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

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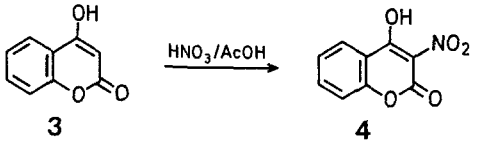
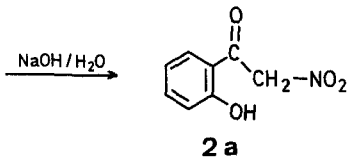
We recently required 2-hydroxy-3,4-dimethoxy-α-nitroacetophenone **(2e)**. Although 2-hydroxy-α-nitroacetophenone **(2a)** has been synthesized from 4-hydroxycoumarin **(3)** via nitration ($\rightarrow$**4**) and ring cleavage[1],



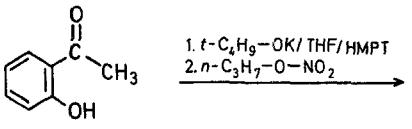


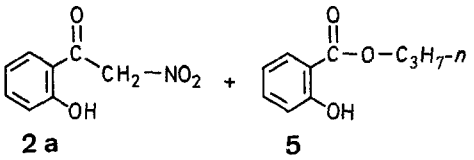
the method does not appear to be suitable for preparation of **2e** owing to the indirect nature of the route and the ease of nitration of aromatic rings activated by oxygen substituents. The methods currently available for synthesis of 1-nitroalkyl ketones are:

- *C*-acylation of nitronate anions with acyl cyanides[2], heptafluoroisopropyl ketones[3], *N*-acylimidazoles[4], phenyl esters[5], phthalic anhydride[6], and benzil[7];
- *C*-acylation of α,α-doubly deprotonated nitroalkanes[8,9];
- decomposition of 2-nitroalkyl peroxynitrates derived from olefin nitration with dinitrogen tetroxide and oxygen[10];
- the oxidation of 2-nitroalkanols[11–15];
- the oxidation of α-ketooximes with trifluoroperacetic acid[16];
- the reaction of enol acetates and enol ethers with nitryl chloride[17];
- the reaction of vinyloxysilanes with nitronium tetrafluoroborate[18];
- aqueous hydrochloric acid decomposition of β-nitrosonitroalkanes derived from the nitrous acid treatment of alkenes[19];
- the nitration of potassium enolates with alkyl nitrates[20,21,22].

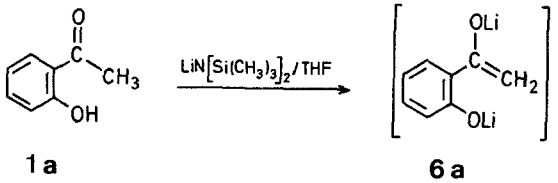
Of these possibilities, the last method appears to be the most attractive because of the ready availability of the acetophenone **1e**[23,24].

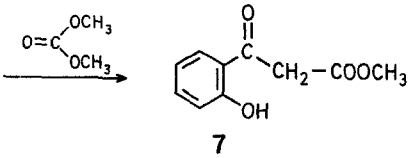
It was previously reported that the nitration of propiophenone with potassium *t*-butoxide and ethyl nitrate in tetrahydrofuran at $-30\,^{\circ}C$ affords α-nitropropiophenone in 16% yield[22]. A 59% yield of the starting material was recovered even though the nitration was carried out at a higher temperature and for a longer reaction time than usually employed for this nitration procedure[22]. *o*-Hydroxyacetophenone **(1a)** was accordingly treated with 4 equivalents of potassium *t*-butoxide in tetrahydrofuran/hexamethylphosphoric triamide (HMPT) followed by addition of 1.6 equivalents of propyl nitrate. This resulted in the isolation of a 23% yield of the desired *o*-hydroxy-α-nitroacetophenone **(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.





