

On the Purity of 2-[*ortho*-Aniliny]l]-1,3-benzoxazole Derived from
2*H*-3,1-Benzoxazine-2,4(1*H*)dione (Isatoic Anhydride) [1,2]

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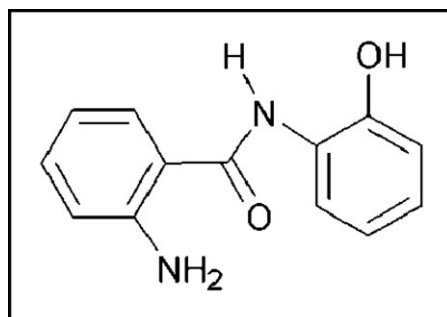
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The Lewis acid catalyzed synthesis and chromatographic purification of isatoic anhydride-derived 2-(2'-aniliny]l)-1,3-benzoxazole (**2**) can result in the co-isolation of **2** and a light pink colored impurity (<5%). This latter species has been identified (NMR, single crystal X-ray diffraction, mp) as 2'-hydroxy-2-aminobenzanilide (**3**), which represents a predictable intermediate in the formation of **2**. Compound **3** crystallizes in an orthorhombic crystal system of space group $P2_12_12_1$ with four molecules in the unit cell ($\alpha = \beta = \gamma = 90^\circ$; $a = 6.715$ (2) Å, $b = 12.100$ (4) Å, $c = 13.321$ (4) Å; $V = 1082.2$ (6) Å³). Pure **2** is characterized as a colorless, high-melting solid; unlike the dark colored oil that is isolated if **2** contains traces of **3**.

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INTRODUCTION

Oxazoles, 2-oxazolines (*i.e.*, 4,5-dihydro-1,3-oxazoles) and 1,3-benzoxazoles represent an important group of organic heterocyclic compounds. These materials have found widespread applications as ligands in transition metal and main group coordination chemistry and as important monomers in polymer science. In addition, these heterocycles are used in medicinal chemistry and in regio-selective and enantio-selective synthesis [3–12]. Our own interests lie in the design and application of novel oxazoles for metal-mediated catalysis and in fundamental studies of inorganic structural chemistry [13–18]. Several years ago, Gajare *et al.* demonstrated that isatoic anhydride (*i.e.*, 2*H*-3,1-benzoxazine-2,4(1*H*)dione: **1**; Scheme 1) [19–21] can be used as a useful synthon for the production of *o*-aniliny]l-oxazolines, -oxazines, and -benzoxazoles [22]. Their coupling strategy involved the application of kaolinitic clay as a Lewis acid promoter of decarboxylative coupling and subsequent dehydrative ring formation reactions between **1** and *o*-aminoalcohols (Scheme 1; $E = -(CRR')_n-$

($n = 2$ or 3), $o-C_6H_4$). Our independent study of this reaction using $ZnCl_2$ [23] or $ZnBr_2$ [24,25] as catalyst had revealed that the desired product of the above reaction between **1** and *o*-aminophenol, *viz.* 2-(1,3-benzoxazol-2-yl)aniline (**2**; *i.e.*, 2-[*o*-aniliny]l]-1,3-benzoxazole: Scheme 1), can be problematic to isolate in pure form by these reaction protocols [22,23]. Details of this investigation are reported herein.

RESULTS AND DISCUSSION

We were perplexed by the earlier disclosure (and indeed in our own synthesis and purification by similar means) [23,24] that compound **2**, following chromatographic isolation, often takes the form of a dark colored analytically pure oil. Compared with the variety of other structurally analogous materials that we had made, it seemed unusual that this compound should exist as a liquid under ambient conditions. A thorough search of the literature reveals that compound **2** has in fact been previously reported by several different synthetic

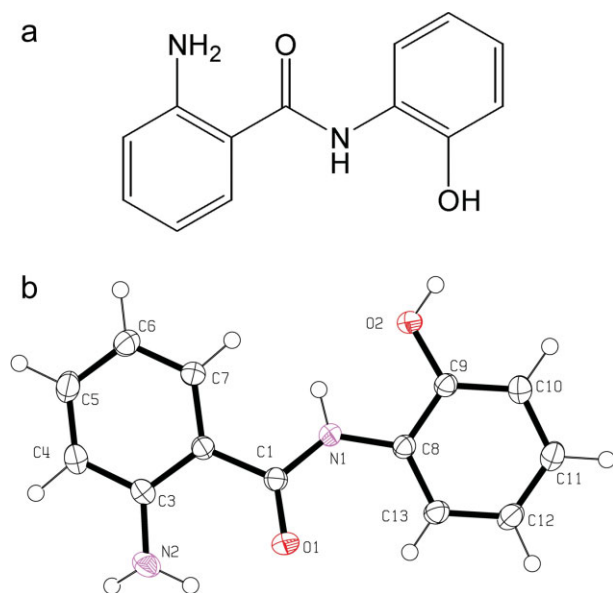


Figure 1. (a) A molecular representation of **3**. (b) An ORTEP diagram of a molecule of **3** found in the unit cell. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

