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Synthesis of Hexyl (amino(4-aminophenyl)methylene)carbamate or its salts

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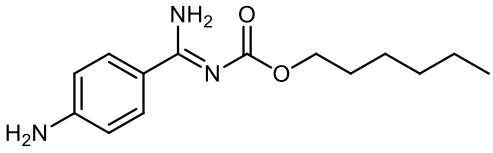
Process for the preparation of Hexyl (amino(4-aminophenyl) methylene)- carbamate (I) or its salts has been developed, which is used as an intermediate in the synthesis of N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate, also known as Dabigatran etexilate mesylate.

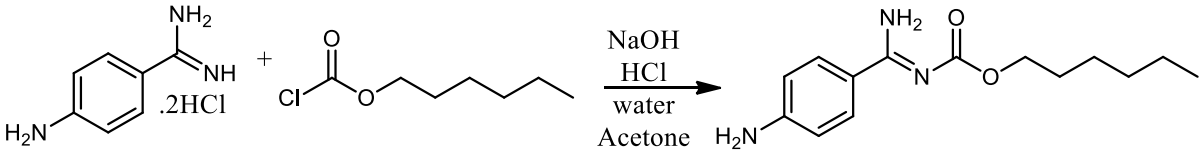


(I)

Compound (I), a known intermediate disclosed in US6242466B1 is prepared by the hydrogenation of 4-(hexyloxycarbonylamidino)-nitrobenzene in the presence of palladium on charcoal under hydrogen pressure.

Preparation of compound (I), is also disclosed in US8399678B2 by the coupling of 4-aminobenzimidamide dihydrochloride with n-hexylchloroformate in the presence of sodium hydroxide in acetone.

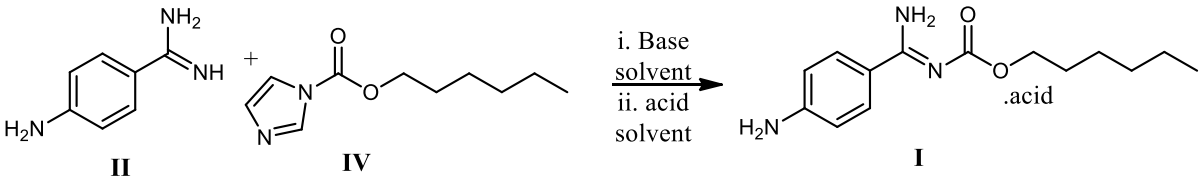
The above process is depicted in scheme-I as follows:



IIa **III** **I**

Scheme-I

The present disclosure provides a process for Hexyl (amino(4-aminophenyl) methylene)- carbamate (I) or its salts by coupling of 4-aminobenzimidamide with hexyl *1H*-imidazole-1-carboxylate in presence of a base in a solvent and converted to its salt by treating with an acid in a solvent; where in the suitable base is selected from organic base or inorganic base.

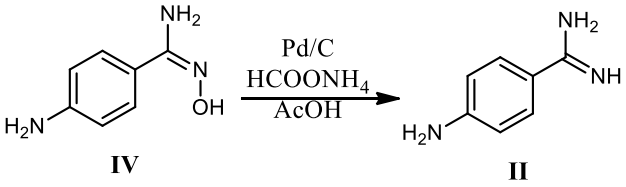


II **IV** **I**

Scheme-II

Preparation of compound-(II) from 4-amino-N'-hydroxybenzimidamide using palladium on carbon, ammonium formate and acetic acid was disclosed in Bioorganic & Medicinal Chemistry 2015, 23(13), 3013-3032.

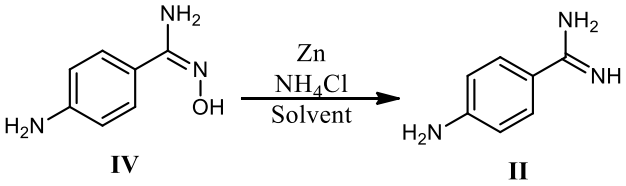
The above process is depicted in scheme-III as follows:



IV **II**

Scheme-III

Further present disclosure also provides an improved process for the preparation of 4-aminobenzimidamide compound-(II) or its salts. 4-aminobenzimidamide is prepared by treating 4-amino-N'-hydroxybenzimidamide compound-(IV) with zinc in presence of ammonium chloride in a solvent. Optionally, 4-aminobenzimidamide is converted to its salts by treating with acid.



IV **II**

Scheme-IV

Hexyl (amino(4-aminophenyl) methylene)- carbamate or its salts obtained according to present disclosure, can be converted into Dabigatran etexilate or its salts by the known process in the literature.

Example-1: Preparation of Hexyl (amino(4-aminophenyl) methylene)- carbamate hydrochloride.

Step-A)

Mixture of 4-amino-N'-hydroxybenzimidamide (100 g), tetrahydrofuran (300 ml) and zinc (129.7 g) stirred at 25-30°C. Aqueous ammonium chloride solution (106.1 g of ammonium chloride in 300 ml of water) was added to reaction mixture at 25-30°C and stirred. Heated the reaction mixture to 55-60°C and stirred. Cooled the reaction mixture to 25-30°C and filtered the resultant mixture.

Step-B)

n-Hexanol (101.4 g) was added to solution of N,N-carbonyldiimidazole (160.9 g) in dichloromethane (400 ml) at 25-30°C and stirred. Water was added to the reaction mixture. The organic layer was collected and washed with aqueous sodium chloride solution. The

solvent was distilled off from organic layer under reduced pressure to obtained hexyl 1*H*-imidazole-1-carboxylate. Tetrahydrofuran (100 ml) was added to obtained hexyl 1H-imidazole-1-carboxylate.

Step-C)

Potassium carbonate (182.8 g) was added to the filtrate obtained in Step-A) at 25-30°C and stirred. Hexyl 1H-imidazole-1-carboxylate in tetrahydrofuran obtained in step-B) was added to the reaction mixture at 25-30°C. Heated to 50-55°C the reaction mixture and stirred. Cooled the reaction mixture to 25-30°C and stirred. Filtered the reaction mixture and washed with tetrahydrofuran. The organic layer was collected and distilled off solvent. Water and dichloromethane were added to resultant compound at 25-30°C and stirred. Hydrochloric acid solution was added to the mixture. The organic layer was collected and washed with aqueous sodium chloride solution. Distilled off solvent completely from organic layer and co-distilled with acetone. Acetone (1000 ml) was added to the obtained residue at 25-30°C and stirred. Cooled the mixture to 0-5°C and hydrochloric acid in ethyl acetate (300 ml) was added and stirred. Filtered the precipitated solid and washed with acetone. Purified the obtained compound using acetone to get the pure Hexyl (amino(4-aminophenyl) methylene)-carbamate hydrochloride.

Yield: 88.74% and M.R: 150-155°C.

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