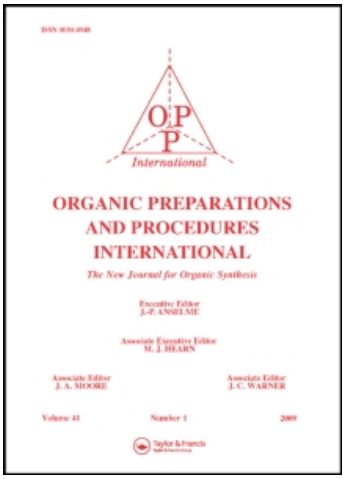

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A RELIABLE MULTIGRAM SYNTHESIS OF (±) DOXAZOSIN

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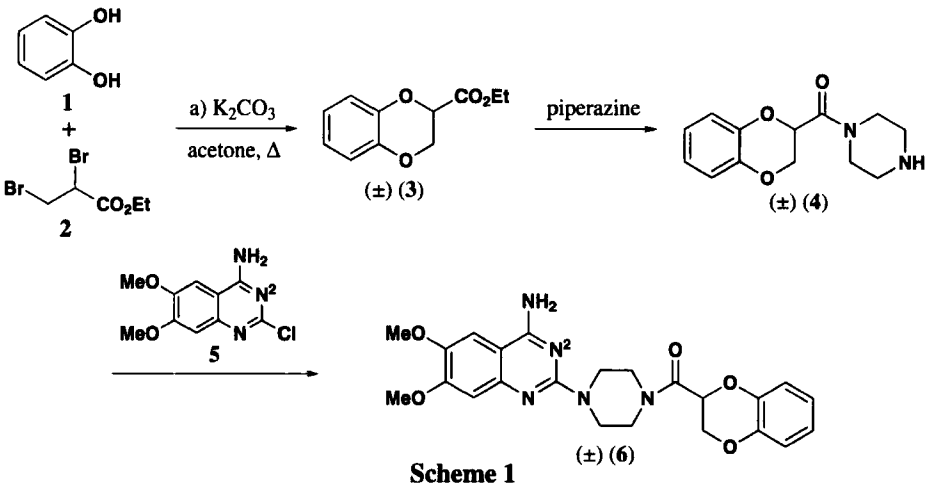
(±) Doxazosin mesylate (6•mesylate), an important drug of the quinazoline family in current use for the treatment of hypertension has also been proven effective for the treatment of benign prostatic hyperplasia (BPH). Doxazosin mesylate displays high binding affinity for α_1-adrenoceptor, with no significant activity at α_2-sites. This mode of action provides appropriate therapy which is being increasingly employed in order to ameliorate hemodynamic derangements without affecting normal physiological functions.[1] The advantages and limitations of the original method[2] are discussed herein and we report an alternative route of preparation for the intermediate (±) ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**3**) and a simple work-up procedure for the separation of the *bis*-amide impurity as well as optimum conditions for the synthesis of intermediate (±) N-(2,3-dihydro[1,4]-dioxin-2-carbonyl)piperazine (**4**).

Several routes have been described for the synthesis of (±) doxazosin (**6**). The most studied method[2] shown in *Scheme 1*, involves crucial intermediates (±) ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**3**) and (±) N-(2,3-dihydro[1,4]dioxin-2-carbonyl)piperazine (**4**). After our initial efforts toward the synthesis of these intermediates, we made the following observations. The purity and crystalline nature of (±) doxazosin mesylate (**6**•mesylate) depends on the purity of doxazosin which, in turn, depends on the purity of (±) N-(2,3-dihydro-[1,4]dioxin-2-carbonyl)piperazine (**4**). The product obtained by condensation of (±) ethyl 2,3-di-hydrobenzo[1,4]dioxin-2-carboxylate (**3**) with piperazine contained substantial amounts of the *bis*-amide [from the reaction of piperazine with *two* molecules of (±) **3**] as impurity and further purification of the doxazosin proved to be very difficult due to its polymorphic nature.[7]



Scheme 1

(±) Ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**3**) was obtained in only 30% yield by the condensation of catechol and ethyl 2,3-dibromopropionate in dry acetone in the presence of anhydrous potassium carbonate. The major impurity isolated was the highly lachrymatory ethyl 2-bromoacrylate and undistillable polymeric material.[3] These observations led us to develop an alternative method for intermediate (±) **3**, and a facile method for the removal of *bis*-amide from intermediate (±) **4**.

