

## Henry Reaction and 1,4-Addition of Nitroalkanes to $\alpha,\beta$ -Unsaturated Carbonyl Compounds under the Influence of MS 4 Å in DMSO

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In the presence of MS 4 Å in DMSO (dimethyl sulfoxide), Henry reaction with various carbonyl compounds and nitroalkanes proceeded smoothly to give the corresponding  $\beta$ -nitroalcohol without a base catalyst. Moreover, 1,4-addition of nitroalkane to  $\alpha,\beta$ -unsaturated ketones was also performed in DMSO.

Our recent investigations documented the silylation of alcohols with trialkylsilyl chloride in DMSO–hexane without a catalyst,<sup>1</sup> cyanobenzoylation of aldehydes with benzoyl cyanide in DMSO,<sup>2</sup> and cyanocarbonylation of aldehydes with cyanofornate in DMSO.<sup>3</sup> And more recently, we have discovered a trifluoromethylation of carbonyl compounds using TMSCF<sub>3</sub> in DMSO without a catalyst.<sup>4</sup> On the basis of this background in the papers, we would like to report another new DMSO-promoted efficient reaction, Henry reaction of aldehydes in DMSO.

The Henry reaction is a fundamental carbon–carbon bond-forming reaction in synthetic organic chemistry.<sup>5</sup> The continuous discovery of new and efficient Henry reactions is one of the key steps in the development of simpler, cheaper, and more environment-friendly synthesis of complex molecules.<sup>6</sup> A catalytic Henry reaction is especially very important, because it leads to the benign creation of new chemical bonds.<sup>7–9</sup>

In the first place, we tried the reaction of benzaldehyde (0.3 mmol) with 5 equiv. of nitromethane in DMSO. The reaction mixture was stirred at room temperature for 24 h. The usual work-up afforded the corresponding product, 1-phenyl-2-nitroethanol, in 10% isolated yield (Table 1, Run 1). On the other hand, a similar reaction in the presence of molecular sieves

(MS) 4 Å (50 mg) proceeded very smoothly to afford the desired product in 88% yield (Run 2). When the reaction was performed in the presence of MS 3 Å and 13X, the yield was slightly decreased (Runs 9 and 11). It was also demonstrated that DMSO is the most suitable solvent for this transformation as shown in Table 1. Although use of DMF as a solvent afforded the desired product in 52% yield, MeCN, CH<sub>2</sub>Cl<sub>2</sub>, hexane, and THF were not effective for this reaction (Runs 3–7). As a whole, we found that a reaction using MS 4 Å in DMSO gave the product in 91% yield.

The substrate scope of this reaction was examined and the successful results are summarized in Table 2.<sup>10</sup> Good to high yield of Henry reaction products was achieved for many aromatic aldehydes containing different substituents on the benzene ring and several aliphatic aldehydes. The reaction of aliphatic aldehydes proceeded in shorter reaction time as compared to aromatic aldehydes (Runs 15 and 16). Even in the case of sterically hindered aliphatic aldehyde, the desired product was obtained in 61% yield (Run 17). Additionally, the reaction of ethyl pyruvate with nitromethane was similarly performed to give

