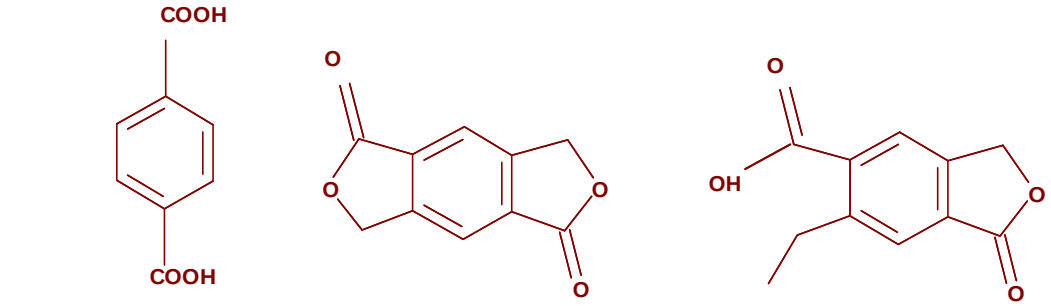
Title: **Novel polymorph of 5-cyanopthalide high purity intermediate for the preparation of citalopram and escitalopram.**

Abstract: The present invention relates to obtaining a new polymorph of 5 – Cyanophthalide in highly pure form (99.5 to 99.99%), which is an intermediate used for the synthesis of citalopram& escitalopram both of which are potent antidepressant drugs. Moreover this new polymorph of 5-cyanophthalide does not contain impurities like terephthalic acid & diphthalide derivatives.



KEYWORDS:
5-Cyanophthalide, high purity, new polymorph, terephthalic acid, diphthalide derivatives.

AUTHOR'S NAME:
Dr. Krishna Sharma. Pathy*, Mr. Sadashiv Shetty, Mr.V.Paleria, Miss. Drashti.P. Gondalia.
Shakti Bioscience Limited. Plot no: 411/1, L.I.C.Sector, Silvassa Road, G.I.D.C, Vapi, Dist-Valsad, Gujarat-396 195. INDIA.
* Author to whom correspondence should be addressed
Email: dr.pathy@shaktibioscience.com

INTRODUCTION:
5-cyanophthalide is an important intermediate for manufacture of citalopram and escitalopram. It is important to produce this product in adequate quality, in a highly pure form by convenient process and in cost effective way.
The impurities obtained during preparation of 5-cyanophthalide are terephthalic acid and dipthalide derivatives .This impurities need to be removed or else they will interfere in the further reactions for the preparation of citalopram & escitalopram and thereby resulting in the decrease in yield & purity of final product.
The present invention relates to a novel process for preparing crystalline form-A of 5-cyanopthalide.

RESULTS AND DISCUSSIONS:
The crystalline form – form A of 5-cyanopthalide was confirmed on the basis of XRD, IR,HPLC purity and melting point tabulated as follows:
Characterization by X-ray diffraction pattern having peaks at degree 2 theta & relative intensities (%) are as follows:

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

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

IR Analysis Pattern:

S.NO	BAND REGION(cm-1)	ASSIGNMENT
1	3494.8	C=0 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=0 Asymmetric stretch(carboxyl ate ion)

HPLC PURITY : 99.9%
Analysis conditions :
Column: C_{18} 250mm x 4.6mm (5 particle size)
Mobile phase: 500ml HPLC water, 2.5 pH with orthophosphoric acid and 410 ml acetonitrile. Mix and filter with 0.45 filter and sonicate it
Temp: room temperature
Flow rate: 1.2ml/minute
Detection: UV239nm
Injection volume: 20 µl
Melting point: 199^0C -204^0C

The method provides for the synthesis of 5-cyanophthalide from 5-carboxyphthalide by reaction of terephthalic acid with paraformaldehdye and oleum. The method provides for the reaction between 5-carboxyphthalide and a chlorinating agent like thionylchloride and dimethyl formaldehyde. This produces chlorocarbonyl derivative which is then reacted with ammonia to give corresponding acetamidophthalide. When subjected to dehydration reaction, acetamidophthalide forms 5-cyanophthalide.

