Conjugate Additions of α,β-Unsaturated Ketones with Arylzinc Species That Form in situ from Diethylzinc and Arylboronic Acids

Lin Dong, Yan-Jun Xu, Liu-Zhu Gong,* Ai-Qiao Mi, Yao-Zhong Jiang

Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, P. R. China
E-mail: gonglz@cioc.ac.cn

Received 10 December 2003; revised 16 March 2004

SYNTHESIS 2004, No. 7, pp 1057–1061 xx.x .2 0 0 4
Advanced online publication: 14.04.2004
© Georg Thieme Verlag Stuttgart · New York

Abstract: Conjugate addition of α,β-unsaturated ketones with arylzinc species that form in situ from diethylzinc and a series of arylboronic acids by boron-zinc exchange reactions were investigated. 1,4-Addition products were formed in yields of 34–93%.

Keywords: conjugate addition, α,β-unsaturated ketone, arylboronic acid, boron-zinc exchange reaction

Conjugate addition of organometallic reagents to electron-deficient olefins is one of the most versatile methods for forming carbon-carbon bonds. Due to the importance of the resulting β-substituted carbonyl compounds in organic synthesis, many conjugate additions of organometallic reagents, such as those of lithium, magnesium, zinc, and boron, to enones have been extensively studied. Recently, important advances have been made regarding asymmetric conjugate additions of arylboronic acids and the corresponding esters, and related reactions with alkylzincs. These reactions generally require the use of transition-metal complexes as catalysts. Since arylzinc species can be formed by boron-zinc exchange reactions, we started a project to prepare β-aryl carbonyl compounds via the conjugate addition of arylzinc, generated in situ from arylboronic acids and diethylzinc, to α,β-unsaturated ketones.

We first studied the reaction of chalcone (1a) with the combination of phenylboronic acid and diethylzinc. The phenylzinc species was prepared by stirring a mixture of phenylboronic acid and a 3-fold excess of Et₂Zn in toluene at 60 °C under argon for 12 hours. It was then reacted with chalcone (1a) at 0 °C to give 3a in 92% yield (Table 1, entry 1). The use of several commercial arylboronic acids 2a–f and an ester 2g in the 1,4-addition of chalcone (1a) under the above reaction conditions was then investigated. The results are summarized in Table 1.

As shown in Table 1, 1,4-additions are highly dependent on the structures of the arylboronic acids. Boronic acid with two strongly electron-withdrawing trifluoromethyl groups was not good for 1,4-addition (entry 6). This is probably due to an incomplete boron-zinc exchange. Boronic acid also gave a low yield of 34% for 1,4-addition, which might be the result of steric hindrance by the 2-chlorophenyl group (entry 5). Arylzincs formed from other arylboronic acids, such as phenylboronic acid and 4-substituted phenylboronic acids, reacted well with chalcone (1a) to furnish 1,4-adducts 3a–d in high yields (entries 1–4). Pinacol phenylboronate (2g, entry 7) gave a lower yield than its analogue 2a.

Table 1 1,4-Addition to Chalcone 1a by the Combination of Aromatic Boronic Acids and Diethylzinc

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArB(OH)₂</th>
<th>Product 3, (Ar =)</th>
<th>Yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (2a)</td>
<td>Ph (3a)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-ClPh (2b)</td>
<td>4-Cl-Ph (3b)</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>4-CH₃OPh (2c)</td>
<td>4-CH₃OPh (3c)</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>4-F-Ph (2d)</td>
<td>4-F-Ph (3d)</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>2-ClPh (2e)</td>
<td>2-Cl-Ph (3e)</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>(2f)</td>
<td>(3f)</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>(2g)</td>
<td>Ph (3a)</td>
<td>44</td>
</tr>
</tbody>
</table>

² Isolated yield based on 1a.

Scheme 1  Reactions of 1a with Ph₂Zn and Ph₂Zn–Et₂Zn
To understand whether the EtB(OZnEt)$_2$ generated in situ from diethylzinc and arylboronic acid acts as a catalyst to promote the 1,4-addition of EtZnAr to $\alpha,\beta$-unsaturated ketone, chalcone (1a) was treated with Ph$_2$Zn and an organozinc species formed in situ from Et$_2$Zn–Ph$_2$Zn.$^7$ No 1,4-addition adduct 3a was produced in either reaction (Scheme 1). However, the combination of Et$_2$Zn and phenylboronic acid reacted smoothly with chalcone (1a) to give 3a in 92% yield (Table 1, entry 1). In addition, reactions of 1a with Ph$_2$Zn in the presence of a mixture of MeB(OH)$_2$ and Et$_2$Zn proceeded well to give 3a in 77% yield (Scheme 2). These results demonstrated that EtB(OZnEt)$_2$ might catalyze the 1,4-addition.

