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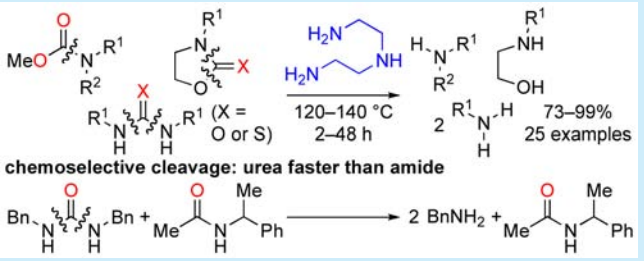
Diethylenetriamine-Mediated Direct Cleavage of Unactivated Carbamates and Ureas

Megumi Noshita, Yuhei Shimizu, Hiroyuki Morimoto,* and Takashi Ohshima*

Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan

Supporting Information

ABSTRACT: Diethylenetriamine is effective for the direct cleavage of unactivated carbamates and ureas without additional reagents and catalysts. Various carbamates and ureas were cleaved to afford products in good yield, and the reactions were not affected by air or moisture. Unique chemoselective cleavage of carbamate and urea in the presence of amides was also achieved.

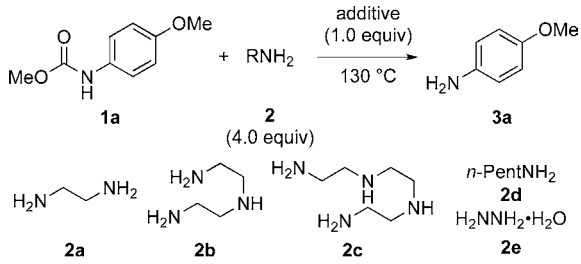


Carbamates and ureas are common structural motifs in biologically active compounds such as pharmaceuticals and pesticides.[1] Their high stability makes them useful protecting groups for amines in organic synthesis.[2] Furthermore, carbamates and ureas are key structural motifs in chiral auxiliaries[3] and C−H functionalization reactions.[4]

Despite their utility, cleavage of simple unactivated carbamates and ureas is not always facile due to the low reactivity of these functional groups. For example, the half-life of methyl *N*-phenylcarbamate (MeO_2CNHPh) for hydrolysis is 4000 years at 25 °C, pH 7, similar to that of acetamide.[5] Therefore, except for chemically designed carbamates, such as Boc, Cbz, and Fmoc groups, simple unactivated carbamates, such as methyl carbamates and oxazolidinones, are inert under many reaction conditions. To avoid harsh reaction conditions, installation of activating groups such as a Boc group on the nitrogen atom of carbamates is often required before cleavage,[2] but this strategy is not applicable for *N*,*N*-disubstituted carbamates. Furthermore, it is more difficult to cleave unactivated ureas than carbamates because they are highly stable.[6] Recent efforts to overcome these limitations have provided straightforward solutions,[7−9] but most of these solutions require air-/moisture-sensitive reagents and catalysts or are not broadly applicable. Therefore, the development of an operationally simple and robust method to cleave a range of unactivated carbamates and ureas is highly desirable. Herein, we report diethylenetriamine-mediated direct cleavage of unactivated carbamates and ureas. Various carbamates and ureas were cleaved to give products in good yield without consideration of air and moisture conditions. Highly chemoselective cleavage of carbamate and urea in the presence of amide is also demonstrated.

We recently reported the cleavage of unactivated amide bonds using combinations of ammonium salts and nitrogen nucleophiles.[10] These reaction conditions eliminate the need for strong acids and bases because nitrogen nucleophiles are more nucleophilic than oxygen nucleophiles, such as alcohols and water. Therefore, we envisioned that similar conditions would be applicable for cleaving unactivated carbamates and ureas. Initial screening of the reaction conditions using methyl *N*-(4-methoxyphenyl)carbamate (**1a**) as a model substrate revealed that a combination of ethylenediamine (**2a**) and ammonium bromide[10a] afforded product **3a** in moderate yield (Table 1, entry 1). The reactivity, however, was unchanged even in the absence of the ammonium salt (entry 2), which is in contrast to our previous observations that the addition of

Table 1. Optimization of Reaction Conditions[a]



entry	nitrogen nucleophile	additive	time (h)	yield[b] (%)
1	**2a**	NH_4Br	2	43
2	**2a**	none	2	44
3	**2b**	none	2	42
4	**2c**	none	2	39
5	**2d**	none	2	11
6	**2e**	none	2	57
7	**2b**	none	12	97 (95[c])
8[d]	**2b**	none	12	97 (94[c])

[a]Reaction conditions: methyl carbamate **1a** and nitrogen nucleophile **2** (4.0 molar equiv) at 130 °C. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield. [d]H_2O (1.0 equiv) was added.

