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Note

Synthesis of *N*-[2-benzyloxy-5-(2-oxiranyl)-phenyl]formamide: Formal synthesis of formoterol

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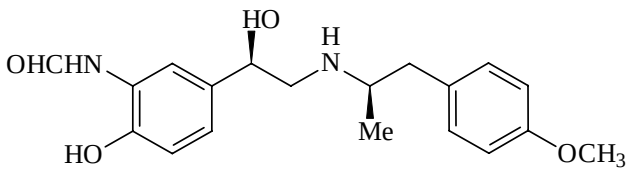
Nitration, benzylation followed by bromination of 4- hydroxyacetophenone is described to obtain nitrobenzyloxyphenacyl bromide derivative **3**. Sodiumborohydride reduction of **3** gives rise to the diol **6**. Reaction of **6** with Ph_3P/I_2/imidazole yields styrene derivative **7**. Compound **7** on selective reduction of the nitro group followed by *N*-formylation and epoxidation affords the key intermediate *N-[2*-benzyloxy-5-(2-oxiranyl)phenyl]formamide **4**.

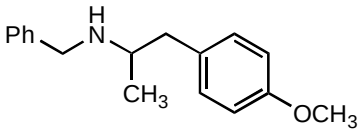
IPC: **Int.Cl.**[7] **C 07 C**

Formoterol **1** is a highly potent β_2-selective adrenoceptor agonist with a long effect duration when inhaled[1]. The isomer with *(R)*-configuration at both chiral centres was the most potent, the other being less potent[2]. The generic name formoterol refers to the enantiomeric mixture, which is currently marketed (Foradil) as a racemate, as are the β_2-agonists albuterol, salmeterol or terbutaline. Enantioselective[3] and chemoenzymatic[4] synthesis of all the four stereoisomers of formoterol **1** has been described.

In spite of its interesting properties, a very few syntheses of **1** have been reported. Synthesis of **1** has earlier been described by condensation of *N*-benzyl-(*p*-methoxy-α-methylphenethyl)amine[2a,5] **2** with 4-benzyloxy-3-nitrophenacylbromide[6] **3** and 4-benzyloxy-3-formamidophenyl oxirane[7] **4**. Preparation of **4** starting from 4-hydroxy benzaldehyde in five steps is described in patented literature[7].



Formoterol (*R,R*)-**1**



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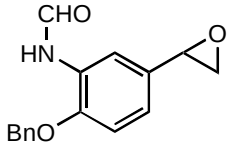

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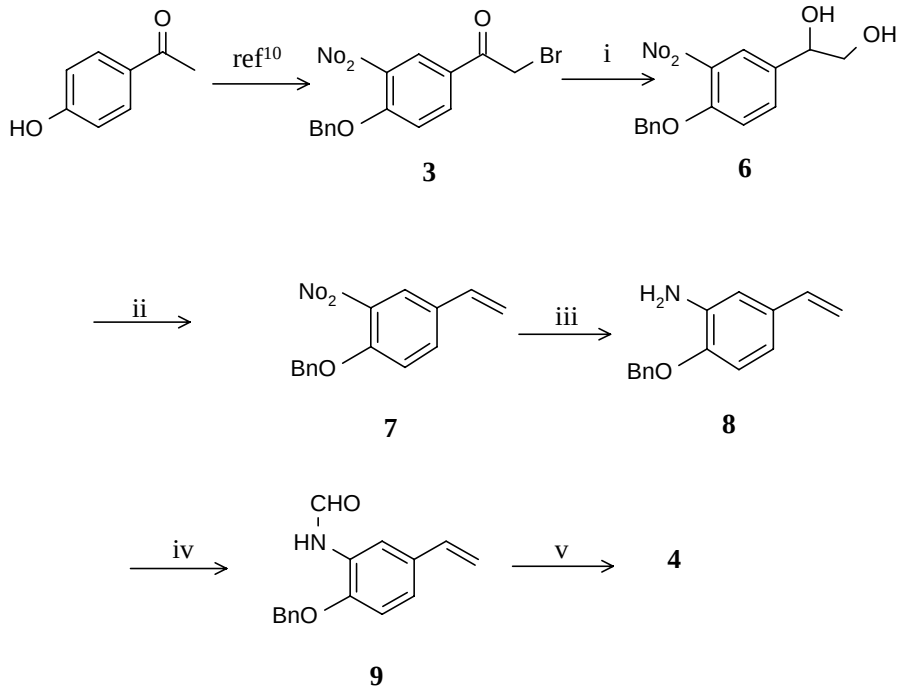
Earlier we have described a simple synthesis of right side fragment **2**[8] from *p*-anisaldehyde and now in this communication an alternative method for the synthesis of left side fragment 4-benzyloxy-3-formamidophenyloxirane **4** thereby completing the formal synthesis of **1**. 4-Hydroxyacetophenone was converted to the known 3-nitro-4-benzyloxyphenacyl bromide derivative **3** (**Scheme I**). Compound **3** on reduction with $NaBH_4$/MeOH at room temperature followed by treatment with glacial HOAc in a one pot reaction gave the styrene diol **6** in high yield (84%) as a crystalline solid, m.p. 72-74°C. Attempted isolation of the styrene oxide intermediate **5** in good yield was always difficult due to the formation of diol **6** during the workup of the reaction. The diol **6** on reaction with Ph_3P/I_2/imidazole/toluene[9] at 50°C for 4 hr gave the nitrostyrene derivative **7** as a crystalline solid in 91.7% yield, m.p. 92°C. Nitro derivative **7** on reduction with Fe powder in glacial HOAc at reflux temperature for 2 hr gave the amine **8** as a solid, m.p. 50°C in 79.5% yield. The amino compound **8** on reaction with Ac_2O/HCO_2H at 0°C gave the formamido derivative **9** as a syrup in 81.7% yield. Formamido derivative **9** was characterized from the ^{1}H NMR spectrum by the appearance of *N*-formyl group at δ 8.40, 8.50 (2s, 1H, NC*H*O) and styrene protons at δ 5.05-5.12 (m, 3H, PhCH_2O, H-2′), 5.65 (d, 1H, *J*=12.0Hz, H-2″) and δ 6.61 (dd, 1H, *J*=11.0Hz, H-1′). Formamido derivative **9** on reaction with *m*-CPBA/aq. $NaHCO_3$ at room temperature for 3 hr gave the formamido styreneoxide **4** as a syrup in 85% yield. Condensation of the epoxide **4** with the amine **2** has been reported earlier, thereby completing formal synthesis of formoterol **1**.

