

Acid-Free, Aminoborane-Mediated Ugi-Type Reaction Leading to General Utilization of Secondary Amines

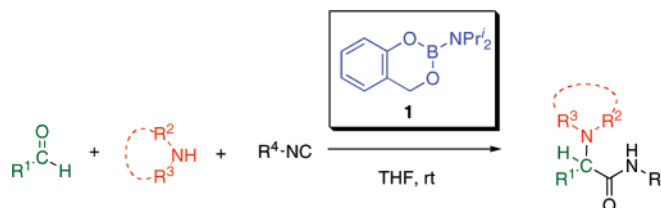
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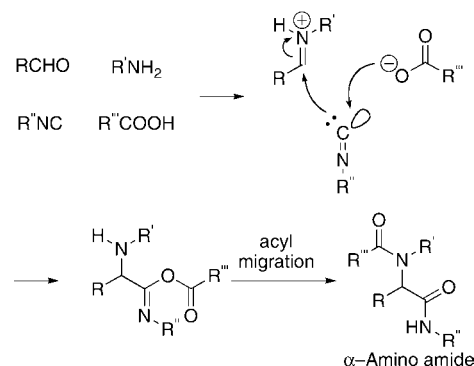
ABSTRACT



A variety of secondary amines have become utilized in the Ugi reaction by using aminoborane **1** as an iminium ion generator. Aldehydes, secondary amines, and isocyanides are coupled in the presence of **1** at room temperature, giving the corresponding α -amino amides in good yields. The nonacidic reaction conditions are beneficial for unique chemoselectivity, where the aldimine functionality is left intact in the present Ugi-type reaction.

The Ugi reaction is one of the most intensively studied multicomponent reactions, affording α -amino amides via coupling of aldehydes, amines, isocyanides, and carboxylic acids (Scheme 1).^{1,2} The reaction primarily relies on the unique reactivity of isocyanides, which have carbene-like carbon atoms.³ The reaction's usefulness in the combinatorial synthesis of α -amino acid derivatives prompted its application in polymer-supported solid-phase synthesis.⁴ From the mechanistic point of view, the fourth component, i.e., the

Scheme 1. Acid-Mediated Ugi Four-Component Coupling Reaction



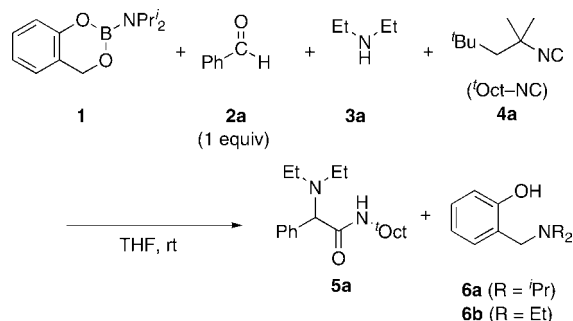
carboxylic acid, plays a dual role in the Ugi reaction. It serves as a Brønsted acid in the formation of iminium ion intermediates and as a donor of an acyl group, which finally migrates to the α -amino group in the products. Because the acyl migration is involved as the key step, the typical Ugi reaction requires primary amines, nitrogen atoms of which

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(2) Recent examples: (a) Trifilenkov, A. S.; Ilyin, A. P.; Kyril, V. M.; Sandulenko, Y. B.; Ivachtchenko, A. V. *Tetrahedron Lett.* **2007**, *48*, 2563–2567. (b) Akritopolou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 1299–1302. (c) Kaïm, L. E.; Grimaud, L.; Obie, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961–7964.

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Scheme 2. Reaction of Benzaldehyde, Diethylamine, and *tert*-Octyl Isocyanide in the Presence of Aminoborane **1**



are able to accept the acyl group through amide formation. This mechanism-based requirement makes it difficult to use secondary amines as the amine component in the Ugi reaction, although the use of secondary amines has partly been achieved by the use of excess dimethylamines⁵ or by the use of secondary amines that carry additional functional groups, such as OH and NHR groups, which serve as intramolecular acyl group receptors.⁶ Secondary amines also took part in a certain Ugi-type reaction, where formaldehyde was used as a highly reactive carbonyl component.⁷ Because α -dialkylamino acid derivatives, including those with cyclic amino groups, attract much attention as potential drugs or biologically active substances,⁸ it is highly desirable to develop entirely new reaction conditions that allow utilization of secondary amines.

