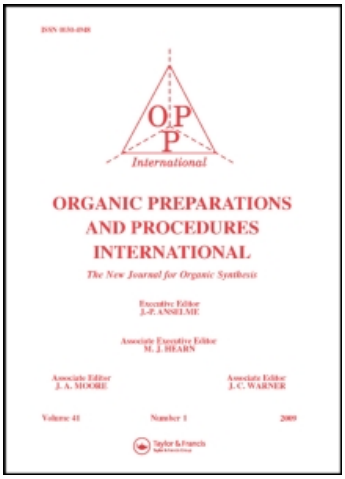

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A PRACTICAL SYNTHESIS OF 4-HYDROXYETHYL-2,3-DIHYDROBENZOFURAN

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OPPI BRIEFS

A PRACTICAL SYNTHESIS OF 4-HYDROXYETHYL-2,3-DIHYDROBENZOFURAN

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(01/17/08)

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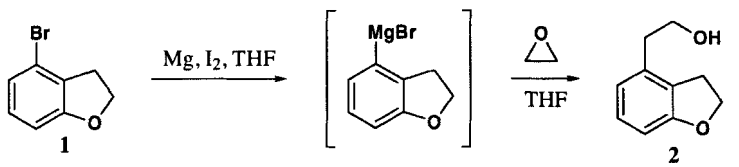
4-Hydroxyethyl-2,3-dihydrobenzofuran (**2**) is a versatile early intermediate in the preparation of several melatonin agonists containing substituted dihydrobenzofurans.[1,2] Though it is a useful molecule, a review of the literature, including patents, indicated the absence of an easily-performed synthesis. As part of our research program on the study of ethylene oxide,[3] we have developed a practical pilot-scale method for the preparation of 4-hydroxyethyl-2,3-dihydrobenzofuran from ethylene oxide and 4-bromo-2,3-dihydrobenzofuran (*Scheme 1*). The latter compound was prepared by cyclization of 2,6-dibromo- phenylethanol obtained by reduction of 2,6-dibromophenylacetic acid according to literature procedure.[4-6] The obvious advantages of this process are efficiency, speed and ease of workup.



Scheme 1

Treatment of the Grignard reagent from 4-bromo-2,3-dihydrobenzofuran with ethylene oxide under various conditions led to very little conversion when performed at –20°C and 2-bromoethanol was obtained as the major product in over 70% yield.[7] Further investigation indicated that the temperature is the key factor and the yield of 4-hydroxyethyl-2,3-dihydrobenzofuran (**2**) increased to 93% when the temperature was raised to 45°C. However, the yield decreased when the reaction was performed above 55°C because of polymerization of ethylene oxide. To our surprise, unlike the literature data[7] and our previous report,[3] no 2-bromoethanol was obtained when the reaction was performed above 40°C.

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected. The purity of products was established on a HPLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 (400 MHz) instrument with TMS as internal standard. Infrared spectra were obtained on a Shimadzu IR-408 instrument. All chemicals were reagent grade and available commercially. The elemental analysis was performed on a Flash EA1112 instrument.

4-Hydroxyethyl-2,3-dihydrobenzofuran.- In a 500 mL round-bottomed flask, fitted with a stirrer, an addition funnel, and a reflux condenser fitted with a calcium chloride tube, was placed 8.0 g (0.33 mol) of magnesium chips, a small crystal of iodine and 200 mL anhydrous tetrahydrofuran. A solution of 5.0 g (0.025 mol) 4-bromo-2,3-dihydro- benzofuran in 10 mL of anhydrous tetrahydrofuran was added and the temperature was raised to 75°C. As soon as the reaction started, the remainder of the 4-bromo-2,3- dihydrobenzofuran (44.8 g, 0.25 mol in all), dissolved in 90 mL of anhydrous tetrahydrofuran solution, was dropwise added at such a rate that the mixture boiled continuously. The mixture was stirred at 80°C for another 0.5 h then cooled to 45°C. Then a solution of ethylene oxide (13.2 g, 0.30 mol) in 60 mL of anhydrous tetrahydrofuran was added over 2-3 h. When the addition was complete, the mixture was stirred for another 1.5 h at 55°C. Evaporation of tetrahydrofuran gave a pale yellow solid which was treated with 50 mL 1 M hydrobromic acid. The mixture was extracted with ether (50 mL x 3) and dried over $MgSO_4$. Evaporation of the solvent gave a liquid which was fractionally distilled to afford 38.1 g (93%) of a colorless oil, bp. 110-113°C/20 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.85 (1 H, b), 2.80 (2 H, t, J = 6.6 Hz), 3.16 (2 H, t, J = 8.2 Hz), 3.82 (2 H, t, J = 6.6 Hz), 4.54 (2 H, t, J = 8.2 Hz), 6.66 (1 H, d, J = 7.6 Hz), 6.69 (1 H, d, J = 7.6 Hz), 7.06 (1 H, t, J = 7.6 Hz).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.28; H, 7.45.

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AN IMPROVED SYNTHETIC PROCESS FOR YF-6, A PROMISING ANTI-HBV DRUG CANDIDATE

Submitted by Sai Hong Jiang, Peng Lu, Xiao Zhong Fu, Yu She Yang* and Ru Yun Ji
(12/14/07)

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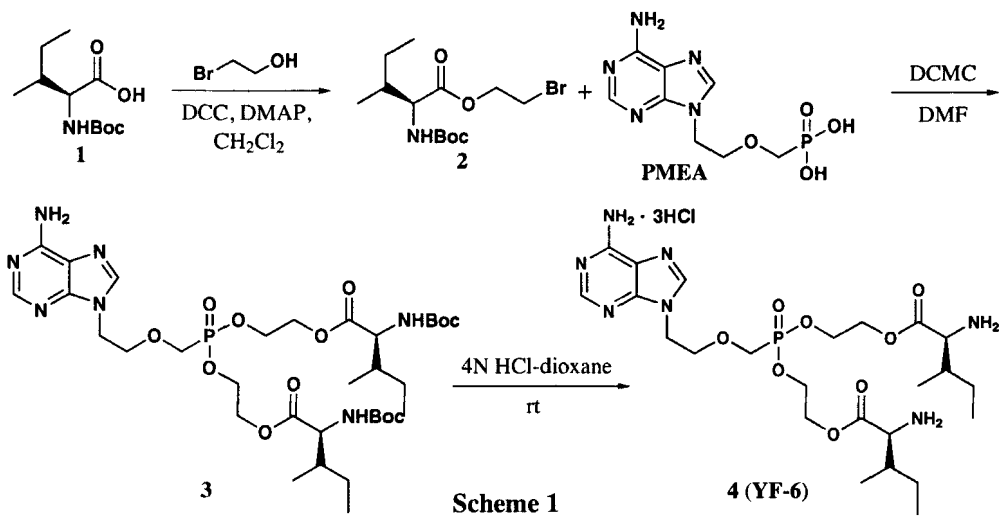
YF-6 (**4**), an ethylene glycol-linked L-amino acid conjugate of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), is a promising anti-HBV drug candidate which has been reported from our laboratory, albeit in less than 2% overall yield (*Scheme 1*).[1] Condensation of



Scheme 1