New and Efficient Conversion of Benzoic Acids into Salicylic Acids via Copper Mediated Hydroxylation Process

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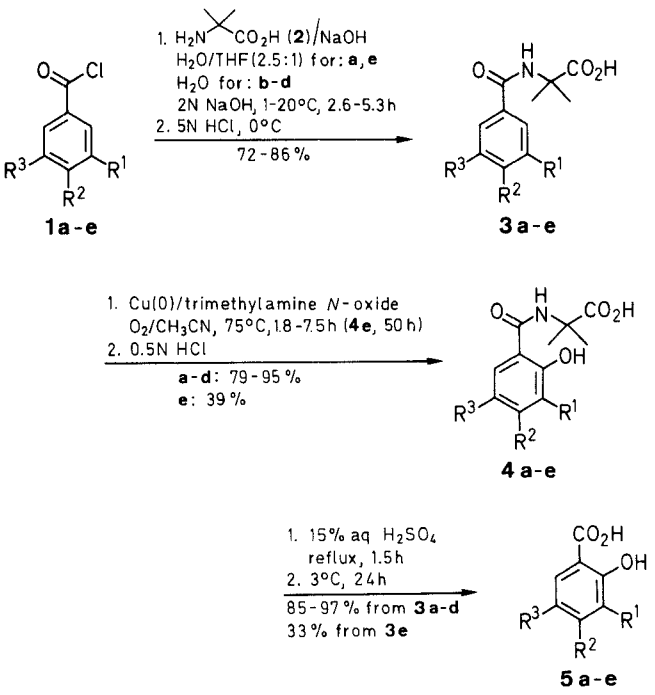
N-benzoyl-2-methylalanines **3**, obtained through condensation of aroyl chlorides **1** with sodium 2-methylalaninate are *ortho*-hydroxylated by the new Cu(0)/O_2/trimethylamine *N*-oxide system. Acid hydrolysis of the so-obtained salicylamides **4** provides salicylic acids **5** in excellent yield. When the substrate contains three electron-releasing groups the yields are moderate.

Salicylic acids are prepared with difficulty from the corresponding benzoic acids by direct introduction of an hydroxyl group.[1] Hydroxylations by the $KMnO_4$/H_2SO_4 system[2] or HO• produced by X-Ray radiolysis[3] are not selective and afford a mixture of *ortho*, *meta* and *para* isomers. The classical (Fe^{2+}/H_2O_2),[4] or the modified (Fe^{2+}, Cu^+, Co^{2+} or Mn^{2+}/H_2O_2/EDTA/ascorbate)[5] Fenton's reagent as Udenfriend's type system (Fe^{3+} or Cu^{2+}/O_2/ascorbate)[6] gave very low yields of salicylic acids. This can be explained by the lack of regioselectivity in bimolecular processes and by the high oxidizability of the product compared with the starting material. However, thermal decomposition (200–220 °C) of the basic cupric salt of benzoic acid ($PhCO_2Cu(II)OH$)[7] allows an *ortho*-selective hydroxylation owing to the intramolecular nature of the reaction. This procedure has limited preparative value due to the unsatisfactory preparation of the basic salt and formation of decarboxylation byproducts. Pyrolysis of the neutral cupric benzoate [$(PhCO_2)_2Cu(II)$][8] can give better yields but conversion ratios (50% in theory) remain low (**5a**: 19%, yield = 100%; **5c**: 40%, yield: 87%; **5d**: 41%, yield = 70%) (substituents are explained in Scheme).

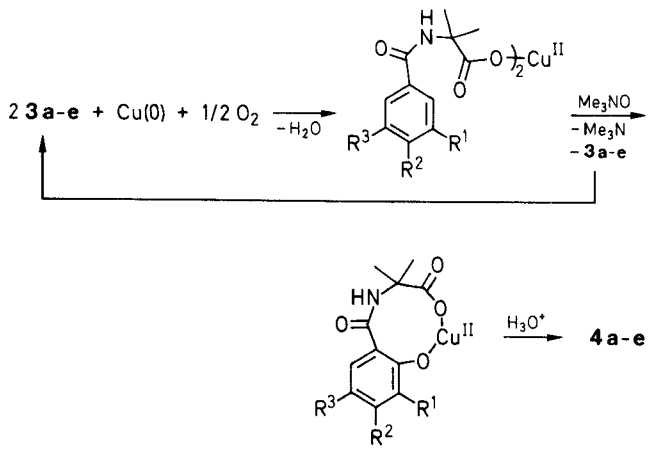
We report herein a new method for the conversion of benzoic acids to salicylic acids in three steps, which gives high yields of the final product with a high conversion ratio and is completely regioselective.