Recently, we reported that dialkylaminoboranes serve as iminium ion generators under mild reaction conditions.⁹ The use of these aminoborane derivatives has allowed Strecker-type reaction,^{10a} Mannich-type β -amino ketone and ester synthesis,^{10b,c} and reductive amination using NaBH_4 ^{10d} under nonacidic reaction conditions. In these reactions, the use of secondary amines gave more satisfactory results than the use of primary amines. We have so far presumed that the aminoborane derivatives efficiently promote the generation

of iminium ion intermediates, thus leading to the success of a variety of amination reactions in nonacidic media. These successful examples of the amination reaction prompted us to use aminoboranes as a promoter for secondary amine-based Ugi reactions.

In the presence of aminoborane **1**, benzaldehyde (**2a**) was reacted with diethylamine (**3a**) and *tert*-octyl isocyanide (**4a**) in THF at room temperature (Scheme 2). When a reagent ratio of 1:1:1.5 was used, the reaction successfully gave the Ugi product, *N,N*-diethylphenylglycine amide **5a**, in 86% yield (Table 1, entry 1). The formation of the product **5a**

Table 1. Reactions of Benzaldehyde (**2a**) with Diethylamine (**3a**) and *tert*-Octyl Isocyanide (**4a**) in the Presence of Aminoborane **1**^a (Scheme 2)

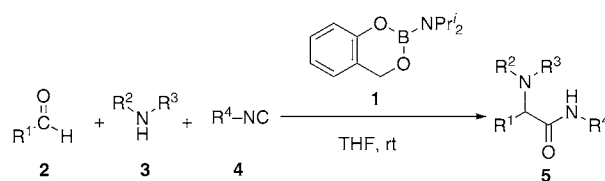
entry	equiv of 1	equiv of 3a	equiv of 4a	% yield of 5a ^{b,c}	% yield of 6 ^b
1	1	1	1.5	86	88 (6a/6b = 4:1)
2	1	1.5	1.5	94	89 (6a/6b = 3:1)
3	1	2	1.5	89	59 (6b)
4	1	1.5	2	77	67 (6a/6b = 1:4)
5	1.2	1.2	1.5	94	90 (6a/6b = 4:1)
6	1.5	1.5	1.5	99 (82)	89 (6a/6b = 4:1)
7 ^d	0	2	1.5	0	0

^a Benzaldehyde (0.2 mmol), Et_2NH , and *t*-octyl isocyanide were reacted with aminoborane **1** in THF at rt, unless otherwise noted. ^b NMR yield. ^c Isolated yield in the parentheses. ^d At 80 °C.

was accompanied by the formation of *o*-(dialkylaminomethyl)phenol byproducts **6**, which were derived from the salicyl alcohol-derived ligand of aminoborane **1**. We optimized the reaction conditions of the new Ugi-type reaction by varying the molar ratios of the reagents used (Table 1). Although no remarkable difference was found among the reaction conditions examined, the use of a slight excess of aminoborane, amines, and isocyanide afforded the desired **5a** in excellent yields (entries 5 and 6). It should be also noted that no reaction took place in the absence of **1** even at 80 °C (entry 7).

Under the optimized reaction conditions, various aldehydes were reacted with secondary amines in the presence of **1** and isocyanides (Scheme 3). Benzaldehydes with electron-

Scheme 3. Acid-Free Ugi-Type Reaction of Aldehydes, Secondary Amines, and Isocyanides in the Presence of Aminoborane **1**



withdrawing (Table 2, entries 1 and 2) or electron-donating (entries 3 and 4) groups at their *para*-positions afforded the

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Table 2. Reactions of Aldehydes (R^1CHO) with Diethylamine (**3a**) and *tert*-Octyl Isocyanide (**4a**) in the Ugi Reaction Mediated by **1**^a









entry	R^1CHO	% yield ^b
1	4-BrC ₆ H ₄ CHO (2b)	81 (5b)
2	4-NO ₂ C ₆ H ₄ CHO (2c)	94 (5c)
3	4-MeOC ₆ H ₄ CHO (2d)	87 (5d)
4	4-BocNHC ₆ H ₄ CHO (2e)	83 (5e)
5	1-NapCHO (2f)	92 (5f)
6	2-PyrCHO (2g)	61 (5g)
7 ^c	PhCH ₂ CH ₂ CHO (2h)	61 (5h)

^a Aldehydes (0.4 mmol), diethylamine (0.6 mmol), and *tert*-octyl isocyanide (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12–16 h, unless otherwise noted. ^b Isolated yield (silica gel column chromatography). ^c At 60 °C.

