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## Fischer's base<sup>†</sup> as a protecting group: protection and deprotection of 2-hydroxybenzaldehydes

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### Abstract

The hydroxyl and aldehyde groups of 2-hydroxybenzaldehydes were protected by the reaction with Fischer's base and deprotected by the ozonolysis in methanol at  $-78^{\circ}\text{C}$  to give the corresponding 2-hydroxybenzaldehydes in good to high yields. © 2000 Elsevier Science Ltd. All rights reserved.

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The selective chemical modifications of 2-hydroxybenzaldehydes having other functional groups are very important, because 2-hydroxybenzaldehydes have been known as good substrates for salen Schiff's base derivatives which were useful in various fields.<sup>1</sup> However, the selective chemical modification of 2-hydroxybenzaldehydes having hydroxyl and/or aldehyde groups is not easy due to the preexistence of these functional groups in these molecules. One reported method for the selective functional transformation of 2,4-dihydroxybenzaldehydes is limited to the alkylation at the 4-hydroxyl group using so called regioselective modification under basic conditions.<sup>2</sup> This selective method is very specific and limited to the 2,4-dihydroxybenzaldehyde. Therefore, the development of the selective and general protecting groups for 2-hydroxybenzaldehydes might be very useful.

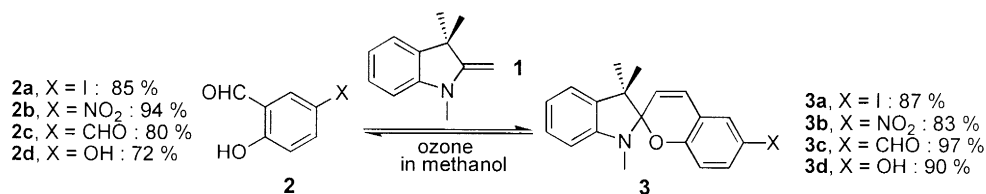
Here we report an efficient protecting method of 2-hydroxybenzaldehydes **2** using Fischer's base **1**: the protection and deprotection of the hydroxyl and aldehyde group of 2-hydroxybenzaldehydes is also reported.

The reaction of 2-hydroxybenzaldehydes **2** with Fischer's base **1** in ethanol under reflux gave the corresponding spiropyrans **3** in high yield by the known conditions<sup>3</sup> (Scheme 1). The treatment of spiropyran **3a** with reagents such as  $\text{KMnO}_4$ <sup>4a</sup> or  $\text{NaIO}_4$ <sup>4b</sup> gave a 2-hydroxybenzaldehyde **2a** in various solvent systems in low yield (less than 20%) and unidentified side products. However, when spiropyran

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<sup>†</sup> Fischer's base is available commercially as 2-methylene-1,3,3-trimethylindoline.

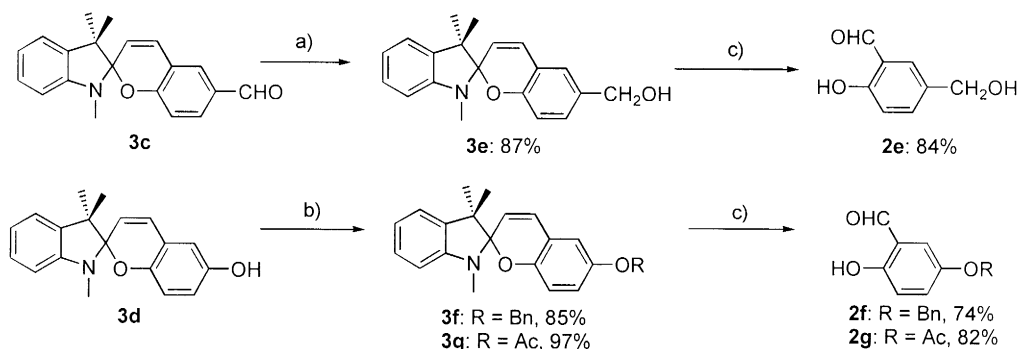
**3a** was treated with ozone at  $-78^{\circ}\text{C}$  in methanol, 2-hydroxybenzaldehyde **2a** was obtained in 85% yield.<sup>5</sup> The results for the protection and the deprotection are shown in Scheme 1.



Scheme 1.

A representative experimental procedure for the deprotection is as follows: Ozone was passed through a solution of spiropyran **3a** (100 mg, 0.248 mmol) in methanol (5 ml), cooled to  $-78^{\circ}\text{C}$  for 5 min. Excess ozone was then purged from the system by bubbling oxygen through the reaction mixture for 10 min, quenched by addition of excess amount of methyl sulfide. The solvent was then removed by the evaporation under reduced pressure. The concentrate was chromatographed on silica gel column using a mixture of ethyl acetate and *n*-hexane (1:30) to give a 2-hydroxyaldehyde **2a**.

The chemical transformations of spiropyrans as protected forms followed by the deprotection were tried (Scheme 2). The formylspiropyran **3c** was reduced using sodium borohydride in ethanol at room temperature to give an alcohol **3e**,<sup>6</sup> which was treated with ozone in methanol at  $-78^{\circ}\text{C}$  to give 2-hydroxy-5-hydroxymethylbenzaldehyde **2e** in 84%. The 6-hydroxyspiropyran **3d** was benzylated by the reaction with benzyl bromide in the presence of potassium carbonate in acetonitrile at reflux to give an ether **3f** in 85% yield<sup>7</sup> and acetylated using acetic anhydride in the presence of triethylamine in methylene chloride at rt to give an ester **3g** in 97% yield.<sup>8</sup> The ozonolysis of the ether **3f** and the ester **3g** gave the corresponding 2-hydroxybenzaldehydes **2f** and **2g** in 74% and 82% yield, respectively.



Scheme 2. (a) NaBH<sub>4</sub> in ethanol at rt, 5 min; (b) benzyl bromide and K<sub>2</sub>CO<sub>3</sub> in acetonitrile at reflux, 3 h /Ac<sub>2</sub>O and Et<sub>3</sub>N in methylene chloride at rt, 30 min; (c) ozonolysis in methanol at  $-78^{\circ}\text{C}$

In conclusion, the hydroxyl and aldehyde group of 2-hydroxybenzaldehydes were protected at the same time by their reaction with Fischer's base in ethanol under reflux to give the corresponding spiropyrans, the protected form of 2-hydroxybenzaldehydes. The spiropyrans were efficiently cleaved by ozonolysis to give the corresponding 2-hydroxybenzaldehydes in high yields.

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