Mild condition synthesis of α, β-U n s a t u r a t e d esters derivatives through copper catalyst

AFG Masud Rezaa and Dr. Mohd. Amirul Islam

Abstract
Copper (II) triflate catalyzed reactions of ethylene diazo acetate with aldehyde derivatives are presented in this report. Based on modification of the Wittig reaction, a practical and highly efficient synthesis of α, β-unsaturated esters with good to excellent yields were obtained. A variety of substituted aromatic aldehydes were smoothly converted to the corresponding derivatives of acrylic acid with ethyl ester for the reaction of ethyl diazoacetate using Cu (II) triflate as catalyst in the presence of triphenylphosphine as a reducing agent. Yields of the products obtained were found to be good to excellent, under mild reaction conditions and in a narrow range of solvents.

Keywords: α, β-unsaturated esters, Olefination, Wittig reactions, Cu (II) triflate, triphenylphosphine

Introduction
Catalyst can be used to enhance the reactivity and selectivity of specific chemical transformations, as well as decreasing the amount of energy consumed by these processes. Most catalytic reactions fulfill the criteria for a sustainable transformation on the macroscopic scale, and a wide variety of efficient catalytic systems have been developed in both industry and academia that are capable of affecting a broad range of chemical transformations.

Unfortunately, however, most of the popular and frequently used catalysts are based on precious metals such as copper, palladium, rhodium, ruthenium, iridium, and osmium, which are becoming increasingly expensive because they are derived from dwindling resources. Catalytic asymmetric multi-component reactions (CAMCRs), in which three or more reactants are combined in a single chemical step to stereoselectivity products have received considerable attention [1a]. The synthesis of α, β-unsaturated esters from aldehydes is very common carbon-carbon bond forming reaction, especially Wittig reaction variants are widely used [1b]. But almost in every case the problem with these approaches is their unsatisfactory atom economy resulting in significant by-product formation. Alternative approaches have been suggested by different research groups, e.g., modified Horner-Wadsworth-Emmons reaction [2]. An alternative yet rarely used methodology for the synthesis of α, β-unsaturated esters from aldehydes is the decarboxylative Knoevenagel reaction using malonate half esters which leads to the formation of H2O & CO2 as the only by-product [3] (Benjamin et al., 1945). Benjamin et al explored the formation of α, β-unsaturated esters from malonate half esters with aldehyde which leads to the formation of H2O & CO2 as the only by-product (scheme 1) [3].

![Scheme 1](image-url)

**Scheme 1.**
Moreover, half-esters of malonates are as inexpensive as the corresponding phosphorous based reagents and can also be obtained from inexpensive diethyl malonate. In addition, by this method (E) vs (Z) selectivity varies and, most importantly, in the reaction with enolizable aldehydes, not $\alpha$, $\beta$-unsaturated esters (or their mixtures) are commonly obtained [4]. Benjamin et al reported the formation of $\alpha$, $\beta$-unsaturated esters from malonate half esters with aldehyde and the reaction was carried out in the presence of catalytic amount of 4-dimethylaminopyridine (4-DMAP, 10 mol %) at room temperature which provided the corresponding unsaturated esters with the remarkable result [5]. A number of transition metal complexes derived from Mo, Ru, Co, and Ir are known to catalyze the olefination of carbonyl compounds with diazoacetate derivatives. Recently, a research group reported the formation of esters from the reaction of carbonyl compounds with diazoacetate using lanthanide triflates as catalyst [13]. Among the various metal triflates, copper (II) triflate [Cu(OTf)$_2$], plays an indispensable role in the discovery of novel and improved reaction process. copper (II) triflate has been known to promote elimination reactions, oxidative coupling reactions and reactions of diazo-compounds [14]. In the present letter we wish to report Cu (OTf)$_2$ efficiently catalyses the olefination of variety of compounds [14]. In the present letter we wish to report Cu (OTf)$_2$ efficiently catalyses the olefination of variety of compounds.

Experimental Section

General procedure

A mixture of aldehyde (1.0 mmol) and EDA (2.0 mmol) in the presence of Cu(OTf)$_2$ (0.3 mmol) and chloroform (7.0 mL) was stirred at 70 °C for 7-10h. After completion of the reaction (TLC-checked), the solvent was removed under reduced pressure to obtain the crude product. Then the crude product was purified by column chromatography (hexane-EtOAc) on silica gel to give corresponding $\alpha$, $\beta$-unsaturated ester.

General procedure for the preparation of $\alpha$, $\beta$-unsaturated ester

A mixture of aldehyde (1.0 mmol) and EDA (2.0 mmol) in the presence of Cu(OTf)$_2$ (0.3 mmol) and chloroform (7.0 mL) was stirred at 70 °C for 7-10h. After completion of the reaction (TLC-checked), the solvent was removed under reduced pressure to obtain the crude product. Then the crude product was purified by column chromatography (hexane-EtOAc) on silica gel to give corresponding $\alpha$, $\beta$-unsaturated ester.

