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Regioselective preparation of 5-amino- and 6-amino-1,3-benzoxazole-4,7-diones from symmetrical diaminophenol and aminoresorcinol

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Abstract—Regioisomeric 5-amino- and 6-amino- 1,3-benzoxazole-4,7-diones were prepared from 2,6-diamino-4-methoxyphenol and 2-amino-5-methoxyresorcinol, respectively. These symmetrical precursors have the property to be antisymmetrical to each other with respect to their amino and hydroxy substituents.

A series of compounds based on the 1,3-benzoxazole-4,7-dione template (**1**, Fig. 1) has been prepared and screened against dual specificity phosphatases CDC25. These enzymes are involved in the regulation of the cell cycle and their synthetic inhibitors are currently investigated as cytostatic agents for oncological applications.[1–3] Biological assays revealed that amines at positions 5 and 6 were substituents of choice for an improved activity. A few heterocyclic quinones such as **1** are reported in the literature. They are generally fused within tricyclic or tetracyclic systems,[4–13] and standalone bicyclic structures as in **1** are encountered just sporadically.[14–16] The present communication discloses the regioselective synthesis of 5- and 6-amino-1,3-benzoxazole-4,7-diones.

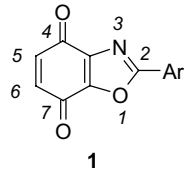

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Figure 1.

As shown on Scheme 1, either an amino or a hydroxy substituent can provide a handle to oxidize a given benzenoid to its corresponding quinone. The initial route to benzoxazolediones **1** consisted in the condensation of 2-amino-3-nitrophenol (**2**) with either carboxylic acids[17,18] or orthoesters[19] to give substituted nitrobenzoxazoles **3**. A subsequent reduction of the nitro group[19] provided aminobenzoxazoles such as **4a** which were oxidized with either Fremy's salt [potassium nitrosodisulfonate, $(KO_3S)_2NO$],[20] or BTI [bis(trifluoroacetoxy)iodobenzene][21] to the corresponding quinone **1a**. Alternatively, the rhodium catalyzed cycloaddition of 2-diazo-1,3-cyclohexanedione (**5**) to diversely substituted nitriles gave cyclohexenones such as **6b**[22] which were then aromatized to hydroxybenzoxazoles such as **4b** by a bromination–elimination[23,24] sequence. These latter phenolic intermediates were readily converted to quinones such as **1** by oxidation with Fremy's salt or BTI.[21] Further experimental details for Scheme 1 can be found in the patent literature.[25]

We then turned our attention to the addition of amino substituents to benzoxazolediones **1**. Amines are known to add in a 1,4-mode to quinones.[26–28] In the case of non-symmetrical molecules such as 5,8-quinolinedione, two regioisomeric adducts are generally obtained in varying ratios depending on the reaction conditions.[29] In the present case, the addition of *N*,*N*-dimethylethylenediamine to 3-bromophenylbenzoxalonedione **1c** gave in low yield a mixture of regioisomers **7** and **8** (6-N and 5-N, respectively, as shown on Scheme 2), in a 1:1.9 ratio as measured by ^{1}H NMR. Although the

