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Generation of Carbamoyl- and Thiocarbamoyllithium Synthons Having a Hydrogen(s) or an Aryl Group on the Nitrogen and Their Trapping with Carbonyl Electrophiles

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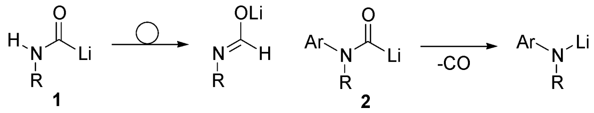
Adding carbonyl functions into organic molecules is a significantly important transformation in organic synthesis, and much effort has been focused on the development of new and useful carbonyl transfer reagents.[1] Carbamoyllithium ($R_2NC(O)Li$) is one of the most straightforward reagents for the nucleophilic introduction of carbamoyl moieties into organic compounds, and several methods have been developed for the generation of carbamoyllithiums.[2−7] Among them, we already disclosed that carbamoyllithiums were generated efficiently by tellurium−lithium exchange reaction[8] of carbamotelluroates with organolithium reagents, and many amide derivatives were obtained by the trapping with various electrophiles.[5] This reaction is of great synthetic value since one-pot operation starting from carbamoyl chlorides in a large scale has been established and easy isolation of the products is possible.[5b]

During the course of our study on the generation and synthetic use of carbamoyllithiums, we faced two problems: (i) carbamoyllithiums **1**, having a hydrogen(s) on the nitrogen, rapidly rearrange to azaenolates of the corresponding formamides;[9] and (ii) carbamoyllithiums **2**, having an aromatic substituent on the nitrogen, release CO rapidly even at low temperatures.[5b]

Scheme 1. Two Problems of Carbamoyllithiums



As the synthons of carbamoyllithiums having a hydrogen on the nitrogen, tripropylcarbazoyllithium[10a] and *N*-methoxymethylcarbamoyllithium[10b] were reported so far; however, removal of the protecting groups is troublesome.

To overcome these disadvantages, we examined utilization of aluminum azaenolates of carbamoyllithiums such as **5** as a synthon of carbamoyllithiums having a hydrogen on the nitrogen. Dianions **5** can be generated by tellurium−lithium exchange reaction of aluminum azaenolate of carbamotelluroate **4** with organolithium reagents; they have azaenolate structures, hence resist decarbonylation, and deprotection is not necessary (Scheme 2).

To prepare **3**, we carried out the reaction of butyl isocyanate with $^{i}Bu_2AlTe^{n}Bu$,[11] and carbamotelluroate **4a** was obtained in 88% yield after proton quench. This shows that aluminum azaenolate **3a** (R = ^{n}Bu) was formed efficiently in situ.[12] Then **3a** was allowed to react with ^{n}BuLi at −105 °C for 30 min, and the mixture was trapped with benzaldehyde. As the result, α-hydroxyamide **6a** was obtained in 81% yield (Table 1, run 1).[13] From this result, dianion **5** can be utilized as a useful synthon of a hydrogen possessing carbamoyllithiums **1**.

Scheme 2. Generation of Aluminum Azaenolates **5** as a Carbamoyllithium Synthon and Their Trapping

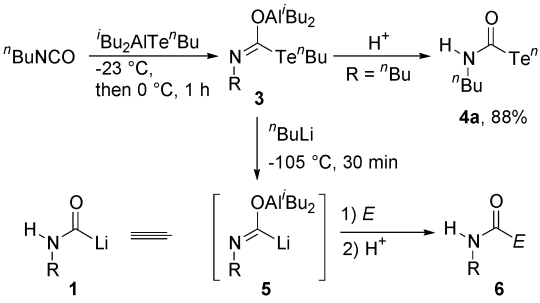
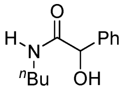
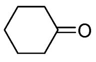
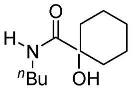
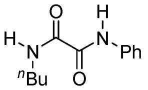
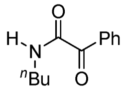
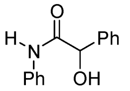
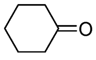
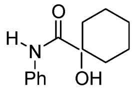
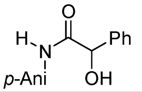


Table 1. Conversion of Isocyanates to Carbamoyllithium Synthons and Their Trapping with Carbonyl Electrophiles[a]

run	R	electrophile	product	yield, %
1	^{n}Bu	PhCHO		**6a,** 81
2	^{n}Bu			**6b,** 68
3	^{n}Bu	PhNCO		**6c,** 74
4	^{n}Bu	$PhCO_2Me$		**6d,** 53
5	Ph	PhCHO		**6e,** 90
6	Ph			**6f,** 74
7	p-$MeOC_6H_4$	PhCHO		**6g,** 88

[a] Conditions: isocyanate (1 mmol), $^{i}Bu_2AlTe^{n}Bu$ (1 mmol), −23 °C, then 0 °C, 1 h, THF (2 mL); ^{n}BuLi (1.1 mmol), −105 °C, 30 min, THF (3 mL), Et_2O (4 mL); electrophile (1.5 mmol), −105 °C, then 25 °C, 2 h.

