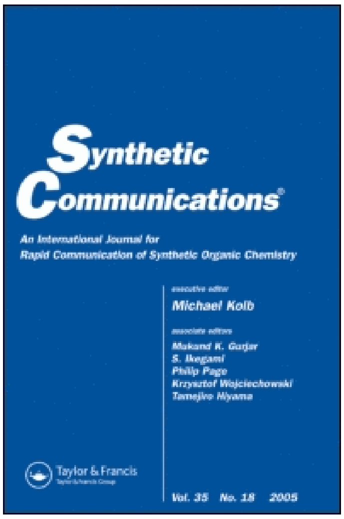

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M. K. Gurjar[a]; Shreerang V. Joshi[a]; B. S. Sastry[a]; A. V. Rama Rao[a]
[a] Indian Institute of Chemical Technology, Hyderabad, India

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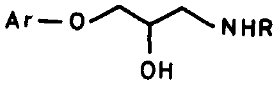
A NEW ROUTE TO (±) METOPROLOL

M.K. Gurjar*, Shreerang V Joshi, B.S. Sastry and A V Rama Rao
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract *Synthesis of 4-(2-methoxyethyl)phenol* (**5**) *from phenol is described. The derived aryloxyallyl ether* (**6**) *is converted into (±)-metoprolol* (**10**) *by involving dihydroxylation reaction with* OsO_4 *and NMO.*

Interest[1] in β-blocker drugs particularly belonging to the aryloxypropanolamine skeleton (1) has been stimulated since the introduction of propranolol in 1968. The general approach adopted[2] for the preparation of racemic β-blocker involves the condensation of substituted phenol derivative with epichlorohydrin followed by treatment with a suitable alkylamine.



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4-(2-Methoxyethyl)phenol (5) is the aromatic segment of metoprolol (10). Although several routes[3] to the preparation of 5 have been described, we felt the scope to devise a simple approach

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* To whom correspondence should be addressed.

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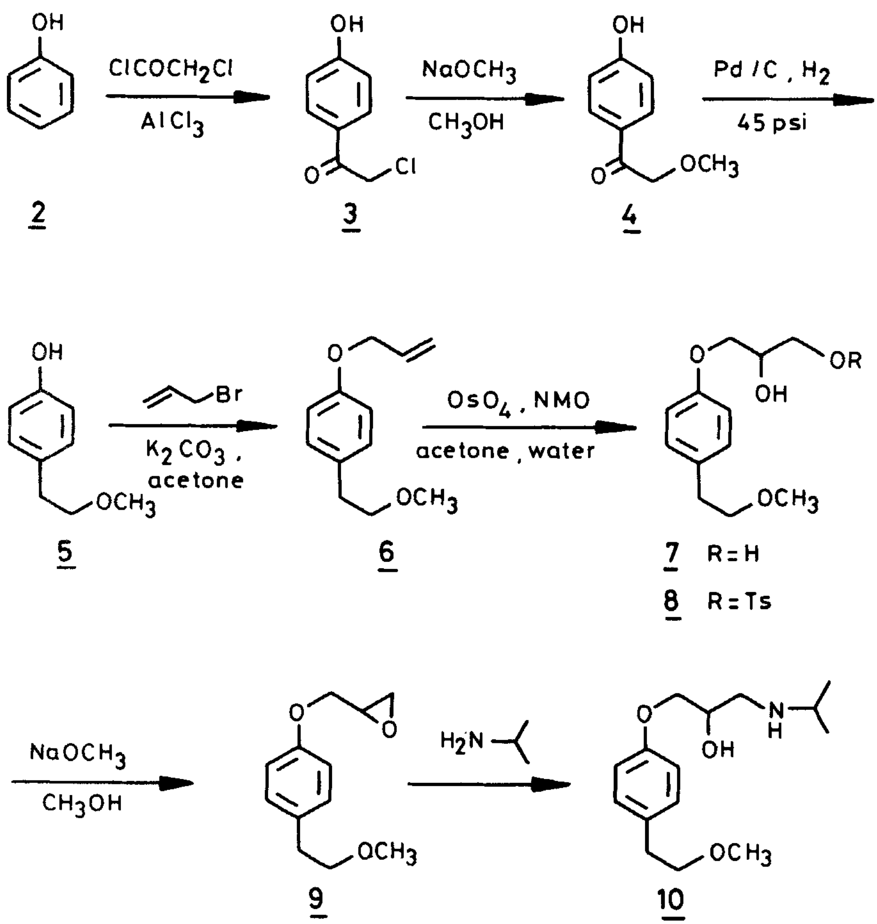
still existed. The route described here undoubtedly is suited for large scale manufacture of **5** and to the best of our knowledge has not been described. The dihydroxylation[4] of aryloxyallyl ether (**6**) leading to the formation of side-chain of metoprolol (**10**) is also presented.