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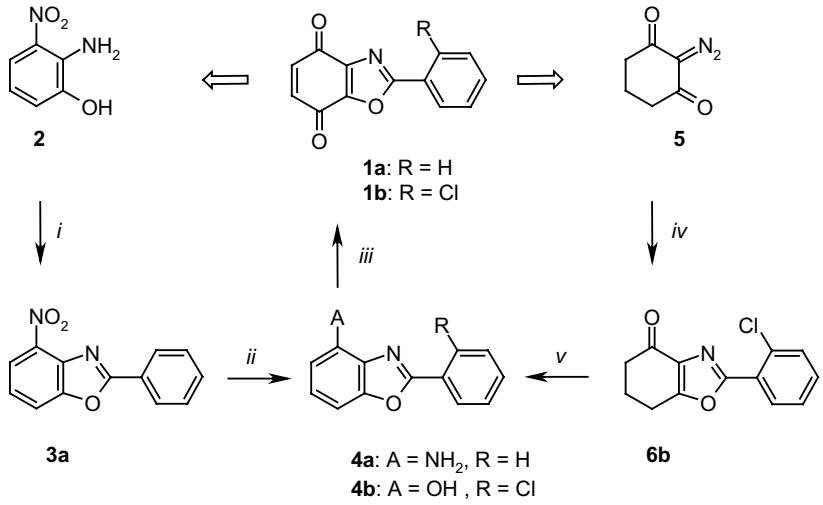
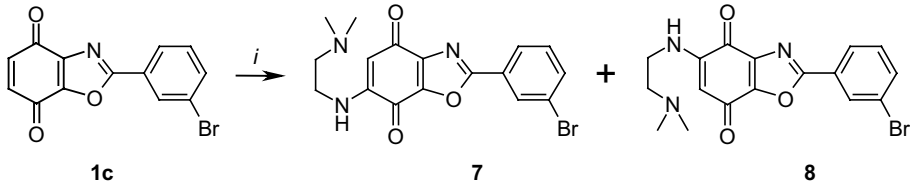


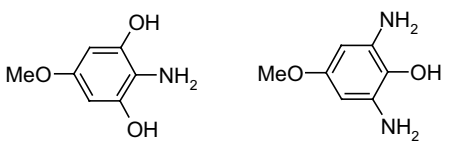
Scheme 1. Reagents and conditions: (i) $PhC(OMe)_3$ (2 equiv), neat, PTSA (cat), 110 °C, 2 h, 82%; (ii) H_2 (8 atm) 10%Pd/C (cat), MeOH, 70%; (iii) BTI (2.2 equiv), $MeCN/H_2O$, −5 °C, 30 min, **1a**: 42%, **1b**: 67%; (iv) 2-Cl–C_6H_4CN (1.5 equiv), $((AcO)_2Rh)_2$ (0.02 equiv) 60 °C, 1 h, 36%; (v) (a) Br_2, AcOH, rt, 27 h, 84%, (b) DBU (1.5 equiv), THF, 1.5 h, 87%.



Scheme 2. Reagents and conditions: (i) $Me_2NCH_2CH_2NH_2$ (2 equiv), $CeCl_3{\cdot}7H_2O$ (1 equiv), EtOH/THF, rt, 1 h, 19%.

regioisomers could be separated by chromatography, a general regioselective preparation was desirable.

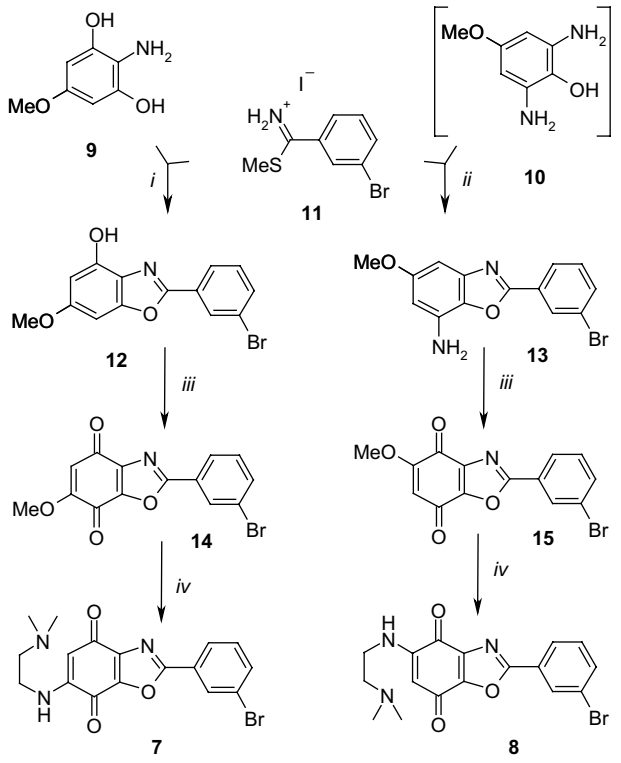
Aminated quinones can also be obtained by displacement of the corresponding alkoxy substituents.[30,31] Such a process, which can be formally seen as a 'vinylogous' *trans*-esterification or a 1,4-addition–elimination, has the merit of being regiospecific.[31,32] Combining the requirement of a methoxy group *para* to the nitrogen and with the convenience of a symmetrical starting material such as **5**, aminoresorcinol **9** was identified as a possible precursor for 6-amino-benzoxazoles such as **8**. Conversely, diaminophenol **10** could lead to 5-amino-benzoxazole **7** since both anilines and phenols can be oxidized to quinones. These two tetra-substituted benzenes, **9** and **10** are readily obtained by applying a nitration and reduction sequence to commercially available starting material.[33,34] Another refinement in this method consisted in engaging thioimidate salts as activated carboxylic synthons in the condensation reaction with either **9** or **10**. These salts are readily obtained from



