Joseph M. Muchowski* and Michael L. Maddox

Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304, U.S.A.

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Dedicated to the memory of Dr. Raymundo Cruz Almanza, a distinguished organic chemist, a true patriot, and a steadfast friend.

Abstract. Ethyl acetate solutions of o-hydroxylaminobenzaldehydes (1a, 8c, 8d) can be generated by reduction of the corresponding nitro compounds with zinc and ammonium chloride in a two phase ethyl acetate-water system at room temperature, but 2-nitro-3,6-dimethoxybenzaldehyde (4b) is converted into the anthranil 11 under these conditions. The N-acylated compounds derived from 1a and 8c exist exclusively as the cyclic tautomers (6a-c and 9a) in solution and in the solid state, whereas the N-acetyl compound 9b is in equilibrium with the open chain form 10 in solution, but only the cyclic form is present in the solid state. The N-acetylo-hydroxylaminobenzaldehydes undergo a novel internal redox reaction on thermolysis generating o-acetyloaminoenzoic acids which are converted into 2-substituted-4H-3,1-benzoxazin-4-ones (e.g., 6b→12b→13b) to a greater or lesser extent under the reaction conditions. Keywords: O-hydroxyminobenzaldehydes, reduction, anthranil, N-acyl, benzoxazinones.

Introduction

o-Hydroxylaminobenzaldehydes and/or the N-acylated derivatives thereof were required as intermediates for another study. Pure o-Hydroxylaminobenzaldehyde (1a, Scheme 1) itself has never been isolated, but its existence as an intermediate during the reduction of o-nitrobenzaldehyde (1b) to anthranil (2) [1] or to the so-called agnotobenzaldehyde (3) [2], the precise structure of which is not known [3], is secure. Furthermore, the presence of 1a in solution during controlled potential reduction of 1b is well documented [4]. The only other o-hydroxylaminobenzaldehyde derivative for which data exists in the literature is the dimethoxy compound 4a, which remarkably was reported [5] to be a stable, crystalline, solid generated by the catalytic reduction of the corresponding nitro compound 4b.

The N-acetyl derivative 5 is the sole N-acetylo-hydroxylaminobenzaldehyde described to date. This compound was first obtained by Bamberger [2] as one of the products of the acetylation of agnotobenzaldehyde with acetic anhydride, and was subsequently shown by Bakke and Engan [3] to exist in the cyclic form 6a.

Results and Discussion

Given the fragile nature of o-hydroxylaminobenzaldehyde, it was assumed that all congeners of this compound would have a similar lack of stability, the reported [5] robust nature of 4a notwithstanding. Therefore, a very mild procedure for the reduction of aryl nitro compounds to arylhydroxylamines was devised using nitrobenzene (7a, Scheme 2) as a model system. The process was based on the use of the well known zinc/ammonium chloride combination for the reduction of aromatic nitro compounds to hydroxylamines [6], except that the reaction was effected at room temperature in a two phase ethyl acetate-water system. Under these conditions overreduction to aniline was minimized and pure phenylhydroxylamine (7b, Scheme 2) was isolated in at least 75 % yield, after a reaction time of ca 5 h. When these conditions were applied to o-nitrobenzaldehyde, TLC (thin layer chromatography) showed that the nitro compound disappeared rapidly (< 2 h) and was replaced by a major, more polar material. Rapid removal of the solvent from an aliquot of the organic phase in vacuo below room temperature, and immediate measurement of the NMR spectrum of the residue, showed that a mixture contain-
Hydroxylaminobenzaldehydes and the N-Acylated Derivatives Thereof

1a, R = NHOOH
1b, R = NO₂
1c, R = NH₂

2

3

4a, R = NHOOH
4b, R = NO₂
4c, R = NH₂
4d, R = H

5

6a, R = Me
6b, R = Ph
6c, R = OCH₂Ph

Scheme 1

7a, R = NO₂
7b, R = NHOOH

8a, R¹ = NO₂, R² = H, R³ = Cl
8b, R¹ = NO₂, R² = MeO, R³ = H
8c, R¹ = NHOOH, R² = H, R³ = Cl
8d, R¹ = NHOOH, R² = MeO, R³ = H

