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Technical Notes

A New and Improved Process for Celiprolol Hydrochloride

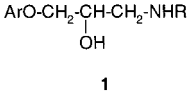
Ramesh A. Joshi, Mukund K. Gurjar*, and Narendra K. Tripathy
National Chemical Laboratory, Pune 411 008, India

Mukund S. Chorghade*
Chorghade Enterprises, 14 Carlson Circle, Natick, Massachusetts 01760, U.S.A.

Abstract:
Celiprolol hydrochloride, a β-blocker drug, has been synthesized by a new approach. How this new process offers distinctive advantages over the existing one will be described.

Introduction

Drugs belonging to the class of aryloxypropanolamine (**1**) are useful β-blockers.[1] A large number of β-blockers are currently marketed and include propranolol, atenolol, metoprolol, nadolol, cervidolol, celiprolol etc. The drug of our interest, celiprolol hydrochloride (**2**), contains a unique *N*,*N*-diethyl urea in its structural framework.[2,3]



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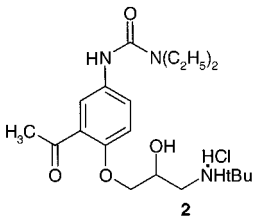
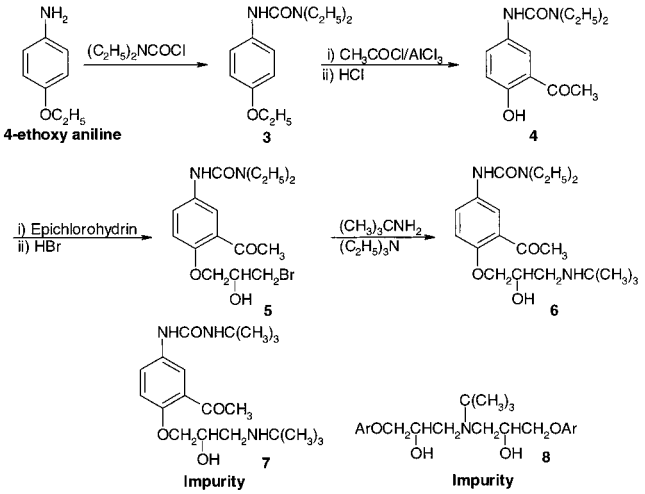


2

The existing process[4] of celiprolol (**2**) is fraught with difficulties (Scheme 1).[5] 4-Ethoxy aniline is treated with diethyl carbamoyl chloride in the presence of potassium bicarbonate to give *N*-*p*-ethoxyphenylacetamide (**3**). Friedel–Crafts acylation using acetyl chloride and anhydrous aluminium chloride gives urea derivative **4**. Reaction of the urea derivative with epicholorohydrin followed by treatment with hydrobromic acid gives bromohydrin (**5**). The celiprolol base **6** is obtained by reaction of bromohydrin with *tert*-butylamine, in the presence of triethylamine, and converted to the hydrochloride salt. The introduction of *N*,*N*-diethyl urea is carried out at a fairly early stage of the process by using expensive reagent, diethyl carbamoyl chloride (DECC).

Scheme 1. **Existing Process**



Being labile, this unit undergoes side-reactions resulting in by-products **7** and **8** that require extensive purification, and this adds to the overall cost of the drug. These compelling factors attracted our attention for a need to develop a new approach, which could circumvent most of the above-mentioned difficulties. Introduction of the *N*,*N*-diethylurea segment as late as possible would be critical to our success.

This report deals with a new synthesis of **2** starting from 4-nitrophenol. The presence of the nitro group in the aromatic ring provided crystalline intermediates, making their purification simple.

Results and Discussion

The key intermediate in the synthetic sequence was 2-acetyl-4-nitrophenol (**10**). The literature offers two methods for its preparation: (a) the Fries migration[6] of 4-nitrophenyl acetate (**9**) and (b) nitration of *o*-hydroxy acetophenone.[7] The Fries migration of 4-nitrophenyl acetate (**9**) using 2.2 equiv of anhydrous $AlCl_3$ in dry nitrobenzene gave a 25% yield of **10** after steam distillation to remove nitrobenzene.

