzyl *S*-thiocarbamate was separately synthesized and reacted with P_2S_5 in refluxing toluene to form the corresponding thiol. Furthermore, involvement of the dithiocarbamate was indicated indirectly by treating the thiocyanate with P_2S_5 in refluxing toluene to obtain the thiol. It is thought that the thiocyanate, by analogy with the thionation of nitriles to thioamides with P_2S_5,[10] will also furnish the dithiocarbamate that will ultimately give the corresponding thiol through acid-mediated cleavage. Additionally, *S*-thiocarbamates are also known to undergo acid-mediated cleavage to thiols.[11] Hence, the thiols could be formed by the acid-mediated cleavage of both *S*-thiocarbamate and dithiocarbamate intermediates.

In summary, the method described in this paper presents an efficient and direct route for the conversion of primary carbamates into thiols.[12] In this way, it provides an alternate route for converting alcohols into the thiols through their carbamate derivatives.

Table 2 Conversion of Carbamates into Thiols with P_2S_5[a]

Entry	Reactant	Time (h)	Product	Yield (%)[b]
1		3		75
2		2		78
3		2		76
4		2		72
5		3		71
6		2.5		77
7		2.25		79
8		8		74

Entry	Reactant	Time (h)	Product	Yield (%)[b]
9		5		71
10		4.5		72
11		6		72
12		5		71
13		4.5		73
14		4		69
15		4		67

[a] Reaction conditions: carbamate (10 mmol), P_2S_5 (15 mmol), toluene (25 mL).[10]
[b] Known compounds were identified by comparison with authentic thiols.

Acknowledgment

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References and Notes

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(12) **Conversion of Carbamate into Thiol – Typical Procedure**
In a three-neck round-bottom flask, to a solution of carbamate (10 mmol) in toluene (25 mL), P_2S_5 (3.33 g, 15 mmol) was added, and the resulting suspension was heated to reflux until complete consumption of the starting material (TLC). After the reaction was complete, the reaction mixture was quenched by careful addition of water (10 mL), extracted with EtOAc (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to obtain the crude product that was purified by flash chromatography (hexane–EtOAc) to give the pure thiol.
3-Phenoxybenzyl Thiol
Oil, yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.34 (m, 3 H), 6.87–7.10 (m, 6 H), 3.87 (d, $^3J_{H-H}$ = 4.0 Hz, 2 H), 1.75 (t, $^3J_{H-H}$ = 4.0 Hz, 1 H). ^{13}CNMR (100 MHz, $CDCl_3$): δ = 28.70, 117.29, 118.34, 119.01, 122.77, 123.37, 129.76, 129.92, 143.11, 156.94, 157.50. ESI-HRMS: *m/z* calcd for $C_{13}H_{12}OS$ [M + Na]$^+$: 239.0609; found: 239.0611