Synthesis of 2-Hydroxy-1-naphthoic Acid Derivatives by Oxidative Cyclization of Esters of 5-Aryl-3-oxopentanoic Acid by Mn(III) and Ce(IV) Salts

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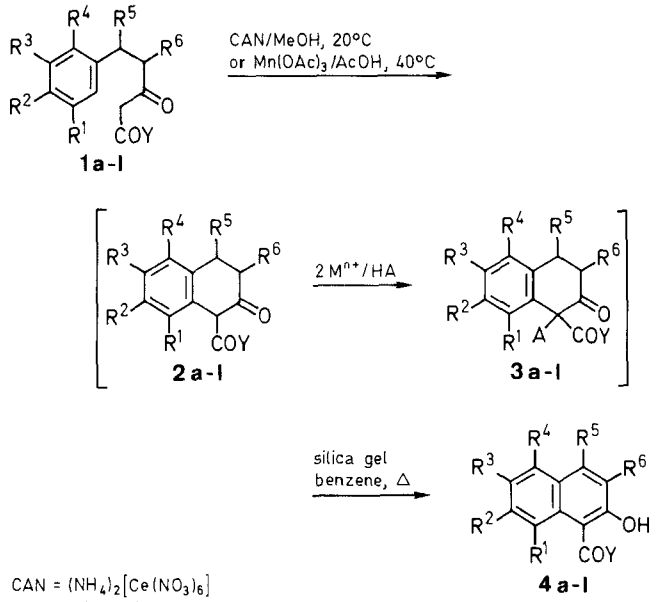
A new synthesis of substituted 2-hydroxy-1-naphthoic acid esters and amides **4** by oxidation of 5-aryl-3-oxopentanoic acid esters or amides **1** with manganese(III) acetate or cerium(IV) ammonium nitrate has been developed, based on the intramolecular homolytic substitution by α-dicarbonylalkyl radicals generated from high-valent metal β-dicarbonyl complexes.

There are few recent published examples of inter- and intramolecular homolytic alkylation of aromatic compounds by oxidation of alkanes, 1,1-disubstituted with electron-withdrawing groups, with manganese(III) acetate/acetic acid,[1] cerium(IV) ammonium nitrate (CAN)/methanol,[2] or iron(III) perchlorate/acetonitrile.[3] These reactions have extended the methodology applied to the oxidation at the methylene group of 1,3-dicarbonyl compounds by high-valent metal salts; thus increasing the synthetic potential of the well documented olefinic series[4] to that of the aromatic series.[4]



CAN = $(NH_4)_2[Ce(NO_3)_6]$
$M^{n+} = Ce^{4+}, Mn^{3+}$
HA = HOAc, MeOH, HNO_3, H_2O

1–4	R^1	R^2	R^3	R^4	R^5	R^6	Y
a	H	H	H	H	H	H	OMe
b	H	H	H	H	H	H	OEt
c	H	H	H	H	H	H	NH_2
d	H	H	H	H	H	CH_3	OEt
e	H	F	H	H	H	CH_3	OMe
f	OMe	H	H	H	H	CH_3	OMe
f'	H	H	OMe	H	H	CH_3	OMe
g	CH_3	H	H	CH_3	H	H	OEt
h	H	CN	H	H	H	CH_3	OEt
i	H	H	H	H	Ph	H	OEt
j	H	CH_3	H	OMe	H	H	OMe
k	H	OMe	H	CH_3	H	H	OMe
l	H	H	$-(CH=CH)_2-$		H	H	OEt

We now report a further application of this strategy to the synthesis of 2-hydroxy-1-naphthoic acid derivatives **4** by four-electron oxidation of 5-aryl-3-oxopentanoic acid derivatives **1** by manganese(III) acetate in acetic acid or CAN in methanol, through the cyclic intermediates **2** and **3**.

