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Article

Addition of Thiols to Isocyanates Catalyzed by Simple Rare-Earth-Metal Amides: Synthesis of S-Alkyl Thiocarbamates and Dithiocarbamates

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S Supporting Information

ABSTRACT: Simple additions of thiols to isocyanates/ isothiocyanates under mild conditions led to the efficient preparation of various S-alkyl thiocarbamates and dithiocarbamates, respectively. The lanthanum complex La[N- $(SiMe_3)_2]_3$ was found to be active to give thiocarbamates and dithiocarbamates in medium to excellent yields with a good group tolerance. A plausible mechanism of the catalytic transformation was proposed on the basis of both experimental observations and DFT calculations.



INTRODUCTION

Thiocarbamates are useful compounds in biological medicine,¹ agricultural chemistry,² and organic sysnthesis.³ Up to now, several strategies for the preparation of thiocarbamates were established. First, the intramolecular rearrangement of thiocarbonyl compounds under illumination was explored, while the relatively narrow substrate scope limited its application.⁴ A few multistep methods of thiocarbamate formation were developed, mainly using the carbonylation of amines, elemental sulfur, and carbon monoxide, followed by a reaction with alkyl halides.⁵ The requirement of a large amount of solvents and raw materials was unsatisfactory. A carbonylation of anilines, thiols, and carbon monoxide mediated by selenium or palladium was developed; the substrate anilines can also be replaced by nitroarenes.⁶ The only fly in the ointment there was that the method was not suitable for thiols with large steric hindrance. An oxidative coupling of amines, thiols, and carbon monoxide yielded thiocarbamates successfully by Jones' group. However, a side reaction under the same catalytic circumstances could not be avoided. The search for an environmentally friendly and atom-economical method to synthesize thiocarbamates is urgent. Hence, a method of intermolecular addition of thiols and isocyanates was established in succession. Though S-aryl-substituted thiocarbamates^{8a} and N-alkyl-substituted thiocarbamates^{8b,c} were easily available, the more challenging preparation of S-alkylsubstituted thiocarbamates is worthy of attention. Eisen realized the catalytic addition of thiols to phenyl isocyanates efficiently using early actinide amides.⁹ Nevertheless, the radioactive catalysts they employed are slightly structurally complicated and must be prepared under harsh conditions in advance. Therefore, it is still meaningful to develop simple and efficient catalytic systems to produce thiocarbamates with a good functional group tolerance.

To the best of our knowledge, rare-earth-metal amides have acted as active catalysts in a wide range of transformations.¹⁰ Very recently, the handy rare-earth-metal amides RE[N- $(SiMe_3)_2$, were used successfully by our group to catalyze guanylation/cyclization of carbodiimides and amino acid esters and intermolecular addition of alcohols to carbodiimides.¹¹ As a continuation of our research on the rare-earth-metalmediated transformation, we herein report the addition of thiols to phenyl isocyanates catalyzed by rare-earth-metal amides. Furthermore, to get a deep insight into the plausible mechanism of the current addition reaction, DFT calculations were carried out.

RESULTS AND DISCUSSION

Four complexes $RE[N(SiMe_3)_2]_3$ (RE = La, Sm, Yb, Y) were synthesized according to a previous work.^{10t} As expected, the model addition reaction of phenyl isocyanate (1a) with benzyl thiol (2a) was catalyzed by 10 mol % $La[N(SiMe_3)_2]_3$ to obtain 83% of the desired product 3aa at 30 °C after 24 h (Table 1, entry 1). A routine screening of the main factors that may influence the transformation, including center metals of the catalysts, catalyst loading, reaction time, temperature, and solvent were conducted in turn. Different rare-earth-metal amides were investigated, and all of the amides catalyzed the model reaction smoothly (Table 1, entries 1-4). The lanthanum amide La[N(SiMe₃)₂]₃ shows the highest activity among the catalysts. When the temperature decreased from 75 to 10 °C, the yields of the target product 3aa varied from 59% to 86% (Table 1, entries 1 and 5-8). Some representative polar and nonpolar solvents were also tested. Toluene was

