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AN EFFICIENT AND CONVENIENT SYNTHESIS OF 5-FORMYLSALICYLALDEHYDE

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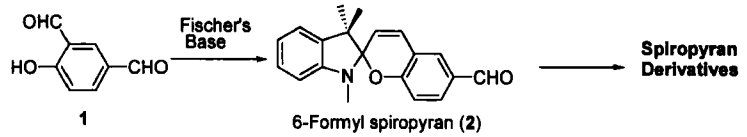
Abstract: 5-Formylsalicylaldehyde **1**, which is a key intermediate of spiropyran dye and a recently developed insulin sensitivity enhancer (ISE) compounds, was prepared from 5-iodosalicylaldehyde by the palladium-catalyzed coupling reaction with ethyl acrylate followed by ozonolysis in high overall yield (92%).

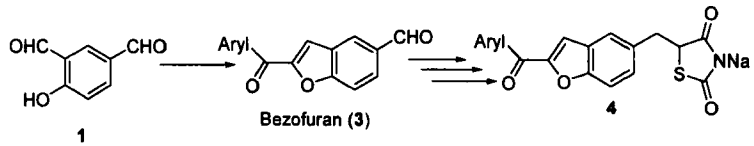
5-Formylsalicylaldehyde **1** is a starting material for the synthesis of 6-formylspiropyran **2**, which could be a key substrate for a variety of photochromic spiropyran derivatives, which have been paid considerable attention, due to their potential application in many new technologies, including the area of high-density optical data storage, optical switching, displays, and non-linear optics (Scheme 1).[1-3]

5-Formylsalicylaldehyde **1** is also a key intermediate for the synthesis of the various 2,5-disubstituted benzofuran spacers **3**, which are a key substrate for the parent compound of several derivatives, insulin sensitivity enhancer(ISE) compounds **4**, prepared by Beecham Group PLC and



1 6-Formyl spiropyran (2)

Scheme 1



1 Bezofuran (3) 4

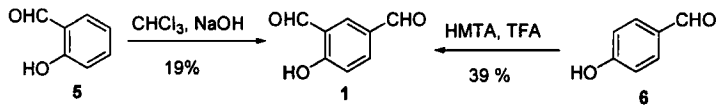
Scheme 2

developed through parallel efforts in a collaboration between Tanabe Seiyaku Co., Ltd. and Eli Lilly and Co. (Scheme 2).[4]

Two previous methods for the synthesis of 5-formylsalicylaldehyde have been known (Scheme 3). The first one is Reimer-Tiemann methodology for the synthesis of 5-formylsalicylaldehyde from salicylaldehyde **5**, which is generally ineffective. After column chromatography on silica gel, 5-formylsalicylaldehyde **1** of satisfactory purity was obtained only in 19 % yield.[5] The reaction of 4-hydroxybenzaldehyde **6** under the same condition lead to the similar result.

The second method is the reaction of 4-hydroxybenzaldehyde **6** with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) at reflux. The reaction gave 5-formylsalicylaldehyde **1** as the major component of the crude mixture. Treatment of the extracted product with ethanol led to crystalline material in 39% yield.[6] This method is better than Reimer-Tiemann methodology in yield respect.

However, it has a problem to follow because a large scale of strong acid (HCl) should be used during work-up and too inefficient to do because trifluoroacetic acid used as solvent is expensive and corrosive, and dangerous to do in large scale in the Lab because HMTA is cancer suspect reagent.

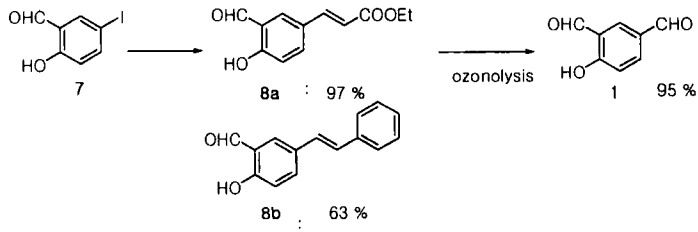


Scheme 3

Here, we report one of the very convenient and efficient method for the synthesis of 5-formylsalicylaldehyde, which can apply to the small or large scale preparation of salicylaldehyde. Our approach to 5-formylsalicylaldehyde is palladium catalyzed coupling reaction with olefins followed by ozonolysis and summarized in Scheme 4. 5-Iodosalicylaldehyde[7] in acetonitrile was coupled with styrene or ethyl acrylate using palladium acetate as catalyst in the presence of tri-*o*-tolylphosphine as ligand and triethylamine as base to give ethyl 3-(3-formyl-4-hydroxyphenyl)prop-2-enoate **8a** and 2-hydroxy-5-(2-phenylvinyl)benzaldehyde **8b** in 97% and 63% isolated yields, respectively. The yield of the coupling reaction with styrene was much lower than that of coupling reaction with ethyl acrylate. The starting material was left in the reaction with styrene even if the reaction time was extended. The purification of **8a** is simple: the reaction mixture was concentrated and run a short pad of silica gel using a mixture of ethyl acetate and hexane (1:20). The column chromatography on silica gel was needed to get a reasonably pure material of **8b** due to the remaining starting material **7**. The ester **8a** was ozonized in methylene chloride at -78 °C to give 5-formylsalicylaldehyde in 95% isolated yield. These two steps are very simple and efficient (overall yield for these two steps is 92%).

