An Efficient Synthesis of 6-Hydroxyanthranilic Acid via Ortho-Directed Metalation

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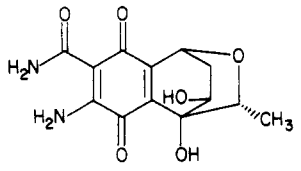
In conjunction with our studies to identify possible intermediates in the biosynthetic pathway leading to sarubicin A,[2] **1**, an antibiotic produced by *Streptomyces helicus*, we were in need of 6-hydroxyanthranilic acid (**2**) and its ^{13}C-labeled carboxyl analogue. Several methods for



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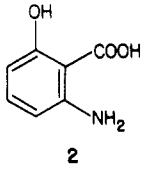
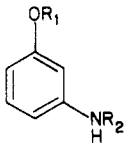


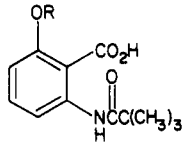
2

the synthesis of **2** have been reported,[3] but they suffer from poor to modest overall yields and lack the adaptability for introduction of a ^{13}C label. Therefore, we now report a new higher yielding method of preparing **2** that includes the capability of utilizing $^{13}CO_2$ to prepare ^{13}C-carboxyl-labeled 6-hydroxyanthranilic acid.

Our initial synthesis of **2** began with the ortho-directed metalation of dimethyl propionanilide **3**.[4] Lithiation (*n*-BuLi, THF, ~0 °C) followed by quenching (CO_2) afforded methoxy acid **4** (75%). However, attempts to cleave the methyl ether of **4** proved quite troublesome. Reaction of **4** with HI,[5] trimethylsilyl iodide,[6] BBr_3,[7] $NaCN/Me_2SO$,[8] or $AlCl_3/CH_3CN$[9] gave tars, decarboxylated products, and/or unreacted starting material. Demethylation and subsequent pivalamide hydrolysis was eventually achieved by treatment of **4** with $AlCl_3$/ethanethiol[10] followed immediately by HCl/AcOH (3:2) at 45 °C to yield **2** (30%) as the hydrochloride salt (23% from **3**).



3, R_1=CH_3; R_2=$COC(CH_3)_3$
5, R_1=R_2=H
6, R_1=H; R_2=$COC(CH_3)_3$
7, R_1=CH_2OCH_3; R_2=$COC(CH_3)_3$



4, R=CH_3
8, R=H

Due to the problem encountered with demethylation of **4**, a more efficient synthesis was designed starting with 3-aminophenol (**5**). This involved transforming **5** ($NaHCO_3$, $(CH_3)_3COCl$) into pivalamide **6**[11] (95%) which upon reaction with chloromethyl methyl ether gave the MOM-protected pivaloylanilide **7** (82%). Lithiation of **7** (*n*-BuLi, THF, 0 °C), quenching (CO_2), and acidic workup afforded hydroxy acid **8** (97%). Removal of the pivaloyl protecting group of **8** (HCl/AcOH/48 °C) yielded **2** (72%) as a crystalline hydrochloride salt (55% from **5**).

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. UV spectra were taken on a IBM 9420 UV/vis spectrophotometer. IR spectra were recorded on a Perkin-Elmer 727B infrared spectrophotometer. ^1H NMR spectra were determined on a Varian FT-80A instrument using Me_4Si (δ 0.0) as an internal standard. ^{13}C NMR spectra were determined on either the Varian FT-80A spectrometer (20.00 MHz) or on a Bruker AM 400 spectrometer (100.61 MHz). Mass spectra were obtained on a Varian MAT CH7 spectrometer with a System Industries 150 data system. All solvents were distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Precoated silica gel 60 F_{254} (E. Merck) glass supported plates were used for the purposes of analytical (0.25 mm) and preparative (2 mm) thin layer chromatography. Elemental analyses were performed by MicAnal, Organic Microanalysis, Tucson, AZ.