The low yields of (±) **3** are due to a partial hydrolysis of the ester group and the β-elimination reaction leading to the formation of ethyl 2-bromoacrylate. We modified the procedure by azeotropic removal of the water generated, thereby favoring the formation of monopotassium salt of catechol. This change not only avoids hydrolysis of the ester but also increases the strength of the nucleophile (anion), thus facilitating substitution on the ethyl 2,3-dibromopropionate. Accordingly, the monopotassium salt of catechol **1** was generated by refluxing with potassium hydroxide powder in toluene with azeotropic removal of water. Polyethylene glycol-400, followed by ethyl 2,3-dibromopropionate and solid potassium carbonate were then added while water was removed azeotropically. Reflux of the reaction mixture was continued for an additional 3 h. Filtration and evaporation of the organic layer gave the crude product which was subjected to high vacuum distillation to give pure compound (±) **3** in 85% yield.[4,5] The use of two equivalents of KOH or of potassium carbonate as the base gave poor yield of (±) **3**. Furthermore, the sequence of base addition had a significant effect on the yield. The use of PEG-400 as phase-transfer catalyst increased the yields by 15-20%. This process led to improved yields of the desired product in 3 h (instead of 24) and minimal (2-3%) formation of ethyl 2-bromoacrylate. In addition, the solvent used in the reaction can be recovered.

Recently, Chou *et al.*,[6] described a high yield (94%) condensation of piperazine with (±) **3** under reflux conditions (3 h). However, our attempt to carry out this reaction under identical conditions failed to give pure doxazosin. Analysis of the reaction mixture showed the

presence of (±) doxazosin (**6**) and of the *bis*-amide in a 70:30 ratio. All efforts to purify the doxazosin at this stage failed, again because of its polymorphic nature.[7]

We decided to study the effect of temperature and time. We found that the internal temperature of the reaction should be maintained at 70-80°C (oil bath temperature 120-150°C) and we examined the yield of the products (±) (**4**) and *bis*-amide at 3, 6 and 10 h duration. At 3 h duration, the isolated yield of (±) **4** was 45% along with 10% of each *bis*-amide and starting material. After 6 h, 65% yield of (±) (**4**), 12% of *bis*-amide and 5% of starting material were obtained, respectively. The desired product (±) (**4**) was isolated in 89% yield after 10 h, in addition to 11% of the *bis*-amide with no trace of starting material. The pure product (±) (**4**) was obtained by simple acid-base extraction. The organic layer was acidified to pH 2 with 6N HCl and the layers were separated. Basification of the aqueous layer with solid $NaHCO_3$ followed by extraction gave pure (±) piperamide (**4**) in 89% yield.[8] The *bis*-amide recovered from the organic layer was subjected to hydrolysis followed by esterification to give the starting material (±) **3**.[9]

Attempts to prepare doxazosin from (±) doxazosin.HCl salt[2a] proved to be very cumbersome and led to unsatisfactory results. This is due to the presence of large proportions of the aprotic polar solvent DMF and water, which were used for basification. It was also found that the basification by either a strong base (NaOH) or a weak base (K_2CO_3) led to poor yields. Strongly basic conditions cause racemization of the pure (*S*)-isomer.[10] Moreover from the pharmaceutical stand point, DMF is an undesirable residual solvent in substances used medicinally.[11] Therefore, we developed a simple and economically viable method of basification in which (±) doxazosin•HCl and aqueous ammonium hydroxide (25% solution) were refluxed for 2 h followed by filtration to give 99.95% pure (±) doxazosin (**6**). This simple procedure not only avoids costly DMF but also simplifies the work-up procedure. The free base was further converted to its mesylate salt by the literature procedure to give pharmaceutical grade doxazosin mesylate (99.99% purity)[12,2b]. Thus, an efficient, practical and economically viable route has been developed for (±) doxazosin (**6**) from **1** and **2** in 51% overall yield.

EXPERIMENTAL SECTION

Mps were determined on an Electrothermall-9100 melting apparatus and are uncorrected. Commercial reagent grade solvents were used. ^{1}H NMR spectra were recorded on a Gemini 200 MHz Varian or Bruker 300 MHz. Mass spectra were obtained on a VG-AUTOSPEM.M (FAB) and VG-70704 (EI) instrument. HPLC analysis was performed using SHIMADZU-LC 10AVP APP instrument. YMC ODS 25cms, 5μ column was used. A 50:50 mixture of acetonitrile and methanol (modified with 0.05% v/v TEA in water) at a flow rate of 1 mL min^{-1} was used as the mobile phase. Detection wavelength was 254 nm.

(±) Ethyl 2,3-Dihydrobenzo[1,4]dioxin-2-carboxylate (3).- A 3L round bottom flask fitted with a stirrer, Dean-Stark trap and thermowell was charged with 112 g (1.0 mole) of catechol,

56.11 g (1.0mole) of potassium hydroxide and 600 mL of toluene. The reaction mixture was heated to reflux and the water formed was removed azeotropically. Then, 5.5 g of polyethylene glycol-400 was added in one portion followed by the dropwise addition of 286 g (1.1 mole) of ethyl 2,3-dibromopropionate over a period of 45 min and the mixture was refluxed. To the reaction mixture 138 g (1.0 mole) of solid potassium carbonate was added portionwise (to control the frothing). Simultaneously the water formed was removed azeotropically. After the addition of potassium carbonate, the mixture was refluxed for 3 h.The solids were filtered off and the filtrate was washed with water. The organic layer was concentrated to give a liquid which was distilled to afford 180 g (85%) of **3** as colorless liquid, bp.105 –115°C / 0.2 mm, [*lit.*,[3a] 105-107°C (0.15 mm)].

