

PROCESS FOR THE PREPARATION OF 5-CYANOPHTHALIDE AND INTERMEDIATES USEFUL THEREIN.

ABSTRACT:

Process for the preparation of 5-cyanophthalide is disclosed which comprises reacting a pharmaceutically acceptable salts of 5-carboxyphthalide with an alkyl carbomate to obtain 5-carboxycarbonyl phthalide. Latter was reacted with 30% HBr in acetic acid to obtain an amide. The latter is further reacted with a chloride so as to obtain substantially pure 5-Cyanophthalide.

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KEY WORDS:

5-Cyanophthalide; high purity; terephthalic acid & diphtalide derivatives; alkyl carbomate;

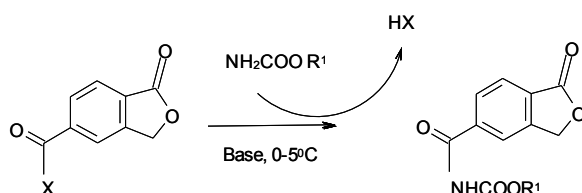
INTRODUCTION:

The present invention relates to a process for the preparation of 5-Cyanophthalide and intermediates useful therein.

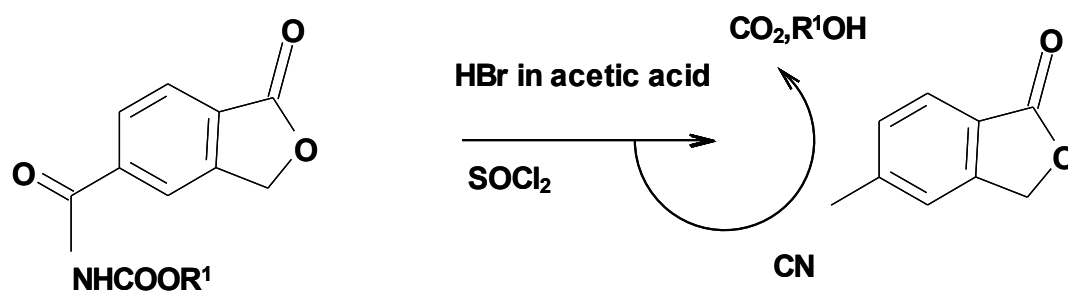
5-Cyanophthalide is a key intermediate used in the preparation of citalopram which is a well known antidepressant drug. Citalopram is a selective serotonin reuptake inhibitor used as an antidepressant and in the cure of obesity and alcoholism as well.

The present invention concerns a process for the preparation of 5-Cyanophthalide comprising:

- reacting a pharmaceutically acceptable salt of 5-carboxyphthalide with an acid chloride and alkyl carbomate to obtain 5-carboxy carbonyl phthalide



b) reacting the latter formed in the above step with HBr in acetic acid and then with an acid chloride to obtain 5-Cyanophthalide



Furthermore, the method of invention comprises purifying crude 5-Cyanophthalide by dissolving it in DMF, followed by filtration. The residue is further subjected to toluene and recrystallized in methanol.

Terephthalic acid and diphtalide impurities generally formed during the preparation of 5-Cyanophthalide are preferably removed. This has resulted in the increase in purity to about 99.5% to 99.9% and also increase in quality of the product.

Number of processes have been described for preparation of 5-Cyanophthalide. However, there remains a need in the art for additional processes that can be prepared at a quality specification required for use in pharmaceutical application.

W0 00/39112 discloses the synthesis of 5-Cyanophthalide via, a two step procedure, wherein 5-carboxyphthalide is first transformed into a secondary amine, preferable with ammonia or a C_{1-6} primary amine. The ester used is not as reactive as acid chloride and requires long reaction time and high temperature.

W0 00/44738 discloses a one-pot synthesis of 5-cyanophthalide. The method comprises reacting 5-Cyanophthalide with a dehydrating agent and a sulfoamide preferably using sulfolane or acetonitrile as solvents, at 135°C . The reaction provides the formation of correspondent haloformyl derivative, optionally isolated, then converted into amide derivative thereof, which decomposes at high temperature.

EP 1321 464A1 which discloses a method that uses 5-carboxyphthalide and reacts it with an alkyl chloroformate so to obtain a mixed anhydride, the latter being reacted with alkyl disilazane so as to obtain

amide and finally with a chloride to obtain pure 5-Cyanophthalide. The alkyl disilazane used is very costly and the process requires long reaction time.

The methods mentioned above describe processes in which it is necessary to isolate the reaction intermediates and/or to use potentially dangerous reagents like ammonia or alkylamines.

