Stereoselective Synthesis of trans-β-Substituted γ-Ferrocenyl-γ-butyrolactones via Ammonium Ylides

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Abstract: trans-β-substituted γ-ferrocenyl-γ-butyrolactones were prepared via the reaction of quaternary ammonium salts with electron-deficient trisubstituted alkene 1 under the optimum conditions. Moderate to good yields and excellent trans stereoselectivity were achieved for the new compounds 2-10. The X-ray crystal structure of 2a was determined and all the products were characterized by 1H NMR, 13C NMR, FAB-MS, IR and HRMS spectra.

Key words: trans-β-substituted γ-ferrocenyl-γ-butyrolactones, ammonium ylides, electron-deficient, stereoselectivity, mechanism

Much attention has been focused on compounds bearing the substituted γ-butyrolactone moiety because of their far-ranging existence in natural products.1 Moreover, functionalized γ-butyrolactones have been also employed as key intermediates for the synthesis of a wide range of bioactive compounds.2 Ferrocene derivatives have found a number of applications in organic synthesis, as well as in materials science.3 A large number of papers have been published on the characterization of mono- and disubstituted derivatives of ferrocene as typical organometallic species.4 In the course of a research program devoted to the synthesis of ferrocene derivatives as potentially valuable material,5 we were interested in introducing butyrolactone moiety to ferrocene derivatives. Cao et al. reported that β,γ-trans-disubstituted γ-butyrolactone can be prepared via the reaction of arsenic ylides with 2,2-dialkyl-1,3-dioxo-5-substituted-benzylidene-4,6-diones.6 Recently, a growing amount of attention has been paid to the application of nitrogen ylides owing to the vast range of tertiary amines that are commercially available.7 Our group also reported some efficient synthesis methods based on ammonium ylides.8 To our knowledge, there are no nitrogen ylide-attended versions of the synthesis of trans-β-substituted γ-ferrocenyl-γ-butyrolactones.

We present here a strategy for the efficient and highly stereoselective synthesis of trans-β-substituted γ-ferrocenyl-γ-butyrolactones via ammonium ylide routes. This strategy for the synthesis of ferrocenyl butyrolactones has a number of advantages over common methods of generating β,γ-trans-disubstituted γ-butyrolactones:9 there are no transition metals involved in the reaction, and the starting materials are readily available and conveniently handled. We also discuss the structures of these ferrocenyl butyrolactones. Specially, the configuration of product 2a was determined by the X-ray structural analysis.

Our work started by treating electron-deficient trisubstituted alkene 1 with salt 2 in the presence of base under different conditions to mainly form β,γ-trans-disubstituted γ-butyrolactone as shown in Scheme 1. After optimizing the conditions, good yield (87%) and high stereoselectivity (the ratio of trans to cis diastereoisomer was above 99:1) were obtained under reflux in dichloromethane and DMSO (4:1). Anhydrous K2CO3 proved to be the most effective and convenient base to the reaction in the solvent system. There was little or no reaction observed at room temperature. The results of the synthesis of ferrocenyl butyrolactones are summarized in Table 1.

The reaction worked as well for most of the salts. In entries 1–5 and 7–9, the products formed were the β,γ-trans-disubstituted γ-butyrolactones in good to excellent yield and with high stereoselectivity (the ratios of trans to cis diastereoisomers were above 99:1). The trans isomers were formed preferentially probably due to the major thermodynamic stability. It was also noticed that different

Scheme 1
substituted groups of the phenyl ring resulted in dramatic change in yields (entries 1–4). In particular, entries 2 and 4 showed quite different yields of 62 and 90%, respectively. In entry 6 only a moderate stereoselectivity (the ratio of trans diastereoisomer to cis one was 66:11) was obtained due to the small steric hindrance of the cyano group.

To increase the range of the salts, other ylides prepared from corresponding halides were examined. Some selected examples are shown in Figure 1. All these substrates could not undergo the reaction. We got ferrocenyl aldehyde as decomposed product of the substrate 1 in most of the experiments. These results strongly indicated that the methylene of the salts must attach to an electron-withdrawing group, such as carbonyl, cyano-, and the reaction is retarded by the substituents at the methylene due to the steric hindrance.

The reaction mechanism for the formation of compound 2a is proposed as follows (Scheme 2):\(^6\) Firstly, the ylide 11, derived from ammonium salt 2, reacts with olefin 1 to form the trans-cyclopropane derivative 12. Compound 12 reacts further with water to form trans-β-benzoyl-γ-ferrocenyl-γ-butyrolactone 2a.