thioamides, either of commercial origin or derived from commercial benzonitriles,[35] by treatment with methyl iodide in acetone.[36]

This new method was validated and applied to a lead optimization program.[37] The operating procedure is exemplified here with 3-bromo-phenyl at position 2 of the benzoxazole and *N*,*N*-dimethylethylenediamino at position 5 or 6 (Scheme 3). Obtained by nitration and subsequent reduction of the corresponding resorcinol (Scheme 4),[33] aminoresorcinol **9** was condensed with bromophenylthioimidate **11** in refluxing ethanol to give hydroxybenzoxazole **12**. BTI oxidation furnished the expected methoxybenzoxazoledione **14**, which was treated in refluxing ethanol with *N*,*N*-dimethylethylenediamine to give the desired 6-aminated benzoxazoledione **7**.

As shown on Scheme 3, regioisomeric 5-amino-benzoxazoledione **8** was obtained similarly from diaminophenol **10**, although the experimental procedure had to be modified to accommodate the high instability of **10** to air. The condensation of **10** to **11** was therefore performed under nitrogen, in the same vessel used for the previous hydrogenation and without removal of the palladium catalyst to avoid exposition to ambient atmosphere. Furthermore, the dinitrophenol precursor of **10**, obtained by nitration of 2-hydroxy-5-methoxy-benzoic acid (Scheme 5),[34] must be considered as *shock-sensitive* and, as such, should neither be dried too thoroughly, nor triturated unduly. Taking these pre-



Scheme 3. Reagents and conditions: (i) EtOH, rt, 2 h, 29%; (ii) EtOH, rt, 16 h, 75% from dinitro precursor; (iii) BTI, $MeCN/H_2O$, −5 °C, 20 min, **14**: 76%, **15**: 8%); (iv) $Me_2NCH_2CH_2NH_2$, EtOH, reflux, 1 h, **7**: 54%, **8**: 38%.

cautions into account, 5-aminated benzoxazoledione **8** was obtained via 5-methoxy-benzoxazoledione **15**, thus providing the counterpart of 6-amino compound **7**. The observation that BTI oxidation proceeded with much lower yields on anilines such as **13** compared to phenols such as **12** (5–15% vs 40–76%) may be related to the higher instability of **10** compared to **9**.

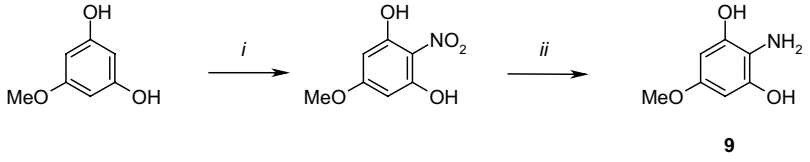
In summary, a novel strategy was developed to obtain regioisomerically pure 5- and 6-aminated benzoxazoquinones without chromatographic separation. This new procedure takes advantage of the symmetry found in aminoresorcinol **9** and diaminophenol **10** which tends to simplify their structure and availability. Interestingly **9** and **10** are also antisymmetrical to each other as the amino and hydroxyl groups are interchanged between their structures. Both compounds lead to benzoxazolediones structures because both phenols and anilines can be oxidized to quinoid structures. No significant difference in activity was observed between the two regioisomeric products **7** and **8**, either in respect to their inhibition of CDC25 phosphatases or in their antiproliferative effect. However, 6-amino-benzoxazoles such as **7** are preferred for their safer and easier preparation.

