Regiocontrol in the $\alpha,\alpha$-dialkylation of ketones

Alan R. Katritzky,* Zuoquan Wang, Yu Ji, and Yunfeng Fang

Center for Heterocyclic Compounds, University of Florida, Department of Chemistry,
Gainesville, Florida 32611-7200, USA
E-mail: Katritzky@chem.ufl.edu

Abstract
Refluxing $\alpha$-halo ketones $1, 5, 8, 11$ with benzotriazole gave the corresponding $\alpha$-benzotriazolyl ketones $2, 6, 9, 12$ in high yields. Regioselective introduction of an alkyl group into the $\alpha$-position of these $\alpha$-benzotriazolyl ketones using an appropriate halide under basic conditions gave $\alpha$-alkyl-$\alpha$-benzotriazolyl ketones $4a-e, 7a-c, 10a-c$ and $13a-c$. Removal of the benzotriazole group by lithium naphthalenide and the introduction of another alkyl group were illustrated for $4c$ and $13c$, which gave compounds $14$ and $15$.

Keywords: Benzotriazole, $\alpha,\alpha$-dialkylation, ketones, regiocontrol, $\alpha$-haloketones

Introduction

The regioselective introduction of one or two alkyl groups at the carbon $\alpha$ to a ketone carbonyl is important synthetically. Published general procedures for achieving this include controlling the site of alkylation by diverse activating substituents at the $\alpha$-position, including: (i) another carbonyl group; $^{1a-d}$ (ii) an $\alpha$-alkylthio group, which could be further reductively substituted; $^{2a-d}$ (iii) an $\alpha$-benzenesulfonyl group; $^{3a-c}$ (iv) an $\alpha$-cyano group. $^{4}$ There are several published procedures for introduction of two identical alkyl groups at the $\alpha$-carbon of a ketone; $^{5a-c}$ however, few procedures for the introduction of two different alkyl groups at the $\alpha$-carbon of a ketone have been published. $^{6a-c}$

We now disclose a method for the regioselective $\alpha$-alkylation of ketones via benzotriazole intermediates, which allows the introduction of two different $\alpha$-substituents. The sequence involved three steps (Schemes 1 and 2): (i) preparation of an $\alpha$-benzotriazolyl ketone; (ii) introduction of an alkyl group into the $\alpha$-position using 2N or 5N NaOH aqueous solution; (iii) removal of benzotriazole by lithium naphthalenide and simultaneous introduction of another

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$^a$ Present addresses: Triad Therapeutics, 5820 Nancy Ridge Drive, #200, San Diego, CA 92121.
alkyl group. This new approach is convenient, with mild reaction conditions, applies commercial or readily available reagents. It complements previous routes for the α-alkylation of ketones.

![Chemical Structures]

Scheme 1

**Results and Discussion**

Halo ketones 1, 5, 8, 11 were treated with benzotriazole in toluene with (for 1, 8) or without triethylamine (for 5, 11) as a base to afford α-benzotriazolyl ketones 2, 6, 9, 12 in 73%, 81%, 87% and 78% total yields respectively (Scheme 1). These easy to handle reactions often give isomeric mixtures of the 1- and 2-N-alkylated benzotriazole (RBt1 and RBt2; 2, 6, 9) with 12 as an exception, where only RBt1 was obtained. The RBt1 and RBt2 isomers were separated for characterisation and for use in further reactions. Structures 2, 6, 9, 12 are supported by 1H NMR spectra which show a new set of signals at 7.0–8.2 ppm assigned to the N-substituted benzotriazole group. The 13C NMR spectra of 2, 6, 9, 12 show signals between 110 ppm and 146 ppm corresponding to the N-substituted benzotriazole.
Intermediates 2, 6, 9, 12, on treatment with 2 equivalents of NaOH and an alkyl halide 3a-g in acetonitrile at 20 °C, give the corresponding α-alkyl-α-benzotriazolyl ketones 4a-e, 7a-c, 10a-c and 13a-c in average 65% yields (Scheme 1) (Table 1). Monoalkylation compounds are the major products, but dialkylation products 10a’-c’ and 13b’,c’ are also formed from the acyclic starting materials 9 and 12 in 5–16% yields. Dialkylation product 13a’ was not detected. The structures of α-alkyl-α-benzotriazolyl ketones 4a-e, 7a-c, 10a-c and 13a-c are supported by their \(^1\)H NMR spectra which for products 4a-e and 7a-c show the appearance of a new set of signals corresponding to the introduced alkyl groups in place of the doublet of doublets at 5.5–6.5 ppm characteristic for the α-H to the benzotriazole group in the starting materials. The \(^{13}\)C NMR spectra of 4a-e and 7a-c also show new signals corresponding to the introduced alkyl groups. The \(^1\)H NMR spectra of products 10a-c and 13a-c show the appearance of a new doublet of doublets characteristic for the single α-H to the benzotriazole group and a new set of signals characteristic for the alkyl group introduced. The singlets at 5.0–6.0 ppm in the starting materials 9, 12 for the two α-H to the benzotriazole group are gone. The \(^{13}\)C NMR spectra of 10a-c and 13a-c also show new signals corresponding to the alkyl groups introduced.

