Tetrahedron Letters 52 (2011) 415–417

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of selenoureas and selenocarbamates via selenation of isocyanates with bis(dimethylaluminum) selenide

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ARTICLE INFO

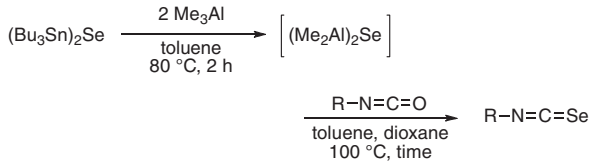
Article history:
Received 28 September 2010
Revised 10 November 2010
Accepted 15 November 2010
Available online 18 November 2010

ABSTRACT

Isocyanates were efficiently selenated by the reaction with bis(dimethylaluminum) selenide to give the corresponding isoselenocyanates. One-pot synthesis of unsymmetrical selenoureas and selenocarbamates was achieved in high yields by the subsequent addition of amines and alcoholates to the reaction mixture.

Recent advances of heteroatom chemistry enabled to design and synthesize various heteroatom-containing organic molecules. Among them, compounds having carbon-heteroatom double bonds play significant roles for organic syntheses as synthetic intermediates due to their high reactivities. We have developed a useful selenating reagent, bis(dimethylaluminum) selenide,[1] which can transform various carbonyl compounds and related compounds such as ketones,[2] aldehydes,[2b,c,3] amides,[4] and acetals,[5] directly to selenocarbonyl compounds in high yields. During the course of our study about the synthetic utility of the reagent, we found that direct conversion of isocyanates to isoselenocyanates could be achieved. Moreover, selenoureas and selenocarbamates were obtained in one-pot reactions by the subsequent trapping with amines and alcoholates without isolation of isoselenocyanates. Herein, the results of this study are described.

For the preparation of bis(dimethylaluminum) selenide, a hexane solution of trimethylaluminum (2.2 equiv) was added to a toluene solution of bis(tributylstannyl) selenide and stirred at 80 °C for 2 h (Scheme 1). White-suspended solution was obtained, that indicates the formation of bis(dimethylaluminum) selenide. After cooling to room temperature, 1,4-dioxane was added to give a clear homogeneous colorless solution. Addition of *n*-butyl isocyanate (1.2 equiv) and stirring at 100 °C for 3 h followed by aqueous workup gave a yellow residue. Purification by a silica gel column chromatography gave *n*-butyl isoselenocyanate in 86% isolated yield (Table 1, entry 1).[6] Reaction of cyclohexyl, *p*-chlorophenyl, and 1-naphthyl isocyanates also proceeded in a similar manner to give the corresponding isoselenocyanates in 90–95% isolated yields (entries 2–4).



Scheme 1. Synthesis of isoselenocyanates.

These successful results impelled us to examine the one-pot synthesis of unsymmetrical selenoureas without isolation of isoselenocyanates, by the addition of amines before aqueous workup (Scheme 2, Table 2). *p*-Chlorophenyl isoselenocyanate, generated in situ from *p*-chlorophenyl isocyanate and $(Me_2Al)_2Se$ under the conditions described above, was allowed to react with *n*-propylamine (2 equiv) at 70 °C for 0.5 h before aqueous workup to give *N*-*p*-chlorophenyl-*N*′-propylselenourea in 93% isolated yield (Table 2, entry 1). This synthetic method could be applied to the reaction with other primary and secondary amines (entries 2–6), and the reaction of 1-naphthyl (entries 7–11) and *n*-butyl isocyanates (entries 12–15). The use of isopropylamine (entries 2, 8, and 13) slightly improved the yields than that of *n*-propylamine (entries 1, 7, and 12). Decreasing yields when *tert*-butylamine was used are attributable to the bulkiness of the nucleophile (entries 3 and 14). Secondary amines such as diethylamine, di-*n*-propylamine, and diisopropylamine could be used for the synthesis of selenoureas

Table 1
Synthesis of isoselenocyanates by the reaction of bis(dimethylaluminum) selenide with isocyanates

Entry	R	Time (h)	Yield[a] (%)
1	*n*-Bu	3	86
2	Cyclohexyl	2	93
3	*p*-ClC_6H_4	5	95
4	1-Naphthyl	5	90

[a] Isolated yield.

