A Novel Synthesis of Clonidine, an Anti-Hypertensive Drug from *o*-Chloronitrobenzene[1]

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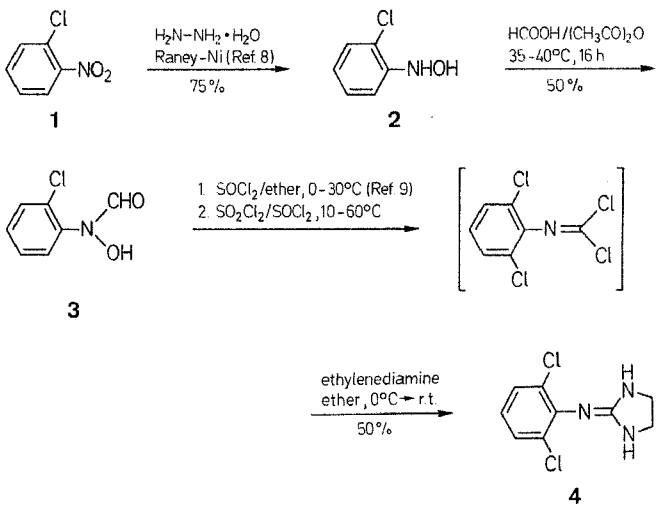
An elegant, cost-effective synthesis of clonidine **(4)** is reported from readily available starting materials. *o*-Chlorophenylhydroxylamine **(2)**, obtained from *o*-chloronitrobenzene, is formylated to *N*-(2-chlorophenyl)-N-hydroxyformamide **(3)**. In a one-pot procedure, **3** is converted to clonidine by chlorination with thionyl chloride and then with thionyl chloride/sulfuryl chloride, followed by condensation with ethylenediamine.

Clonidine **(4)**, originally conceived as a vasoconstrictor, became the most potent centrally acting drug to lower blood-pressure, and was subsequently found to be a cure for several diseases such as glaucoma, migraine, and Torrett's syndrome, as well as for the symptoms of opiate withdrawal.[2-7]

The facile transfer-reduction of nitroarenes to *N*-arylhydroxylamines with hydrazine in the presence of Raney nickel has been recently reported by us.[8] We have also described the facile synthesis of *o*-chloroarylamines from nitroarenes by a novel *ortho*-halogenation reaction on *N*-substituted benzo- and aceto-hydroxamic acids.[9-11] The ingeneous application of the above methodologies has resulted in an elegant, cost-effective and newer synthesis of clonidine, which is reported in the present communication.

The earlier approaches to the synthesis of clonidine make use of 2,6-dichloroaniline as the starting material.[12-14] The methods described for the synthesis of 2,6-dichloroaniline involve cumbersome multistage processes giving lower yields (15–50%).[15,16] The present approach makes use of the readily available and less expensive *o*-chloronitrobenzene **(1)** as the starting material.

Conversion of **1** into *o*-chlorophenylhydroxylamine **(2)** in 75% yield by the partial transfer-hydrogenation process was reported by us.[8] **2** was then formylated to *N*-(2-chlorophenyl)-*N*-hydroxyformamide **(3)** by acetic-formic anhydride. The 2'-chloro-*N*-hydroxyformanilide **3** was *ortho*-halogenated[9] with thionyl chloride and then halogenated with sulphuryl chloride-/thionyl chloride, and was finally condensed with ethylenediamine, all in a one-pot operation to yield clonidine **(4)** as the free base in 50% yield.



Features of the present method are: (1) a readily available starting material (*o*-chloronitrobenzene), thus avoiding the use of 2,6-dichloroaniline, synthesis of which requires cumbersome multi-stage processes, (2) a one-pot operation to prepare clonidine directly from **3**, (3) Simple work-up procedures, and (4) cost-effectiveness.

