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Highly efficient synthesis and chemical separation of 5-amino- and 7-amino-4-hydroxy-2-naphthoic acids

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Abstract—5-Amino- and 7-amino-4-hydroxy-2-naphthoic acids were synthesized for the first time via a microwave-assisted pathway. The separation of the two isomers was then conveniently achieved by exploiting their different reactivities with CDI.

Aminonaphthol sulfonic acids,[1] as 7-amino-4-naphthol-2-sulfonic acid (J acid, Fig. 1) and 5-amino-4-naphthol-2-sulfonic acid (H monoacid, Fig. 1), have been widely used as intermediates in the manufacture of direct dyes (dyes used without mordant) for a long time.[2] In addition to this application, they recently also emerged as synthetic intermediates for a number of biologically active compounds and pharmaceutical candidates.[3–9]

As part of a project aimed at discovering novel small-molecule inhibitors of arginine methyltransferases,[9] we were interested in the synthesis of the carboxy- analogues of the aminonaphthol sulfonic acids. We then realized that, while a successful pathway leading to the preparation of 6-amino-4-hydroxy-2-naphthoic acid was described,[4] only failed attempted syntheses of 7-amino-4-hydroxy-2-naphthoic acid **1a** (Fig. 1) are reported.[10,11] Moreover, to the best of our knowledge, there is no literature report of the synthesis of 5-amino-4-hydroxy-2-naphthoic acid **1b**. Thus we decided to set up a convenient single method for the synthesis of both these building blocks.

In this work we describe, for the first time, the preparation of compounds **1a** and **1b** and their successful separation.

As nitrobenzaldehydes are reported to resinify under alkaline Stobbe conditions,[12] we used a Wittig reaction between 3-nitrobenzaldehyde and carboxyphosphorane **2**[13] to regioselectively[14] prepare the (*E*)-nitrophenylitaconate **3**,[12,15] which was selectively reduced with zinc dust in acetic acid to amino derivative **4** (Scheme 1).[16] The

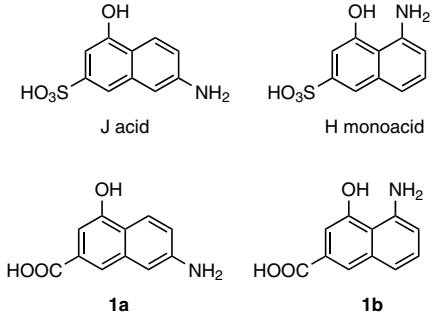
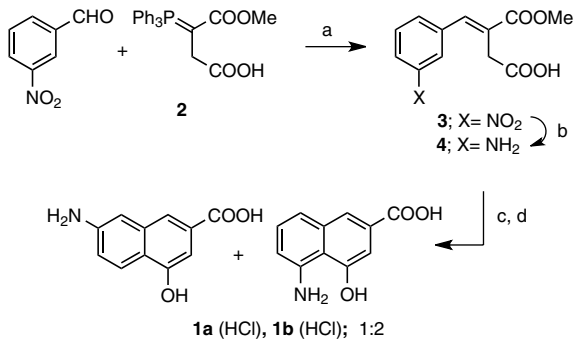


Figure 1. J acid, H monoacid and their carboxy- analogues **1a** and **1b.**



Scheme 1. Reagents and conditions: (a) benzene, rt, 24 h; (b) Zn (6 mol equiv), AcOH, rt, 24 h; (c) AcONa (1.5 mol equiv), Ac_2O, MW (300 W, 5 min); (d) HCl 8 N, 5 h.

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subsequent ring closure via Friedel–Crafts acylation was successfully performed by using a single-mode microwave irradiation[17] at a constant irradiation power during a short reaction time (1.5 equiv NaOAc, Ac_2O, 300 W, 5 min).[18] Hydrolysis of the crude furnished a mixture of title acids **1a** and **1b** (1:2 ratio, determined by NMR) in a satisfactory 70% overall yield, without intentional purification of the intermediates.[19]

With the mixture of the two isomeric acids in our hands, we turned our attention to their separation. As a matter of fact, accordingly to what was previously reported for similar derivatives,[10,11] this task revealed to be not easy. After the failure of fractionated crystallization and both conventional and flash chromatography (data not shown), we were able to separate the mixture only through analytical RP-HPLC (Fig. 2).[20]

Unfortunately, this result was not reproducible on a preparative scale (preparative RP-HPLC, same conditions, data not shown). For this reason we decided to investigate if the expected difference in reactivity resulting from the relative positions of the amino and the hydroxy group in the two compounds could be exploited for their separation. Actually, the reaction[21] of the mixture of ethyl esters **5a** and **5b** (from **1a** and **1b**, respectively) with CDI in THF at 0 °C for 3 h converted **5b**[22] into the cyclic carbamate **6** (Scheme 2), leaving **5a** unreacted (33% and 55% yield, respectively). The two derivatives were easily separated by double extraction and then quantitatively converted into acids **1a** and **1b** by hydrolysis with 8 N hydrochloric acid.