3-Phenyl-acrylic acid ethyl ester (10)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.67 (d, $J$ = 16.0Hz, =CH, 1H), 7.52-7.48 (m, 2H), 7.38-7.34 (m, 3H), 6.43 (d, $J$ =16.0Hz, =CH, 1H), 4.25 (q, $J$ = 7.1Hz, -CH$_2$, 2H), 1.32 (t, $J$ = 7.1Hz, CH$_3$, 3H).

IR (neat): 2928, 2855, 1721, 1640, 1451, 1368, 1300, 1267, 1177, 1038, 890, 828 cm$^{-1}$.

3-p-Toly-diacid acid ethyl ester (11)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.64 (d, $J$ = 16.0Hz, 1H), 7.40 (d, $J$ = 8.1Hz, 2H), 7.17 (d, $J$ = 8.1Hz, 2H), 6.37 (d, $J$ = 16.0Hz, 1H), 4.24 (q, $J$ = 7.1Hz, 2H), 2.35 (s, 3H), 1.34 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2982, 1713, 1638, 1609, 1514, 1368, 1312, 1267, 1206, 1175, 1038, 984, 814 cm$^{-1}$.

3-Phenyl-acrylic acid ethyl ester (12)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.64 (d, $J$ = 16.0Hz, 1H), 7.31 (d, $J$ = 6.1Hz, 2H), 7.25 (t, $J$ = 7.4Hz, 1H), 7.18 (d, $J$ = 7.4Hz, 1H), 6.40 (d, $J$ = 16.0Hz, 1H), 4.24 (q, $J$ = 7.1Hz, 2H), 2.35 (s, 3H), 1.32 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2982, 1713, 1640, 1447, 1368, 1312, 1265, 1236, 1179, 1038, 984, 787 cm$^{-1}$.

3-(2,5-Dimethyl-phenyl)-acrylic acid ethyl ester (13)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.93 (d, $J$ = 15.9Hz, 1H), 7.35 (s, 1H), 7.07 (d, $J$ =1.0Hz, 2H), 6.33 (d, $J$ = 15.9Hz, 1H), 4.24 (q, $J$ = 7.1Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 1.32 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2980, 2928, 1715, 1636, 1497, 1449, 1368, 1314, 1177, 1038, 982, 814 cm$^{-1}$.

3-(4-Methoxy-phenyl)-acrylic acid ethyl ester (14)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.62 (d, $J$ = 16.0Hz, 1H), 7.45 (dq, $J$ = 8.8Hz, 2.9Hz, 2H), 6.88 (dq, $J$ = 8.8, 2.9Hz, 2H), 6.28 (d, $J$ = 16.0Hz, 1H), 4.23 (q, $J$ = 7.1Hz, 2H), 3.28 (s, 3H), 1.31 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2982, 1709, 1634, 1605, 1514, 1464, 1304, 1254, 1206, 1173, 1032, 984, 829 cm$^{-1}$.

3-Benz[d1]oxol-5-yl-acrylic acid ethyl ester (15)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.56 (J = 15.9Hz, 1H), 7.01-6.96 (m, 2H), 6.79 (d, $J$ = 7.9Hz, 1H), 6.24 (d, $J$ = 15.9Hz, 1H), 5.98 (s, 2H), 4.22 (q, $J$ = 7.1Hz, 2H), 1.30 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2990, 2905, 1703, 1642, 1611, 1491, 1449, 1369, 1246, 1175, 1098, 1034, 930, 806 cm$^{-1}$.

3-Naphthalen-2-yl-acrylic acid ethyl ester (16)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.91 (s, 1H), 7.86 -7.80 (m, 4H), 7.65 (dd, $J$ = 8.6Hz, 1.7Hz, 1H), 7.52-7.44 (m, 4H), 6.53 (d, $J$ = 16.0 Hz, 1H), 4.27 (q, $J$ = 7.1 Hz, 2H), 1.34 (t, $J$ = 7.1 Hz, 3H).

IR (neat): 2980, 1709, 1634, 1370, 1298, 1262, 1200, 1175, 1038, 990, 860, 822, 752 cm$^{-1}$.

5-Phenyl-penta-2,4-dienoic acid ethyl ester (17)

$^1$H NMR (300 MHz, CDCl$_3$) δ = 7.46 (q, $J$ = 2.1Hz, 1H), 7.43-7.28 (m, 5H), 6.88-6.80 (m, 2H), 5.98 (d, $J$ = 15.2Hz, 1H), 4.21 (q, $J$ = 7.1Hz, 2H), 1.30 (t, $J$ = 7.1Hz, 3H).

IR (neat): 2982, 1709, 1626, 1449, 1368, 1298, 1240, 1134, 1038, 1001, 756, 691 cm$^{-1}$.
4-Phenyl-pent-2-enoic acid ethyl ester (18)

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54 (d, $J = 7.4$Hz, 1H), 7.07 (dd, $J = 15.7, 7.4$Hz, 1H), 5.78 (dd, $J = 15.7, 16.1$Hz, 1H), 4.23 (q, $J = 7.1$Hz, 2H), 2.59 (2H, s), 1.30 (t, $J = 7.1$Hz, 3H).

