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Preparation of 2-hydroxybenzamidines from 3-aminobenzisoxazoles

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Abstract—2-Hydroxybenzamidines have been prepared from 3-aminobenzisoxazoles by reductive cleavage of the nitrogen–oxygen bond using catalytic hydrogenation, Zn/AcOH or $NiCl_2/NaBH_4$. This ring-opening reaction can be accomplished chemoselectively in the presence of a variety of hydrogenation-sensitive functional groups including an aryl bromide, benzyl carbamate, and olefin.

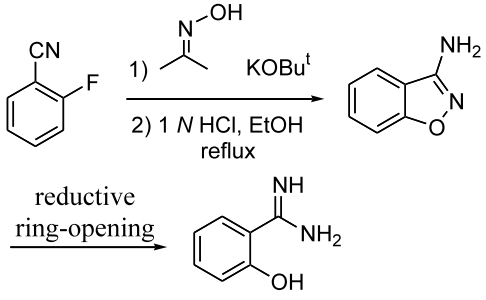
As a part of a program to develop novel anticoagulants for the treatment of thrombotic disorders, we have prepared a variety of benzamidine-based inhibitors of coagulation enzymes.[1] Although the amidinium ion helps produce high binding affinity with such enzymes due to its interaction with Asp189 in the S1 specificity pocket, this positively charged functional group can provide a barrier to good oral absorption. Among the strategies we have pursued to enhance the membrane permeability of such enzyme inhibitors,[2] we have evaluated 2-hydroxybenzamidines as a means both to neutralize and internally solvate the positive charge.[3]

The few examples of 2-hydroxybenzamidines reported to date have been prepared from 2-hydroxybenzonitriles, employing the Pinner reaction followed by treatment of the resulting imidate with ammonia.[4,5] When the free hydroxyl is carried through the reaction sequence, low yields of the desired product result. One strategy for improving the outcome is to protect the phenolic oxygen. Then, if the amidine needs to be introduced early in a synthetic sequence, an additional amidine protecting group will likely be required.

As an alternative, we envisioned that 2-hydroxybenzamidines could be obtained through the reductive ring-opening of 3-aminobenzisoxazoles (Scheme 1). These heterocycles can be readily prepared from a variety of substituted 2-fluorobenzonitriles by the methods of either Palermo[6] or Shutsky.[7,8] 3-Aminobenzisoxazoles are stable to a variety of reaction conditions and can be easily isolated using silica gel chromatography techniques.

As an initial test of the feasibility of this approach, 3-aminobenzisoxazole (**1**) was prepared[7] and treated with hydrogen and 5% Pd on carbon (Pd/C) in methanol for 12 h.[9] After filtration of the catalyst and removal of the solvent, 2-hydroxybenzamidine (**2**)[10] was isolated in 92% yield and >96% purity (Table 1, entry 1). Under these conditions, 6-methoxy-3-aminobenzisoxazole (**3**) and the 6-methoxycarbonyl-3-aminobenzisoxazole (**5**) were also converted to the corresponding hydroxybenzamidines **4** (93%) and **6** (90%) in high yield.

To extend the utility of this method, additional reduction conditions were evaluated that would be compatible with functional groups sensitive to hydrogenation. As expected, the arylbromide **7**, the benzylcarbamate **9**,



Scheme 1. Reductive ring-opening strategy for the synthesis of 2-hydroxybenzamidines.

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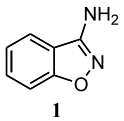
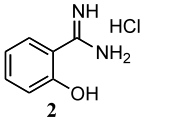
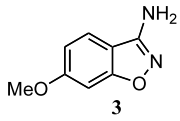
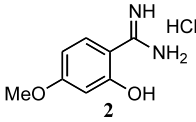
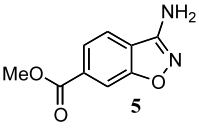
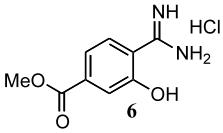
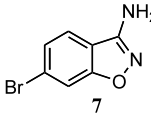
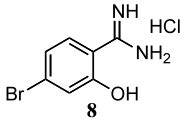
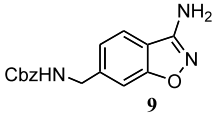
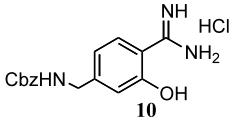
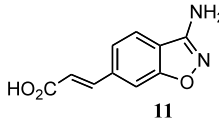
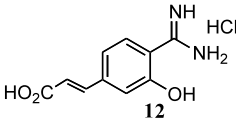
Table 1. Comparison of reduction conditions in the ring-opening reaction of a variety of 3-amino-benzisoxazoles