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Table 1. Screening of the Optimal Conditions of the Addition of 2a to $1a^a$

Ĺ	SH SH	x mol% cat. T, t, Sol.	→ C	ys√	
	la 2a		\checkmark	3aa	
entry	cat. (loading/mol %)	$T/^{\circ}C$	sol	t/h	yield/% ^E
1	La[N(SiMe_3)_2]_3 (10)	30		24	83
2	$Sm[N(SiMe_3)_2]_3$ (10)	30		24	79
3	$Yb[N(SiMe_3)_2]_3$ (10)	30		24	75
4	$Y[N(SiMe_3)_2]_3$ (10)	30		24	79
5	La[N(SiMe_3)_2]_3 (10)	10		24	81
6	La[N(SiMe_3)_2]_3 (10)	40		24	86
7	La[N(SiMe_3)_2]_3 (10)	60		24	67
8	La[N(SiMe_3)_2]_3 (10)	75		24	59
9	La[N(SiMe_3)_2]_3 (10)	40	toluene	24	97
10	La[N(SiMe_3)_2]_3 (10)	40	PhCl	24	92
11	La[N(SiMe_3)_2]_3 (10)	40	CHCl ₃	24	89
12	La[N(SiMe_3)_2]_3 (10)	40	DMSO	24	22
13	La[N(SiMe_3)_2]_3 (10)	40	DMF	24	58
14	La[N(SiMe_3)_2]_3 (10)	40	THF	24	86
15	La[N(SiMe_3)_2]_3 (10)	40	TBME	24	81
16	La[N(SiMe_3)_2]_3 (10)	40	CH ₃ CN	24	52
17	La[N(SiMe_3)_2]_3 (5)	40	toluene	24	98
18	La[N(SiMe_3)_2]_3 (3)	40	toluene	24	85
19	La[N(SiMe_3)_2]_3 (2)	40	toluene	24	81
20	La[N(SiMe_3)_2]_3 (1)	40	toluene	24	81
21	La[N(SiMe_3)_2]_3 (1)	40	toluene	30	96
22	La[N(SiMe_3)_2]_3 (1)	40	toluene	36	97
23	La[N(SiMe_3)_2]_3 (1)	40		30	21
24	ate form $complex^{c}(10)$	40	THF	24	82

^{*a*}Conditions: phenyl isocyanate (1 mmol), benzyl thiol (1 mmol), 1 mL of solvent. ^{*b*}Determined by ¹H NMR of the crude reaction mixture. ^{*c*}The corresponding ate form complex $[(Me_3Si)_2N]_3La(\mu-Cl)Li(THF)_3$ was used.

proved to be the optimal solvent, for a 97% yield of **3aa** was obtained at 40 °C (Table 1, entries 9–16 and 24). Even though the catalyst loading of amide $La[N(SiMe_3)_2]_3$ was reduced to 1 mol %, an 81% yield of **3aa** was detected (Table 1, entries 17–20). Prolonging the reaction time to 30 and 36 h leads to increases in the yield of **3aa** to 96% and 97%, respectively (Table 1, entries 21 and 22). Thus, the ideal reaction time was chosen as 30 h, while the yield of **3aa** was only 21% at 30 h with 1 mol % catalyst loading under solvent-free conditions (Table 1, entry 23).

