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Process for the preparation of Dofetilide intermediates

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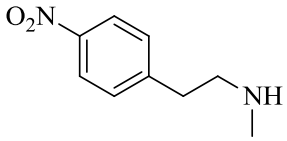
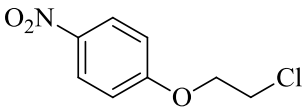
N-methyl-2-(4-nitrophenyl)ethanamine of Formula-1 or its salt and 1-(2-chloroethoxy)-4-nitrobenzene are the key intermediates in the preparation of N-[4-(2-{[2-(4-methane sulfonamidophenoxy)ethyl] (methyl)amino}ethyl)phenyl]methanesulfonamide, is also known as Dofetilide. Current invention provides a process for the preparation of N-methyl-2-(4-nitrophenyl)ethanamine of Formula-1 or its salt and 1-(2-chloroethoxy)-4-nitrobenzene of formula-2.



Formula-1



Formula-2.

Compound of Formula-1 is a known intermediate which was disclosed in Journal of the American Chemical Society 1910, 32, 761-770. Compound of Formula-1 as HCl salt was disclosed in WO 9606084 A1.

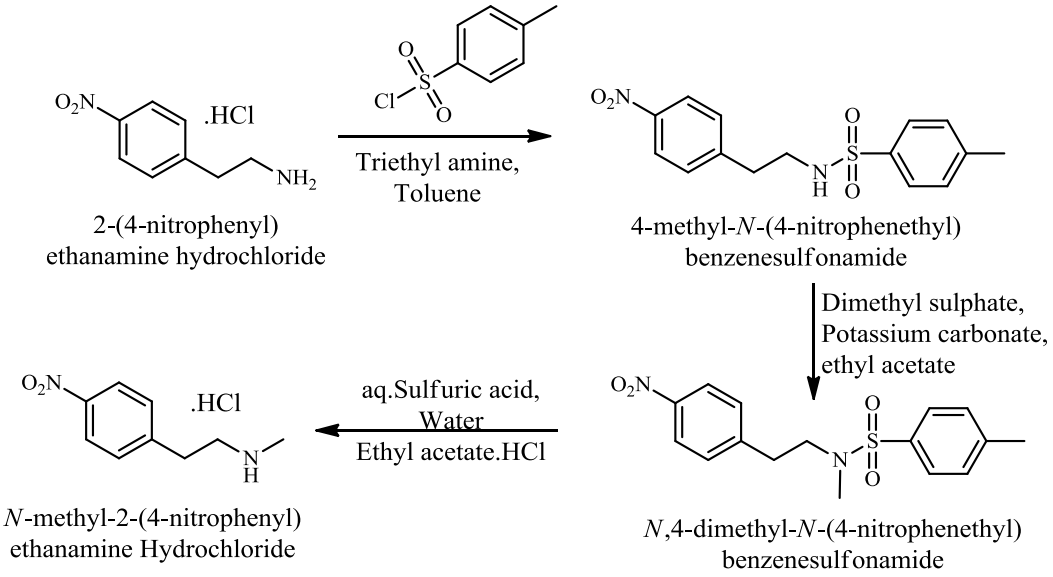
The present disclosure provides a process for the preparation of N-methyl-2-(4-nitrophenyl)ethanamine hydrochloride of Formula-1a by

(i) protecting 2-(4-Nitrophenyl)ethanamine hydrochloride with para-toluene sulfonyl chloride in the presence of triethylamine in toluene to provide 4-methyl-N-(4-nitrophenethyl)benzenesulfonamide,

(ii) reacting 4-methyl-N-(4-nitrophenethyl)benzenesulfonamide with dimethyl sulphate in presence potassium carbonate in ethyl acetate to provide N,4-dimethyl-N-(4-nitrophenethyl)benzenesulfonamide,

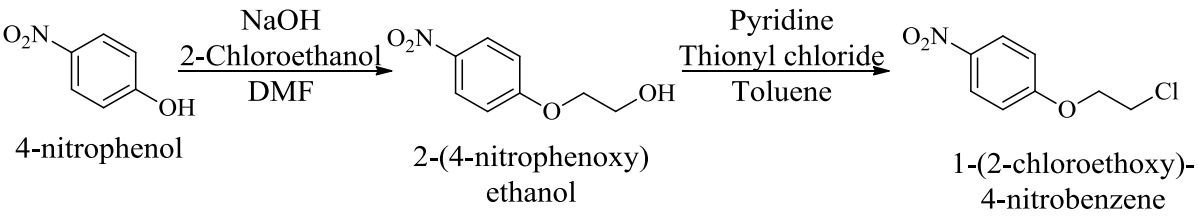
(iii) de-protecting N,4-dimethyl-N-(4-nitrophenethyl)benzenesulfonamide with aqueous sulphuric acid to provide N-methyl-2-(4-nitrophenyl)ethanamine and further treating with ethyl acetate.HCl to provide N-methyl-2-(4-nitrophenyl)ethanamine hydrochloric acid salt.

