Expedient Mukaiyama-Type Mannich Reaction Catalyzed by Lithium Chloride

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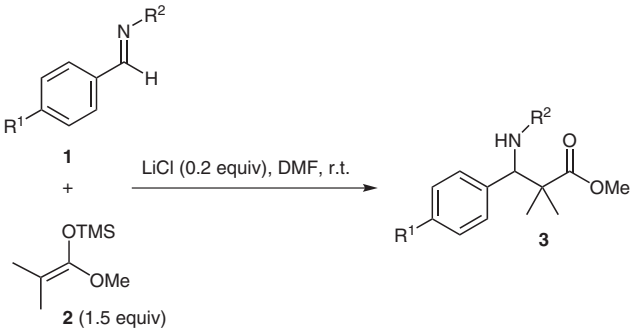
Abstract: The Mannich reaction of methylsilyl enol ether with arylaldimine proceeded in the presence of a catalytic amount of lithium chloride in dimethylformamide at room temperature. The reaction was mild enough to apply to aldimines having the AcO, TBDMSO, or MeS group. Microwave irradiation accelerated the reaction substantially to reduce reaction time.

Keywords: Mannich reaction, aldimines, trimethylsilyl ketene acetal, microwave heating, lithium chloride

The development of environmentally benign synthesis of an organic substance is currently of great interest in the chemical community for applications to promote a sustainable society.[1] The Mannich reaction and its related reactions are among the most basic C–C bond-forming reactions, especially for the synthesis of biologically active β-amino acids along with β-lactams,[2] and thus more benign reaction conditions are always desired. Recently, nucleophilic reaction via a hypervalent silicate intermediate has attracted much attention in the aldol[3] or Mannich reaction,[4] which directly activates silyl enol ether differently from the activation of the carbonyl group with Lewis acid in the original Mukaiyama reaction.[5]

The new Mukaiyama aldol and Mannich reaction protocols[3,4] employ a catalytic amount of Lewis base such as lithium carboxylate or lithium amide, and thus are much more mild, general and environmentally benign, since a stoichiometric amount of a strong Lewis acid is not required. Based on the concept on the new Mukaiyama reaction, we previously reported the practical and benign aldol reaction of silyl ketene acetal with aldehyde catalyzed by a Lewis basic organomolecular catalyst such as pyridine *N*-oxide or *N*-methylimidazole in the presence of lithium chloride,[6] in which the role of lithium chloride was proposed to replace the organomolecular catalyst on a hypervalent alkoxysilicate intermediate after the aldol reaction, thereby facilitating turnover of a catalytic cycle.

In this letter, we report a new environmentally benign Mannich reaction of arylaldimine **1** with silyl enol ether **2** catalyzed by lithium chloride in dimethylformamide (DMF).



Scheme 1 Mukaiyama-type Mannich reaction catalyzed by lithium chloride

Employing the Mannich reaction of *N*-tosyl-*p*-chlorophenylaldimine **1** (R^1 = Cl, R^2 = Ts) with trimethylsilyl ketene acetal **2** as a probe to optimize the reaction conditions, an optimum catalyst was investigated initially (Scheme 1).

Based on our previous result on the aldol reaction, *N*-methylimidazole or pyridine *N*-oxide in combination with lithium chloride was employed in initial attempts (Table 1, entries 1–4). However, during the course of our investigation, we found that only lithium chloride was sufficient to catalyze the Mannich reaction more efficiently at room temperature (Table 1, entries 5 and 6).

Subsequently, employing lithium chloride as the catalyst, an optimum solvent was investigated and DMF exhibited better results among the other solvents tested (Table 2, entries 5 and 6). The addition of H_2O afforded lower yield (Table 2, entry 6) due to hydrolysis of aldimine **1**, which is different from the results obtained by Mukaiyama et al.[3] Although the reaction takes a longer time at room temperature, microwave irradiation was effective in accelerating the reaction substantially (Table 2, entry 7), while conventional heating in an oil bath provided lower yield (Table 2, entry 8).

The optimum reaction conditions (Table 2, entries 5 and 7) were general for various substrates, as shown in Table 3. Since the catalyst (lithium chloride) is a neutral salt, acid- or base-sensitive groups on aldimine **1** remained intact in product **3** (Table 3, entries 9–12). The

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Table 1 Investigation of Optimum Catalyst in the Reaction of Aldimine **1** (R^1 = Cl, R^2 = Ts) and Silyl Ketene Acetal **2**[a]

Entry	Additive	Temp (°C)	Time (h)	Yield (%)
1	*N*-Methylimidazole (0.1 equiv) + LiCl (0.2 equiv)	r.t.	19	71
2[b]	*N*-Methylimidazole (0.1 equiv) + LiCl (0.2 equiv)	70	1.5	87
3	Pyridine *N*-oxide (0.1 equiv) + LiCl (0.2 equiv)	r.t.	19	83
4[b]	Pyridine *N*-oxide (0.1 equiv) + LiCl (0.2 equiv)	70	1.5	86
5	LiCl (0.2 equiv)	r.t.	13	91
6[b]	LiCl (0.2 equiv)	70	1.5	87

[a] Reaction was carried out as described in ref.[8] in DMF. Yield is an isolated pure product based on aldimine **1**.
[b] Heated by microwave irradiation (300 W).