Compounds **1a–l**, easily available from benzyl halides and the dianions of β-keto esters,[5] are oxidized by manganese(III) acetate/acetic acid at 40–70 °C to give **3** (A = OAc) in significant yield only when an electron-releasing group is present on the aromatic ring in the *meta* position. With other substituents the yields were lower and several products were formed arising from further unselective oxidation of the cyclic product **2**, which was generally observed in trace amounts.

CAN in methanol or acetic acid/water (9:1) is more efficient than manganese(III) acetate and gave **3** (A = OMe, ONO_2 or OH, in variable proportions depending on the substituent) in moderate yield.

In all cases, aromatization of **3** to substituted 2-hydroxy-1-naphthoic acid esters or amides was achieved by adsorption on silica gel (0.032–0.063 mesh) and heating in benzene. This procedure can be applied to the crude reaction mixture, followed by flash chromatography to obtain pure **4**, generally as the first compound eluted. However, the aromatization of the *ortho*-addition product **3f'** needs more drastic conditions.

Lower temperatures and reaction times were necessary for compounds **1f**, **1g**, **1j** and **1k** having electron-releasing groups. The conversion of **1** was 85–90% using two equivalents of the metal salt, and attempts to improve the yield by using higher amounts of the oxidant or by inverse addition were unsuccessful.

However, compared with previous approaches to the synthesis of this class of compounds, the reaction appears to be synthetically useful. For instance, compound **4k**, the naphthalene chromophore of the antitumor antibiotics neocarzinostatin and carzinophilitin, was previously prepared in seven steps in 4.5% overall yield.[6]

The reaction can be interpreted as an intramolecular homolytic aromatic substitution by α-dicarbonylalkyl radicals, generated by inner-sphere electron transfer from high-valent metal complexes, followed by further oxidation of the benzylic position of **2** to give **3**.[1,2]

The factors which determine the possibility of stopping the reaction at the oxidation stage of compound **2**, i.e. with substrate **1l**, appear to be related to the low enol content of **2l**.

The different behavior observed between CAN and Mn(III) acetate is related to a higher rate of ligand-

Table. Cerium(IV) Ammonium Nitrate (CAN) and Manganese(III) Acetate Oxidation of **1** to 2-Hydroxy-1-naphthoic Acid Derivatives **4**.