Table 1. Preparation of α-alkylated α-benzotriazolyl ketones 4a-e, 7a-c, 10a-c (a’-c’-c’) and 13a-c (b’-c’)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Reaction Time, h</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>CH₃</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>4b</td>
<td>CH₂=CHCH₂</td>
<td>30</td>
<td>68</td>
</tr>
<tr>
<td>4c</td>
<td>PhCH₂</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>4d</td>
<td>4-Br-C₆H₄CH₂</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>4e</td>
<td>PhCH=CHCH₂</td>
<td>35</td>
<td>77</td>
</tr>
<tr>
<td>7a</td>
<td>CH₃</td>
<td>39</td>
<td>70</td>
</tr>
<tr>
<td>7b</td>
<td>CH₂=CHCH₂</td>
<td>39</td>
<td>73</td>
</tr>
<tr>
<td>7c</td>
<td>PhCH=CHCH₂</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td>10a (a’)</td>
<td>PhCH₂</td>
<td>48</td>
<td>45 (11)</td>
</tr>
<tr>
<td>10b (b’)</td>
<td>4-Br-C₆H₄CH₂</td>
<td>42</td>
<td>44 (16)</td>
</tr>
</tbody>
</table>

* The isolated yields.

Cyclic compound 4c and acyclic compound 13c were chosen as starting materials to test the benzotriazolyl group elimination and the introduction of another alkyl group. Intermediates 4c or 13c were treated with 5 equivalents of lithium naphthalenide in THF at –40 °C for 4 h, then the corresponding alkyl iodide was added and the mixture was stirred for 6 h at the same temperature. After general work-up, compound 14 and 15 were obtained in 51% and 56% yields, respectively. Structures 14 and 15 are supported by their \(^1\)H NMR spectra which show the appearance of a new set of signals corresponding to the introduced alkyl group in place of the signals at 7.0–8.2 ppm assigned to the benzotriazolyl group. The \(^{13}\)C NMR spectra of 14 and 15 also show new signals corresponding to the alkyl groups introduced.
In summary, a novel, simple route for the regioselective α,α-dialkylation of ketones was developed.

Scheme 2

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and were uncorrected. NMR spectra were recorded in CDCl₃ with TMS as the internal standard for ¹H (300 MHz) or a solvent as the internal standard for ¹³C (75 MHz). Microanalyses were performed on a Carlo Erba -1106 elemental analyzer. Benzene and toluene were dried over molecular sieves. Column chromatography was conducted with silica gel 200–425 mesh.

General procedure for the preparation of α-benzotriazolyl ketones 2, 6, 9, 12

The α-halo ketone 1, 5, 8, or 11 (10 mmol) and benzotriazole (1.79 g, 15 mmol) in toluene (50 mL) and triethylamine (for 1: 50 mmol; for 8: 15 mmol) were heated under reflux for 24 h. Toluene was removed in vacuo. The residue was purified by column chromatography to afford an analytically pure sample.

