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Synthesis of (3-Aminophenyl)(morpholino)methanone from Benzotrichloride as Precursor

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(3-Aminophenyl)(morpholino)methanone derivatives are key intermediates in the preparation of active pharmaceutical ingredients. In this synthesis benzotrichloride is selected as a precursor for the preparation of target molecule, the precursor is easily available raw material. The present synthesis consisting of four steps, in the first step we are nitrating the benzotrichloride to obtain the *meta*-nitrobenzoic acid, which on chlorinated with thionyl chloride to obtain *meta* nitro benzoyl chloride, which on condensing with morpholine, further reduction with iron and HCl for the formation of the target molecule.

Keywords: Benzotrichloride, Thionyl chloride, Morpholine, Iron.

INTRODUCTION

The generation of diverse compound libraries plays an important role in the development of potential drug and pesticide molecules [1], in addition to high flexibility, selectivity and atom economy, multi component reactions are one of the most powerful and convenient synthetic routes for building of small library molecules.

The morpholine structural core is present in many bioactive compounds [2], which have shown promising biological properties, such as antidepressant, anticancer, antioxidant, anti-inflammatory and fungicidal activities. Although a variety of synthetic protocols for morpholine derivatives are reported [3], most of them need to use elevated temperature, functionalized pre-synthesized starting materials, and often suffer from drawbacks such as poor yield and tedious work up process. Mean while, there are less reports on the straight synthesis of morpholines which may have potential biological value [4]. Therefore the development of a straight forward high-yielding protocol for the synthesis of morpholines at room temperature from easily available raw materials is of our great interest [5,6].

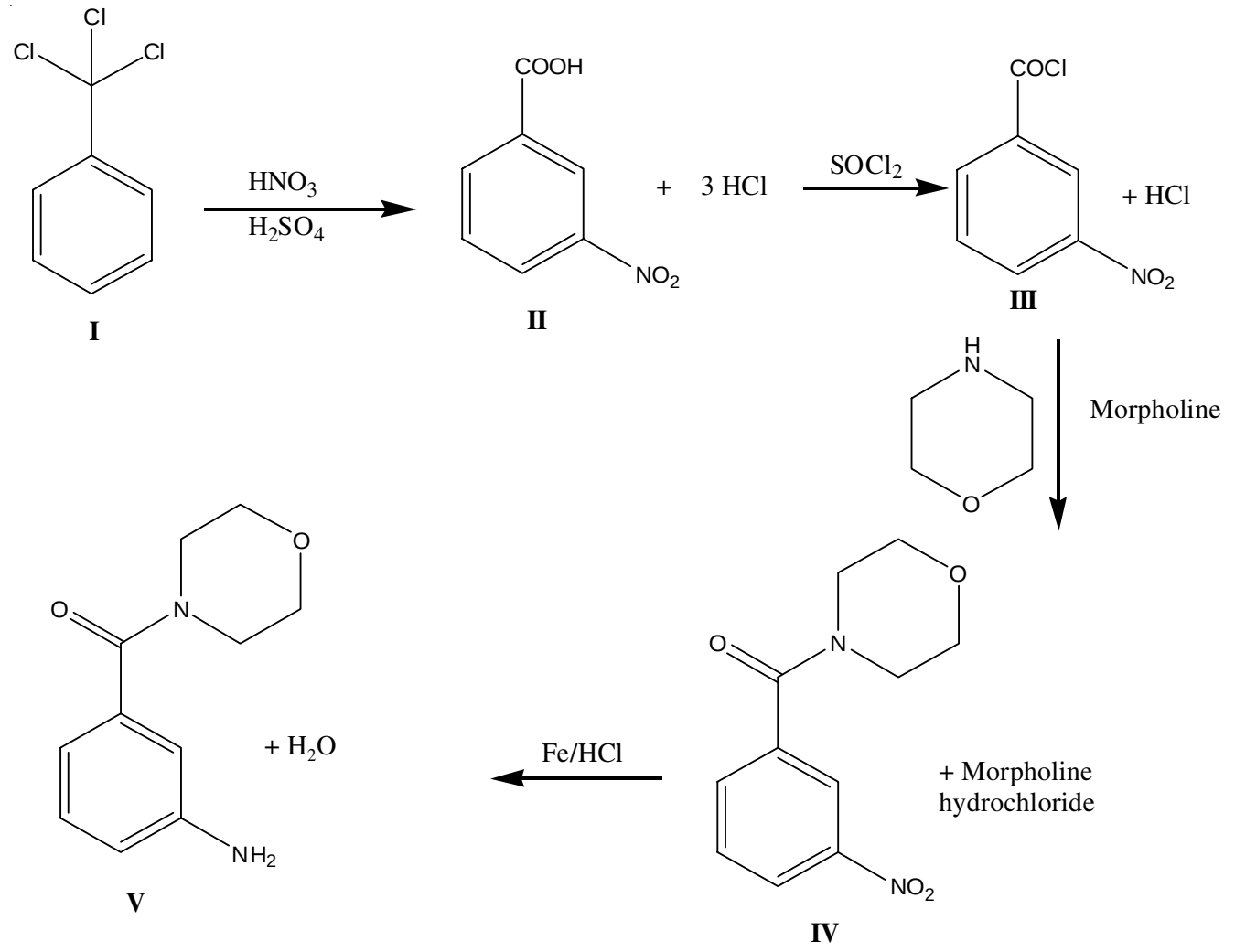
(3-Aminophenyl) (morpholino) methanone is a key intermediate in the synthesis of API Intermediates and their derivatives, earlier authors are reported similar moieties with their own choice, exact literature for this molecule not available in our known sources. Morpholine derivatives are using in the preparation of tyrosine kinase inhibitors and other biologically active agents [7,8] and the synthesis of (3-aminophenyl) (morpholino) methanone from benzotrichloride presented in the **Scheme-I**.

