Phase-Transfer Mediated Heteroaromatic Nucleophilic Substitution: Introduction of a β-Adrenergic Blocking Moiety

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The advantages of phase-transfer catalyzed (PTC) reactions have been widely discussed1,2. We sought to replace sodium hydride/dimethylformamide as base/solvent in the preparation of the antihypertensive agent, di-S-2-[(3-[(1,1-dimethyl)ethyl]-amino]-2-hydroxypropoxy]-3-pyridinecarbonitrile fumarate (5)3. 2-Chloro-3-cyanopyridine4 (1) and the alkoxide of S-3-tert-butyl-5-hydroxymethyl-2-phenylazolidine (2; containing 1% of the isomeric dioxolane)5 generate 3 which is converted by acid hydrolysis to free base 4 and isolated as the fumarate salt, 5 (Scheme A). Application of PTC conditions allowed us to effect the heteroaromatic nucleophilic substitution rapidly at 20–25°C with toluene/alkali metal hydroxide in excellent yield (Table 1).

\[
\begin{align*}
\text{CN} & \quad \text{CN} + \quad \text{HO-CH}_2\text{CH}_2\text{O-CH}_2\text{H} & \quad \text{H}_2\text{N-CH}_2\text{NH-C}_6\text{H}_5\text{-t} \\
\text{C}_6\text{H}_5 & \quad \text{H} & \quad \text{N-C}_6\text{H}_5\text{-t} \\
1 & \quad 2 & \quad 3 \\
\text{Aliquat 336/} & \quad \text{toluene/50% NaOH} & \quad \text{normal HCl/} & \quad \text{pH 3.5, 50°C} \\
\text{CN} & \quad \text{H}_2\text{C-CH}_2\text{NH-C}_6\text{H}_5\text{-t} & \quad \text{CN} & \quad \text{H}_2\text{CH}_2\text{OH} \\
\text{O-CH}_2\text{CH}_2\text{H} & \quad \text{OH} & \quad \text{H}_2\text{N-CH}_2\text{NH-C}_6\text{H}_5\text{-t} & \quad \text{H}_2\text{O} \\
4 \text{a (major)} & \quad 4 \text{b (minor)}
\end{align*}
\]

Scheme A

Liquid-liquid catalysis using Aliquat 336 (tricaprylmethyl-ammonium chloride) or 15-Crown-5 in equal volumes of toluene and 50% aqueous sodium hydroxide afforded 5 in 84% yield. Solid-liquid catalysis in toluene/potassium hydroxide with 18-Crown-6 resulted in a comparable yield.
but offered no advantage for large scale reactions. Aliquat 336 has no catalytic effect in solid-liquid catalysis since similar yields and rates were observed with and without catalyst, and potassium carbonate/toluene was ineffective with 18-Crown 6 or Aliquat 336.

The rate of nucleophilic substitution is dependent on the amount of phase-transfer catalyst. A molar ratio of 0.05 equivalents of Aliquat 336 to 1.0 of 2-chloro-3-cyanopyridine (1) completed the reaction in 1 h at 25 °C. This was comparable to reaction of the alkoxide of 2 with 1 in dimethylformamide. Competitive displacement by hydroxide did not occur. Control experiments in the absence of 2 confirmed the stability of 1 to the reaction conditions, and 2-chloro-3-cyanopyridine (1) was recovered quantitatively.

Competitive reactivity of primary to secondary alcohols towards 2-chloro-3-cyanopyridine was evaluated using the unprotected analogue of 2, (S)-3-(4-butylnamino-1,2-propanediol, at 25 °C in toluene/50% aqueous sodium hydroxide with Aliquat 336. After 3 h, a 4:1 mixture of 4a and the 2'-isomer, 2-[3-[(1,1-dimethyllethylamino)-1-hydroxypropoxy]-3-pyridinecarbonitrile (4b) was observed. Control experiments in aqueous base at pH 11 indicate negligible (-0.5%) 4a to 4b isomer equilibration. Thus, primary alkoxide is at least four times more reactive than secondary alkoxide in the PTC-mediated nucleophilic displacement reaction for this case.

Application of this methodology to simple alcohols is indicated in Table 2. Primary alkoxide displacement of 2-chloro-3-cyanopyridine (1) with 18-Crown-6 proceeds within 3 h at 25 °C, but less reactive 2-chloropyridine required heating. As expected, a longer reaction time was necessary for 2-propanol and t-butyl alcohol was inert. Although a similar yield of 8e was obtained with liquid-liquid and solid-liquid catalysis, it is prudent to employ solid-liquid PTC for alcohols which exhibit appreciable water solubility.

