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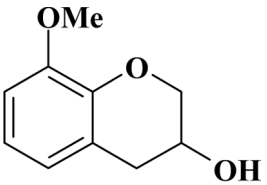
EFFICIENT SYNTHESIS OF 8-METHOXY-3,4-DIHYDRO-2H-1-BENZOPYRAN-3-OL

A. V. Shindikar and C. L. Viswanathan
Bombay College of Pharmacy, Mumbai, India

GRAPHICAL ABSTRACT



(1)

Abstract *The article reports a practical, simple, and inexpensive procedure for the synthesis of 8-methoxy-3,4-dihydro-2H-1-benzopyran-3-ol (**1**). 2-Methoxy phenol on treatment offers the oxirane compound, which undergoes ring cleavage under acidic conditions to give a chlorohydrin, which on acylation and cyclization in the presence of stannic chloride followed by hydrolysis of the acetyl group, yields the desired compound (**1**).*

Keywords Benzopyranol; 3-chromanol; nipradilol; vasodilator

INTRODUCTION

Benzopyranols have emerged as an important class of heterocycles and have attracted significant synthetic interest because of their pharmacological and therapeutic properties.[1–3] Several bioactive natural products containing benzopyranol moieties exibit antibacterial, antioxidant, and photoprotective action.[4,5] Additionally, 8-methoxy-3,4-dihydro-2H-1-benzopyran-3-ol (**1**) is a key intermediate in the synthesis of Nipradilol (**A**), a β-adrenoreceptor blocking agent with vasodilator action.[6,7]

Methods for the synthesis of 8-methoxy-3,4-dihydro-2H-1-benzopyran-3-ol are reported in the literature. These include, for example, sodium borohydride reduction of 3-chromanone,[8] epoxidation of methoxy-2-allyl phenyl acetates followed by breaking of the epoxide ring, cyclization of chlorohydrin in the presence of a base to get benzopyranol,[7,9] and oxidative cyclization of p-substituted allylphenyl ether

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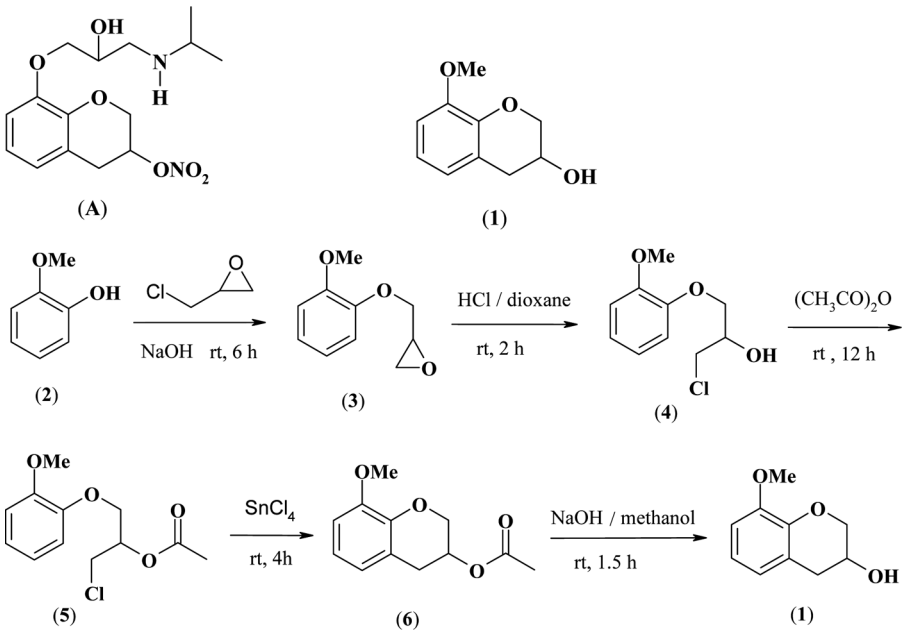
Address correspondence to A. V. Shindikar, Bombay College of Pharmacy, Kalina, Santacruz (E), Mumbai 400 098, India. E-mail: anandshindikar@gmail.com

derivatives using $Ti_2(SO_4)_3$-H_2SO_4.[10] These methods have disadvantages such as a large number of steps, harsh reaction conditions, or tedious procedures. We therefore aimed at overcoming the disadvantages of the reported methods and provide a simple and efficient synthetic protocol for **1**.