2′-Carboxy-3′-methoxy-2,2-dimethylpropionanilide (4). To a solution of pivalamide **3**[4] (3.082 g, 14.89 mmol) in 75 mL of dry THF under an argon atmosphere at 0 °C was added dropwise 14.2 mL (2.3 M in hexane, 32.7 mmol) of *n*-butyllithium, and the reaction was stirred at 0 °C for 2 h. Carbon dioxide was then bubbled for 1 h through the yellow solution. The resulting mixture containing a yellow precipitate was diluted with chloroform and extracted with 5% aqueous NaOH. The aqueous layers were combined, acidified to pH 1 (HCl), and extracted with three portions of chloroform. Combining the organic layers, drying ($MgSO_4$), removal of solvent at aspirator pressure, and crystallization (MeOH–H_2O) afforded 2.794 g (74.8%) of **4** as colorless plates: mp 114–115 °C; IR ($CHCl_3$) 3650–3600, 2970, 1715, 1695, 1610, 1590, 1470, 1380, 1280, 1160, 1070, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 9 H), 4.09 (s, 3 H), 6.76 (dd, 1 H, J = 8.4 and 0.9 Hz), 7.47 (t, 1 H, J = 8 Hz[12]), 8.54 (dd, 1 H, J = 8.6 and 1.0 Hz), 11.15 (br s, 1 H), 11.97 (br s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) 27.5, 40.6, 57.3, 104.1, 105.6, 114.8, 134.9, 144.2, 158.8, 168.5, 178.3; MS (70 eV), m/z (relative intensity) 251 (M^+, 24), 194 (20), 176 (42), 149 (100), 61 (28), 57 (51); UV (MeOH) 221 nm (ϵ 27 873), 250 (ϵ 9432). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 61.83; H, 6.69; N, 5.92.

3′-Hydroxy-2,2-dimethylpropionanilide (6). To a heterogeneous solution of 3-aminophenol (**5**) (3.982 g, 36.53 mmol), sodium bicarbonate (9.20 g, 109.5 mmol), ethyl acetate (125 mL), and water (150 mL) was added trimethylacetyl chloride (4.72 mL, d 0.979, 38.35 mmol). The two-phased system was stirred for 2 h and then the organic phase was separated, washed (1 N HCl, water, brine), dried (Na_2SO_4), and concentrated at reduced pressure. Crystallization of the residue (dichloromethane–hexane) afforded 6.729 g (95.4%) of **6**[11] as colorless plates: mp 144–145 °C; IR ($CHCl_3$) 3650–3000, 3470, 2960, 1660, 1605, 1520, 1440, 1270, 1140 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 1.27 (s, 9 H), 6.54 (m, 1 H), 7.06 (m, 2 H), 7.39 (m, 1 H), 8.26 (s, 1 H), 8.40 (br s, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) 27.1, 39.1, 107.4, 110.1, 110.9, 128.8, 140.3, 157.3, 176.2; UV (MeOH) 211 nm (ϵ 29 571), 243 (ϵ 10 895).

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(12) At 79.54-MHz field strength, accurate coupling constants of this slightly broad triplet could not be obtained.

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3′-[(Methoxymethyl)oxy]-2,2-dimethylpropionanilide (7). To a mixture of sodium hydride (0.419 g, 17.46 mmol) and 50 mL of dry THF under nitrogen at 0 °C was added phenol **6** (3.067 g, 15.89 mmol). After stirring at 0 °C for 3 h, chloromethyl methyl ether (1.35 mL, 17.78 mmol) was added, and the reaction was allowed to come to room temperature overnight. The solution containing precipitated NaCl was diluted with ether, washed (5% aqueous NaOH, water, brine), and dried (Na_2SO_4), and the solvent was removed at aspirator pressure. Crystallization of the residue (dichloromethane–hexane) yielded 3.092 g (82.1%) of **7** as colorless needles: mp 70–71 °C; IR ($CHCl_3$) 3470, 2960, 1680, 1600, 1520, 1480, 1420, 1140, 1060, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 9 H), 3.47 (s, 3 H), 5.16 (s, 2 H), 6.76 (m, 1 H), 7.23 (m, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 27.4, 39.5, 55.8, 94.3, 108.1, 112.0, 113.4, 129.5, 139.2, 157.6, 176.5 ppm; MS (70 eV), *m/z* (relative intensity) 237 (M^+, 87), 205 (11), 153 (13), 121 (18), 61 (17), 57 (97), 45 (100); UV (MeOH) 209 nm (ϵ 30 283), 243 (ϵ 11 465). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.82; H, 8.02; N, 5.91. Found: C, 65.82; H, 8.20; N, 5.74.