**Table 2.** Henry reaction with various carbonyl compounds<sup>a</sup>

$R^1-\overset{\text{O}}{\parallel}{C}-R^2 + \text{MeNO}_2 \xrightarrow[\text{rt, 24 h}]{\text{MS 4 Å, DMSO}} R^1-\overset{\text{OH}}{\underset{\text{R}^2}{\text{C}}}-\text{CH}_2-\text{NO}_2$		
Run	Substrate	Yield/% <sup>b</sup>
1	PhCHO	91
2	2-MeC <sub>6</sub> H <sub>4</sub> CHO	84
3	3-MeC <sub>6</sub> H <sub>4</sub> CHO	88
4	4-MeC <sub>6</sub> H <sub>4</sub> CHO	83
5	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CHO	38
6	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	67
7	4-BrC <sub>6</sub> H <sub>4</sub> CHO	91
8	4-NCC <sub>6</sub> H <sub>4</sub> CHO	82
9	4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> CHO	93
10	4-AcC <sub>6</sub> H <sub>4</sub> CHO	64
11	1-Naphthaldehyde	90
12	2-Naphthaldehyde	89
13	PhCH <sub>2</sub> CH <sub>2</sub> CHO	35 <sup>c</sup>
14	PhCH <sub>2</sub> CH <sub>2</sub> CHO	trace <sup>c,d</sup>
15	PhCH <sub>2</sub> CH <sub>2</sub> CHO	79 <sup>e</sup>
16	cyclo-C <sub>6</sub> H <sub>11</sub> CHO	93 <sup>e</sup>
17	BnOCH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> CHO	61
18	AcCO <sub>2</sub> Et	84

<sup>a</sup>All reactions were performed using benzaldehyde (0.3 mmol) and nitromethane (1.5 mmol) in DMSO (2 mL) in the presence of MS 4 Å (60 mg). <sup>b</sup>Yield of isolated product after chromatographic purification. <sup>c</sup>Without MS 4 Å. <sup>d</sup>H<sub>2</sub>O (100  $\mu$ L) was added. <sup>e</sup>The reaction time was 6 h.

**Table 1.** Optimization of the reaction conditions<sup>a</sup>

$\text{PhCHO} + \text{MeNO}_2 \xrightarrow[\text{rt, 24 h}]{\text{DMSO}} \text{Ph}-\overset{\text{OH}}{\text{CH}}-\text{CH}_2-\text{NO}_2$			
Run	Solvent	Molecular sieves	Yield/% <sup>b</sup>
1	DMSO	none	10
2	DMSO	4 Å (50 mg)	88
3	DMF	4 Å (50 mg)	52
4	MeCN	4 Å (50 mg)	trace
5	CH <sub>2</sub> Cl <sub>2</sub>	4 Å (50 mg)	0
6	Hexane	4 Å (50 mg)	trace
7	THF	4 Å (50 mg)	trace
8	DMSO	4 Å (60 mg)	91
9	DMSO	3 Å (60 mg)	88
10	DMSO	5 Å (60 mg)	28
11	DMSO	13X (60 mg)	84

<sup>a</sup>All reactions were performed using benzaldehyde (0.3 mmol) and nitromethane (1.5 mmol) in DMSO (2 mL).

<sup>b</sup>Yield of isolated product after chromatographic purification.

**Table 3.** Henry reaction with various nitroalkanes<sup>a</sup>

$$\text{RCHO} + \text{R}'\text{CH}_2\text{NO}_2 \xrightarrow[\text{rt, 24 h}]{\text{MS 4 \AA, DMSO}} \text{RCH(OH)CH(R)CH}_2\text{NO}_2$$

Run	Substrate	Nitroalkane	Yield/% <sup>b</sup>
1	PhCHO	MeNO <sub>2</sub>	91
2	PhCH <sub>2</sub> CH <sub>2</sub> CHO	MeNO <sub>2</sub>	79 <sup>c</sup>
3	PhCHO	EtNO <sub>2</sub>	84 <sup>d</sup>
4	PhCH <sub>2</sub> CH <sub>2</sub> CHO	EtNO <sub>2</sub>	88 <sup>c,e</sup>
5	PhCHO	<i>i</i> -PrNO <sub>2</sub>	2
6	PhCH <sub>2</sub> CH <sub>2</sub> CHO	<i>i</i> -PrNO <sub>2</sub>	53

<sup>a</sup>All reactions were performed using benzaldehyde (0.3 mmol) and nitroalkane (1.5 mmol) in DMSO (2 mL) in the presence of MS 4 Å (60 mg). <sup>b</sup>Yield of isolated product after chromatographic purification. <sup>c</sup>The reaction time was 6 h. <sup>d</sup>The ratio of diastereomers was 2:3. <sup>e</sup>The ratio of diastereomers was 1:1.

