Reaction of 4-(N,N-Dimethylamino)-2-phenyl-2-(2-pyridyl)butenenitrile and Related Compounds with Ethyl Chloroformate; Formation of Indolizinium and Quinolinizinium Chlorides

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4-(N,N-Dialkylamino)-2-phenyl-2-(2-pyridyl)butenenitriles (10, 11 and 12) and 5-(N,N-dimethylamino)-2-phenyl-2-(2-pyridyl)pentenitrile (13) react with ethyl chloroformate, via a cyclization–N-dealkylation process, to give indolizinium and quinolinizinium salts (1 and 2). Compounds 1 and 2 are also obtained by reaction of the alcohol derivatives 14 and 15 with thionyl chloride. Reaction of 2-phenyl-2-(2-pyridyl)ethenenitrile (9) in the presence of potassium hydroxide in dimethyl sulfoxide, leading to [2-hydroxy-2-phenyl-2-(2-pyridyl)ethyl]methylsulfoxide (21), is also described.

Keywords 1-cyano-2,3-dihydro-1-phenyl-1H-indolizinium chloride; 1-cyano-1-phenyl-1,2,3,4-tetrahydroquinolinizinium chloride; N-dealkylation; cyclization

As part of an extensive research program on the preparation of anticholinergic and antihistaminergic agents, we needed relatively large quantities of 4-(N-methylamino)-2-phenyl-2-(2-pyridyl)butenenitrile. Reaction of chloroformate with tertiary aliphatic and allicyclic bases often provides a convenient method for promoting dealkylation. When 4-(N,N-dimethylamino)-2-phenyl-2-(2-pyridyl)butenenitrile (10) was allowed to react with ethyl chloroformate in refluxing CH₂Cl₂, an unexpected cyclization–N-dealkylation product, 1-cyano-2,3-dihydro-1-phenyl-1H-indolizinium chloride (1) was obtained along with the normal N-demethylation product (3). In this paper we would like to report the reaction of 10 and related compounds with ethyl chloroformate, leading to indolizinium (1) and quinolinizinium (2) salts. The reaction of 2-phenyl-2-(2-pyridyl)ethenenitrile (9) in the presence of potassium hydroxide (KOH) in dimethyl sulfoxide (DMSO), leading to [2-hydroxy-2-phenyl-2-(2-pyridyl)ethyl]methylsulfoxide (21), is also described.

Results and Discussion

Reaction of 10 with ethyl chloroformate in CH₂Cl₂ was complete after 7 h under reflux to give the normal N-demethylation product 3 in 13% yield and the indolizinium chloride 1 as a viscous oil in 51% yield. The 90 MHz proton nuclear magnetic resonance (¹H-NMR) spectrum of 1 in a mixed solvent of CDCl₃ and D₂O is shown in Fig. 1. Signals between δ 7.72 and 9.1 were allocated to nine aromatic protons, among which four protons at δ 7.80, 8.10, 8.53 and 9.02 ppm were assigned to the pyridine ring. One of the CH₃ moieties in the CH₃CH₂ entity of 1 gave rise to an AA'XX' type spectrum. A good resolved multiplet centered at δ 3.14 was assigned to the CH₂ adjacent to the carbon atom at the 1-position. A triplet centered at δ 5.08 (J = 7.2 Hz) was assigned to the CH₂ connected to nitrogen. Thus, the structure of 1 was determined as 1-cyano-2,3-dihydro-1-phenyl-1H-indolizinium chloride. As can be seen in Table 1, similar treatment of N,N-diethy lamino (11) and piperidino (12) derivatives with ethyl chloroformate gave 1 in high yields. Reaction of 5-(N,N-dimethylamino)-2-phenyl-2-(2-pyridyl)pentenitrile (13) with ethyl chloroformate yielded quinolinizinium chloride 2 in a poor yield of 4% along with the normal N-demethylation product (5). Reaction of the alcohol 14 with thionyl chloride (SOCl₂) yielded 1. Reaction of 15 with SOCl₂ gave 2 along with the chloro derivative 7. Compound 7 was converted into 2 on standing at room temperature for 48 h in benzene. When 15 was treated with SOCl₂ in refluxing benzene, 2 was obtained in 85% yield without giving the chloro derivative 7.

The cyclization–N-dealkylation observed in this series is depicted in Chart 2. First, a quaternary ammonium chloride intermediate (A) is formed. Then, the intermediate A is converted into the carbamate ester 3 (path iii) or has no net effect on the amine (path iv). Concerning the formation of 1 (or 2), the reaction appears to proceed through

Fig. 1. ¹H-NMR Spectrum of 1

CDCl₃ + D₂O, 90 MHz.

