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A Practical Pilot-Scale Synthesis of 4-Vinyl-2,3-dihydrobenzofuran Using Imidate Ester Chemistry and Phase-Transfer Catalysis

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Abstract:

A two-step telescoped synthesis of 4-vinyl-2,3-dihydrobenzofuran (2) was demonstrated using imidate ester chemistry and phase-transfer catalysis. Treatment of 2,3-bis(2-hydroxyethyl)-phenol (1) with the Vilsmeier reagent resulted in an in situ generation of a bis-imidate intermediate 4, which was converted to 4-(2-chloroethyl)-2,3-dihydrobenzofuran (6) via a sequential ring closure and chloride displacement reactions. Further dehydrohalogenation of 6 using a phase-transfer catalyst provided an excellent, cost-effective method to prepare high quality 4-vinyl-2,3-dihydrobenzofuran (2). The yields for the two-step telescoped process ranged from 83 to 90%.

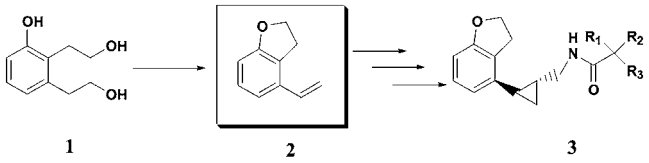
Introduction

Recently, several melatonin agonists containing substituted dihydrobenzofurans having generic structure **3** (Scheme 1) have been identified at Bristol−Myers Squibb.[1] For the synthesis of these compounds, 4-vinyl-2,3-dihydrobenzofuran (**2**) is a versatile early intermediate, allowing further manipulation at the vinyl group. As this program moved into larger clinical studies, the requirements for the active pharmaceutical ingredient increased to multikilogram quantities, requiring hundreds of kilograms of **2** per year. Therefore, an efficient synthesis of the 4-vinyl2,3-dihydrobenzofuran (**2**) became essential. In this paper, we describe a practical and scaleable synthesis of **2**.

Early in the development of this project, 2,3-bis(2-hydroxyethyl)phenol (**1**) (triol) was used as the starting material because of its ready availability from the industrial intermediate 5,8-dihydro-1-naphthol via ozonolysis and reduction.[2] At the outset, **2** was prepared via bis-tosylation of the triol **1** followed by cyclization and elimination.[3] This approach was not pursued for the large-scale preparation of **2** because of the moderate yield (69%), lack of atom efficiency, and low temperature requirements (−40 °C) during the bis-tosylation step.

A published method for the synthesis of **2** involves the Cu-catalyzed intramolecular cyclization of 2-(2′-chlorophenyl)ethanol using NaH as the base followed by palladium-catalyzed vinyl tin coupling.[4] Although this is an interesting approach, we felt that it was not practical for multikilogram synthesis, particularly because of potential metal waste disposal issues.

Scheme 1



Recently, Procopiou[5,6] and Barrett[7] have reported use of the Vilsmeier reagent for the cyclization of hydroxyphenols to afford dihydrobenzofurans via formation of an imidate ester followed by displacement with phenoxide. This chemistry was especially attractive to us for large-scale operations because of its atom efficiency and environmentally acceptable byproducts such as DMF and triethylamine hydrochloride. Application of these conditions with **1** (Scheme 2) resulted in an intermediate chloroethyldihydrobenzofuran **6**, which, on subsequent dehydrohalogenation using a phase-transfer catalyst in the presence of a base, afforded the desired 4-vinyl-2,3-dihydrobenzofuran (**2**). Besides the obvious advantages of efficiency, speed, and ease of workup, this approach led to high overall conversion and produced high quality material which did not require further purification. This two-step method yielded **2** in 83−90% yield and ≥98% purity. Furthermore, this "one-pot" approach was accomplished without isolating any intermediates.

