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A simple synthesis of 4-substituted 2,3-benzoxazinones from C-2 arylated 1,3-indanediones

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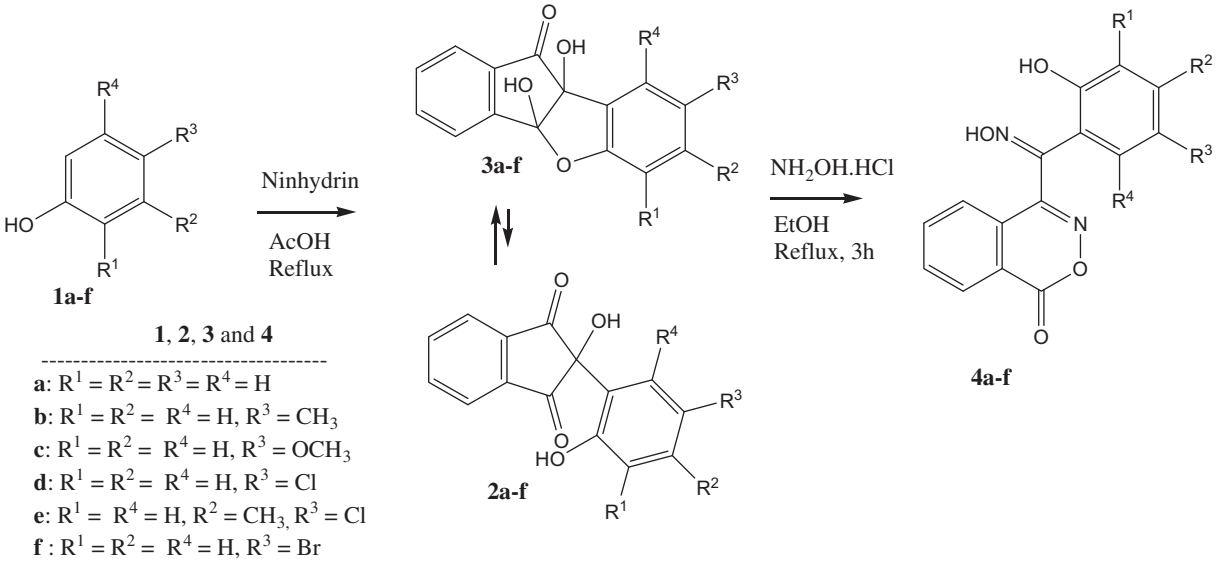
ABSTRACT

A simple one-pot procedure for the conversion of 2-hydroxy-2-(2′-hydroxy-aryl)-1,3-indanediones to 4-substituted benzoxazinones has been developed. The process constitutes an interesting acid-catalyzed rearrangement followed by condensation with hydroxylamine.

Benzoxazinones are an important class of naturally occurring heterocycles with interesting biological properties. For example, 2-substituted 4*H*-3,1-benzoxazin-4-ones are found in nature as phytoalexins avenalumin I[1] and dianthalexin.[2] Efavirenz (Trade name Sustiva(R)) is a marketed human immunodeficiency virus type 1 (HIV-1) specific non-nucleoside reverse transcriptase



Scheme 1. Synthesis of 4-substituted 2,3-benzoxazinones **4a–f**.

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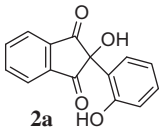
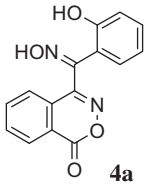
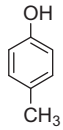
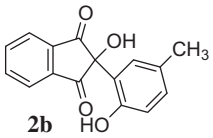
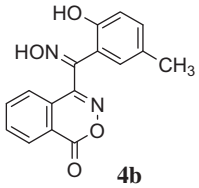
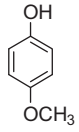
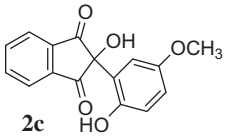
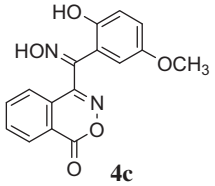
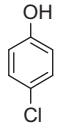
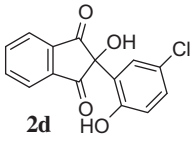
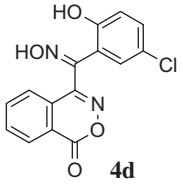
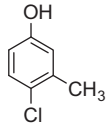
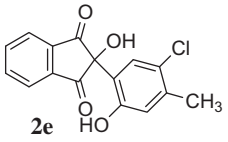
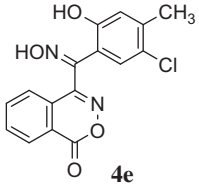
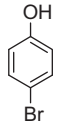
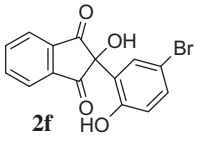
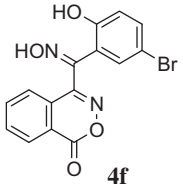
Table 1
Preparation of 4-substituted 2,3-benzoxazinones **4a–f** from **2a–f**