1	 **1**	A	 **2**	92
2		B		94
3		C		98
4		D		78
5		E		10[c]
6		F		no rxn
7	 **3**	A	 **2**	93
8		C		93
9		D		30
10	 **5**	A	 **6**	90
11		C		74
12		D		98
13	 **7**	A	 **8**	0[d]
14		B		17[e]
15		C		78
16		D		99
17	 **9**	B	 **10**	96[f]
18		C		89
19		D		92
20	 **11**	B	 **12**	97[g]
21		C		85
22		D		30[h]

[a]Method A = H_2/Pd(C), EtOH, 1.0 *N* HCl, rt, 12 h. B = H_2, Lindlar's catalyst, MeOH, rt, 12 h. C = Zn, AcOH, 70°C, 12 h. D = $NaBH_4$, $NiCl_2$, MeOH, 0 °C, 15 min. E = SmI_2 (2.2 equiv.), THF, 0 °C, 15 min. F = H_2NNH_2, EtOH, reflux, 12 h.

[b] All product yields are based on the HCl salt of the product obtained after filtration through celite (Methods A & B) or SCX filtration (Methods C - E). See representative procedures in the notes. Unless otherwise indicated, all products were >96% pure based on HPLC analysis of the product after filtration. [c] Mostly starting material remaining. [d] Nearly complete conversion (91%) to hydro-debrominated product. [e] Conversion after reaction time of 2.5 days. [f] Reaction time = 1 h in this case. [g] Reaction time = 3 days in this case. [h] These conditions led to a significant percentage of olefin reduction product (41%).

and the olefin **11** all gave undesirable side reactions upon hydrogenation with 5% Pd/C. Entries 2–6 in the table illustrate the results obtained for the treatment of compound **1** with several reducing agents precedented for the cleavage of N–O bonds. The Lindlar reduction[11] of **1** produced hydroxybenzamidine (**2**) in 94% yield after 12 h (entry 2). Reduction with Zn/AcOH[12] (entry 3) also proceeded in high yield (98%) over a 12 h period. Unlike the heterogeneous hydrogenation reactions, the soluble contaminants produced in this reaction cannot be removed by simple filtration. However ion-exchange chromatography was found to provide a very simple and effective means of purification of the final products when necessary. For example, a solution of **2** (25 mg) in methanol and acetic acid was loaded onto an SCX column (1 g) and rinsed with two column volumes of methanol. Subsequent elution with one column volume of 2 M NH_3 in MeOH gave >98% recovery of **2**. Using this purification procedure to facilitate the workup, $NiCl_2/NaBH_4$[13] (entry 4) gave the desired product (**2**) in 78% isolated yield and required only 15 min at 0°C to go to completion. On the other hand, suitable reaction conditions were not identified for SmI_2[14] (entry 5), which gave only 10% conversion to the desired product, or for hydrazine[15] (entry 6), which gave no reaction with **1** even after extended reaction times.

Table entries 13–22 illustrate the results observed for reduction of the Pd/hydrogen-sensitive substrates **7**, **9** and **11**. Treatment of the aryl bromide **7** with H_2/Pd/C led to complete reductive debromination[16] in addition to the ring-opening reaction, and provided **2** as the undesired product (entry 13). In this case, the Lindlar reduction proceeded very slowly, with only 17% conversion of **7** to the desired product **8** after 2.5 days (entry 14).

Alternatively, both Zn/AcOH and $NiCl_2/NaBH_4$ gave **8** (entries 15 and 16) in reasonable isolated yield (78% and 99%, respectively). With the benzyl carbamate-containing substrate **9**, Pd/C-mediated hydrogenation led to ring-opening with concomitant Cbz-removal (results not shown). In this case, Lindlar's catalyst (entry 17) gave the desired hydroxybenzamidine product **10** in 96% yield (>96% purity), provided the reaction time was kept under 1 h. Longer exposure to the reaction conditions led to the formation of some Cbz-deprotected hydroxybenzamidine product. Zn/AcOH and $NiCl_2/NaBH_4$ (entries 18 and 19) also gave excellent yields and purities of compound **10**. Finally, as expected, reduction of the olefin-containing substrate **11** with H_2/Pd/C led exclusively to the over-reduction product. Similar to the reaction with the bromobenzisoxazole substrate **7**, the Lindlar reduction of **11** proceeded very slowly. After a reaction time of 3 days, a 97% isolated yield (>96% purity) of the desired ring-opening product **12** was obtained (entry 20).[17] Treatment of **11** with Zn/AcOH led to an 85% yield of the desired ring-opening product **12** after ion exchange chromatography (entry 21). Reduction of compound **11** with $NiCl_2/NaBH_4$ provided **12** in only 30% isolated yield (entry 22) along with 41% of the over-reduction product. No improvements in the selectivity were achieved with variations in the reaction time, temperature or $NiCl_2$ addition rate.