(1) Elks, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapman and Hall, Ltd.: New York, 1990; Vol. 1.
(2) U.S. Patent 4,034,009, 1997.
(3) Mazzo, D. J.; Obetz, C. L.; Shuster, J. E. *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1991; Vol. 20, pp 237−301.
(4) Zolss, G. *Arzneim. Forsch.* **1983**, *33*, 1.
(5) Schloyl, K.; Hofer, V. O. *Arzneim. Forsch.* **1986**, *36*, 1157.
(6) Chaughuley, A. S. U. *Sci. Cul.* **1954**, *19*, 614.
(7) Szell, T.; Brand, A.; Ratanathanawngs, S. *J. Chem. Eng. Data* **1981**, *26*, 230.

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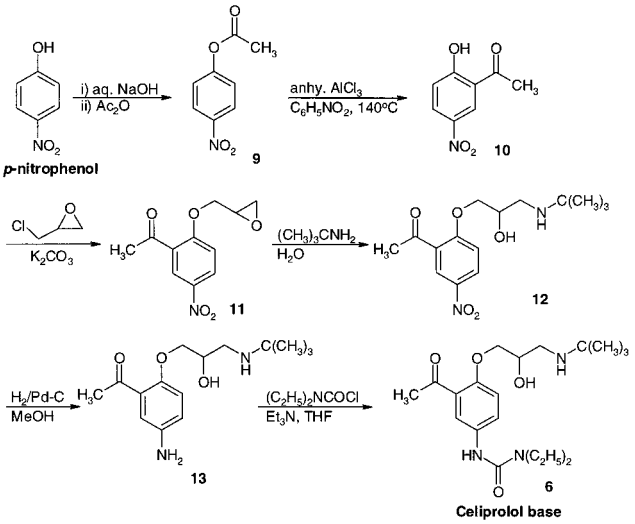
Scheme 2



Attempts to carry out the migration by heating a concentrated mixture of reactants not only failed to give **10** but resulted in decomposition with slight ignition. The nitration of *o*-hydroxy acetophenone using 10 N nitric acid has been reported to give mixture of 4-nitro-2-acetyl phenol and 6-nitro-2-acetyl phenol.

The methods described above were not suitable for the preparation of large quantities of **10** and warrant investigation. The Fries migration of **9** was targeted first. The acetylation of 4-nitrophenol was carried out using a modified procedure.[8] A solution of sodium salt of 4-nitrophenol was treated with acetic anhydride (1.5 equiv), and the crystallized product (**9**) was isolated by filtration in good yields. The Fries migration of 4-nitrophenyl acetate (**9**) was attempted under various modified conditions and worked well using nitrobenzene as the solvent. The reaction was exothermic when a slurry of **9** and anhydrous $AlCl_3$ were combined. The exothermic reaction was controlled by slow addition of $AlCl_3$ in nitrobenzene to a solution of **9** in nitrobenzene at room temperature (25 °C), followed by heating the clear solution at 140 °C. The isolation of **10** by steam distillation was found to be time-consuming, and therefore the isolation procedure was modified by extracting the product with aqueous alkali to separate nitrobenzene. Acidification of the aqueous solution followed by extraction of **10** into ethyl acetate gave **10** in a 70% yield (Scheme 2).

O-Alkylation of *p*-nitrophenol by epichlorhydrin has been reported in high yields under PTC conditions.[9] Treatment of **10** with an excess of epichlorohydrin in the presence of potassium carbonate and a catalytic amount of triethyl benzylammoniumchloride gave the crystalline aryl glycidol derivative (**11**) as a solid in 96% yield. The ring-opening of the epoxide **11** with *tert*-butylamine in water gave the solid amino alcohol derivative **12** in 86% yield. Finally the nitro group was reduced over catalytic Pd/C in methanol to afford the amine **13** in 92% yield.

The introduction of *N*,*N*-diethyl urea moiety was carried out using DECC in the presence of Et_3N in THF for 48 h to give 90% yield which was characterized by comparison with the authentic sample. Although two amino groups are present in substrate **13,** the predominant formation of celiprolol base (**6**) was due to steric hindrance of *tert*-butyl group of **13**. Compound **6** was converted to celiprolol hydrochloride (**2**) by the reported[4] procedure.