Reduction of *o*-Chloronitrobenzene 1 to *o*-Chlorophenylhydroxylamine (2):

The reduction was carried out by the method already reported by us.[8]

Formylation of *o*-Chlorophenylhydroxylamine (2) to *N*-(2-Chlorophenyl)-*N*-hydroxyformamide (3):

To a stirred mixture of acetic anhydride (32 ml, 0.31 mol) and 80% formic acid (11 ml, 0.19 mol), the *N*-arylhydroxylamine **2** (14.3 g, 0.10 mol) is added over 0.5 h maintaining the reaction temperature at 35–40°C. The reaction mixture is stirred at 35–40°C for 16 h and poured into water (200 ml). The solution is saturated with sodium chloride and extracted with ether (200 ml). The ether layer is extracted with 5% sodium hydroxide solution (700 ml). The aqueous alkaline solution is acidified with 10% hydrochloric acid solution (320 ml). The acidic solution is saturated with sodium chloride and extracted with ether (300 ml). The ether is dried with anhydrous sodium sulphate, and the solvent is distilled leaving behind a thick gummy mass. The gummy mass is triturated with petroleum ether to get a solid mass which is recrystallized from benzene petroleum ether (1:1) to give **3**; yield: 8.6 g (50%); m.p. 80°C.

$C_7H_6ClNO_2$	calc.	C 48.97	H 3.49	N 8.16	Cl 20.69
(171.5)	found	49.29	3.86	8.21	20.48

UV (CH_3OH): λ_{max} (log ε) = 245 nm (3.74).

IR (nujol): ν = 3140, 1680, 1635, 1610, 1490, 1340, 1140, 1080, 1000, 860, 770, 730 cm^{-1}.

^{1}H-NMR (90 MHz, $CDCl_3/TMS_{int}$): δ = 7.25–7.55 (m, 4 H_{arom}); 8.20 (s, 1 H, CHO); 9.60 ppm (bs, 1 H, OH, exchangeable with D_2O).

MS (70 eV): *m/e* (rel. int., %) = 173 (26), 171 (85), 143 (100), 125 (80).

One-pot Conversion of *N*-(Chlorophenyl)-*N*-hydroxyformamide (3) to Clonidine(4):

3 (2.75 g, 0.016 mol) is dissolved in dry ether (25 ml) and cooled to 0 °C with an ice-bath. Thionyl chloride (2 g, 0.016 mol) in dry ether (10 ml) is added dropwise with stirring over 0.5 h. The ice-bath is removed. The reaction mixture warms to 30 °C over 1 h. It is stirred at this temperature for 2 h. The ether is distilled off, thionyl chloride (9 ml) is added, and the reaction mixture is cooled to 0 °C. Sulphuryl chloride (2.24 g, 0.016 mol) is added dropwise over 0.5 h such that the reaction temperature remains below 10 °C. The reaction temperature is slowly raised to 30 °C (over 1 h), then raised further to 60 °C and maintained at 60 °C with stirring for 16 h. Thionyl chloride is removed completely by distillation under reduced pressure. Ether (50 ml) is added to the residual mass and the solution is cooled to 0 °C. Ethylenediamine (6 g, 0.1 mol), previously cooled to 0 °C, is added at a rate so as to maintain the reaction temperature below 5 °C. The reaction mixture is stirred without external cooling for 2 h and then poured into water (100 ml). The aqueous layer is separated and further extracted with ether (100 ml). The combined ether layer is dried with anhydrous sodium sulphate and the ether is distilled off. The residue is column chromatographed on silica gel (benzene/ethyl acetate as eluent; the percentage of ethyl acetate is varied from 10 to 50) to give clonidine **4** as the free base; yield = 1.85 g (50%); m.p. 138–139 °C (Lit.[16] m.p. 137–138 °C).

$C_9H_9Cl_2N_3$	calc.	C 46.95	H 3.91	N 18.26	Cl 30.87
(230.1)	found	47.04	4.26	17.84	30.80

IR (Nujol): ν = 3460, 3170, 1650, 1580, 1450, 1380, 1282, 1090, 1040, 895, 820, 720 cm^{-1}.

^{1}H-NMR (90 MHz, $CDCl_3/TMS_{int}$): δ = 3.47 (s, 4 H, CH_2); 5.10 (bs, 2 H, NH, exchangeable with D_2O); 6.57–7.30 ppm (m, 3 H)

MS (70 eV): *m/e* (rel. int., %) = 231 (44), 229 (100), 194 (42), 172 (28), 159 (10), 145 (12), 124 (13), 109 (14).

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