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B(OMe)₃ as a Nonacidic Iminium Ion Generator in Mannich- and Ugi-Type Reactions

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Mannich-type reactions of aldehydes with secondary amines and a ketene silyl acetal were promoted by trimethoxyborane in DMSO to afford the corresponding β -amino esters in good yields. B(OMe)₃ also promoted Ugi-type reactions of aldehydes with secondary amines and isocyanides in 1,2-dichloroethane, which leads to the formation of α -amino

Introduction

Aminative C-C bond formation via generation of iminium ion intermediates are widely utilized as reliable, general, and efficient methods for the synthesis of amine derivatives. Mannich reactions^[1] and Ugi reactions^[2] are among this classification and are utilized frequently in the preparation of amines. These reactions are typically carried out in the presence of Brønsted acids or Lewis acids for activation of carbonyl compounds.^[3] The requirement of acidic conditions often makes it difficult to retain acid-sensitive functional groups during the transformations. To avoid this difficulty, nonacidic reaction systems for the generation of iminium ion intermediates have been reported. For example, iminium ions were generated by α -fragmentation of amine derivatives bearing a leaving group α to the amino groups.^[4] Although iminium ions are generated under nonacidic reaction conditions with this strategy, it requires preparation of the α -modified amine precursors. It is highly desirable to develop new synthesis methods for amine derivatives from easily available starting materials under functional-grouptolerable reaction conditions.

We previously reported that aminoborane derivative **1** acted as an iminium ion generator under nonacidic conditions,^[5] and mediated a Mannich-type reaction,^[6] reductive amination,^[7] and Ugi-type reaction.^[8,9] The attractive aspect of the aminative reactions is that the iminium ions can be generated directly from secondary amines and carbonyl compounds without the need for preparation of special precursors. However, this nonacidic system for the generation

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amides. In these reactions, trimethoxyborane serves as an inexpensive, commercially available, and virtually nonacidic iminium ion generator.

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of iminium ions suffers from the requirement of commercially unavailable boron reagents. Although we recently reported new nonacidic, "catalytic" iminium ion generators,^[10,11] these boron-based catalysts were still not easily available in large quantities. It seems desirable to use commercially available, inexpensive boron compounds as a practical iminium ion generator. In this paper, we report on the Mannich- and Ugi-type reactions mediated by B(OMe)₃, which is one of the most inexpensive boron compounds.



Results and Discussion

Reactions of benzaldehyde 2a, diethylamine 3a, and ketene silvl acetal (4) were carried out in the presence of BF_3 ·OEt₂ and B(OMe)₃, both of which are easily available (Table 1). In the absence of an additive, the reaction afforded only a trace amount of aldol product 6 as judged by ¹H NMR spectroscopy (Entry 1). The use of boron trifluoride etherate resulted in the formation of β-amino ester 5aa in 33% yield along with the aldol product 6 in 7% yield (Entry 2). In the presence of an increased amount of BF₃·OEt₂, exclusive formation of the aldol product was observed (Entry 3). We then found that the use of 1-3 equiv. B(OMe)₃ gave the Mannich-type product selectively in 69-91% yield without any formation of the aldol product (Entries 4-6). It should be noted that we previously reported that a catalytic amount of B(OMe)₃ failed to promote the reaction.^[10] The use of 2 equiv. B(OMe)₃ afforded the highest yield for the Mannich product (Entry 5). The requirement of excess B(OMe)₃ suggests that it may also serve as a dehydrating reagent and that the efficiency of the genera-

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tion of the iminium ion was not as high as that previously reported for the catalytic iminium ion generator (Ph_2BOMe) .^[10] Among the solvents we examined, DMSO was found to be the highest-yielding solvent for this reaction (Entries 6–10).

Table 1. Reaction of benzaldehyde, diethylamine, and silyl ketene acetal in the presence of boron compounds. $^{\left[a\right] }$

	O ∐ + Et₂N	отв: Н + Д	BF ₃ •OEt ₂ or	B(OMe) ₃
	Ph H		Me r.t.	
	2a 3a	4		
		Et_N_Et	₂Me ⁺ Ph → OH	CO ₂ Me
		5aa	6	
Entry	Boron compound ^[b]	Solvent	Yield (5aa) [%] ^[c]	Yield (6) [%] ^[c]
1	none	DMSO	0	trace
2	$BF_3 \cdot OEt_2(1)$	DMSO	33	7
3	$BF_3 \cdot OEt_2$ (2)	DMSO	0	77
4	$B(OMe)_{3}(1)$	DMSO	69	0
5	$B(OMe)_{3}(2)$	DMSO	91	0
6	$B(OMe)_{3}(3)$	DMSO	80	0
7 ^[d]	$B(OMe)_{3}(3)$	DMF	55	0
8 ^[d]	$B(OMe)_3$ (3)	toluene	42	0
9 ^[d]	$B(OMe)_{3}(3)$	THF	30	0
10 ^[d]	$B(OMe)_3(3)$	DCE ^[e]	43	0

[a] Benzaldehyde (0.30 mmol), diethylamine (0.20 mmol), and silyl ketene acetal (0.30 mmol) were treated with boron compounds at room temperature for 5 h unless otherwise noted. [b] Number of equivalents in parentheses. [c] NMR yield. [d] 23 h. [e] 1,2-Dichloro-ethane.