EXPERIMENTAL

Synthesis of 3-nitrobenzoic acid(II) from benzotrichloride: In a four neck-round bottom flask equipped with a condenser and thermopacket, charged benzotrichloride (0.1 mol) at room temperature, charged dichloromethane (5 V) at room temperature, cooled to 15-20 °C, slowly added 90 % nitric acid (0.15 mol) and sulphuric acid (0.3 mol) at 15-20 °C for 1 h. The temperature, maintained at room temperature until evolution of HCl gas is ceases, once evolution of HCl gas ceases quench the reaction mass in ice water (200 mL), settled and separated layers. The aqueous layer extracted with dichloromethane, combined total organic layer. The organic layer is washed with sodium chloride solution until the solution of sodium chloride is colourless, organic layer is dried over sodium sulphate, concentrated organic layer under rotovapour, 3-nitrobenzoic acid a pale yellow crystalline powder obtained, yield is 85 %, compound purified with column chromatography.

Melting point: 139-141 °C. IR spectra (ν_{mac}, KBr pellet, cm^{-1}): 3086 (=C-H), 1692 (C=O), 1616 (C=C), 1530 (C=C), 1478 (C=C); NMR-Data (500 MHz,$CDCl_3$): 11.67 (1H, s), 8.960 (1H, d), 8.49 (1H, dd), 8.47 (1H, dd), 7.737 (1H, dd). GC-MS data (*m/e*): 167, 121, 93, 65.1, 28.1

Synthesis of 3-nitrobenzoyl chloride(III) from 3-nitrobenzoic acid: In a 250 mL four-necked flask equipped with a thermo pocket, condenser and a guard tube, charged 3-nitro benzoic acid (0.1 mol) at 30 °C, charged with dichloromethane (5 V) at 30 °C, slowly heated to 40 °C, slowly added thionyl chloride (0.15 mol) at 40 °C for 1 h, maintained 2 h at 40-



Scheme-I

45 °C, distilled out dichloromethane and thionyl chloride with vacuum, obtained 3-nitrobenzoyl chloride with 80 % yield.