Table 2 Investigation of Optimum Solvent in the Reaction of Aldimine **1** (R^1 = Cl, R^2 = Ts) and Silyl Ketene Acetal **2**[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	THF	r.t.	24	–
2[b]	THF	50	4	–
3	MeCN	r.t.	18.5	79
4[b]	MeCN	50	4	74
5	DMF	r.t.	13	91
6	DMF–H_2O[d]	r.t.	12	62
7[b]	DMF	70	1.5	87
8[c]	DMF	70	1.5	73
9[e]	DMF	70	1.5	75

[a] Reaction was carried out as described in ref.[8] in the presence of LiCl (0.2 equiv). Yield is an isolated pure product based on aldimine **1**.
[b] Heated by microwave irradiation (300 W).
[c] Conventional heating in an oil bath.
[d] Volume ratio of DMF and H_2O was 50:1.
[e] An equivalent amount of aldimine **1** and silyl ketene acetal **2** was employed.

aldimine **1** having a coordinative methylthio group toward Lewis acid afforded Mannich product **3** for the first time (Table 3, entries 13 and 14). Not only aldimine **1** bearing electron-withdrawing substituents (Table 3, entries 3–6) but also electron-donating substituents (Table 3, entries 7–10) provided β-amino ester **3** in satisfactory yields.

The present reaction condition is applicable to *N*-phenylsulfonyl-, *N*-benzoyl- or *N*-*tert*-butoxycarbonyl aldimine **1** (Table 3, entries 15–21), while the yield was moderate due to low stability of the starting *N*-benzoylaldimine **1** (Table 3, entries 19 and 20).

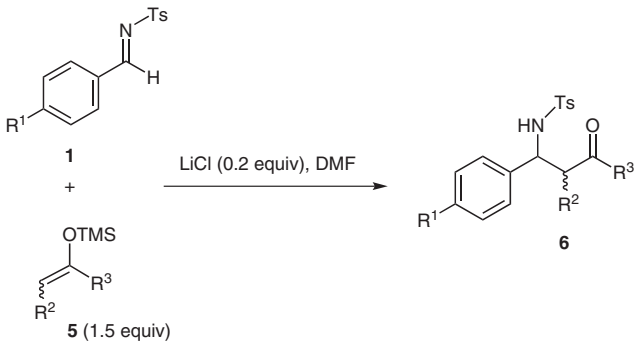
Table 3 Generality of the Reaction Conditions at Room Temperature with Various Types of Aldimine **1** and Silyl Ketene Acetal **2**[a]

Entry	R^1	R^2	Temp (°C)	Time (h)	Yield (%)
1	H	Ts	r.t.	40	84
2[b]	H	Ts	70	3	75
3	NO_2	Ts	r.t.	1	95
4[b]	NO_2	Ts	70	0.25	83
5	Cl	Ts	r.t.	13	91
6[b]	Cl	Ts	70	1.5	87
7	MeO	Ts	r.t.	72	76
8[b]	MeO	Ts	70	4	77
9	TBDMSO	Ts	r.t.	24	70
10[b]	TBDMSO	Ts	70	2	51
11	AcO	Ts	r.t.	72	90
12[b]	AcO	Ts	70	5	89
13	MeS	Ts	r.t.	120	74
14[b]	MeS	Ts	70	10	77
15	H	SO_2Ph	r.t.	29	70
16[b]	H	SO_2Ph	70	2.5	74
17	Cl	SO_2Ph	r.t.	12	93
18[b]	Cl	SO_2Ph	70	3.5	86
19	H	Bz	r.t.	23	58
20[b]	H	Bz	70	1.5	51
21	H	Boc	r.t.	38	76

[a] Reaction was carried out as described in ref.[8] employing 0.2 equiv of LiCl. Yield is an isolated pure product based on aldimine.
[b] Heated by microwave irradiation (300 W).

