Nitrations of the Lithium Potassium Dianions of Phenolic Alkyl Aryl Ketones with Propyl Nitrates: Synthesis of 1-Nitroalkyl Hydroxyphenyl Ketones

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We recently required 2-hydroxy-3,4-dimethoxy-α-nitrocatechophenone (2e). Although 2-hydroxy-α-nitrocatechophenone (2a) has been synthesized from 4-hydroxycoumarin (3) via nitration (→4) and ring cleavage1, the method does not appear to be suitable for preparation of 2e owing to the indirect nature of the route and the ease of nitration of aromatic rings activated by oxygen substituents. The methods currently available for synthesis of 1-nitroalkyl ketones are:

- C-acylation of nitronate anions with acyl cyanides2, heptafluoroisopropyl ketones3, N-acylimidazoles4, phenyl esters5, phthalic anhydride6, and benzil7;
- C-acylation of α,α-doubly deprotonated nitroalkanes8,9;
- decomposition of 2-nitroalkyl peroxynitritates derived from olefin nitration with dinitrogen tetroxide and oxygen10;
- the oxidation of 2-nitroalkanols11,12;
- the oxidation of α-ketoximes with trifluoroperacetic acid13;
- the reaction of enol acetates and enol ethers with nitril chloride14;
- the reaction of vinyloxysilanes with nitronium tetrafluoroborate15;
- aqueous hydrochloric acid decomposition of β-nitrosomethylketones derived from the nitrous acid treatment of alkenes16;
- the nitration of potassium enolates with alkyl nitrates20,21,22.

Of these possibilities, the last method appears to be the most attractive because of the ready availability of the acetophenone 1e23,24.

It was previously reported that the nitration of propiophenone with potassium t-butoxide and ethyl nitrate in tetrahydrofuran at −30°C affords α-nitropropiophenone in 16% yield22. A 59% yield of the starting material was recovered even though the nitration was carried out at a higher temperature and for a longer reaction time than usually employed for this nitration procedure22. α-Hydroxyacetophenone (1a) was accordingly treated with 4 equivalents of potassium t-butoxide in tetrahydrofuran/hexamethylen phosphoric triamide (HMPT) followed by addition of 1.6 equivalents of propyl nitrate. This resulted in the isolation of a 23% yield of the desired α-hydroxy-α-nitrocatechophenone (2a) along with 39% recovered 1a and 19% of the cleavage product 5. The low yield of the α-nitroketone 2a may be attributed to the insolubility of the dipotassium salt of enolized 1a in the reaction medium.

Use of the soluble dilitium salt 6a25 in this procedure resulted in failure to obtain any of the desired α-nitroketone 2a. Although 6a was unreactive toward propyl nitrate, it could be methoxycarbonylated with dimethyl carbonate after generation from 1a using 3 equivalents of lithium bis(trimethylsilyl)amide in tetrahydrofuran at −25°C to afford the oxoester 7.

In an alternative attempt to synthesize 2e, compound 1e was brominated with copper(I) bromide in ethyl acetate26 and the resultant bromomethyl ketone 8 subjected to the reaction with sodium nitrite in dimethylformamide. Instead of the desired nitroketone 2e, the hydroxymethyl ketone 9 was obtained in 33% yield. Evidently, the O-atom rather than the N-atom of the nitrite displaces the Br-atom.
A satisfactory compromise between the reactivity of the dipotassium salt and the solubility of the dilithium salt (6e) was finally found by use of the lithium potassium salt 11e. This procedure resulted in the isolation of a 45% yield of nitromethyl ketone 2e.

This method was also applied to several other alkyl hydroxyphenyl ketones (1a–d). The moderate yields of the desired nitroketones (2a–d) were in all cases accompanied by significant amounts of starting material and ester (e.g. 5) resulting from C–C bond cleavage by alkoxide ion.

