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5-Formyl Salicylaldehyde as a Linker for the Synthesis of Benzofuran Containing Insulin Sensitivity Enhancer Compounds

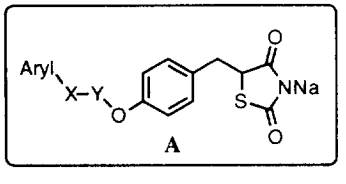
John R. Stille,* Jeffrey A. Ward, Cindy Leffelman, and Kevin A. Sullivan

Chemical Process Research and Development, Lilly Research Laboratories, Indianapolis, IN 46285-4813

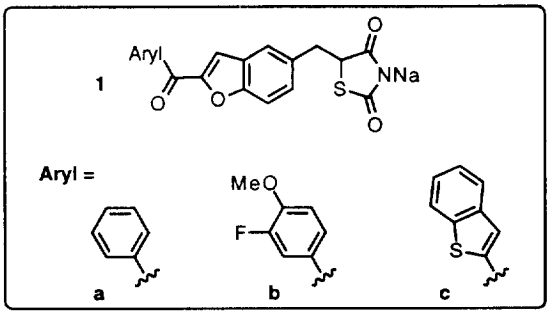
Abstract: 5-Formyl salicylaldehyde was prepared by treatment of 4-hydroxybenzaldehyde with HMTA in TFA. Reaction of this dialdehyde with α-haloacetyl aryl compounds gave 2,5-disubstituted benzofurans, from which an Insulin Sensitivity Enhancer compound was prepared.

Non-insulin dependent diabetes mellitus (NIDDM, Type II) is a chronic, progressive disease in which patients exhibit peripheral insulin resistance, obesity, and hyperglycemia.[1] Current treatment for Type II diabetes is a balanced program of exercise, controlled diet, and sulphonylurea drug therapy for improved glycemic control. Sulphonylurea compounds act through stimulation of insulin secretion, which has the potential to induce fatal hypoglycemia. In contrast, a series of 2,4-thiazolidinedione compounds were found to act as insulin sensitivity enhancers in the peripheral tissue and did not lower plasma glucose beyond acceptable levels, even in nondiabetic animal models.

Most insulin sensitivity enhancer (ISE) compounds have the general structure **A**, which consists of the 2,4-thiazolidinedione analog of tyrosine, a tether (-X-Y-), and an aromatic moiety (Aryl). Recent efforts have found that conformational control of the Y-O-Ph linkage, through use of bicyclic dihydrobenzopyran,[2] dihydrobenzofuran,[2] benzoxazine,[3] benzoxazole,[4] benzofuran,[5] or a more complex ring system[6] as aromatic spacers, has led to improved pharmacological activity. Of particular interest are compounds **1a**, the parent compound of several derivatives prepared by Beecham Group PLC,[5] and **1b** and **1c**, developed through parallel efforts in a collaboration between Tanabe Seiyaku Co., Ltd. and Eli Lilly and Co.

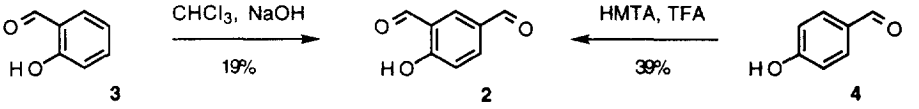


A



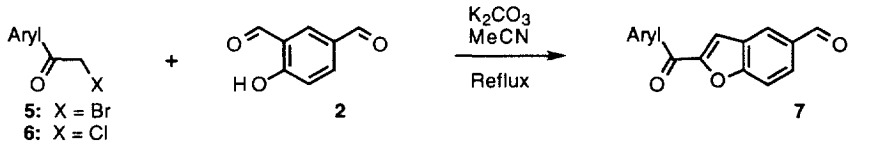
Route development for the synthesis of the various 2,5-disubstituted benzofuran spacers required an economical and efficient means of generating significant quantities of 5-formyl salicylaldehyde (**2**).[5] Previous methods for the synthesis of **2** were problematic for large scale synthesis. Established Reimer-Tiemann methodology for the synthesis of **2** from **3** by consecutive formylation was generally ineffective.[7] In these

systems, chromatography was required to obtain material of satisfactory purity in 19% isolated yield (eq. 1).[8] Treatment of **4** under similar conditions led to the same results, however, reaction with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA)[9] at reflux gave **2** as the major component of the crude mixture.[10] The key to the utility of this reaction centered around the work up procedure. Treatment of the extracted product with EtOH led to crystalline material in 39% yield without the need for chromatographic purification.[11]