In conclusion, the new improved process for celiprolol offers distinctive advantages over the published procedure. Relocation of the diethylcarbamoyl chloride reaction toward the end offers potential cost and purity advantages. The new intermediates are all crystalline, offering multiple purification points for control.

Experimental Section

Melting points were determined on Buchi melting point B 540 apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated Merck silica gel 60 F_{254} plates. Products were visualized with UV light. All NMR spectra were recorded (Brucker AC200 model spectrometer) in deuteriochloroform, unless otherwise specified. Chemical shifts are reported in ppm (δ) relative to TMS. High performance liquid chromatography (HPLC) was performed on a Shimadzu LC 8A equipped with a variable wavelength λ_{max} 254, column Merck Lichrosphere RP 18e (5 μm) 250 × 4 mm, mobile phase acetonitrile−methanol: buffer. Mass spectra were recorded on a Finnigan MAT 1020 spectrophotometer. Elemental analysis was carried out using Karlo-Erba automatic analyzer. The use of hexane and diisopropyl ether can be replaced by heptane and methyl *tert*-butyl ether, respectively.

4-Nitro-phenylaceate (9). 4-Nitrophenol (308 g, 2.21 mol) was slowly added to a solution of NaOH (132 g, 3.3 mol, 1650 mL water). The reaction mixture was heated at 90−95 °C with stirring until a homogeneous solution was obtained. Acetic anhydride (300 mL, 3.2 mol) was added in 10 min to the above hot solution. Then the reaction mixture was immediately cooled to 20 °C. The product was crystallized and collected by filtration. The isolated solid was washed with water to give **9** (350 g, 87%), mp 81 °C, lit.[8] mp 83 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H, Ac), 7.30 (d, J = 8.7 Hz, 2 H, Ar), 8.27 (d, J = 8.7 Hz, 2 H, Ar).

2-Hydroxy-5-nitroacetophenone (10). To a stirred solution of acetate (**9**) (100 g, 0.55 mol) in 400 mL of nitrobenzene was added a solution of anhydrous $AlCl_3$ (73.6 g, 0.55 mol) in 220 mL of nitrobenzene over a period of 30 min at room temperature. The reaction mixture was heated at 140 °C for 6 h, allowed to cool to room temperature, and then poured into 500 g crushed ice and 300 mL of concentrated HCl with vigorous stirring. The nitrobenzene layer was separated and washed with water (300 mL) followed by 10% NaOH (2 × 300 mL). The combined alkali layers were acidified to pH 5 with concentrated HCl and extracted with ethyl acetate (2 × 300 mL). The combined ethyl acetate layers were concentrated to a residue which was subjected to Soxhlet extraction using *n*-hexane as a solvent to yield **10** (70 g, 70%) as an off-white solid, mp 102 °C, lit.[10] mp 102−103 °C; ^{1}H NMR (200 MHz, $CDCl_3$)

(8) Chattaway, F. D. *J. Chem. Soc.* **1931**, 2495.
(9) Liu, Z.-Z.; chen, H.-C.; Cao, S.-Li.; Li, R.-T. *Synth. Commun.* **1994**, *24*, 833.
(10) Szell, T. *Chem. Ber.* **1958**, *91*, 2609.

δ 2.73 (s, 3H, Ac), 7.04 (d, J = 9.0, Hz, 1 H, Ar), 8.34 (dd, J = 2.0, 9.0 Hz, 1 H, Ar), 8.69 (d, J = 2.0 Hz, 1H, Ar), 12.84 (s, 1H, OH).

2-[(2′,3′-Epoxy)-propoxyl-5-nitro-acetophenone (11). A mixture of **10** (60 g, 0.33 mol), K_2CO_3 (92 g, 0.66 mol), benzyltriethylammonium chloride (4.0 g, 0.017 mol), and epichlorohydrin (700 mL) were heated at 75 °C with stirring for 10 h, cooled to room temperature, and filtered. The filtrate was concentrated under vacuum to afford **11** (75 g, 96%) (500 mL of epichlorohydrin is recovered). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.67 (s, 3H, Ac), 2.80 (m, 1H), 2.99 (m, 1H), 3.46 (m, 1H), 4.08 (dd, J = 7.4, 13.7 Hz, 1 H), 4.58 (dd, J = 3.1, 13.7 Hz, 1 H), 7.08 (d, J = 9.0 Hz, 1 H, Ar), 8.31 (dd, J = 2.0, 9.0 Hz, 1 H, Ar), 8.58 (d, J = 2.0 Hz, 1 H, Ar). Mass: 237(M^+).