Table. 1-Nitroalkyl Hydroxyphenyl Ketones (2)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Yield</th>
<th>m.p.</th>
<th>m.p. [°C]</th>
<th>δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[%]</td>
<td>[°C]</td>
<td>reported or</td>
<td>¹H-N.M.R. (CDCl₃/TMS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Molecular formula</td>
<td>δ [ppm]</td>
</tr>
<tr>
<td>a</td>
<td></td>
<td>42</td>
<td>106°</td>
<td>106°¹</td>
<td>11.35 (s, 1 H); 7.95–6.95 (m, 4 H); 6.05 (s, 2 H)</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>41°²</td>
<td>115°</td>
<td>C₇H₅NO₄ (181.1)</td>
<td>11.05 (s, 1 H); 7.45 (m, 4 H); 6.15 (s, 2 H)</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>15°³</td>
<td>109°</td>
<td>C₉H₇NO₄ (195.2)</td>
<td>8.90 (broad s, 2 H); 8.20–7.05 (m, 4 H); 2.40 (s, 3 H)³</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>20°³</td>
<td>52°</td>
<td>C₁₀H₁₁NO₄ (209.2)</td>
<td>12.25 (s, 1 H); 8.30 (d, 1 H); 7.70–6.80 (m, 3 H); 1.70 (s, 6 H)</td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>45</td>
<td>155°</td>
<td>C₁₀H₁₁NO₄ (241.2)</td>
<td>10.95 (s, 1 H); 7.50 (d, 1 H, J= 9 Hz); 6.70 (d, 1 H, J= 9 Hz); 5.95 (s, 2 H); 4.05 (s, 3 H); 3.95 (s, 3 H)</td>
</tr>
</tbody>
</table>

¹ The microanalyses showed the following maximum deviations from the calculated values: C, ±0.23; H, ±0.24; N, ±0.29.
² Compound 2b was isolated from the reaction mixture by extraction with aqueous 10% sodium hydrogen carbonate followed by acidification of the aqueous extract to pH 3–4. An analytical sample was obtained by chromatography on silica gel (chloroform as eluent).
³ The starting material 1b was isolated in 23% yield and the cleavage product, propyl 3-hydroxybenzoate (5), was isolated in 26% yield.
⁴ The starting material 1c was isolated in 14% yield whereas the cleavage products, propyl 2-hydroxybenzoate (5) and 2-hydroxybenzoic acid, were obtained in 48% and 10% yields, respectively.
⁵ The ¹H-N.M.R. spectrum displays only the methyl singlet of the enol form of the product (2e) which was isolated from the reaction mixture by extraction with aqueous 10% sodium hydrogen carbonate followed by acidification to pH 3-4. Analytically pure product 2e was obtained by preparative T.L.C. on silica gel (using chloroform).
⁶ The starting material 1d was prepared in 60% yield by alklylation of the dilithium salt of enolated 2-hydroxypropiophenone (6c; from 1c and 2.5 equiv of lithium disopropylamide in tetrahydrofuran at −30°C) with 1 equiv of methyl iodide.
⁷ Compound 2d was isolated by acidification of the reaction mixture, pouring it into ether, extracting the mixture with aqueous 10% potassium hydroxide (1 × 50 ml), and acidifying the alkaline extract to pH 1-2. The analytical sample was obtained by preparative T.L.C. on silica gel (using chloroform).
⁸ The cleavage product, propyl 2-hydroxybenzoate (5), was obtained in 22% yield and 2-hydroxybenzoic acid in 8% yield.
Hydroxynyl-1-Nitroalkyl Ketones (2a–e); General Procedure:
A 2.4 mol solution of butylthiium in hexane (8.2 ml, 0.02 mol) is added dropwise to a stirred, dry solution of disopropylamine (2.2 g, 0.021 mol) in tetrahydrofuran (10 ml) at −33 °C under a nitrogen atmosphere. Stirring is continued for 15 min and a solution of the appropriate alkyl hydroxynyl ketone 1 (0.02 mol) in dry tetrahydrofuran (10 ml) is added dropwise. The pale yellow suspension is stirred for 10 min before addition of dry hexamethyldisilazane-triethylamine (1:1:1) (10 ml). The clear yellow solution is stirred at 0°C for 10 min and then added dropwise by syringe to a stirred suspension of potassium tert-butoxide (6.72 g, 0.06 mol) in tetrahydrofuran (20 ml) at −33 °C under a nitrogen atmosphere. The orange solution is stirred at −33 °C for 30 min. Propyl nitrate (Aldrich; 3 g, 0.028 mol) is then added dropwise. The reaction mixture is stirred at room temperature for 30 min. The thick red suspension is decomposed by addition of ice-cold 10% sulfuric acid (25 ml). The aqueous layer is extracted with ether (3 × 15 ml). The ether extract is washed with water (3 × 10 ml) and then dried with magnesium sulfate. Evaporation of the solvent gives a yellow powder which is purified by titration with ethanol and filtration. Analytical samples are obtained by recrystallization from ethanol unless otherwise stated.