9a, R¹ = H, R² = Cl
9b, R¹ = MeO, R² = H

Scheme 2

Although the utilization of 1a as such for synthetic purposes was not practical, the ethyl acetate solutions thereof functioned reasonably well in this respect. For example, N-acylation could be effected with acyl halides in the presence of aqueous sodium bicarbonate at ca – 5 °C [7]. The N-acetyl (6a), N-benzoyl (6b), and N-benzoxycarbonyl (6c) derivatives were prepared in this way in 52 %, 45-53 %, and 21 % yields, respectively. As judged from the NMR and IR spectra, these compounds exist in the cyclic forms 6a-c to an extent of at least 95 % both in solution (DMSO) and in the solid state. This methodology could also be used to prepare the N-acetyl compounds 9a and 9b from the nitro compounds 8a and 8b.
Whereas 9a also exists predominantly in the cyclic form (\( \geq 95 \% \)) in solution and in the solid state, the \(^1\)H NMR (DMSO) spectrum of the dimethoxy compound 9b shows that it is a 2:3 mixture of the cyclic and open chain forms 9b and 10, respectively. Both forms are also clearly recognizable in the \(^{13}\)C NMR spectrum (see experimental section). In CD\(_2\)CN solution, equal amounts of the two forms are present at room temperature, but the aldehyde form is favored over the cyclic form (3:2) at 330 °K. As judged by the absence of an aldehyde carbonyl stretching band in the IR spectrum, this substance exists totally as the cyclic tautomer in the solid state.

The generation of the putative hydroxylamino compound 4a was investigated next. This substance is reported to be a stable crystalline solid, mp 87 ºC, which was isolated by column chromatography on silica gel, and was converted into the amine 4c on catalytic reduction. All of the reported spectroscopic data are consistent with that expected for 4a, except that the aldehyde CH is found at δ 9.09 in the NMR spectrum. This is > 1 δ upfield of the chemical shift for the vast majority of aldehydes (δ 10-10.5). Reduction of the nitro compound 4b with the zinc/ammonium chloride system gave a solution which by TLC, contained a little of the amino compound 4c and a major amount of a more polar material. Separation of this mixture by column chromatography on silica gel gave the aldehyde 4c (20 %) and a stable crystalline compound, mp 91.5-93 º C (ca 70 %). Both the crystalline material, and the ethyl acetal solution of the crude reduction mixture were completely inert to acylation with acetyl chloride under conditions which were successful for the synthesis of 6a-c, 9a, and 9b. The \(^1\)H NMR spectrum of the pure material precisely matched that reported by Blanco, et. al. [5] except for a broad absorption at δ 5.40, which was not found in the material described in this work. Furthermore, the \(^{13}\)C NMR spectrum also matched well with that described, but the reported absorption for the aldehyde carbon (δ 191.73) was not observed in our material. An absorption at δ 152.58, not reported by Blanco, et. al. was, however, present in the material described herein. All of the spectroscopic and chemical properties of this crystalline compound are consistent with the antranil structure 11. The δ 9.09 absorption is assignable to H-3, and is found in all of the 3-unsubstituted antranils (δ 8.8-9.2) that we and others [8] have studied. In addition, the δ 152.58 absorption is due to C-3 and is also present in the \(^{13}\)C spectra of the 3-unsubstituted antranil derivatives (δ 152.0-155.2) that we and Kim, et. al. [8] have examined. In addition, the 1650 cm\(^{-1}\) IR band which Blanco, et. al. [5] assigned to the aldehyde carbonyl stretching absorption of 4a, is present in 3-unsubstituted antranils (1655-1635 cm\(^{-1}\)). Finally, Fernández, et. al. [9] reported that the antranil 11, was obtained as an intermediate on catalytic reduction of 4b to the amine 4c. The data (IR, \(^1\)H NMR) which they list, match ours closely, although their melting point (62-64 ºC) differs considerably from what we and Blanco, et. al. [5] observed.