Results and Discussion

In the previous reports,[6,7] the imidate esters were prepared at room temperature, and cyclization was accomplished after addition of a base followed by refluxing for more than 15 h. In our case, we found that a proper temperature control during imidate formation was very critical for the quality and yield of **2**. Also, the cyclization required lower temperatures and shorter reaction times than those indicated in the original papers. A detailed investigation of the reaction parameters such as the temperature, solvent, and stoichiom-

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(2) Ellis, F.; Panchal, T.; North, P.; Cooke, J.; Smith, C. (Glaxo Wellcome) W00743272 A2 19971120.

(3) At Bristol−Myers Squibb, the preparation of 4-vinyl-2,3-dihydrobenzofuran via the tosylation approach was developed and optimized by W. Li, J. Thornton, Z. Guo, J. Zhu, W. Yang, T. Vu, A. Singh, V. Rosso, D. Lust, S. Prasad, M. Yang, and D. Kacsur.

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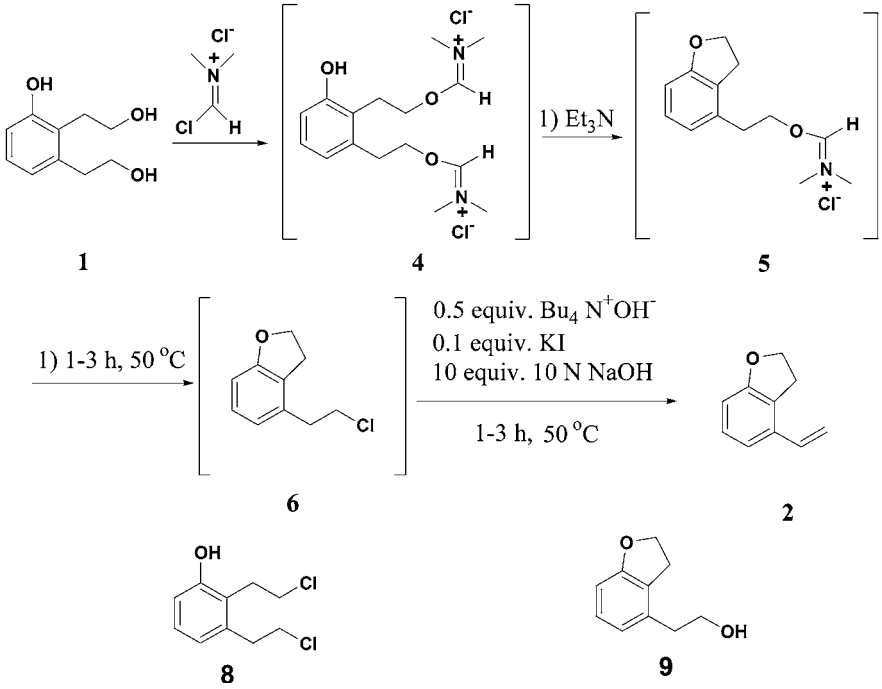
Scheme 2