methodologies and in all cases reported as a colorless solid. However, there is considerable discrepancy as to the exact mp of **2** (reported mps: 126°C [26]; 113–115°C [27]; 105–105.5°C [28]; 105°C [29]). On one occasion in our own laboratories, we also obtained the said material as an off-white solid with a mp of 103–105°C (which we likewise reported in 2003 [23]), a property consistent with that reported independently by both Culbertson et al. [29] and Igeta and coworkers [28]. These conflicting observations promoted us to re-examine both **2** and the “oil” material more closely, and we have thus found that flash chromatographic isolation of **2** using EtOAc/hexanes (v/v: 50/50 or 25/75) mixtures often leads [22,23] to the contamination of **2** with a small amount of a second light pink-colored compound (**3**). When this impurity is present, impure **2** does indeed take the form of a viscous tar-like oil which is typically dark in color. This material is usually isolated when the accompanying solvent is removed expeditiously by, for example, rotary evaporation. An interesting facet of this oil is the acceptable level of analytical purity (calculated for C₁₃H₁₀N₂O: C 74.28, H 4.76,

Table 1

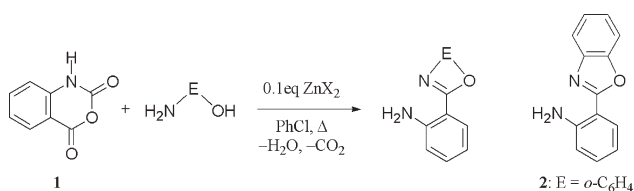
Selected bond distances (Å), bond angles (deg), and dihedral angles (deg) for compound **3** with estimated standard deviations in parentheses (see Fig. 1).

| | |
|----------------|-------------|
| Bond distances | |
| O1–C1 | 1.235 (2) |
| O2–C9 | 1.364 (2) |
| N1–C1 | 1.349 (2) |
| N1–C8 | 1.410 (2) |
| N2–C3 | 1.371 (2) |
| Bond angles | |
| C8–N1–C1 | 129.68 (11) |
| O1–C1–N1 | 121.86 (11) |
| Dihedral angle | |
| C8–N1–C1–C2 | 173.11 (11) |

N 13.33; found [22]: C 74.48, H 4.26, N 13.61%). We have succeeded in isolating **2** that is free of **3** by careful fractional crystallization of the resulting mixture dissolved in EtOAc/hexanes. Slow solvent removal by evaporation under ambient conditions (in open test tubes) leads to the gradual precipitation of a white material in the form of needles (identified as **2**) and a second crystalline light pink-colored solid (**3**), which is present in quite small amounts relative to that of **2**. Investigation of this latter material isolated in this way *via* ¹H NMR spectroscopy and mp measurements (mp: 136–136.5°C) reveals very similar properties to those reported [30] some 40 years ago for 2'-hydroxy-2-aminobenzanilide (lit. mp: 139–140°C; Fig. 1). This compound is an obvious and predictable intermediate [19–21,23] in the synthesis of **2** from **1**. To obtain unequivocal evidence on the nature of **3**, a single crystal X-ray diffraction study was carried out. Compound **3**, 2'-hydroxy-2-aminobenzanilide (Fig. 1), crystallizes in the *P*₂₁₂₁ space group with four molecules in the unit cell (see Table 1). The molecules contain virtually co-planar aromatic groupings and intra-molecular *H*-bonding between the amide oxygen atom (O1) and the NH₂ group (O1...H–N2 = 2.024 Å) and the amide *H*-atom and the *O*-atom of the phenolic –OH functionality (O2...H1–N1 = 2.132 Å). In addition, a close inter-molecular contact is found between the *H* of this –OH group (*i.e.*, H2c) and O1 (O1...H2c = 1.773 Å). An ORTEP representation of a molecule of **3** from the unit cell is shown in Figure 1.

The off-white needle form of **2** (mp: 103–105°C) isolated above was subjected to recrystallization from boiling pet. spirit (60–80°C bp range) to yield initially a cream colored material in the form of very thin needles (mp: 106–108°C). This crop was subsequently recrystallized a second time from the same solvent to give colorless needles (mp: 109–111°C). The variability in mp behavior of **2** may be due to its sensitivity to gradual yellowing (presumably oxidation) under ambient

Scheme 1



conditions. We have been unable to recrystallize **2** from hydrocarbon media to a point in which the measured mp mimics that disclosed by Padmaja *et al.* (126°C: to our knowledge the highest mp reported for **2**) [26]. Their method used glacial acetic acid for recrystallization. Using this solvent gave white material of mp 113–114°C. It should also be noted that the analytical purity of **2**, as described in [22], could contain traces of **3**. For example, the contamination of a sample of **2** by 1% by weight of **3** (corresponding to 9.3 molecules of **3** per 100 that of **2**) gives a calculated elemental analysis (calc.: C 74.16; H 4.79; N 13.38%) consistent with **2** (*vide supra*) and this concentration of impurity makes it unlikely that **3** would be easily spotted by NMR spectroscopy. Despite these facts, it does appear as if all these levels of purity of **2** are still of sufficient quality for the use of this material in subsequent syntheses [23,31,32].