2-(3′-*tert*-Butylamino-2′-hydroxy-propoxy)-5-nitro-acetophenone (12). Glycidyl ether (**11**) (75 g, 0.316 mole), *tert*-butylamine (100 mL, 0.95 mol) and water (300 mL) were combined and stirred at room temperature for 12 h. Excess of *tert*-butylamine was removed under reduced pressure, and the resulting residue was extracted with ethyl acetate (2 × 300 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated to give **12** (84 g, 86%). The intermediate **12** was recrystallized from diisopropyl ether and ethyl acetate (5:1), mp 105−107 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 2.30 (bs, 1H, OH), 2.70 (m, 4H, Ac and NCH), 2.90 (dd, J = 4.0, 13.5 Hz, 1H, NCH), 4.0 (m, 1H, CHO), 4.20 (m, 2H, OCH_2), 7.06 (d, J = 9.0 Hz, 1H, Ar), 8.30 (dd, J = 2.0, 9.0 Hz, 1H, Ar), 8.58 (d, J = 2.0 Hz, 1H, Ar). Analysis. Calcd. For $C_{15}H_{22}O_5N_2$: C, 58.06; H, 7.09. Found: C, 57.83; H, 7.21.

Celiprolol Base (6). Compound **12** (30, 0.096 mol) in methanol (180 mL) was hydrogenated at 20 psi with 10% Pd/C (3 g) at room temperature. The reaction was monitored by HPLC. After complete reduction (5−6 h), the catalyst was filtered, and the filtrate was concentrated under vacuum to afford the amino compound (**13**) (25 g, 92%).

^{1}HNMR (200 MHz, $CDCl_3$) δ 1.15 (s, 9H, *t*-Bu), 2.50−2.75 (m, 5H, Ac, NCH and OH), 2.86 (m, 1H, NCH), 3.60 (m, 1H, CHO), 4.0 (m, 2H, OCH_2), 4.85 (bs, 1H, NH), 6.80 (bs, 2H, Ar), 7.05 (s, 1H, Ar).

To the amine (**13**) (20 g, 0.071 mole) in THF (100 mL) containing Et_3N (25 mL, 0.18 mol) and maintained at 40 °C, was added DECC (15 mL), and the reaction progress was monitored by HPLC. After 48 h the reaction mixture was concentrated, extracted with ethyl acetate (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in acetone (200 mL) and filtered through a short bed of neutral alumina. The filtrate was concentrated under vacuum to afford celiprolol base (**6**) (24.3 g, 90%) and crystallized from acetone, mp 116−118 °C lit.[4] (117−118 °C), TLC: homogeneous with authentic specimen; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 9H, *t*-Bu), 1.20 (t, J = 8.0 Hz, 6 H, 2 x CH_3), 2.20 (bs, 1 H, OH), 2.55−2.70 (m, 4H, Ac and NCH), 2.85 (dd, J = 4.0, 13.5 Hz, 1H, NCH), 3.34 (q, J = 8.0 Hz, 4H, 2 x CH_3), 3.85−4.05 (m, 3H, OCH_2 and CHO), 6.36 (s, 1H, NH), 6.86 (d, J = 9.0 Hz, 1H, Ar), 7.44 (d, J = 2.0 Hz, 1H, Ar), 7.75 (dd, J = 2.0, 9.0 Hz, 1H, Ar).

Celiprolol Hydrochloride (2). Celiprolol base **6** (24 g, 0.0615 mol) was dissolved in 100 mL acetone and cooled to 20 °C. 4 N HCl (20 mL) was added until the pH is 5.5−6.0 and stirred for 90 min. The separated salt was filtered and washed with acetone and dried to give the title compound **2** (21 g, 80%), mp 197−198 °C, lit.[2,3] mp 197−200 °C.

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