Table 1 Synthesis of trans-β-Substituted γ-Ferrocenyl-γ-butyrolactones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Product</th>
<th>trans/cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_3)Cl (_2)-DMSO (4:1)</td>
<td>87</td>
<td>2a</td>
<td>&gt;99:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>MeCN</td>
<td>62</td>
<td>3a</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)Cl (_2)-DMSO (4:1)</td>
<td>82</td>
<td>4a</td>
<td>&gt;99:1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1  Synthesis of trans-β-Substituted γ-Ferrocenyl-γ-butyrolactones (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>trans/cis&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td>Br</td>
<td>CH₂Cl₂–DMSO</td>
<td>90</td>
<td>5a</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Br</td>
<td>CH₂Cl₂–DMSO</td>
<td>55</td>
<td>6a</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>NC—</td>
<td>Cl</td>
<td>CH₂Cl₂–DMSO</td>
<td>66</td>
<td>7a</td>
<td>66:11&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Br</td>
<td>acetone</td>
<td>47</td>
<td>8a</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Br</td>
<td>CH₂Cl₂–DMSO</td>
<td>65</td>
<td>9a</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Br</td>
<td>CH₂Cl₂–DMSO</td>
<td>64</td>
<td>10a</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated product.
<sup>b</sup> Fc = ferrocenyl.
<sup>c</sup> Determined by 1H NMR spectroscopy.
<sup>d</sup> Determined by isolated yield.
Products 2–10 are air-stable compounds and are characterized by $^1$H and $^{13}$C NMR, FAB mass, IR and HRMS spectra. The $^1$H NMR spectra of products 2a–10a show that the ferrocenyl and $\gamma$-substituted groups are placed trans to each other. The configuration of the product 2a was assigned on the basis of the X-ray structural analysis. An ORTEP diagram of the structure of 2a is shown in Figure 2. In the molecule of compound 2a, the benzoyl group and the ferrocenyl group orient in opposite directions on the central five-membered ring. The C=O, Fe–C and C–C bonds of the butyrolactone as well as the geometrical parameters of the ferrocene sandwiches, are close to standard values.

Further investigations into this process to find more effective nitrogen ylides and to prepare substituted $\gamma$-butyrolactones are currently underway in our laboratory.

Melting points were determined on a microscopic apparatus and are uncorrected. Column chromatography was carried out on silica gel. The NMR spectra were recorded on a Mercury 4N-PFG $^1$H sensitivity (plus-300) spectrometer, using CDCl$_3$ as solvent and TMS as internal standard. The FAB mass spectra were measured on VG ZAB-HS Mass spectrometer. Nicolet AVATAR 360 FT-IR spectrometer was used for IR spectra and only major peaks are reported in cm$^{-1}$. HRMS spectra were obtained with a Bruker APEX instrument.

All reagents were used directly as obtained commercially unless otherwise noted. All mixed solvent systems are reported as v/v solutions. The electron-deficient trisubstituted alkene 1 was easily prepared according to the literature procedures.

**Ammonium Ylides; Ammonium Salt 2; Typical Procedure**

A solution of DABCO (1.12 g, 10 mmol) in THF (10 mL) was added to a solution of phenacyl bromide (1.99 g, 10 mmol) in THF (30 mL) with stirring at r.t. until the starting material had disappeared (monitored by TLC). The mixture was filtered and the precipitates were washed with THF (3 × 10 mL) and petroleum ether (bp 40–60 °C, 3 × 10 mL) to give the pure salt 1 as a white solid in 95% yield.

**Reaction of the Electron-Deficient Trisubstituted Alkene 1 with Ammonium Ylides To Give trans-$\beta$-Substituted $\gamma$-Ferrocenyl-$\gamma$-butyrolactones; General Procedure**

A suspension of the appropriate ammonium salt (0.75 mmol, Table 1) and anhyd K$_2$CO$_3$ (1.5 mmol) in CH$_2$Cl$_2$–DMSO (4:1, 10 mL) was stirred vigorously at r.t. for 0.5 h. A solution of alkene 1 (0.5 mmol) in CH$_2$Cl$_2$–DMSO (4:1, 10 mL) was added to the previous mixture and the stirring continued at reflux temperature until the reaction was completed according to TLC. The reaction was quenched with H$_2$O (10–15 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with H$_2$O, brine, and dried (MgSO$_4$). The crude product was purified by silica gel column chromatography using petroleum ether and EtOAc as eluent to give the pure product (Table 1).

2a
Orange solid; mp 121–122 °C.

IR (KBr): 3070, 1759, 1688, 1598, 1581, 1447, 1196, 905 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.88 (d, $J$ = 7.8 Hz, 2 H), 7.62 (t, $J$ = 7.2 Hz, 1 H), 7.48 (t, $J$ = 7.5 Hz, 2 H), 5.60 (d, $J$ = 6.9 Hz, 1 H), 4.24 (s, 2 H), 4.17 (br s, 8 H), 2.94 (dd, $J$ = 2.4, 8.7 Hz, 2 H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 196.7, 174.2, 135.1, 134.1, 128.9, 128.5, 85.3, 80.3, 68.9, 68.4, 66.7, 65.4, 49.5, 33.6.

FAB$^+$-MS: $m/z$ = 374.