**Table 2 1,4-Addition of 1b–m with PhB(OH)$_2$–Et$_2$Zn**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone (1b–m)</th>
<th>Yield of 4b–m (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>PhH</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>PhO</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>PhF</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>PhBr</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>PhCl</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>PhNO$_2$</td>
<td>53</td>
</tr>
</tbody>
</table>

1,4-Additions of several unsaturated ketones in the presence of Et$_2$Zn and phenylboronic acid were examined. The results are listed in Table 2. Most of the tested ketones underwent 1,4-addition to give the expected product in good yields, except for ketone 1j and 1m. The 1,4-addition of 1j produced 4j in only 38% yield (entry 9). Only trace amount of product was observed with unsaturated ketone 1m (entry 12), which implied that the unsaturated ketone with an aliphatic substituted carbonyl group was less reactive. Compound 1f bearing a 2,6-dichlorophenyl group showed relatively low yield for 1,4-addition (63% yield), probably due to its steric bulk (entry 5). Reactions of $\alpha,\beta$-unsaturated ketones containing a nitro group always gave worse results than those of their structural analogues bearing other electron-withdrawing groups (entries 6 and 9).

In summary, conjugated additions of $\alpha,\beta$-unsaturated ketones with the ary zinc species formed in situ from diethylzinc and arylboronic acids were studied. 1,4-Addition products were formed in yields of 34–93%. The observed 1,4-addition of the $\alpha,\beta$-unsaturated ketones is useful since
it does not require transition-metal catalysts for the aryl transfer reactions. \(^2\)

NMR spectra were recorded on a Bruker-300 MHz spectrometer. El Mass spectra were recorded on a VG-7010E spectrometer. IR spectra were recorded on Nicolet 200SXV spectrometer. Elemental analysis was performed on Italy CARCOERBA 1106 apparatus. All reactions that are air and moisture sensitive were carried out under an anhyd argon atmosphere using standard Schlenk line techniques. Toluene was dried with Na–benzophenone. Petroleum ether (bp 60–90 °C) and EtOAc for column chromatography were distilled before use.

### 1.4-Addition to Generate 3a–e and 4b–m; General Procedure

Under an argon atmosphere, a solution of diethylzinc in hexane (1.0 M, 2.25 mL, 2.25 mmol) was added to a solution of PhB(OH)₂ (91.3 mg, 0.75 mmol) in anhyd toluene (6 mL) in a flame-dried Schlenk flask (25 mL). After being stirred at 60 °C for 12 h, the reaction mixture was cooled to 0 °C and a solution of 1a (62.4 mg, 0.3 mmol) in anhyd toluene (1.5 mL) was added. After stirring at 0 °C for 10 h, the reaction was quenched with sat. aq NH₄Cl (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over anhyd Na₂SO₄. The solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 35:1) to give 3a as white crystals (79 mg, 92% yield); mp 94.4–95.8 °C.

**3b**

Yield: 78%; colorless solid; mp 95.4–96.4 °C.

**3c**

Yield: 79%; colorless solid; mp 95.4–96.4 °C.

**3d**

Yield: 88%; colorless solid; mp 98.2–99.8 °C.

**3e**

Yield: 34%; colorless oil.

**4b**

Yield: 83%; colorless solid; mp 97.4–99.2 °C.

**4e**

Yield: 85%; colorless solid; mp 108.9–109.6 °C.

### Conjugate Additions of \(\alpha,\beta\)-Unsaturated Ketones with Arylzinc Species

Anal. Calcd for \(\text{C}_2\text{H}_5\text{O}_2\): C, 83.51; H, 6.37. Found: C, 83.35; H, 6.57.

Anal. Calcd for \(\text{C}_2\text{H}_5\text{BrOO}\): C, 86.46; H, 5.38. Found: C, 86.21; H, 5.31.

Anal. Calcd for \(\text{C}_2\text{H}_5\text{BrO}_2\): C, 83.51; H, 6.37. Found: C, 83.35; H, 6.57.

\(3d\) Yield: 88%; colorless solid; mp 98.2–99.8 °C.

**MS (EI, 70 eV):** m/z (%) = 286 [M⁺], 167 (36), 105 (100).

**IR (neat):** 3060, 1647, 750, 693 cm⁻¹.

**1H NMR (300 MHz, CDCl₃):** δ = 3.64 (d, \(J = 7.3\) Hz, 2 H), 4.72 (t, \(J = 7.3\) Hz, 1 H), 7.06–7.11 (m, 5 H), 7.16–7.19 (m, 8 H), 7.32–7.37 (m, 2 H), 7.44–7.46 (m, 1 H), 7.83–7.86 (m, 2 H).