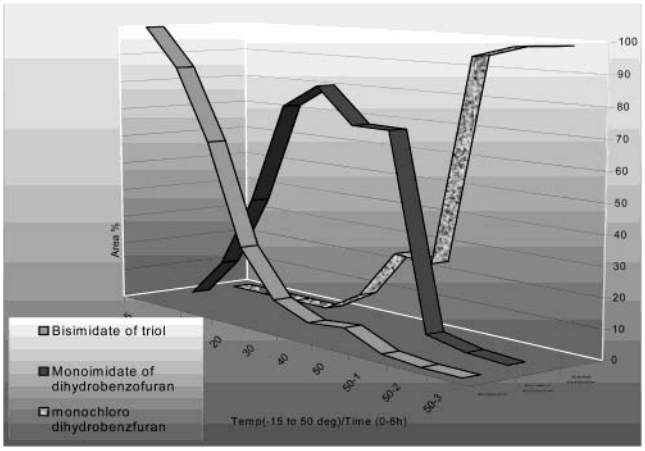


Figure 1. **Kinetics for the conversion of 1 to 2.**

etry of base revealed that formation of **6** occurred via a three-step sequence. The first intermediate in the sequence was bis-imidate **4**, formed within 15 min at an optimum reaction temperature of −20 °C. The second intermediate, monoimidate **5**, was formed via ring closure after addition of 4 equiv of triethylamine at temperatures between −15 °C and −20 °C followed by warming of the reaction mixture to 0 °C. Further heating of the reaction mixture to 50 °C converted **5** to **6**. The various intermediates in the reaction were monitored by HPLC, and the presence of the imidate esters was confirmed by LC/MS as their formate esters. A graphic representation of the HPLC data for conversion of the triol **1** to **6** via various intermediates is shown in Figure 1.

The choice of solvent for the formation of **6** was also critical. Although the reaction of **1** with the Vilsmeier reagent could be carried out in THF, CH_2Cl_2, DMF, or CH_3CN, conversion of the mono-imidate **5** to **6** was successful only in CH_3CN. A possible explanation for this is that the $Et_3NH^+Cl^-$ salt, being soluble in CH_3CN, provided a sufficient concentration of chloride ions and the polar nature of CH_3CN favored the substitution. After 3 h, the reaction was complete, the chloroethyldihydrobenzofuran was dissolved in MTBE, and the salts were removed by aqueous washes.

The stoichiometry of triethylamine in the cyclization step was a factor in controlling the formation of impurities. More than 4 equiv of Et_3N resulted in 2−10% of 4-(2-hydroxyethyl)-2,3-dihydrobenzofuran (**9**), and less than 3.8 equiv of Et_3N gave 4−7% of 2,3-bis(2-chloroethyl)phenol (**8**) and 1% of **9**. Since 4−7% of 2,3-bis(2-chloroethyl)phenol (**8**) cyclized and eliminated to the desired **2** in the next step, **9** became the major impurity in the final product. Since we preferred to avoid purification **2** via distillation, it was important to keep the levels of impurity as low as possible. This was accomplished by the use of 3.9 equiv of Et_3N. The impurity **9** was observed as the major product when *t*-NaOBu was used as the base instead of Et_3N.

A number of bases, such as IRA 68, IRA-400, NaOH, NH_4OH, Na_2CO_3, K_2HPO_4, DIPEA, DBU, *t*-NaOBu, and $Bu_4N^+OH^-$, were screened for the dehydrohalogenation of **6**. Of all the bases tried, only $Bu_4N^+OH^-$ and *t*-NaOBu were found to convert the chloroethyldihydrobenzofuran to 4-vinyl-2,3-dihydrobenzofuran (**2**) cleanly. Since $Bu_4N^+OH^-$ worked, phase-transfer catalysis was pursued because of its simplicity. Initially, under phase-transfer conditions, even with equimolar amounts of $Bu_4N^+OH^-$, the reaction was found to be very slow and was incomplete after 24 h. However, the addition of catalytic amounts of KI significantly improved the rate of reaction. Finally the reaction conditions were optimized where only 0.15 equiv of $Bu_4N^+OH^-$, 0.1 equiv of KI, and 10 equiv of NaOH were required to complete the reaction in 3 h at 50 °C. The phase-transfer catalyzed elimination was nearly quantitative and could be carried out in MTBE, toluene, or 2-methyltetrahydrofuran. It did not work in polar

Table 1. **Yields of 4-Vinyl-2,3,-dihydrobenzofuran**

run	input **1** (triol), kg	output **2**, kg	M % yield	% purity HPLC
1	0.0115	0.083	90	99
2	0.16	0.11	83	98
3	65	44.2	85	99
3	65	44.5	85	98

solvents such as CH_3CN or THF but tolerated a maximum of 20% of CH_3CN in MTBE without slowing significantly. Excess *t*-NaOBu could also be used for dehydrohalogenation to 4-vinyl-2,3,-dihydrobenzofuran (**2**); however, yields using the base were 70−75%, and the product was more colored, which proved detrimental to the subsequent chemistry.[8]

4-Vinyl-2,3-dihydrobenzofuran (**2**) was purified by vacuum distillation[9] (40 °C at 0.5 mmHg) on a laboratory scale. However, we preferred to avoid this operation on scale due to the potential risk of polymerization of **2** at high temperatures for an extended period. Polymerization of **2** was a significant stability issue and was shown to occur under neutral or acidic conditions. However, under basic conditions, **2** can be stored without any degradation for several weeks.