Conversion of 2-Hydroxyacetophenone (1a) into 2-Hydroxy-α-nitroacetophenone (2a) and Propyl 2-Hydroxyphenyl (5): A solution of 2-hydroxyacetophenone (1a; 1.36 g, 0.01 mol) in dry tetrahydrofuran (5 ml) is added dropwise to a stirred suspension of potassium tert-butoxide (4.48 g, 0.04 mol) in tetrahydrofuran (20 ml) at −33 °C under a nitrogen atmosphere. The pale orange suspension is stirred for 10 min before addition of dry HMPT (5 ml). The deep orange-red suspension is stirred at −33 °C for 30 min. Propyl nitrate (1.2 g) is then added dropwise. The mixture is stirred at room temperature for 15 min, and then ice-cold 5% sulfuric acid (20 ml) is added. The mixture is extracted with ether (3 × 25 ml) and the combined extract washed with water (3 × 10 ml). The organic solution is extracted with aqueous 10% sodium hydrogen carbonate (3 × 15 ml). The combined aqueous extract is acidified with 2 normal hydrochloric acid to give nitroketone 2a (0.71 g, 39%). The original organic extract is washed with water (2 × 5 ml) and dried with magnesium sulfate. The solvent is evaporated and the residual brown oil column-chromatographed on silica gel using chloroform/methanol (9:1) eluent to give ester 5 (0.34 g, 19%) and recovered starting material (0.51 g, 38%).

Conversion of 2-Hydroxyacetophenone (1a) into Methyl 3-(2-Hydroxy-phenyl)-3-oxopropionate (7): A 1.48 mol solution of butylthiium in hexane (9.8 ml, 0.015 mol) is added to a stirred solution of 1,1,3,3-tetramethylsilolane (3.0 ml, 0.014 mol) in dry tetrahydrofuran (10 ml) at −25 °C under a nitrogen atmosphere. The mixture is stirred for 15 min before a solution of α-hydroxyacetophenone (0.647 g, 0.00425 mol) in dry tetrahydrofuran (10 ml) is added dropwise. The orange solution is stirred at −25 °C for 60 min and then warmed to 0°C using an ice bath. The solution is stirred at 0°C for 15 min and then cooled again to −25°C. Dimethyl carbonate (0.420 g, 0.0066 mol) is added rapidly. The mixture is then stirred at room temperature for 30 min. The yellow suspension is poured into a mixture of concentrated hydrochloric acid (3 ml) and ice/water (40 ml). The resulting solution is extracted with ether (2 × 50 ml). The ether extract is washed with water (3 × 15 ml) and dried with magnesium sulfate. Evaporation of the solvent yields a yellow oil which solidifies at room temperature. Ether (1 ml) and pentane (0.5 ml) are added. The pale yellow powder (0.35 g, 38%) is filtered and washed with pentane (1 ml). The analytical sample is prepared by titration with cold ether; mp 36 °C.

C11H12O4 calc. C 61.85 H 5.19 found 61.85 5.27

1H-N.M.R. (CDCl3/TMS): δ = 11.75 (s, 1H); 1.76-1.83 (m, 4H); 3.93 (s, 2H); 3.70 ppm (s, 3H).

Attempted Conversion of Bromometallated Ketone 8 into Nitromethyl Ketone 2c: Formation of 2α-Dihydroxy-3,4-dimethoxycarboxylic acid (9): α-Bromo-3,4-dimethoxy-2-hydroxyacetophenone (8) is prepared from ketone 1e using copper(I) bromide in ethyl acetate according to the procedure of Ref. 37; yield 47%; mp 140-141°C (Ref. 37); mp 140-142.5°C (this procedure).

H-N.M.R. (CDCl3/TMS): δ = 12.05 (s, 1H); 6.78 (d, 1H, J = 9 Hz); 6.55 (d, 1H, J = 9 Hz); 4.47 (s, 2H); 4.02 (s, 3H); 3.95 ppm (s, 3H).

2α-Dihydroxy-3,4-dimethoxycarboxylic acid (9): The ketone 8 (0.27 g, 0.001 mol) is added to a stirred mixture of sodium nitrite (0.12 g, 0.0017 mol) and phosphoric acid dihydrate (0.17 g, 0.001 mol) in dimethylformamide (2 ml). The pale orange solution is stirred at room temperature for 3 and then poured into ice water (5 ml) and extracted with ether (3 × 10 ml). The aqueous layer is extracted with chloroform (10 ml) and the combined organic extract is washed with water (10 ml) and dried with magnesium sulfate. Evaporation of the solvent yields an oil which is purified by 1.1L. on silica gel, eluting with chloroform (ethyl acetate 9:1). Isolation of the second-most polar compound affords the dihydroxymethyl ketone 9; yield 0.07 g (33%); mp 99-100 °C.

C11H12O4 calc. C 56.60 H 5.70
(212.2) found 56.57 5.84

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