2-(Benzotriazol-2-yl)cyclohexanone and 2-(benzotriazol-1-yl)cyclohexanone (2). The ratio of the two isomers is 1.2 : 1.

2-(Benzotriazol-2-yl)cyclohexanone. colorless flakes (ethanol), mp 131–133 °C, 8 (40%); ¹H NMR (CDCl₃) δ 1.70–2.00 (m, 2H), 2.04–2.24 (m, 2H), 2.44–2.72 (m, 3H), 2.78–2.90 (m, 1H), 5.59 (dd, J = 12.6, 5.7 Hz, 1H), 7.37–7.40 (m, 2H), 7.87–7.90 (m, 2H); ¹³C NMR (CDCl₃) δ 24.1, 26.7, 33.0, 41.0, 73.1, 118.2, 126.4, 144.2, 202.7.
2-(Benzotriazol-1-yl)cyclohexanone. colorless prisms (ethanol), mp 128–129 °C (33%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.82–2.04 (m, 2H), 2.18–2.31 (m, 2H), 2.54–2.80 (m, 4H), 5.59 (dd, 12.6, 6.3 Hz, 1H), 7.33–7.48 (m, 3H), 8.08 (d, \(J = 8.4\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 24.6, 26.9, 33.0, 41.2, 66.6, 110.3, 120.1, 123.8, 127.2, 132.9, 146.2, 202.7. Anal. Calcd for C\(_{12}\)H\(_{13}\)N\(_3\)O: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.97; H, 6.30; N, 19.60.

2-(Benzotriazol-2-yl)cyclopentanone and 2-(benzotriazol-1-yl)cyclopentanone (6). the ratio of the two isomers is 2 : 1.

2-(Benzotriazol-2-yl)cyclopentanone. colorless prisms (ethanol), mp 72–74 °C (54%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.98–2.15 (m, 1H), 2.33–2.43 (m, 1H), 2.50–2.62 (m, 2H), 2.70–2.90 (m, 2H), 5.38 (t, \(J = 9.8\) Hz, 1H), 7.30–7.42 (m, 2H), 7.78–7.90 (m, 2H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 18.8, 30.2, 36.2, 70.7, 118.0, 126.6, 144.5, 209.5. Anal. Calcd for C\(_{11}\)H\(_{11}\)N\(_3\)O: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.78; H, 5.64; N, 21.04.

2-(Benzotriazol-1-yl)cyclopentanone. colorless prisms (ethanol) mp 62–64 °C (27%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.00–2.22 (m, 1H), 2.28–2.44 (m, 1H), 2.45–2.63 (m, 2H), 2.66–2.84 (m, 2H), 5.28 (t, \(J = 9.9\) Hz, 1H), 7.32–7.52 (m, 3H), 8.06 (d, \(J = 8.4\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 18.6, 28.9, 35.9, 63.8, 109.4, 119.9, 123.9, 127.4, 132.8, 145.7, 210.2. Anal. Calcd for C\(_{11}\)H\(_{11}\)N\(_3\)O: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.68; H, 5.72; N, 20.85.

1-(Benzotriazol-1-yl)propan-2-one and 1-(benzotriazol-2-yl)propan-2-one (9). the ratio of the two isomers is 4 : 1.

1-(Benzotriazol-1-yl)propan-2-one. colorless flakes (ethanol), mp 120–122 °C, [mp 126–127 °C\(^3\)] (65%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.21 (s, 3H), 5.45 (s, 2H), 7.32–7.41 (m, 2H), 7.48 (t, \(J = 7.5\) Hz, 1H), 8.06 (d, \(J = 8.4\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 27.0, 56.6, 109.1, 119.9, 124.0, 127.8, 133.3, 145.8, 199.8. 1-(Benzotriazol-2-yl)propan-2-one. colorless prisms (ethanol), mp 143–144 °C,\(^{10}\) (16%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.15 (s, 3H), 5.52 (s, 2H), 7.41–7.44 (m, 2H), 7.88–7.91 (m, 2H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 27.0, 64.7, 118.2, 126.9, 144.9, 199.7.