In conclusion, we developed an efficient and convenient synthetic methodology of 5-formylsalicylaldehyde **1**, which needed two steps from 5-iodosalicylaldehyde **7**. The two steps include palladium-catalyzed coupling reaction and ozonolysis.

Further study for the synthesis of spiropyran derivative is under way and will be reported in due course.



Scheme 4

Experimental

Melting points were determined using a Electrothermal IA 900 and are uncorrected. IR spectra were taken with an Analet Instrument FT-IR (MAP-60) spectrometer using KBr pellets. The ^{1}H NMR spectra were recorded on a Bruker Ac 200. Electron Impact mass spectra were recorded on a Schimadzu GCMS-QP1000 spectro- photometer. Silica gel 60 (70-230 mesh, Merck) was used for column chromatography, and silica gel 60F_{254} plates (0.25 mm, Merck) were used for TLC.

Ethyl 3-(3-formyl-4-hydroxyphenyl)prop-2-enoate (8a): A mixture of 5-iodosalicylaldehyde (1 g, 4.03 mmol), ethyl acrylate (0.81 g, 2 equiv.), palladium acetate (46 mg, 0.1 mmol), tri-*o*-tolylphosphine (122 mg, 0.2 mmol) and triethylamine (4 ml) in acetonitrile (50 ml) was heated to reflux for 2 h. It was concentrated under reduced pressure and run a short pad of silica gel using a mixture of ethyl acetate and hexane (1:20). The concentration gave a pale yellow product (864 mg) in 97% yield. mp : 67.7-69.5 °C. IR (KBr Pellet, cm^{-1}): 1702 (C=O ester), 1638 (C=C alkene), 1582 (C=C aromatic), 1182 (C-O), ^{1}H NMR ($CDCl_3$): δ 1.34 (q, 3H, J = 6.9 Hz), 4.27 (t, 2H, J = 6.9), 6.37 (d, 1H, J = 8.1 Hz), 7.03 (d, 1H, J = 9.0 Hz), 7.62-7.75 (m, 3H), 9.93 (s, 1H), 11.20 (s, 1H). Mass m/z (relative intensity)(EI, 70 eV) : 220 (M^+, 89), 192 (24), 176 (14), 175 (100), 148 (42), 147 (46), 146 (26), 145 (14), 119 (18), 91 (36), 89 (27), 65 (38).

2-Hydroxy-5-(2-phenylvinyl)benzaldehyde (8b): A mixture of 5-iodosalicylaldehyde (330 mg, 1.33 mmol), styrene (0.15 ml, 2 equiv.), palladium acetate (15 mg, 0.1 mmol), tri-*o*-tolylphosphine (40 mg, 0.2 mmol), and triethylamine (1.3 ml) in acetonitrile (30 ml) was heated to reflux for 3 h. It was then concentrated under reduced pressure, and chromatographed on silica gel using a mixture of ethyl acetate and hexane (1:10). The eluate was concentrated to give a yellow product in 63% yield (190 mg). mp : 108.2-200.0 ℃ IR (KBr Pellet, cm^{-1}): 1662 (C=C alkene), 1586 (C=C aromatic) ^1H NMR ($CDCl_3$) δ 6.99-7.13 (m, 2H), 7.31-7.52 (m, 6H), 7.66 (s, 1H), 7.73 (d, 1H, J = 8.8 Hz), 9.95 (s, 1H), 11.02 (s, 1H). Mass m/z (relative intensity) : 224 (M^+, 100), 204 (24), 178 (30), 177 (22), 165 (26), 152 (16), 115 (8), 89 (8).

5-Formylsalicylaldehyde 1: Ozone was passed through a mixture of ethyl 3-(3-formyl-4-hydroxyphenyl)prop-2-enoate **8a** (600 mg, 2.72 mmol) in methylene chloride (40 ml), cooled to -78 ℃, until a blue color persisted. Excess ozone was then purged from the system by bubbling oxygen through the reaction mixture for 15 min, followed by addition of methyl sulfide. The solvent was then removed by the evaporation under reduced pressure to give a reasonably pure 5-formylsalicyaldehdye in 95% yield (390 mg). The spectral data are consistent with the reported one.[6] ^1H NMR ($CDCl_3$) δ 7.15 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 8.8 Hz), 8.15 (s, 1H), 9.95 (s, 1H), 10.01 (s, 1H).

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