Substituted *N*-aroyl-2-methylalanines **3a–e** are synthesized according to the previously described procedure for **3c**[9] which has been adapted for **3a,b,d,e**: aroyl chlorides **1a–e** (readily prepared from benzoic acids with thionyl chloride according to the classical procedure[10] if not commercially available) are condensed with 2-methylalanine **(2)** at low temperature in a sodium hydroxide solution with addition of tetrahydrofuran for **1a,e** in order to ensure partial solubility (Table 1). The nonquantitative yields are due to competitive hydrolysis of acid chlorides **1a–e** giving the corresponding sodium benzoates, but recovered materials could be recycled into benzoic chlorides **1a–e**. Amides **3a–e** are then *ortho*-hydroxylated in dry acetonitrile at 75 °C, in the presence of copper(0) powder (1.1 equiv) and excess trimethylamine *N*-oxide (TMAO, 5 equiv.) under an oxygen atmosphere.[11] A mild hydrolysis (0.5 N hydrochloric



1, 3–5	R^1	R^2	R^3
a	H	NO_2	H
b	H	Cl	H
c	H	H	H
d	H	Me	H
e	OMe	OMe	OMe

Scheme A



acid) provides salicylamides **4a–e** which can be either purified by recrystallization or directly converted into salicylic acids **5a–e** in refluxing 15% aq. sulfuric acid in excellent yield (see Table 2). Tables 1 and 2 emphasize the diversity of substrates to which the method was applied and the overall high yield obtained after three steps was: **5a–d**: 67–71%, except **5e**: 29%. The reactions were easy to perform and were carried out on a scale from 0.5 to 50 mmol.

This synthetic pathway consists of an original key step: the *ortho*-hydroxylation of benzamides **3a–e**. This oxidation proceeds through conversion of metallic copper into copper(II) salts by acidic compounds **3a–e** and molecular oxygen, followed by their *ortho*-hydroxylation

Table 1. *N*-Aroyl-2-methylalanines **3** Prepared

Product	Reaction Time (h)/ Temperature (°C)	Solvent	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	^{1}H-NMR (DMSO-d_6/TMS)[c] δ, J(Hz)
3a	2.5/1; 1/20	H_2O/THF	79	194	183.5[17]	1.48 (s, 6H, $2CH_3$), 8.11 and 8.35 (2d, $4H_{arom}$, J = 8.5), 8.83 (s, 1H, NH)
3b	2.5/12; 1/20	H_2O	72	221	$C_{11}H_{12}ClNO_3$ (241.7)	1.47 (s, 6H, $2CH_3$), 7.54 and 7.92 (2d, $4H_{arom}$, J = 8), 8.54 (s, 1H, NH)
3c	2.5/1; 0.1/20	H_2O	79	201	202[9]	1.48 (s, 6H, $2CH_3$), 7.4–7.55 (m, $3H_{arom}$), 7.83–7.93 (m, $2H_{arom}$), 8.45 (s, 1H, NH)
3d	5/1; 0.3/20	H_2O	81	217	$C_{12}H_{15}NO_3$ (221.2)	1.47 (s, 6H, $2CH_3$), 2.37 (s, 3H, CH_3), 7.29 and 7.82 (2d, $4H_{arom}$, J = 8.5), 8.38 (s, 1H, NH)
3e	3.5/1; 1/20	H_2O/THF	86	184	$C_{14}H_{19}NO_6$ (297.3)	1.48 (s, 6H, $2CH_3$), 3.73 (s, 3H, OCH_3), 3.87 (s, 6H, $2OCH_3$), 7.23 (s, $2H_{arom}$), 8.42 (s, 1H, NH)

[a] Yield of isolated product **3** based on **1**.
[b] Satisfactory microanalyses obtained: C ±0.06, H ±0.06, Cl +0.11, N ±0.07, O ±0.28.
[c] Obtained on a Varian EM-390 (90 MHz) spectrometer.