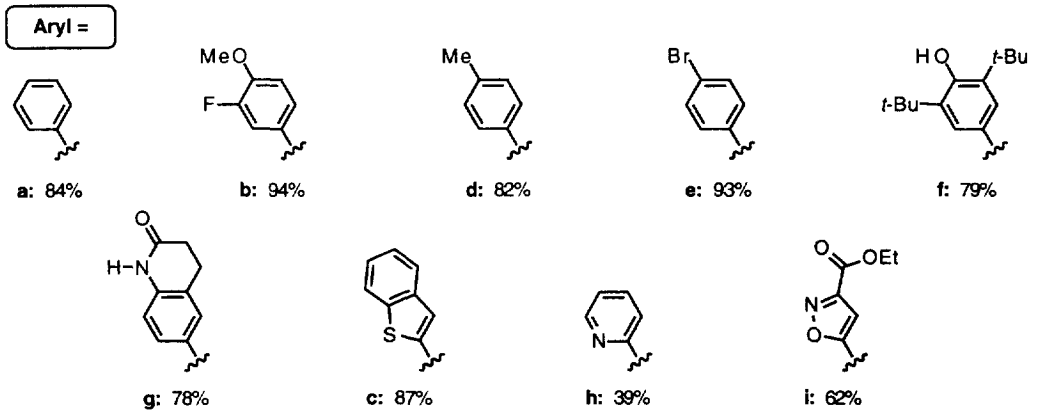


(1)

Benzofuran formation from **2** was accomplished with K_2CO_3 in MeCN. Typical reaction conditions for the synthesis of benzofurans utilize K_2CO_3 in either acetone, 2-butanone, DMF,[12] or under phase transfer conditions.[13] However, the use of MeCN as the solvent for benzofuran formation resulted in a cleaner reaction profile, easier product isolation, higher yields, and lower levels of residual solvent (eq. 2). When MeCN was employed, minor complications due to acetone aldol condensation and self-condensation were circumvented, and problems due to product isolation (greater product solubility in DMF) and the presence of residual DMF were avoided. The use of MeCN provided general conditions for the efficient reaction of **2** with a variety of haloacetyl aryl species **5** or **6** to give 2-aroyl-5-formylbenzofuran products.

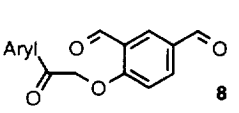


(2)

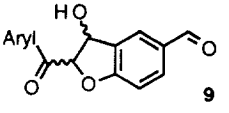


Reaction of **2** with **5**, promoted by K_2CO_3 in MeCN at reflux, led to benzofuran formation in high yield (eq. 2).[14] During this process, the initial alkylation of the phenol was found to occur almost immediately to give **8**. Formation of diastereomeric β-hydroxy ketone intermediates **9** was then observed prior to dehydration to generate **7**. Benzofuran formation under these conditions proceeded well for unfunctionalized aromatic

groups (**a** and **d**), as well as for **e**, which has potential for subsequent transition metal coupling reactions. Compound **7b**, an intermediate for one of the targeted ISE compounds, was generated in 94% yield from **5b**. Substrates that contained O-H (**5f**) and N-H (**5g**) functionality also gave benzofuran formation in good yield.