Entry	Phenols	Substrates	Products	Time (h)	Yield[a] (%)	Mp[b] (°C)
1		 **2a**	 **4a**	3.0	45	189–190
2		 **2b**	 **4b**	2.5	50	193–194
3		 **2c**	 **4c**	3.0	52	186–187
4		 **2d**	 **4d**	3.5	48	173–174
5		 **2e**	 **4e**	3.0	46	183–185
6		 **2f**	 **4f**	3.5	42	193–194

[a] Yields are for isolated products.
[b] Mps are uncorrected.

inhibitor (NNRTI) that contains benzoxazinone moiety.[3] Some derivatives of 3,1-benzoxazinones act as competitive inhibitors[4] or potent inactivators[5] of chymotrypsin and other serine proteases, or are inhibitors of human leukocyte elastase (HLE),[6] neutrophil elastase,[7] herpes simplex virus type 1 (HSV-1) protease,[8] and C1r serine protease.[9] Bioactivity and ecological role of 1,4-benzoxazinone systems has recently been explored.[10,11] Although there are several methods for the synthesis of substituted 3,1- and 1,4-benzoxazinones, very few methods are available for the synthesis of 2,3-benzoxazinone skeletons.[12] Herein we report an efficient and novel procedure for the synthesis of 4-substituted 2,3-benzoxazinones from easily available starting materials.

When ninhydrin is refluxed in a mixture of phenols **1** and acetic acid, 2-hydroxy-2-(2′-hydroxy-aryl)-1,3-indanediones **2** are formed.[13,14a] The adducts so formed preferentially remain in the cyclic hemiketal form **3**.[13a–c] On the basis of our previous experience in the preparation of various heterocyclic skeletons[14] from ninhydrin, we thought that 2-hydroxy-2-(2′-hydroxy-aryl)-1,3-indanediones **2** could be a flexible precursor for the synthesis of heterocycles containing both nitrogen and oxygen. To achieve this, hydroxylamine was chosen as nucleophile for the reaction. Interestingly we found that upon refluxing 2-hydroxy-2-(2′-hydroxy-aryl)-1,3-indanediones **2a–f** with hydroxylamine hydrochloride in ethanol, 4-substituted 2,3-benzoxazinones **4a–f** are formed in moderate yields through sequence of reactions within 3 h (Scheme 1, Table 1). The current one-pot protocol possesses a simple work-up and purification procedure, requiring only filtration followed by crystallization from acetone.[15] All the compounds were characterized by ^{1}H and ^{13}C NMR specta.[16] In the ^{1}H NMR spectra of compound **4c**, for example, phenolic proton comes to resonate at $\delta = 9.56$ ppm and the oxime proton appears at $\delta = 12.23$ ppm as a singlet. The ^{13}C NMR spectrum of compound **4c** shows lactone carbonyl signal at

δ = 163.0 ppm. X-ray crystal structure of **4b** is shown in Figure 1 which confirms the product formation.[17] In the structure the intramolecular hydrogen bonding is indicated by a broken line.