Under the optimized conditions, various aldehydes 2 and amines 3 were treated with ketene silvl acetal 4 (Table 2). Diethylamine and diallylamine gave the corresponding Mannich-type products in high yield (Entries 1 and 2). Reactions of dibenzylamine and N-methyl aniline also afforded β -amino esters **5ac** and **5ad** (Entries 3 and 4). Cyclic amines such as pyrrolidine (3e), piperidine derivatives (3f and 3h), hexamethyleneimine (3g), and tetrahydroisoquinoline (3i) afforded the corresponding amino esters in good yields, although reaction of tetrahydroquinoline (3i), an aniline derivative like 3d, gave the Mannich-type product only in moderate yield (Entries 5-10). In the reaction of amine derivative **3h**, the acetal group was compatible with the reaction conditions (Entry 8). p-Substituted benzaldehydes (2b and 2c) and 1-naphthaldehyde 2d afforded the desired products in their reactions with diethylamine (Entries 11-13). No remarkable reactivity difference was observed among these aldehydes. B(OMe)₃-mediated Mannich-type reactions were also applicable to the aliphatic aldehydes 2e-2g (Entries 14–16). Acid-sensitive protective groups such as THP and trityl groups could tolerate the reaction conditions (Entries 15 and 16). Paraformaldehyde (2h) also afforded the corresponding Mannich-type product 5hk in the reaction with dicyclohexylamine (Entry 17).

In sharp contrast to the reaction of the secondary amines, the primary amines did not give the corresponding



0 II	R ¹ R ² OTBS	B(OMe) ₃ R	¹ N ²
к∕́н	+ H + OMe	DMSO, r.t. R	└CO₂Me
2	3 4		5
Entry	Aldehydes	Amine	Yield [%] ^[b]
1	PhCHO (2a)	Et ₂ NH (3a)	80 (5aa)
2	2a	(allyl) ₂ NH (3b)	80 (5ab)
3 ^[c]	2a	$Bn_2NH(3c)$	76 (5ac)
4 ^[c]	2a	Ph(Me)NH (3d)	69 (5ad)
5	2a	(3e)	87 (5ae)
6	2a		87 (83) ^[d]
		\ (3f)	(5af)
7	2a	NH	88 (5ag)
		(3 g)	
8	2a	(3h)	77 (5ah)
9	2a	NH	84 (5ai)
	-	(3i)	
10	2a	N N	51 (5aj)
		(3j)	
11	<i>p</i> –MeOC ₆ H ₄ CHO (2b)	3a	74 (5ba)
12	<i>p</i> –NO ₂ C ₆ H ₄ CHO (2c)	3a	83 (5ca)
13 ^[c]	1-NapCHO (2d)	3a	77 (5da)
14	PhCH ₂ CH ₂ CHO (2e)	3a	80 (5ea)
15	THPO(CH ₂) ₃ CHO (2f)	3a	77 (5fa)
16 ^[e]	Ph ₃ CO(CH ₂) ₃ CHO (2g)	3a	76 (5ga)
17	$H_2CO^{[f]}(\mathbf{2h})$	Cy ₂ NH (3k)	75 (5hk)

[a] Aldehyde 2 (0.60 mmol), amine 3 (0.40 mmol), and silyl ketene acetal 4 (0.60 mmol) were treated with $B(OMe)_3$ (0.80 mol) at room temperature unless otherwise noted. [b] Isolated yield. [c] Use of 0.80 mmol 4. [d] Isolated yield for 10 mmol-scale reaction in parentheses. [e] Use of 0.40 mmol $B(OMe)_3$. [f] Paraformaldehyde (1.2 mmol) was used.

Mannich-type product, but gave imines in the reactions with benzaldehyde. As postulated in our previous reports,[8,10] our reaction system can hardly activate imine derivatives, because of the nonacidic nature of the reaction conditions. This fact can be utilized for selective C-C bond formation at the iminium carbon rather than at the imino carbon atom. Secondary amine 31 bearing an NH₂ group was treated with 4 under the B(OMe)₃-mediated Mannichtype reaction conditions (Scheme 1). The Mannich reaction proceeded at the iminium carbon, which was generated with the secondary amine moiety, with conversion of the NH₂ group into the imino group to give 7a. This result clearly indicates that trimethoxyborane is not acidic enough to mediate addition of the ketene silyl acetal to aldimines. This prompted us to examine the selective Mannich-type reaction of amine-imine conjugates 3m and 3n. The secondary amines 3m and 3n, bearing imine moieties, were subjected to reaction with benzaldehyde and ketene silyl acetal in the presence of B(OMe)₃ (Scheme 2). Mannich reaction took place selectively at the secondary amine moiety to provide the β -amino esters **7a** and **7b** bearing an imine moiety.