In conclusion, we have developed an efficient route to the synthesis of 2-hydroxybenzamidines via reductive ring-opening of 3-aminobenzisoxazoles. The Pd/C-mediated hydrogenation provides a mild and efficient

protocol for the reduction of most 3-aminobenzisoxazole substrates on large scale. The Lindlar reduction, Zn/AcOH and $NiCl_2/NaBH_4$ can complement the Pd catalyzed hydrogenolysis by allowing for the reduction of a variety of hydrogenation-sensitive functional groups. Furthermore, the application of ion exchange chromatography facilitates purification and allows rapid parallel processing of samples. Thus, this methodology in combination with our previously reported solid phase synthesis of 3-aminobenzisoxazoles,[8] comprises a useful method for the preparation of libraries of 2-hydroxybenzamidines.[18]

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10. All new compounds have been characterized by mass spectral, elemental, and NMR analysis. Experimental procedures A–D for the formation of 3-aminobenzisoxazole (**2**). **Method A**: to a flask containing 3-aminobenzisoxazole (**1**) (25 mg, 0.187 mmol) was added 5% Pd/C (20 mg, 0.009 mmol Pd) and methanol (2 mL). The reaction vessel was then placed under a mild vacuum (10 mmHg) and released to a hydrogen atmosphere. The reaction was allowed to proceed for 12 h or until the TLC showed complete disappearance of **1** (R_f of **1** approx. 0.5 in 50% EtOAc/hexanes). The palladium catalyst was filtered off by filtration of the reaction mixture through a celite column (2 g) rinsing with methanol. The filtrate was concentrated and redissolved in 1N HCl. This solution was again concentrated to give the HCl salt of **2** (30 mg, 92% yield). HPLC analysis (2–15% MeCN/H_2O with TFA buffer, 1 mL/min, C_{18} column) gave only one peak at 9.4 min (>96% purity). **Method B**: same procedure as Method A except use 20 mg of Lindlar's catalyst (94% yield, >96% purity). **Method C**: to a flask containing **1** (25 mg, 0.187 mmol) was added zinc metal (20 mg, 0.30 mmol), acetic acid (1 mL) and H_2O (2 mL). The reaction was heated to 70°C for 12 h with vigorous stirring. The reaction was allowed to cool and poured onto a 2 g SCX column pretreated with 5% AcOH/MeOH and the column was rinsed with 7 MeOH (7 mL). Product was removed from the ion-exchange resin by rinsing with 2 M NH_3 in MeOH (2×7 mL). The ammonia/methanol rinses were collected and concentrated and redissolved in 1N HCl. This solution was again concentrated to give the HCl salt of **2** (32 mg, 98% yield, >96% purity). **Method D**: to a flask containing **1** (25 mg, 0.187 mmol) was added $NiCl_2 \cdot 6H_2O$ (47 mg, 0.196 mmol) and methanol (2 mL). The reaction was cooled to 0°C and $NaBH_4$ (15 mg) was added in several portions producing a vigorous evolution of gas in the reaction. After 15 min, the reaction was purified as in Method C to give the HCl salt of **2** (25 mg, 78% yield, >96% purity).
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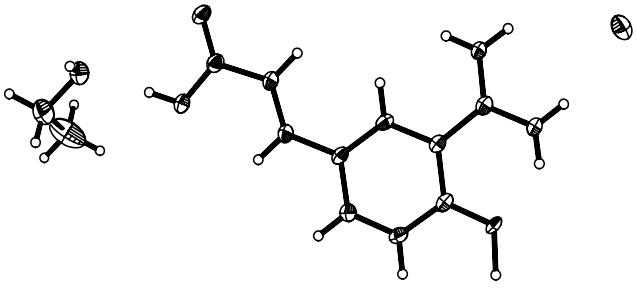
17. Compound **12** was recently reported as the natural product phyllurine, a leaf-opening substance isolated from the leaves of *Phyllanthus urinaria*: (a) Ueda, M.; Asano, M.; Yamamura, S. *Tetrahedron Lett.* **1998**, *39*, 9731; (b) Ueda, M.; Asano, M.; Sawai, S.; Yamamura, S. *Tetrahedron* **1999**, *55*, 5781. However, our NMR spectra for compound **12** are inconsistent with the published data for phyllurine: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (br, 1H), 11.5 (br, 1H), 9.19 (s, 2H), 8.95 (s, 2H), 7.87 (s, 1H), 7.77 (s, 1H), 7.52 (d, J=16.0 Hz, 1H), 7.04 (s, 1H), 6.43 (d, J=16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.64, 163.82, 158.78, 142.72, 133.53, 129.72, 124.79, 117.63, 117.13, 115.56. X-ray crystallography also confirms the structure of synthetic material **12**. An ORTEP of the X-ray structure is shown below. In the unit cell is also contained 1 molecule of ethanol and the chloride counterion.



18. The physical chemical and biological properties of representative 2-hydroxybenzamidienes will be reported separately.