The present invention deal with a process which is a two step method of preparation of 5-Cyanophthalide in a convenient and cost effective manner from 5-carboxyphthalide. Moreover the reaction takes very less time to get completed. Also, the impurities generally formed during the preparation of 5-Cyanophthalide are terephthalic acid and diphthalide derivatives. These impurities need to be removed or else they interfere in the further reactions for the preparation of citalopram and thereby resulting in the decrease in yield & purity of final product.

RESULTS AND DISCUSSIONS:

5-Cyanophthalide was confirmed on the basis of XRD, IR, HPLC purity and melting point tabulated as follows: Characterization of X-ray diffraction pattern having peaks at degree 2 theta & relative intensities (%) are as follows:

SR.NO	Pos (2)	Relative Intensities (%)
1	6.3	48.95
2	12.3	100
3	14.8	34.47
4	18.3	40.37
5	24.8	64.87
6	26.0	42.02
7	27.2	29.56
8	28.5	35.65
9	29.5	14.2
10	33.2	4.93
11	34.2	4.74
12	36.2	5.19
13	40.2	34.2
14	41.9	3.87
15	44.1	8.6
16	50.66	7.69
17	53.08	14.43
18	57.6	5.54
19	72.2	33.38

IR Analysis Pattern:

SR.NO	BAND REGION(cm-1)	ASSIGNMENT
1	3494.8	C=O Stretch overtone bond (lactonic ring)
2	3111, 3091	C-H Stretch (Aromatic ring)
3	2962	C-H Stretch (Aliphatic)
4	2231	C=N Stretch
5	1757	C=O Stretch (lactonic ring)
6	1679, 1620	C=C Stretch (Aromatic ring)
7	1552	C=O Asymmetric Stretch (Carboxylate ion)

HPLC PURITY:

Purity of about 99.5% to 99.9% obtained.

Analysis Conditions:

Column: C₁₈ 250 mm x 4.6 mm (5 μ particle size)

Mobile Phase: 500 ml HPLC water, 2.5 pH with orthophosphoric acid and 410 ml acetonitrile. Mix and filter with 0.45 μ filter and sonicate it.

Temperature: Room Temperature

Flow Rate: 1.2 ml/min

Detection: U.V. 239 nm

Injection volume: 20 μl

Melting Point: 199-204°C

SUPPORTING INFORMATION:

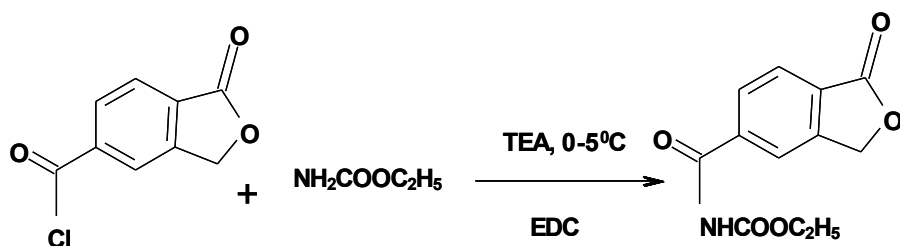
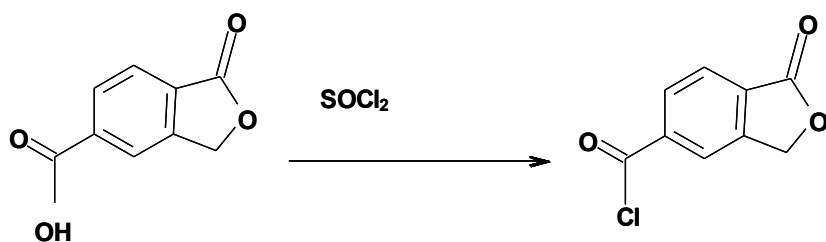
Accordingly the present invention provides for the manufacture of 5-Cyanophthalide which comprises of following steps:

- a) Conversion of 5-carboxyphthalide to 5-Acetamidophthalide
- b) Subsequent formation of 5- Cyanophthalide from 5- Acetamidophthalide

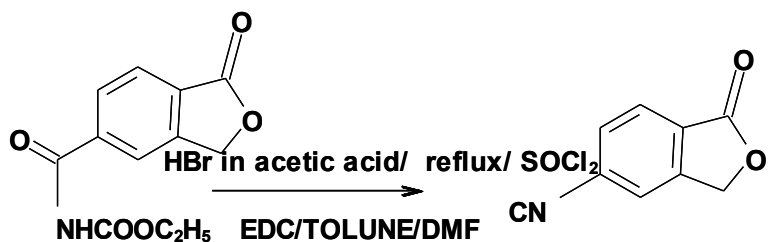
METHOD OF PREPARATION:

The process of invention is briefly described as follows:

A) 5-Carboxyphthalide of formula-I get converted into an acid chloride of formula-II in presence of a dehydrating agent & this then get converted into 5-Carboxy carbomylphthalide of formula-III in presence of triethylamine & ethyl carbomate.



