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1-Methylimidazole 3-*N*-oxide as a new promoter for the Morita–Baylis–Hillman reaction

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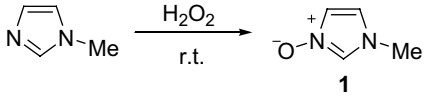
Abstract—The Morita–Baylis–Hillman reaction of aldehydes with α,β-unsaturated ketones can be affected by the Lewis bases. We have found that 1-methylimidazole 3-*N*-oxide promoted the Morita–Baylis–Hillman reaction of various activated aldehyde compounds in non-solvent system. This is a mild reaction condition and requires no special equipment to give the Morita–Baylis–Hillman adducts.

The Morita–Baylis–Hillman reaction is an important carbon–carbon formation process and has drawn considerable attention over the past few years. The condensation reaction of an acrylate or otherwise activated terminal olefin with an aldehyde, provides a simple and convenient route to a very useful class of functionalized olefins. This reaction involves three components: an activated alkene, electrophile and tertiary amine, respectively. Lewis bases such as 1,4-diazabicyclo[2.2.2]-octane (DABCO),[1] DMAP,[2] DBU,[3] phosphines,[4] chalcogen species[5] and imidazole[6] are frequently used in these reactions as catalysts. Besides, Lewis acid-accelerated reactions were also reported, such as $TiCl_4$,[7] Et_2AlI[8] and BF_3.[9] In addition to variations of catalysts and solvent,[10] modifications such as the use of high pressure,[11] microwave[12] and ultrasound[13] have given some promising results. On the other hand, the solvent also has a significant effect on the reaction rate[10a,14] and even different salt effects[15] on the Morita–Baylis–Hillman reaction. This prompted us to develop a new series of catalysts to replace the Lewis bases in the traditional Morita–Baylis–Hillman reaction.

In general, *N*-oxide compounds are a weak base and a good nucleophile. And the *N*-oxide compounds are easy to prepare and to preserve. 1-Methyl imidazole as a starting material followed by the oxidation of H_2O_2 at room temperature to yield the 1-methylimidazole 3-*N*-oxide (**1**) (Scheme 1). In addition, compound **1**, a non-hindered base has been reasonably versatile, working for a range of substrates and easily to remove. In general process, the Morita–Baylis–Hillman reaction suffers from poor reaction rates and long reaction time using DABCO or other strong Lewis bases. In our process, we used methyl vinyl ketone (MVK), methyl acrylate with various aldehydes in the presence of compound **1**, which not only produced the desired product in moderate to high yield but also reduced the side products. For example, in the reaction of *p*-nitrobenzaldehyde (1.0 equiv) with MVK (2.0 equiv), (Table 1, entry 1) can be obtained in 95% yield in the presence of 1-methylimidazole 3-*N*-oxide (2.0 equiv)[17] for 0.7 h at room temperature. Our condition goes very smoothly without any solvent and these reactions take place to give high yields and accelerate the reaction rate. The best results were obtained when aldehyde on *para*- or *ortho*-position have an electron withdrawal groups such as (Table 1, entries 1–3, 7 and 10). On the other hand, if these positions have electron donating groups such as (Table 1, entries 11–13), the yields are not good enough (25–56%). For this reason, we set up the reaction under microwave irradiation.[18] The results were rather unfortunate in that the yield of this process did not show improvement. In addition, a plausible mechanism using tertiary amine



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Scheme 1. Synthesis of 1-methylimidazole 3-*N*-oxide.[16]

Keywords: *N*-oxide; Morita–Baylis–Hillman reaction.
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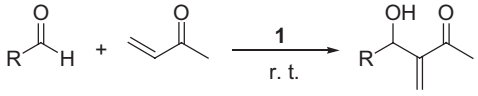
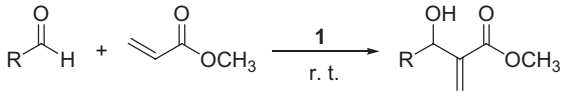
Table 1. Reaction of various aldehydes with MVK in the presence of 1-methyl-imidazole 3-*N*-oxide[a]



Entry	Aldehyde	Time (h)	Yield[b] (%)
1	*p*-Nitrobenzaldehyde	0.7	95
2	Methyl 4-formylbenzoate	2	87
3	4-(Trifluoromethyl)benzaldehyde	3.5	89
4	1-Naphthaldehyde	35	67
5	2-Naphthaldehyde	2.7	63
6	Piperonal	12	72
7	4-Biphenylcarboxaldehyde	6	68
8	2-Fluorobenzaldehyde	18	52
9	2-Bromobenzaldehyde	4.5	83
10	4-Chlorobenzaldehyde	4	88
11	4-Methoxybenzaldehyde	22	35
12	3,4,5-Trimethoxybenzaldehyde	44	56
13	4-Hydroxybenzaldehyde	26	25
14	4-(Methylthio)benzaldehyde	19	76
15	2-Quinolinecarbaldehyde	18	79
16	4-Quinolinecarbaldehyde	23.5	58
17	2-Pyridinecarboxaldehyde	17	78
18	3-Pyridinecarboxaldehyde	23	51
19	4-Bromo-2-thiophenecarbozaldehyde	18	85
20	5-(3-Chlorophenyl)furfural	3.5	89

[a] All reactions were conducted using 1:2 ratio of MVK and aldehyde at room temperature in the presence of compound **1** (2 equiv).
[b] Isolated yield.

