Base-Promoted Reactions of Bridged Ketones and 1,3- and 1,4-Haloalkyl Azides:

Competitive Alkylation vs. Azidation Reactions of Ketone Enolates

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Supporting Information

Experimental Section........................................................................................................................................S2

Copies of $^1$H and $^{13}$C spectrum of new compounds.............................................................................S13

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**General.** Compounds 1 and 2 have been previously reported.\textsuperscript{1} **CAUTION:** Although we have not experienced any explosions, alkyl azides can be hazardous compounds. Accordingly, alkyl azides A–D were not distilled and in some cases used in crude form for safety reasons. We strongly recommend the use of these compounds with appropriate precautions, including the use of safety shields and the avoidance of very large-scale reactions.

\[
\begin{array}{c}
\text{N}_3 \\
\text{Cl}\end{array}
\]

\[A\]

**1-Azido-3-chloropropane (A).** NaN\textsubscript{3} (1.0 g, 6.35 mmol) was added to a solution of 1-bromo-3-chloropropane (0.41 g, 6.35 mmol) in 20 mL of DMF at room temperature. The reaction mixture was allowed to stir for 20 h. The reaction mixture was partitioned between ether and water, and the organic layer was washed with water 3x, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to give A (0.71 g, 94%) as a colorless oil. The material was approximately 90% pure by NMR and used as obtained. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \[2.03 \text{ (m, 2H), 3.51 \text{ (t, } J = 6.2 \text{ Hz, 2H), 3.65 \text{ (t, } J = 6.2 \text{ Hz, 2H); }^{13}\text{C NMR (100.6 MHz, CDCl\textsubscript{3}}) \[32.3, 42.0, 48.7; IR \text{ (neat) 2100 cm}^{-1}; MS \text{ (Cl) } m/z 120 \text{ (M}^+\text{+1); HRMS calcd for C}_3\text{H}_7\text{ClN}_3 \text{ (M}^+\text{+1): 120.0344, found 120.0355.}]}
1-Azido-3-iodopropane (B). NaI (768 mg, 5.12 mmol) was added to a solution of A (306 mg, 2.56 mmol) in 15 mL of acetone and heated to reflux for 24 h. The reaction mixture was partitioned between EtOAc and water. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to give an oil. Flash chromatography (10% EtOAc/hexane) afforded B (461 mg, 85%) as an oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 2.09 (m, 2H), 3.27 (t, $J$ = 6.6 Hz, 2H), 3.46 (t, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 2.8, 32.7, 51.9; IR (neat) 2098 cm$^{-1}$; MS (Cl) m/z 211 (M$^+$+1); HRMS calcd for C$_3$H$_7$IN$_3$ (M$^+$+1): 211.9685, found 211.9672.

1-Azido-4-chlorobutane (C). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.76 (m, 2H), 1.87 (m, 2H), 3.36 (t, $J$ = 6.6 Hz, 2H), 3.53 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 26.6, 30.0, 44.8, 51.1; IR (neat) 2100 cm$^{-1}$; MS (Cl) m/z 134 (M$^+$+1); HRMS calcd for C$_4$H$_9$ClN$_3$ (M$^+$+1): 134.0445, found 134.0428.

