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An environmentally friendly procedure for Mukaiyama aldol and Mukaiyama–Michael reactions using a catalytic amount of DBU under solvent- and metal-free conditions

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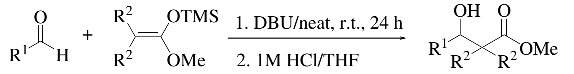
Abstract—Mukaiyama aldol and Mukaiyama–Michael reactions can proceed smoothly in the presence of a catalytic amount of DBU (20% mmol), to afford the corresponding products in moderate to good yields. This solvent- and metal-free approach provides an environmentally friendly procedure for Mukaiyama reactions.

In recent years, much efforts have been directed towards the development of new organic transformations under environmentally friendly conditions. In relation to this, much studies have been focused on the development of new C–C bond formation reactions in green media without the use of metal catalyst.[1] For example, our group has established an efficient method to promote the Mukaiyama aldol reaction without metal catalyst in water[2] as well as in ionic liquids.[3] In connection with our efforts to develop new organic transformations without the use of metal complexes, we would like to report that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzes Mukaiyama aldol[4] and Mukaiyama–Michael[4] reactions under solvent-free condition.

Initial studies were focused on the Mukaiyama aldol reaction of aldehydes with ketene silyl acetals. The reactions were conducted at room temperature using a catalytic amount of DBU (20% mmol) under solvent-free condition. All the results are summarized in Table 1.

As shown in Table 1, we could observe that the solvent-free reactions proceeded efficiently in all cases in the presence of DBU to afford the desired products in moderate to good yields.

Table 1. DBU-catalyzed Mukaiyama aldol reaction of ketene silyl acetals with different aldehydes under solvent-free conditions[a,5]



Entry	R^1	R^2	Product	Yield (%)[b]
1	2-$NO_2C_6H_4$	CH_3	**1a**	67
2	2-$NO_2C_6H_4$	H	**1b**	60[c]
3	4-ClC_6H_4	CH_3	**1c**	73
4	4-ClC_6H_4	H	**1d**	60
5	C_6H_5	CH_3	**1e**	77
6	C_6H_5	H	**1f**	51
7	4-MeC_6H_4	CH_3	**1g**	79
8	4-MeC_6H_4	H	**1h**	55
9	2-$OMeC_6H_4$	CH_3	**1i**	68
10	2-$OMeC_6H_4$	H	**1j**	33
11	$C_6H_5CH{=}CH$	CH_3	**1k**	83
12	$C_6H_5CH{=}CH$	H	**1l**	65
13	3-C_5H_4N	CH_3	**1m**	63[d]
14	3-C_5H_4N	H	**1n**	79[d]
15	*n*-C_8H_{17}	CH_3	**1o**	58
16	*n*-C_8H_{17}	H	**1p**	64

[a] The reactions were carried out at room temperature for 24 h using aldehydes (1 mmol), ketene silyl acetals (2 mmol), DBU (0.2 mmol).
[b] Isolated yield.
[c] An aldol condensation product was obtained in 22% yield.
[d] Including TMS protected aldol product.

Keywords: Mukaiyama reaction; DBU; Organic catalyst; Solvent-free condition; Metal-free.

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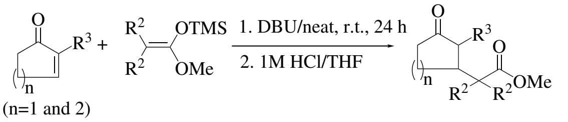
Table 2. DBU-catalyzed Mukaiyama–Michael reaction of enones with ketene silyl acetals under solvent-free condition[a,5]



Entry	R^2	R^3	*n*	Product	Yield (%)[b]
1	Me	H	2	**2a**	76
2	H	H	2	**2b**	70
3	Me	H	1	**2c**	71
4	H	H	1	**2d**	81
5	Me	Me	1	**2e**	68[c]
6	H	Me	1	**2f**	61[c]

[a] The reactions were carried out at room temperature for 24 h using enone (1 mmol), ketene silyl acetals (2 mmol), DBU (0.2 mmol).

[b] Isolated yield.

[c] Diastereoselectivity was not determined.

It was worthy to note that the reaction system also worked well with aliphatic aldehydes such as nonyl aldehyde (Table 1, entries 15 and 16). For conjugated aldehyde (Table 1, entries 11 and 12), a good yield of aldol product was selectively obtained without detection of the 1,4-adduct. Similar results were obtained with 1-methoxy-1-[(trimethylsilyl)oxy]ethane.

In addition, we also carried out the DBU-catalyzed Mukaiyama aldol reaction in different organic solvents using benzaldehyde as substrate, however, low yields were obtained in organic solvents (MeOH: 5% yield; THF: 53% yield; CH_2Cl_2: 32% yield; DMF: 67% yield) in comparison with neat condition (77% yield).

Next, we extended this method to Mukaiyama–Michael reactions involving α,β-unsaturated carbonyl compounds. The results are summarized in Table 2.

As shown in Table 2, the reactions proceeded smoothly under solvent-free conditions with the addition of a catalytic amount (20% mmol) of DBU.

It is assumed that the Mukaiyama reactions might proceed via the activation of trimethylsilyl enol ether by forming a hypervalent silicate between nitrogen atom of DBU and silicon atom of the enolate.

In summary, we have developed an efficient and environmentally friendly protocol for Mukaiyama reactions, employing a catalytic amount of DBU under solvent-free conditions at room temperature. Mild reaction conditions, environmental benign catalytic system, cheap organic catalyst, good selectivity and a moderate to high yields of the products can make this procedure an attractive alternative to conventional methodologies, which using organic solvents and metal-containing Lewis acids or bases with inherent limitations.

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5. *Representative experimental procedure*: A mixture of benzaldehyde (1 mmol), 1-methoxy-2-methyl-1-trimethylsilyloxypropene (2 mmol) and DBU (0.2 mmol) was stirred at room temperature for 24 h. After that, 2 mL of 1 M aqueous HCl and 2 mL THF were added to the reaction system. After stirring vigorously for a while, the product was extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated in vaccuo followed by the purification using flash silica gel chromatography to give desired products. All the new products are characterized by ^1H NMR, ^{13}C NMR, FTIR and mass spectrometry.