Ugi-type products **5b–5e** in high yields. Moderately sterically demanding aromatic aldehyde also afforded **5f** in high yield (entry 5). Reactions of 2-pyridylaldehyde and 3-phenylpropanal gave **5g** and **5h**, respectively, in moderate yields (entries 6 and 7). In the reaction of 3-phenylpropanal, formation of a significant amount of enamine was responsible for the observed moderate yield. It should be noted that Passerini-type reactions were not detected in these reactions, even in the reactions that gave the desired products in moderate yields.

We then varied the secondary amines in the reactions with benzaldehyde and *tert*-octyl isocyanide (Table 3). Dibenzyl-

Table 3. Reactions of Secondary Amines (R^2R^3NH) with Benzaldehyde (**2a**) and *tert*-Octyl Isocyanide (**4a**) in the Ugi Reaction Mediated by **1**^a



entry	R^2R^3NH	% yield ^b
1	Bn ₂ NH (3b) ^c	85 (5i)
2	(allyl) ₂ NH (3c)	81 (5j)
3	Ph(Me)NH (3d) ^c	86 (5k)
4	^t Pr ₂ NH (3e)	58 (5l)
5	 (3f)	85 (5m)
6	 (3g)	94 (5n)
7	 (3h)	83 (5o)
8	 (3i)	83 (5p)
9	 (3j)	96 (5q)
10	 (3k) ^c	53 (5r)
11	 (3l) ^c	65 (5s)
12	 (3m)	87 (5t)

^a **2** (0.4 mmol), **3** (0.6 mmol), and **4** (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12–16 h, unless otherwise noted. ^b Isolated yield (silica gel column chromatography or preparative GPC (for **5r**)). ^c 0.8 mmol of the amine was used.

amine, diallylamine, and *N*-methylaniline gave Ugi-type products **5i–5k** in good yields (entries 1–3). In the reaction of diisopropylamine, the desired product **5l** was isolated only in moderate yield (entry 4). Reactions of cyclic amines with benzaldehyde and *tert*-octyl isocyanide also gave products **5m–5p** having five-, six-, and seven-membered cyclic amino groups in high yields (entries 5–8). Reaction of a cyclic amine bearing an acetal protective group also afforded **5q** in good yield (entry 9). *N*-Methylpiperazine, tetrahydroquinoline, and tetrahydroisoquinoline took part in the Ugi-type reaction, affording the corresponding α -amino amides **5r–5t** in moderate to good yields (entries 10–12).

The scope of the isocyanide component was then examined (Table 4). The reaction of benzaldehyde and diethylamine

Table 4. Reactions of Isocyanides (R^4-NC) with Benzaldehyde (**2a**) and Diethylamine (**3a**) in the Ugi Reaction Mediated by **1**^a

entry	R^4-NC	% yield ^b
1	4-MeOC ₆ H ₄ CH ₂ NC (4b)	95 (5u)
2	1-Adamantyl-NC (4c)	87 (5v)
3	4-EtOCOC ₆ H ₄ NC (4d)	94 (5w)
4	4-NO ₂ -2-Me-C ₆ H ₃ CHO(4e)	95 (5x)
5	4-MeOC ₆ H ₄ NC (4f)	96 (5y) ^c
6	4-TBSOOC ₆ H ₄ NC (4g)	90 (5z) ^c
7	MesNC (4h)	79 (5aa)
8	 (4i)	88 (5ab)
9	 (4j)	87(5ac)

^a Benzaldehyde (0.4 mmol), diethylamine (0.6 mmol), and isocyanides (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12–16 h, unless otherwise noted. ^b Isolated yield (silica gel column chromatography). ^c 0.8 mmol of diethylamine was used.

