ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Straightforward and Highly Efficient Synthesis of Diselenocarbamates

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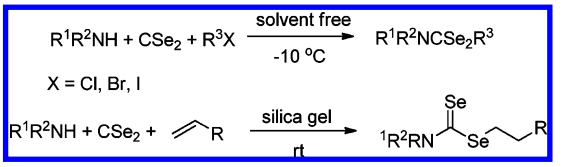
Received October 17, 2012

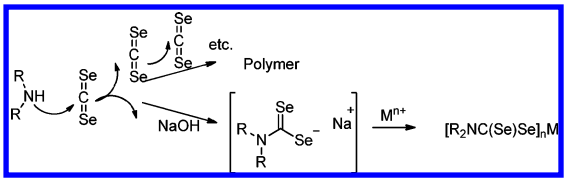
ABSTRACT



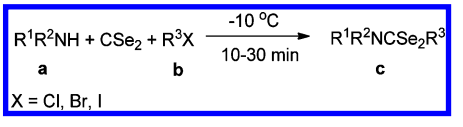
A highly efficient and simple synthesis of diselenocarbamates, based on a one-pot reaction of amines, CSe_2, and alkyl halides in the absence of a catalyst under solvent-free conditions, is reported. The first efficient synthesis of diselenocarbamates via Michael addition of electron-deficient alkenes with aliphatic amines and CSe_2 in solid media silica gel is also presented.

During the last few decades, many syntheses of compounds containing selenium have been reported because of their interesting reactivity and potential biological activity.[1] The biological and pharmacological activity of selenium and organoselenium compounds are of increasing interest because of their antioxidant, antitumor, and antiviral properties.[2] The selenium compounds have also shown the ability to control the free-radical polymerization of vinyl monomers.[3] A number of methods for the synthesis of organoselenium compounds have been published in the literature.[4] Among the organoselenium compounds, diselenocarbamates have received less attention,[5] and the synthesis of diselenocarbamates has rarely been reported. General methods for their synthesis involve the reaction of an amine with isoselenocyanate[6] or the reaction of *N*,*N*-dimethylselenocarbamoyl chloride with lithium alkylselenolate.[7]

Scheme 1. Reaction of Amines and CSe_2



Scheme 2. One-Pot Synthesis of *Se*-Alkyl Diselenocarbamates



(1) (a) Jensen, K. A.; Kjaer, A. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1987; Vol. 1, pp 13. (b) Klayman, D. L.; Shine, R. J. *J. Org. Chem.* **1969**, *34*, 3549. (c) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373. (d) Li, G. M.; Zingaro, R. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 647. (e) Koketsu, M.; Suzuki, N.; Ishihara, H. *J. Org. Chem.* **1999**, *64*, 6473.

(2) (a) Mugesh, G.; Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255. (c) Mukherjee, A. J.; Zade, S. S.; Singh, H. B.; Sunoj, R. B. *Chem. Rev.* **2010**, *110*, 4357.

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(4) (a) Perin, G.; Lenardão, E. J.; Jacob, R. G.; Panatieri, R. B. *Chem. Rev.* **2009**, *109*, 1277. (b) Murai, T.; Kato, S. In *Organoselenium Chemistry. Modern Developments in Organic Synthesis*; Springer-Verlag: New York, 2000; p 177.

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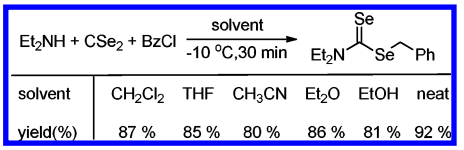
10.1021/ol3028626

Carbon diselenide can be used as the key reagent for the synthesis of diselenocarbamates[5] but is rarely mentioned in the literature. Carbon diselenide can polymerize in the presence of amines,[5a] and some transition-metal diselenocarbamate complex can be prepared by the reaction of carbon diselenide (CSe_2) with secondary amines and metal salts (Scheme 1).[5b] However, the efficient synthesis of diselenocarbamates from CSe_2 has rarely been described.[5c]

During the course of a study aimed at improving the ecocompatibility of certain organic processes, some organic transformations under solvent-free conditions were performed to develop environmentally benign reactions.[8] Herein, an efficient, novel, and highly simple procedure for the direct synthesis of diselenocarbamates from a one-pot reaction of simple compounds (e.g., amines, CSe_2, and alkyl halides) without the use of a catalyst and under solvent-free conditions at low temperature is described (Scheme 2).