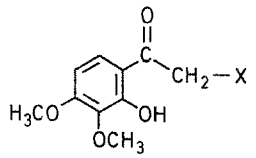
Use of the soluble dilithium salt **6a**[25] in this procedure resulted in failure to obtain any of the desired α-nitroketone **2a**. Although **6a** was unreactive toward propyl nitrate, it could be methoxycarbonylated with dimethyl carbonate after generation from **1a** using 3 equivalents of lithium bis[trimethylsilyl]amide in tetrahydrofuran at $-25\,^{\circ}C$ to afford the oxoester **7**.





In an alternative attempt to synthesize **2e**, compound **1e** was brominated with copper(I) bromide in ethyl acetate[26] 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.

0039-7881/82/0532-0397 $ 03.00



1e X = H **8** X = Br
2e X = NO_2 **9** X = OH

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.

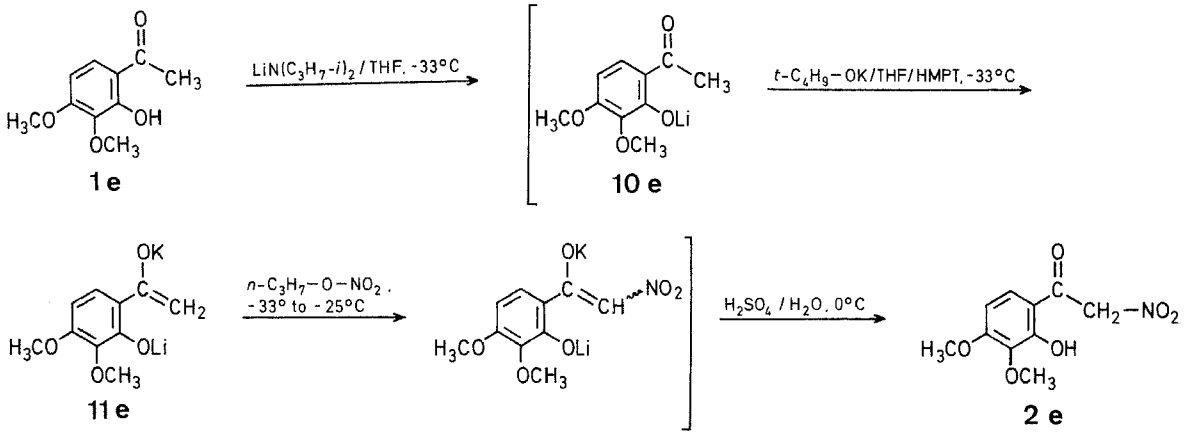
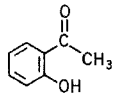
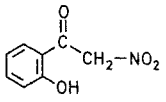
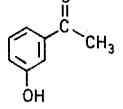
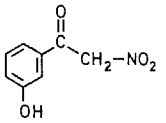
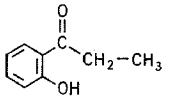
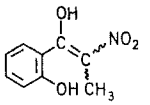
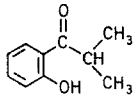
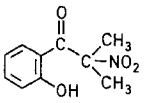
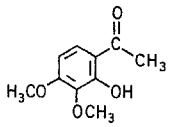
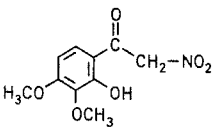


Table. 1-Nitroalkyl Hydroxyphenyl Ketones **(2)**

	1	2	Yield [%]	m.p. [°C]	m.p. [°C] reported or Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
a			42	106°	106°[1]	11.35 (s, 1H); 7.95–6.95 (m, 4H); 6.05 (s, 2H)
b			41[b,c]	115°	$C_8H_7NO_4$ (181.1)	11.05 (s, 1H); 7.45 (m, 4H); 6.15 (s, 2H)
c			15[d,e]	109°	$C_9H_9NO_4$ (195.2)	8.90 (broad s, 2H); 8.20–7.05 (m, 4H); 2.40 (s, 3H)[e]
d			20[f,g,h]	52°	$C_{10}H_{11}NO_4$ (209.2)	12.25 (s, 1H); 8.30 (d, 1H); 7.70–6.80 (m, 3H); 1.70 (s, 6H)
e			45	155°	$C_{10}H_{11}NO_6$ (241.2)	10.95 (s, 1H); 7.50 (d, 1H, J=9 Hz); 6.70 (d, 1H, J=9 Hz); 5.95 (s, 2H); 4.05 (s, 3H); 3.95 (s, 3H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.23; H, ±0.24; N, ±0.29.