During the course of determining the melting points of the N-acylated o-hydroxylaminobenz-aldehydes, it was observed that these substances melted with decomposition, and in all cases the so-produced melt resolidified giving a material with a very different melting point. A preparative scale thermal decomposition of the N-benzoyl compound 6b at its melting point (132 ºC) gave a less polar, crystalline solid, mp 121-122 ºC (68 % yield) which clearly was not antranil. The IR spectrum possessed an intense band at 1765 cm\(^{-1}\), and the mass spectrum showed that the new compound differed from 6b by 18 mass units. These data were uniquely consistent with those expected [10] for the benzoazinonine 13b (Scheme 3), which was confirmed by direct comparison with an authentic specimen. The formation of 13b from 6b is suggested to take place by an internal redox process to give N-benzoxylanthranilic acid 12b as an intermediate, which then under goes intramolecular dehydration (Scheme 3). The thermal dehydration of N-benzoxylanthranilic acid 12b to 13b is a well recognized phenomenon [11]. The above redox dehydration sequence on 6b could also be effected, although much more slowly, in boiling m-xylene, in which case both the benzoazinonine 13b and a small amount of the anthranilic acid 12b (8 %) were obtained. The N-acetyl compound 6a similarly underwent the above sequence of reactions in m-xylene to give N-acetylanthranilic acid 12a and the expected benzoazinonine 13a in ca 21 % and 65 % yields, respectively. Furthermore, 12a was converted into 13a under these conditions. The thermolysis of 9a and 9b was examined only in a cursory manner. When heated neat at its melting point, the chloro compound 9a was converted into the anthranilic acid derivative 14a (38 %), and a small amount of the antranil 15a, but none of the benzoazinozine 16a was formed. Thermolysis of 9b in the same way gave the anthranilic acid 14b (22 %), the benzoazinonine 16b (45 %), but none of the antranil 15b.

The first, and to date only, reported example of the above interesting internal redox process was described by Bamberger [2] who obtained N-acetylanthranilic acid 12a in 55 % yield upon brief heating of 6a slightly above its melting point. He did not, however, observe the intramolecular dehydration of 12a to the benzoazinonine 13a.

A few comments regarding the synthesis of 2-nitro-3,6-dimethoxybenzaldehyde (4b), the precursor of antranil 11, are in order. This compound was first prepared by Rubenstein [12], by the nitration of 2,5-dimethoxybenzaldehyde (4d) with concentrated nitric acid (0 ºC - room temp.). This nitration (room temp.) was repeated by Blanco, et. al. [13, 14]), was said to be difficult to reproduce, not easily scaled up, and was reported to give a 2.5 : 1 mixture of 4b and the isometric nitro compound 17 (Scheme 4, Table 1, Entry 1). They also describe conditions for this nitration in acetic acid-ether solution, which are said to be free of the above problems, and provided a 2:1 mixture of 4b and 17 (Entry 2). Thummel, et. al. [15] disclosed conditions for the nitration of 4d using nitric acid supported on silica gel in dichloromethane solution at room temperature, under ultrasonic irradiation, which generated a mixture in which 4b was favored over 17 by a factor of 4.3 (\( > 95 % \) yield; Entry 3). In our hands, none of these procedures gave precisely the results reported. The nitration in acetic acid-ether solution had a long induction period (24 h),...
Table 1. Nitration of 2,5-Dimethoxybenzaldehyde (4d).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitration method</th>
<th>Temp.</th>
<th>% 4b</th>
<th>% 17</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>conc. HNO₃</td>
<td>r.t.</td>
<td>64</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>HNO₃ - Ether - HOAc</td>
<td>r.t.</td>
<td>60</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>HNO₃ on SiO₂ in CH₂Cl₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>r.t.</td>
<td>78</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>HNO₃ - Ether - HOAc</td>
<td>r.t.</td>
<td>40</td>
<td>26</td>
<td>This work</td>
</tr>
<tr>
<td>5</td>
<td>Add 4d in CH₂Cl₂ to HNO₃ on SiO₂</td>
<td>r.t.</td>
<td>37</td>
<td>25</td>
<td>This work</td>
</tr>
<tr>
<td>6</td>
<td>Add HNO₃ on SiO₂ to 4d in CH₂Cl₂</td>
<td>r.t.</td>
<td>49</td>
<td>27</td>
<td>This work</td>
</tr>
<tr>
<td>7</td>
<td>conc. HNO₃</td>
<td>3-8 °C</td>
<td>67</td>
<td>11</td>
<td>This work</td>
</tr>
</tbody>
</table>