2′-Carboxy-3′-hydroxy-2,2-dimethylpropionanilide (8). To a solution of **7** (1.519 g, 6.41 mmol) in 75 mL of dry THF at 0 °C under nitrogen was added dropwise 5.3 mL (2.6 M in hexane, 13.8 mmol) of *n*-butyllithium. After the mixture was stirred for 2 h, carbon dioxide was bubbled continuously through the mixture for an additional 2 h. The resulting yellow solution was diluted with ethyl acetate and extracted with two portions of 5% aqueous NaOH. The aqueous layers were combined, acidified to pH 1 (HCl), and extracted twice with ethyl acetate. Combining the organic extracts, washing (H_2O and brine), drying (Na_2SO_4), and concentrating in vacuo gave 1.478 g (97.3%) of **8** as a synthetically pure red-brown oil which crystallized slowly upon standing. A small sample was subjected to preparative TLC on silica gel (10% methanol–ethyl acetate) to afford a clear oil (R_f 0.28–0.41). Crystallization (dichloromethane–hexane) gave colorless crystals: mp 208–209 °C dec; IR (Nujol) 3650–2600, 1675, 1590, 1540, 1290, 1240, 1160, 910 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 1.25 (s, 9 H), 6.45 (dd, 1 H, J = 8.2 and 1.2 Hz), 7.09 (t, 1 H, J = 8.2 Hz), 8.13 (dd, 1 H, J = 8.2 and 1.2 Hz), 10.03 (br s, 2 H), 12.88 (s, 1 H); ^{13}C NMR (20 MHz, $(CD_3)_2CO$) 28.1, 40.7, 106.9, 109.4, 111.3, 132.2, 143.6, 164.3, 177.1, 177.6 ppm; MS (70 eV), *m/z* (relative intensity) 193 ($M^+ - CO_2$, 21), 109 (81), 80 (16), 57 (100), 41 (35); UV (MeOH) 222 nm (ϵ 24 179), 261 (ϵ 8831). Combustion analysis was performed on the dimethyl derivative, 2′-(carboxymethyl)-3′-methoxy-2,2-dimethylpropionanilide, obtained from the acid by treatment with diazomethane: mp 72.5–74 °C. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.40; H, 7.17; N, 5.28. Found: C, 63.47; H, 7.31; N, 5.32.

6-Hydroxyanthranilic Acid (2) Hydrochloride. A. From 4. To a solution of 10 mL of ethanethiol at 0 °C under nitrogen was added sequentially aluminum chloride (0.654 g, 49.2 mmol) and **4** (0.988 g, 3.94 mmol). An immediate precipitate developed and the mixture was diluted with an additional 15 mL of ethanethiol. The mixture was stirred at room temperature for 1.5 h, poured into 5% aqueous HCl, and stirred an additional 20 min. Extracting with three 75-mL portions of dichloromethane, combining the organic extracts, drying (Na_2SO_4), and concentrating at aspirator pressure gave a brown residue. The oil was added to a solution consisting of 6 N HCl (12 mL) and acetic acid (8 mL), heated at 45 °C for 16 h, cooled, and filtered (suction) to yield 0.244 g (30.0%) of **2** as the hydrochloride salt.