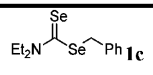
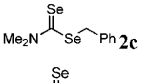
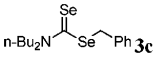
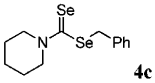
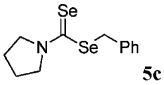
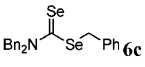
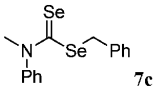
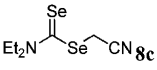
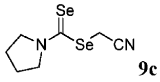
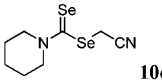
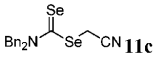
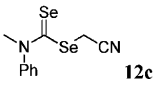
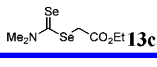
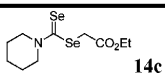
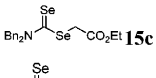
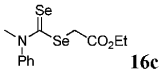
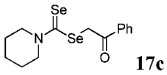
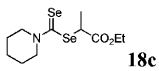
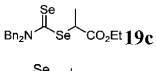
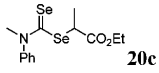
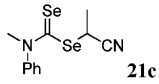
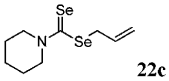
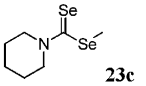
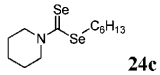
In our approach, CSe_2 was prepared by reaction of Se with an excess of CH_2Cl_2 according to a previously published protocol.[9] First, the treatment of CSe_2 (1 mmol) and benzyl chloride (1 mmol) with diethylamine (2 mmol)

Scheme 3. Screening of Solvents



solvent	CH_2Cl_2	THF	CH_3CN	Et_2O	EtOH	neat
yield(%)	87 %	85 %	80 %	86 %	81 %	92 %

Table 1. One-Pot Synthesis of *Se*-Alkyl Diselenocarbamates without a Catalyst under Solvent-Free Conditions[a]

entry	amine	halide	product	yield (%)
1	Et_2NH	$PhCH_2Cl$	 **1c**	92
2	Me_2NH	$PhCH_2Br$	 **2c**	90
3	*n*-Bu_2NH	$PhCH_2Cl$	 **3c**	90
4	Piperidine	$PhCH_2Br$	 **4c**	85
5	Pyrrolidine	$PhCH_2Br$	 **5c**	88
6	$(PhCH_2)_2NH$	$PhCH_2Br$	 **6c**	86
7	$PhNHCH_3$	$PhCH_2Br$	 **7c**	82
8	Et_2NH	Br CN	 **8c**	85
9	Pyrrolidine	Br CN	 **9c**	89
10	Piperidine	Br CN	 **10c**	80
11	$(PhCH_2)_2NH$	Br CN	 **11c**	81
12	$PhNHCH_3$	Br CN	 **12c**	78
13	Me_2NH	Br CO_2Et	 **13c**	90
14	Piperidine	Br CO_2Et	 **14c**	85
15	$(PhCH_2)_2NH$	Br CO_2Et	 **15c**	95
16	$PhNHCH_3$	Br CO_2Et	 **16c**	92
17	Piperidine	Br Ph O	 **17c**	87
18	Piperidine	Br CO_2Et	 **18c**	75
19	$(PhCH_2)_2NH$	Br CO_2Et	 **19c**	72
20	$PhNHCH_3$	Br CO_2Et	 **20c**	76
21	$PhNHCH_3$	Br CN	 **21c**	75
22	Piperidine	Br	 **22c**	84
23	Piperidine	CH_3I	 **23c**	85
24	Piperidine	$C_6H_{13}Br$	 **24c**	81
25	Piperidine	Br CO_2Et	**complex**	-
26	$PhNH_2$	Br CN	**complex**	-

[a] Reaction conditions: amine (2 mmol), CSe_2 (1 mmol), alkyl halide (1 mmol), −10 °C. Isolated yields are based on the alkyl halide. For a detailed experimental procedure, see the Supporting Information.