<sup>a</sup>Sonication.
then required a further 24 h for completion, and generated a 1.5:1 mixture of 4b and 17 (Entry 4). When nitric acid on silica gel was used, both the reaction rate and the product distribution were dependant on the addition order. Addition of 2,5-dimethoxybenzaldehyde in a small volume of dichloromethane (4 mL/g) to the supported nitrating reagent (20 g/g 4d), and subsequent mechanical agitation, resulted in completion of the reaction in < 10 min, and favored 4b over 17 by a factor of 1.5 (Entry 5). Addition of the supported nitrating agent to a dichloromethane solution of 4d (40 mL/g), resulted in a slow reaction (8 h), which was not accelerated by ultra sound, and gave a 1.8:1 mixture of 4b and 17 (Entry 6). Nitration in concentrated nitric acid at room temperature, as described by Blanco, et al. [13] was complicated by the formation of polynitrination products such as 18. In contrast, when this nitration was effected at ice-bath temperature, the reaction was essentially complete in 10 min, gave a 6:1 mixture of 4b and 17 from which 4b could be isolated in nearly 70 % yield (Entry 7). This is an easily reproducible, and rapid method for the generation of substantial quantities of 4b.

**Experimental**

For general procedures, see reference 16. The 1H NMR spectra were measured at 300 MHz. Column chromatographic separations were effected using 230-400 mesh silica gel. The columns were packed dry, successively layered with the crude reaction mixture (absorbed onto silica gel), and a small amount of sand, and then eluted with the appropriate solvent system. The mixtures absorbed on silica gel were prepared by dissolving the reaction mixture in dichloromethane, adding the solution to silica gel, and then removing the solvent in vacuo. Commercial 2-nitro-4,5-dimethoxybenzaldehyde (8b) contains 10-20% of 1,2-dinitro-4,5-dimethoxybenzene (19) which cannot be readily removed by crystallization or by column chromatography. Pure 8b, is readily obtained, however, by vigorously stirring a dichloromethane solution of the mixture with aqueous sodium bisulfite (2 equiv) for 3-4 h. The pure aldehyde is recovered from the aqueous phase, by the addition of excess sodium carbonate, extraction with dichloromethane and crystallization of the crude product from ethanol. About 85 % of the pure aldehyde is recovered in this way.

2-Nitro-3,6-dimethoxybenzaldehyde (4b). Finely ground 2,5-dimethoxybenzaldehyde (4d, 1.0 g, 6.02 mmol) was added in one portion to concentrated nitric acid (12 mL) cooled in an ice bath. The reaction temperature rose from 3 ºC to 8 ºC (Larger scale reactions required portionwise addition to prevent the temperature from exceeding 10 ºC), the aldehyde dissolved, and almost immediately a yellow solid began to separate from solution. The starting material was no longer detectable by TLC after 10 min, and the mixture was poured onto crushed ice. The mixture was extracted with dichloromethane, the extract was washed to neutrality with water, dried, and the solvent was removed in vacuo. The usual yellow solid (1.18 g) was absorbed onto silica gel (6 g) and purified by column (4.2 x 18 cm) chromatography on silica gel (120 g) using ethyl acetate-hexane (25:75; 25 mL fractions) as the eluant. Fractions 1 and 2 contained the 4-nitro compound 17 (0.235 g), and fractions 9-26 contained 4b (0.857 g, 67.4 %), mp 165-167 ºC, reptd. [15] mp 163-165 ºC. Crystallization of the crude 4-nitro compound from ethanol gave pure material (0.145 g, 11.4 %) mp 170-171 ºC, reptd. [15] mp 157-161 ºC.

