Selenium-Assisted One-Pot Synthesis of Carbodiimides from Isocyanides and Primary Amines

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Abstract: Reaction of isocyanides with primary amines in the presence of selenium and DBU, followed by introduction of molecular oxygen in refluxing THF affords carbodiimides in high yields.

Key words: carbodiimide, selenourea, selenium, isocyanide

Carbodiimides² are important condensing reagents for the construction of functional groups such as peptides, nucleotides, amides, acid anhydrides, and esters. They are also useful intermediates for the preparation of a variety of heterocycles. Elimination of hydrogen sulfide from thioureas is a classical and still the most commonly employed method for the synthesis of carbodiimides. Since selenocarbonyl compounds are generally more reactive than the corresponding thiocarbonyl compounds, similar elimination of hydrogen selenide from selenoureas **1** is expected to proceed under somewhat milder conditions. After several preliminary experiments, we have found that carbodiimides **2** were obtained in high yields from **1** by the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in the presence of molecular oxygen (eq 1).



For example, selenourea $1a^3$ (R = *t*-Bu, R' = *n*-Bu, 2 mmol) was treated with 4 equiv of DBU in THF (5 mL) under reflux in the presence of molecular oxygen, feeded by a peristaltic pump at 20 mL/min, for 6 h. After removal of the deposited selenium by filtration, the filtrate was diluted with Et_2O (50 mL), washed with brine (50 mL x 2), dried with MgSO₄, and concentrated to afford carbodiimide $2a^{4,5}$ in 78% yield. DBU and molecular oxygen are both essential for the present reaction. Thus, without molecular oxygen the reaction proceeded sluggishly to afford 2a only in 10% yield, and when Et_3N or *N*-methylpyrrolidine (NMP) was used instead of DBU, **1a** was recovered unchanged. It is also noticeable that under the same conditions the corresponding thiourea⁶ did not afford **2a** and was recovered unchanged.

Since selenoureas 1 can be formed by the reaction of isocyanides with selenium and amines,³ we then attempted one-pot synthesis of carbodiimides 2 from isocyanides and primary amines in the presence of selenium (eq 2).⁷

2

RNC + R'NH₂ $\xrightarrow{\text{Se, DBU}}$ $\xrightarrow{\text{reflux, 1 h}}$ $\xrightarrow{\text{O}_2}$ RN=C=NR' (2)

Equation 2

A mixture of t-BuNC (2 mmol), n-BuNH₂ (2 mmol), selenium (2 mmol) and DBU (8 mmol) was stirred for 1 h in refluxing THF (5 mL). Then molecular oxygen was introduced by a peristaltic pump at 20 mL/min for 5 h under reflux. After deposited selenium was filtered off, the filtrate was diluted with Et_2O (50 mL), washed with brine (50 mL x 3), dried over MgSO₄, and concentrated *in vacuo* to give essentially pure 2a in 82% yield (Table 1, Run 1). The reaction also proceeded efficiently with 2 equiv of DBU (Run 2). However, the use of only 1 equiv of DBU resulted in a low yield of 2a (Run 3). A stoichiometric amount of selenium is needed in the present transformation, and attempts for catalytic use of selenium failed. The reaction proceeded in acetonitrile as well as in THF (Run 4), but 2a was obtained in a moderate yield in benzene (Run 5). In a similar manner, carbodiimides 2b-d^{4,5} were also obtained in good to high yields (Runs 6-9).

A plausible reaction pathway is shown in Scheme 1. Isocyanides react with selenium to yield isoselenocyanates,^{3,8} which react with amines to give selenoureas 1. Proton abstraction from selenoureas 1 with DBU affords azaselenoenolates 3. Oxidation of 3 with molecular oxygen followed by homocoupling gives diselenides $4.^9$ Attempts for isolation or detection of 4 in the present reaction failed, probably due to the rapid proton abstraction from 4 with another molecule of DBU giving rise to carbodiimides 2 and 5. The subsequent elimination of selenium from 5 regenerates 3. This pathway accounts for the fact that two equivalents of DBU are required for the generation of 2 in the present reaction.

In summary, selenoureas were found to readily undergo formal elimination of hydrogen selenide in the presence of



Scheme 1. A Plausible Reaction Pathway

DBU and molecular oxygen to give carbodiimides. By the use of this reaction, a new one-pot procedure for the synthesis of carbodiimides from isocyanides and primary amines has been developed.

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References and Notes

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- (5) ¹H and ¹³C NMR spectral data of **2a** and **2d**: Butyl-*tert*-butylcarbodiimide (**2a**): ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.28 (s, 9 H), 1.41 (sext, J = 7.3 Hz, 2 H), 1.57 (quint, J = 7.3 Hz, 2 H), 3.21 (t, J = 7.3Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 13.6, 20.0, 31.3, 33.5, 46.5, 54.8, 139.6. *tert*-Butylphenylcarbodiimide(**2d**):¹HNMR(400MHz,CDCl₃) δ 1.40 (s, 9 H), 7.05-7.12 (m, 3 H), 7.28 (t, J = 7.6 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 31.5, 57.3, 122.9, 124.3, 129.0, 135.9, 140.6.
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Run	Isocyanide	Amine	DBU (equiv)	Solvent	Product	Yield (%) ^a
1	t-BuNC	n-BuNH ₂	4	THF	<i>t</i> -BuN=C=NBu- <i>n</i> (2a)	82(93)
2			2		2a	(93)
3			1		2a	(36) ^b
4			4	CH₃CN	2a	(92)
5			4	benzene	2 a	(67)
6		t-BuNH ₂	4	THF	t-BuN=C=NBu-t (2b)	62(83)
7	<i>cyclo</i> -C ₆ H ₁₁ NC	cyclo-C ₆ H ₁₁ NH ₂	4		<i>cyclo</i> -C ₆ H ₁₁ N=C=NC ₆ H ₁₁ - <i>cyclo</i> (2c)	87
8	t-BuNC	PhNH ₂	4		t-BuN=C=NPh (2d)	58(66)
9	PhNC	t-BuNH ₂	4		2d	(41)

Table 1. One-pot synthesis of carbodiimides

Conditions: isocyanide (2 mmol), amine (2 mmol), selenium (2 mmol), DBU (2-8 mmol as shown in Table), solvent (5 mL), reflux, 1 h; molecular oxygen feeded at 20 mL/min, reflux, 5 h. a) Isolated yields. Yields in parentheses were determined by ¹H NMR.

b) Selenourea 1a (48%) was also formed.