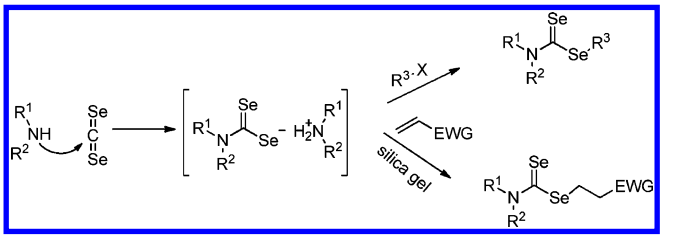
was examined (Table 1, entry 1). Surprisingly, the reaction occurred readily at −10 °C, and product **1c** was obtained in 92% yield after workup of the reaction mixture (Table 1, entry 1). The reaction was also performed in organic solvents, such as CH_2Cl_2, THF, diethyl ether, CH_3CN, and ethanol, for comparison. Moderate yields of the product were obtained in organic solvents, such as CH_3CN and CH_2Cl_2, after 30 min (Scheme 3). However, the best result was obtained from a one-pot reaction under solvent-free conditions at −10 °C affording the *Se*-alkyl diselenocarbamate in excellent yield without the use of a catalyst. The structure of **1c** was elucidated by ^{1}H NMR, ^{13}C NMR, and LCMS studies.

Next, the scope and limitations of this simple process were explored using a wide range of alkyl halides and secondary amines. A variety of structurally diverse amines and alkyl halides, including chloride, bromide, and iodide, were employed in the one-pot reaction in the absence of a catalyst or solvent to afford the corresponding *Se*-alkyl diselenocarbamate derivatives in moderate to high yields (higher than 72%). The results are summarized in Table 1. The generality of the present method was also extended to primary amines. However, unidentified side products were obtained in the reaction of aniline (Table 1, entry 26). Monosubstituted diselenocarbamate has been reported to be unstable and could decompose or undergo nucleophilic addition with another primary amine to afford selenourea or other byproducts.[10]

The reactions reached completion after 10−30 min with 72−95% yields. Commercially available alkyl halides and secondary amines were employed under the same conditions for both reactive and unreactive alkyl halides and amines. Therefore, a diverse set of synthetically useful diselencarbamate products can potentially be prepared in one step by this method. In this reaction, CSe_2 was first attacked by the secondary amine to yield the aminium diselenocarbamate, which converted directly to the diselenocarbamate derivatives with the alkyl halide (Scheme 4). The yield of this reaction was controlled by the steric hindrance in the alkyl halides, which decreased in the following order: primary alkyl halides > secondary alkyl halides, with tertiary alkyl halides yielding trace amounts of diselenocarbamate (Table 1, entry 25). Many of the synthesized diselenocarbamates are yellow solids and display good stability in the refrigerator but slowly decompose at room temperature.

To exploit the in situ generated aminium diselenocarbamate for other useful reactions, we explored a Michael-type addition to conjugated alkenes (Scheme 4).[11] First,

Scheme 4. Mechanism of the One-Pot Reaction



Scheme 5. Nucleophilic Addition of Aminium Diselenocarbamate to Michael Acceptors