Table I. Preparation of Indolizinium and Quinolinizinium Chlorides (1 and 2)

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Product (%) isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>ref</td>
<td>7</td>
<td>1 (51), 3 (13)</td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>ref</td>
<td>2</td>
<td>1 (81), 4 (9)</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>ref</td>
<td>2</td>
<td>1 (93)</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>CH₂Cl₂</td>
<td>ref</td>
<td>5</td>
<td>2 (4), 5 (62)</td>
</tr>
<tr>
<td>14</td>
<td>B</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>2</td>
<td>1 (78)</td>
</tr>
<tr>
<td>15</td>
<td>B</td>
<td>C₆H₆</td>
<td>rt</td>
<td>2</td>
<td>2 (54), 7 (36)</td>
</tr>
<tr>
<td>15</td>
<td>B</td>
<td>C₆H₆</td>
<td>ref</td>
<td>1</td>
<td>2 (85)</td>
</tr>
</tbody>
</table>

a) A, ethyl chloroformate; B, thionyl chloride; ref, refluxing solvent; rt, room temperature.

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cyclization–N-dealkylation involving intramolecular nucleophilic attack by nitrogen of the pyridine ring (path i), giving the indolizinium chloride 1 (or quinolinium chloride 2) along with N-ethoxycarbonyl-N,N-dimethyamine. However, we can not rule out completely the possibility that the chloro derivative 6 (or 7) is converted into 1 (or 2).

**Synthesis of Intermediates** Intermediates employed in this study are listed in Chart 3. Alkylation of 2-phenyl-ethanenitrile (8) and 2-phenyl-2-(2-pyridyl)ethanenitrile (9) was effected in the presence of KOH in DMSO. A key intermediate 9 was prepared by the reaction of 8 with 2-bromopyridine in 70% yield. Compounds 10, 11, 12, 13, 14 and 15 were prepared in good yields by the reaction of 9 with corresponding alkyl chlorides. Compound 14 was prepared in 75% yield by lithium borohydride (LiBH₄) reduction of 16 in refluxing toluene.

When reaction of 9 with 2-chloroethanol was carried out
in the presence of KOH in DMSO, 2-benzoylpyridine (20)\(^{20}\) and [2-hydroxy-2-phenyl-2-(2-pyridyl)ethyl]methylsulfoxide\(^{40}\) (21) were obtained in 11% and 67% yields, respectively, without formation of the desired alcohol 14. In order to estimate conversion of 9 into 20 and 21 several reaction runs were conducted (Chart 4). When 9 was heated at 50°C for 24 h in the presence of KOH in dimethylformamide (DMF), 20 was obtained in a quantitative yield. However, 9 was recovered unchanged after heating in the absence of KOH in DMSO and DMF at 50°C for 24 h. Treatment of the alcohol 19\(^{10}\) with KOH in DMSO at 70°C for 16 h gave 20 and 21 in 21% and 74% yields, respectively. When the alcohol 19 was treated with KOH in DMF, the ketone 20 was obtained in a qualitative yield. When 20 was treated with KOH in DMSO, 21 was obtained in 82% yield. From these findings, a plausible mechanism for the formation of 20 and 21 may be as follows (Chart 4). First, the methylsulfinyl carbamation\(^{17}\) (17) is formed by the reaction of DMSO with KOH, with release of water. Anion exchange between 9 and the anion 17 gives the carbamation 18 and DMSO. The anion 18 reacts with alkyl halide to give the desired C-alkyl derivative. On the other hand, the cyano group of 9 is replaced with hydroxy anion to give the alcohol 19, which is oxidized in the presence of KOH and gives the ketone 20. Compound 20 reacts with 17 to yield 21.

Similar treatment of 3- and 4-benzoylpyridines gave [2-hydroxy-2-phenyl-2-(3-pyridyl)ethyl]- and [2-hydroxy-2-phenyl-2-(4-pyridyl)ethyl]methylsulfoxides\(^{40}\) in 13% and 38% yield, respectively. Reaction of benzhydryl with KOH in DMSO also gave benzophenone, which was not converted into [2-hydroxy-2,2-diphenylethyl]methylsulfoxide\(^{7}\) under the conditions used in this series. It is an interesting observation that the methylsulfinyl carbamation (17) was produced by the reaction of DMSO with KOH, compared with the reaction of DMSO with such strong bases as sodium hydride and sodium amide,\(^{7}\) although the reaction was limited to a series of benzoylpyridines.

**Experimental**

Melting points were measured in a Gallenkamp melting point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 IR spectrophotometer and \(^1\)H-NMR spectra were measured on Hitachi R-90H (90 MHz) and Bruker AM360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), m (multiplet) or br (broad). All spectra were consistent with the assigned structures. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained on a JMS-DX300 spectrometer operating at an ionization potential of 70 eV. Combustion analyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

Solutions were dried over Molecular Sieves 4A. 2-Bromopyridine, 2-, 3- and 4-benzoylpyridines, benzhydrol and benzophenone were commercial products.

**Reaction of Dialkylamino Derivatives 10, 11, 12 and 13 with Ethyl Chloroformate**

*General Procedure*: A mixture of 10 (2.2 g, 8.3 mmol) and ethyl chloroformate (1.5 g, 13.8 mmol) in CH\(_2\)Cl\(_2\) (15 ml) was refluxed for 7 h. The CH\(_2\)Cl\(_2\) layer was extracted with 1 N HCl and the aqueous layer was washed with CH\(_2\)Cl\(_2\) and evaporated to dryness in high vacuum to give an oil, which was dried over concentrated HSO\(_4\) to give 1-cyano-2,3-dihydro-1-phenyl-1H-indolizinium chloride (1) as a viscous oil.

