Aliphatic C–H Activation with Aluminium Trichloride–Acetyl Chloride: Expanding the Scope of the Baddeley Reaction for the Functionalisation of Saturated Hydrocarbons

Catherine L. Lyall, Mario Uosis-Martin, John P. Lowe, Mary F. Mahon,* G. Dan Pantoş and Simon E. Lewis*

ELECTRONIC SUPPORTING INFORMATION

Experimental Procedures Page 2
NMR Spectra Page 8
Chart of isomeric enol ethers from isopropylcyclohexane Page 22
EXPERIMENTAL PROCEDURES

Large-Scale Synthesis of Baddeley’s enol ether 6

This reaction was performed in accordance with Baddeley’s literature procedure.\(^{5b-f}\) Acetyl chloride (85.45 mL, 1.197 mol, 2.40 equiv) was gradually added with stirring to a cooled (<25 °C) mixture of aluminium chloride (100.0 g, 0.75 mol, 1.50 equiv) in DCM (225 mL). The resulting yellow-brown solution was decanted into a flask, cooled to <10 °C, and decalin 1 (80.9 mL, 0.51 mol, 1.00 equiv) was gradually added over 30 min with stirring and cooling to keep the temperature of the reaction mixture below 10 °C. After a further 2 h at 10-15°C, the mixture was gradually added to a vigorously stirred slurry of crushed ice (1 kg) and water. The lower organic layer was separated and, together with DCM extracts of the aqueous layer, washed several times with ice-cold water and dried over MgSO\(_4\), then filtered. The filtrate was concentrated under reduced pressure. Fractional distillation of the residual brown oil gave (1S\(^*\),4aR\(^*\),8aR\(^*\))-9-methyleneoctahydro-1H-1,4a-(epoxymethano)naphthalene 6 (b.p. 82-85 °C / 5.8 Torr) which was then further purified by refluxing with LiAlH\(_4\) (0.5 g) in dry diethyl ether (30 mL) for 30 min. Excess of hydride was destroyed by cautious addition of ethyl acetate (5 mL), and ice-cold dilute sulphuric acid (50 mL, 0.5 N) was gradually added to the cooled mixture. The ethereal layer was rapidly separated and, with further ethereal extracts of aqueous layer, was washed with water (2 × 50 mL) and dried over MgSO\(_4\), then filtered. The filtrate was concentrated under reduced pressure. Further distillation afforded pure (1S\(^*\),4aR\(^*\),8aR\(^*\))-9-methyleneoctahydro-1H-1,4a-(epoxymethano)naphthalene 6 (22.81 g, 25%) as a pale yellow oil; b.p. 65 °C / 1.5 Torr; \(\delta\)\(_H\) (250 MHz, CDCl\(_3\)) 4.22 (1H, dt, \(J\) 1.0, 0.5 Hz, >CH-O-), 4.03 (1H, d, \(J\) 4.5 Hz, =CH\(_2\)), 3.66 (1H, d, \(J\) 1.5 Hz, =CH\(_2\)), 1.88-1.07 (15H, m, cy-CH); \(\delta\)\(_C\) (75 MHz, CDCl\(_3\)) 166.0 (>C=CH\(_2\)), 80.4 (>CH-O-), 76.9 (=CH\(_2\)), 50.0 (3\(^*\)), 46.2 (4\(^*\)), 39.5 (2\(^*\)), 31.3 (2\(^*\)), 30.2 (2\(^*\)), 26.5 (2\(^*\)), 24.9 (2\(^*\)), 22.1 (2\(^*\)), 18.9 (2\(^*\)); \(\nu\)\(_{max}\) (film) 2927, 2860, 1679, 1455, 1369, 1198, 1106 cm\(^{-1}\); TOF-ESI+ m/z calculated for \((\text{C}_{12}\text{H}_{18}\text{O} + \text{H})^+\), 179.1435, found, 179.1422.