Boiling point: 275-278 °C; IR spectra (ν_{mac}, KBr pellet, cm^{-1}): 3090 (=C-H), 1766 (C=O), 1653 (C=C), 1614 (C=C), 1585 (C=C); NMR data (500 MHz, $CDCl_3$): 8.930 (1H, d), 8.57 (1H, dd), 8.50 (1H, dd), 7.737 (dd); GC-MS data (*m/e*): 185, 150, 104, 76.0, 50.

Synthesis of morpholino(3-nitrophenyl)methanone (IV): In a 250 mL 4 neck flask equipped with magnetic stirrer, thermo pocket, condenser and $CaCl_2$ guard tube, charged diethyl ether at 25 °C, charged 3-nitrobenzoyl chloride (0.1 mol) at 25 °C, slowly added morpholine (0.22 mol) at 25-30 °C for 1 h, maintained 1 h at 30 °C for 1 h filtered morpho line hydrochloride salt, the filtrate is distilled out with vacuum, obtained the crude morpholino(3-nitrophenyl)methanone with 80 % yield, the above product is purified with column chromatography.

Melting point: 85-88 °C; IR spectra (ν_{mac}, KBr pellet, cm^{-1}): 3080 (=C-H), 1774 (C=O), 1643 (C=C), 1614 (C=C), 1582 (C=C), 1526 (C-N), 1382 (N-O). NMR data (500 MHz, $CDCl_3$): 8.930 (1H, d), 8.42 (1H, dd), 8.41 (1H, dd), 7.69 (1H, dd), 3.41 (4H, t), 3.64 (4H, t). GC-MS data (*m/e*): 235, 205, 189, 150, 134, 104, 76, 56, 28.

Synthesis of (3-aminophenyl)(morpholino)methanone (V): In a 250 mL 4 neck flask equipped with magnetic stirrer, thermopocket, condenser and $CaCl_2$ guard tube, charged methanol (5 V) at 25 °C, charged morpholino(3-nitrophenyl)-methanone (0.1 mol) at 25 °C, charged Fe (0.9 mol) at 25 °C, slowly heated to 60-65 °C, conc. HCl (100 mL) added at 65 °C, maintained 1 h at 65 °C, cooled to 30 °C, filtered the mass through hyflow, washed hyflow bed with methanol, the filtrate is basified with 10 % NaOH solution and extracted with dichloromethane two times, washed dichloromethane with water, separated the dichloromethane layer and concentrated the dichloromethane layer with vacuum, purified the crude compound with column chromatography, yield 70 %.

Boiling point: 290-295 °C; IR spectra (ν_{mac}, KBr pellet, cm^{-1}): 3334 (N-H), 3302 (N-H), 3080 (=C-H), 1760 (C=O), 1656 (C=C), 1614 (C=C), 1270 (C-N), 1225 (C-O); NMR data (500 MHz, $CDCl_3$): 8.91 (1H, s), 8.57 (1H, dd), 8.47 (1H, dd), 7.64 (1H, dd), 4.0 (2H, s), 3.43 (4H, t), 3.71 (4H, t). GC-MS data (*m/e*): 206, 120, 92, 65, 42, 28.

RESULTS AND DISCUSSION

The molecule is prepared from the benzotrichloride, nitration of benzotrichloride gives 3-nitro benzoic acid, in this reaction nitration and hydrolysis happening at one time, which

on treatment with thionyl chloride forming 3-nitrobenzoyl chloride, which on treatment with morpholine forming the subject molecule.

Conclusion

(3-Aminophenyl)(morpholino)methanone is prepared from benzotrichloride, in nitration of benzotrichloride with 90 % nitric acid achieved 90-95 % selectivity of *meta*-nitrobenzoic acid, *meta*-nitrobenzoic acid is separated by column chromatography, *meta*-nitrobenzoyl chloride is prepared from *meta*-nitrobenzoic acid reacting with thionyl chloride with 80 % yield, morpholine is coupled with step 2 product achieved 80 % yield of morpholino(3-nitrophenyl)methanone, which on reduction with iron and hydrochloric acid forming the subject molecule of morpholino(3-nitrophenyl)methanone with 80 % yield.

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