RESULTS AND DISCUSSION

Synthesis of **1** was carried out as shown in Scheme 1. 2-Methoxyphenol (**2**) on treatment with epichlorhydrin in alkaline conditions afforded (**3**), which led to chlorohydrin (**4**) with the opening of the epoxide ring by treatment with HCl. Then **4** was acetylated using acetic anhydride to get **5**. Ring closure of **5** with stannic chloride gave **6**, which on hydrolysis of the 3-acetyl group gave the desired 8-methoxy-3,4-dihydro-2H-1-benzopyran-3-ol (**1**). The advantages offered by this method are (i) easily available starting material, (ii) simple operation (e.g., no high-temperature reactions are involved), and insensitivity to air, (iii) cost-effectiveness (e.g., avoids use of costly reagents such as m-chloroperbenzoic acid, used in other methods), and (iv) good product yields.

Friedel–Craft's alkyation using stannic chloride as the catalyst, which offers good yields, is reported in the literature.[11,12] Thus, in the present method, the ability of stannic chloride to effect alkylation/ring closure with less possibility of generation of undesired material resulted in good yields. These advantages make the present method useful for large-scale operations.



Scheme 1. Synthesis of 8-methoxy-3,4-dihydro-2H-1-benzopyran-3-ol.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) using silica-gel GF-254 precoated plates from Merck. Infrared (IR) spectra were recorded on a Shimadzu IR spectrometer. ^{1}H NMR spectra were recorded using tetramethylsilane (TMS) as an internal standard on a Varian 300-MHz instrument.

Procedure for Compound 3

Epichlorhydrin (83.25 g, 0.9 M) was added to a solution of guaiacol (**2**) (37.2 g, 0.3 M) in 2 N aqueous sodium hydroxide (150 ml), and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (150 ml) and extracted with chloroform (3 × 150 ml). The chloroform layer was washed with aqueous sodium hydroxide solution (2 × 100 ml), dried over $MgSO_4$, and evaporated in vacuo to afford compound **3**.

Procedure for Compound 4

A solution of **3** (34 g, 0.19 M) in tetrahydrofuran (THF; 210 ml) was cooled to 5 °C in an ice bath. To it was added 210 ml of HCl in dioxane (dry dioxane containing 18.5% w/w of hydrogen chloride), and the mixture was stirred at 5–10 °C for 2 h. The reaction mixture was poured into cold water (450 ml) and extracted with ethyl acetate (3 × 200 ml). The ethyl acetate layer was washed with water (2 × 100 ml), dried over $MgSO_4$, and evaporated in vacuo to give the compound **4**.

Procedure for Compound 5

Triethylamine (0.9 g, 0.009 M) and acetic anhydride (9.18 g, 0.09 M) were successively added to a solution of **4** (20 g, 0.09 M) in 200 ml of chloroform, and the mixture was stirred at room temperature for 12 h. Then 100 ml of 10% aqueous K_2CO_3 was added to the reaction mixture, and the layers were separated. The chloroform layer was washed with water (2 × 100 ml), dried over $MgSO_4$, and evaporated in vacuo to give compound **5**.

Procedure for Compound 6

Stannic chloride (26.20 g, 0.1 M) was added to a solution of **5** (20 g, 0.07 M) in 100 ml benzene, and the mixture was stirred at room temperature for 4 h under a nitrogen stream. The reaction mixture was then poured over ice-cold water (200 ml) and extracted with chloroform (3 × 100 ml). The organic layer was washed with diluted HCl (100 ml), saturated $NaHCO_3$ (100 ml), and water (2 × 100 ml); dried over $MgSO_4$; and evaporated in vacuo to give compound **6**.