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**Scheme 2**

**Figure 2 X-ray crystal structure of 2a**

Further investigations into this process to find more effective nitrogen ylides and to prepare substituted $\gamma$-butyrolactones are currently underway in our laboratory.
HRMS: m/z [M + H] calcd for C_{30}H_{24}FeO_{3}: 375.0678; found: 375.0678.

3a
Orange solid; mp 156–157 °C.
IR (KBr): 3095, 1757, 1684, 1583, 1417, 1205, 1150, 1069, 813 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 8.4 Hz, 2 H), 5.53 (d, J = 6.9 Hz, 1 H), 4.26 (s, 2 H), 4.18 (s, 7 H), 4.07 (br s, 1 H), 2.96 (d, J = 6.9 Hz, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 195.8, 174.0, 133.9, 132.3, 130.0, 129.7, 85.4, 80.4, 69.2, 68.5, 67.0, 65.2, 50.0, 33.5.
FAB⁻-MS: m/z = 454, 452.
HRMS: m/z [M + H] calcd for C_{30}H_{24}BrFeO_{3}: 452.9783; found: 452.9777.

4a
Orange solid; mp 120–121 °C.
IR (KBr): 3075, 1754, 1687, 1608, 1406, 1204, 1102, 833, 813 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.78 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 5.60 (d, J = 6.9 Hz, 1 H), 4.23 (s, 2 H), 4.14–4.19 (m, 8 H), 2.94 (d, J = 8.7 Hz, 2 H), 2.42 (s, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 196.3, 174.3, 145.3, 132.7, 129.6, 128.7, 85.4, 80.5, 68.8, 68.4, 66.7, 65.5, 49.5, 33.8, 21.7.
FAB⁻-MS: m/z = 388.
HRMS: m/z [M + H] calcd for C_{22}H_{18}FeO_{4}: 389.0834; found: 389.0827.

5a
Orange solid; mp 80–81 °C.
IR (KBr): 3094, 1779, 1669, 1599, 1417, 1316, 1175, 840, 816 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.86 (d, J = 8.7 Hz, 2 H), 6.94 (d, J = 9.0 Hz, 2 H), 5.57 (d, J = 6.6 Hz, 1 H), 4.24 (s, 2 H), 4.14 (s, 7 H), 4.09 (br s, 1 H), 3.88 (s, 3 H), 2.94 (dd, J = 3.6, 8.7 Hz, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 195.1, 174.5, 164.3, 131.0, 128.3, 114.2, 85.5, 80.7, 69.0, 68.4, 66.9, 65.5, 55.6, 49.4, 33.9.
FAB⁻-MS: m/z = 404.
HRMS: m/z [M + H] calcd for C_{22}H_{18}FeO_{4}: 389.0834; found: 389.0827.

6a
Orange solid; mp 57–58 °C.
IR (KBr): 1783, 1733, 1414, 1189, 1105 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.49 (d, J = 6.0 Hz, 1 H), 4.22–4.29 (m, 11 H), 3.33–3.41 (m, 1 H), 2.84–3.02 (m, 2 H), 1.32 (t, J = 6.9 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 174.3, 171.2, 85.2, 80.5, 69.0, 68.8, 66.5, 66.3, 61.8, 47.1, 32.6, 14.1.
FAB⁻-MS: m/z = 342.
HRMS: m/z [M + H] calcd for C_{21}H_{18}FeO_{3}: 343.0627; found: 343.0619.

7a
Orange solid; mp 130–131 °C.
IR (KBr): 2248, 1781, 1415, 1183 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.47 (d, J = 6.9 Hz, 1 H), 4.33 (br s, 9 H), 3.68 (dd, J = 7.5, 15 Hz, 1 H), 2.93–2.96 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 172.1, 116.5, 81.2, 78.5, 69.4, 67.9, 65.4, 33.3, 32.5.
FAB⁻-MS: m/z = 295.
HRMS: m/z [M + H] calcd for C_{16}H_{18}FeO_{3}S: 381.0242; found: 381.0237.
Acknowledgment

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References


(10) Crystal Data for 2a; C7H8FeO2, MW = 374.20, monoclinic, space group P2(1)/c (a = 21.048(3)Å, b = 7.480(1)Å, c = 11.020(1)Å, α = 90.00°, β = 90.45(1)°, γ = 90.00°, V = 1716.19(38)Å3, Z = 4, Dc = 1.448 mg/m3, F(000) = 776, crystal size 0.58×0.56×0.36mm. Intensity data were collected at 291 (2) K with a Siemens P4 diffractometer with graphite monochromator, and MoKα radiation (λ = 0.71073 Å). A total of 3731 independent reflections were measured in range 1.96 < θ < 26.00° and 2293 reflections were considered as observed applying the condition I >2σ(I). The crystal used for X-ray diffraction was grown in a solution of acetone and petroleum ether. All calculations were performed using the SHELXL-97 program. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included but not refined. The final cycle of full matrix least-square refinement was based on F2. The final R and wR values were 0.0328 and 0.0765 respectively. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 266936 for compound 2a. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, Fax (int. code): +44 (1223)336 033; email:deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.