Table 2. *N*-Salicyloyl-2-methylalanines **4** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
4a	1.8	79 (98)	245 (239)	$C_{11}H_{12}N_2O_6$ (268.2)	1.52 (s, 6H, $2CH_3$), 7.71 (s, $1H_{arom}$), 7.72 and 8.12 (2d, $2H_{arom}$, J = 8.7), 9.02 (s, 1H, NH), 12.51 (br s, 2H, OH and CO_2H)
4b	4	95 (>100)	207 (190)	$C_{11}H_{12}ClNO_4$ (257.7)	1.50 (s, 6H, $2CH_3$), 6.97 and 7.96 (2d, $2H_{arom}$, J = 7.4), 6.99 (s, $1H_{arom}$), 8.84 (s, 1H, NH), 12.48 (br s, 2H, OH and CO_2H)
4c	6	88 (98)	184 (180)	$C_{11}H_{13}NO_4$ (223.2)	1.49 (s, 6H, $2CH_3$), 6.90 (m, $2H_{arom}$), 7.36 (t, $1H_{arom}$, J = 7.7), 7.94 (d, $1H_{arom}$, J = 7.2), 8.80 (s, 1H, NH), 12.11 (s, 1H, OH), 12.43 (br s, 1H, CO_2H)
4d	7.5	87 (>100)	179 (174)	$C_{12}H_{15}NO_4$ (237.2)	1.48 (s, 6H, $2CH_3$), 2.27 (s, 3H, CH_3), 6.71 and 7.83 (2d, $2H_{arom}$, J = 8.4), 6.72 (s, $1H_{arom}$), 8.70 (s, 1H, NH), 12.16 (s, 1H, OH), 12.38 (br s, 1H, CO_2H)
4e	50	39	209	$C_{14}H_{19}NO_7$ (313.3)	1.49 (s, 6H, $2CH_3$), 3.75, 3.78 and 3.81 (3s, 9H, $3OCH_3$), 7.30 (s, $1H_{arom}$), 8.70 (s, 1H, NH), 12.02 (s, 1H, OH), 12.44 (br s, 1H, CO_2H)

[a] Yield of purified product **4** (recrystallization) based on **3**. Apparent yield of isolated crude product **4** is shown in parenthesis, and can exceed 100%.
[b] Melting point of purified product **4**. Melting point of crude product **4** are shown in parenthesis.
[c] Satisfactory microanalyses obtained: C ±0.33, H ±0.13, Cl ±0.01, N ±0.20, O ±0.21; exception: **4a:** N −0.32, O −0.39.
[d] Obtained on a Bruker AM-250 (250 MHz) spectrometer.

by trimethylamine *N*-oxide to give the blue copper(II) salts of salicylamides **4a–e** and trimethylamine (TMA).[11]

The reaction is selective with complete conversion to **4** (for **a–d**) as detected either by HPLC, TLC or NMR spectroscopy of the crude product after hydrolysis. Under these conditions, neither benzoic acid or the *N*-methyl derivative of **3c** suffer any hydroxylation. Consequently, the 2-methylalaninamide group is essential for this reaction for two reasons: (i) the copper(II) ion has to be at the proper distance from the aromatic nucleus to allow intramolecular hydroxylation, which accounts for the complete *ortho*-selectivity; (ii) an N–H amidic bond is required for adequate oxidative activity of the Cu(II)/TMAO couple. This is confirmed by the observed correlation between the acidity of the NH group and the reactivity; electron-withdrawing substituents R^2 greatly enhance the hydroxylation rate (Table 2, from **3e** to **3a**). With three methoxy electron-releasing substituents, substrate **3e** represents the most unfavorable situation and consequently a relatively low yield is obtained. However, it should be noted that this is the first reaction that allows direct introduction of only one hydroxyl group onto such an oxidizable aromatic moiety. High stability of salicylamide **4a–e** copper(II) salts under these experimental conditions account for the moderate yield of **5e** to the almost quantitative yield of **5c**.