In conclusion, a simple method for the preparation of aminostyrene epoxide, an intermediate required for the preparation of **1** from 4-hydroxyacetophenone has been achieved.



i) $NaBH_4$, MeOH, RT, 3hr; ii) Ph_3P, imidazole, I2, PhMe, 50°C, 2hr; iii) Fe powder, AcOH, MeOH, reflux, 2hr; iv) CH_2Cl_2, Ac_2O, HCO_2H, 1.5hr; v) m-CPBA, aq.$NaHCO_3$, RT, 3hr.

Scheme I

Experimental Section

General. All the products were characterised by ^{1}H NMR spectroscopy. ^{1}H NMR spectra were recorded on an FT NMR, Varian 200 MHz spectrometer. The solvents and other chemicals used for the reactions were purified and/or dried as per the standard literature methods.

(4-Benzyloxy-3-nitrophenyl)ethane-1,2-diol 6. To a solution of **3** (35.0g, 0.1mmole) in methanol (125 mL) was added $NaBH_4$(3.8g, 0.1mmole) and the mixture stirred at room temperature for 3 hr. After completion of the reaction, the reaction mixture was diluted with methanol (30 mL) and acidified with glacial HOAc (6.2 mL). The reaction mixture was concentrated on a rotary evaporator to remove methanol, diluted with water (500 mL) and extracted into chloroform (200 mL). The organic phase was separated, washed with water (200 mL), dried (Na_2SO_4) and concentrated to isolate the title diol in 84% yield (24.0g), m.p. 72-74°C; ^{1}H NMR ($CDCl_3$): δ 2.80-3.20 (2H, brs,OH), 3.75-4.00 (m, 2H, H-2′,H-2″), 4.90 (t, 1H, *J* = 7.0 Hz, H-1′), 5.22 (s, 2H, PhC*H*$_2$O), 7.18 (d, 1H, *J*= 16.0Hz, H-5),7.25-7.50 (m, 5H, Ar-H), 7.59 (dd, 1H, *J*=10.0Hz, H-6), 7.89 (d, 1H, *J* = 3.0Hz, H-2); EIMS: m/z 289 (M^+); Anal. Calcd for $C_{15}H_{15}NO_3$:C, 62.28; H, 5.23; N, 4.85. Found: C, 62.12; H, 5.27; N, 4.98%.

