Michael Addition of Active Methylene Compounds to α,β-Unsaturated Carbonyl Compounds under the Influence of Molecular Sieves in Dimethyl Sulfoxide

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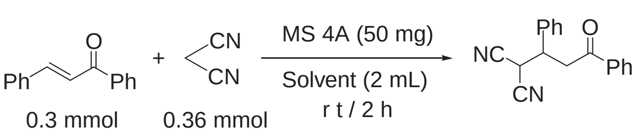
The Michael addition of active methylene compounds to α,β-unsaturated carbonyl compounds in the presence of MS 4A in dimethyl sulfoxide proceeds smoothly to afford the corresponding 1,4-addition products in good to high yields.

The Michael addition is an important and useful class of reactions in organic synthesis, and generally requires a catalyst such as K_2CO_3, piperidine or LiI.[1,2] On the other hand, Shirakawa and Shimizu very recently reported that the catalyst-free Michael addition was efficiently promoted in ethanol by hydrogen-bonding activation.[3] Much attention has been focused on catalyst-free reactions, because reducing the use of catalyst is environmentally friendly.

In recent years, dimethyl sulfoxide (DMSO) has received renewed attention as a polar solvent and a promoter of efficient organic reactions.[4] We also developed several effective reactions in DMSO. For example, cyanocarbonation of aldehydes[5] and trifluoromethylation of carbonyl compounds[6] were documented. During the course of our research to promote fundamental carbon–carbon bond-forming reactions without catalysts in DMSO,[7] a novel Henry reaction was developed successfully in 2007.[8] The Henry reaction of various carbonyl compounds with nitroalkanes proceeded very smoothly to afford the corresponding β-nitroalcohol without a base catalyst. Furthermore, the 1,4-addition of nitroalkane to α,β-unsaturated ketones was also performed in DMSO. These results suggested that a similar Michael addition of other active methylene compounds, such as malononitrile and malonate, having larger pK_a values than those of nitroalkanes, could be performed in DMSO.

First, we chose the reaction of chalcone (0.3 mmol) with malononitrile (0.36 mmol) in the presence of molecular sieves (MS) 4A (50 mg) as a model case for the optimization of the solvent. As can be seen in Table 1, toluene, dichloromethane, THF, and acetonitrile were found to be ineffective for this reaction. The desired reaction proceeded moderately in DMF and chloroform, but we discovered that DMSO was the best solvent. The corresponding 1,4-addition product was obtained in a 71% isolated yield (Entry 7).

Table 1. Effect of solvents

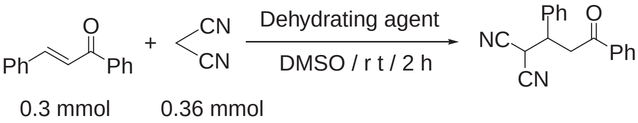


Entry	Solvent	Yield/%[a]
1	Toluene	0
2	CH_2Cl_2	1
3	THF	1
4	CH_3CN	0
5	DMF	46
6	$CHCl_3$	59
7	DMSO	71

[a] Isolated yield of purified product.

Next, we attempted Michael additions in the presence of various dehydrating agents as additives in DMSO (Table 2). When the reaction was carried out without an additive, we obtained the desired compound in only 6% yield. On the other hand, the additions of MS led to dramatic increases in the yield. In particular, we found MS 4A, MS 13X, and Drierite ($CaSO_4$) to be extremely effective.[9] A longer reaction time (12 h) improved yields of the product as described in Entry 9.

Table 2. Effect of dehydrating agents



Entry	Dehydrating agent	Yield/%[a]
1	None	6
2	MS 3A (50 mg)	60
3	MS 4A (50 mg)	71
4	MS 5A (50 mg)	30
5	MS 13X (50 mg)	70
6	Drierite (50 mg)	72
7	$MgSO_4$ (50 mg)	34
8	MS 4A (100 mg)	73
9	MS 4A (100 mg)	92[b]

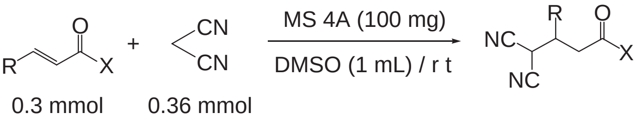
[a] Isolated yield of purified product. [b] The reaction was carried out for 12 h.