Procedure for Compound 1

To a solution of **6** (6.6 g, 0.03 M) in methanol (65 ml) was added 2 N aqueous sodium hydroxide (20 ml). The mixture was stirred at room temperature for 1.5 h and

then neutralized with 1 N hydrochloric acid. The neutralized mixture was extracted with chloroform (3×100 ml). The chloroform layer was dried over $MgSO_4$ and evaporated in vacuo to give a viscous residue, which on stirring with benzene–hexane mixture gave a crystalline product (**1**).

SPECTRAL DATA

2-(2-Methoxyphenoxymethyl)oxirane (3)

Yield 70%; colorless liquid; IR (KBr) ν: 1255 (C-O), 1224 (C-O-C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ ppm): 6.98–6.92 (2H, m, ArH), 6.80–6.76 (2H, m, ArH), 4.24 (2H, d, -CH_2-), 3.85 (3H, m, O-CH_3), 3.34–3.32 (1H, m, C-H), 2.85–2.72 (2H, m, -CH_2-). Anal. calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67; O, 26.66. Found: C, 66.60; H, 6.70; O, 26.59.

1-Chloro-3-(2-methoxyphenoxy)propan-2-ol (4)

Yield 51%; colorless liquid; IR (KBr) ν: 3427 (O-H), 1255 (C-O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ ppm): 6.98–6.94 (2H, m, ArH), 6.82–6.74 (2H, m, ArH), 4.24 (2H, d, -CH_2-), 4.10 (1H, m, C-H), 3.85 (3H, s, O-CH_3), 3.81–3.79 (2H, d, -CH_2-), 3.02 (1H, s, O-H). Anal. calcd. for $C_{10}H_{13}ClO_3$: C, 55.55; H, 6.02; Cl, 16.43; O, 22.22. Found: C, 55.60; H, 5.97; Cl, 16.50; O, 22.31.

1-Chloro-3-(2-methoxyphenoxy)propan-2-yl Acetate (5)

Yield 85%; colorless liquid; IR (KBr) ν: 1745 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ ppm): 6.98–6.89 (2H, m, ArH), 6.82–6.75 (2H, m, ArH), 4.34 (2H, d, -CH_2-), 3.85 (3H, s, O-CH_3), 3.74–3.69 (2H, d, -CH_2-), 2.03 (1H, s, O-H). Anal. calcd. for $C_{12}H_{15}ClO_4$: C, 55.70; H, 5.81; Cl, 13.76; O, 24.81. Found: C, 55.81; H, 5.89; Cl, 13.68; O, 24.71.

8-Methoxy-3,4-dihydro-2H-1-benzopyran-3-yl Acetate (6)

Yield 72%; pale yellow liquid; IR (KBr) ν: 1745 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ ppm): 6.98–6.89 (2H, m, ArH), 6.82–6.75 (2H, m, ArH), 4.34 (2H, d, -CH_2-), 3.85 (3H, s, O-CH_3), 3.74–3.69 (2H, d, -CH_2-), 2.03 (1H, s, O-H). Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30; O, 28.83. Found: C, 64.98; H, 6.41; O, 28.70.

8-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ol (1)

Yield 73%; mp 77–79°C; IR (KBr) ν: 3427 (O-H), 1269 (C-O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (δ ppm): 7.00–6.86 (2H, m, ArH), 6.77–6.73 (1H, m, ArH), 4.30–4.25 (1H, m, C-H), 3.88 (3H, s, O-CH_3), 2.96–2.92 (2H, m, -CH_2-), 2.91–2.86 (2H, m, -CH_2-), 2.10 (1H, m, O-H). Anal. calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67; O, 26.66. Found: C, 66.59; H, 6.58; O, 26.60.

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