Silyl enol ether of methyl propionate **5** (R^2 = Me, R^3 = OMe, *E*/*Z* = 3:1) provided Mannich product **6** in good yield (Scheme 2 and Table 4, entries 1–4). The reaction of silyl enol ether of acetophenone **5** (R^2 = H, R^3 = Ph) or propiophenone **5** (R^2 = Me, R^3 = Ph, *Z*-isomer) proceeded in the same manner to afford Mannich product **6** (Table 4, entries 5–8). Moderate *anti* selectivity might be explained by an acyclic transition-state model proposed by Mukaiyama et al.[4] The low yield in entry 6 was due to the β-elimination of *N*-tosylamine at elevated temperature to afford 4-aryl-3-buten-2-one as a side product. In the reaction of enol ether of propiophenone **5**, undesired β-elimination was suppressed to proceed with moderate *anti* selectivity[4] (Table 4, entries 7 and 8).

The reaction of the sterically less demanding dimethylsilylketene acetal **7**,[7] which was anticipated to facilitate the formation of a hypervalent silicate intermediate

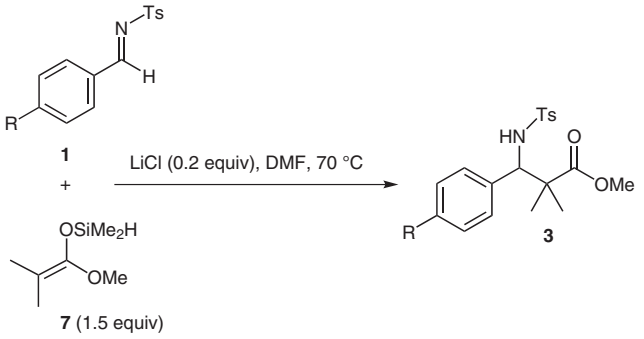


Scheme 2 Mukaiyama-type Mannich reaction of various types of silyl enol ether

Table 4 Mukaiyama-Type Mannich Reaction of Silyl Enol Ether **5**[a]

Entry	R^1	R^2	R^3	Temp (°C)	Time	Yield (%)	*anti*/*syn*
1	Cl	Me	OMe	r.t.	2 h	88	3.9:1
2[b]	Cl	Me	OMe	70	25 min	90	3.3:1
3	H	Me	OMe	r.t.	1 h	91	3.4:1
4[b]	H	Me	OMe	70	20 min	80	2.5:1
5	Cl	H	Ph	r.t.	42 h	80	
6[b]	Cl	H	Ph	70	3	45	
7	Cl	Me	Ph	r.t.	5 d	78	2.3:1
8[b]	Cl	Me	Ph	70	9.5 h	80	1.6:1

[a] Reaction was carried out as described in ref.[8] employing 0.2 equiv of LiCl. Yield is an isolated pure product based on aldimine **1**.
[b] Heated by microwave irradiation (300 W).



Scheme 3 Mukaiyama-type Mannich reaction of dimethylsilyl ketene acetal **7** under microwave irradiation

(Scheme 3) proceeded more readily than the reaction of trimethylsilyl ketene acetal **2**, as shown in Table 5.

In summary, we have demonstrated a new Mannich reaction of readily available and stable methylsilyl enol ether with various arylaldimines catalyzed by lithium chloride in DMF. Since lithium chloride is a neutral, cheap, nontoxic, and shelf-stable catalyst compared to lithium carboxylate or amide which requires methyllithium for its preparation,[4] the present reaction offers a mild, practical, environmentally and economically benign method for synthesizing β-amino carbonyl compounds, which are versatile building blocks for the synthesis of various biologically important products.

Table 5 Mukaiyama-Type Mannich Reaction of Dimethylsilyl Ketene Acetal **7**[a]

Entry	R	Time	Yield (%)
1	H	5 h	73
2	Cl	75 min	87
3	NO_2	15 min	89
4	MeO	5.5 h	76

[a] Reaction was carried out as described in ref.[8] employing 0.2 equiv of LiCl under microwave irradiation at 70 °C. Yield is an isolated pure product based on aldimine **1**.

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(8) **Typical Experimental Procedure**
To a stirred solution of *N*-*p*-toluenesulfonyl-*p*-chlorophenylaldimine (**1**, 118 mg, 0.4 mmol) and LiCl (3.4 mg, 0.08 mmol) in DMF (1.5 mL) was added trimethylsilyl ketene acetal **2** (130 μL, 0.6 mmol) at r.t. under nitrogen atmosphere. After stirring for 13 h, the reaction was quenched by adding H_2O. The product was extracted with EtOAc twice and the combined organic layer was washed with H_2O and brine, and then evaporated to dryness. Column chromatography of the residue (eluent, EtOAc–*n*-hexane, 1:2) afforded β-amino ester **3** (145 mg, 91%).