Table 2. Reaction of various aldehydes with methyl acrylate in the presence of 1-methylimidazole 3-*N*-oxide[a]



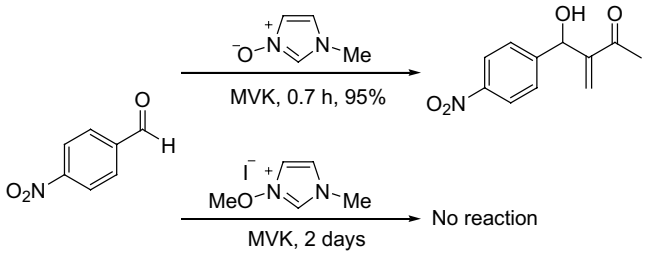
Entry	Aldehyde	Time (h)	Yield[b] (%)
21	*p*-Nitrobenzaldehyde	6	92
22	Methyl 4-formylbenzoate	27	81
23	4-(Trifluoromethyl)benzaldehyde	3	86
24	1-Naphthaldehyde	119	73
25	2-Naphthaldehyde	56	82
26	Piperonal	35	76
27	4-Biphenylcarboxaldehyde	40	57
28	2-Fluorobenzaldehyde	22	69
29	2-Bromobenzaldehyde	19	71
30	4-Chlorobenzaldehyde	25	43
31	4-Methoxybenzaldehyde	56	32
32	3,4,5-Trimethoxybenzaldehyde	27	56
33	4-Hydroxybenzaldehyde	—	—[c]
34	4-(Methylthio)benzaldehyde	110	75
35	2-Quinolinecarbaldehyde	15	65
36	4-Quinolinecarbaldehyde	19.5	82
37	2-Pyridinecarboxaldehyde	56	72
38	3-Pyridinecarboxaldehyde	47	58
39	4-Bromo-2-thiophenecarbozaldehyde	23	96
40	5-(3-Chlorophenyl)furfural	3.5	91

[a] All reactions were conducted using 1:2 ratio of methyl acrylate and aldehyde at room temperature in the presence of compound **1** (2 equiv).
[b] Isolated yield.
[c] No reaction.

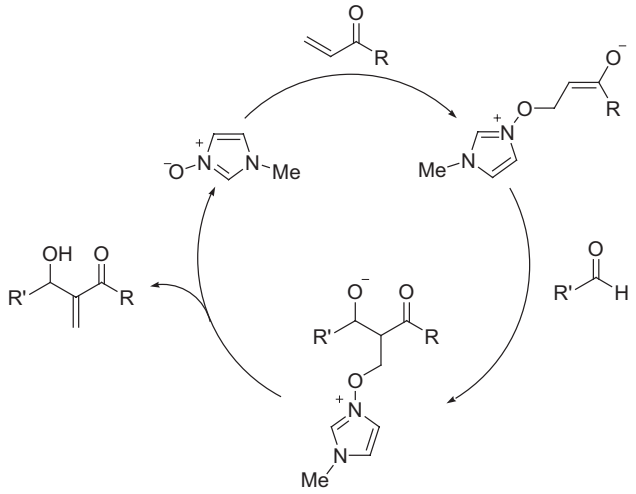
as a nucleophile for the Morita–Baylis–Hillman reaction has been proposed and the addition of ammonium enolate with an aldehyde is believed to be the rate-determining step.[19] 1-Methyl 3-*N*-methoxy imidazole, prepared by the methylation of compound **1** with methyl iodide, is subjected to the Morita–Baylis–Hillman reaction under the same condition as compound **1**. After two days, TLC shows no formation of any product (Scheme 2), Table 2.

Therefore, we propose a mechanism for the Morita–Baylis–Hillman reaction with compound **1** as the Scheme 3.

In conclusion, we have shown that 1-methylimidazole 3-*N*-oxide is a good promoter and it can be used to replace the strong Lewis bases for the Morita–Baylis–Hillman reaction. An efficient and simple route to α-(hydroxyalkyl)ketones or α-(hydroxyalkyl)acrylates can be prepared easily.



Scheme 2.



Scheme 3.

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16. Preparation of 1-methylimidazole 3-*N*-oxide **1**: To a stirred solution of 1-methyl imidazole (8.50 g, 0.1 mol) in THF (200 mL), 30% H_2O_2 (13.6 mL, 0.12 mol) was added. The reaction mixture was stirred at room temperature for 3 h. Then, the mixture was washed with water (2×200 mL) and water layer extracted with 300 mL dichloromethane. The organic layer were combined, dried over anhydrous $MgSO_4$ and concentrated. A light yellow oil, 1-methylimidazole 3-*N*-oxide, was obtained (8.93 g, 95%).
17. In order to reduce the reaction time, we tried to increase the catalyst amount of compound **1** (0.5–5 equiv). The use of a small amount of 3-*N*-oxide (0.5–1 equiv) resulted in lower conversion yield and longer reaction time. We found 2 equiv of compound **1** is the best condition for the Morita–Baylis–Hillman reaction.
18. For example, 4-methoxybenzaldehyde (136 mg, 1 mmol), MVK (140 mg, 2 mmol) and 1-methylimidazole 3-*N*-oxide (196 mg, 2 mmol) were added a 10 mL flask. The reaction mixture was exposed to microwave irradiation (600 W) for 30 min.
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