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Convenient synthesis of carbamates, *S*-alkyl thiocarbamates, and *N,N′*-disubstituted urea derivatives of methoxycarbonylsulfenyl isocyanate

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ABSTRACT

Convenient simple and suitable methods for the synthesis of carbamates, *N,N′*-unsymmetrically disubstituted ureas, and *S*-alkyl thiocarbamates derived from $CH_3OC(O)SNCO$ in one-step are provided. Reactions are operationally simple and have high selectivity toward nitrogen, oxygen, and sulfur nucleophiles. The absence of solvents coupled with high yields and short reaction times make these procedures very attractive for synthesis.

The chemistry of isocyanates has been thoroughly covered in review articles.[1,2] The reactions of isocyanates with active hydrogen compounds involve attack by a nucleophile at the electrophilic carbon of the isocyanate.[1] The reaction of isocyanates with compounds containing nitrogen—hydrogen bonds is governed primarily by the basicity or nucleophilicity of the N—H bond and yields urea derivatives.[3] Reactions of isocyanates with compounds containing an O—H bond represent one of the most important areas of isocyanate chemistry.[4–6] Thus, organic carbamates are a class of compounds that has received special attention because of their multiple applications as protecting groups for amine functions in amino acids in peptide chemistry.[7] In addition, they play an important role in the synthesis of pharmaceuticals, agricultural chemicals, and in the chemical industry.[8,9] It is also known that the thiol group reacts in the same way as its oxygen analog, except that it is less reactive.[10] Thus, condensation of a thiol with an isocyanate affords the corresponding thiocarbamate.[11] *S*-alkyl thiocarbamates have received considerable attention in the literature mainly because they are potent herbicides[12,13] and due to their wide biological effects[14] with anesthetic,[15] bactericidal,[11] pesticidal, and antiviral activities.[1,16–22]

In the present work, we describe the reactivity of the recently synthesized methoxycarbonylsulfenyl isocyanate, $CH_3OC(O)SNCO$,[1,23] toward addition reactions with alcohols, amines and thiols (see Scheme 1). The synthesis of novel carbamate, urea, and *S*-alkyl thiocarbamate derivatives is achieved in a simple way without the use of solvents.

Synthesis of carbamates

Large-scale synthesis of carbamates involves either the reaction of urea with an alcohol, or the amination of an alkyl chloroformate or the transesterification of an alkyl carbamate with a higher boiling alcohol. However, these reactions require drastic conditions (e.g., high temperatures) or more than one-step.[24] Therefore, alternative synthetic methods were investigated.[25–27] For instance, Feroci et al. reported a synthesis of carbamates[28] via a cyanomethyl anion/carbon dioxide system, and Abbate et al. studied the catalytic reaction of *n*-butyl alcohol with isocyanates using organometallic derivatives,[29] and other catalytic processes based on alcohols and isocyanates were also reported.[2,30]

The reaction of **1** with alcohols (**2a–c**) involves the attack of the nucleophilic center (oxygen atom) at the electrophilic carbon of the isocyanate group. Reactions must be performed in anhydrous conditions because compound **1** reacts readily with water at ordinary temperatures, yielding 1,3-disubstituted urea and carbon dioxide.[31,32] The corresponding carbamate derivatives **3a–c** can be obtained in high yields (93–98%) as can be seen in Table 1. Primary alcohols **2a,b** react expeditiously with compound **1**. However, the faster rate is more difficult to control and can lead to by-products. The reaction runs more cleanly with tertiary alcohols offering the best yields for **3c**.

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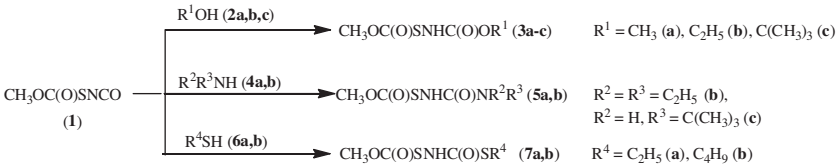

Scheme 1. General reaction scheme for addition reactions of methoxycarbonylsulfenyl isocyanate with alcohols, amines, and thiols.

Table 1
Optimized conditions for the addition reactions of $CH_3OC(O)SNCO$ with alcohols (**2a–c**), amines (**4a**,**b**), and thiols (**6a**,**b**)

Nucleophile	Temperature (°C)	Time (min)	Product	Yield (%)[a]
2a	−20	60	**3a**	93
2b	−20	60	**3b**	95
2c	−20	90	**3c**	98
4a	−60	60	**5a**	80
4b	−60	30	**5b**	85
6a	−60	60	**7a**	85
6b	−50	60	**7b**	90

[a] Overall yield from reactions shown in the Scheme 1 based on GC–MS analysis.

Synthesis of *N,N′*-unsymmetrically disubstituted ureas

Preparation methods for the synthesis of ureas have been extensively developed. The general procedures for the synthesis of unsymmetrical ureas involve the reaction of isocyanates with primary or secondary amines.[2] Well-known alternative methods for the preparation of unsymmetrical ureas are based on chloroformate derivatives.[33,34] More recently, the synthesis of symmetrical ureas by oxidative carbonylation of amines by means of carbon monoxide and a transition-metal catalyst was reported.[35–38] In general, all previously reported methods for preparing *N,N′*-disubstituted ureas require the preparation of reagents, long reaction time, use of large excess of reagents and usually drastic conditions.

Avoiding organic solvents during the reactions, compound **1** reacts with different aliphatic amines yielding *N,N′*-unsymmetrically disubstituted ureas (**5a,b**) in relatively high yields (80–85%). The reaction with the amine is exothermic and the temperature must be lowered in order to obtain the addition product. The condition that furnished the best yields of product **5a** uses an equimolar mixture of amine and isocyanate at low temperatures (−60 °C).

Synthesis of *S*-alkyl thiocarbamates

There are several suitable methods for the preparation of *S*-alkyl thiocarbamates.[16,39,40] The reaction of an amine with phosgene and a thiol or with carbonyl sulfide followed by alkylation[41] with alkyl halides has been well known as the general synthetic method.[21,42,43] Here, novel *S*-alkyl thiocarbamates were obtained in high yield from **1** and different aliphatic thiols (Scheme 1). The reaction conditions that provided the best yields of product **7a** use a 1:1 ratio of thiol and isocyanate **1**, respectively. The reaction mixture was kept with stirring at temperatures near −60 °C for usually not more than 30 min, followed by slow warm-up to room temperature. The products, *S*-alkyl *N*-substituted thiocarbamates **7a,b**, were obtained in high yields (85–90%), as shown in Table 1.

In summary, convenient one-pot procedures for the synthesis of carbamates, *N,N′*-methoxycarbonyl disubstituted ureas, and *S*-alkyl thiocarbamates utilizing commercially available reagents are provided. Reactions are operationally simple, offer high yields, short reaction times, and high selectivity toward nitrogen, oxygen, and sulfur nucleophiles. The higher yield of carbamate with a tertiary alcohol suggests that primary alcohols are more reactive in nucleophilic additions than tertiary alcohols.[30]

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Supplementary data

Supplementary data: experimental procedures and product characterization (^{1}H NMR, ^{13}C{^{1}H} NMR and FTIR spectra) for compounds **3a–c**, **5a,b** and **7a,b** associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.027.

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