1-Azido-4-iodobutane (D). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.73 (m, 2H), 1.91 (m, 2H), 3.23 (t, $J$ = 6.8 Hz, 2H), 3.36 (t, $J$ = 6.6 Hz, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 6.1, 30.1, 30.8, 50.8; IR (neat) 2100 cm$^{-1}$; MS (Cl) m/z 225 (M$^+$+1); HRMS calcd for C$_4$H$_8$IN$_3$ (M$^+$+1): 225.3953 found 225.3939.
Triazoline 3. A 2.5 M solution of n-butyllithium in hexanes (0.31 mL, 0.78 mmol) was added dropwise to a solution of THF (8 mL) and diisopropylamine (0.086 g, 0.85 mmol) at 0 °C and allowed to stir under argon for 10 min. The mixture was cooled to -78 °C and ketone\(^1\) (117 mg, 0.65 mmol) was added. After stirring for 1 h, 1-azido-4-iodobutane D (294 mg, 1.31 mmol) was added dropwise. After 30 min at -78 °C, the reaction mixture was allowed to warm to 0 °C for 2 h. The reaction mixture was quenched with saturated NaHCO\(_3\), extracted with EtOAc, dried over Na\(_2\)SO\(_4\), and concentrated to give an oil. Flash chromatography (40% EtOAc/hexane) afforded 107 mg (60%) of 3 as an oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \[1.12-1.20 (m, 2H), 1.28-1.31 (m, 2H), 1.49-1.54 (m, 3H), 1.66-1.71 (m, 4H), 1.86 (m, 1H), 1.96-1.98 (m, 2H), 2.14-2.20 (m, 2H), 2.44 (s, 1H), 2.67 (m, 1H), 2.83 (m, 1H), 2.99 (m, 1H), 3.16 (m, 1H), 3.89 (m, 1H), 4.14 (m, 1H), 4.36 (s, 1H); \(^13\)C NMR (500 MHz, CDCl\(_3\)) \[25.0, 25.5, 28.2, 30.2, 30.4, 36.1, 40.9, 45.3, 47.8 (2C), 56.3, 62.1, 66.3, 85.3, 102.9; IR (neat) 2940, 2750 cm\(^{-1}\); MS (Cl) \(m/z\) 277 (M\(^+1\)): 97; HRMS calcd for C\(_{15}\)H\(_{23}\)N\(_4\)O (M\(^+1\)): 277.2028, found 277.2016. A sample solidified on standing; the structure of compound 3 was confirmed through X-ray crystallography.
3,4,7,8,9,10-Hexahydro-2H,6aH-1-oxa-4a,5,6-triaza-7,10-methano-
benzo[c]indene (4). Prepared using the same procedure as above from norcamphor (555 mg, 5.04 mmol) and 1-azido-3-iodopropane (1.06 g, 7.56 mmol). Flash chromatography (50% EtOAc/hexane) afforded 917 mg (94%) of triazoline 4 as an oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.21-1.22 (m, 2H), 1.45-1.47 (m, 2H), 1.61-1.71 (complex, 3H), 1.95-2.01 (m, 1H), 2.66-2.67 (m, 1H), 2.79-2.80 (m, 1H), 3.66-3.88 (m, 4H), 4.36-4.40 (m, 1H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 21.9, 26.6, 27.5, 35.7, 40.6, 42.5, 42.8, 62.8, 91.4, 96.4; IR (neat) 2950 cm$^{-1}$; MS (CI) m/z 194 (M$^+$+1): 97; HRMS calcd for C$_{10}$H$_{16}$N$_3$O (M$^+$+1): 194.1215, found 194.1222.

1-(4'-Chlorobutyl)-7a-hydroxyl-4,7-methano-1H-benzotriazole (5). Prepared using the same procedure as above from norcamphor and alkyl azide C. Yield 91%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.17 (m, 2H), 1.50 (m, 2H), 1.70 (m, 1H), 1.89-1.97 (complex, 5H), 2.40 (s, 1H), 2.58 (m, 1H), 3.58-3.65 (m, 5H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 23.1, 27.1, 27.7, 30.4, 34.6, 43.7, 43.8, 44.9, 45.0, 87.4, 96.4; IR (neat) 3168 cm$^{-1}$; MS (CI) m/z 244 (M$^+$+1); HRMS calcd for C$_{11}$H$_{18}$N$_3$OCl (M$^+$+1): 244.1217, found 244.1205.
Spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane (E). E was made from norcamphor and 1,3-propanediol using a procedure of Gassman\textsuperscript{2} et al. Yield: 90%. Bp 65-66 °C (0.2 mm Hg), \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \[1.22 (m, 2H), 1.38 (m, 2H), 1.60-1.64 (complex, 4H), 1.75-1.83 (m, 2H), 2.33 (s, 1H), 2.68 (s, 1H), 3.80-3.95 (complex, 4H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \[21.8, 26.0, 28.8, 36.0, 37.4, 42.1, 44.4, 60.9, 62.6, 108.3; IR (neat) 2983 cm\textsuperscript{-1}; MS (CI) \textit{m/z} 169 (M\textsuperscript{+}+1); HRMS calcd for C\textsubscript{10}H\textsubscript{17}O\textsubscript{2}: 169.1229, found 169.1233.