The results of the intermolecular addition between various phenyl isocyanates and benzyl thiols catalyzed by LaN- $(SiMe_3)_2$ are presented in Chart 1. Phenyl isocyanates bearing different substituents were first investigated under the optimal reaction conditions of 1 mol % catalyst at 40 °C for 30 h. To our delight, most phenyl isocyanates gave high to excellent yields, varying from 89% to 95%. Whether the groups directly attached on the phenyl ring are electron donating or electron withdrawing, the yields are nearly invariable (Chart 1, **3ba-ha**). However, the steric hindrance of the substituent on the ortho position of the phenyl isocyanates has a significant effect on the outcomes, since the corresponding yields of products 3ja-ma decreased after 30 h. A better yield can be obtained by both prolonging the reaction time and increasing the feed ratio of substrates (Chart 1, 3ja-ma). Several thiols, including substituted benzyl thiols (2b-e), furan-2Chart 1. Intermolecular Addition of Thiols and Phenyl Isocyanates Catalyzed by $La[N(SiMe_3)_2]_3^{a,b}$



^{*a*}Conditions unless specified otherwise: 1a-m (1 mmol), 2a-h (1 mmol). ^{*b*}Isolated yield. ^{*c*}48 h. ^{*d*}1 (1 mmol), 2 (1.5 mmol). ^{*e*}1 (1 mmol), 2 (2 mmol).

ylmethanethiol (2f), and cyclohexanethiol (2g), were tested under the optimal reaction conditions as well. Different thiols show excellent reactivities in the current catalytic system, which gives satisfying yields of the corresponding thiocarbamates (Chart 1, 3ab-ag). The steric hindrance effect of thiols also emerges, for the yield of product 3ah starting from bulky thiols dropped significantly to 58% after 48 h (Chart 1, 3ah). These results demonstrate an alternative approach to the preparation of new thiocarbamates but more importantly presents a novel reactivity for rare-earth-metal-mediated catalysis.

Phenyl isothiocyanate is a sulfur-substituted analogue of phenyl isocyanate; it is a valuable biological activated species¹² and is vital in polymer chemistry,¹³ coordinate chemistry,¹⁴ and environmental chemistry.¹⁵ Naturally, the model addition of benzyl thiol and phenyl isothiocyanate was studied under the same conditions as the above transformation. The reaction went smoothly, as expected; however, the isolated yield of dithiocarbamate **5aa** was only 75%. This revealed that the reactivity of phenyl isothiocyanate is slightly less than that of phenyl isocyanate (isolated yield of 90% for **3aa**), and so the reaction conditions for phenyl isothiocyanate required further optimization. The main influencing factors, such as catalyst loading and the ratio of the two reactants, were subsequently modified. The results are given in Table 2.

Table 2. Screening of the Optimal Conditions of the Addition of 2a to 4a⁴

y constants 2a	$SH + z$ $N_C S = 4a$	x mol%	6 La[N(SiMe ₃) ₂] ₃	H S Saa	
entry	x	у	z	yield/% ^b	
1		1	1		
2	1	1	1	83 (75 [°])	
3	2	1	1	82	
4	3	1	1	83	
5	5	1	1	79	
6	1	1.2	1	73	
7	1	1	1.2	89	
8	1	1	1.5	94	
9	1	1	2	96	

^aConditions: benzyl thiol (y mmol), phenyl isothiocyanate (z mmol), 1 mL of toluene. ^bDetermined by ¹H NMR of the crude reaction mixture. ^cIsolated yield.

The yields of product **5aa** were almost the same (79-83%)when the catalyst dosage was increased from 1 to 5 mol % (Table 2, entries 2-5). Things started to change when the molar ratio of the substrates changed. Finally, the optimal feed of benzyl thiol to phenyl isothiocyanate was proved to be 1:2, and the yield of dithiocarbamate 5aa reached 96% (Table 2, entries 6-9).