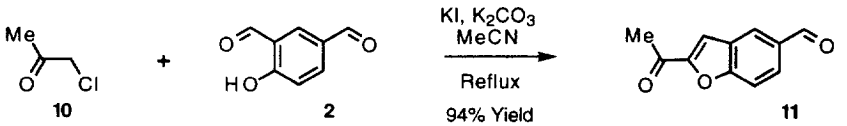


8



9

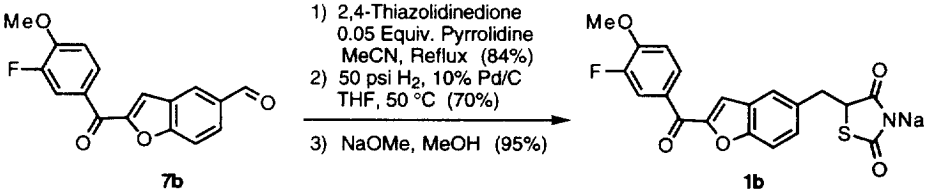
The use of heterocyclic aromatic species for benzofuran formation was equally successful. Reaction of **6c** with **2** was slow, and the addition of KI to the mixture was required to promote generation of the desired product. Presumably, metathesis to the corresponding iodoacetyl species occurred during the reaction, which facilitated alkylation of the phenol and provided an 87% yield of the desired product. Reaction with heterocyclic derivatives **5h**[15] and **5i** gave the corresponding products in somewhat lower yield.[16]



10 **2** **11** (3)

Reaction of **2** with **10** was slow in MeCN, but again the reaction rate was accelerated by the addition of KI to the mixture, and **11** was isolated in 94% yield (eq. 3).

Extension of this benzofuran chemistry to form **7b** led to the synthesis of insulin sensitivity enhancer **1b** (eq. 4). Condensation with 2,4-thiazolidinedione was catalyzed with 0.05 equiv. of pyrrolidine in MeCN. Subsequent catalytic hydrogenation and salt formation led to the synthesis of **1b**. Overall, the four-step synthesis of **1b** from **2** was accomplished in 53% yield, which represents an overall five-step process from **4** in 20% yield.



7b **1b** (4)

In this study, an efficient synthesis of **2** was developed, and conditions for effective utilization of **2** in the general synthesis of a variety of 2-aroyl-5-formylbenzophenone products was established, including **7a**, which led to the efficient synthesis of the ISE compound **1b**.

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10. Typical procedure for the synthesis of **2**: To a solution of **4** (119.8 g, 981 mmol) in 988 mL of TFA was added HMTA (137.5 g, 981 mmol) in one portion under nitrogen. After the addition was complete, the solution temperature had reached 65 °C (mild exotherm), and then external heating was used to reflux (≈98 °C) the reaction mixture for 24 h. The reaction was then quenched by the addition of 1550 mL of 3 *N* HCl, and the heat source was removed and the mixture was allowed to cool to 40 °C over the course of 3 h. The mixture was extracted with CH_2Cl_2 (4 x 1865 mL), and the combined organic layers were concentrated to an oil. Addition of 135 mL of EtOH resulted in the crystallization of **2** as a light yellow solid, which was then washed with cold EtOH (2 x 50 mL), filtered, and dried to give **2** (56.64 g, 377 mmol) in 38.5% yield. The resultant filtrate was concentrated to a slurry, filtered, washed with EtOH (3 x 20 mL), and dried to give additional **2** (13.93 g, 93 mmol, 9.5% yield), which had a lower potency.
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14. Typical procedure for the synthesis of **7**: A mixture of α-bromo compound **5b** (376 g, 1.52 mol), **2** (229 g, 1.52 mol), and K_2CO_3 (211 g, 1.52 mol) was taken up in MeCN (5.4 L) and stirred with overhead mechanical stirring. The heterogeneous mixture was heated at reflux for 3 h under an atmosphere of N_2 until the transformation was complete (HPLC). After the heat source was removed, 10.8 L of H_2O was added, and the stirred mixture was allowed to cool to ambient temperature overnight (due to the reaction scale). The mixture was filtered, washed with H_2O/MeCN; 2:1 (2 x 1.5 L), MeCN (2 x 1.5 L), and then dried *in vacuo* at 50-60 °C overnight to give **7b** (425 g, 1.42 mol) in 94% yield.
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