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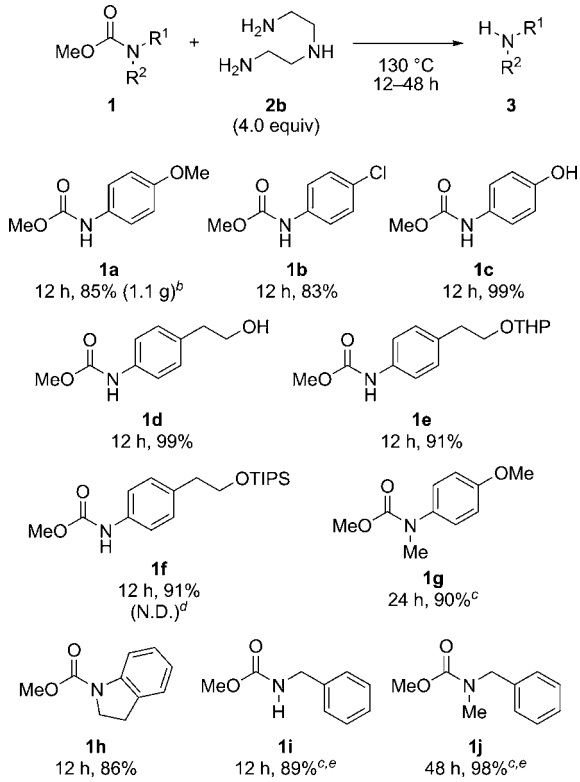
ammonium salts significantly accelerated the cleavage reaction of amide bonds.[10] Further screening of the nitrogen nucleophiles **2** revealed that diethylenetriamine (**2b**), triethylenetetramine (**2c**), and hydrazine hydrate (**2e**) were also reactive, while pentylamine (**2d**) gave inferior results (entries 3−6). Although **2e** exhibited the highest reactivity, we selected **2b** because of the facile purification of the products **3** from the reaction mixture and the applicability of the reagent to both carbamates and ureas (vide infra). Finally, extending the reaction time to 12 h afforded product **3a** in 95% isolated yield (entry 7). This reaction system was not affected by the addition of 1 equiv of water (entry 8). The reported conditions[8b,c] in which similar nitrogen nucleophiles are used as cleaving reagent of carbamates did not provide **3a**.[11]

With the optimized conditions in hand, we first examined the substrate scope of methyl carbamates (Scheme 1). All of the

Scheme 1. Scope of the Cleavage of Methyl Carbamates[a]



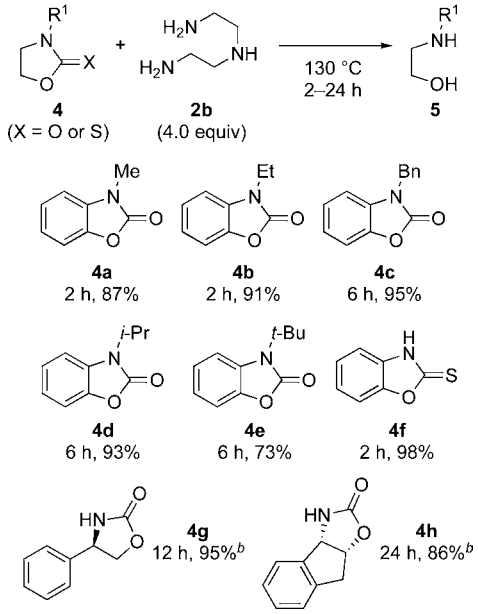
[a]Reaction conditions: methyl carbamate **1** and diethylenetriamine **2b** (4.0 molar equiv) at 130 °C. [b]On a 10 mmol scale. [c]At 140 °C. [d]Under the reported conditions ($H_2NNH_2{\cdot}H_2O$, KOH, ethylene glycol, reflux, 1.5 h),[8a] 84% of de-TIPS byproduct was obtained.[11] [e]Isolated as HCl salt.