PTC catalysis has been demonstrated to be an economical and efficient means of effecting displacement reactions. To our knowledge this represents the first application in heteroaromatic nucleophilic substitution employing alkoxide anions. Extension of this methodology to heterocycles other than pyridine, i.e., thiadiazole, has been confirmed.

Table 1. Phase Transfer-Catalyzed Nucleophilic Heteroaromatic Substitution of 2-Chloro-3-cyanopyridine (1) with S-3-(1,5-Butyl-5-hydroxymethyl-2-phenylazo)ximinol (2a)

<table>
<thead>
<tr>
<th>Catalyst*</th>
<th>Solvent*</th>
<th>Base*</th>
<th>Yield* [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliquat 336</td>
<td>toluene</td>
<td>50% aqueous NaOH</td>
<td>85</td>
</tr>
<tr>
<td>Aliquat 336</td>
<td>80% cyclohexane/20% toluene</td>
<td>50% aqueous NaOH</td>
<td>83</td>
</tr>
<tr>
<td>Aliquat 336</td>
<td>cyclohexane</td>
<td>50% aqueous NaOH</td>
<td>70</td>
</tr>
<tr>
<td>15-Crown-5</td>
<td>toluene</td>
<td>50% aqueous NaOH</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 2. Solid-Liquid PTC Alcohol Displacement Reactions

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Yield [%]</th>
<th>b.p. [°C]/torr</th>
<th>Molecular formulaa</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>H</td>
<td>C₃H₇CH₂</td>
<td>80°</td>
<td>98-100°/0.25</td>
<td>C₃H₆NO (185.2)</td>
</tr>
<tr>
<td>8b</td>
<td>CN</td>
<td>C₃H₇CH₂</td>
<td>85°</td>
<td>128-129°/0.25</td>
<td>C₃H₆N₂O (210.2)</td>
</tr>
<tr>
<td>8c</td>
<td>CN</td>
<td>n-C₃H₇</td>
<td>85°</td>
<td>135-138°/0.5</td>
<td>C₃H₆N₂O (232.3)</td>
</tr>
<tr>
<td>8d</td>
<td>CN</td>
<td>i-C₃H₇</td>
<td>67°</td>
<td>68-70°/0.5</td>
<td>C₄H₆N₂O (162.2)</td>
</tr>
<tr>
<td>8e</td>
<td>CN</td>
<td>i-C₃H₇</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Di-S-2-3-[1,1-dimethyl]amino]-2-hydroxypyroxy; 3-pyridinecarbonitrile Fumurate (5): Method A: Liquid-Liquid Catalysis: A solution of (S)-3-4-butylnamino-5-hydroxymethyl-2-phenylazoaline (1) (2 189 g, 804 mol) in toluene (190 ml) is added at 20-30 °C over 0.5 h to a well-stirred mixture of 2-chloro-3-cyanopyridine (1; 100 g, 0.722 mol), Aliquat 336 (19 g, 0.0379 mol), toluene (1.5 l), and 50% aqueous sodium hydroxide (1.4 l). The reaction mixture is stirred for 1 h at 25 °C; the layers are allowed to settle, and then separated. The aqueous layer, which contains the interface, is extracted with toluene (350 ml). Combined toluene extracts and interface are washed with water (2 x 400 ml) and then extracted with 1 normal aqueous hydrochloric acid (2 x 725 ml). Combined acid extracts are adjusted to pH 3.5 with solid sodium acetate (91.3 g), heated at 50°C for 3 h, and extracted at 25 °C with cyclohexane (2 x 300 ml). The aqueous layer is stirred with ethyl acetate (800 ml), and adjusted to pH 12 with 50% aqueous sodium hydroxide (79 ml). Layers are separated, and the aqueous portion extracted with ethyl acetate (400 ml). Combined extracts are treated with Calgon-PWA 20 charcoal (25 g) and anhydrous sodium sulfate (125 g), and filtered through Soper-Cel. The filtrate is concentrated in vacuo to 160 ml and flushed with absolute ethanol (2 x 250 ml) to afford 4 (final volume 145 ml). Conversion to the fumurate salt is achieved by heating a mixture of 4, absolute ethanol (1.25 l), and fumaric acid (42 g, 0.362 mol) at 65-75 °C for 30 min and cooling at 0-5 °C for 2 h. Solids are filtered, washed with absolute ethanol (3 x 90 ml), and dried at 35 °C to afford 5; yield: 186.4 g (84%); m.p. 216-218 °C; [α]D25° = -25.5° (0.1 normal hydrochloric acid).
July 1980

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C_{16}H_{22}N_{5}O_{6} calc. C 58.62 H 6.89 N 13.67 (614.7) found 58.29 6.91 13.62

I.R. (Nujol): ν = 2250, 1675 cm⁻¹

U.V. (methanol): λmax = 211 (ε = 25235); 287 nm (ε = 13815).