1-(Benzotriazol-1-yl)-2-butanone (12). obtained as just one isomer, colorless needles (ethanol), mp 101–103 °C (78%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.10 (t, \(J = 7.2\) Hz, 3H), 2.49 (q, \(J = 7.2\) Hz, 2H), 5.44 (s, 2H), 7.37–7.43 (m, 2H), 7.51 (t, \(J = 7.7\) Hz, 1H), 8.10 (d, \(J = 8.4\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 7.1, 33.2, 56.0, 109.1, 120.2, 124.1, 128.0, 133.4, 146.0, 202.8. Anal. Calcd for C\(_{10}\)H\(_{11}\)N\(_3\)O: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.62; H, 6.03; N, 22.39.

General procedure for the preparation of \(\alpha\)-alkyl \(\alpha\)-benzotriazolyl ketones 4a-e, 7a-c, 10a-c and 13a-c

To a solution of \(\alpha\)-benzotriazolyl ketones 2, 6, 9, or 12 (3 mmol) and the corresponding alkyl halide 3a-g (3.3 mmol) in CH\(_3\)CN (15 mL), 2 N aqueous NaOH solution (3 mL, 6 mmol) was added. The reaction mixture was stirred at room temperature for about 48 h. The reaction was monitored by TLC. The solvent was removed in vacuo and water was added to the residue. The mixture was extracted with ether. The combined ether extracts were dried over anhydrous MgSO\(_4\). Ether was removed in vacuo. The residue was purified by column chromatography to afford an analytically pure sample.
2-(Benzotriazol-1-yl)-2-methylocyclohexanone (4a). yellow oil (54%); $^1$H NMR (CDCl$_3$) $\delta$ 1.73 (s, 3H), 1.79–2.18 (m, 5H), 2.22–2.38 (m, 1H), 2.42–2.58 (m, 1H), 3.35–3.50 (m, 1H), 7.30–7.47 (m, 3H), 8.10 (d, $J = 8.1$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.2, 23.0, 27.9, 39.0, 39.5, 70.0, 110.6, 120.2, 123.9, 127.5, 131.8, 146.6, 207.1. Anal. Calcd for C$_{13}$H$_{15}$N$_3$O: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.82; H, 6.83; N, 18.43.

2-Allyl-2-(benzotriazol-2-yl)cyclohexanone (4b). colorless prisms (ethanol), mp 47–49 °C (68%); $^1$H NMR (CDCl$_3$) $\delta$ 1.65–2.06 (m, 5H), 2.30–2.60 (m, 2H), 2.76 (dd, $J = 14.1$, 7.8 Hz, 1H), 2.98 (dd, $J = 14.1$, 6.6 Hz, 1H), 3.36 (dd, $J = 14.7$, 2.7 Hz, 1H), 4.84–4.95 (m, 2H), 5.48–5.64 (m, 1H), 7.38–7.48 (m, 2H), 7.84–8.00 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.0, 27.5, 36.7, 39.6, 42.0, 76.2, 118.2, 119.2, 126.5, 131.5, 144.0, 204.2. Anal. Calcd for C$_{15}$H$_{17}$N$_3$O: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.34; H, 6.60; N, 16.48.

2-(Benzotriazol-2-yl)-2-benzylcyclohexanone (4c). white prisms (ethanol), mp 91–93 °C (67%); $^1$H NMR (CDCl$_3$) $\delta$ 0.94–1.81 (m, 3H), 1.21–1.77 (m, 2H), 1.49–1.59 (m, 1H), 1.62–2.40 (m, 2H), 2.49–3.25 (m, 1H), 3.26 (d, $J = 13.7$ Hz, 1H), 3.42 (d, $J = 14.3$ Hz, 1H), 6.30 (d, $J = 13.7$ Hz, 1H), 6.52 (d, $J = 7.8$ Hz, 2H), 7.00–7.14 (m, 3H), 7.36–7.41 (m, 2H), 7.84–7.87 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 20.9, 27.5, 36.4, 39.4, 43.5, 76.4, 118.2, 126.5, 126.7, 127.7, 129.9, 134.7, 143.9, 204.3. Anal. Calcd for C$_{19}$H$_{19}$N$_3$O: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.40; H, 6.35; N, 13.97.