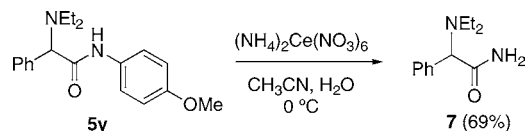
with *p*-methoxybenzyl or adamantly isocyanides gave **5u** and **5v** in high yields (entries 1 and 2). Aromatic isocyanides bearing electron-withdrawing (entries 3 and 4), electron-donating (entries 5 and 6), and sterically demanding groups (entry 7) also gave the Ugi products **5w–5aa** in high yields. An isocyanide designed for ready hydrolysis of the amide functionality successfully gave **5ab** in good yields (entry 8).¹¹ Dipeptide derivative **5ac** was obtained in high yield in the reaction of α -amino acid-derived isocyanide **4j** (entry 9). Note that *para*-methoxyphenyl amide **5y** was converted to primary amide **7** by treatment with CAN (cerium(IV) ammonium nitrate) (Scheme 4).¹²

It should be noted that use of primary amines in the aminoborane-mediated Ugi-type reaction resulted in the formation of imines as major products. Because of the

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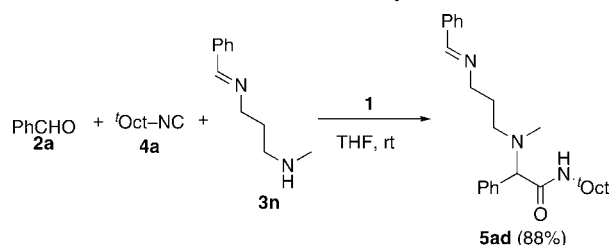
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Scheme 4. Deprotection of *p*-Methoxyphenyl Amide by Treatment with CAN



nonacidic nature of the reaction system, the formed imines are not able to undergo further reaction with isocyanides. This seems to be the major practical difference between our system and the ordinary acidic system for the Ugi reaction. To take advantage of this feature, we examined the reaction of the secondary amine bearing an imine functionality in the molecule. The secondary amine **3n**, bearing an imine moiety, was subjected to reaction with benzaldehyde with *tert*-octyl isocyanide in the presence of aminoborane **1** (Scheme 5).

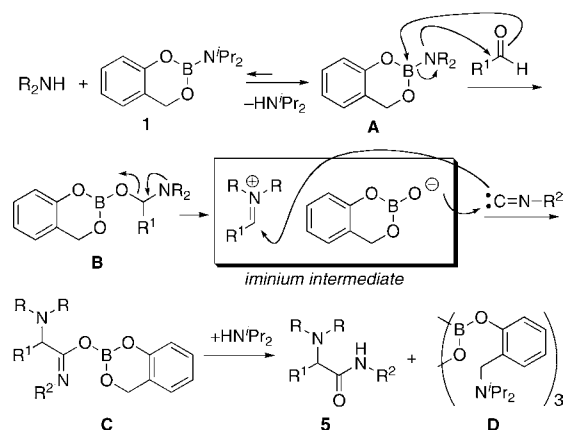
Scheme 5. Ugi-Type Reaction of Secondary Amine-Bearing Imine Functionality



The Ugi reaction took place selectively at the secondary amine moiety, providing the product **5ad** in which the imine moiety was left intact. This result is in sharp contrast with the reaction of the same reactants under the ordinary Ugi reaction conditions using acetic acid. The reaction afforded several products, none of which was the imine compound **5ad**.

One of the possible reaction mechanisms is shown in Scheme 6. Aminoborane **A** is generated from the free amine and **1**, which is less reactive toward aldehydes than **A**, via reversible amine exchange reaction. This amine exchange was indeed observed in the reaction of **1** with diethylamine (1 equiv) in CDCl_3 at rt, which resulted in 91% conversion

Scheme 6. Possible Reaction Mechanism



to **A** ($R = \text{Et}$) after 7 h. The intermediate **A** then reacts with aldehydes through nucleophilic attack of its amino group to the carbonyl group and the subsequent B–O bond formation, giving intermediate **B**. The cleavage of the C–O bond in **B** leads to the formation of the iminium ion intermediate, which undergoes the reaction with isocyanides, giving the Ugi-type products **5** and byproduct **D** through the aminolysis of **C**. Hydrolysis of **D** leads to the formation of the byproducts **6**.

In summary, we have demonstrated a new Ugi-type reaction of secondary amines using aminoborane **1** as an iminium ion generator under nonacidic conditions. This reaction system can be regarded as a three-component Ugi-type reaction, in which the fourth component, i.e., the acid component, was not used. As shown by the selective reaction of the imine–amine conjugate, our new reaction system may open up new possibilities for the Ugi reaction.

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Supporting Information Available: Experimental procedures and spectral data for new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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