Preparation of aryl benzyl ketones by [1,2]-Wittig rearrangement

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Dedicated to Professor S. V. Kessar on the occasion of his 70th birthday
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Abstract

α-(Benzotriazol-1-yl)benzyl ethers 4a–f were readily prepared by condensation of benzotriazole, aryl aldehydes and benzyl alcohols. A one-pot reaction involving deprotonation of 4 followed by [1,2]-Wittig rearrangement and departure of the benzotriazolyl group resulted in aryl benzyl ketones 6a–f in good yields.

Keywords: α-(Benzotriazol-1-yl)benzyl ethers, [1,2]-Wittig rearrangement, aryl benzyl ketones

Introduction

The [1,2]-Wittig rearrangement1 has been reviewed extensively.2 It is now widely accepted that the rearrangement proceeds via a radical dissociation-recombination mechanism,3,4 with configuration retention at the migrating carbon and inversion at the Li-bearing terminus.5

Substituted ethers 1, in which G can function as a leaving group as well as an electron-withdrawing group, eliminate group G after [1,2]-Wittig rearrangement to form the carbonyl compounds 3 (Scheme 1). Such reactions have been reported for G = cyano,6 imidazolium and benzimidazolium7 groups. α-(Benzotriazol-1-yl)alkyl allyl ethers have been successfully utilized in the synthesis of homoallylic ketones and alcohols via [2,3]-Wittig rearrangements.8 We now report an extension of this methodology: [1,2]-Wittig rearrangements of α-(benzotriazol-1-yl)arylmethyl ethers to give aromatic ketones.

Results and Discussion

Condensation of an aromatic aldehyde, an aliphatic alcohol and benzotriazole in the presence of a catalytic amount of p-TsOH and 4Å molecular sieves in methylene chloride at room temperature as expected,8,9 gave the α-(benzotriazol-1-yl)alkyl ethers 4a–f in 60–78% yield.
Novel ethers 4b–f were fully characterized by their $^1$H, $^{13}$C NMR spectra and elemental analyses or HRMS data.

\[
\begin{align*}
\text{Scheme 1} \\
\text{The acidic benzotriazole-activated } \alpha\text{-proton in the } \alpha\text{-}(benzotriazol-1-yl)alkyl benzyl ethers 4a–f on treatment with LDA at –78 °C readily gives the } \alpha\text{-lithiated intermediates 5a–f, which eliminate the benzotriazole anion to give, by [1,2]-Wittig rearrangement, the carbonyl products 6a–f in 53–63% yield. The structures of 6a–f were confirmed by } ^1\text{H and } ^{13}\text{C NMR spectroscopy. } ^1\text{H NMR spectra of all of the ketones 6a–f displayed a similar pattern including the disappearance of the } \alpha\text{-proton and benzotriazolyl signals from the aromatic region. The benzylic protons in 6a–f resonated around 4.2 ppm and the } ^{13}\text{C NMR signal for this carbon appeared around 45 ppm. The aromatic signals in all of the ketones 6a–f experienced a negligible change in the chemical shift values from those in the } ^1\text{H and } ^{13}\text{C NMR spectra of starting ethers 4a–f. The disappearance of the } \alpha\text{-carbon signal around 88 ppm and the appearance of a carbonyl signal near 197 ppm in the } ^{13}\text{C NMR spectra further confirmed the formation of ketones 6a–f (Scheme 2), (Table 1).}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 2} \\
\text{Bt = benzotriazol-1-yl}
\end{align*}
\]
Table 1. Synthesis of \(\alpha\)-(benzotriazol-1-yl) ethers 4a–f and aryl benzyl ketones 6a–f

| Entry | Ar | Ar' | 4 (%yield)
\(a\) | 6 (%yield)
\(a\) |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>Ph</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>b</td>
<td>4-F-C(_6)H(_4)</td>
<td>Ph</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>c</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>Ph</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>d</td>
<td>3-MeO-C(_6)H(_4)</td>
<td>Ph</td>
<td>72</td>
<td>53</td>
</tr>
<tr>
<td>e</td>
<td>Ph</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>f</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>63</td>
<td>63</td>
</tr>
</tbody>
</table>

\(a\) Isolated yields.

General methods for the preparation of ketones from aldehydes include (i) nucleophilic addition of an organometallic reagent followed by oxidation of the secondary alcohol;\(^{10}\) (ii) transformation into a carbonyl anion equivalent such as an \((\alpha\)-benzotriazol-1-ylalkyl)methyl ether followed by lithiation, alkylation and deprotection.\(^{9}\) The present two-step [1,2]-Wittig rearrangement procedure provides access to aryl benzyl ketones from an aromatic aldehyde and a benzyl alcohol.