The process reported here for the synthesis of **2** is a two-step telescoped process. Prior to this, attempts had been made to develop a single-step, one-pot process for the conversion of the imidate intermediates to **2**. Several bases were examined instead of Et_3N such as NMM, DIEA, proton sponge, DBU, *t*-NaOBu, and DMAP. Only DBU was successful in converting the bis-imidate to 4-vinyl-2,3-dihydrobenzofuran (**2**), albeit in low yields (60%). The 4-vinyl-2,3-dihydrobenzofuran (**2**) obtained by this process was highly colored and required purification by vacuum distillation. The cost of DBU, the modest yields, and the requirement for purification ended interest in the single-step approach.

Summary

The two-step telescoped process for the synthesis of 4-vinyl-2,3-dihydrobenzofuran (**2**) proceeds via **6**, which was not isolated. An aqueous extraction is efficient in the removal of most process impurities. Phase-transfer catalyzed dehydrohalogenation proved to be an excellent, cost-effective method for obtaining high quality **2** without distillation. The yields for the two-step process on a laboratory scale ranged from 83 to 90%; results on a pilot plant scale[10] are summarized in Table 1.

Experimental Section

General. The triol, 2,3-bis(2-hydroxyethyl)phenol was obtained from DSM-Andeno and had a minimum of 91.4 area % by HPLC. The Vilsmeier reagent, 40% tetra-*n*-butylammonium hydroxide, and potassium iodide were commercially available and used as is. MTBE and CH_3CN were used without any purification or drying. The moisture content in CH_3CN should be ≤0.05% w/w. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a w/w basis. Melting points were obtained using a Thomas−Hoover melting point apparatus and are uncorrected. Proton and carbon NMR were recorded on a Bruker AC-300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C in $CDCl_3$ solution using Me_4Si as an internal standard. HPLC analysis was performed under the following conditions: column = YMC Phenyl, S 5 μm; 120 A°, 3.0 × 150 mm^2, flow rate 0.5 mL/min, detector 225 nm, injection volume 10 μL, column temperature = rt. Mobile phase A: 10% CH_3CN, 90% H_2O (0.1% v/v TFA). Mobile phase B: 90% CH_3CN, 10% H_2O (0.08% v/v TFA) according to the timetable below:

time (min)	% A	% B
0	70	30
25	30	70

Typical retention times are 2.22 min for triol **1**, 4.08 min for hydroxyethyl dihydrobenzofuran **9**, 6.62 min for the bis-imidate **4**, 8.41 min for the mono-imidate **5**, 11.94 min for the product **2**, 15.22 min for the chloroethyldihydrobenzofuran **6**, and 19.07 min for the di(chloroethyl)dihydrobenzofuran **8**.

Purity and potency of the products obtained were determined by comparison with purified authentic samples using quantitative HPLC. Gas chromatography was performed under the following conditions: column Restek Rt-X1, 30 m, ID 0.32 mm, T_i = 40 °C (hold for 5 min), T_f = 275 °C (hold for 4 min), heating rate = 10 °C/min. The retention times are 2.22 min for CH_3CN, 3.08 min for MTBE, and 1.58 min for MeOH.