2-(Benzotriazol-2-yl)-2-(4-bromobenzyl)cyclohexanone (4d). white prisms (ethanol) mp 139–141 °C (84%); $^1$H NMR (CDCl$_3$) $\delta$ 1.60–1.83 (m, 3H), 1.83–2.05 (m, 2H), 2.15–2.35 (m, 1H), 2.52 (d, $J = 12.6$ Hz, 1H), 3.10–3.30 (m, 2H), 3.56 (d, $J = 14.4$ Hz, 1H), 6.39 (d, $J = 8.3$ Hz, 2H), 7.14 (d, $J = 8.3$ Hz, 2H), 7.35–7.50 (m, 2H), 7.78–7.98 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 20.9, 27.6, 36.6, 39.4, 43.0, 76.2, 118.2, 121.0, 126.7, 130.9, 131.6, 133.8, 144.0, 204.2. Anal. Calcd for C$_{19}$H$_{19}$BrN$_3$O: C, 59.39; H, 4.72; N, 10.93. Found: C, 59.33; H, 4.72; N, 10.90.

2-(Benzotriazol-2-yl)-2-[(E)-3-phenyl-2-propenyl]cyclohexanone (4e). white needles (ethanol), mp 138–140 °C (77%); $^1$H NMR (CDCl$_3$) $\delta$ 1.68–1.88 (m, 3H), 1.91–2.13 (m, 2H), 2.39–2.62 (m, 2H), 2.89–2.97 (m, 1H), 3.04–3.12 (m 1H), 3.34–3.44 (m, 1H), 5.89–5.99 (m, 1H), 6.21 (d, $J = 15.9$ Hz, 1H), 7.15–7.26 (m, 5H), 7.36–7.43 (m, 2H), 7.86–7.93 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.0, 27.5, 36.8, 39.6, 41.3, 76.6, 118.2, 123.3, 126.1, 126.6, 127.2, 128.3, 134.0, 136.9, 144.1, 204.3. Anal. Calcd for C$_{21}$H$_{21}$N$_3$O: C, 76.11; H, 6.39; N, 12.68. Found: C, 75.94; H, 6.52; N, 12.65.

2-(Benzotriazol-2-yl)-2-methylocyclopentanone (7a). colorless prisms (ethanol), mp 81–82 °C (70%); $^1$H NMR (CDCl$_3$) $\delta$ 1.95 (s, 3H), 2.00–2.22 (m, 2H), 2.30–2.39 (m, 1H), 2.48–2.59 (m, 1H), 2.67–2.79 (m, 1H), 2.98–3.08 (m, 1H), 7.36–7.39 (m, 2H), 7.85–7.88 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 18.3, 21.0, 36.3, 38.2, 72.9, 118.1, 126.4, 144.0, 211.7. Anal. Calcd for C$_{13}$H$_{13}$N$_3$O: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.67; H, 6.18; N, 19.61.

2-Allyl-2-(benzotriazol-2-yl)cyclopentanone (7b). colorless oil (73%); $^1$H NMR (CDCl$_3$) $\delta$ 2.00–2.21 (m, 2H), 2.43–2.55 (m, 2H), 2.64–2.75 (m, 1H), 2.93 (dd, $J = 14.3$, 7.5 Hz, 1H), 3.07–3.16 (m, 1H), 3.37 (dd, $J = 14.3$, 6.9 Hz, 1H), 5.17–5.27 (m, 2H), 5.73–5.87 (m, 1H), 7.40–7.44 (m, 2H), 7.90–7.93 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 18.2, 34.2, 36.6, 38.8, 75.3, 118.2, 120.3, 126.4, 131.3, 144.0, 210.5. Anal. Calcd for C$_{14}$H$_{15}$N$_3$O: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.33; H, 6.38; N, 17.76.
2-(Benzotriazol-2-yl)-2-[(E)-3-phenyl-2-propenyl]cyclopentanone (7c). Colorless prisms (ethanol), mp 106–107 °C (100%); 1H NMR (CDCl3) δ 1.97–2.15 (m, 2H), 2.39–2.56 (m, 2H), 2.60–2.72 (m, 1H), 3.01–3.08 (m, 2H), 3.49 (dd, J = 14.3, 6.8 Hz, 1H), 6.09–6.19 (m, 1H), 6.54 (d, J = 15.6 Hz, 1H), 7.17–7.32 (m, 5H), 7.33–7.43 (m, 2H), 7.82–7.93 (m, 2H); 13C NMR (CDCl3) δ 18.3, 34.3, 36.6, 38.0, 75.6, 118.2, 122.7, 126.2, 126.5, 127.6, 128.5, 132.5, 136.7, 144.0, 210.7. Anal. Calcd for C20H19N3O: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.31; H, 6.17; N, 13.23.