**Experimental Section**

**General Procedures.** Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. \(^1\)H NMR (300 MHz) and \(^{13}\)C NMR (75 MHz) spectra were recorded on a Gemini 300 NMR spectrometer in CDCl\(_3\) (with TMS for \(^1\)H and chloroform-\(d\) for \(^{13}\)C as the internal reference). HRMS were measured on an AEI-30 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. THF was distilled from sodium/benzophenone and dichloromethane from calcium hydride prior to use. All of the reactions were carried out under N\(_2\).

**General procedure for the preparation of \(\alpha\)-(benzotriazol-1-yl)alkyl ethers 4**

A mixture of an aldehyde (20 mmol), an alcohol (20 mmol), benzotriazole (25 mmol), \(p\)-TsOH (10 mmol) and 4Å molecular sieves (10 g) in dry methylene chloride (60 mL) was stirred at 25 °C for 2 days. After filtration, the undissolved solid was washed with methylene chloride (3×30 mL). The solvent of the combined filtrate was removed in vacuo and the residue was purified by column chromatography using hexanes/EtOAc (9:1) as eluent to afford the pure products 4a–f.

**1-[(Benzyloxy)(phenyl)methyl]-1\(\text{H}-1,2,3\)-benzotriazole (4a).** Colorless oil;\(^{11}\) yield, 78%; \(^1\)H NMR \(\delta\) 8.10–8.04 (m, 1H), 7.44–7.42 (m, 2H), 7.34–7.25 (m, 12H), 4.58 (s, 2H); \(^{13}\)C NMR \(\delta\) 147.0, 136.0, 131.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.5, 126.0, 124.2, 119.9, 111.9, 88.3, 70.7.

**1-[(Benzyloxy)(4-fluorophenyl)methyl]-1\(\text{H}-1,2,3\)-benzotriazole (4b).** Colorless oil; yield, 63%; \(^1\)H NMR \(\delta\) 8.12–8.05 (m, 1H), 7.46–7.22 (m, 11H), 7.04 (t, \(J = 8.5\) Hz, 2H), 4.57 (s, 2H); \(^{13}\)C NMR \(\delta\) 163.1 (d, \(J = 248.5\) Hz), 147.3, 136.1, 132.2 (d, \(J = 3.4\) Hz), 131.2, 128.9, 128.3 (d, \(J = 8.5\) Hz), 70.7.
1-[(Benzyloxy)(4-chlorophenyl)methyl]-1H-1,2,3-benzotriazole (4c). Colorless oil; yield, 60%; \(^1\)H NMR \(\delta\) 8.12–8.05 (m, 1H), 7.40–7.24 (m, 13H), 4.57 (s, 2H); \(^{13}\)C NMR \(\delta\) 147.3, 136.0, 135.3, 134.9, 131.2, 129.0, 128.8, 128.4, 127.9, 127.7, 127.6, 124.6, 120.3, 111.7, 87.9, 87.7. Anal. Calcd for C\(_{20}\)H\(_{17}\)FN\(_3\)O\(_2\): C, 68.67; H, 4.61; N, 12.01. Found: C, 68.54; H, 4.83; N, 12.16.

1-[(Benzyloxy)(3-methoxyphenyl)methyl]-1H-1,2,3-benzotriazole (4d). Colorless oil; yield, 72%; \(^1\)H NMR \(\delta\) 8.10–8.04 (m, 1H), 7.40–7.20 (m, 10H), 7.04 (s, 1H), 6.98 (d, \(J = 7.7\) Hz, 1H), 6.86 (dd, \(J = 8.2, 2.2\) Hz, 1H), 4.57 (s, 2H), 3.74 (s, 3H); \(^{13}\)C NMR \(\delta\) 159.9, 147.2, 137.8, 136.2, 131.3, 129.9, 128.7, 128.4, 128.3, 127.7, 124.5, 120.1, 118.4, 114.5, 112.0, 111.9, 88.3, 71.0, 55.5. Anal. Calcd for C\(_{21}\)H\(_{19}\)N\(_3\)O\(_2\): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.79; H, 5.69; N, 11.96.

1-{(4-Methoxybenzyl)oxy}(phenyl)methyl]-1H-1,2,3-benzotriazole (4e). Colorless oil; yield, 73%; \(^1\)H NMR \(\delta\) 8.20–8.00 (m, 1H), 7.45–7.37 (m, 2H), 7.35–7.22 (m, 9H), 6.86 (d, \(J = 7.5\) Hz, 2H), 4.53 (d, \(J = 11.7\) Hz, 1H), 4.47 (d, \(J = 11.7\) Hz, 1H), 3.77 (s, 3H); \(^{13}\)C NMR \(\delta\) 159.8, 147.1, 136.4, 131.3, 130.2, 129.1, 128.7, 128.2, 127.7, 126.1, 124.4, 120.1, 114.1, 111.9, 88.1, 70.6, 55.4. Anal. Calcd for C\(_{21}\)H\(_{19}\)N\(_3\)O\(_2\): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.84; H, 5.75; N, 12.17.