4-(2-Chloroethyl)-2,3-dihydrobenzofuran (6). To a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermocouple, and N_2 was added Vilsmeier reagent (19.3 g, 151 mmol, 2.5 equiv). The flask was cooled to an internal temperature −15 °C to −20 °C and then charged with 76 mL of CH_3CN. To the cooled yellow slurry was added 2,3-bis(2-hydroxyethyl)phenol (**1**) (10.97 g, 60 mmol, 1 equiv) in portions over 20 min. The reaction was exothermic, and careful control of the temperature to ≤−15 °C was required. The reaction was stirred for 30 min until it was complete as judged by the disappearance of the triol by HPLC. A dilute solution of Et_3N (24.39 g, 241 mmol, 4.0 equiv) in acetonitrile (1:1 by volume) was added slowly while the temperature was maintained between −15 °C and − 20 °C. The reaction was heated to 50 °C for 3 h until the mono-imidate was completely converted to the chloroethyldihydrobenzofuran. The reaction mixture was cooled to room temperature and quenched with 25 mL of water; all the salts dissolved. The mixture was concentrated to one-half the original volume and charged with 80 mL of MTBE

(8) In the subsequent chemistry, an asymmetric cyclopropanation was accomplished by treating the vinyl-dihydrobenzofuran with ethyl diazoacetate in the presence of a chiral auxiliary. The author would like to thank Drs. James H. Simpson and Atul Kotnis for evaluating several laboratory-scale batches of the vinyl-dihydrobenzofuran in the cyclopropanation chemistry and helping us in identifying optimized parameters for the preparation of the vinyl-dihydrobenzofuran.

(9) Unpublished information, Dr. James H. Simpson of Bristol-Myers Squibb.

(10) Authors would like to thank Doris Chen and the New Brunswick Pilot Plant staff for helping the authors in successful scale-up operations.

and 35 mL of water. The organic phase was separated and washed twice with 55 mL of 10% w/v H_3PO_4 solution in 10% w/v brine. The MTBE phase was then assayed by GC and quantitated against a 4-(2-chloroethyl)-2,3-dihydrobenzofuran (**6**) standard and found to contain 10.1 g of **6** (92%). Samples for NMR assays were prepared by removing MTBE under reduced pressure. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, 2 H), 3.15 (t, 2 H), 3.70 (t, 2 H), 4.45 (t, 2 H), 6.60 (d, 1H), 6.70 (d, 1H), 7.05 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 30, 37.5, 46, 72.5, 110, 122.5, 128, 130, 137.5, 162. HRMS [M + H] calcd for $C_{10}H_{11}ClO$, 182.05; found, 183.05.

4-Vinyl-2,3-dihydrobenzofuran (2). To a 500-mL, three-necked flask containing the MTBE solution of 4-(2-chloroethyl)-2,3-dihydrobenzofuran (**6**), 28 mL of water, 31.7 mL (600 mmol, 10 equiv) of 50% w/w NaOH, 13.8 mL (21 mmol, 0.35 equiv) of 40% w/v tetrabutylammonium hydroxide, and 1.0 g (6.0 mmol, 0.1 equiv) of solid KI were added. The reaction mixture was heated to 50 °C for 3 h until the reaction was found to be complete by HPLC (<1 relative area % of **6** remaining). On completion of the reaction, the phases were separated at 50 °C to minimize the loss of the product into the rag layer. The rag layer was discarded. The organic phase was cooled and washed once with 45 mL of 0.5 M sodium thiosulfate in 10% w/v brine followed by a wash with 45 mL of 1 N sodium hydroxide in 10% w/v brine. The MTBE solution contained 7.3 g (83%) of 4-vinyl-2,3-dihydrobenzofuran (**2**). Samples for NMR assays were prepared by removing MTBE under reduced pressure or by distilling crude oil as mentioned in the text. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (m, 2 H), 4.45 (t, 2 H), 5.25 (d, 1 H), 5.65 (d, 1H), 6.6 (d, 1H), 6.7(d, 1H), 6.95 (d, 1H), 7.05 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 28.84, 70.78, 108.25, 115.33, 117.48, 124.65, 127.87, 134.15, 134.52, 160.09. HRMS [M + H] calcd for $C_{10}H_{10}O$, 146.07; found, 147.07.

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