In conclusion, we have developed a convenient pathway leading to the first synthesis of 5-amino- and 7-amino-4-hydroxy-2-naphthoic acids. An efficient microwave-assisted transformation, together with a relatively straightforward separation process exploiting the different chemical reactivities of the two isomers, makes this protocol useful for the preparation of building blocks for the drug discovery process as well of intermediates in the manufacture of dyes.

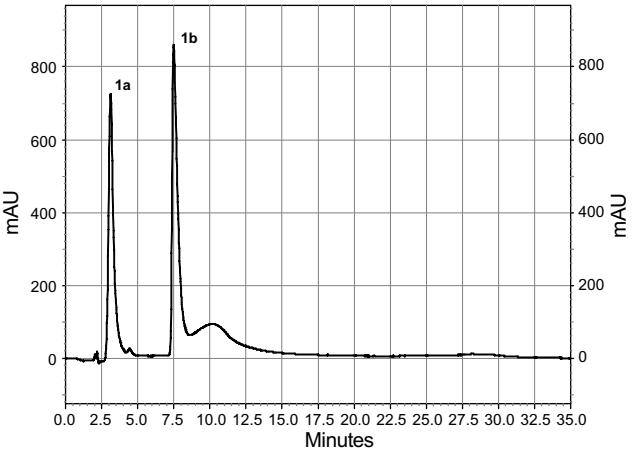
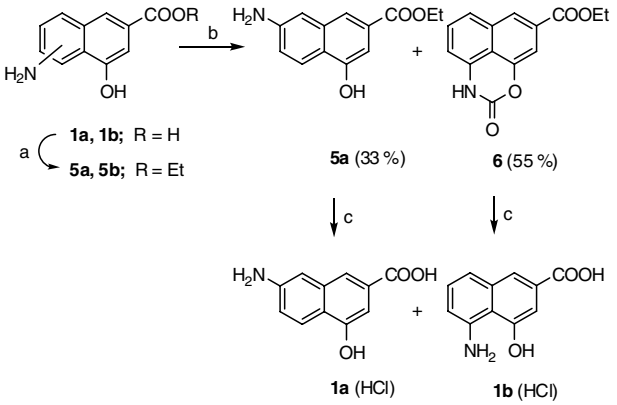


Figure 2. Analytical RP-HPLC separation of isomers **1a** and **1b** was performed on C18 column (Vydac 218TP152010) using a gradient of acetonitrile (40–70% acetonitrile in 30 min) in 0.1% aqueous TFA at 1 mL/min.



Scheme 2. Reagents and conditions: (a) EtOH, H_2SO_4, reflux, 24 h; (b) CDI, THF, 0 °C, 3 h; (c) HCl 8 N, 5 h.