Phenyldihydroxylamine (7b). A mixture of nitrobenzene (2.46 g, 20 mmol), zinc powder (4.82 g, 75.3 mmol), ammonium chloride (6.72 g, 125.6 mmol), water (120 mL), and ethyl acetate (200 mL) was vigorously stirred at room temperature for 5 h. The organic phase was separated, the aqueous phase was saturated with NaCl, and extracted with ethyl acetate. The organic phases were combined, washed with saturated NaCl solution, and dried over Na2SO4. The crude product was slurried with hexane, purified with a glass rod, and cooled in the refrigerator. Phenyldihydroxylamine (1.71 g, 78.3 %) was obtained as a white, needle shaped, crystalline solid, mp 81-83 ºC, reptd. [17] mp 80-81 ºC.

**Synthesis of o-hydroxyaminobenzaldehyde (1a).** A mixture of o-nitrobenzaldehyde (1b) (1.51 g, 10 mmol), zinc powder (2.46 g, 37.6 mmol), ammonium chloride (3.36 g, 62.8 mmol), water (60 mL), and ethyl acetate (100 mL), was stirred vigorously at room temperature for 1.5 h. The organic phase was separated, combined with an ethyl acetate extract of the aqueous phase, the extract was washed with saturated NaCl solution, and dried. Ethyl acetate solutions of the hydroxylaminobenzaldehyd compound can be kept at 5 ºC for several days without significant decomposition. An aliquot of this solution was rapidly evaporated in vacuo below room temperature and the NMR spectral measurements were made immediately. Integration of the appropriate resonances showed that the mixture consisted of 1a (65.5 %), o-nitrobenzaldehyde (1b, 7 %), 2-aminobenzaldehyde (1c, 5.5 %), and anthranil (2, 21.5 %). 2-Hydroxylaminobenzaldehyde had the following NMR spectral data. 1H NMR (CDCl3) δ 6.98 (td, 1H, J = 7.4, 1.1 Hz), 7.35 (d, 1H, J = 7.4 Hz), 7.53 (td, 1H), 7.60 (dd, 1H, J = 7.7, 1.5 Hz), 9.74 (bs, 1H, exchanged with D2O), 9.83 (s, 1H); 13C NMR (CDCl3) δ 113.54, 119.39, 124.81, 135.80, 136.13, 152.65, 194.25.

2-Hydroxyaminobenzaldehyde (8c) and 2-hydroxyaminobenzaldehyde (8d). Ethyl acetate solutions of these compounds were prepared from the corresponding nitro compounds 8a and 8b in exactly the same manner as described for the synthesis of 1a, except that the reduction required 3-4 h to reach completion. These solutions were used immediately to prepare the N-acetyl compounds.

N-Acetylation of the o-hydroxyaminobenzaldehydes. Synthesis of the N-acetyl compound 6a. o-Nitrobenzaldehyde was reduced on a 20 mmol scale as
described above. The ethyl acetate solution was cooled in an ice-salt bath and a solution of NaHCO₃ (18 mmol) in water (20 mL) was added with vigorous stirring. When the aqueous phase had frozen, a solution of acetyl chloride (1.0 mL, 110 g, 14.06 mmol) in ethyl acetate (25 mL) was added over a 5 min period. The mixture was then stirred at ice-bath temperature for 1 h and at room temperature for 1 h. The organic phase was separated, and combined with an ethyl acetate extract of the aqueous phase. The ethyl acetate solution was washed with saturated NaCl solution, dried, and the solvent was removed in vacuo to give a semi-solid residue (2.71 g). This was dissolved in hot ethyl acetate (5 mL), diluted with hexane (5 mL) and seeded. A solid (0.957 g, mp 120-122 °C, dec), which gave a strong positive test with 1% methanolic ferric chloride solution [18], was obtained. The mother liquor was evaporated and the residue (1.75 g) was absorbed onto silica gel (30; 50 mL fractions). Fractions 6-8 contained anthranil (0.515 g), and the desired product (0.236 g) was found in fractions 40-50 °C. Crystallization of this material from 1:1 ethyl acetate-hexane gave a further 0.167 g of the product, mp 122-123 °C, dec [yield, 1.124 g, 52.3% (based on an assumed 60% yield (12 mmol) of the hydroxylamino compound 1a]. A specimen of this material on recrystallization and drying in vacuo at 50 °C for 16 h had mp 122.5-124 °C; IR (KBr) 3312, 1641 cm⁻¹; 1H NMR (DMSO, d₆) δ 2.23 (s, 3H), 6.65 (d, 1H, J = 8.1 Hz, singlet after D₂O exchange), 7.49 (td, 1H, J = 7.2, 0.95 Hz), 7.44 (m, 2H), 7.94 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 8.1 Hz, exchanged with D₂O); 13C NMR δ 22.01, 99.24, 113.61, 124.02, 124.92, 129.00, 130.15, 136.74, 166.98. Anal. calcd. for C₇H₆NO₄: C 63.76, H 4.85, N 5.27. The presence of ca 0.07 mol toluene was confirmed by a singlet at δ 2.30 in the NMR spectrum.