**13C NMR (75 MHz, CDCl₃):** δ = 20.9, 44.7, 45.5, 126.2, 126.6, 127.6, 127.7, 128.0, 128.5, 128.9, 133.0, 137.0, 197.3.

**MS (EI, 70 eV):** m/z (%) = 320 [M⁺], 105 (100).

Anal. Calcd for \(\text{C}_2\text{H}_5\text{BrO}_2\): C, 83.51; H, 6.37. Found: C, 83.35; H, 6.57.

**MS (EI, 70 eV):** m/z (%) = 304 [M⁺], 185 (38), 105 (100).

Anal. Calcd for \(\text{C}_2\text{H}_5\text{FO}:\) C, 82.87; H, 5.63. Found: C, 82.72; H, 5.73.

**MS (EI, 70 eV):** m/z (%) = 301 [M⁺], 184 (38), 105 (100).

Anal. Calcd for \(\text{C}_2\text{H}_5\text{BrO}_2\): C, 83.51; H, 6.37. Found: C, 83.35; H, 6.57.

**MS (EI, 70 eV):** m/z (%) = 301 [M⁺], 184 (38), 105 (100).

Anal. Calcd for \(\text{C}_2\text{H}_5\text{ClO}:\) C, 78.62; H, 5.34. Found: C, 78.93; H, 5.44.
8.29 (m, 2 H).

8.23 (m, 4 H).

\( \delta = 7.83 \) (m, 1 H), 7.91–7.94 (m, 2 H), 8.15–8.18 (m, 1 H).

\( \delta = 7.3 \) Hz, 1 H), 7.01–7.33 (m, 10 H), 7.47–7.51 (m, 3 H), 7.76–7.83 (m, 1 H), 7.91–7.94 (m, 2 H), 8.15–8.18 (m, 1 H).

\( \delta = 44.1, 45.0, 123.8, 127.0, 127.7, 128.0, 128.7, 129.1, 131.4, 136.5, 142.5, 146.4, 151.7, 197.1. \)

MS (EI, 70 eV): \( m/z \) (%) = 331 [M+], 167 (100).

Anal. Calcd for C\(_{21}\)H\(_{16}\)Cl\(_2\)O: C, 71.20; H, 5.30; N, 4.32.

\( \delta = 4.72 \) (q, \( J = 6.6 \) Hz, 3 H), 0.99 (d, \( J = 6.6 \) Hz, 1 H), 1.79–2.31 (m, 9 H), 5.22 (d, \( J = 17.6 \) Hz, 1 H).

13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 45.8, 46.3, 124.2, 125.6, 126.3, 126.4, 126.7, 127.6, 128.2, 128.5, 129.9, 132.3, 133.8, 136.5, 143.8, 202.5.

MS (EI, 70 eV): \( m/z \) (%) = 336 [M+] 155 (100).


4f Yield: 85%; colorless solid; mp 124.1–125.5 °C.

IR (KBBr): 3056, 1677, 1596, 1468, 1200, 779, 759, 699 cm\(^{-1}\).

\( \delta = 3.77 \) (t, \( J = 6.0 \) Hz, 2 H), 4.91 (t, \( J = 7.3 \) Hz, 1 H), 7.22–7.32 (m, 5 H), 7.47–7.48 (m, 4 H), 7.55–7.60 (m, 1 H), 7.93–7.96 (m, 2 H), 8.10–8.14 (m, 2 H).

13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 41.3, 45.0, 123.7, 124.3, 125.1, 125.4, 126.1, 126.3, 127.2, 127.9, 128.0, 128.4, 128.7, 131.5, 133.0, 134.0, 136.9, 139.6, 143.8, 197.8.

MS (EI, 70 eV): \( m/z \) (%) = 336 [M+], 217 (100), 85 (78).

4h Yield: 74%; colorless solid.

IR (neat): 3059, 2958, 2928, 2870, 1684, 1593, 1447, 1474, 1396, 1347, 1270, 1260, 1178, 1161, 1144, 1061, 1034, 929, 869 cm\(^{-1}\).

\( \delta = 3.82 \) (q, \( J = 7.3 \) Hz, 2 H), 5.63 (t, \( J = 7.3 \) Hz, 1 H), 7.13–7.58 (m, 12 H), 7.70–7.73 (m, 1 H), 7.76–7.83 (m, 1 H), 7.91–7.94 (m, 2 H), 8.15–8.18 (m, 1 H).

13C NMR (75 MHz, CDCl\(_3\)): \( \delta = 40.5, 45.7, 123.8, 127.0, 127.7, 128.0, 128.7, 129.1, 133.4, 136.5, 142.5, 146.4, 151.7, 197.1.

MS (EI, 70 eV): \( m/z \) (%) = 331 [M+], 167 (100).

Acknowledgment

We are grateful to the National Natural Science Foundation of China for the financial support (projects 20325211 and 203900505).

References


Conjugate Additions of α,β-Unsaturated Ketones with Arylzinc Species


(6) Decreasing the amount of Et₂Zn led to an incomplete reaction.