2-Chloro-1-(4-hydroxyphenyl)ethanone (**3**) was prepared by a modified Friedel Crafts acylation[5] of phenol (**2**) with chloroacetyl chloride (yield 50%). Subsequent reaction of **3** with methanolic sodium methoxide at room temperature afforded **4** in 90% yield. The reduction of **4** over 10% Pd-C at 45 psi for 4 h gave **5** in 96% yield. The IR and NMR spectra of **5** were in good agreement with the spectrum of the authentic sample[3a,c].

Having prepared the requisite phenol derivative (**5**), the next concern was to introduce the propanolamine side chain. The dihydroxylation reaction of olefins in the presence of cat. OsO_4 and N-methylmorpholine-N-oxide (NMO) is a suitable technique for obtaining the corresponding diols. The recent modification[6] of employing $K_3Fe(CN)_6$ instead of NMO is a fruitful demonstration to appreciate the value of this reaction. Treatment of **5** with allyl bromide in the presence of potassium carbonate in refluxing acetone afforded **6** in 85% yield. The dihydroxylation reaction[4] of **6** with OsO_4-NMO (0.025 eq) (1.2 eq) in the presence of 2:1 water-acetone mixture at room temperature led to the formation of the diol (**7**) (80%). The diol was subsequently monotosylated by the conventional procedure to **8** followed by the epoxide (**9**) formation in the presence of sodium methoxide in methanol. The epoxide (**9**) was identical with the authentic specimen prepared by the literature procedure. Transformation of **9** into (±)-metoprolol was done by the reported procedure.[7]



In conclusion we have developed a simple strategy to the aromatic segment[3] of metoprolol. In addition, the route to realise the side-chain from the corresponding allyl ether precursor (**6**) by employing OsO_4 catalysed dihydroxylation is particularly useful for developing chiral synthesis[8] of β-blocker drugs.

EXPERIMENTAL

2-Chloro-1-(4-hydroxyphenyl)ethanone (2)

To a cooled and mechanically stirred mixture containing phenol (9.4 g, 100.0 mmol) and ethylenedichloride (25 ml) was added aluminium chloride (26.7 g, 230.0 mmol) over the period of 10-15 min. After the addition was over, the reaction mixture was allowed to attain room temperature and then it was heated at 70° with the help of a preheated oil bath. The resulting solution was stirred at 70° and then chloroacetyl chloride (12.4 g, 110.0 mmol) was added dropwise over the period of 1 h. The reaction mixture was stirred further for 5 h at 70° and then at room temperature for 12 h. It was then poured on crushed ice, hydrochloric acid mixture. 2-Chloro-1-(4-hydroxyphenyl)ethanone (**2**) separated out and was filtered. The solid was crystallized from methanol. Yield 8.52 g (50%), m.p. 151° (lit.[5] m.p. 151-152°). IR : (KBr) 1655 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.58 (s, 2H); 6.8 (d, 2H, J = 9 Hz); 7.72 (d, 2H, J = 9 Hz). MS : M^+ 120.5.

2-Methoxy-1-(4-hydroxyphenyl)ethanone (3)

A solution of sodium methoxide (prepared from 1.02 g of sodium, 44.0 mmol and 20 ml of methanol) and **2** (3.41 g, 20.0 mmol) was stirred at room temperature for 24 h and then concentrated. The resulting residue was treated with dilute HCl, extracted with chloroform and washed with water, dried (Na_2SO_4) and concentrated to give 2-methoxy-1-(4-hydroxyphenyl)ethanone (**3**) (2.98 g, 90%) as white solid. m.p. 133-135°. IR : (KBr) 3300, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.4 (s, 3H); 4.55 (s, 2H); 6.8 (d, 2H, J = 9 Hz); 7.75 (d, 2H, J = 9 Hz); 9.6 (bs, 1H, -OH). MS : M^+ 166. Analysis calculated for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found : C, 64.88; H, 6.27%.