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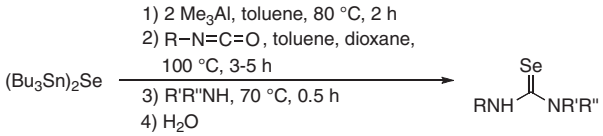
doi:10.1016/j.tetlet.2010.11.069

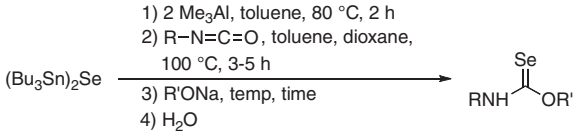


Scheme 2. One-pot synthesis of unsymmetrical selenoureas.

Table 2
One-pot synthesis of unsymmetrical selenoureas

Entry	R	R′	R″	Yield[a] (%)
1	*p*-ClC$_6$H$_4$	H	*n*-Pr	93
2	*p*-ClC$_6$H$_4$	H	*i*-Pr	98
3	*p*-ClC$_6$H$_4$	H	*t*-Bu	65
4	*p*-ClC$_6$H$_4$	Et	Et	76
5	*p*-ClC$_6$H$_4$	*n*-Pr	*n*-Pr	72
6	*p*-ClC$_6$H$_4$	*i*-Bu	*i*-Bu	84
7	1-Naphthyl	H	*n*-Pr	70
8	1-Naphthyl	H	*i*-Pr	96
9	1-Naphthyl	Et	Et	74
10	1-Naphthyl	*n*-Pr	*n*-Pr	97
11	1-Naphthyl	*i*-Bu	*i*-Bu	79
12	*n*-Bu	H	*n*-Pr	79
13	*n*-Bu	H	*i*-Pr	84
14	*n*-Bu	H	*t*-Bu	71
15	*n*-Bu	Et	Et	69

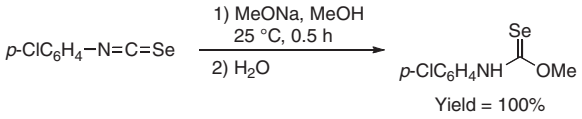
[a] Isolated yield.



Scheme 3. One-pot synthesis of selenocarbamates.

in high to excellent yields (entries 4–6, 9–11, and 15). It is demonstrated that nucleophilic addition of amines to isoselenocyanates proceeded even in the presence of Lewis acidic aluminum species.

One-pot synthesis of selenocarbamates could be achieved by the addition of sodium alkoxides instead of amines (Scheme 3, Table 3). To a toluene-dioxane solution containing *n*-butyl isoselenocyanate, generated by the reaction of *n*-butyl isocyanate with $(Me_2Al)_2Se$ under the conditions described above, was added sodium methoxide (3 equiv) prepared from methanol and sodium in another flask. Stirring at 25 °C for 24 h followed by aqueous workup and purification by silica gel column chromatography gave *N*-*n*-butyl *O*-methyl selenocarbamate in 50% yield (entry 1). Increased stoichiometry of MeONa (5 equiv) and temperature



Scheme 4. Reaction of *p*-chlorophenyl isoselenocyanate with sodium methoxide.