1-{(4-Chlorophenyl)\[(4-methoxybenzyl)oxy\]methyl}-1H-1,2,3-benzotriazole (4f). Colorless oil; yield, 63%; \(^1\)H NMR \(\delta\) 8.12–8.04 (m, 1H), 7.40–7.20 (m, 10H), 6.86 (d, \(J = 8.5\) Hz, 2H), 4.53 (d, \(J = 11.7\) Hz, 1H), 4.47 (d, \(J = 11.7\) Hz, 1H), 3.79 (s, 3H); \(^{13}\)C NMR \(\delta\) 159.9, 147.2, 135.2, 135.0, 131.2, 130.2, 129.0, 127.9, 127.8, 127.6, 124.6, 120.2, 114.1, 111.7, 87.4, 70.7, 55.4. Anal. Calcd for C\(_{21}\)H\(_{18}\)ClN\(_3\)O\(_2\): C, 66.40; H, 4.78; N, 11.06. Found: C, 66.04; H, 4.66; N, 10.84.

General procedure for the preparation of ketones (6a–f) via [1,2]-Wittig rearrangement

To a solution of 4a–f (2 mmol) in dry THF (10 mL) at –78 °C was added dropwise LDA (2.2 mmol). The solution was stirred at –78 °C for 3 hours and then allowed to warm up to room temperature overnight. The reaction was quenched using water (5 mL) and then extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\). After removal of the solvent in vacuo the residue was purified by column chromatography using hexanes/EtOAc (20:1) as eluent to afford the pure ketones 6a–f.

1,2-Diphenyl-1-ethanone (6a). White prisms (pentane); mp 53.0–55.0 °C (Lit.\(^{12}\) mp 55.0–56.0 °C); yield, 63%; \(^1\)H NMR \(\delta\) 8.01 (d, \(J = 7.7\) Hz, 2H), 7.57–7.42 (m, 3H), 7.35–7.24 (m, 5H), 4.28 (s, 2H); \(^{13}\)C NMR \(\delta\) 197.4, 136.4, 133.0, 129.3, 128.5, 128.5, 126.7, 45.3.

1-(4-Fluorophenyl)-2-phenyl-1-ethanone (6b). White microcrystals (hexane); mp 77.5–78.5 °C (Lit.\(^{13}\) mp 83.0 °C); yield, 54%; \(^1\)H NMR \(\delta\) 8.03 (dd, \(J = 8.8, 5.5\) Hz, 2H), 7.38–7.22 (m, 5H), 7.11 (t, \(J = 8.5\) Hz, 2H), 4.25 (s, 2H); \(^{13}\)C NMR \(\delta\) 196.2, 165.9 (d, \(J = 254.8\) Hz), 134.5, 133.1, 131.5, 131.4, 129.2 (d, \(J = 48.1\) Hz), 127.2, 115.9 (d, \(J = 11.8\) Hz), 45.7.

1-(4-chlorophenyl)-2-phenyl-1-ethanone (6c). White needles (hexane); mp 102.0–103.0 °C (Lit.\(^{14}\) mp 107.5 °C); yield, 62%; \(^1\)H NMR \(\delta\) 7.94 (d, \(J = 8.4\) Hz, 2H), 7.42 (d, \(J = 8.5\) Hz, 2H),
7.38–7.20 (m, 5H), 4.25 (s, 2H); $^{13}$C NMR δ 196.6, 139.8, 135.0, 134.4, 130.2, 129.6, 129.2, 129.0, 127.2, 45.8.

1-(3-Methoxyphenyl)-2-phenyl-1-ethanone (6d). Colorless oil; $^{1}$H NMR δ 7.60 (d, $J = 7.7$ Hz, 1H), 7.55–7.51 (m, 1H), 7.40–7.22 (m, 6H), 7.10 (dd, $J = 8.2$, 2.2 Hz, 1H), 4.27 (s, 2H), 3.84 (m, 3H); $^{13}$C NMR δ 196.6, 139.8, 135.0, 134.4, 130.2, 129.6, 129.2, 127.1, 121.5, 119.9, 113.0, 55.6, 45.8.

2-(4-Methoxyphenyl)-1-phenyl-1-ethanone (6e). White powder (hexane); mp 92.0 °C (Lit. mp 99.5–100.5 °C); yield, 61%; $^{1}$H NMR δ 8.01 (d, $J = 7.1$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 4.22 (s, 2H), 3.78 (s, 3H); $^{13}$C NMR δ 197.7, 160.0, 138.2, 134.8, 129.8, 129.6, 128.9, 127.1, 121.5, 114.3, 55.4, 44.8.

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1-ethanone (6f). White prisms (hexane); mp 107.5 °C (Lit. mp 111.0 °C); yield, 63%; $^{1}$H NMR δ 7.93 (d, $J = 8.5$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 4.19 (s, 2H), 3.78 (s, 3H); $^{13}$C NMR δ 196.7, 158.6, 139.6, 134.9, 130.4, 130.1, 129.0, 126.1, 114.2, 55.3, 44.7.

References