In conclusion, this new synthesis of salicylic acids is complementary to the classical *ortho*-directed sodium phenoxide carboxylation, the Kolbe–Schmitt[12] reaction which affords 5-substituted salicylic acids from *para*-substituted phenols, although poor yields are obtained with strong electron-withdrawing (nitro) or releasing (methoxy) groups,[13] whilst our method allows the easy synthesis of 4-substituted derivatives. The mechanism of this oxidation is under investigation.

Table 3. Salicylic Acids Prepared

Product	Yield[a] (%)	mp (°C) found	reported
5a	85	240	235[14]
5b	97	219	216–218[15]
5c	90	157	154[14]
5d	88	175	177[14]
5e	33	99	104[16]

[a] Yield of isolated product **5** based on **3**.

Most reagents are commercially available. CH_3CN was distilled from P_4O_{10} and kept over molecular sieves (3 Å). Dry TMAO was obtained by azeotropic distillation of TMAO. 2 H_2O with toluene and kept as a 1 M solution in anhydrous CH_3CN. Melting points are determined on a Kofler (Reichert) apparatus.

Benzamides 3; General Procedure:

2-Methylalanine (**2**, 5.16 g, 50 mmol) and NaOH (2 g, 50 mmol) are required temperature (cf Table 1). Half of the neat **b–d** or THF-dissolved (**a,e**, 30 mL) aroyl chloride **1** (50 mmol) is added within 30 minutes. The addition of the other half (over 1.5 h) is carried out with simultaneous dropping of a 2 N NaOH solution (25 mL) in order to maintain a basic reaction medium. After the time indicated in Table 1 the temperature is raised to r.t., and maintained until all aroyl chloride **1** has reacted (HPLC). THF (if present) is distilled off under reduced pressure. Careful (ice-cooling) acid hydrolysis with 5 N HCl (10 mL) affords a white precipitate, which is collected by filtration and washed with ice-cold water (4 × 10 mL). The crude product is dried in a vacuum dessicator over KOH, then is dried over P_4O_{10}. It is then suspended in boiling Et_2O (30 mL) for 15 min (in order to remove the benzoic acid produced by the hydrolysis of aroyl chloride **1**), filtered after cooling and finally recrystallized from hot EtOAc/EtOH.

***N*-(4-Chloro-2-hydroxybenzoyl)-2-methylalanine (4b; $R^1 = R^3 = H$, $R^2 = Cl$); Typical Procedure:**

A mixture of *N*-(4-chlorobenzoyl)-2-methylalanine (**3b**, 12.1 g, 50 mmol) and Cu(0) powder (200 mesh, 3.5 g, 0.55 mmole, 1.1 equiv.) is vigorously stirred, with O_2 bubbling, in dry CH_3CN (50 mL). A 1 M CH_3CN solution of TMAO (250 mL, 5 equiv.) is then added and temperature set at 75 °C. Within 4 h, the reaction mixture turns from green to blue. The solution is allowed to cool to r.t., poured on ice-cold 0.5 N HCl (600 mL), saturated with NaCl and extracted with EtOAc (2 × 400 mL then 2 × 200 mL). The collected organic layers are washed with brine (2 × 100 mL then 50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford crude benzamide **4b** as light tan crystals (13.34 g; mp 190 °C) which can be recrystallized from $EtOH/H_2O$, yield: 12.26 g (95 %); mp 207 °C. For **4e**, an additional TMAO equivalent is added after the 24 first hours.

4-Chloro-2-hydroxybenzoic acid (5b; $R^1 = R^3 = H$, $R^2 = Cl$); Typical Procedure:

Crude salicylamide **4b** (1 g) is stirred in refluxing 15 % aq H_2SO_4 (70 mL) for 1.5 h and then cooled for 24 h at 3 °C. Pure salicylic acid **5b** (630 mg; mp 219 °C) is obtained by filtration, washing with ice-cold water (3 × 5 mL) and drying under vacuum over P_4O_{10}. Yield based on **3b**: 97 %.

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