The formation of **4** can be explained from the proposed mechanism depicted in Scheme 2 and in accordance with our previous results.[14a] In the acidic condition, protonation of the carbonyl group of the bicyclo[3.3.0]octano system **3** initiates the breaking of the central C–C bond to afford an eight-membered lactone intermediate **5** which undergoes the tautomeric keto form. Then the ketonic carbonyl preferentially condenses with hydroxylamine to furnish the oxime intermediate **6**. Subsequently the intramolecular nucleophilic attack of hydroxyl group of oxime on the lactone carbonyl results in the formation of 2,3-benzoxazinone skeleton **7**. Under the reaction conditions **7** spontaneously is oxidized to ketone **8** which finally condenses with hydroxylamine to furnish compound **4**. It was not possible to isolate any of the intermediates 5–**8** under the reaction conditions.

In summary, we have developed a simple and efficient procedure for the synthesis of benzoxazinones from 2-hydroxy-2-(2′-hydroxy-aryl)-1,3-indanediones through an acid catalyzed rearrangement followed by condensation with hydroxylamine. The present method constitutes a one-pot reaction from easily prepared starting materials and easy work-up procedure. To the best of our knowledge, this is the first time the synthesis of benzoxazinone skeleton from C2-arylated 1,3-indanediones has been accomplished.

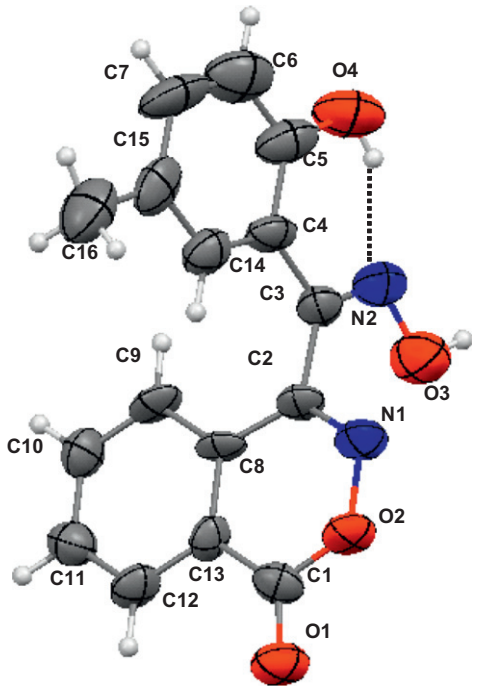


Figure 1. ORTEP diagram of **4b** with atom numbering scheme. Thermal ellipsoids are shown at the 50% probability. Intramolecular hydrogen bond is shown as dotted line. Color code: red, oxygen; blue, nitrogen; gray, carbon; light gray, hydrogen.

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Supplementary data

Supplementary data (IR, ^{1}H, ^{13}C data of compounds **4a**, **4d**, and **4f** and crystallographic data for **4b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.076.

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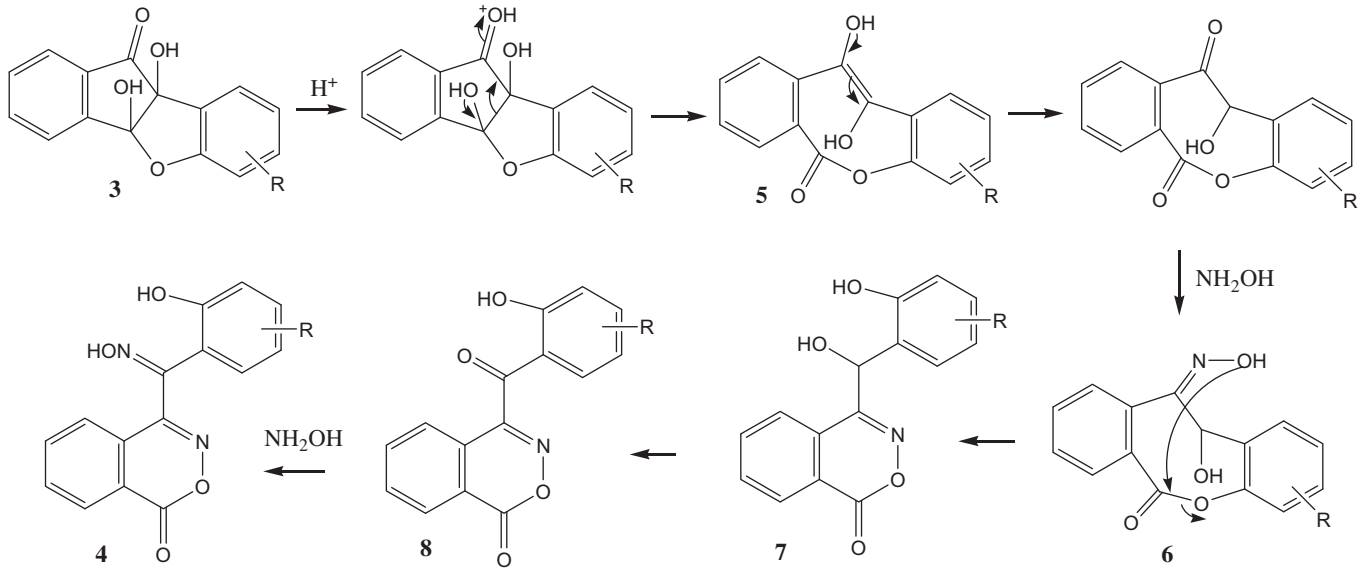