Use of different Lewis acids

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Reaction with 1 and AcCl under Baddeley conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FeCl(_3)</td>
<td>9% yield of 6</td>
</tr>
<tr>
<td>ZnCl(_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td>BF(_3).Et(_2)O</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
6,7,8,9-tetrahydro-5H-benzo[7]annulene, \textbf{38}

\begin{center}
\begin{tikzpicture}

\begin{scope}
\node at (0,0) (a) {\includegraphics[width=1.5cm]{image1.png}};
\node at (2,0) (b) {\includegraphics[width=1.5cm]{image2.png}};
\draw[->,thick] (a) -- (b);
\end{scope}
\end{tikzpicture}
\end{center}

\begin{itemize}
\item Reaction performed in accordance with a literature procedure\textsuperscript{24a}.
\end{itemize}

4,5,6,7,8,9-hexahydro-1H-benzo[7]annulene, \textbf{40} and 2,5,6,7,8,9-hexahydro-1H-benzo[7]annulene, \textbf{39}

\begin{center}
\begin{tikzpicture}

\begin{scope}
\node at (0,0) (a) {\includegraphics[width=1.5cm]{image3.png}};
\node at (2,0) (b) {\includegraphics[width=1.5cm]{image4.png}};
\node at (4,0) (c) {\includegraphics[width=1.5cm]{image5.png}};
\draw[->,thick] (a) -- (b) -- (c);
\end{scope}
\end{tikzpicture}
\end{center}

\begin{itemize}
\item This reaction was adapted from a literature procedure\textsuperscript{24b}.
\end{itemize}

2-necked 1 L flask and cold finger were oven dried and flushed with Ar, then cooled to -78 °C in a dry ice/acetone bath. Ammonia (200 mL) was condensed into the flask, then a mixture of tBuOH (78 mL), Et₂O (14 mL) and 6,7,8,9-tetrahydro-5H-benzo[7]annulene (10.8 g, 0.074 mol, 1.0 eq.) was added slowly, with stirring. Over 6 h, Li (3.85 g, 0.555 mol, 7.5 eq.) was added piecewise to the RM, turning a distinctive blue colour. After addition of Li, RM stirred at -78 °C for a further 5 h, then ice bath removed and NH₃ was allowed to evaporate overnight. The solid residue was quenched by gradual addition of iPrOH, MeOH and then H₂O over 2 h, then cooled to rt, transferred to separating funnel and extracted with petrol (3 x 100 mL). Organic layers combined and washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure. The crude product was flushed through a silica pad with hexanes to give a mixture of dialkenes (\textbf{39} and \textbf{40}, 10.71 g, 98%) as a colourless oil. The mixture was taken forward to hydrogenation without further purification.
**2,3,4,5,6,7,8,9-octahydro-1H-benzo[7]annulene, 41 and 2,3,5,6,7,8,9,9a-octahydro-1H-benzo[7]annulene, 42**

\[
\begin{align*}
\text{39} & \quad \text{+} \quad \text{40} \\
& \quad \overset{\text{H}_2, \text{Pd/C}}{\xrightarrow{\text{EtOAc, rt, o/n,}}}
\end{align*}
\]

74% (41 and 42)

To a mixture of dienes 39 and 40 (5.42 g) dissolved in EtOAc (100 mL) was added Pd/C (100 mg). The reaction was allowed to stir at room temperature overnight under 1 atmosphere of H\(_2\). Gas was removed under vacuum and reaction vessel flushed with N\(_2\). Pd/C removed by filtering through a celite pad and filtrate concentrated under reduced pressure. Column chromatography (100% petrol) gave a mixture of alkenes 41 and 42 (colourless oil, visualised by KMnO\(_4\) stain, R\(_f\) 0.98, 4.08 g, 74%) and 6,7,8,9-tetrahydro-5H-benzo[7]annulene (colourless oil, visualised by UV, R\(_f\) 0.83, 0.25 g, 5%). The mixture of alkenes was taken forward to further hydrogenation without separation.

