Nitration of steroidal olefins with sodium nitrite

Papori Goswami & P K Chowdhury
Natural Products Chemistry Division, Regional Research Laboratory Jorhat 785 006, India

Received 18 February 1999; accepted (revised) 27 August 1999

$\Delta^1$-Steroidal olefins react with the sodium nitrite-acetyl chloride system to furnish 5α-chloro-6β-nitro derivatives in good yields while $\Delta^1,16$-20-oxosteroids furnish regioselectively vinyl nitro derivatives $\Delta^1,16$-6-nitro-20-oxosteroids.

Nitration of olefins and α, β-unsaturated carbonyl compounds with various nitrating agents is a useful reaction in synthetic organic chemistry because of the application of nitro group in various chemical transformations.\(^1\)\(^-\)\(^4\)

In continuation of our work on steroids,\(^5\)\(^,\)\(^6\) we present here some nitration reactions on steroids through in situ generation of nitrosyl chloride which is a good source of NO\(^+\) under mild reaction conditions using sodium nitrite in the presence of acetyl chloride (stoichiometric amount). The generation of nitrosyl chloride by using NaNO\(_2\) in the presence of concentrated hydrochloric acid has been described.\(^6\)\(^,\)\(^8\) The other nitrating agents used generally involve conc. nitric acid alone or in combination with acetic anhydride or acetic acid and sodium nitrite or acyl nitrate etc.\(^9\). The condition for all these methods is harsh sometimes being explosive and interferes also with acid labile functional group present in a molecule. The use of sodium nitrite in presence of acetyl chloride which is cheap furnishes the nitro derivatives of various steroidal olefins under milder reaction conditions at room temperature. The ease of handling of the reagent system is also another advantage. Several $\Delta^1$-steroids (at entries 1-5) furnished their 5α-chloro-6β-nitro derivatives (5-7 and 9) in good yield (Table-I). It is believed that sodium nitrite in presence of acetyl chloride generates nitrosyl chloride via acetyl nitrite (Scheme I) to give the desired results.

The product might be formed from the addition of nitrosyl chloride to the double bond followed by oxidation of nitroso to nitro group.\(^7\) The formation of the nitrosyl chloride in the reaction was evident from the deoximating reaction of various oximes to their respective ketones by this reagent system.\(^10\)

However in case of substrates containing an α, β-unsaturated carbonyl group in addition to the 5, 6-double bond, the olefinic bond in conjugation with the

Table I

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>m.p.</th>
<th>Yield (^a)</th>
<th>(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>144</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>143</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>112</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>92</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>145</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>155</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>152</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Yields refer to pure isolated products.

\(^b\) All compounds are confirmed by IR, \(^1\)H NMR and mass spectral data and by direct comparison with the authentic samples for the chloro-nitro derivatives.

Scheme I

\[ \text{NaNNO}_2 + \text{CH}_3\text{COCl} \rightarrow \text{CH}_3\text{COONO} + \text{NaCl} \]

\[ \text{CH}_3\text{COONO} + \text{CH}_3\text{COCl} \rightarrow \text{NOCl} + (\text{CH}_3\text{CO})_2\text{O} \]

\[ 2\text{H}_2\text{O} \rightarrow \text{2CH}_3\text{COOH} \]
carbonyl function is selectively attacked to give their vinyl nitro derivatives as the major product. Thus, when compound 10 was treated with the reagent system, it furnished vinyl nitro compound 12 as the major isolable compound along with some other minor products. Similarly, compound 11 furnished nitro compound 13 as the major isolable compound. The formation of 12 or 13 demonstrates the evidence for build-up of positive charge (at C-17) adjacent to a carbonyl functionality due to attack by NO₂⁻. The elimination of the proton at C-16 followed by oxidation led to the formation of compounds 12 or 13 (Scheme II).

Both these compounds showed the addition of only NO₂⁻ group to the parent olefins in their mass spectra while in the IR spectra they exhibited strong nitro group absorption at 1550 cm⁻¹ in addition to the band for α, β-unsaturated carbonyl system at 1680 cm⁻¹. The NMR spectra of compounds 12 and 13 are devoid of any signal under chlorine or nitro group and displayed absorption for a single olefinic proton at δ 5.3 for C-6 olefinic proton. Besides, all these nitrochlorides (5-7, 9) upon treatment with zinc in acetic acid furnished the corresponding Δ⁴-steroids in quantitative yield while compounds 12 and 13 remain unaffected. Ready reductive elimination of these chloro-nitro compounds to regenerate Δ⁴-steroids confirms the trans-diaxial (5α, 6β) orientation for the chloro-nitro group.

Moreover, all the chloro-nitro compounds formed were easily converted to their vinyl nitro derivatives under mild basic conditions.

Experimental Section

Mps were determined on a Metler FP 62 instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 B spectrophotometer for solutions in chloroform. 'H NMR spectra were recorded in CDCl₃ on a Varian T-60 and Brucker 300 MHz NMR instruments using TMS as the internal standard. Mass spectra were scanned on an INCOS 50 GC MS instrument. TLC was performed on silica gel (E Merck) and the plates were activated at 100°C before use. Satisfactory microanalyses were obtained for the products.

Nitration of Δ⁴-steroids and Δ⁴,16-20-oxosteroids with NaNO₂-CH₃COCl system : General procedure:

To a solution of the substrate (200 mg) in 10 mL of dichloromethane was added 200 mg of NaNO₂ and 0.5 mL of acetyl chloride. The reaction mixture was stirred at room temperature for a period of 4 hr, during which the reaction mixture turned yellow. The reaction mixture was poured into cold water (150 mL) and was extracted with pet. ether (60-80°C) (3×100 mL) which after drying over anhyd. Na₂SO₄ was evaporated under reduced pressure to get a residue which was purified by preparative TLC (Pet.ether:EtOAc :: 10:1) to get pure nitro steroids.

**Compound 12 :** Compound 10 (200 mg) yielded 12 (100 mg, 45%). MS: m/z (%) 401 (M⁺), 355 (M⁺-NO₂⁻, 40), 341 (M⁺-NO₂⁻, 15.2), 295 (24.6) and 252 (30); IR: 1735, 1680, 1550, 1350 and 1250 cm⁻¹; ¹H NMR: δ 0.9 (s, 3H, Me-19), 1.2 (s, 3H, Me-18), 0.9 (s, 3H, COCH₃), 2.2 (s, 3H, Me-21); 4.3 (m, 1H, H-3); 5.3 (m, 1H, H-6), m.p. 155°C. Anal. Caled. for C₂₂H₂₈O₃N: C, 73.46; H, 8.45. Found: C, 73.3; H, 8.34.

**Compound 13 :** Compound 11 (200 mg) yielded 13 (110 mg, 48%). MS: m/z (%) 343 (M⁺), 303 (M⁺-NO₂⁻, 5.2) 283 (M⁺-NO₂⁻, 16.2) and 243 (20.3); IR: 1680, 1550, 1345, 1250 and 850 cm⁻¹; ¹H NMR: δ 0.8 (s, 3H, Me-19), 1.2 (s, 3H, Me-18), 2.2 (s, 3H, Me-21), 5.3 (m, 1H, H-6), m.p. 132°C. Anal. Caled. for C₂₂H₂₆O₂N: C, 73.46; H, 8.45. Found: C, 73.3; H, 8.34.

References