(65 °C) enabled to shorten the reaction time to 0.5 h and increased the yield to 63% (entry 2). Further increment of the stoichiometry of methanol to 10 equiv was not effective (entry 3). Reaction with sodium ethoxide at 25 °C also proceeded to give *O*-ethyl derivative in 77% isolated yield (entry 4). Reaction with sodium ethoxide under ethanol-refluxing conditions shortened the reaction time to 1 h (entry 5). Reaction using allyl alcohol smoothly proceeded even at 25 °C for 1 h (entry 6). One-pot reaction from *p*-chlorophenyl isocyanate also proceeded but the yields were poor and the formation of unidentified by-products was observed (entries 7–9). Lowering of the reaction temperature from 25 °C to 0 °C improved the yield to 22% (entry 10). Reaction of isolated *p*-chlorophenyl isoselenocyanate with MeONa at 25 °C for 0.5 h gave the corresponding selenocarbamate in quantitative yield (Scheme 4), so it is unclear why the one-pot procedure is not suitable for the preparation of *N*-aryl selenocarbamate.[7]

There are many synthetic methods for the preparation of isoselenocyanates.[8] They are roughly classified into seven categories, those are (i) reaction of isocyanides with elemental selenium,[9] (ii) nucleophilic substitution of alkyl halides or related compounds by selenocyanate anion,[10] (iii) photochemical and thermal conversion of alkyl selenocyanates,[11] (iv) reaction of amines with CSe_2 to give diselenocarbamates followed by the reaction with electrophiles,[12] (v) reaction of imidoyl dichlorides with alkali metal selenocyanates followed by elimination of cyanogen chloride,[13] (vi) insertion reaction of diazoalkanes to arylselenenyl selenocyanates.[14] Those methods often have inevitable problems such as bad smell of isocyanides, difficulty of separation of products from selenocyanates, and the use of hazardous metals and reagents. The seventh category is the direct selenation of isocyanate to isoselenocyanate, which is closely related with this study. However, to the best of our knowledge, there is only one literature in this category by using diphosphorus pentaselenide under severe conditions (160 °C, 3–4 h) in extremely low yields (<10%).[15] Our method described herein is easily handled from commercially available substrates under mild conditions. So the synthetic method developed here will be a useful one in the preparation of isoselenocyanates, selenoureas, and selenocarbamates.

In conclusion, we developed direct selenation reaction of isocyanates to isoselenocyanates by using $(Me_2Al)_2Se$. One-pot synthesis of selenoureas and selenocarbamates can also be achieved by the subsequent addition of amines and alcoholates in high yields.

Table 3
One-pot synthesis of selenocarbamates

Entry	R	Alcohol (mL)	Na (equiv)	Temp (°C)	Time (h)	Yield[a] (%)
1	*n*-Bu	MeOH (1.5)	3	25	24	50
2	*n*-Bu	MeOH (3.0)	5	65	0.5	63
3	*n*-Bu	MeOH (6.0)	10	65	0.5	64
4	*n*-Bu	EtOH (3.0)	5	25	20	77
5	*n*-Bu	EtOH (3.0)	5	78	1	79
6	*n*-Bu	Allyl-OH (3.0)	5	25	1	83
7	*p*-ClC$_6$H$_4$	MeOH (3.0)	5	25	0.5	<1
8	*p*-ClC$_6$H$_4$	MeOH (3.0)	5	25	2	<1
9	*p*-ClC$_6$H$_4$	MeOH (10)	10	25	0.5	13
10	*p*-ClC$_6$H$_4$	MeOH (3.0)	5	0	0.5	22

[a] Isolated yield.

Acknowledgment

This work was partially supported by the Grant-in-Aids for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supplementary data

Supplementary data (general experimental procedures, ^{1}H and ^{13}C NMR data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.069.

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6. General procedure: To a flame-dried, argon-purged flask, $(Bu_3Sn)_2Se$ (660 mg, 1.0 mmol) and toluene (10 mL) were placed. Me_3Al solution in hexane (1.0 M, 2.2 mL, 2.2 mmol) was added and stirred at 80 °C for 2 h. After cooling to room temperature, 1,4-dioxane (10 mL) and isocyanate (1.2 mmol) were added and the mixture was stirred at 100 °C for 2-5 h. After cooling to 0 °C by an ice bath, water (10 mL) was added. The product was extracted with ether (three times). The organic layers were combined, washed with brine (three times), dried over $MgSO_4$, and evaporated in vacuo. Purification by silica gel column chromatography gave pure isoselenocyanates.
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