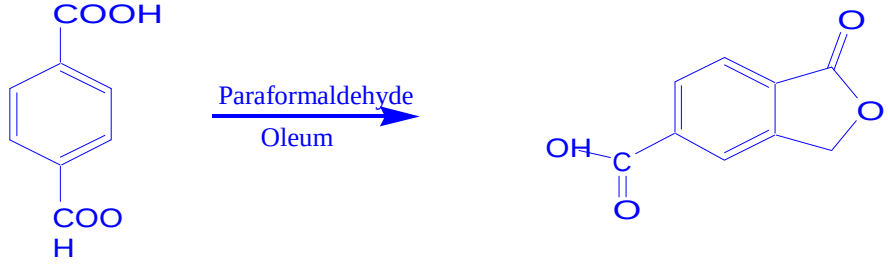
Furthermore, the method of invention comprises purifying crude 5-cyanophthalide by dissolving it in DMF, followed by filtration and distillation of DMF. Then toluene is added to the resulting residue. Further purification is performed by recrystallization in methanol.

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

Terephthalic acid and diphthalide 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 in the increase in quality and % yield of about 90% to 95%.

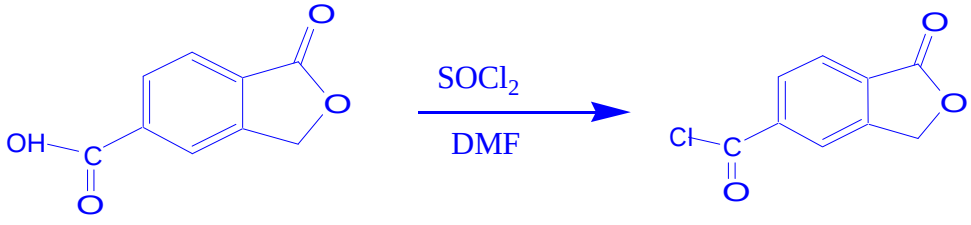
SUPPORTING INFORMATION:
Accordingly, the present invention provides for the manufacture of 5-cyanophthalide which comprises of following steps:
a] Formation of 5-carboxyphthalide.
b] Conversion of 5-carboxyphthalide to 5-acetamidophthalide
c] Subsequent conversion of 5-acetamidophthalide to 5-cyanophthalide.

METHOD OF PREPARATION:
The process of invention is briefly explained which is as follows:
A] Terephthalic acid of formula I reacts with Paraformaldehyde and oleum to form 5-carboxyphthalide of formula II.



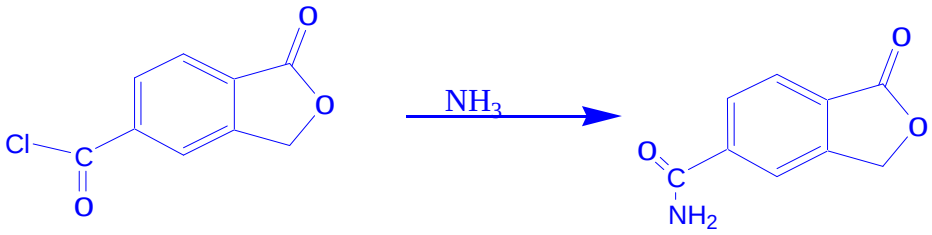
Formula1 Formula II

B] Then formula II compound gets converted into an acid chloride of formula III in presence of a dehydrating agent and this is then converted into an amide of formula IV by amidation with ammonia.



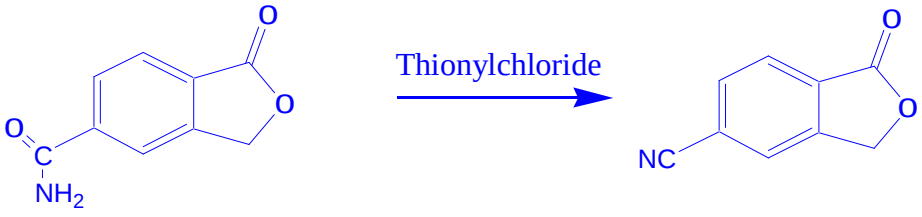
Formula II Formula III

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional



Formula-III Formula-IV

C] Then finally amide of formula IV is converted into 5-cyanophthalide of formula V in presence of dehydrating agent.



Formula-IV Formula-V

The above mentioned reaction is carried out in the presence of polar, organic solvents like DMF, DMSO, toluene or mixtures thereof, at reflux temperature. The chlorinating agent is preferably selected from thionyl chloride, phosphorus pentachloride, sulphuryl chloride or mixtures thereof.