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Scheme 1. Selective Mannich-type reaction of secondary amines bearing a primary amine.



Scheme 2. Selective Mannich-type reaction of amine-imine conjugates.

We then examined the Ugi-type reaction using $B(OMe)_3$ as an iminium ion generator. In the presence of $B(OMe)_3$, reaction of benzaldehyde (**2a**), diethylamine (**3a**), and *tert*octyl isocyanide (**8**) in THF proceeded at 80 °C to give the corresponding phenylglycine derivative **9aa** in 68% yield, while no reaction took place at room temperature (Table 3, Entries 1 and 2). Among the solvents tested for the Ugitype reaction, nonpolar solvents such as THF, toluene, and 1,2-dichloroethane gave good yields of the α -amino amides (Entries 2, 5, and 6), while DMSO, which was the solvent of choice in the Mannich-type reaction, resulted in a lower yield (Entry 3). The use of $B(OMe)_3$ as a solvent resulted in a lower yield for the formation of **9aa** (Entry 7).

Reactions of 2a with isocyanide 8 and secondary amines in 1,2-dichloroethane afforded the corresponding Ugi-type products in good yields (Table 4, Entries 1 and 2). The present reaction conditions with trimethoxyborane were also effective for the aliphatic aldehydes. Reaction of 3-phenylpropanal (2e) with 3a and 8 afforded the corresponding Ugitype product in 79% yield (Table 4, Entry 3). The successful use of the aliphatic aldehydes is the significant advantage of the present system over the previously reported aminoborane system that uses 1,^[8] in which the aliphatic aldehydes gave poor yields in the Ugi-type reactions. Secondary amines such as dibutylamine, piperidine, and hexamethyleneimine are involved in the Ugi-type reactions with 3phenylpropanal, which give the corresponding α-amino amides in good yields (Entries 4-6). The reactions of butyraldehyde and propionaldehyde also afforded the Ugi-type

Table 3. Reaction of benzaldehyde, diethylamine, and *tert*-octyl isocyanide in the presence of B(OMe)₃.^[a]



Ениу	Solvent	Temperature [C]	
1	THF	r.t.	trace
2	THF	80	68
3	DMSO	80	25
4	MeOH	80	17
5	toluene	80	61
6	ClCH ₂ CH ₂ Cl	80	70
7	B(OMe) ₃	80	42

[a] Benzaldehyde (2a, 0.20 mmol), diethylamine (3a, 0.30 mmol), and *tert*-octyl isocyanide (8, 0.30 mmol) were treated with trimethoxyborane (0.60 mmol) in the solvent (0.5 mL). [b] NMR yield.

products in high yields (Entries 7 and 8). α -Amino amides containing acid-sensitive THP ether was obtained in 78% yield (Entry 9).

Table 4. Reactions of aldehydes, amines, and isocyanide in the presence of $B(OMe)_3.^{\left[n \right]}$



[a] Aldehyde (2, 0.40 mmol), amine (3, 0.60 mmol), and *tert*-octyl isocyanide (8, 0.60 mmol) were treated with trimethoxyborane (1.2 mmol) in dichloromethane (1.0 mL). [b] Isolated yield. [c] 0.80 mmol of the amine was used.

Conclusions

In summary, we have demonstrated nonacidic Mannichand Ugi-type amination reactions mediated by 1–3 equiv. trimethoxyborane as an iminium ion generator. Because trimethoxyborane is inexpensive, commercially available, and virtually nonacidic, the present reaction system offers a new access to amine derivatives through generation of iminium ions under mild reaction conditions.

Experimental Section

General Procedure for the B(OMe)₃-Mediated Mannich-Type Reaction: A solution of B(OMe)₃ (89 µL, 83 mg, 0.80 mmol), secondary amine (0.40 mmol), and aldehyde (0.60 mmol) in DMSO (1.0 mL) was stirred for 10 min at room temperature. To the solution was added ketene silyl acetal **4** (0.60 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, quenched with ice water, and extracted with ethyl acetate. The organic layer was washed with water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with Na₂SO₄ and filtered, and the solvents evaporated under vacuum. The crude material was purified by silica gel column chromatography to give β-amino esters **5**. For the synthesis of **5hk** and the 10 mmol-scale reactions, the products were isolated by acid–base extraction [0.5 N HCl (aq.)/28% NH₃ (aq.)]. See Supporting Information for details.

General Procedure for the B(OMe)₃-Mediated Ugi-Type Reaction: A solution of B(OMe)₃ (134 μ L, 125 mg, 1.2 mmol), secondary amine (0.60 mmol), aldehyde (0.40 mmol), and isocyanide 8 (0.60 mmol) in 1,2-dichloroethane (1.0 mL) was stirred at 80 °C for 12 h. The mixture was cooled to room temperature, quenched with ice water, and extracted with ethyl acetate. The organic layer was washed with water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with Na₂SO₄ and filtered, and the solvents evaporated under vacuum. The crude material was purified by silica gel column chromatography to give α -amino amides 9.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization of the new compounds are described.

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