3-(Benzotriazol-1-yl)-4-phenyl-2-butanone (10a). Colorless oil (45%); 1H NMR (CDCl3) δ 2.03 (s, 3H), 3.55 (dd, J = 14.3, 5.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.3 Hz, 2H), 7.28–7.49 (m, 3H), 8.07 (d, J = 8.1 Hz, 1H); 13C NMR (CDCl3) δ 26.9, 35.1, 69.0, 109.0, 120.4, 121.0, 124.4, 128.1, 130.4, 131.7, 132.8, 134.9, 146.0, 201.8. HRMS (FAB) Calcd for C16H15N3O: 269.1108. Found: 269.1107.

3-(Benzotriazol-1-yl)-4-(4-bromophenyl)-2-butanone (10b). Colorless oil (44%); 1H NMR (CDCl3) δ 2.02 (s, 3H), 3.53 (dd, J = 14.3, 10.2 Hz, 1H), 3.76 (dd, J = 14.3, 5.3 Hz, 1H), 5.60 (dd, J = 10.2, 5.3 Hz, 1H), 6.94–6.98 (m, 2H), 7.10–7.13 (m, 3H), 7.27–7.44 (m, 3H), 8.04–8.08 (m, 1H); 13C NMR (CDCl3) δ 27.0, 35.8, 69.4, 109.2, 120.2, 124.2, 127.0, 127.9, 128.6, 128.7, 132.9, 135.9, 146.0, 202.1. Anal. Calcd for C16H15BrN3O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.52; H, 5.86; N, 15.91.

3-(Benzotriazol-1-yl)-4-(4-methylphenyl)-2-butanone (10c). Colorless oil (45%); 1H NMR (CDCl3) δ 2.03 (s, 3H), 2.20 (s, 3H), 3.52 (dd, J = 14.3, 9.9 Hz, 1H), 3.72 (dd, J = 14.3, 5.4 Hz, 1H), 5.59 (dd, J = 9.9, 5.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.32–7.47 (m, 3H), 8.06 (d, J = 8.1 Hz, 1H); 13C NMR (CDCl3) δ 20.9, 27.1, 35.3, 69.6, 109.4, 120.2, 124.2, 127.9, 128.6, 129.3, 132.7, 133.0, 146.1, 202.3. Anal. Calcd for C17H17N3O: C, 73.10; H, 6.13; N, 15.04. Found: C, 72.74; H, 6.34; N, 15.39.