**Table 4.** 1,4-Addition of nitroalkanes to various  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>a</sup>

$$\text{R}^1\text{CH=CHC(=O)R}^2 + \text{MeNO}_2 \xrightarrow[\text{rt, 24 h}]{\text{MS 4 \AA, DMSO}} \text{R}^1\text{CH}_2\text{CH(R)C(=O)R}^2$$

Run	R <sup>1</sup>	R <sup>2</sup>	Yield/% <sup>b</sup>
1	Ph	Me	26
2	Ph	Ph	92
3	2-MeC <sub>6</sub> H <sub>4</sub>	Ph	85
4	3-MeC <sub>6</sub> H <sub>4</sub>	Ph	84
5	4-MeC <sub>6</sub> H <sub>4</sub>	Ph	83
6	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	Ph	26
7	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	45
8	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	84
9	1-Naphthyl	Ph	65
10	2-Naphthyl	Ph	88
11	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	83
12	Diethyl benzylidenemalonate		46
13	Ph	Ph	74 <sup>c</sup>
14	Ph	Ph	6 <sup>d</sup>

<sup>a</sup>All reactions were performed using enone (0.3 mmol) and nitroalkane (1.5 mmol) in DMSO (2 mL) in the presence of MS 4 Å (30 mg). <sup>b</sup>Yield of isolated product after chromatographic purification. <sup>c</sup>Nitroethane was used. The ratio of diastereomers was 1:1. <sup>d</sup>2-Nitropropane was used.

the corresponding 1,2-addition product of a carbonyl group (Run 18). At the present time, the role of MS 4 Å is supposed to be a dehydrating agent, because the reaction with a small amount of water in the absence of MS 4 Å has scarcely occurred (Run 14).<sup>11</sup>

In order to determine the scope and limitation of this reaction, the Henry reaction was tested using other nitroalkanes. The reaction of aldehydes with nitroethane gave the desired products in good yields (Table 3, Runs 3 and 4). In contrast, the reaction with rather sterically bulky, 2-nitropropane, afforded lower yield of products (Runs 5 and 6).

The reaction also occurred with  $\alpha,\beta$ -unsaturated ketones.<sup>12</sup> 1,4-Addition products were uniformly obtained in moderate to high yields as shown in Table 4. Especially, the reaction of

chalcone and the various substituted chalcones gave the desired products in high yields. However, the reaction of sterically hindered chalcone (Run 6) or *p*-methoxy-substituted chalcone on the  $\beta$ -phenyl group (Run 7) provided poor results. In addition, the reaction of chalcone with nitroethane also gave the corresponding 1,4-adduct in moderate yield (Run 13).

While the mechanism of this new reaction is still being investigated, we have developed an efficient and convenient method for the Henry reaction in DMSO. This reaction has the following synthetic advantages: (1) in contrast to the known Henry reaction, the present reaction does not need an additional base as an activator, (2) a broad range of carbonyl compounds including sterically hindered aldehydes and  $\alpha$ -keto ester can be applied, (3) 1,4-addition of nitroalkanes to various  $\alpha,\beta$ -unsaturated carbonyl compounds also proceeds smoothly. Further studies for the development of DMSO-promoted benign reactions are currently underway in our laboratory.

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## References and Notes

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- 10 Typical experimental procedure is as follows: A solution of benzaldehyde (30  $\mu$ L, 0.30 mmol) and CH<sub>3</sub>NO<sub>2</sub> (81  $\mu$ L, 1.5 mmol) in DMSO (2 mL) in the presence of powdered MS 4 Å (60 mg) was stirred at room temperature under an argon atmosphere. After 24 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<sub>4</sub>. 2-Nitro-1-phenylethanol (45.5 mg, 91%) was isolated by TLC on silica gel.
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