Product	Yield (%)[a]		mp (°C)[b]	Molecular Formula[c] or lit. mp (°C)	IR (Nujol)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	MS (70 eV)[f] m/z (%)
	CAN	Mn(III)					
4a	31	–	78–79	78–9[8]	–	–	–
4b	62	24	56–57	58–60[8]	–	–	–
4c	42	–	177–178	178[8]	–	–	–
4d	40	30	69–70	$C_{14}H_{14}O_3$ (230.26)	1657, 1646, 1625	1.55, 2.42 (s, 3H); 4.61 (q, 2H); 7.2–7.85 (m, 4H); 8.82 (dd, 1H, J = 10.2); 12.6 (s, 1H)	230 (M^+, 19), 184 (100)
4e	42	10	87–88	$C_{13}H_{11}FO_3$ (234.2)	1656, 1645, 1638	2.39, 4.12 (s, 3H); 7.11 (ddd, 1H, J = 9, 9.1, 2.5); 7.66 (dd, 1H, J = 9.91); 7.73 (m, 1H); 2.33 (dd, 1H, J = 13.5, 2.5)	234 (M^+, 43), 202 (100)
4f	28	41	98–99	$C_{14}H_{14}O_4$ (246.3)	1655, 1645, 1618	2.48, 3.88, 4.08 (s, 3H); 7.03 (d, 1H, J = 2.8); 7.15 (dd, 1H, J = 9.6, 2.8); 7.66 (s, 1H); 8.59 (d, 1H, J = 9.6); 12.4 (s, 1H)	246 (M^+, 27), 214 (100)
4f'	32	36	114–115	$C_{14}H_{14}O_4$ (246.3)	1658, 1645	2.46 (s, 3H); 3.92 (s, 3H); 4.12 (s, 3H); 7.1–7.8 (m, 4H); 10.2 (s, 1H)	246 (M^+, 38), 231 (100)
4g	39	–	129–130	$C_{15}H_{16}O_3$ (244.3)	1640	1.39, 2.5, 2.67 (s, 3H); 6.48 (q, 2H); 7.2 (d, m); 7.23 (d, 1H); 7.30 (d, 1H); 8.10 (d, 1H); 9.40 (s, 1H)	244 (M^+, 35), 198 (100)
4h	21	0	121–122	$C_{15}H_{13}NO_3$ (255.3)	2225, 1655, 1618	2.48, 4.17 (s, 3H); 7.17 (s, 1H); 7.51 (dd, 1H, J = 9.2); 7.76 (d, 1H); 9.10 (d, 1H); 12.86 (s, 1H)	241 (M^+, 8), 209 (100)
4i	38	–	143–144	$C_{19}H_{16}O_3$	1658, 1640	1.38 (t, 3H); 4.45 (d, 2H); 7.2–7.9 (m, 10H); 12.7 (s, 1H)	292 (M^+, 100)
4j	55	–	112–113	113–114[6]	1657, 1648, 1623	2.68, 3.87, 4.08 (s, 3H); 6.95 (dd, 1H, J = 2.5, 0.6); 7.05 (d, 1H, J = 9.1); 7.74 (d, 1H); 7.9 (d, 1H, J = 9.1); 12.4 (s, 1H)	246 (M^+, 51), 231 (100)
4k	62	–	104–105	104–105[6]	1655, 1645, 1620	2.62, 3.90, 4.09 (s, 3H); 6.86 (dd, 1H, J = 2.7, 0.7); 7.01 (d, 1H, J = 9.3); 8.00 (d, 1H); 8.05 (d, 1H, J = 2.7); 12.2 (s, 1H)	246 (M^+, 31), 214 (100)
2l	38	–	89–90	$C_{17}H_{16}O_3$ (268.3)	1735, 1705	1.24 (t, 3H); 2.78 (ddd, 1H, J = 2.3, 13, 18.5); 3.06 and 3.17 (ddd, 2H, J = 19, 2.5, 4.5); 3.56 (ddd, 1H, J = 19, 2.5, 2.3); 4.3 (m, 2H); 4.59 (s, 1H); 7.2–7.9 (m, 6H)	268 (M^+, 10), 165 (100)

[a] Yield of isolated product **4** based on **1** and metal salt.
[b] Uncorrected, measured with a Koffler Apparatus.
[c] Satisfactory microanalyses obtained: C ±0.2, H ±0.1, N ±0.3.
[d] Recorded on a Perkin Elmer 177 Grating Infrared Spectrometer.
[e] Obtained on a Bruker A-200 Spectrometer.
[f] Recorder on a Hitachi RMU Spectrometer.

transfer oxidation of free carbon radicals by Ce(IV). In fact, only free carbon radicals substituted at the radical center with strongly electron-releasing groups, i.e. hydroxy-, alkoxy-, or *o,p*-dialkoxyaryl groups, are known to be oxidized selectively by Mn(III) acetate.[7]

Ethyl 3-Methyl-2-hydroxy-1-naphthoate (4d); Typical Procedure with CAN:

CAN (9.36 g, 17.1 mmol) is dissolved in MeOH (20 mL) at 15 °C and the resulting solution added with stirring at 5–10 °C to a solution of **1d** (1.01 g, 4.3 mmol) in MeOH (5 mL). The solution is stirred for 0.5 h, then diluted with Et_2O (50 mL) and filtered through silica gel (6 g). The resulting solution is evaporated to dryness, the residue taken up with benzene and silica gel (6 g) added. The mixture is refluxed for 2 h, then concentrated and submitted to flash chromatography on a silica gel column (25 cm × 5 cm; 230–400 mesh), to give compound **4d** as a colorless solid; yield: 0.39 g (40 %); mp 69–70 °C.

