Catalytic phosphorylation using a bifunctional imidazole derived nucleophilic catalyst

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General Experimental
THF and diethyl ether were freshly distilled over sodium and CH2Cl2 was distilled over CaH2. All reagents were used as supplied without purification unless stated. Column chromatography was carried out on Fluorochem Limited Silica Gel 40-63μ 60A and TLC on aluminium sheets coated with 0.2mm silica gel. Plates were visualised using an UV light and KMnO4 and PMA with heating. 250MHz 1H NMR analysis were carried out on a Bruker AC250 sample changer, 300MHz 1H & 13C NMR were carried out on a Bruker Advance 300 spectrometer and 500MHz 1H & 13C NMR were carried out on a JEOL λ.500MHz spectrometer. Residual signals from the deuterated solvents were used as reference. Coupling constants were measured in Hz. Mass spectra were recorded on a VG Autospec spectrometer.

(1-Methylimidazol-2-yl) methanol 3'

\[
\text{OH} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N}
\]
N-Methylimidazole (10.0g, 9.6 cm³, 0.12 mol) and paraformaldehyde (10.0 g, 0.33 mol) were refluxed at 160 °C for 1 h. The brown solution was dissolved in methanol (12 cm³) and cooled to -78 °C and triturated to precipitate a brown solid that was filtered off. The product was recrystallized from CH₂Cl₂ / petrol (40:60) to give (1-methylimidazol-2-yl) methanol 3 (8.7 g, 0.07 mol, 63%) as a light brown solid. Mpt 115 °C (lit. 114 °C); δH (300MHz, CDCl3) 6.81 (1H, d, J 1.2, CH=CH), 6.75 (1H, d, J 1.2, CH=CH), 5.45 (1H, br s, O/H), 4.55 (2H, s, CH₂OH), 3.66 (3H, s, CH₃N); δC (75MHz, CDCl₃) 148.4, 127.0, 121.9, 56.1, 33.2. All NMR data was in accordance with the literature.

2-[2-(2-Methoxy-ethoxy)-ethoxymethyl]-1-methyl-1H-imidazole 1

NaH (0.16 g, 4 mmol) was washed with petrol (3 × 5 cm³) and dried under vacuum. This was suspended in dry THF (10 cm³) and stirred under N₂ for 5 mins. (1-Methyl imidazol-2-yl) methanol 3 (0.11 g, 1.0 mmol) was added and after 30 mins 1-bromo-2-(2-methoxy ethoxy)ethane² (0.36 g, 2.0 mmol) was added. The brown mixture was left to stir for 20 h at rt. Methanol (5 cm³) was added followed by water (3 cm³) to quench excess NaH. The brown solution was extracted with CH₂Cl₂ (10 × 15 cm³). The organic layer dried over MgSO₄ and the solvent removed giving a crude yellow oil. Purification by column chromatography on silica gel with an eluent of CH₂Cl₂:MeOH (9.5:0.5) gave a yellow oil 1 (0.134 g, 0.65 mmol, 63%). νmax cm⁻¹ (film) 2878, 1654, 1501, 1453, 1096; δH (500MHz, CDCl₃) 6.86 (1H, s, CH=CH), 6.80 (1H, s, CH=CH), 4.57 (2H, s, ArCH₂O), 3.64 (3H, s, NCH₃), 3.54 (6H, m, CH₂O), 3.47 (2H, m, CH₂O), 3.30 (3H, s, OCH₃); δC (125MHz, CDCl₃) 144.5, 127.3, 122.0, 71.9, 70.4, 69.0, 65.0, 59.0, 32.8; m/z (EI) 215.1389 (1.4%; MH⁺, C₁₀H₁₉N₂O₃ requires 215.1396), 199 (16), 183 (2), 169 (4), 139 (3), 125 (7), 111 (96), 95 (100).

General procedure for the kinetic evaluation of the catalyst for the phosphorylation of cyclohexanol in CH₂Cl₂

Et₃N (4.0 cm³, 4.72 mmol from a stock solution in dry CH₂Cl₂) and cyclohexanol (4.0 cm³, 4.72 mmol from a stock solution in dry CH₂Cl₂) were stirred under nitrogen for 15 min with or without catalyst (4.0 cm³, 0.472 mmol from a stock solution in dry CH₂Cl₂) and with or without MPF₆ (0.472 mmol) as appropriate. Diphenyl chlorophosphate (4.0 cm³, 4.72 mmol from a stock solution in dry CH₂Cl₂) was added and stirred for 24 h at 30 °C. Samples (1 cm³) were removed at timed intervals and quenched with water (10 cm³) and extracted with CH₂Cl₂ (10 cm³). The organic layer
was separated, washed with water (2 × 5 cm³) and dried with MgSO₄. The solvent was removed and the crude oil was dried under vacuum. The samples were analysed by ¹H NMR spectroscopy.

Data from kinetic plots (Figure 2)

<table>
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<th>Time (min)</th>
<th>Product 6 (%)ᵃ</th>
</tr>
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<tr>
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<td>0</td>
</tr>
<tr>
<td>5</td>
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<tr>
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<td>10 (8)</td>
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<tr>
<td>60</td>
<td>21 (24)</td>
</tr>
<tr>
<td>120</td>
<td>27 (21)</td>
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<tr>
<td>540</td>
<td>37 (34)</td>
</tr>
<tr>
<td>1440</td>
<td>46 (49)</td>
</tr>
</tbody>
</table>

ᵃ Amount of product determined from comparison of the integrals of the ¹H nmr spectrum. Figures in parenthesis refer to results obtained in a duplicate experiment to validate the data.