2-Benzyloxy-5-vinylnitrobenzene 7. To a solution of diol **6** (13 g, 45.3 mmoles) in toluene (100 mL) was added triphenylphosphine (43.25 g, 164.5 mmoles) and imidazole (10.4 g, 152.5 mmoles) and the mixture heated to 50°C. Crystalline iodine (33.8 g, 133 mmoles) was added to the reaction mixture in small portions in about 20 min maintaining the temperature of the reaction mixture between 55-60°C for 1hr and then was heated to reflux for 2 hr. After completion of the reaction, the reaction mixture was cooled to room temperature, solvent removed and the residue obtained was extracted into ethyl acetate (100 mL). A second lot of iodine (7 g) was added to the organic layer followed by 5% aq. NaOH solution (60 mL) and stirred for 15 min at room temperature. The organic phase was separated and washed with 10% sodium thiosulphate solution (2×50 mL). Organic phase was dried ($NaSO_4$), concentrated and filtered on a bed of silica [60-120 mesh, hexane-ethyl acetate (1:1)] to obtain the title compound **7** in 91.7% (10.6 g) yield as a crystalline solid, m.p. 92°C; ^{1}H NMR ($CDCl_3$): δ 5.10-5.35 (m, 3H, PhC*H*$_2$O, H-2′), 5.15 (d, 1H,

J=16.0Hz, H-2′′), 6.60 (dd, 1H, *J*=11.0Hz, H-1′), 7.00(d, 1H, *J*=7.0Hz, H-3), 7.20-7.55 (m, 6H, 5 Ar-H, H-4), 7.82 (d, 1H, *J*=2.5Hz, H-6); EIMS: m/z 255 (M^+); Anal.Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.38; H,5.14; N,5.39%.

2-Benzyloxy-5-vinylaniline 8. To a solution of compound **7** (5 g, 19.6 mmoles) in methanol (20 mL) was added Fe powder (7 g, 125 mmoles) and HOAc (15 mL) and the mixture heated to reflux for 2hr. After completion of the reaction, the reaction mixture was poured into water and extracted into CH_2Cl_2 (2×50 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to syrupy residue and filtered on silica gel [SiO_2, 60-120 mesh; hexane-ethyl acetate (1:1)] to obtain the title compound **8** (3.5 g) as a crystalline solid in 79.5% yield, m.p.50°C; ^{1}H NMR ($CDCl_3$): δ 3.80 (brs, 2H, NH_2), 5.00-5.05 (m, 3H, PhC*H*$_2$O, H-2′), 5.50(d,1H,*J*=14.0Hz,H-2′′), 6.51 (dd, 1H, *J*=10.0 Hz, H-1′′), 6.65-6.80 (m, 3H, H-3,4,6), 7.25-7.45 (m, 5H, Ar-H); EIMS: m/z 225 (M^+): Anal. Calcd for $C_{15}H_{15}NO$: C, 79.95; H, 6.71; N, 6.22. Found: C, 79.78; H, 6.75; N, 6.18%.

***N*-(2-Benzyloxy-5-vinylphenyl)formamide 9**. To a solution of compound **8** (6.6 g, 26.05 mmoles) in CH_2Cl_2 (25 mL) under N_2 atmosphere at 0°C, was added a mixture of formic acid and acetic anhydride (2:5 v/v, 5 mL) and stirred for 1.5hr. After completion of the reaction, the reaction mixture was poured into water and extracted into CH_2Cl_2 (2×50mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to obtain the title compound **9** in 81.7% (6.05 g) yield as a syrup; ^{1}H NMR ($CDCl_3$): δ 5.05-5.12 (m, 3H, PhC*H*$_2$O, H-2′), 5.65 (d, 1H, *J*=12.0Hz, H-2′′), 6.61 (dd, 1H, *J*=10.0Hz, H-1′), 6.75-7.15 (m, 3H, H-3,4,6), 7.30-7.45 (m, 5H, Ar-H), 7.75 (brs, 1H, NH), 8.40-8.50 (2s, 1H, CHO); FABMS: m/z 253 (M^+); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.67; H, 5.88; N, 5.48%.

***N*-[2-Benzyloxy-5-(2-oxiranyl)phenyl]formamide 4**. To a solution of compound **9** (3 g, 11.2 mmoles) in CH_2Cl_2 (30 mL) was added *m*-CPBA (7.75 g, 44 mmoles) and saturated aqueous $NaHCO_3$ solution (20 mL) and stirred at room temperature for 3 hr. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed thoroughly with saturated aqueous $NaHCO_3$ solution. The organic phase was separated, concentrated, dried (Na_2SO_4) and filtered on a bed of silica gel [60-120 mesh eluted with hexane-ethyl acetate (7:3)] to obtain the title compound **4** in 85% (1.15g) yield as a syrup[7]. ^{1}H NMR ($CDCl_3$): δ 3.80-4.20 (m, 2 H, H-2′,H-2′′), 5.12 (s, 2H, PhC*H*$_2$O), 5.90-6.10 (m, 1H, H-1′), 6.85-7.20 (m, 2 H, H-3, 4), 7.30-7.60 (m, 6 H, Ar-H,H-6), 7.65-7.85 (m, 1H, NH), 8.40-8.55 (2s, 1H, CHO); FABMS: m/z 270(M+1). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.19; H, 5.64; N, 5.23%.

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