Some thiols and phenyl isothiocyanates were detected using 1 mol % of the amide La[N(SiMe₃)₂]₃ at 40 °C for 30 h. When the phenyl rings in benzyl thiol molecules were substituted by hydrocarbyl, halogen, and methyloxy groups, high yields of the desired dithiocarbamates were obtained (Chart 2, 5ab-ae). A

Chart 2. Intermolecular Addition of Thiols and Phenyl Isothiocyanates Catalyzed by $La[N(SiMe_3)_2]_3^{a,b}$



^aConditions: 2a-g (1 mmol), 4a-d (2 mmol). ^bIsolated yield.

slightly decreased yield was observed on the addition of phenyl isothiocyanate and thiols such as furan-2-ylmethanethiol and cyclohexanethiol, dropping to 82% and 75%, respectively (Chart 2, 5af,ag). Also, when 2-isothiocyanato-1,3-dimethylbenzene (4d) was used as the starting material, the yield decreased significantly (Chart 2, 5da).

A possible mechanism of the catalytic transformation was proposed and is shown in Scheme 1. Initially, on the basis of some cases of rare-earth-metal amide catalytic processes, ^{10f,g,i,q}





the protonolysis of a rare-earth-metal amide by a thiol affords thiolate A. A stoichiometric reaction between the precatalyst $La[N(SiMe_3)_2]_3$ and benzyl thiol was detected by ¹H NMR analysis, and the results are illustrated in Figure 1. The peak at



Figure 1. ¹H NMR monitoring of the stoichiometric reaction between La[N(SiMe₃)₂]₃ and benzyl thiol: (a) spectrum of catalyst La[N- $(SiMe_3)_2]_{3i}$ (b) spectrum of $-[N(SiMe_3)_2]_3$ after the addition of benzyl thiol for 30 min.

 δ 0.2768 ascribed to the coordinated (SiMe₃)₂N– disappeared after 30 min; meanwhile the peak ascribed to methyl protons in HN(SiMe₃)₂ was observed at δ 0.1025 (Figure 1). The change of chemical shifts of (SiMe₃)₂N- groups during the reaction indicates the metathesis reaction in the first stage. The powder A isolated from the above reaction mixture was then used as a catalyst to initiate the model addition reaction. The isolated yield of thiocarbamate 3aa was 86%, matching the outcome of the reaction in situ much better.

Subsequently, the oxygen atom of an isocyanate molecule coordinates to the rare-earth metal of catalyst A, which helps the insertion of the O-C-N moiety of isocyanate to the RE-S bond in A to produce Int-1. The nitrogen atom of the O-C–N moiety coordinates to the central metal to fully complete the insertion of isocyanate into the RE-S bond. Obviously, the phenyl isocyanates and thiols substituted with larger groups retard both their coordination to catalyst A and the generation of the corresponding key intermediates Int-1 and Int-2. Therefore, steric hindrance effects of isocyanates and thiols were observed. Then, a second thiol molecule attacks Int-2 to

give complex **D**, which liberates the desired thiocarbamate **3**. Meanwhile, the rare-earth-metal thiolate **A** is regenerated and the catalytic cycle **I** is complete.

If at this time Int-2 is attacked by a second isocyanate molecule, the insertion of isocyanate into the RE–N bond of Int-2 may occur to produce Int-3. An intramolecular nucleophilic attack happens in Int-3 to give Int-4, which quickly undergoes protonolysis with thiol to produce the nitrogen-containing heterocyclic compound P; meanwhile the rare-earth-metal thiolate A is free. A set of experiments were designed to prove the transformation from P to thiocarbamate. Under the optimum conditions, 2 equiv of *o*-methyl isocyanate was treated with 1 equiv of thiol to give P with an isolated yield of 84%. Continuous addition of 1 equiv of thiol to P yields 30% of the target molecule 3ja. When the molar ratio of thiol to P is increased to 1.2:1, a 63% yield of 3ja is acquired (Scheme 2, eq 1). Thus, it is believed that the addition of thiol





and isocyanate catalyzed by amide $RE[N(SiMe_3)_2]_3$ adopts the reversible path II as well. If the initial molar ratio of thiol to *o*-methyl isocyanate is 1.5:1, without the separation of compound P, an excellent yield (96%) of the corresponding product **3ja** is obtained (Scheme 2, eq 2).