We then conducted the reaction using other electrophiles and aryl isocyanates, and the results are also summarized in Table 1. As for electrophiles, trapping of dianion **5a** (R = ^{n}Bu) with cyclohexanone, phenyl isocyanate, and methyl benzoate gave the corresponding carbamoylated products in good yields (runs 2−4). The successful result of run 3 demonstrates the utility of the present method for the preparation of unsymmetrical oxalamides starting from two different isocyanates. When aryl isocyanates were

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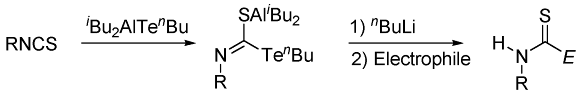
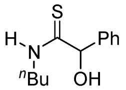
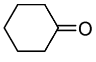
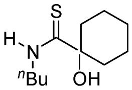
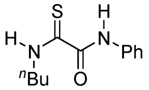
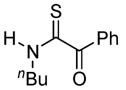
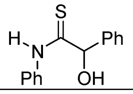
Table 2. Conversion of Isothiocyanates to Thiocarbamoyllithium Synthons and Their Trapping with Carbonyl Electrophiles[a]

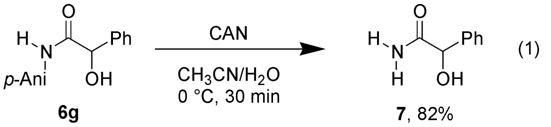


run	R	electrophile	product	yield, %
1	${}^nBu$	PhCHO		**8a**, 81
2	${}^nBu$			**8b**, 60
3	${}^nBu$	PhNCO		**8c**, 85
4	${}^nBu$	$PhCO_2Me$		**8d**, 73
5	Ph	PhCHO		**8e**, 91

[a] Similar reaction conditions employed in Table 1 were used.

employed, α-hydroxyamides were also obtained in high yields by trapping with benzaldehyde and cyclohexanone (runs 5−7). These results indicate that dianions **5** (R = aryl) served as synthons of carbamoyllithiums having an aryl group on the nitrogen.

Removal of the *p*-methoxyphenyl group on the nitrogen in **6g** was then performed by the use of ceric ammonium nitrate (CAN).[14] As a result, deprotected amide **7** was obtained in 81% yield (eq 1). By combining this method, the present reaction can be employed for nucleophilic introduction of an unsubstituted carbamoyl group "$H_2NC(O)$" into organic compounds.



(1)

6g

7, 82%

Thiocarbamoyllithiums are also useful compounds for the nucleophilic introduction of thiocarbamoyl moieties. However, generation methods of them are limited to the reaction of thioformamides with LDA[15] and reduction of thiocarbamoyl chloride with lithium naphthalenide.[6] There are no reports on thiocarbamoyllithiums having a hydrogen on the nitrogen or their synthons. Thus, the conversion of isothiocyanates to thiocarbamoyllithium synthons having a hydrogen on the nitrogen was examined. As summarized in Table 2, the reactions proceeded efficiently, and the corresponding thioamides were obtained by the trapping with various carbonyl electrophiles. Since thioamides are an important class of compounds not only in synthetic chemistry[16] but also in the biological field,[17] this transformation provides a novel efficient synthetic method of them.

In summary, the reaction of isocyanates with ${}^iBu_2AlTe^nBu$ affords aluminum azaenolates of carbamotelluroates **3**. Tellurium−lithium exchange reaction of **3** and subsequent trapping with electrophiles gives the corresponding amide derivatives. These results reveal that carbamoyllithium synthons having an aryl group and/or a hydrogen on the nitrogen, dianions **5**, are generated efficiently from isocyanates by one-pot operation. In a similar manner, thiocarbamoyllithium synthons can be generated from isothiocyanates. The present method would provide new access to a variety of amide families, including unsymmetrical oxalamides and their sulfur derivatives.

Supporting Information Available: Characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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