3-(Benzotriazol-1-yl)-2-(4-methylbenzyl)-4-(4-methylphenyl)-2-butanone (10c'). Colorless needles (ethanol), mp 113–115 °C (11%); 1H NMR (CDCl3) δ 1.76 (s, 3H), 2.24 (s, 6H), 3.66–3.82 (m, 4H), 6.71 (d, J = 7.8 Hz, 4H), 6.94 (d, J = 7.8 Hz, 4H), 7.16 (d, J = 7.2 Hz, 1H), 7.37–7.40 (m, 2H), 8.11–8.15 (m, 1H); 13C NMR (CDCl3) δ 20.9, 26.8, 39.3, 76.9, 110.6, 120.5, 124.0, 127.6, 128.9, 130.0, 131.0, 132.8, 136.8, 146.5, 205.4. HRMS (FAB) Calcd for C25H26N3O: 384.2076. Found: 384.2074.
4-(Benzotriazol-1-yl)-6-hepten-3-one (13a). yellow oil (57%); \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) 0.98 (t, \( J = 7.2 \) Hz, 3H), 2.20–2.40 (m, 2H), 3.03–3.22 (m, 2H), 4.94–5.05 (m, 2H), 5.51 (dd, \( J = 9.6, 6.0 \) Hz, 1H), 5.57–5.71 (m, 1H), 7.38–7.54 (m, 3H), 8.10 (d, \( J = 8.4 \) Hz, 1H); \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) 7.2, 32.7, 33.8, 67.1, 109.5, 119.3, 120.3, 124.3, 127.9, 131.9, 132.7, 146.2, 205.1. Anal. Calcd for C\(_{13}\)H\(_{15}\)N\(_3\)O: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.85; H, 6.80; N, 18.71.

2-(Benzotriazol-1-yl)-1-(4-bromophenyl)-3-pentanone (13b). colorless prisms (ethanol), mp 84–86 °C (42%); \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) 0.97 (t, \( J = 7.1 \) Hz, 3H), 2.13–2.38 (m, 2H), 3.53 (dd, \( J = 14.5, 10.1 \) Hz, 1H), 3.71 (dd, \( J = 14.5, 5.4 \) Hz, 1H), 5.60 (dd, \( J = 10.1, 5.4 \) Hz, 1H), 6.85 (d, \( J = 8.3 \) Hz, 2H), 7.23 (d, \( J = 8.3 \) Hz, 2H), 7.33–7.41 (m, 2H), 7.46 (t, \( J = 7.5 \) Hz, 1H), 8.06 (d, \( J = 8.4 \) Hz, 1H); \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) 7.2, 32.9, 35.2, 68.4, 109.1, 120.3, 121.0, 124.3, 128.1, 130.5, 131.7, 132.8, 135.0, 136.0, 204.8. Anal. Calcd for C\(_{17}\)H\(_{16}\)BrN\(_3\)O: C, 57.00; H, 4.50; N, 11.73. Found: C, 57.00; H, 4.44; N, 11.55.

2-(Benzotriazol-1-yl)-2-(4-bromobenzyl)-1-(4-bromophenyl)-3-pentanone (13b'). yellow oil (7%); \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) 0.83 (t, \( J = 7.1 \) Hz, 3H), 1.96 (q, \( J = 7.1 \) Hz, 2H), 3.64 (d, \( J = 14.7 \) Hz, 2H), 3.80 (d, \( J = 14.7 \) Hz, 2H), 6.65 (d, \( J = 8.6 \) Hz, 4H), 7.11–7.15 (m, 1H), 7.27 (d, \( J = 8.6 \) Hz, 4H), 7.40–7.50 (m, 2H), 8.15–8.18 (m, 1H); \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) 7.4, 32.4, 39.8, 76.3, 110.5, 120.9, 121.6, 124.4, 128.1, 131.5, 131.9, 132.7, 133.1, 146.7, 208.0. Anal. Calcd for C\(_{24}\)H\(_{21}\)Br\(_2\)N\(_3\)O: C, 54.67; H, 4.01; N, 7.97. Found: C, 55.00; H, 4.57; N, 7.57.

2-(Benzotriazol-1-yl)-1-(3-methylphenyl)-3-pentanone (13c). white prisms (ethanol), mp 81–83 °C (50%); \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) 0.97 (t, \( J = 7.1 \) Hz, 3H), 2.16 (s, 3H), 2.19–2.42 (m, 2H), 3.50 (dd, \( J = 14.0, 9.9 \) Hz, 1H), 3.72 (dd, \( J = 14.0, 5.4 \) Hz, 1H), 5.62 (dd, \( J = 9.9, 5.4 \) Hz, 1H), 6.77 (s, 2H), 6.90–6.93 (m, 1H), 7.01 (t, \( J = 7.8 \) Hz, 1H), 7.33–7.46 (m, 3H), 8.05 (d, \( J = 7.5 \) Hz, 1H); \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) 7.3, 21.1, 33.1, 35.9, 68.9, 109.5, 120.2, 124.2, 125.7, 127.7, 127.8, 128.5, 129.5, 132.9, 135.9, 138.2, 146.1, 205.1. Anal. Calcd for C\(_{18}\)H\(_{19}\)N\(_3\)O: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.56; H, 6.66; N, 14.39.

