Synthesis of aryl β-ketoesters by opening of aryl epoxides with ethyl diazoacetate catalyzed by BF₃OEt₂

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A facile synthesis of 4-aryl substituted β-ketoesters from the reaction aryl epoxides with ethyl diazoacetate, in presence of BF₃OEt₂ has been described with excellent yields.

Keywords: Aryl epoxides, ethyl diazoacetate, BF₃OEt₂, β-ketoesters

Aryl β-ketoesters are versatile intermediates in the synthesis of many natural products and for construction heterocyclic compound. A wide range of methods are available for synthesis of β-ketoesters but with low yields and 3-hydroxyl acrylates as by-products due to enolisation of the β-ketoesters with Lewis acids. Familiar methods for synthesizing β-ketoesters are hydration of acetylenic ester, acylation of acetylacetone or ethyl acetoacetate and their substituted derivatives by acyl halides or esters followed by base promoted cleavage of carbonyl group, and reaction of acylbenzotriazoles with ethyl acetoacetate in presence of sodium hydride and very recently, reaction of benzaldehydes with diazoacetate in presence of triphenylborane and triethylborane with moderate yields. It has been reported in literature that conversion of aryl epoxides to aldehydes can be effected with lithium perchlorate. In continuation of the work on reactions with epoxides, a reaction of ethyl diazoacetate with substituted 2-phenyloxiranes has been carried out in presence of Lewis acids to afford aryl β-ketoesters (Scheme I).

Results and Discussion
Various Lewis acids such as ZrOCl₂, FeCl₃, InBr₃, ZrCl₄, and TMSOTf, have been screened to favour the reaction of ethyl diazoacetate with substituted 2-phenyloxiranes to afford aryl β-ketoesters without success except with BF₃OEt₂. However, with ferric chloride and indium bromide, corresponding halohydrins were obtained.

Initially, a reaction of 2-phenyloxirane and ethyl diazoacetate in presence of BF₃OEt₂ was carried out to afford ethyl-3-oxo-4-phenylbutanoate in excellent yield (98%, Table I, entry 1). Encouraged by the success of the reaction, various electron withdrawing and donating substituted 2-phenyloxiranes were reacted with ethyl diazoacetate in presence of BF₃OEt₂ to afford β-ketoesters in excellent yields.

It has been observed that boron Lewis acids are much more effective for this conversion than any other Lewis acid. Similar results were obtained with moistened sodium tetraflouroborate in ether. A plausible reaction mechanism has been given in Scheme II, where initially the 2-phenyloxirane reacts with ethyl diazoacetate to give the corresponding aldehyde which reacts with ethyl diazoacetate to afford β-ketoesters.

Experimental Section

General experimental procedure
To a solution of 2-phenyloxirane (1 mmol) and ethyl diazoacetate (1 mmol) in ether (10 mL) was added BF₃OEt₂ (0.2 equivalents) and the reaction stirred at RT as noted in Table II. After completion of the reaction, the reaction mass was diluted with water and extracted into ethyl acetate and the organic phase was concentrated under reduced pressure. The crude product was purified over silica gel column to obtain pure products.

Spectral data for selected compounds

| Ethyl 3-oxo-4-phenyl butanoate, 1. IR (Neat): 2922, 2853, 1733, 1451, 1372, 1250, 771 and 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.34-7.16 (m, 5H), 4.14 (q, J = 6.7, 2H), 3.7 (s, 2H), 3.3 (s, 2H), 1.26 (t, J = 6.7, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 199.8, 166.7, 135.5, 129.5, 128.5, 127.3, 61.2, 49.9, 48.0, 14.1; ESI-MS: m/z 229 [M+Na]⁺. |
| Ethyl 4-(4-chlorophenyl)-3-oxobutanoate, 2. IR (Neat): 2937, 2894, 1744, 1627, 1492, 1317, 1243, 1091, 1017, 797, 772 and 494 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.30-7.25 (d, J = 8.0 2H), 7.13-7.10 (d, J = 8.0, 2H), 4.15 (q, J = 7.0, 2H), 3.7 (s, 2H), 3.3 (s, 2H), 1.26 (t, J = 7.0, 3H); ¹³C NMR |
**Scheme I**

**Table 1** — Reactions of 2-phenyloxiranes and ethyl diazoacetate in presence of $\text{BF}_3\text{OEt}_2$

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
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<td>$\text{O} $</td>
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<td>$\text{O}$</td>
<td>98</td>
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<tr>
<td>2</td>
<td>Cl</td>
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<td>Cl</td>
<td>98</td>
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<tr>
<td>3</td>
<td>F</td>
<td>0.5</td>
<td>F</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>BnO</td>
<td>1.0</td>
<td>BnO</td>
<td>85</td>
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<tr>
<td>5</td>
<td>NO$_2$</td>
<td>0.5</td>
<td>NO$_2$</td>
<td>95</td>
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<tr>
<td>6</td>
<td>H$_3$C</td>
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<td>H$_3$C</td>
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<tr>
<td>7</td>
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<td>0.5</td>
<td>Cl</td>
<td>97</td>
</tr>
</tbody>
</table>
(75 MHz, CDCl$_3$): δ 199.8, 166.9, 133.2, 131.5, 130.8, 128.8, 61.4, 48.9, 48.3, 13.9; ESI-MS: m/z 241 [M$^+$.]

**Ethyl 4-(4-flourophenyl)-3-oxobutanoate, 3.** IR (Neat): 2984, 2927, 2853, 1738, 1603, 1510, 1415, 1370, 1316, 1224, 1158, 1029, 837, 775 and 510 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.16 (dd, $J = 9.009$, $J = 6.006$, 2H), 7.0 (t, $J = 9.009$, 2H), 4.16 (q, $J = 7.0$, 2H), 3.7 (s, 2H), 3.3 (s, 2H), 1.27 (t, $J = 7.0$, 3H); ESI-MS: m/z 225 [M$^+$].

**Ethyl 4-(4-benzyloxy) phenyl)-3-oxobutanoate, 4.** IR (Neat): 2978, 2923, 2853, 1735, 1610, 1513, 1448, 1369, 1307, 1262, 1290, 1281, 1261, 1159, 61.3, 48.3, 13.9; ESI-MS: m/z 335 [M+Na$^+$.]

**Ethyl 4-(3-nitro phenyl)-3-oxobutanoate, 5.** IR (Neat): 2983, 2933, 2874, 1746, 1563, 1437, 1311, 1260, 1090, 1030, 777, 567 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.16 (dd, $J = 9.009$, $J = 6.006$, 2H), 7.0 (t, $J = 9.009$, 2H), 4.16 (q, $J = 7.0$, 2H), 3.7 (s, 2H), 3.3 (s, 2H), 1.27 (t, $J = 7.0$, 3H); ESI-MS: m/z 274 [M+Na$^+$.]

**Ethyl 3-oxo-4-p-tolylbutanoate, 6.** $^1$H NMR (300 MHz, CDCl$_3$): δ 7.24-7.07 (m, 4H), 4.17 (q, $J = 6.7$, 2H), 3.7 (s, 2H), 3.4 (s, 2H), 2.3 (s, 3H), 1.26 (t, $J = 6.7$, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 199.0, 167.8, 137.0, 130.2, 129.5, 129.3, 61.3, 49.6, 48.1, 21.0, and 14.0; ESI-MS: m/z 221 [M+1$^+$].

**Conclusion**

In conclusion, a simple and versatile method for preparation of aryl β-ketoesters has been developed by reacting 2-phenyloxiranes with ethyl diazoacetate in presence of BF$_3$OEt$_2$ in excellent yields.

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**References**