reactions were performed without excluding air or moisture, demonstrating the robustness of the reaction conditions. The reaction was readily scaled up to 10 mmol to give 1.1 g of **3a**. Carbamates **1b** with an electron-withdrawing group gave **3b** in 89% yield. Protic functionalities such as phenol (**1c**) and alcohol (**1d**) were compatible. Notably, an acid-sensitive THP group (**1e**) and base-sensitive TIPS group (**1f**) were tolerated under these reaction conditions. The reaction of **1f** under the reported conditions using hydrazine hydrate as one of the cleaving reagents[8a] did not afford the desired product **3f** and produced the undesired product as the major species,[11] suggesting the mildness of the present reaction conditions.

N,N-Disubstituted methyl carbamates **1g** and **1h** were also cleaved, for which the installation of activating groups such as a Boc group on the nitrogen atom was not applicable. Finally, methyl carbamates **1i** and **1j** derived from aliphatic amines also gave the products in good yield at a slightly elevated temperature.

Next, cyclic carbamates **4** were treated under the reaction conditions to afford amino alcohols **5** (Scheme 2). A series of

Scheme 2. Scope of the Cleavage of Cyclic Carbamates[a]



[a]Reaction conditions: cyclic carbamate or thiocarbamate **4** and diethylenetriamine **2b** (4.0 mol equiv) at 130 °C. [b]At 140 °C.

N-alkylated cyclic carbamates **4a−e** gave the desired amino-alcohols **5a−e** in good yield. Notably, thiocarbamate **4f**, which may be difficult to cleave under the conditions of transition-metal catalysis, also gave the product **5f** without problems. Furthermore, cyclic carbamates **4g** and **4h**, both of which are the products of catalytic reactions,[12] were cleaved to give amino alcohols **5g** and **5h**, respectively.

The same reaction conditions were applicable to less reactive ureas and thioureas **6** (Scheme 3). While hydrazine hydrate (**2e**) was not suitable for the reaction of ureas, presumably because of the limited solubility of these substrates,[11] diethylenetriamine (**2b**) efficiently solubilized these substrates to afford product **7** in good yield.

The reactivity difference between carbamates and amides was disclosed during the optimization study in Table 1, leading us to examine the chemoselective cleavage of unactivated carbamate in the presence of amide.[13] The results shown in Scheme 4 revealed that, under the present reaction conditions, carbamate **4g** was selectively cleaved in the presence of amide **8a**.[14] Similar results were observed between even less reactive unactivated urea **6b** and amide **8b**.[15] Notably, the opposite chemoselectivity was observed under the conventional acidic or basic reaction conditions, where amide **8b** was cleaved faster than urea **6b**,[11] suggesting the uniqueness of the present reaction conditions.[16]

Finally, we applied the reaction conditions to functionalized compounds (Scheme 5). Albendazole (**1k**), a drug used to treat parasitic diseases, reacted under the standard conditions to give

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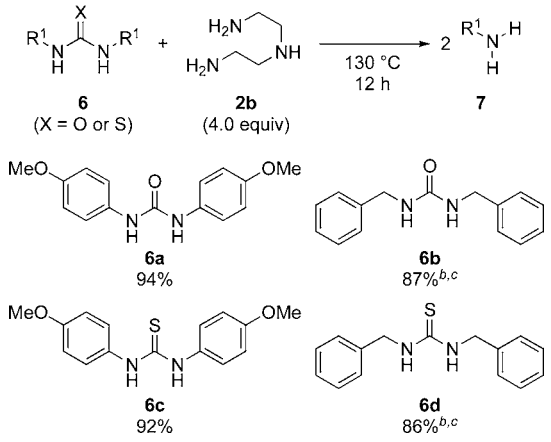
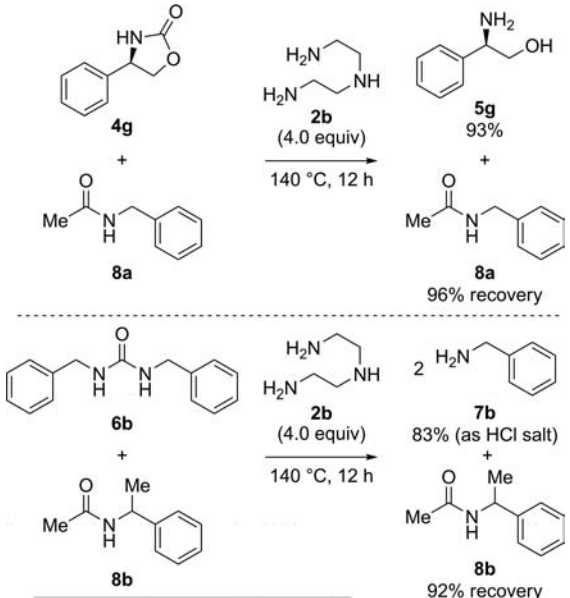
Scheme 3. Scope of the Cleavage of Ureas and Thioureas[a]