In order to further support both the observed reactivity and the possible mechanism raised, DFT calculations¹⁶ were performed with the Gaussian 16 software package and the reaction profiles were determined in silico for phenyl isocyanate and benzyl thiol promoted by precatalyst La[N(SiMe₃)₂]₃ in toluene (Figure 2). Initially, the protonolysis energy of precatalyst La[N(SiMe₃)₂]₃ to real active species **A** is calculated to be thermodynamically favored (Figure S1 in the Supporting Information). The coordination of isocyanate via its oxygen atom to the La center of **A** forms complex **B** with a relative energy of 0.6 kcal mol⁻¹, which surmounts an energy barrier (TS-1) of 4.0 kcal mol⁻¹ to give Int-1 with a relative energy of -6.0 kcal mol⁻¹. The full insertion of isocyanate into the La–S bond is calculated as the rate-determining step of the addition, overcoming an energy barrier of 17.1 kcal mol⁻¹ to give Int-2. Then, the relative energies of complex **C** and **D** decrease to -21.6 and -19.9 kcal mol⁻¹, respectively. Finally, liberating the target molecule **3aa** from complex **D** overcomes an energy barrier of 16.5 kcal mol⁻¹.

In comparison, the approximate relative energy decrease (8.7 and 7.0 kcal mol⁻¹) for isocyanate insertion (Int-2 \rightarrow complex F \rightarrow TS-5 \rightarrow Int-3) and thiol insertion (Int-2 \rightarrow complex C \rightarrow TS-3 \rightarrow complex D) suggest that these two processes are kinetically competitive. The slight thermodynamic advantage of Int-3 makes the isocyanate insertion possible. Each energy barrier for the following steps from Int-3 to compound P' is relatively low. Therefore, the reverse reaction from compound P' to Int-3 and further to Int-2 (the energy barrier for Int-3 to Int-2 is 8.7 kcal mol⁻¹) is feasible. This theoretical result is in line with the experimental observation that compound P' can further undergo a transformation to the target molecule.

Furthermore, the theoretical calculation suggests the possibility of catalytic cycle III. The competitive step is an intermolecular attack of another thiol molecule to complex **B** to yield complex **C** with a relative energy of 9.3 kcal mol⁻¹, instead of the intramolecular migration to **Int-1**. To overcome an energy barrier of 12.9 kcal mol⁻¹, complex **E** transforms to complex **D** via **TS-4**. Thus, an overall step from complex **B** to **D** is exergonic by 20.5 kcal mol⁻¹. Path III is energetically unfavorable.



Figure 2. Plausible reaction profile of benzyl thiol addition to phenyl isocyanate mediated by catalyst $La[N(SiMe_3)_2]_3$: path I (black curve), path II (blue curve), and path III (red curve)

In terms of relative energies, the key step of the addition of benzyl thiolto phenyl isocyanate is more likely to proceed by intramolecular migration of the BnS- moiety to the carbon atom of isocyanate, as path I demonstrated.

CONCLUSION

Rare-earth-metal amides $RE[N(SiMe_3)_2]_3$ are found to be efficient catalysts for the intermolecular addition of thiols to phenyl isocyanates and phenyl isothiocyanates. The lanthanum amide is the optimal choice, and *S*-alkyl thiocarbamates and dithiocarbamates bearing different substituents are obtained in good to excellent yields under moderate conditions. The unknown N-containing four-membered heterocycle P is found in the transformation and can further transfer to the corresponding thiocarbamates. A plausible mechanism of the reactions catalyzed by rare-earth-metal amide is proposed, which is confirmed by both experimental observations and DFT calculations. More importantly, this work presents a novel reactivity for rare-earth-metal-mediated catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.9b00147.

Additional experimental procedures, full spectroscopy data for all the products, and computational methods (PDF)

Cartesian coordinates and energies (XYZ)

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Notes

The authors declare no competing financial interest.

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