[b] 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).

[c] The starting material **1b** was isolated in 23% yield and the cleavage product, propyl 3-hydroxybenzoate **(5),** was isolated in 26% yield.

[d] 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.

[e] The ^{1}H-N.M.R. spectrum displays only the methyl singlet of the enol form of the product **(2c)** 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 **2c** was obtained by preparative T.L.C. on silica gel (using chloroform).

[f] The starting material **1d**[29] was prepared in 60% yield by alkylation of the dilithium salt of enolized 2-hydroxypropiophenone **(6c;** from **1c** and 2.5 equiv of lithium diisopropylamide in tetrahydrofuran at −30°C) with 1 equiv of methyl iodide.

[g] 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).

[h] The cleavage product, propyl 2-hydroxybenzoate **(5),** was obtained in 22% yield and 2-hydroxybenzoic acid in 8% yield.

Hydroxyphenyl 1-Nitroalkyl Ketones (2a–e); General Procedure:
A 2.4 molar solution of butyllithium in hexane (8.2 ml, 0.02 mol) is added dropwise to a stirred, dry solution of diisopropylamine (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 hydroxyphenyl 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 hexamethylphosphoric triamide (HMPT; 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 *t*-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 trituration 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-Hydroxybenzoate (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 *t*-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 (1.71 g, 0.016 mol) 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) as 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-oxopropanoate (7):**
A 1.48 molar solution of butyllithium in hexane (9.8 ml, 0.015 mol) is added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (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 *o*-hydroxyacetophenone (0.647 g, 0.00475 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, 0.00466 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 trituration with cold ether; mp. 56 °C.

$C_{10}H_{10}O_4$	calc.	C 61.85	H 5.19
(194.2)	found	61.83	5.27

^{1}H-N.M.R. ($CDCl_3$/TMS); δ = 11.75 (s, 1 H); 7.67–6.63 (m, 4 H); 3.93 (s, 2 H); 3.70 ppm (s, 3 H).

Attempted Conversion of Bromomethyl Ketone 8 *into* Nitromethyl Ketone 2e; Formation of 2,α-Dihydroxy-3,4-dimethoxyacetophenone (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.[26]; yield: 47%; m.p. 140–141 °C (Ref.[26], m.p. 140–142.5 °C).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 12.05 (s, 1 H); 7.68 (d, 1 H, J = 9 Hz); 6.55 (d, 1 H, J = 9 Hz); 4.47 (s, 2 H); 4.02 (s, 3 H); 3.95 ppm (s, 3 H).

2,α-Dihydroxy-3,4-dimethoxyacetophenone (**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 phloroglucinol dihdyrate (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 T.L.C. on silica gel, eluting with chloroform/ethyl acetate (9:1). Isolation of the second-most polar compound affords the hydroxymethyl ketone **9**; yield 0.07 g (33%); m.p. 99–100 °C.

$C_{10}H_{12}O_5$	calc.	C 56.60	H 5.70
(212.2)	found	56.57	5.84

^{1}H-N.M.R. (acetone-d_6): δ = 11.51 (br s, 1 H); 7.30 (d, 1 H, J = 9 Hz); 6.50 (d, 1 H, J = 9 Hz); 4.81 (s, 2 H); 3.91 (s, 3 H); 3.89 ppm (s, 3 H).

This investigation was supported by Grant CA-27512, awarded by the National Cancer Institute, DHHS.

Received: May 6, 1981
(Revised form: July 22, 1981)

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