Synthesis of the N-benzyloxyacarbonyl compound 6c. The crude product (0.77 g) obtained from a 5 mmol scale reduction of 1b, was absorbed onto silica gel (4 g) and subjected to chromatographic purification on a column (6 x 16.5 cm) of silica gel (232 g) using ethyl acetate-hexane (25:75; 50 mL fractions) as the eluting solvent. The crystalline product (0.174 g, 21.4% yield based on an assumed 60% yield in the reduction) was twice crystallized from toluene to give analytically pure material, mp 143-143.5 °C; IR (KBr) 3418, 1682 cm⁻¹; 1H NMR (DMSO, d₆) δ 5.31 (s, 2H), 6.60 (d, 1H, J = 7.6 Hz, singlet after D₂O exchange), 7.17-7.22 (m, 2H), 7.36-7.48 (m, 7H), 7.73 (d, 1H, J = 7.6 Hz, exchanged with D₂O); 13C NMR δ 67.81, 99.09, 113.08, 124.04, 124.65, 128.59, 128.77, 128.91, 130.16, 136.07, 137.82, 151.93. Anal. calcd. for C₁₅H₁₂NO₄: C 69.70, H 4.60, N 5.81; found: C 69.81, H 4.99, N 5.27.

Synthesis of the N-acetyl chloro compound 9a. The crude, solid acetylation product (1.60 g) obtained from a 10 mmol scale reduction of 8a, was slurried with ethyl acetate and the insoluble material (0.433 g, mp 135-137 °C) was collected by filtration and dried in vacuo. The mother liquor was evaporated in vacuo, and slurried with dichloromethane to give additional product (0.082 g, mp 139-139.5 °C; total yield, 0.485 g; 37.8% based on an assumed 60% yield of 8c). This compound cannot be purified by column chromatography on silica gel; it is converted into the corresponding anthranil 15a. Crystallization from ethyl acetate gave analytically pure material, mp 143-143.5 °C; IR (KBr) 3234, 1640 cm⁻¹; 1H NMR (DMSO, d₆) δ 2.25 (s, 3H), 6.64 (d, 1H, J = 8.1 Hz, singlet after D₂O exchange), 7.26 (dd, 1H, J = 8.0, 0.91 Hz), 7.47 (t, 1H), 7.63 (d, 1H, J = 7.85 Hz), 8.02 (d, 1H, J = 8.1 Hz, exchanged with D₂O); 13C NMR δ 72.01, 98.31, 112.51, 124.97, 126.68, 128.68, 132.25, 136.32, 167.54. Anal. calcd. for C₁₄H₁₁NO₃: C 69.70, H 4.60, N 5.86; found: C 69.70, H 4.96, N 5.49.