Spectral data: Compound **14** (6-OMe): IR (KBr) 1033, 1539, 1565, 1601, 1660, 1692. ^{1}H NMR (d_6-DMSO): 3.86 (br, 3H); 6.20 (br, 1H); 7.59 (t, 1H); 7.89 (d, 1H); 8.13 (d, 1H); 8.23 (s, 1H). ^{13}C NMR (d_6-DMSO) 57.83; 106.65; 122.76; 126.70; 127.38; 129.87; 132.05; 135.77; 142.03; 148.17; 159.82; 163.26; 169.09; 180.09.

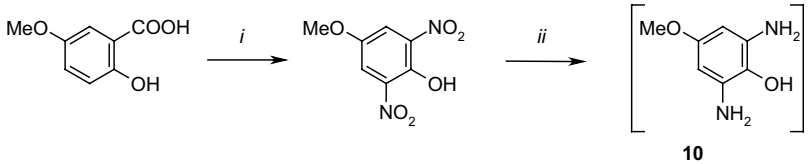
Compound **15** (5-OMe): IR (KBr) 1034, 1543, 1563, 1600, 1656, 1703. ^{1}H NMR (d_6-DMSO): 3.85 (br, 3H); 6.15 (br, 1H); 7.59 (t, 1H); 7.88 (d, 1H); 8.12 (d, 1H); 8.22 (s, 1H). ^{13}C NMR (d_6-DMSO): 57.62; 106.01; 122.73; 126.56; 127.40; 129.75; 132.03; 135.59; 139.64; 149.64; 160.35; 162.43; 174.45; 175.23.

Compound **7** (6-N): IR (KBr) 1046, 1531, 1576, 1599, 1635, 1693. ^{1}H NMR (d_6-DMSO): 2.18 (s, 6H); 2.47 (m, 2H); 3.25 (m, 2H); 5.39 (s, 1H); 7.40 (br, 1H); 7.59 (t, 1H); 7.87 (d, 1H); 8.13 (d, 1H); 8.23 (s, 1H); ^{13}C NMR (d_6-DMSO): 40.38; 45.08; 56.08; 95.68; 122.64; 126.65; 127.55; 129.83; 131.92; 135.57; 144.48; 146.65; 148.13; 163.59; 170.46; 177.85.

Compound **8** (5-N): IR (KBr) 1042, 1547, 1571, 1603, 1637, 1703. ^{1}H NMR (d_6-DMSO): 2.19 (s, 6H); 2.52 (m, 2H); 3.26 (m, 2H); 5.41 (s, 1H); 7.53 (br, 1H); 7.58 (t, 1H); 7.85 (d, 1H); 8.09 (d, 1H); 8.19 (s, 1H); ^{13}C NMR (d_6-DMSO): 40.45; 45.12; 56.08; 95.05; 122.59; 126.23; 127.60; 129.48; 131.87; 135.12; 137.62; 148.97; 152.39; 161.32; 173.09; 176.06.



Scheme 4. Reagents and conditions: (i) HNO_3 (d 1.42, 1.3 equiv), $AcOH/Ac_2O$, 5 °C, 1 h, 23%; (ii) H_2 (1 atm) 10%Pd/C cat, EtOH, 70%.



Scheme 5. Reagents and conditions: (i) HNO_3 (d 1.42, 2.4 equiv), AcOH, 10 °C, 2 h, 50%; (ii) H_2 (1 atm) 10%Pd/C cat, EtOH.

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