2-Heptyloxymethyl-1-methyl-1H-imidazole 4

KH (0.11 g, 2.5 mmol) was suspended in dry THF (10 cm³) and stirred under N₂ for 5 mins. (1-Methyl imidazol-2-yl) methanol 3 (0.28 g, 2.5 mmol) was added and after 30 mins 1-heptyl p-toluene sulphonate¹ (0.67g, 2.5mmol) was added. The mixture was left to stir for 20 h at rt and ethanol (5 cm³) was added followed by water (3 cm³) to quench excess KH. The brown solution was extracted with CH₂Cl₂ (10 × 15 cm³). The organic layer was dried over MgSO₄ and the solvent removed giving a crude yellow oil. Purification by column chromatography on silica gel eluting with CH₂Cl₂:MeOH (9.5:0.5) gave a yellow oil 4 (0.29 g, 1.38 mmol, 55%). νmax cm⁻¹ (film) 2929, 2857, 1500, 1095; δH (250 MHz, CDCl₃) 6.93 (1H, s, CH=C₄H), 6.86 (1H, s, CH=CH₂), 4.56 (2H, s, ArCH₂O), 3.69 (3H, s, NCH₃), 3.41 (2H, t, J 6.6, OCH₂), 1.61 (2H, m, CH₂), 1.35—1.19 (10H, m, CH₂), 0.78 (3H, t, J 6.6, CH₃CH₂); δC (63 MHz, CDCl₃) 144.8, 127.2, 121.8, 70.2, 64.7, 32.7, 31.7, 29.5, 29.0, 26.0, 22.5, 14.0; m/z (EI) 210.1736 (8%; M⁺, C₁₂H₂₂N₂O requires 210.1732), 112 (21), 111 (34), 96 (100), 95 (58), 81 (13), 57 (6), 54 (23).
General procedure for the preparation of catalysts 7 and 8

NaH (4 eq.) was washed with petrol (3 × 5 cm³) and dried under vacuum. This was suspended in dry THF (10 cm³) and stirred under N₂ for 5 mins. (1-Methyl imidazol-2-yl) methanol 3 (1 eq) was added and after 30 mins the appropriate polyether bromide (2 eq.) was added. The brown mixture was left to stir for 20 h at rt. After such time the reaction was quenched with methanol (5 cm³), followed by water (3 cm³). The brown solution was extracted with CH₂Cl₂ (5 × 15 cm³), the organic layer dried over MgSO₄ and the solvent removed giving a crude product. This was purified by column chromatography on silica gel with an eluent of CH₂Cl₂:MeOH (9.5:0.5) to give the desired product.

2-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxymethyl}-1-methyl-1H-imidazole 7

Catalyst 7 was obtained as a yellow oil (68%) using 1-[2-(2-bromo-ethoxy)-ethoxy]-2-methoxy-ethane⁴ in accordance with the general procedure. νmax cm⁻¹ (film) 2876, 1648, 1501, 1454, 1103; δH (500 MHz, CDCl₃) 6.86 (1H, s, ArCH), 6.80 (1H, s, ArCH), 4.57 (3H, s, CH₃N), 3.50–3.58 (10H, m, 5 × CH₂O), 3.46 (2H, m, CH₂), 3.29 (3H, s, OCH₃); δC (126 MHz, CDCl₃) 144.3, 127.0, 121.9, 71.7, 70.3, 70.2, 70.1, 68.9, 64.8, 58.7, 32.6; m/z (EI) 258.1589 (12%, M⁺ C₁₂H₂₂N₂O₄ requires 258.1579), 258 (12), 183 (7), 155 (9), 139 (13), 111 (100), 95 (84), 81 (7), 59 (42).

2-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxymethyl]-1-methyl-1H-imidazole 8

Catalyst 8 was obtained as a yellow oil (71%) using 1-{2-[2-(2-bromo-ethoxy)-ethoxy]-ethoxy}-2-methoxy-ethane⁵ in accordance with the general procedure. νmax cm⁻¹ (film) 2874, 1500, 1453; 1104; δH (250MHz, CDCl₃) 6.84 (1H, s, ArCH), 6.79 (1H, s, ArCH), 4.54 (2H, s, ArCH₂), 3.62 (3H, s, CH₃N), 3.52–3.56 (14H, m, 7 × CH₂O), 3.45 (2H, m, CH₂O), 3.28 (3H, s, CH₃O); δC (63MHz,
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CDCl₃) 144.5, 127.3, 122.0, 71.8, 70.5, 70.4, 70.2, 69.0, 64.9, 58.9, 32.8; m/z (ES) 303.1911 (100%; MH⁺, C₁₄H₂₇N₂O₅ requires 303.1920), 325 (M⁺+Na), 493; m/z (EI) 302 (6%), 257 (4), 227 (4), 199 (3), 139 (10), 111 (100), 95 (93), 59 (44).

References