F

2-[3-[(Trimethylsilyl)oxy]propoxy]bicyclo[2.2.1]hep-2-ene (F). F was made from E by procedure of Gassman\textsuperscript{2} et al. Yield: 90%. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \[0.14 (s, 9H), 1.08 (d, \textit{J} = 7.9 Hz, 1H), 1.13-1.25 (m, 2H), 1.47-1.50 (m, 1H), 1.66-1.70 (m, 2H), 1.89 (pentet, \textit{J} = 5.9 Hz, 2H), 2.67-2.68 (m, 1H), 2.82-2.83 (m, 1H), 3.53-3.80 (complex, 4H), 4.54 (d, \textit{J} = 3.1 Hz, 1H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \[−0.2, 25.2, 28.7, 32.4, 41.2, 44.4, 47.4, 59.5, 65.6, 97.7, 116.6; IR (neat) 1614 cm\textsuperscript{-1}; MS (CI) \textit{m/z} 241 (M\textsuperscript{+}+1); HRMS calcd for C\textsubscript{13}H\textsubscript{25}O\textsubscript{2}Si (M\textsuperscript{+}+1): 241.1526, found 241.1545.
3- (Bicyclo[2.2.1]hept-2-en-2-yloxy)-propan-1-ol (G). To a solution of F (2.80 g, 11.7 mmol) in methanol was added K$_2$CO$_3$ (1.61 g, 11.7 mmol) at 0 °C, and the solution allowed to stir for 1 h. After filtration and evaporation, the residue was partitioned between water and CH$_2$Cl$_2$, and the organic layer was dried with Na$_2$SO$_4$. Removal of solvent gave G 1.90 g (98%) as a brown oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.07 (d, $J = 7.9$ Hz, 1H), 1.13-1.30 (m, 2H), 1.47-1.51 (m, 1H), 1.63-1.75 (m, 2H), 1.87 (t, $J = 5.5$ Hz, 1H), 1.94 (pentet, $J = 5.9$ Hz, 2H), 2.67-2.68 (m, 1H), 2.82-2.83 (m, 1H), 3.70-3.90 (complex, 4H), 4.55 (d, $J = 3.2$ Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 25.2, 28.6, 32.1, 41.2, 44.4, 47.4, 61.3, 67.2, 196.3; IR (neat) 3418, 1614 cm$^{-1}$; MS (CI) m/z 169 (M$^+$+1); HRMS calcd for C$_{10}$H$_{17}$O$_2$ (M$^+$+1): 169.1229, found 169.1220.

2-[3-Azido-propoxy]bicyclo[2.2.1]hept-2-ene (6). To a solution of G (200 mg, 1.2 mmol), Zn(N$_3$)$_2$•2Py$^3$ (275 mg, 0.9 mmol) and PPh$_3$ (620 mg, 2.4 mmol) in dry THF, was added diisopropylazodicarbonate (470 mg, 2.4 mmol) dropwise at room temperature, and the reaction mixture was allowed to stir overnight. The reaction was poured through Celite and concentrated to afford compound 6 (200 mg, 90%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.07-1.96 (complex, 8H), 2.68-2.83 (m, 2H), 3.45 (t, $J = 6.6$ Hz, 2H), 3.65-3.78 (m, 2H), 4.54 (d, $J = 3.2$ Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 25.3, 28.6, 28.9, 41.2,
44.3, 47.4, 48.8, 65.6, 98.1, 166.3; IR (neat) 2098, 1613 cm\(^{-1}\); MS (Cl) \(m/z\) 194 (M\(^+\)+1); HRMS calcd for C\(_{10}\)H\(_{16}\)N\(_3\)O (M\(^+\)+1): 194.1215, found 194.1222.

1-Benzyl-7a-hydroxy-4,7-methano-1\(H\)-benzotriazole (7). Prepared by the same procedure described in compound 10 from norcamphor and benzyl azide. Yield 67%; mp 111-118 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.01-1.87 (complex, 6H); 2.08 (d, \(J = 3.0\) Hz, 1H), 2.56 (d, \(J = 3.8\) Hz, 1H), 3.66 (s, 1H), 4.80 (ABq, \(J = 15.2\) Hz, \(\Delta\delta = 4.2\) Hz, 2H), 5.57 (s, 1H), 7.28-7.43 (complex, 5H); \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 22.9, 27.2, 34.6, 43.8, 45.0, 48.5, 87.6, 96.6, 128.0, 128.9, 129.0, 138.2; IR (neat) 3165,1460 cm\(^{-1}\); MS (Cl) \(m/z\) 244 (M\(^+\)+1); HRMS calcd for C\(_{14}\)H\(_{18}\)N\(_3\)O (M\(^+\)+1): 244.1450, found 244.1438.

1-Hexyl-7a-hydroxy-4,7-methano-1\(H\)-benzotriazole (8). Prepared by the same procedure described in compound 10 from norcamphor and 1-azidohexane. Yield 93%; mp 65-67 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.89-1.91 (complex, 18H), 2.22 (d, \(J = 6.9\) Hz, 1H), 2.47 (d, \(J = 6.9\) Hz, 1H), 3.55 (t, \(J = 7.6\) Hz, 2H), 3.60 (br s, 1H); \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 14.5, 23.0, 23.1, 27.1, 27.2, 30.4, 31.9, 34.5, 43.8, 44.7, 44.9,
87.6, 96.4; IR (neat): 3158, 1456, cm⁻¹; MS (Cl) m/z 238 (M⁺+1); HRMS calcd for C₁₃H₂₄N₃O (M⁺+1): 238.1919, found 238.1925.

![9]

1-Cyclohexyl-7a-hydroxyl-4,7-methano-1H-benzotriazole (9). Prepared by the same procedure described in compound 10 from norcamphor and 1-azidocyclohexane.
Yield 69%; mp 184-186 ºC; ¹H NMR (400 MHz, CDCl₃) δ 1.12 (s, 2H), 1.21-2.09 (complex, 14H), 2.38 (d, J = 2.8 Hz, 1H), 2.51 (d, J = 4.2 Hz, 1H), 3.41-3.56 (m, 2H), 6.06 (br s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ 23.2, 25.9, 26.3, 27.1, 34.4, 34.7, 44.0, 45.2, 54.7, 85.9, 97.0; IR (neat) 3157, 1450 cm⁻¹; MS (Cl) m/z 236 (M⁺+1); HRMS calcd for C₁₃H₂₂N₃O (M⁺+1): 236.1763, found 236.1756.

![10]

1-Benzyl-7a-trimethylsilyloxy-4,7-methano-1H-benzotriazole (10). A 2.5 M solution of n-butyllithium in hexanes (0.80 mL, 1.99 mmol) was added dropwise to a solution of THF (10 mL) and diisopropylamine (0.239 g, 2.36 mmol) at 0 ºC and allowed to stir under argon for 10 min. The mixture was cooled to -78 ºC and norcamphor (200 mg, 1.81 mmol) was added. After stirring for 1 h, benzyl azide (480 mg, 3.61 mmol) was added dropwise. After 30 min at -78 ºC, the reaction mixture was allowed to warm to 0
°C for 2 h. TMSCl (256 mg, 3.61 mmol) was added and the solution was stirred for another hour. The reaction mixture was quenched with saturated NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography afforded 542 mg (95%) of 10 as an oil: ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, 9H), 0.86-1.06 (m, 3H), 1.26-1.40 (m, 3H), 1.58-1.71 (m, 2H), 2.02 (m, 1H), 2.62 (d, J = 4.4 Hz, 1H), 3.90 (s, 1H), 4.55 (d, J = 15.1 Hz, 1H), 4.83 (d, J = 15.1 Hz, 1H), 7.29-7.40 (m, 5H); ¹³C NMR (100.6 MHz, CDCl₃) δ 1.3, 23.0, 27.3, 33.4, 43.7, 46.4, 48.8, 87.2, 97.4, 128.0, 128.9, 129.0, 138.1; IR (neat) 2980 cm⁻¹; MS (CI) m/z 316 (M⁺+1): 258, 91; HRMS calcd for C₁₇H₂₆N₃OSi (M⁺+1): 316.1845, found 316.1831.

\[ \text{N-N-C} \]

1-N-(4'-Chlorobutyl)-4,5,6,7-tetrahydro-1H-benzotriazole (Table 1, entry 1).

The same procedure was followed as described above (no trapping agent was used). Yield: 95%; oil. ¹H NMR (400 MHz, CDCl₃) δ 1.71-1.88 (complex, 6H), 2.03 (m, 2H), 2.61 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 5.6 Hz, 2H), 3.58 (t, J = 6.3 Hz, 2H), 4.26 (t, J = 6.9 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 20.5, 22.3, 22.9, 23.0, 27.3, 29.7, 44.6, 47.2, 132.0, 143.9; IR (neat) 1588, 1460 cm⁻¹; MS (CI) m/z 214 (M⁺+1); HRMS calcd for C₁₀H₁₇N₃Cl (M⁺+1): 214.0955, found 214.0931.

\[ \text{N-N-C} \]

3'-Chloropropyl-4,5-dihydro-1H-benzotriazole (Table 1, entry 2). Yield 52%; oil. ¹H NMR (400 MHz, CDCl₃) δ 2.38 (pentet, J = 6.5 Hz, 2H), 2.54 (ddt, J = 2.0, 4.3,
9.0 Hz, 2H), 2.95 (t, J = 9.0 Hz, 2H), 3.53 (t, J = 6.5 Hz, 2H), 4.44 (t, J = 6.5 Hz, 2H),
6.08 (dt, J = 4.3, 9.8 Hz, 1H), 6.44 (dt, J = 2.0, 9.8 Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 20.1, 24.7, 33.0, 41.8, 44.8, 113.7, 132.0, 132.1, 142.8; IR (neat) 1572, 1449 cm$^{-1}$; MS (Cl) m/z 198 (M$^+$+1); HRMS calcd for C$_5$H$_{13}$N$_3$Cl (M$^+$+1): 198.0798, found 198.0788.

![3'-Chloropropyl-4,6-dimethyl-4,5-dihydro-1H-benzotriazole](image.png)

3'-Chloropropyl-4,6-dimethyl-4,5-dihydro-1H-benzotriazole (Table 1, entry 3). Yield 69%; oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.33 (d, J = 6.9 Hz, 3H), 1.94 (s, 3H), 2.15 (dd, J = 8.0, 17.3 Hz, 1H), 2.35 (pentet, J = 9.7 Hz, 2H), 2.52 (dd, J = 8.0, 17.3 Hz, 1H), 3.17-3.22 (m, 1H), 3.51 (t, J = 6.1 Hz, 2H), 4.39 (t, J = 9.7 Hz, 2H), 6.13 (d, J = 1.4 Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 19.5, 24.2, 27.1, 33.2, 39.7, 41.9, 44.7, 108.4, 132.5, 142.3, 146.0; IR (neat) 1567, 1444 cm$^{-1}$; MS (Cl) m/z 226 (M$^+$+1); HRMS calcd for C$_{11}$H$_{17}$N$_3$Cl (M$^+$+1): 226.1111, found 226.1132.

![4-Methyl-5-ethyl-1-(4'-chlorobutyl)-1H-1,2,3-triazole](image.png)

4-Methyl-5-ethyl-1-(4'-chlorobutyl)-1H-1,2,3-triazole (Table 1, entry 4). Yield 32%; oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.17 (t, J = 7.6 Hz, 3H), 1.79-1.86 (m, 2H), 2.02-2.09 (m, 2H), 2.29 (s, 3H), 2.64 (q, J = 7.6 Hz, 2H), 3.57 (t, J = 6.3 Hz, 2H), 4.25 (t, J = 7.1 Hz, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 10.8, 13.8, 16.4, 27.8, 29.7, 44.6, 47.4, 134.5, 140.7; IR (neat) 1567, 1444 cm$^{-1}$; MS (Cl) m/z 202 (M$^+$+1); HRMS calcd for C$_9$H$_{17}$N$_3$Cl (M$^+$+1): 202.1111, found 202.1097.
N-(4-Chlorobutyl)-2-methyl Butanamide (Table 1, entry 4). Yield 30%; oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 0.91\) (t, \(J = 7.4\) Hz, 3H), \(1.13\) (d, \(J = 6.9\) Hz, 3H), \(1.39-1.46\) (m, 1H), \(1.60-1.71\) (m, 3H), \(1.78-1.85\) (m, 2H), \(2.07-2.11\) (m, 1H), \(3.20-3.66\) (m, 2H), \(3.58\) (t, \(J = 6.4\) Hz, 2H); \(5.66\) (br s, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta 12.4, 18.0, 27.6, 27.7, 30.2, 38.9, 43.7, 45.0, 177.0\); IR (neat) 3288, 1649 cm\(^{-1}\); MS (Cl) \(m/z\) 192 (M\(^+\)+1); HRMS calcd for C\(_9\)H\(_{18}\)ClNO (M\(^+\)+1): 192.1155, found 192.1158.

References