IR (neat): 2982, 1723, 1688, 1451, 1368, 1300, 1265, 1157, 1036, 762, 692 cm$^{-1}$.

Results and discussion

In our initial experiment, the reaction of EDA with aldehyde was carried out under various conditions to find optimum conditions (Table 1). As shown in Table 1, the best results were obtained when the reaction was carried out using Cu(OTf)$_2$ as a catalyst in the presence of Ph$_3$P in CHCl$_3$ at 70 °C temperature.

Table 1. Reactions of EDA with aldehydes under various conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (equiv)</th>
<th>Condition</th>
<th>Yieldb(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ag$_2$O (1.0)</td>
<td>CHCl$_3$, 70 °C</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu$_2$O (0.3)</td>
<td>CHCl$_3$, 70 °C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc (1.0)</td>
<td>CHCl$_3$, 70 °C</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>CuBr (1.0)</td>
<td>CHCl$_3$, 70 °C</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)$_2$ (0.3)</td>
<td>CH$_2$Cl$_2$, rt</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)$_2$ (0.3)</td>
<td>CHCl$_3$, rt</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)$_2$ (0.3)</td>
<td>THF, rt</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)$_2$ (0.3)</td>
<td>CHCl$_3$, 70 °C</td>
<td>73</td>
</tr>
</tbody>
</table>

* Isolated yields (not optimized)

In order to obtain the further clue, we studied the reaction of EDA (2.0 equiv) with several aldehydes (1.0 equiv) using Cu(OTf)$_2$ as a catalyst (0.3 equiv) in the presence of Ph$_3$P [15]. In all cases, the corresponding conjugated ester was obtained in good to excellent yields [16]. The results are listed in Table 2.

Table 2: Reactions of EDA with aldehydes in the presence of Cu(OTf)$_2$/Ph$_3$P

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Aldehyde 1]</td>
<td>![Product 1]</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>![Aldehyde 2]</td>
<td>![Product 2]</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>![Aldehyde 3]</td>
<td>![Product 3]</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>![Aldehyde 4]</td>
<td>![Product 4]</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>![Aldehyde 5]</td>
<td>![Product 5]</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>![Aldehyde 6]</td>
<td>![Product 6]</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>![Aldehyde 7]</td>
<td>![Product 7]</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>![Aldehyde 8]</td>
<td>![Product 8]</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>![Aldehyde 9]</td>
<td>![Product 9]</td>
<td>30</td>
</tr>
</tbody>
</table>

* Isolated yields (not optimized)
Next, the reaction was carried out without PPh₃, but the olefination did not proceed. In case of small amount or absence of catalyst, the reaction afforded azine as major product when the reaction mixture was stirred for 2 days (Scheme 2) \(^{16}\).

\[
\begin{align*}
\text{O} & \quad \text{H} + \quad \text{N} & \quad \text{OEt} \\
\text{CHCl}_3, 70^\circ \text{C} & \rightarrow \\
\text{N} & \quad \text{N} & \quad \text{OEt}
\end{align*}
\]

Scheme 2

The structure of the products has been confirmed by the spectral data (IR, \(^1\)H-NMR) and elemental analyses. The \(^1\)H NMR spectra of the products were not identical, but the characteristic spectra of two double bond hydrogen of those compounds were similar in all cases. Two geminal protons appeared nearly at 7.6 ppm and 6.4 ppm as doublets and the coupling constant was about 16 Hz, while the other protons appeared nearly at 7.6 ppm and 6.4 ppm as doublets and the other protons were found to be practically unreactive. The obtained product also can be confirmed by the following mechanism. The olefination process can be explained by the formation of copper yield firstly and the next step formed the very stable phosphine oxide as the bye product. The probable mechanism for the formation of \(\alpha, \beta\)-unsaturated esters will be depicted as shown in Scheme 3.

\[
\begin{align*}
\text{N} & \quad \text{OEt} \quad \text{Cu(II)} \quad \text{Cu} \\
\text{Cl} & \quad \text{H} \quad \text{C} & \quad \text{OEt} \quad \text{PPh}_3 \\
\text{R} & \quad \text{H} \quad \text{OEt} \quad \text{PPh}_3
\end{align*}
\]

Scheme 3. Probable mechanism for the formation of \(\alpha, \beta\)-unsaturated ester

Conclusion

In conclusion, we have developed a simple and efficient method to prepare \(\alpha, \beta\)-unsaturated esters from aldehyde by the reaction with EDA and PPh₃ in the presence of a catalytic amount of Cu (OTf)₂ and established Wittig reagents through a one-pot process. By optimizing the reaction conditions, this catalyst proved to be a fairly good catalyst in mild condition with good to excellent yields (85%), also cost effective, and highly selective (E >95%) compounds. In addition, a salient feature of copper (II) triflate is inherent stable in aqueous solvents that open the way to environmental chemistry. These allow the carbonyl compounds to react under the mild reaction conditions. The desired goal is achieved using the copper-catalyzed olefination reaction as a key step. We are now undergoing to make clear the scope and limitations of the reaction using various carbonyl compounds.

References