**Bicyclo[5,4,0]undecane, 28**

\[
\begin{align*}
\text{41} & \quad \text{+} \quad \text{42} \\
& \quad \overset{\text{H}_2, \text{Pd/C}}{\xrightarrow{\text{EtOAc, rt, 72 h,}}}
\end{align*}
\]

68%

To a mixture of alkenes 41 and 42 (3.51 g, 0.023 mol, 1.0 eq) dissolved in EtOAc (100 mL) was added Pd/C (80 mg). The reaction was allowed to stir at room temperature for 3 days under 1 atmosphere of H\(_2\). Gas was removed under vacuum and reaction vessel flushed with N\(_2\). Pd/C removed by filtering through a celite pad and filtrate concentrated under reduced pressure. A mixture of cis and trans decahydro-1H-benzo[7]annulene 28 was obtained as a colourless oil (3.03 g, 85%). δ\(_H\) (250 MHz, CDCl\(_3\)) 0.82 – 1.79 (40H, m); δ\(_C\) (75 MHz, CDCl\(_3\)) 46.1, 38.6, 36.1, 36.0, 32.7, 32.4, 31.2, 27.5, 26.8, 26.5, 25.8, 24.4; ν\(_{max}\) 2917, 2850, 1446, 1260, 1099, 1018, 805 cm\(^{-1}\)
Reaction performed in accordance with a literature procedure\textsuperscript{26a}.

\textbf{\(\Delta^{1,9}\) octalin, \(\Delta^{9,10}\) octalin, \(\Delta^{1,9}\) octalin, \(\Delta^{9,10}\) octalin, 7}

Reaction performed in accordance with a literature procedure\textsuperscript{26a}.

\textbf{\(\Delta^{9,10}\) octalin, 7}

Reaction performed in accordance with a literature procedure\textsuperscript{26b}.

\textbf{Cyclodecane-1,6-dione, 47}

This reaction was performed in accordance with a literature procedure\textsuperscript{26c}.
2,3,5,6,7,8-hexahydroazulen-4(1H)-one, 48

This reaction was performed in accordance with a literature procedure26c.

1,2,3,4,5,6,7,8-octahydroazulene, 49 and 1,2,3,3a,5,6,7,8-octahydroazulene, 50

To a mixture of 2,3,5,6,7,8-hexahydroazulen-4(1H)-one 48 (4.50 g, 0.03 mol, 1.0 eq.) and zinc powder (45 g, 0.69 mol, 23.0 eq.) was gradually added an HCl solution (9 M in H2O, 187mL). Reaction mixture heated to reflux at 100 °C for 3 h. After cooling to rt, reaction mixture was carefully diluted by addition to 300 mL of water and transferred to a separating funnel. Organic layer extracted with pentane (3 x 100 mL), dried over MgSO4 and concentrated under reduced pressure. The mixture of alkenes, 49 and 50 (2.58g, 63%, colourless oil) were taken forward to hydrogenation without further purification.
Bicyclo[5.3.0]undecane, 30

A mixture of alkenes, 49 and 50, (2.80 g, 0.021 mol, 1.0 eq.) were dissolved in EtOAc (80 mL) to which Pd/C (230 mg) was added. The reaction was allowed to stir at room temperature overnight under 1 atmosphere of H₂. Gas was then removed under vacuum, Pd/C removed by flushing reaction mixture through a celite pad and EtOAc removed under reduced pressure. A mixture of cis and trans bicyclo[5.3.0]undecane 30 was identified as a colourless oil (2.74 g, 96%). δₜ (300 MHz, CDCl₃) 2.49 – 1.02 (36 H, m); δₛ (75 MHz, CDCl₃) 46.3, 43.4, 35.8, 35.1, 34.3, 32.9, 31.7, 29.7, 28.0, 26.6, 26.5, 24.0; vₘₐₓ 2917, 2850, 1449, 1358, 1156, 949 cm⁻¹
HMBC (300MHz, CDCl₃)

DEPT-135 (100MHz, CDCl₃)
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2013
Multiplicity edited HSQC (400 MHz, CDCl$_3$): red = CH/CH$_3$; blue = CH$_2$
NOESY (400 MHz, CDCl₃)
COSY (400 MHz, CDCl₃)
CRUDE SPECTRA
Note: Only those pathways that involved tertiary carbocations were considered, both at the point of initial hydride abstraction and attack on the 2nd equivalent of acylium ion by the alkene.