Scheme 2. Proposed mechanism for the formation of 2,3-benzoxazinone derivatives **4**.

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15. General procedure for the preparation of benzoxazinones **4a**–**f**: The appropriate substrate **2a**–**f** (1.4 mmol) was added to ethanol (15 ml) followed by the addition of hydroxylamine hydrochloride (650 mg, 9.4 mmol). The reaction mixture was refluxed for about 3 h. The cold reaction mixture was then poured into 50–60 ml ice cold water. The solid product separated was filtered and washed with water. The resulting solids were purified by crystallization from acetone to give pure products **4a**–**f**.
16. 4-((2-Hydroxy-5-methylphenyl)(hydroxyimino)methyl)-1*H*-benzo[*d*][1,2]oxazin-1-one **4b**: IR (KBr): 3322, 3214, 1710 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.20 (1H, s), 9.91 (1H, s), 8.29 (1H, dd, J = 7.6, 1.2 Hz), 8.04–7.93 (2H, m), 7.53 (1H, dd, J = 7.3, 1.0 Hz), 7.28 (1H, d, J = 1.5 Hz), 7.06 (1H, dd, J = 8.3, 1.8 Hz), 6.71 (1H, d, J = 8.4 Hz), 2.16 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.0, 154.0, 153.9, 148.2, 136.3, 134.5, 132.0, 128.9, 128.2, 127.8, 127.2, 126.0, 121.5, 119.4, 116.4, 20.0; Anal Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.80; H, 4.02; N, 9.37. 4-((2-Hydroxy-5-methoxyphenyl)(hydroxyimino)methyl)-1*H*-benzo[*d*][1,2]oxazin-1-one **4c**: IR (KBr): 3345, 3224, 1708 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.23 (1H, s), 9.56 (1H, s), 8.28 (1H, d, J = 7.2 Hz), 8.04–7.93 (2H, m), 7.54 (1H, d, J = 7.5 Hz), 7.06 (1H, d, J = 3.0 Hz), 6.88 (1H, dd, J = 8.7, 3.0 Hz), 6.70 (1H, d, J = 9.0 Hz), 3.66 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.0, 154.4, 152.2, 149.9, 147.4, 136.2, 134.4, 127.7, 127.3, 126.2, 121.3, 120.5, 117.6, 117.4, 112.9, 55.6. Anal Calcd for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.49; H, 3.82; N, 8.93. 4-((5-Chloro-2-hydroxy-4-methylphenyl)(hydroxyimino)methyl)-1*H*-benzo[*d*][1,2]oxazin-1-one **4e**: IR (KBr): 3222, 1707 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.37 (1H, s), 10.28 (1H, s), 8.39 (1H, d, J = 8.4 Hz), 8.03–7.93 (2H, m), 7.62–7.50 (2H, m), 6.76 (1H, s), 2.21 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.9, 154.7, 153.9, 146.6, 138.8, 136.2, 134.5, 128.1, 127.8, 127.2, 126.0, 123.6, 121.5, 119.5, 118.9, 19.7. Anal Calcd for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; N, 8.47. Found: C, 58.04; H, 3.30; N, 8.42.
17. Crystallographic data for the structure **4b** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 809903. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk).