

# Synthesis of closantel experiment



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Abstract:- The paper describes the synthesis of Closantel. It is used as an anthelmintic i. e. an agent that destroys or causes the expulsion of parasitic intestinal worms so it is used as Anti-worm drug. The synthesis of Closantel was carried out using four different hydrotropes. The effect of various hydrotropes on yield, rate constant and activation energy at various temperatures and concentrations are studied.

Keywords :- Hydrotropes, Xylene sulfonic acid (XSA), Cumene sulfonic acid (CSA), (n-BBSA): n-Butyl benzene sulfonic acid (n-BBSA), Isobutyl benzene sulfonic acid (I-BBSA),  $^1\text{H}$  NMR, IR.

### Introduction:-

Almost a Century ago Carl Neuberg <sup>1</sup> conceptualized one such area in the form of hydrotrophy. After a dormancy period of about eight decades this exciting field sprung back into the chemical limelight and today it is regarded as one of the frontiers in the field of applied organic chemistry. The pioneer Carl Neuberg baptized this phenomenon as Hydrotrophy or Hydrotropism. <sup>1, 2</sup> It is enhancement in the solubility of organic molecules in water, which otherwise are sparingly soluble or totally insoluble. <sup>3-6</sup> Hydrotropes or hydrotropic agents are defined as the compounds which possess the property of solubility enhancement of other compounds.

Hydrotropes are surface active, highly water soluble organic salts, which when present at high concentration, can solubilise the otherwise insoluble or sparingly soluble organic compounds in water. Hydrotropes can be differentiated from common surfactants in terms of their hydrophobicity i. e. hydrotropes are poorly hydrophobic as compared to surfactants. The

performance of hydrotropic solutions is found to be efficient, usually at higher concentration ranging from 0.2M to 1.0M. At concentration above 1.0M 'salting out effect' is observed. In the present study, the researchers intend to study the aromatic hydrotropes, especially the aromatic sulphonates which are considered to be superior to the aliphatic counterparts as they are thermally stable and have higher affinity. Hydrotropes are readily biodegradable in water under aerobic conditions studies with cumene, toluene and xylene<sup>7</sup>. This ecofriendly methodology where hydrotropes demonstrate a low level of toxicity on aquatic life. Xylene and cumene sulfonates (ammonium, calcium and sodium salts) have no acute toxicity towards fish and invertebrates at concentrations tested (> 318 mg/L)<sup>7</sup>. The scientists around the globe are adopting environment friendly techniques to conserve flora (environment) & fauna (animal life), also to manufacture & synthesize molecules useful to mankind. Carcinogenicity studies reported for both rats and mice exposed to sodium xylene sulfonate. Hydrotropes demonstrated no carcinogenic response.<sup>7</sup>

One of the great advantages of Hydrotropes is the reusability of solvent media without operations such as distillation etc. thereby reducing operation cost. Hence it is an alternate media to organic solvents include water, ionic liquids, supercritical solvents, hydrotropic solutions etc.<sup>8</sup> Hydrotropic solutions are non-toxic, show no hazards of flammability hence considered as safer solvents. The compatibility of aqueous hydrotropic solutions as safer solvents for microwave assisted reactions has been studied.<sup>9</sup> So there is now a realization that more benign chemical synthesis

is required as an integral part of developing sustainable technologies <sup>10</sup> . Efforts have been made to carry out studies on Hydrotropes as effective reaction media for the certain organic reactions.

#### Reaction Scheme:-

The reaction of 3, 5-diiodosalicyloyl chloride with 5-Chloro-4-[(4-chlorophenyl) cyanomethyl]-2-methyl aniline was conducted in aqueous hydrotropic solutions to yield the titled product which was tested for purity.

Hydrotropes used are:

1. (XSA): Xylene sulfonic acid
2. (CSA): Cumene sulfonic acid
3. (n-BBSA): n-Butyl benzene sulfonic acid
4. (l-BBSA): Isobutyl benzene sulfonic acid

#### Experimental Procedure:

In a 500 mls 3-necked flask fitted with a stirrer, thermowell and an addition funnel, were added (0. 01 moles) of 5-Chloro-4- [(chlorophenyl)-cyanomethyl]-2-methyl aniline, followed by the addition of (0. 01 moles) of 3, 5-diiodosalicyloyl chloride at room temperature dissolved in aqueous solutions of the hydrotrope Xylene sulfonic acid. After the reaction mixture was stirred at 303K and 323K for 8 hours. . The progress of the reaction was monitored by TLC for the completion of reaction. On cooling at room temperature the product precipitated out from the reaction medium and was washed with demineralised water in order to make it free from the traces of the hydrotropic solution adhering to it.

The product was then purified and dried in a vacuum drier. The qualitative estimation of the product was done by TLC using the following system. Chloroform: Methanol (9: 1). The product was found to be pure without the traces of either of the starting materials. This is because of the selective solubilization of the reactants which helps to maintain them in the hydrotropic medium. The product N [5-Chloro-4-[(4-chlorophenyl) cyanomethyl ] -2-methyl phenyl]-2-hydroxyl-3, 5-diiodobenzamide has a melting point/boiling point of 217. 8°C.