4-(2-Methoxyethyl)phenol (4)

A solution of **3** (1.66 g, 10.0 mmol) and 10% palladium-charcoal (86 mg) in ethanol (40 ml) was hydrogenated at 45 psi for 4 h. The solution was filtered, washed with ethanol and concentrated to afford the crude product which was distilled (b.p. 125°/3 mm) to afford pure **4** (1.46 g, 96%). IR : (film) 3300. ^1H NMR ($CDCl_3$) : δ 2.84 (t, 2H, J = 7 Hz); 3.42 (s, 3H); 3.65 (t, 2H, J = 7 Hz); 6.74 (d, 2H, J = 9 Hz); 7.1 (d, 2H, J = 9 Hz); 7.0 (br, 1H). MS: M^+ 152.

4-(2-Methoxyethyl)phenoxyallyl ether (5)

A mixture of **4** (1.52 g, 10.0 mmol), potassium carbonate (1.52 g, 11.0 mmol) and allyl bromide (1.33 g, 11.0 mmol) in acetone (25 ml) was refluxed for 7 h. The reaction mixture filtered. Acetone was removed under reduced pressure. The residue so obtained was dissolved in ethyl acetate. The ethyl acetate layer was washed with 1N NaOH solution, water, dried (Na_2SO_4) and concentrated to afford **5** (1.63 g, 85%) as colourless liquid. ^{1}H NMR ($CDCl_3$) : δ 2.81 (t, 2H, J = 7 Hz); 3.36 (s, 3H); 3.60 (t, 2H, J = 7 Hz); 4.5 (d, 2H); 5.10-5.54 (m, 2H); 5.77-6.32 (m, 1H); 6.83 (d, 2H, J = 9 Hz); 7.13 (d, 2H, J = 9 Hz). MS : M^+ 192.

3-[4-(2-Methoxyethyl)phenoxy]-1,2-propanediol (6)

To a stirred solution of **5** (1.34 g, 7.0 mmol), N-methylmorpholine-N-oxide (980 mg, 8.40 mmol) in 2:1 mixture water:acetone (15 ml) was added osmium tetroxide (7 mg). After 15 h, the brown solution was treated with sodium metabisulfite (1.2 g). The reaction mixture was further stirred for 1 h, filtered through a bed of Celite and washed with acetone. The combined filtrate was concentrated and partitioned between ethyl acetate and 2N HCl. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to afford a residue which was filtered through a short column of silica gel with chloroform:methanol (98:2) as eluent to give **6** as a syrapy liquid (1.26 g, 80%). IR (nujol) : 3300 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 2.8 (t, 2H, J = 7 Hz); 3.3 (s, 3H); 3.55 (t, 2H, J = 7 Hz); 3.62-4.44 (m, 5H); 6.81 (d, 2H, J = 9 Hz); 7.1 (d, 2H, J = 9 Hz). MS : M^+ 226.

3-[4-(2-Methoxyethyl)phenoxy]-1,2-epoxypropane (7)

A solution of p-toluenesulfonyl chloride (1.04 g, 5.50 mmol) in pyridine (20 ml) was added to **6** (1.13 g, 5.00 mmol) in pyridine

(3 ml) at 0°C over a period of 1 h. The reaction mixturetwas further stirred for 24 h at room temperature. Pyridine was removed under reduced pressure and residue was diluted with ethyl acetate. The organic layer was washed with 2N HCl, water, dried (Na_2SO_4) and evaporated. The crude tosylate (1.25 g, 3.60 mmol) and methanolic sodium methoxide (0.2 g of sodium methoxide dissolved in 10 ml of methanol) were heated at 50-60° for 30 min. and then concentrated. The residue was purified by filter column over silica gel with chloroform as eluent to yield **7** (0.50 g) as a gummy liquid. ^1H NMR ($CDCl_3$) : δ 2.74-3.00 (m, 4H); 3.42 (s, 3H); 3.62 (m, 3H); 3.87-4.04 (m, 2H); 6.9 (d, 2H, J = 9 Hz); 7.2 (d, 2H, J = 9 Hz).

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