1H-N.M.R. (100 MHz, DMSO-d₆): δ = 8.46 (d of d, 1H, J = 3 and J = 1 Hz); 8.22 (d of d, 1H, J = 4 and J = 1 Hz); 7.19 (d of d, 1H, J = 5 and J = 3 Hz); 6.40 (s, 1H); 4.40 (d, 2H, J = 3 Hz; 4.09 (br s, 1H); 2.18 (s, 3H); 1.18 ppm (s, 9H).

Method B: Solid-Liquid Catalysis: A solution of 2° (14.6 g, 0.059 mol) in toluene (50 ml) is added at 20–25°C to a well-stirred mixture of 1 (7.8 g, 0.056 mol), benzoyl peroxide (60.7 g, 0.003 mol), potassium hydroxide (8.0 g, 0.12 mol), and toluene (110 ml). Stirring is continued for 2 h at 25°C, and the reaction mixture is quenched with cold water (50 ml). Layers are separated, and the toluene layer is washed with water (2 × 25 ml). The aqueous portion is backwashed with toluene (25 ml); combined toluene extracts are washed with water (25 ml), and extracted with 1 normal hydrochloric acid (2 × 75 ml). Hydrolysis and work up, as indicated in Method A, afford the free base which gives salt 5 after treatment with furmaric acid (3.4 g, 0.0293 mol) in refluxing anhydrous ethanol (90 ml); yield: 14.8 g (86%).

2-Benzoyloxypyridine (8a):
A mixture of 2-chloropyridine (14 g, 0.124 mol), benzyl alcohol (14.7 g, 0.137 mol), potassium hydroxide (16.3 g, 0.248 mol), 18-Crown-6 (1.4 g, 0.005 mol), and toluene (50 ml) is stirred rapidly and refluxed under nitrogen. Water is removed via a Dean Stark apparatus. After 1 h the reaction mixture is cooled and quenched with ice/water (100 ml). The aqueous layer is extracted with toluene (25 ml), the combined toluene extracts are washed with saturated potassium chloride, dried with sodium sulfate, and concentrated. Distillation of the crude residue affords product 8a; yield: 18 g (89%); b.p. 99–100°C/0.25 torr.

C₂₁H₁₇NO₆ calc. C 77.81 H 5.99 N 7.56 (285.2) found 78.15 5.97 7.56

M.S.: m/e (relative intensity) = 385 (M⁺, 49); 383 (10); 381 (100); 79 (62); 65 (36).

I.R. (film): ν = 1600, 1590 cm⁻¹.

1H-N.M.R. (60 MHz, CDCl₃): δ = 8.1 (d of d, 1H, J = 3 and J = 1 Hz); 7.5–7.1 (m, 6H); 6.8–6.6 (m, 2H); 5.3 ppm (s, 2H).

2-Benzoyloxy-3-cyanopyridine (8b):
A mixture of 2-chloro-3-cyanopyridine (14 h, 0.101 mol), benzyl alcohol (11.5 g, 0.106 mol), potassium hydroxide (13.8 g, 0.212 mol), 18-Crown-6 (1.3 g, 0.0052 mol), and toluene (140 ml) is stirred rapidly under nitrogen at 25°C. After 2 h, the reaction mixture is quenched with ice/water (100 ml). The aqueous layer is extracted with toluene (25 ml), and the combined toluene extracts are washed with saturated potassium chloride, dried with sodium sulfate, and concentrated. Distillation of the crude residue affords product 8b; yield: 17.8 g (85%); b.p. 125–129°C/0.25 torr.

C₂₁H₁₇N₂O₂ calc. C 74.27 H 4.79 N 13.33 (210.23) found 74.39 4.70 13.30

M.S.: m/e (relative intensity) = 210 (M⁺, 70); 181 (21); 91 (100); 77 (67); 65 (90).

I.R. (film): ν = 2250; 1520 cm⁻¹.

1H-N.M.R. (60 MHz, CDCl₃): δ = 8.2 (d of d, 1H, J = 3 and J = 1 Hz); 7.7 (d of d, 1H, J = 4 and J = 1 Hz); 6.8 (d of d, 1H, J = 3 and J = 1 Hz); 7.4–7.1 (m, 5H); 5.4 ppm (s, 1H).

We are grateful to Dr. A. Douglas for 100 MHz 1H-N.M.R. spectra, Ms. P. Cala-Tway for mass spectra, and Ms. J. Wu for the microbiological analysis. We also thank Henley and Co., Inc., New York, N. Y. for generous samples of crown ethers.

Received: November 12, 1979

0039-7881/80/0732-0575 $ 03.00 © 1980 Georg Thieme Verlag · Stuttgart · New York