Isolation of Intermediates 3d (A = OMe, ONO_2):

Following the typical procedure with CAN given for **4d**, the reaction mixture, before the dilution with Et_2O, is extracted with EtOAc (15 mL) and water (10 mL). The water is extracted with EtOAc (2 × 10 mL) and the extracts combined and evaporated. The residue is subjected to column chromatograph (conditions as previous experiment) to give **3d** (A = OMe, ONO_2).

*Ethyl 1-Methoxy-3-methyl-2-oxo-1,2,3,4-tetrahydronaphthoate (**3d**, A = OMe):* Colorless liquid; yield: 248 mg (22 %).

$C_{15}H_{18}O_4$ (262.3) calc. C 68.68 H 6.92; found 68.79 7.04

IR (film): ν = 1760 (CO), 1725 cm^{-1} (CO_2Et).

^{1}H-NMR ($CDCl_3$): δ = 1.24 (t, 3 H), 1.28 (d, 3 H), 2.78 (dd, 1 H, J = 15, 4.0 Hz), 3.10 (ddq, 1 H), 3.13 (s, 3 H), 3.23 (dd, 1 H), 4.25 (q, 2 H), 7.2–7.45 (m, 3 H), 7.57 (dd, 1 H).

*(**3d**, A = ONO_2):* Colorless liquid: yield 328 mg (26 %).

$C_{14}H_{15}NO_6$ (293.3) calc. C 57.34 H 5.15; found 55.50 5.02

IR (film): ν = 1765 (CO); 1735 (CO_2Et), 1650 cm^{-1} (NO_2).

^{1}H-NMR ($CDCl_3$): δ = 1.28 (t, 3 H), 1.30 (d, 3 H), 2.9–3.2 (m, 3 H), 4.22 (m, 2 H), 7.2–7.5 (m, 3 H), 7.63 (dd, 1 H).

Methyl 6-Methoxy-3-methyl-2-hydroxy-1-naphthoate (4f); Typical Procedure with Manganese(III) Acetate:

Mn(III) acetate (4.14 g, Merck, 98 % purity by iodometry, 16.0 mmol) is added to a stirred solution of **1f** (1.03 g, 4.0 mmol) in AcOH (20 mL) at r. t.. The solution is heated with stirring to 50 °C for 3 h, then AcOH is evaporated under vacuum (20 mmHg) and the residue taken with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined extracts are washed with water

(5 mL), dried (Na_2SO_4, 1 g), and, after addition of silica gel (0.032–0.06 mesh, 5 g), evaporated to dryness. The residue is taken up in benzene (15 mL) and refluxed for 2 h. Flash-chromatography of the residue on silica gel (20 cm × 4 cm; 230–400 mesh) with hexane/EtOAc (8:2) affords as the first eluted compound the *para*-addition isomer **4f** as a colorless solid; yield: 0.40 g (41%); mp 98–99 °C.

Further elution with hexane/EtOAc (4:6) affords the *ortho*-addition product **3f** (A = OAc); yield: 0.35 g (29%); mp 218 °C;

$C_{16}H_{18}O_6$	calc.	C 62.74	H 5.92
(306.3)		62.94	5.72

IR (KBr): ν = 1750 (CO), 1715 cm^{-1} (OCOMe).

^{1}H-NMR ($CDCl_3$): δ = 1.30 (d, 3 H), 2.06 (t, 3 H), 3.65 (dd, 1 H, J = 15.2, 3.6 Hz), 3.21 (m, 1 H), 3.31 (dd, 1 H, J = 4.1 Hz); 3.82 (s, 3 H); 4.02 (s, 3 H); 7.1–7.4 (m, 3 H).

MS: m/z = 306 (17), 264 (10), 248 (11), 246 (24), 219 (16), 214 (73), 205 (100), 177 (28), 161 (24), 121 (19), 91 (13).

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