Synthesis of Nicorandil: An Antianginal Agent

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Nicorandil, N-[2-nitroxyethyl]-pyridine-3-carboxamide was synthesized by condensing nicotinoyl chloride with 2-nitroxyethylamine in presence of pyridine. 2-Nitroxyethylamine was prepared from 2-aminoethanol by a three step process.This process was less hazardous and comparatively economical than the literature reported methods.

Nicorandil is a potassium channel opener that acts on smooth muscles[1]. It has also been reported to activate guanylate cyclase[2]. Nicorandil has been reported to be more effective than isosorbide dinitrate and nitroglycerine in the management and prophylaxis of angina-pectoris[3,4]. Nicorandil has been synthesised by nitration of N-[2-choroethyl]-pyridine-3-carboxamide using silver nitrate and acetonitrile[5] and from 2-aminoethanol by first nitration using silver nitrate and potassium iodide[6]. The present work aims to synthesize nicorandil by alternate process using cheaper reagents and also to optimize the yield in various steps.

Nicorandil was synthesized from 2-aminoethanol by a four step process. In order to protect the amino group during nitration, 2-aminoethanol was first treated with phthalic anhydride. The amide formed was then nitrated using a nitrating mixture and was subsequently deprotected by reacting with hydrazine hydrate. The 2-nitroxyethylamine obtained was condensed with nicotinoyl chloride in pyridine. Treatment with aqueous sodium bicarbonate solution gave nicorandil as free base (Scheme I).

N-(2-hydroxyethyl)-phthalimide (II): Phthalic anhydride, 148.2 g (1M) was placed in a 1L three necked round bottom flask fitted with dropping funnel, overhead stirrer and a condenser set for distillation. 2-aminoethanol, 61 g (1M) was added to it dropwise with continuous stirring. After the completion of addition the reaction mixture was heated on oil bath at 134° to remove all the water formed during reaction. The solid obtained was cooled and recrystallized from 1L ethanol. Yield : 189 g (98%). Melting point: 127°.

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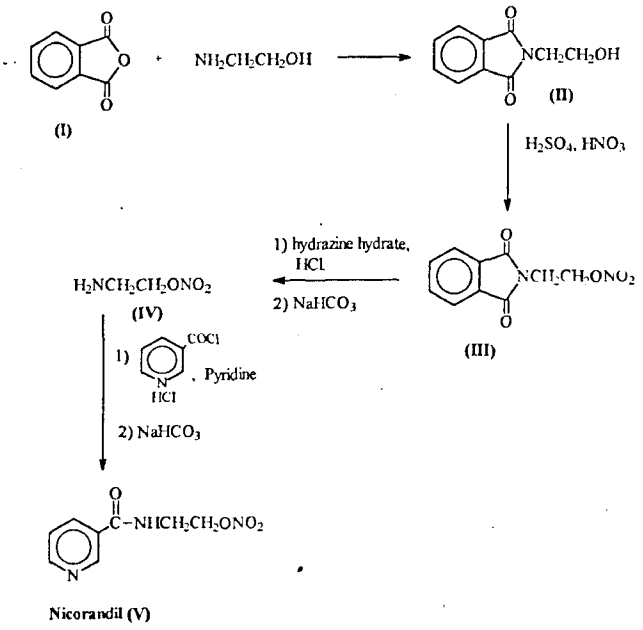

Scheme 1: Synthesis of Nicorandil

[I.R. (KBr) cm^{-1}3474: O-H, aliphatic; 3047: C-H, aromatic ; 2953: C-H, aliphatic; 1768: C=O, phthalimide.]

N-(2-nitroethyl)-phthalimide (III): Compound-II, 189 g (0.98M) was dissolved in 150 ml of conc. sulphuric acid and the mixture was cooled to 15°. Cold fuming nitric acid, 45 ml was added to it dropwise with stirring, maintaining the temperature between 15-20°. The stirring was continued for another six hours with the temperature being maintained at 15-20°. The reaction mixture was then poured into cold water with stirring. The separated solid was filtered and recrystallized from acetone-water (1:4)

mixture. Yield: 195 g (82.6%) Melting Point: 95-100°. [I.R. (KBr) cm^{-1} 3047 : C-H, aromatic; 2950: C-H, aliphatic; 1762: C=O, phthalimide; 1073: C-O, nitrate ester.]

2-nitroethylamine (IV): A mixture of finely powdered compound-III, 195 g (0.8 M) and 45 ml of hydrazine monohydrate in 250 ml of alcohol was warmed when a white precipitate was formed rapidly. After the addition of conc. hydrochloric acid (165 ml) and heating on a steam bath, the phthalylhydrazide formed was filtered and washed with water. The filtrate on concentration under vacuum and on cooling gave the crystals of 2- aminoethylanitrate hydrochloride. The crystals were filtered and treated with saturated solution of sodiumbicarbonate. The free amine formed was filtered and dried. Yield: 75 g (85%). Melting point: 150° (Dec.) [I.R. (KBr) cm^{-1} 3366: N-H, amine, 2928: C-H, aliphatic; 1072:C-O, nitrate ester.]

N-(2-nitroxyethyl)-pyridine-3-carboxamide (Nicorandil) (V): 2-nitroxyethylamine, 75 g (0.8 M) was dissolved in 500 ml of dry pyridine. The solution was cooled to 5-10° and to it was added 143 g of nicotinoyl chloride hydrochloride and stirred for 6 h maintaining the temperature at 5-10°. After completion of reaction, the pyridine was evaporated at vacuum and the residue was treated with saturated solution of sodiumbicarbonate. The product was filtered and washed with little water and dried. It was further recrystallized with ethanol/ether mixture. Yield: 109 g (65%). Melting point: 89-92°. [I.R. (KBr) cm^{-1} 3411, 3395: N-H, amide; 3049: C-H, aromatic; 2980: C-H, aliphatic; 1680: C=O, amide; 1079: C-O nitrate ester] [NMR ($CDCl_3$) δ ppm 8.8, m, 2H (aromatic);' 8.1, m, 1H (aromatic); 7.5, m, 1H (aromatic); 4.7, t, 2H ($-CH_2-ONO_2$); 3.6, q, 2H ($-CONH-CH_2$); 2.5, t, 1H(-CONH-).]

2-Nitroxyethylamine was well prepared from 2-aminoethanol by protecting amino function before nitration and it gave an yield of 70%. Direct nitration of 2-aminoethanol using nitrating mixture was tried but it was unsuccessful. The direct nitration reported in the literature[6] using silver nitrate gave only 50% yield. Higher yield of N-(2-hydroxyethyl)-phthalimide was observed (98%) when the water formed during reaction was simultaneously removed. Temperature during nitration of N-(2-hydroxyethyl)- phthalimide was critically controlled and it was facilitated at 15-20°; while lower temperatures reduced the yield (60%) and higher temperatures resulted in uncontrollable reaction leading to explosion.

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