EXPERIMENTAL

Isolation of 2-(1,3-benzoxazol-2-yl)aniline (2) and 2'-hydroxy-2-aminobenzanilide (3). The synthesis of compounds **2** and **3** was carried out as described in reference [23]. Purification of the reaction mixture *via* flash chromatography (1/1 v/v hexanes/EtOAc) using ~50 g of silica on a column of 2 cm diameter yielded ~40 fractions (~15 mL each in test tubes). These extractions were left to evaporate in open air (fumehood) of which the first 15 contained solid pure (NMR) **2** (yield 36% [23]); fractions 16–18, which were slightly pink in color, yielded about 50 mg of **3** (0.4%) and a small amount of **2**. Compounds **2** and **3** were then separated manually from these fractions. The latter fractions contained species which could not be unequivocally identified (NMR). Properties of **2**: mp 113–114°C (AcOH; lit.: see text); pmr (δ , 400 MHz, deuteriochloroform): data was consistent to within experimental error to that reported (lit. [28]). Properties of **3**: mp: 136–136.5°C (1/1 v/v hexanes/EtOAc; lit. [30] 139–140°C); pmr (δ , 600 MHz, deuteriochloroform containing ~10% hexadeutero-dmso), 9.11 (s, br, 1H, NH), 8.75 (s, br, 1H, OH), 7.71 (dd, 1H, $J = 1.7, 7.8$, ArH), 7.34 (dd, 1H, $J = 1.5, 7.9$, ArH), 7.00 (td, 1H, $J = 1.2, 7.2$, ArH), 6.75 (m, 1H, ArH), 6.72 (dd, 1H, $J = 1.8, 7.8$, ArH), 6.63 (m, 2H, ArH), 6.52 (dd, 1H, $J = 1.2, 7.8$, ArH), 6.46 (td, 1H, $J = 1.2, 7.2$, ArH), 2.60 (s, v. br, NH₂); cmr (δ , 150 MHz, deuteriochloroform containing ~10% hexadeutero-dmso), 167.5 (C=O), 148.7, 147.1, 132.1, 127.6, 126.3, 124.4, 121.0, 119.3, 117.0, 116.0, 115.9, 115.5.

Crystal data for 3. The structure of complex **3** was solved using previously described methods [33]. Formula C₁₃H₁₂N₂O₂, MW: 229.24, orthorhombic, space group *P*2₁2₁2₁, $a = 6.715$ (2) Å, $b = 12.100$ (4) Å, $c = 13.320$ (4) Å, $\alpha = \beta = \gamma = 90^\circ$, $V = 1082.2$ (6) Å³, $D_c = 1.401$ g/cm³, $Z = 4$. Crystal size: 0.80 × 0.71 × 0.56 mm³, light pink. Temperature = 173 (2) K, $\lambda(\text{MoK}\alpha) = 0.71073$ Å, Absolute coefficient = 0.097 mm⁻¹, $F(000) = 480$, θ range for data collection: 2.27–32.46°, hkl range: –4 to 10, –17 to 18, –20 to 18. Reflexions collected: 16,294, Independent reflexions: 3893 [$R(\text{int}) = 0.0581$], Completeness to $\theta = 32.46^\circ$: 99.9%, Absorption corr.: numerical, max. and min. transmission:

0.9479, 0.9265, refinement method: full-matrix least-squares on F^2 , data/restraints/parameters: 3893/0/202, GOF on F^2 : 1.042, final R indices [$I > 2\sigma(I)$] $R1 = 0.0446$, $wR2 = 0.1126$, R indices (all data): $R1 = 0.0544$, $wR2 = 0.1193$, absolute structure parameter: 0.7 (10), largest diff. peak and hole: 0.241–0.272 eÅ⁻³. The molecular representation found in Figure 1 was drawn using ORTEP-III for Windows [34]. CCDC #747662 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

CONCLUSIONS

This investigation has demonstrated that compound **2** (*i.e.*, 2-[1,3-benzoxazol-2-yl]aniline) can be problematic to isolate in very pure form under the reaction conditions described independently by us and Gajare *et al.* Contamination of **2** by its ring opened precursor (2'-hydroxy-2-aminobenzanilide: **3**) can lead to the isolation of analytically “pure” material in an oil-like form. Caution is likewise advised as to the measurement of the purity of solid **2** by mp determination although lower melting point material appears to be of sufficient purity for later synthetic applications. Material with the most pronounced mp behavior is that which has been recrystallized from glacial acetic acid as described previously [26]. The contaminant of **2**, *viz.* **3**, has been fully characterized (mp, NMR, X-ray diffraction).

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