Synthesis of the N-acetyl dimethoxy compound 9b. The crude, solid acetylation product (1.97 g) from a 10 mmol scale reduction of 8b was slurried with ethyl acetate and the insoluble material was collected by filtration, dried, and then crystallized from toluene. A solid (0.576 g, 40.1% yield based on an assumed 60% yield of 8d) which gave a deep purple color with methanolic ferric chloride solution, and which had mp 122-122.5 °C was obtained, IR (KBr) 3400, 3206, 1632 cm⁻¹; 1H NMR (DMSO, d₆) δ 2.20 (s, 1.6H), 2.22 (bs, 1.2H), 3.76 (s, 1.2H), 3.79 (s, 1.2H), 3.84 (s, 1.8H), 3.88 (s, 1.8H), 6.57 (d, 0.4H, J = 8.05 Hz, singlet after D₂O exchange), 7.04 (s, 0.4H), 7.07 (s,
303.0957: found: 303.0971. The ethyl acetate solution was evaporated in vacuo to give a solid which was absorbed onto silica gel (4 g) and then subjected to column (6 pound Synthesis of the anthranil 11. A mixture of the nitro compound 4b (1.056 g, 5.0 mmol), ammonium chloride (2.52 g, 47.1 mmol), zinc powder (1.86 g, 28.4 mmol), ethyl acetate (75 mL), and water (30 mL) was stirred vigorously for 3 h, and then worked up as described above. If the usual quantities of zinc powder and ammonium chloride were used, the reduction was inordinately slow. The ethyl acetate solution was evaporated in vacuo to give a solid which was absorbed onto silica gel (4 g) and then subjected to column (6 x 18.5 cm) chromatographic purification on silica gel (259 g) using ethyl acetate hexane (25:75; 50 mL fractions) as the eluant. The product was found in fractions 20-30 contained the anthranil which by TLC (25:75 EtOAc-hexane) showed the presence of the anthranil solid (.093 g) which by TLC (25:75 EtOAc-hexane) showed none of which corresponded to the benzoxazinone. The carbonate phase was brought to pH 1 with 3M HCl, and extracted with ethyl acetate. The extract was washed successively with water and saturated NaCl solution, dried and evaporated in vacuo. Toluenes was added to the solid residue to remove residual acetic acid, and the mixture was evaporated to dryness in vacuo to give 16b. 13C NMR δ 25.75, 21.85, 21.85, 56.09, 56.20, 56.46, 98.25, 99.69, 107.16, 107.85, 109.15, 119.79, 123.89, 130.82, 138.81, 146.77, 146.82, 150.39, 154.41, 166.26, 188.80; MS [EI] m/z calcd for C11H13NO5 + CH3CN + Na: 188.80; MS [EI] m/z (%) 239 [M+] (57), 197 [M - MeCO + H] (15), 180 (43), 179 (43), 164 (79), 149 (42), 136 (52); HR-ES-CH3CN-MS m/z calcd for C11H13NO5 + CH3CN + Na: 239.0945; found: 239.0971. Solution phase thermolysis of the N-acetylated o-hydroxylaminobenzaldehydes. A solution of the N-acetyl compound in m-xylene (10 mL / 0.1 g substrate) was heated at reflux temperature in an argon atmosphere until TLC showed that the starting material was no longer present. The solvent was removed in vacuo and the residue was then worked up as described below for the particular substrate.

N-Acetyl-4,5-dimethoxyanthranilic acid (14b) and 2-methyl-4H-6,7-dimethoxy-3,1-benzoxazin-4-one (16b). The sodium carbonate soluble material from a 1 mmol scale thermolysis of 9b gave the carboxylic acid 14b as a solid (0.053 g, 22.2 %), mp 221-224 °C, repd. [20] mp 223.5-224.5 °C. 1H NMR (DMSO, d6) δ 2.12 (s, 3H), 7.42 (s, 1H), 8.26 (s, 1H), 11.14 (s, 1H, exchanged with D2O), 13.32 (bs, 1H, exchanged with D2O), 13C NMR δ 25.45, 55.88, 55.94, 103.47, 113.14, 137.24, 143.74, 153.49, 168.61, 169.59. The neutral phase on evaporation gave a solid which was crystallized from ethyl acetate to give 16b as an orange colored solid (0.101 g, 45.7 %) mp 182-183 °C, repd. [20] mp 185-186.5 °C. IR (CHCl3) 1738, 1644, 1610 cm⁻¹; 1H NMR (CDCl3) δ 2.45 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (s, 1H), 7.49 (s, 1H); 13C NMR δ 21.65, 55.94, 91.59, 119.79, 123.89, 124.77, 126.27, 130.21, 136.68, 166.42, 169.14.