Acknowledgments

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15. *Preparation of (E)-3-(methoxycarbonyl)-4-(3-nitrophenyl)but-3-enoic acid* (**3**). To a suspension of **2** (13.0 g, 35.2 mmol) in dry benzene (150 mL) 3-nitrobenzaldehyde (5.74 g, 38.0 mmol) was added and the resulting mixture was stirred at room temperature for 48 h and then extracted with saturated $NaHCO_3$ solution (3×70 mL). The aqueous phase was washed with ethyl ether, acidified with concentrated HCl and extracted with ethyl acetate (3×60 mL). The combined organic phases were washed with brine and dried. Evaporation of the solvent yielded 8.60 g (92%) of **3** as a white solid which was recrystallized from toluene. Mp 160–161 °C (lit. 122–123 °C from benzene, Ref. 12). Anal. Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.44; H, 4.19; N, 5.29. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30–8.10 (m, 2H), 7.92 (s, 1H), 7.78–7.55 (m, 2H), 3.87 (s, 3H), 3.48 (s, 2H). MS (EI, 70 eV) *m*/*z*: 265. ^{1}H NMR experiments confirmed the *E* assignment for compound **3**, as the chemical shift of the vinylic hydrogen atom ($\delta = 7.92$ ppm) is consistent with a cis position respect to the methoxycarbonyl substituent.
16. *Preparation of (E)-3-(methoxycarbonyl)-4-(3-aminophenyl)but-3-enoic acid* (**4**). To a solution of **3** (2.00 g, 7.54 mmol) in glacial acetic acid (100 mL) Zn dust (3.88 g, 60.3 mmol) was added portionwise while keeping the temperature below 20 °C with an ice bath. The resulting mixture was vigorously stirred for 24 h. The solids were filtered off and washed with methanol and the combined filtrates were concentrated and the residue was redissolved in ethanol. The white precipitate formed was filtered off and the solvent was evaporated. The TLC pure crude residue was used immediately for subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) 7.84 (s, 1H), δ 7.22–7.12 (m, 1H), 6.78–6.65 (m, 3H), 5.73 (br s, 3H), 3.84 (s, 3H), 3.58 (s, 2H). MS (EI, 70 eV) *m*/*z*: 235.
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18. The reaction vessel was constantly irradiated at 300 W for 5 min total. The temperature was monitored using the CEM Discover built-in vertically-focused IR temperature sensor. Different reaction conditions such as conventional heating or longer reaction time resulted in lower yields (data not shown).
19. *Preparation of 5-amino- and 7-amino-4-hydroxy-2-naphthoic acids* (**1a** *and* **1b**). A round-bottomed flask containing a magnetic stirring bar and fitted with a reflux condenser was charged with a mixture of **4**, Ac_2O (35 mL) and NaOAc (1.5 equiv). The flask was placed in a CEM Discover Focused Microwave Synthesis and subjected to MW irradiation (power 300 W) for 5 min keeping temperature below 120 °C (air cooling). The crude reaction mixture was evaporated and treated at reflux with HCl 8 N for 5 h. After cooling, the precipitate was collected yielding a pale yellow solid proved to be a 1:2 mixture (NMR determination) of the isomeric amino hydroxyl naphthoic acids hydrochlorides **1a** and **1b** (70% starting from **3**).
20. Compound **1a** (hydrochloride): ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.00 (s, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 1.2$ Hz, 1H), 6.98–6.82 (m, 3H), 6.00 (br s, 2H). Mp >250 °C (dec). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.82; H, 4.45; N, 6.87. MS (+ESI) *m*/*z*: 204; Compound **1b** (hydrochloride): ^{1}H NMR (300 MHz, DMSO-d_6), δ 10.15 (br s, 1H), 7.90 (d, $J = 1.2$ Hz, 1H), 7.57 (dd, $J = 7.8$ Hz, $J = 7.8$ Hz, 1H), 7.58–6.92 (m, 3H), 5.80 (br s, 2H). Mp >250 °C (dec). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.92; H, 4.45; N, 6.88. MS (+ESI) *m*/*z*: 204.
21. *Preparation of ethyl 7-amino-4-hydroxynaphthalene-2-carboxylate* (**5a**) *and ethyl 2,3-dihydro-2-oxonaphtho[1,8-de]-[1,3]oxazine-8-carboxylate* (**6**). Triethylamine (0.626 mL, 4.50 mmol) was added to a solution of esters **5a** and **5b** (1.30 g, 5.62 mmol) in THF (100 mL) stirred at 0 °C. A solution of carbonyldiimidazole (0.730 g, 4.50 mmol) in THF (30 mL) was then added dropwise and the mixture was kept stirring at 0 °C for 3 h. After quenching with water, the mixture was evaporated and the resulting oil was taken up with HCl 1 N (50 mL) and extracted with chloroform (3×20 mL). The combined organic layers were washed with HCl 1 N (2×10 mL) and with brine, then dried and evaporated to furnish compound **6** (0.795 g, 55%) as a white solid: mp >250 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (br s, 1H), 8.25 (d, $J = 1.2$ Hz, 1H), 7.56 (d, $J = 1.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.45 (dd, $J = 8.4$ and 7.2 Hz, 1H), 6.76 (d, $J = 7.2$ Hz, 1H), 4.44 (q, $J = 7.3$ Hz, 2H), 1.34 (t, $J = 7.3$ Hz, 3H). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.24; H, 4.32; N, 5.43. MS (EI, 70 eV) *m*/*z*: 257. The combined aqueous phases were basified with Na_2CO_3 and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried and evaporated to recover unreacted compound **5a** (0.430 g, 33%) which was used immediately for subsequent reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 1.2$ Hz, 1H), 7.18 (d, $J = 1.2$ Hz, 1H), 7.02–6.96 (m, 2H), 5.50 (br s, 2H), 4.40 (q, $J = 7.3$ Hz, 2H), 1.41 (t, $J = 7.3$ Hz, 3H). MS (EI, 70 eV) *m*/*z*: 231.
22. Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J = 1.2$ Hz, 1H), 7.46 (dd, $J = 8.0$ and 1.2 Hz, 1H), 7.37 (d, $J = 1.2$ Hz, 1H), 7.29 (dd, $J = 8.0$ and 7.8 Hz, 1H), 6.91 (dd, $J = 7.8$ and 1.2 Hz, 1H), 5.50 (br s, 2H), 4.38 (q, $J = 7.3$ Hz, 2H), 1.39 (t, $J = 7.3$ Hz, 3H). MS (EI, 70 eV *m*/*z*: 231.