The CH\(_2\)Cl\(_2\) layer was washed with H\(_2\)O and brine, successively, and dried over MgSO\(_4\). After removal of the solvent, the residue was purified by column chromatography on silica gel with a mixture of CH\(_2\)Cl\(_2\) and MeOH (60:1) to give 4-ethylcyclohexylmethylamino)-2-phenyl-2-(2-pyridyl)butanenitrile (3) as a colorless oil.

Reaction of 11, 12 and 13 with ethyl chloroformate was carried out according to a procedure similar to that used for 10. The results are given in Table I. The structures of 1, 2, 3, 4 and 5 were determined on the basis of IR and \(^1\)H NMR spectral data.

1. A viscous oil, IR (neat): 2250, 1630 cm\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)-D\(_2\)O) δ: 2.8–3.5 (2H, m, 2-CH\(_2\)), 5.08 (2H, t, J=7.2 Hz, 3-CH\(_2\)), 7.25 (5H, s, Ph), 7.80 (1H, d, J=7.9 Hz, 8-CH), 8.10 (1H, t, J=7.2 Hz, 6-CH), 8.53 (1H, J=7.9 Hz, 7-CH), 9.02 (1H, d, J=5.4 Hz, 5-CH).
2. A viscous oil, IR (neat): 2240, 1640 cm\(^{-1}\). \(^1\)H-NMR (CD\(_2\)OD) δ: 2.15–2.58 (2H, m), 2.61–2.90 (2H, m), 4.95 (2H, brs, Ph), 8.09 (2H, m), 8.58 (1H, td, J=7.9, 1.7 Hz), 9.06 (1H, m).
3. A colorless oil, IR (neat): 1710 cm\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)) δ: 1.28 (3H, t, J=7.0 Hz, CH\(_3\)), 2.93 (3H, s, NCH\(_3\)), 2.8–3.0 (2H, m, CH\(_2\)CH\(_3\)), 3.2–3.7 (2H, m, CH\(_2\)CH\(_3\)N), 4.42 (2H, q, J=7.0 Hz, CH\(_2\)CH\(_3\)), 7.2–7.8 (8H, m, Ph, Py-3, 4, 5), 8.6–8.8 (1H, m, Py-6).
4. A colorless oil, IR (neat): 2240, 1710 cm\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)) δ: 1.08 (3H, t, J=7.1 Hz), 1.24 (3H, t, J=7.1 Hz), 2.68–3.44 (6H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 4.18 (2H, q, J=7.1 Hz), 7.16–7.77 (8H, m, Ph, Py-3, 4, 5), 8.59–8.67 (1H, m, Py-6).
5. An oil, IR (neat): 2240, 1705 cm\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)) δ: 1.21 (3H, t, J=7.0 Hz, CH\(_3\)), 1.54–1.81 (2H, m), 2.38–2.90 (2H, m), 2.82 (7H, s, NCH\(_3\)), 3.32 (2H, t, J=6.9 Hz, CH\(_2\)), 4.09 (2H, q, J=7.0 Hz, CH\(_2\)CH\(_3\)), 7.12–7.67 (8H, m, Py-3, 4, 5), 8.57–8.64 (1H, m, Py-6).

**Reaction of Alcohol Derivatives 14 and 15 with SOCl\(_2\)**

A solution of 15 (3.0 g, 12 mmol) and SOCl\(_2\) (4 ml, 54 mmol) in CH\(_2\)Cl\(_2\) (30 ml) was
stirred for 2h at room temperature. The CH₂Cl₂ layer was extracted with 1 N HCl solution. The aqueous layer was washed with CH₂Cl₂, evaporated to dryness in high vacuum and dried over concentrated H₂SO₄ to give 2 as a viscous oil.

The CH₂Cl₂ layer was washed with aqueous NaHCO₃ and dried over MgSO₄. After removal of the solvent, the residue was purified by column chromatography on silica gel with CHCl₃ as an eluent to give 3-chloro-2-phenyl-2-(2-pyridyl)pentanenitrile (7) as an oil. IR (neat): 2240 cm⁻¹ (tr). 1H-NMR (CDCl₃) δ: 1.75–2.05 (2H, m, CH₂CH₂CH₂), 2.20–2.89 (2H, m, CH₂CH₂CH₂), 3.57 (2H, t, J = 6.2 Hz, CH₂CH₂CH₂), 7.15–7.78 (8H, m, Ph, Py-3, 4, 5), 8.55–8.60 (1H, m, Py-6). Anal. Caled for C₃₁H₂₈N₂O₂C: 70.98; H, 5.58; N, 10.35. Found: C, 71.01; H, 5.40; N, 10.48.

Reaction of 14 with SOCl₂ was carried out according to a procedure similar to that used for 13. The results are given in Table 1.
References