Molybdenum(VI) Dichloride Dioxide Catalyzed Synthesis of β-Keto Esters by C–H Insertion of Ethyl Diazoacetate into Aldehydes

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Abstract: Synthesis of β-keto esters by condensing various aldehydes with ethyl diazoacetate is achieved by using molybdenum(VI) dichloride dioxide. Aromatic, aliphatic, and heterocyclic aldehydes are successfully condensed with ethyl diazoacetate to obtain corresponding β-keto esters in high yields at room temperature.

Key words: molybdenum, catalyst, β-keto esters, aldehydes, ethyl diazoacetate

Reagents containing multiple functionalities are very important starting materials for organic synthesis as they can be versatile and effective species for the efficient construction of complex organic molecules.1 One important variety of such reagents is represented by β-keto esters, which are multicovalent reagents with electrophilic and nucleophilic centers that have proven to be valuable intermediates in organic synthesis.2 For example, β-keto esters are one of the basic building blocks in the total synthesis of many natural products like thiocolactomycin,3 trichodiene,4 poloxymic acid,5 chokol,6 prostaglandin PGF 2α,7 syncarpic acid,8 and podophyllotoxin.9

Consequently, numerous methods have been developed for the preparation of β-keto esters.2 Among these, one of the simple and most straightforward approaches for the synthesis of β-keto esters is the acid-catalyzed C–H insertion of ethyl diazoacetate into aldehydes9 (see Table 2). Lewis acid catalysts, such as SnCl 4,10a SnCl 2,10b Fe(Cp)(CO) 2,10b ZnCl 2,10b NbCl 5,11 activated alumina,12 zeolites,13 clay,14 BF 3·OEt 2,10b and HBF 4·OEt 210b have been employed for such conversions.

Recently, molybdenum(VI) dichloride dioxide (MoO 2Cl 2) has been used as an efficient catalyst for several organic transformations.15 We have also recently used MoO 2Cl 2 as a mild and selective catalyst for the oxidation of sulfides,16 oxidation of alcohols,17 and ring-opening reactions of epoxides.18 In this article, we wish to report a further application of MoO 2Cl 2 as a catalyst for the synthesis of β-keto esters by condensing various aldehydes with ethyl diazoacetate.

In our preliminary reaction, we studied the condensation of benzaldehyde (1a) with ethyl diazoacetate in various solvents (Table 1) by using 5 mol% of MoO 2Cl 2 at room temperature. The optimum yield of 2a was obtained in dichloromethane with 1.2 equivalents of ethyl diazoacetate.

Using the optimized reaction condition (Table 1, entry 4), we studied the condensation of various aldehydes (1a, 2a, 2b, 2f, 2g) with ethyl diazoacetate and the results are summarized in Table 2. Benzaldehyde (1a) and 2-naphthaldehyde (1b) were converted into the corresponding β-keto esters 2a and 2b in 90% and 73% yields, respectively. Benzaldehydes containing electron-donating groups (e.g., Me and OMe) 1c–e were successfully condensed with ethyl diazoacetate to obtain the corresponding β-keto esters 2c–e in 83–88% yields (Table 2, entries 3–5). Benzaldehydes with electron-withdrawing groups (e.g., NO 2 and Br), 1f and 1g were also converted into the corresponding β-keto esters 2f and 2g in 82 and 92% yields, respectively.

In contrast, when Lewis acids like SnCl 4, Fe(Cp)(CO) 2, ZnCl 2, BF 3·OEt 2, and HBF 4·OEt 2 were employed as catalysts, the aromatic aldehydes gave β-keto esters in low yields together with major amounts of 2-aryl-3-hydroxy-2-acrylic esters (Scheme 1).15b However, such kinds of products were not observed with the MoO 2Cl 2-catalyzed reactions in this work.

Heterocyclic aldehydes pyridine-2-carbaldehyde (1h) and 2-furaldehyde (1i) were successfully converted into the corresponding β-keto esters 2h and 2i at room temperature in 84% and 87% yields, respectively. Aliphatic alde-

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethyl diazoacetate (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>MeCN</td>
<td>3</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>THF</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>MeOH</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>CH 2Cl 2</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>CH 2Cl 2</td>
<td>2.5</td>
<td>91</td>
</tr>
</tbody>
</table>

a Benzaldehyde (1a, 2 mmol), ethyl diazoacetate, MoO 2Cl 2 (5 mol%), solvent (10 mL), stirred, r.t.
hydes, $1j$ and $1k$ gave quantitative yields of the corresponding $\beta$-keto esters $2j$ and $2k$.

Since, MoO$_2$Cl$_2$ has two vacant coordination sites$^{19}$ hence the reaction probably proceeds through the activation of the aldehyde by complexation with MoO$_2$Cl$_2$. The carbon nucleophile attacks on the carbonyl group aldehyde and subsequent 1,2-hydride shift with loss of nitrogen resulting in the formation of the $\beta$-keto ester (Scheme 2). Such a mechanism was proposed earlier by Yadav et al.$^{11}$

In conclusion, molybdenum(VI) dichloride dioxide was successfully used as catalyst for the synthesis of $\beta$-keto esters by condensing aldehydes with ethyl diazoacetate at room temperature. No side products were obtained during the condensation reactions.

Aldehydes 1, ethyl diazoacetate, and MoO$_2$Cl$_2$ were purchased from Aldrich. All the aldehydes and solvents were purified before use for the reactions$^{20}$ and the reactions were performed at r.t. under N$_2$ atmosphere. The products are characterized by $^1$H and $^{13}$C NMR, IR, and melting points using Bruker 400 MHz NMR spectrometer, Jasco FT/IR 660 plus and Toshniwal-India melting point apparatus respectively. The spectral data for products 2 are comparable with the literature data: $2a$,$^{21a}2b$,$^{21b}2c$–$f$,$^{21a}2g$,$^{21c}2h$,$^{10b}2i$,$^{21a}2j$,$^{21d}$ and $2k$.$^{21e}$

### $\beta$-Keto Esters 2a–k; General Procedure

A mixture of aldehyde (2 mmol), ethyl diazoacetate (2.4 mmol) and 5 mol% MoO$_2$Cl$_2$ (0.1 mmol), CH$_2$Cl$_2$ (10 mL), r.t., stirred.

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### Table 2  Synthesis of $\beta$-Keto Esters by Condensing Various Aldehydes with Ethyl Diazoacetate Using Molybdenum(VI) Dichloride Dioxide$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3</td>
<td>$2a$</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>2-naphthyl</td>
<td>3</td>
<td>$2b$</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC$_6$H$_4$</td>
<td>3</td>
<td>$2c$</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC$_6$H$_4$</td>
<td>5</td>
<td>$2d$</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>3,4,5-(MeO)$_3$C$_6$H$_2$</td>
<td>5</td>
<td>$2e$</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>4-O$_2$NC$_6$H$_4$</td>
<td>2</td>
<td>$2f$</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>4-BrC$_6$H$_4$</td>
<td>3</td>
<td>$2g$</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>2-pyridyl</td>
<td>5</td>
<td>$2h$</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>2-furyl</td>
<td>5</td>
<td>$2i$</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>Bn</td>
<td>2</td>
<td>$2j$</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>(CH$_2$)$_2$Me</td>
<td>2.5</td>
<td>$2k$</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ Aldehyde (2 mmol), ethyl diazoacetate (2.4 mmol), MoO$_2$Cl$_2$ (5 mol%), CH$_2$Cl$_2$ (10 mL), r.t., stirred.
References