Similar reactions were carried out using other Hydrotropes such as Cumene Sulfonic Acid, n-Butyl Benzene Sulfonic Acid and Isobutyl Benzene Sulfonic Acid. The concentration range utilized for these hydrotropes was from 0. 2 Mol/dm<sup>3</sup> to 1. 0 Mol/dm<sup>3</sup>. Higher concentration of hydrotropes was avoided due to the salting out of the hydrotropes from the water which is an inherent property of these salts.

Experimental : Melting point are uncorrected. <sup>1</sup> H NMR spectra were recorded at 300 MHz on a Varian spectrometer and IR spectra on a Shimadzu FT/IR-4200 instrument.

Chromatographic System:

Column chromatography: For column chromatography 100 - 200 mesh Acme grade silica gel was used. The crude reaction mixture was concentrated under reduced pressure to yield crude mass which was preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Petroleum ether. The fractions having similar ' R<sub>f</sub> ' values

were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography: TLC plates were prepared using silica gel G (ACME, Mumbai). Pet. Ether : EtOAc (85 : 15) was used as the solvent system.

Radial chromatography: The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

Results: The effect of hydrotrope concentration and temperature on the yield of N [5 - Chloro - 4 - [(4 - chlorophenyl) cyanomethyl] - 2 - methyl phenyl] - 2 - hydroxy - 3, 5 - diiodo

It involves the amidation of 3, 5-diiodo salicyloyl chloride. The lone pair of electrons on nitrogen of amine attacks the carbonyl radical there by liberating the chloride radical in the form of HCl giving the desired amide. This amidation reaction is effected with two iodide group in meta position to the reacting species. The phenomenon of hydrotropy was applied to this synthesis and its effect on yield and reaction dynamics was studied. The hydrotrope used are Xylene sulfonic acid (XSA), Cumene sulfonic acid (CSA), n-Butyl benzene sulfonic acid (n-BBSA), and Isobutyl benzene sulfonic acid (I-BBSA).

The percentage yield obtained for all the four hydrotropes are tabulated in tables VIII (a) to VIII (d) respectively. It was observed that percentage yield

increased from 12.4% to 50.5% at 303K and 17.2% to 56.5% at 323K for XSA. Similarly percentage yield increased from 14.4% to 54% at 303K and from 20.6% to 60.2% at 323K for hydrotrope CSA. For hydrotrope n-BBSA the percentage yield increased from 16% to 70.5% at 303K and from 22.4% to 76% at 323K. For the hydrotrope l-BBSA the percentage yield increased from 20% to 73.7% at 303K and from 26.6% to 80% at 323K.

These were in accordance with the fact that the hydrophobicity of l-BBSA was more than that of XSA, CSA and n-BBSA and the reactants are soluble to a greater extent in l-BBSA. The kinetics of this reaction was studied and rate constant  $K_1$  and  $K_2$  for temperatures 303K and 323K were calculated for all four hydrotropic solutions. The value of  $K_1$  and  $K_2$  obtained are recorded in the tables VIII (e) to VIII (h).

For the hydrotrope XSA the value of  $K_1$  and  $K_2$  increased from 0.0459 to 0.2442 at 303K and from 0.0655 to 0.2898 at 323K. Similarly for CSA the rate constant value increased from 0.0539 to 0.2696 at 303 and from 0.0801 to 0.3199 at 323K. For the hydrotrope n-BBSA the values of  $K_1$  and  $K_2$  increased from 0.0605 to 0.4239 at 303K and from 0.0880 to 0.4955 at 323K. For the hydrotrope l-BBSA the values of rate constants  $K_1$  and  $K_2$  are more than that of XSA, CSA and n-BBSA. It increased from 0.0774 to 0.4638 at 303K and from 0.1073 to 0.5588 at 323K. From above data it is observed that rate constant went on increasing as the concentration of hydrotropes increased.

The activation energy for various concentrations of hydrotropes was tabulated in VIII (e) to VIII (h). The activation energy dropped from 1.4432 to

0. 6966 for hydrotrope XSA and from 1. 6119 to 0. 6965 for hydrotrope CSA. Similarly the value of activation energies dropped for the n-BBSA from 1. 5245 to 0. 6357 and for l-BBSA it decreased from 1. 3291 to 0. 7589 as the concentration of hydrotrope increased. The decrease in activation energy as hydrotrope concentration increased suggest that these hydrotropes also provide some catalytic assistance in shifting the equilibrium towards the product.

#### Conclusion:-

It is evident from the above scheme that at lower hydrotrope concentration, the solubility of organic solutes is less thereby yielding less product. At lower concentration of hydrotrope, the quantity of water is substantially large thereby the reaction are not favorable also resulting in less yields. At higher concentration of hydrotrope, the quantity of water is less and the reaction solubility is more and hence the yields are much better. It is also seen in the above experiment that for lower hydrotrope concentrations the time required for the completion of all reaction is more than that of the time required for a higher hydrotrope concentration.