2-(Benzotriazol-1-yl)-2-(3-methylbenzyl)-1-(3-methylphenyl)-3-pentanone (13c'). colorless oil (5%); \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) 0.83 (t, \( J = 7.1 \) Hz, 3H), 2.03 (q, \( J = 7.1 \) Hz, 2H), 2.17 (s, 6H), 3.69 (d, \( J = 14.7 \) Hz, 2H), 3.82 (d, \( J = 14.7 \) Hz, 2H), 6.56 (s, 2H), 6.62 (d, \( J = 7.5 \) Hz, 2H), 6.96–7.06 (m, 4H), 7.13–7.16 (m, 1H), 7.38–7.42 (m, 2H), 8.13–8.16 (m, 1H); \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) 7.3, 21.2, 32.3, 40.1, 76.8, 110.8, 120.5, 124.1, 127.1, 127.6, 128.0, 128.1, 131.2, 133.0, 134.2, 137.8, 146.6, 208.1. Anal. Calcd for C\(_{26}\)H\(_{27}\)N\(_3\)O: C, 78.56; H, 6.85; N, 10.57. Found: C, 78.25; H, 7.11; N, 10.53.

General procedure for the preparation of \( \alpha, \alpha \)-dialkylketones 14, 15
To a solution of naphthalene (0.6 g, 4.68 mmol) and lithium metal (26 mg, 3.65 mmol) in small pieces was added dry THF (20 mL). The reaction mixture was stirred at room temperature under argon atmosphere until lithium metal completely dissolved (~19.5 h). The resulting dark green solution of lithium naphthalenide (LN) was then cooled to –40 °C by acetonitrile–dry ice bath for 1 h, followed by addition of a solution of the appropriate \( \alpha \)-benzotriazolyl ketone (0.73 mmol) in THF (5 mL) dropwise over 5 min. The reaction mixture was stirred at ~40 °C for 4 h. An appropriate electrophile (21.9 or 7.3 mmol) was then added and the reaction mixture was further stirred at ~40 °C for 6 h. Saturated aqueous ammonium chloride was added into the
reaction mixture, which was then extracted with ether. The solvent was removed in vacuo and the residue was purified by column chromatography to afford the pure sample.

2-Benzyl-2-methyl-cyclohexanone (14). yellow oil,\(^{11}\) (51%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.09 (s, 3H), 1.55–1.64 (m, 1H), 1.72–1.96 (m, 5H), 2.47–2.64 (m, 2H), 2.94 (s, 2H), 7.14–7.18 (m, 2H), 7.23–7.35 (m, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.1, 22.7, 27.2, 38.0, 38.8, 43.0, 49.2, 126.2, 127.9, 130.5, 137.6, 215.4.

4-(3-Methylbenzyl)-6-hepten-3-one (15). yellow oil (56%); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.90 (t, \(J = 7.2\) Hz, 3H), 2.04–2.44 (m, 7H), 2.61–2.70 (m, 1H), 2.78–2.92 (m, 2H), 5.02 (d, \(J = 9.3\) Hz, 1H), 5.03 (d, \(J = 18.0\) Hz, 1H), 5.64–5.78 (m, 1H), 6.92 (d, \(J = 8.1\) Hz, 1H), 6.93 (s, 1H), 7.00 (d, \(J = 7.2\) Hz, 1H), 7.15 (t, overlap of dd, \(J = 7.5\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 7.2, 21.3, 36.1, 37.1, 37.8, 53.4, 117.0, 125.8, 127.0, 128.3, 129.6, 135.4, 138.0, 139.5, 214.2. HRMS (FAB) Calcd for C\(_{15}\)H\(_{21}\)O (M+1): 217.1592. Found: 217.1592.

References