Solution phase thermolysis of the N-acetylated o-hydroxylaminobenzaldehydes. A solution of the N-acetyl compound in m-xylene (10 mL / 0.1 g substrate) was heated at reflux temperature in an argon atmosphere until TLC showed that the starting material was no longer present. The solvent was removed in vacuo and the residue was then worked up as described below for the particular substrate.

N-Acetyl-4,5-dimethoxyanthranilic acid (14b) and 2-methyl-4H-6,7-dimethoxy-3,1-benzoxazin-4-one (16b). The sodium carbonate soluble material from a 1 mmol scale thermolysis of 9b gave the carboxylic acid 14b as a solid (0.053 g, 22.2 %), mp 221-224 °C, repd. [20] mp 223.5-224.5 °C. 1H NMR (DMSO, d6) δ 2.12 (s, 3H), 7.42 (s, 1H), 8.26 (s, 1H), 11.14 (s, 1H, exchanged with D2O), 13.32 (bs, 1H, exchanged with D2O), 13C NMR δ 25.45, 55.88, 55.94, 103.47, 113.14, 137.24, 143.74, 153.49, 168.61, 169.59. The neutral phase on evaporation gave a solid which was crystallized from ethyl acetate to give 16b as an orange colored solid (0.101 g, 45.7 %) mp 182-183 °C, repd. [20] mp 185-186.5 °C. IR (CHCl3) 1738, 1644, 1610 cm⁻¹; 1H NMR (CDCl3) δ 2.45 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (s, 1H), 7.49 (s, 1H); 13C NMR δ 21.65, 55.94, 56.94, 103.47, 113.14, 137.24, 143.74, 153.49, 168.61, 169.59. The neutral phase on evaporation gave a solid which was crystallized from ethyl acetate to give 16b as an orange colored solid (0.101 g, 45.7 %) mp 182-183 °C, repd. [20] mp 185-186.5 °C. IR (CHCl3) 1738, 1644, 1610 cm⁻¹; 1H NMR (CDCl3) δ 2.45 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 6.96 (s, 1H), 7.49 (s, 1H); 13C NMR δ 21.65, 55.94, 56.84, 107.81, 109.49, 149.89, 156.81, 159.93, 160.04.

Solution phase thermolysis of the N-acetylated o-hydroxylaminobenzaldehydes. A solution of the N-acetyl compound in m-xylene (10 mL / 0.1 g substrate) was heated at reflux temperature in an argon atmosphere until TLC showed that the starting material was no longer present. The solvent was removed in vacuo and the residue was then worked up as described below for the particular substrate.

N-Acetylanthranilic acid (12a) and 2-methyl-4H-3,1-benzoazin-4-one (13a). After 6a was heated 6 h at reflux temperature the crude product was partitioned between ethyl acetate and 10 wt. % sodium carbonate solution. The base soluble and neutral phases gave 12a (21.3 %) and 13a (64.9 %) respectively, both of which were spectroscopically identical to commercial samples. A sample of 12a on heating at reflux temperature for 7 h gave 13a in ca 37 % yield, and a considerable amount of 12a was recovered (63 %).

N-Benzylanthranilic acid (12b) and 2-phenyl-4H-3,1-benzoazin-4-one (13b). The crude solid (0.146 g) from a 0.60 mmol scale thermolysis of 6b was absorbed onto silica gel (0.75 g) and purified by column (2.2 x 16.5 cm) chromatography on silica gel (29.3 g) using ethyl acetate-hexane (20:80; 15 mL fractions) as the eluant. The product was found in fractions 3 and 4 and was crystallized from cyclohexane to give 13b (0.081 g, 60.5 %), mp. 121-123 °C. The crude product
from another reaction was partitioned between ethyl acetate and 10 wt. % sodium carbonate solution. N-Benzoylanthranilic acid (12b, 8.3 %), isolated from the basic phase, was spectroscopically identical to an authentic specimen.

References and Notes

14. Compound 4b can also be named 6-nitro-2,5-dimethoxybenzaldehyde [12]. This seems to have led to some confusion in the literature as indicated by the title of the article by Blanco, et. al. [13], viz., “Re-examination of the synthesis of 3,5-dimethoxy-2-nitrobenzaldehyde”.