The above process is depicted in scheme-I as follows:



Scheme-I

The process of 1-(2-chloroethoxy)-4-nitrobenzene of formula-2 is depicted in scheme-II as follows:



Scheme-II

N-methyl-2-(4-nitrophenyl)ethanamine of formula-1 or its HCl salt and 1-(2-chloroethoxy)-4-nitrobenzene of formula-2 obtained according to present disclosure, can be converted into Dofetilide by the known process in the literature.

Example-1: Preparation of 4-Methyl-N-(4-nitrophenethyl) benzene sulfonamide.

Triethylamine (148.8 g) was added to mixture of 2-(4-Nitrophenyl)ethanamine hydrochloride (100 g), toluene (500 ml) at 25-30°C and stirred at the same temperature. Cooled the mixture to 5-10°C, p-toluenesulfonyl chloride (103.8 g) (in 4 equal lots) was slowly added at the same temperature. Heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature, Filtered the solid and slurried in water. Filtered the solid, washed with water and dried to get the title compound. Yield: 147.6 g.

Example-2: Preparation of N,4-Dimethyl-N-(4-nitrophenethyl) benzenesulfonamide

Potassium carbonate (77.68 g) was added to the mixture of 4-Methyl-N-(4-nitrophenethyl) benzene sulfonamide (90 g) and ethyl acetate (450 ml) at 25-30°C and stirred at the same temperature. Dimethyl sulphate (70.92 g) was slowly added to the reaction mixture at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 40-45°C, water was added and stirred at the same temperature. Separated the both organic layer and aqueous layers and the organic layer was washed with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer to get the title compound.

Yield: 90 g.

Example-3: Preparation of N-methyl-2-(4-nitrophenyl) ethanamine hydrochloride.

Sulphuric acid (325 ml) was added to pre-cooled water (175 ml) at 0-5°C and raised the temperature to 25-30°C. N,4-Dimethyl-N-(4-nitrophenethyl) benzenesulfonamide (100 g) was added to above mixture at 25-30°C, heated the reaction mixture to 105-110°C and stirred at the same temperature. Cooled the reaction mixture to 0-5°C, water was added and stirred at the same temperature. Basified reaction mixture with aqueous sodium hydroxide solution at 0-5°C, raised the temperature of the mixture to 25-30°C and stirred at the same temperature. Dichloromethane was added to the reaction mixture at 25-30°C and stirred at the same temperature. Separated the organic layer from the mixture and washed with aqueous sodium chloride solution. Acidified the obtained organic layer with ethyl acetate.HCl solution at 5-10°C and stirred at the same temperature. Filtered the obtained solid, washed with dichloromethane and dried to get the title compound.

Yield: 46.0 g.

Example-4: Preparation of 2-(4-nitrophenoxy) ethanol

Sodium hydroxide (172.6 g) and 2-chloroethanol (356 g) were slowly added to precooled mixture of N,N-Dimethylformamide (600 ml) and 4-Nitrophenol (200 g) and stirred at the same temperature. Heated the reaction mixture to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C. Water followed by ethyl acetate were added to the above mixture and stirred at the same temperature. Separated the organic layer and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with water, further washed with aqueous sodium chloride solution. Distilled off

solvent completely from the organic layer and co-distilled with methyl tertiary-butyl ether. Methyl tertiary-butyl ether was added to the obtained compound at below 50ºC. Cooled the mixture to 25-30ºC and stirred. Filtered the solid, washed with methyl tertiary-butyl ether and dried to get the title compound.
Yield: 210 g.

Example-5: Preparation of 1-(2-chloroethoxy)-4-nitrobenzene

Pyridine (46 ml) was added to mixture of toluene (1000 ml), 2-(4-nitrophenoxy) ethanol(200 g) at 25-30°C and stirred at the same temperature. Cooled the mixture to 15-20°C, thionyl chloride (120 ml) was slowly added at the same temperature. Heated the reaction mixture to 60-65°C and stirred at the same temperature. Cooled the reaction mixture to 5-10°C and water was slowly added to the reaction mixture at 10-15°C. Raised the temperature to 25-30°C. Separated the organic layer and the aqueous layers was extracted with toluene. Combined the organic layers and washed with aqueous sodium chloride solution. Distilled off solvent completely from the organic layer and co-distilled with methanol. Methanol was added to the obtained compound at 35-40ºC. Cooled the mixture to 0-5ºC and stirred. Filtered the solid, washed with chilled methanol and dried to get the title compound.
Yield: 160.6 g.

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