B. From 8. To a 24-mL solution of 6 N HCl–acetic acid (1:1) was added **8** (1.454 g, 6.14 mmol). The reaction mixture was stirred at 48 °C for 96 h. It was then cooled to 0 °C, and the resulting crystalline precipitate was collected via vacuum filtration to afford 0.842 g (72.4%) of **2** as a colorless hydrochloride salt, mp 214–216 °C dec [lit.[3] 216 °C dec]; analytical TLC (25% methanol–ethyl acetate) gave one spot at R_f 0.29; IR (KBr) 3350–2200, 1675, 1630, 1560, 1440, 1180, 1130, 1100, 1080, 780 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 6.73 (dd, 1 H, J = 8.2 and 1.1 Hz), 6.87 (dd, 1 H, J = 8.1 and 1.2 Hz), 7.38 (t, 1 H, J = 8 Hz[12]), 10.91 (br s, 5 H); ^{13}C NMR (20 MHz, $(CD_3)_2SO$) 105.7, 112.4, 134.3, 139.0, 161.6, 170.6, 180.2 ppm; UV (MeOH) 203 nm (ϵ 22 601), 234 (ϵ 13 907).

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Registry No. 1, 75533-14-1; 2·HCl, 94596-96-0; 3, 56619-93-3; 4, 94596-97-1; 5, 591-27-5; 6, 75151-82-5; 7, 94596-98-2; 8, 94596-99-3.

Synthesis of Acyclic, Cis Olefinic Pheromones by Way of Nickel-Catalyzed Grignard Reactions

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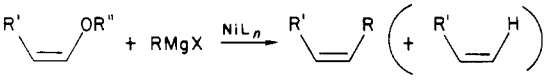
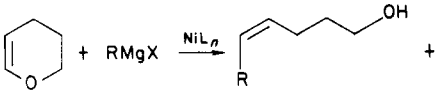
The recent discovery of an olefin synthesis based on the low-valent, nickel-mediated reactions of Grignard reagents with enol ethers and its application to the preparation of *cis*-olefins (eq 1)[3] suggested the use of this new reaction

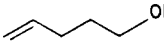


(1)

in the field of pheromone synthesis. The reaction appeared to be especially well suited for the construction of acyclic, cis alkenic pheromones, a large group of natural substances the introduction of whose double bonds had been carried out in the past mostly by Wittig reactions or partial hydrogenations of acetylenes.[4] To illustrate its potential, the olefin synthesis scheme was focused on the use of dihydropyran (1), an inexpensive, readily available enol ether, as general starting material[5] and the interaction of the latter with an array of Grignard reagents (eq 2). Several of the resultant olefinic alcohols **2** then were to be converted into pheromones of several structure types.



a, R = Me
b, R = Et
c, R = *n*-Pr
d, R = *n*-Bu
e, R = *n*-Pent
f, R = *n*-Hex
g, R = *n*-Oct



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In an earlier report[3] the reaction of dihydropyran (1) with methylmagnesium bromide in the presence of [1,3-bis(diphenylphosphino)propane]nickel dichloride ((dppp)$NiCl_2$) has been shown to yield (*Z*)-4-hexen-1-ol (**2a**) and a similar reaction with ethylmagnesium bromide had led to a ca. 5:1 mixture of (*Z*)-4-hepten-1-ol (**2b**) and 4-penten-1-ol (**3**). This alkylation–reduction ratio now dropped to ca. 1:1 on exposure of dihydropyran (1) to the

(1) Conselho Nacional de Pesquisas (Brazil) fellowship holder, 1980–1984.
(2) Postdoctoral fellow, 1983, supported by NATO (Grant RG 094.81) and the Consiglio Nazionale delle Ricerche (Italy).
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(5) For the use of 2,3-dihydrofuran in the same type of reaction leading to two pheromones, see ref 3b.

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