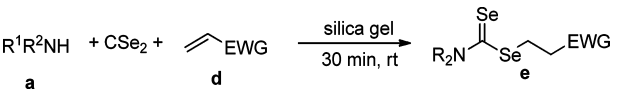
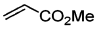
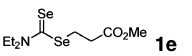
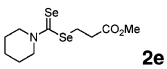
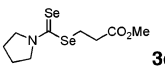
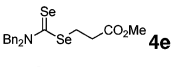
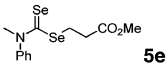
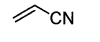
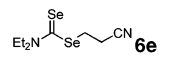
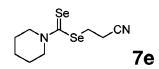
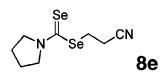
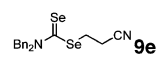
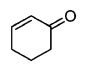
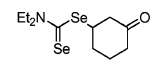
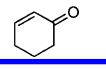
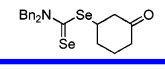


Table 2. One-Pot Synthesis of *Se*-Alkyl Diselenocarbamates under Solvent-Free Conditions[a]

entry	amine	michael acceptors	product	yield (%)
1	Et_2NH	 **1d**	 **1e**	91
2	Piperidine	**1d**	 **2e**	85
3	Pyrrolidine	**1d**	 **3e**	88
4	$(PhCH_2)_2NH$	**1d**	 **4e**	85
5	$PhNHCH_3$	**1d**	 **5e**	83
6	Et_2NH	 **2d**	 **6e**	89
7	Piperidine	**2d**	 **7e**	90
8	Pyrrolidine	**2d**	 **8e**	86
9	$(PhCH_2)_2NH$	**2d**	 **9e**	88
10	Et_2NH			0
11	$(PhCH_2)_2NH$			0

[a] Reaction conditions: amine (2 mmol), CSe_2 (1 mmol), Michael acceptors (1.5 mmol), rt. For a detailed experimental procedure, see the Supporting Information.

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(11) In ref 6, the Michael addition of diselenocarbamate intermediates was studied, and moderate yields were obtained in that reaction.

piperidine was reacted with CSe_2 and methyl acrylate to screen various media. After optimizing the conditions, silica gel exhibited the best result among the screened media, (i.e., silica gel, alkaline Al_2O_3, solvent-free and diverse solvents (CH_2Cl_2, CH_3CN, *n*-hexane, and water)).

With optimal conditions in hand, we examined the generality of these conditions to other substrates by using different amines and α,β-unsaturated compounds. The results are summarized in Table 2. All of the reactions proceeded smoothly under the optimized conditions by stirring all of the reagents together in the presence of silica gel. Using methyl acrylate and acrylonitrile as a Michael receptor, all of the tested aliphatic amines afforded the expected products with good to excellent yields (Table 2, entries 1−9). However, the reactions of primary amines cannot give good results due to the instability of the intermediates. When using substituted α,β-unsaturated compounds, such as cyclohexenone and chalcone, as Michael receptors, the addition reaction does not proceed effectively. The nucleophilicity of the diselenocarbamic anion and the steric hindrance of α,β-unsaturated compounds most likely played a role under these conditions.

In this reaction, the aminium diselenocarbamate is also the key intermediate which was first obtained in the reaction of CSe_2 with the amine and then underwent Michael-type addition to conjugated alkenes to afford the substituted diselenocarbamate. The amine might be absorbed on the surface of the silica gel, and the Lewis acid catalytic activity of silica gel could promote the nucleophilic addition of the intermediate to conjugated alkenes (Scheme 5).

In summary, we have developed a highly practical and reliable procedure for the synthesis of a wide range of diselenocarbamates using CSe_2 and readily available starting materials in one pot. In addition, the Michael-type addition of the aminium diselenocarbamate was reported. In general, the solvent-free reaction is experimentally simple 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; that was not possible via the previously published procedures. Our procedure provides a new route for the assembly of diselenocarbamates from simple starting materials. Further exploitation of this methodology is currently underway in our laboratories. The exploration of these compounds as mediators in the free-radical polymerization of vinyl monomers is also underway in our laboratories.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (No. 21074082), China Postdoctoral Science Foundation (No. 2012M511315), the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Natural Science Foundation of the Jiangsu Higher Education Institutions of China (No. 12KJB150021).

Supporting Information Available. General experimental details and spectral data (IR, ^1H NMR, ^{13}C NMR, LCMS) of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.