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H), 4.23 (q, 2H), 4.38 (d, 2H), 4.78 (t, 1H) , 6.85 (m,2 Ar-H), 6.98 (m, 2 Ar-H); Ms m/z (EI) : 208(68, M^+) , 135 (100), 80 (24), 52(22).

(±) N-(2,3-Dihydrobenzo[1,4]dioxin-2-carbonyl)piperazine (4).- A 1 L round bottom flask fitted with a stirrer, thermowell and set up for distillation was charged with 101.3 g (1.175 mole) of piperazine and 200 g (0.96 mole) of (±) ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**3**). The reaction mixture was heated for 10 h with stirring, while the internal temperature was maintained at 75-80°C. Upon cooling to room temperature, it was dissolved in chloroform (200-300 mL) and washed with saturated bicarbonate solution (1 x 150 mL) followed by water (3 x 150 mL).The organic layer was acidified to pH 2 with 6N HCl. The organic layer was separated and aqueous layer was washed with chloroform (3 x 100 mL). The aqueous portion was made basic with solid sodium bicarbonate to pH 8 and was extracted with chloroform (5 x 150 mL). The combined organic layers were evaporated to yield an amorphous white powder 216.7 g (89%), mp 85-87°C, *lit.*[6] mp. 84-85°C. ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 1H, NH), 2.90-2.95 (m, 2H), 3.56-3.6 (m, 2H), 3.67-3.82 (m, 2H), 4.31 (dd, J =11.9,8.2 Hz, 1H), 4.51 (dd, J = 11.9,2.5Hz, 1H), 4.8(dd, J = 8.2,2.5Hz, 1H), 6.8-6.95 (m, 4H); Ms m/z (FAB): 249 (100,M^+).

***bis*-Amide**: ^{1}H NMR ($CDCl_3$): δ 4.32 (m, 2H), 4.52 (m, 2H), 4.82 (m, 2H), 6.81-6.95 (m, 8H). Ms m/z (FAB^+): 411(100), 249(12), 107(22), 89(16), 77(18).

Synthesis of Doxazosin Hydrochloride Salt.- A 3 L round bottom flask fitted with a stirrer, condenser and a thermowell was charged with 2.5 L of *n*-butanol, 80 g (0.33 mole) of 4-amino-2-chloro-6,7-dimethoxyquinazoline **5** and 100 g (0.4 mole) of (±) N-(2,3-dihydrobenzo[1,4]dioxin-2-carbonyl)piperazine (**4**). The reaction mixture was stirred and refluxed for 5 h. It was cooled to 80°C and the precipitated colorless solid was collected, washed with hot *n*-butanol (500 mL) and dried.

Synthesis of (±) Doxazosin (6).- A 5 L round bottom flask was charged with doxazosin hydrochloride salt and 850 mL of aqueous ammonia (25%) solution. The reaction mixture was heated with stirring under reflux for 1.5 h. The suspension was cooled to room temperature, the solid was collected and washed with 400 mL of water, dried under vacuum to give 126 g

(83%) of doxazosin (purity 99.95% by HPLC), as a white solid, mp 249-251°C. ^{1}H NMR (DMSO-d_6): δ 3.66 (m, 8H), 3.79 (s, 3H), 3.83 (s, 3H), 4.21(m, 1H), 4.41(d, J=11.6 Hz, 1H), 5.24 (m, 1H), 6.84 (m, 5H), 7.17 (s, 2H), 7.44 (s, 1H); Ms m/z(FAB) : 452 (100), 450 (55), 307(14), 233 (15), 107(18), 77(16).

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4. The purity of the product (±) (**3**) was determined by GC and found to be 98% (5% OV-17, 100-250°C, 10 °C /min).

5. The US and Indian patent applications are under review (CSIR Ref. No. NF/538/01).

6. W-C. Chou, C-W. Tan, S. F. Chen, and H. Ku. *J. Org. Chem.* **63**, 10015 (1998).

7. Polymorphic form of doxazosin mesylate (Form I), US Patents 6,130,218; CA, **129**: 45312b (1998) and 6,140,334; CA, **129**: 45310z (1998).

8. The purity of the product (±) **4** was monitored by NMR and TLC. The NMR spectrum shows no trace of the *bis*-amide. We were unable to obtain a HPLC analysis of the product (±) **4** using YMC ODS 25cms, 5μ column (50:50 mixture of acetonitrile and methanol modified with 0.05% v/v TEA in water).

9. The US and Indian patent applications are under review (CSIR Ref. No. NF/428/02). European Patent No. 02021686.7

10. Process optimization for the direct resolution of (±) **4** is in progress.

11. The current ICH guideline for residual solvents in pharmaceutical active substances (ICH Guideline: Residual Solvents, Pharmeuropa, Vol. 8, No. 1, page 103, March 1996).

12. A 100-kg batch production of this drug is currently under progress with Cadila Pharmaceuticals Ltd. Ahmedabad-380 009, Gujarat, India.

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