EXAMPLE:
PREPARATION OF 5-CYANOPHTHALIDE:

PURIFICATION OF CRUDE 5-CYANOPHTHALIDE:
Crude 5-cyanophthalide (100 gms) is suspended in DMF (200 ml) and the mixture is heated to reflux temperature, add charcoal (0.5 gms) and stir for 1 hour. Filter the reaction mixture and wash with DMF. Collect the filtrate and distill out DMF completely. Cool the mixture to about 40^0C, add toluene (150 ml) and stir for 30 minutes. Filter the reaction mass and wash with methanol (25 ml) and dry the crystals in vacuo.
% Purity: 99.8%.
TLC: No secondary spot observed in the chromatogram. (Mobile phase: Ethyl acetate: benzene (20:80); Mix and saturate for 30 mins. Std preparation: 200mg 5-cyanophthalide in 10 ml acetonitrile. Sample preparation: Same as for the standard. Spot the sample and standard on chromatogram and run till the solvent front reaches 75% of chromatogram)
IR analysis: 3494.8 (C=0 Stretch overtone bond (lactonic ring)); 3111,3091(C-H Stretch(Aromatic ring));2962(C-H Stretch (Aliphatic));2231(C=N Stretch);1757 (C=O Stretch(lactonic ring));1679,1620 (C=C Stretch(Aromatic ring)); 1552 (C=0 Asymmetric

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

stretch(carboxyl ate ion)). XRD analysis pattern with peaks at $^{0}2$ are 6.3,12.3,14.8,18.3,24.8,26,27.2,28.5,29.5,33.2,34.2,36.2,40.2,41.9,44.1,50.6,53,57.6,72.2.

PREPARATION OF CRUDE 5-CYANOPHTHALIDE:

5-CARBOXYPHTHALIDE:

Oleum (315ml) is charged into the round bottom flask. Terephthalic acid (100 gms) and then Paraformaldehyde (24 gms) is added. The mixture is then stirred at 110^{0}C to 160 ^{0}C for 8-12 hours. Quench the reaction mixture in ice and water and then temperature is adjusted to about 100^{0} C. The precipitate is filtered off, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with caustic lye. Then adjust the temperature of the reaction mass to about 70^{0}C-100^{0}C and filter it. The pH is adjusted to about 2 with concentrated HCl. The 5-carboxyphthalide precipitated is separated by filtration, washed and dried. %Purity: 98%

5-ACETAMIDOPHTHALIDE:

5-carboxyphthalide (100gms) is suspended in toluene (500 ml) and thionylchloride (75 ml). N, N-dimethylformamide (4ml) is added and the mixture is heated at the reflux temperature for about 3 to 5 hours. Meanwhile prepare a separate mixture of water and liq. ammonia (130ml) and chill it below 12^{0}C. Under stirring slowly start the addition of the above chloro compound to liq. ammonia mixture. Check the pH of the mixture after some time interval. The pH should not be less than 8. Stir the mixture for 1 hour and then distill out toluene and water. The reaction mixture is filtered off and washed with water and dried in vacuo. %Purity: 99%

CRUDE 5-CYANOPHTHALIDE:

5-acetamidophthalide (100 gms) is suspended in thionylchloride (125 gms), ethylene dichloride (1200 ml) and DMF (6ml). Slowly heat the mixture to reflux temperature and keep it for 3-5 hours. Add water and stir the mixture for 1 hour. Collect the EDC layer and wash with (10%, 100ml) soda solution at about 50^{0}C-80^{0}C. Again collect the EDC layer and wash with water and then finally collect the EDC layer and add charcoal (5 gms) and EDTA (1.0 gms) and heat it at reflux temperature for about 1hour. Filter the mixture and wash with EDC (100ml) and then distill out EDC completely. Add methanol (150 ml) and cool the mixture to 10^{0}C-15^{0}C. Then filter and wash with methanol and dry the crystals thus obtained in vacuo. %Purity: 99.5%

REFERENCES:

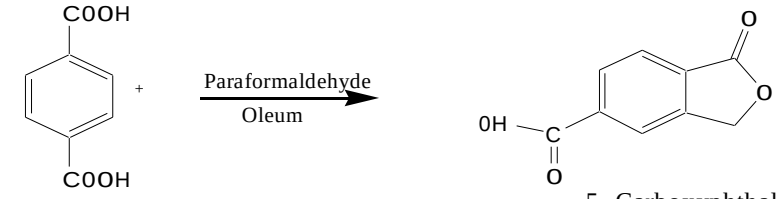
a) Levy, L.F.,"4-Aminophthalide & Some Derivatives", J.Chem.Soc.pp.867-870,(1931).
b) J.Tirouflet,"Phthalide Substitutes en 5,"Bulb.Soc.Sci. de Bretagne,26: 35-43 (1951).
c) Barton, Sir Derek, F,R.S. et al., "vol. 2 Nitrogen compounds, Carboxylic Acids, Phosphorous Compounds", in Comprehensive Organic Chemistry-The Synthesis and Reactions of Organic Compounds, vol. II,pp.1024-1025 (1979).
d) Forney, L. S,J.Org.Chem. 1971, 36, p. 689-693.
e) US Patent No. 3,607,884
f) US Patent No. 6,403,813
g) US Patent No. 6,458,973
e) US Patent No. 3,607,884

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

h) US Patent No. 2007/0117991A1
i) US Patent No. 6,392,060B2
j) US Patent No. 6,403,813B1
k) US Patent No. 2008/0058536A1
l) US Patent No. 3,607,884
m) Buehler, Calvin A. et al., Survey of Organic Syntheses, 951 (John Wiley & Sons, 1970).
n) Forney, L.\ S, J.Org.Chem. 1970, 35, p. 1695-1696.
o) Perregaard, Jens et al., "&σ Ligands with Subnanomolar Affinity and Preference for the & σ_2 Binding Site 1. 3-(-Aminoalkyl)-1H-indoles," J. Med. Chem. 38:1998-2008 (1995). ; 38:1998-2008 (1995).
p) 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).
q) Buehler, Calvin A. et al., "Survey of Organic Syntheses," Wiley-Interscience, John Wiley & Sons, Inc., p. 951 (date unavailable).
r) Barton, Sir Derek, F.R.S. et al., Comprehensive Organic Chemistry. The synthesis and Reactions of Organic Compounds, vol. 2, pp. 1024-1025. (date unavailable).

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

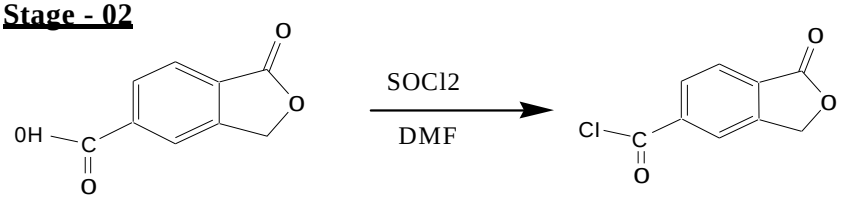
Route of synthesis of 5-Cyanophthalide



Terephthelic acid
M.W : 166.14

5- Carboxyphthalide
M.W : 178.13

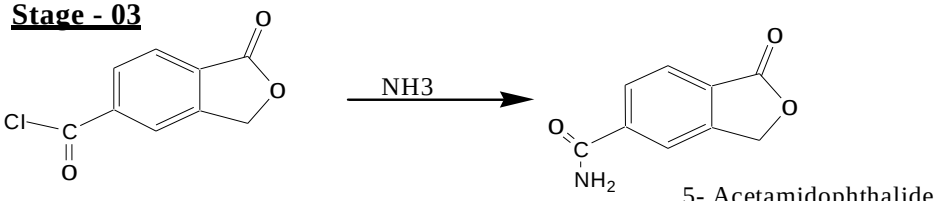
Stage - 02



5- Carboxyphthalide
M.W : 178.13

5- ChloroCarbonylphthalide
M.W : 196.5

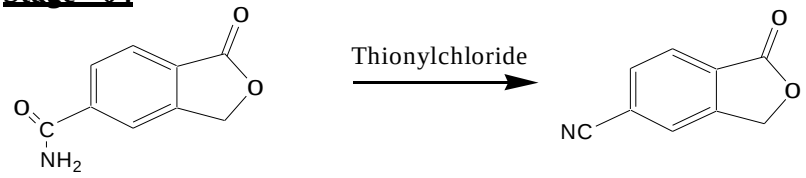
Stage - 03



5- ChloroCarbonylphthalide
M.W : 196.5

5- Acetamidophthalide
M.W : 177

Stage - 04



5- Acetamidophthalide
M.W : 177

5- Cyanophthalide
M.W : 159.15

Created with nitroPDF professional
download the free trial online at nitropdf.com/professional

Created with
nitroPDF professional
download the free trial online at nitropdf.com/professional