[a]Reaction conditions: urea or thiourea **6** and diethylenetriamine **2b** (4.0 molar equiv) at 130 °C. [b]At 140 °C. [c]Isolated as HCl salt.

Scheme 4. Chemoselective Cleavage of Carbamate and Urea in the Presence of Amide

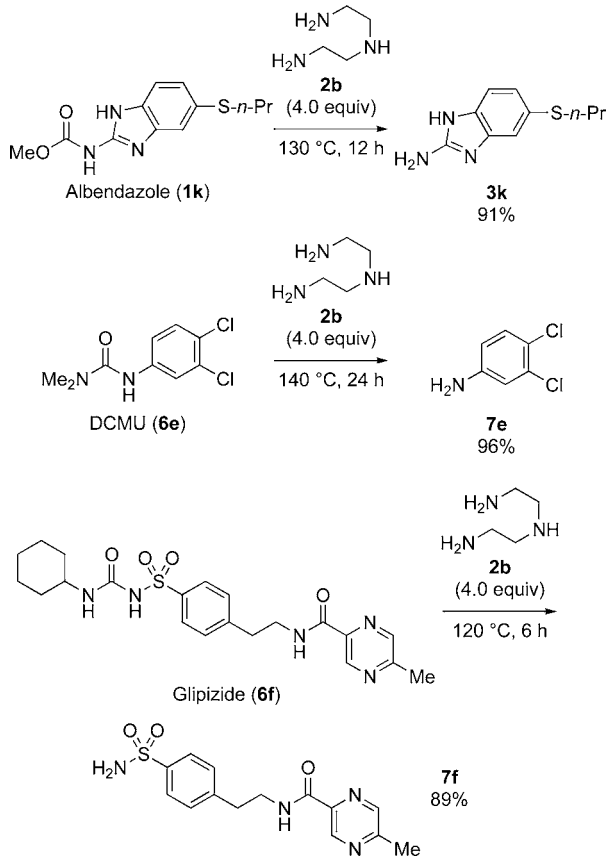


conditions	urea (%)		amide (%)	
	6b	7b	8b	9b
this work	0	83	92	3
aq NaOH	93	0	45	55
aq HCl	97	0	12	82

amine **3k** in good yield. DCMU (**6e**), a well-known herbicide that contains a urea moiety, also gave the cleavage product **7e** in good yield. In addition, glipizide (**6f**), an antidiabetes drug that contains both urea and amide moieties, selectively provided the product **7f** without affecting the amide moiety. These examples demonstrated the high applicability of this method.

In summary, we report a concise method for cleaving unactivated carbamates and ureas. Diethylenetriamine-mediated cleavage was highly effective for a range of carbamates and ureas without the need for additional reagents and catalysts. This method does not require consideration of the air and moisture conditions and is applicable for challenging substrates

Scheme 5. Application to Functionalized Compounds



such as *N,N*-disubstituted carbamates and ureas. The highly chemoselective cleavage of carbamate and urea in the presence of amide also showcases the uniqueness of this protocol. Further expansion of the substrate scope and elucidation of the detailed reaction mechanism are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03016.

Full experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hmorimot@phar.kyushu-u.ac.jp.
*E-mail: ohshima@phar.kyushu-u.ac.jp.

ORCID

Takashi Ohshima: 0000-0001-9817-6984

Notes

The authors declare no competing financial interest.

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(16) Although the reason for the observed chemoselectivity has not yet been clarified, we assume that carbamates and ureas are more prone to react with nitrogen nucleophiles than amides in the absence of Brønsted acids. It is also noted that formation of an isocyanate intermediate as the origin of the chemoselectivity is less likely because a competitive reaction between tertiary carbamate and tertiary amide preferentially cleaved carbamate under the present reaction conditions.[11]

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