Overall, we detemined the optimal conditions as follows: the reaction of enones (0.3 mmol) with malononitrile (0.36 mmol) in the presence of MS 4A (100 mg) in DMSO at room temperature.[10]

We examined Michael additions of malononitrile to various α,β-unsaturated carbonyl compounds, as listed in Table 3. The reactions were uniformly successful for chalcone derivatives (Entries 1–8). In the case of sterically bulky enone, the desired compound was obtained in 52% yield (Entry 6). It was found that ethyl crotonate is also a good Michael acceptor (Entry 10). When the 1,4-addition to cyclic enone was performed under similar reaction conditions, the corresponding product was given in only 36% yield (Entry 11). In addition, when β-nitrostyrene was used as a Michael acceptor, we obtained the desired product in 65% yield (Entry 12).

We also tested various other active methylene compounds (Table 4). Various malonates yielded successful results (Entries 1–3). Acetylacetone was found to be a good Michael donor, as

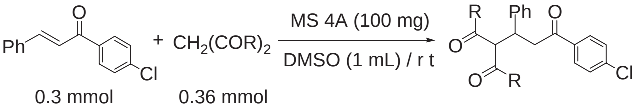
Table 3. Michael addition to various α,β-unsaturated carbonyl compounds



Entry	R	X	Time /h	Yield /%[a]
1	Ph	Ph	12	93
2	4-ClC$_6$H$_4$	Ph	12	91
3	4-BrC$_6$H$_4$	Ph	4	91
4	4-MeC$_6$H$_4$	Ph	12	98
5	4-MeOC$_6$H$_4$	Ph	12	89
6	2,4,6-Me$_3$C$_6$H$_2$	Ph	12	52
7	Ph	4-ClC$_6$H$_4$	2	92
8	Ph	4-MeOC$_6$H$_4$	12	96
9	Me	4-MeC$_6$H$_4$O	10	48
10	Me	OEt	24	65
11	2-Cyclohexenone		12	36
12	β-Nitrostyrene		8	65[b]

[a] Isolated yield of purified product. [b] The reaction was carried out with DMSO (0.3 equiv) in hexane (2 mL).

Table 4. Michael addition of various active methylene compounds



Entry	R	Time/h	Yield/%[a]
1	OMe	12	92
2	OEt	24	88
3	OBn	36	73
4	Me	24	65

[a] Isolated yield of purified product.

evident from Entry 4. Although the detailed reaction mechanism has not been clarified yet, MS 4A played a very important role in promoting the Michael addition.

In conclusion, we have developed a convenient Michael addition of various active methylene compounds to various enones in DMSO under the influence of MS 4A. It should be noted that this very efficient reaction is simpler, cheaper, and more environment-friendly than other available methods. This reaction is very attractive from the standpoint of green chemistry, because the atom economy is extremely high, consuming almost all reagents under very mild reaction conditions. Further studies on the development of DMSO-promoted benign reactions are currently in progress in our laboratory.

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10 Typical experimental procedure is as follows: A mixture of chalcone (62.5 mg, 0.3 mmol) and malononitrile (23.8 mg, 0.36 mmol) in DMSO (1 mL) in the presence of MS 4A (100 mg) was stirred at room temperature under an argon atmosphere. After 12 h, the reaction mixture was quenched with a phosphate buffer (pH 7, 20 mL). The organic materials were extracted with AcOEt and dried over anhydrous MgSO$_4$. 4-Oxo-2,4-diphenylbutane-1,1-dicarbonitrile (76.8 mg, 92%) was isolated by TLC on silica gel.