B) Finally the product of formula-III gets converted into 5-Cyanophthalide of formula-IV in presence of a dehydrating agent.



The higher the purity of starting material reflects on the high purity of 5-Cyanophthalide which is obtained in high yields as well.

The above mentioned reaction is carried out in presence of suitable organic, aprotic or anhydrous solvent; preferred solvents can be selected, for instance among chlorinated hydrocarbons, e.g. dichloromethane, chloroform; aromatic hydrocarbons, e.g. toluene, xylene; amides, e.g. dimethylformamide, dimethylacetamide; ethers, e.g. tetrahydrofuran; or a mixture thereof. Amides are the most preferred solvents.

The chlorinating agent is preferably selected from thionyl chloride, phosphorous pentachloride, sulphuryl chloride, acetyl chloride or mixtures thereof.

EXPERIMENTAL DATA:

EXAMPLE:

Synthesis of 5-Acetamidophthalide from 5-carboxyphthalide:

26 gm of 5-carboxyphthalide was suspended in DMF and thionyl chloride was added. The reaction temperature was held at 80°C for 2 hours. Ethylene Dichloride, ethyl carbamate and triethylamine was added and the mixture was cooled. pH was adjusted to 8.0 with Triethyl amine and the mixture was cooled to RT. The crystalline material was collected and washed with water.

5-Carboxycarbonyl phthalide was suspended in 30% HBr in acetic acid. The reaction mixture was heated to reflux temperature for 5 hours. HBr in acetic acid was removed by distillation and the product was recrystallized.

Synthesis of 5-Cyanophthalide from 5-Acetamidophthalide:

Thionyl chloride and DMF was added into the reaction of 5-Acetamidophthalide in ethylene dichloride and stirred at reflux temperature for 15 hours.

The resulting solution was cooled and poured into water, harvesting the solid so obtained followed by further washing the solid with sodium carbonate and then with water. The crystals thus formed were filtered off and washed with ethylene dichloride which was then removed in vacuo.

The crude solid thus obtained was further purified using solvents like DMF, toluene at reflux temperature. After cooling the crystals were filtered off and washed with methanol. Yield: 22.1 gm, 85%. Melting point: 200-203°C and purity (HPLC) of 99.86%

REFERENCES:

- a) Levy, L.F., "4-Aminophthalide & Some Derivatives", *J. Chem. Soc.* pp.867-870, (1931).
- b) J. Tirouflet, "Phthalide Substitutes en 5", *Bulb. Soc. Sci. de Bretagne*, 26: 35-43 (1951)
- c) Barton, Sir Derek, F.R.S. et al., "vol. 2 Nitrogen compounds, Carboxylic Acids, Phosphorous Compounds", in *Comprehensive Organic Chemistry-The Synthesis & Reactions of Organic Compound*, vol. II, pp.1024-1025 (1979).
- d) Buehler, Calvin A., et al., *Survey of Organic Syntheses*, 951 (John Wiley & Sons, 1970)
- e) Forney, L.S., *J. Org. Chem.* 1970, 35, p. 1695-1696.
- f) Bigler, Allen et al., "Quantitative structure-activity relationship in a series of selective 5-HT uptake inhibitors". *Eur. J. Med. Chem.*, 3:289-295 (1977).
- g) Buehler, Calvin A. et al., "Survey of Organic Syntheses," Wiley-Interscience, John Wiley & Sons, Inc., p. 951 (date unavailable).
- h) Forney, L.S., *J. Org. Chem.* 1971, 36, p. 689-693.
- i) *Acta Psychiatr. Scand.* 478, 75 (1987)
- j) *Can. J. Chem.* 1127, 31 (1953)
- k) *Can. J. Chem.* 1256, 36 (1958)
- l) W0 00/39112
- m) W0 00/44738
- n) W0 01/32642
- o) W0 01/32643
- p) US 3,607,884
- q) US 6,458,973
- r) US 6,403,813
- s) US 6,392,060B2
- t) US 6,403,813B1
- u) US 2007/0117991A1
- v) US 2008/0058536A1