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CHEMICAL WASTE MINIMISATION PROCESS FOR SYNTHESIS OF FEBANTEL BY NEW METHOD

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ABSTRACT

In chemical industries number of routes were followed for synthesis but some of the processes are minimized the waste produced during the synthesis. This paper revels the new synthetic method for synthesis of febantel to minimize the chemical waste.

KEYWORDS:*chemical industries , synthetic method , chemical waste.*

INTRODUCTION:

Febantel is used as an adequate parasite control or helminthes infections .Febantel acts like the drugs called Benzimidazole (BZD) probenzimidazole (pro-BDZ). Antihel minthes are widely used in veterinary and human medicine[1-3].

These compounds are thought to exert their anti-parasite effects by selective binding to parasite tubulin. This produces subsequent disruption of the tubulin-microtubule dynamic equilibrium.

Modes of action and efficiently of the Antihelminthes are feasible and least toxic[4]. Febantel is overall safe to use and hence it is used worldwide over three decades.

This was primarily introduced for the control of gastrointestinal (GI) Nematodes. It is not only used for livestock animals but also for horses, dogs and cats.

Febantel comes under thiabendazole (TBZ) group discovered in 1961. And later on several thousands of benzimidazole and pro- benzimi dazole molecules[5] have been synthesized and screened for antihelmintic activity. However no more than twenty have been commercially developed for use in domestic animals[6] and man. The compound is white crystalline powder with fairly high melting point and insoluble or slightly soluble in water.

Different modifications are done in the position 2 and 5 and most of the antihelmintically drugs are invented, especially the invention of sulphur containing derivatives such as Febantel, Netobimin, Methyltio phanate.

Method and Discussion:

FABANTEL.

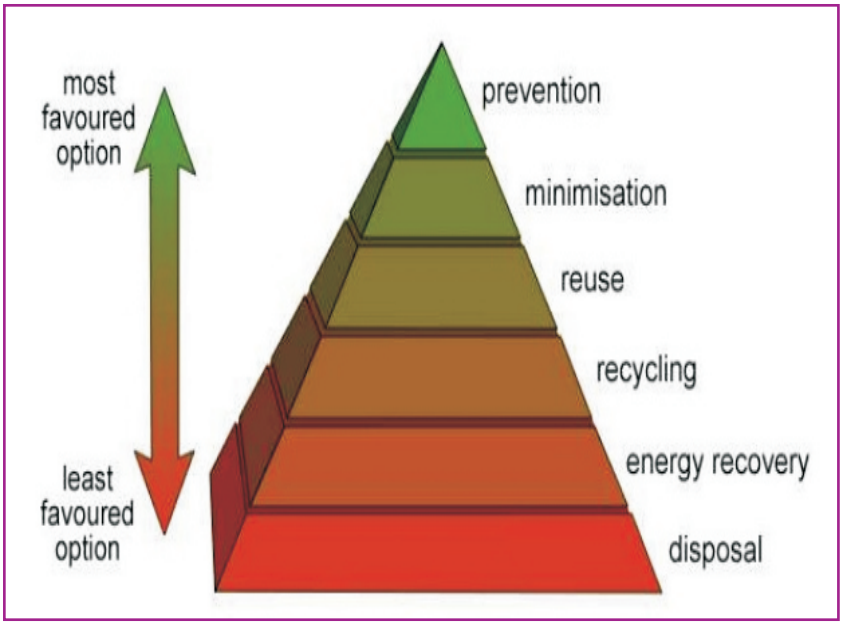
Febantel was prepared by various ways most of methods were produce harmful waste, but another method was adopted to synthesize the febantel to minimize waste.

Step 1st Acylation

m-Chloroaniline is acetylated with Acetic anhydride to protect the Amino group or to reduce the reactivity of the Amino groups.

Step 2nd Nitration

The acylated product is subjected to nitration with fuming nitric acid and sulphuric acid. Resulting in to 3-Chloro-6-nitro acetanilide. Product is centrifuged & suck dried.



Step 3rdDe-acylation

De- acylation of step 2nd is carried by using 6.20%caustic solution at reflux temperature for about five hours.

Step 4th, the 3- Chloro group of step 3rd compound is replaced by Thiophenol group. It involves aromatic nucleophilic substitution using caustic soda flacks in methanol. Stage 4th product is filtered and dried.

Step 5thThe 3-phenyl thio-6- nitro aniline is toMethoxy acetylation using Methoxy acetyl chloride in presence of pyridine and benzene as a solvent. The 3- phenyl thio-6-nitro (N-methoxy acetyl) aniline is separated and dried.

Synthesis of Adduct

Step 6th Thiourea is reacted with dimethyl sulphate in presence of d.m. water and product is crystallized by using methanol.

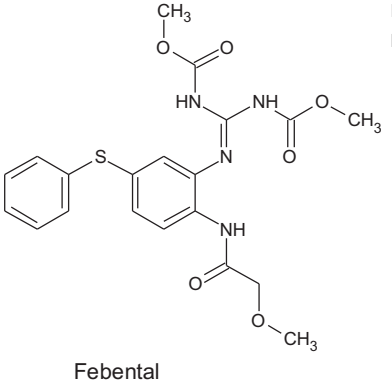
Step 7th The above salt obtained is reacted with methyl chloroformate in presence of aqueous media and resulting hydrochloric acid is neutralized using dilute caustic lye solution.

Resulting adduct is water insoluble and filtered off.

Step 8th step 5th material is reduced with Iron powder in presence of ammonium chloride. Reaction is carried out in presence of methanol. Resulting amino compound is soluble in methanol and hence iron oxide is filtered off form the material.

Setp9th To the above step Adduct of 7th step is added to the amino compound in methanol and mass was refluxed to obtain the final product Febantel. The reactions mass chilled to 0-5'C centrifuged and dried.

Practical yield was obtained 59.18 %.



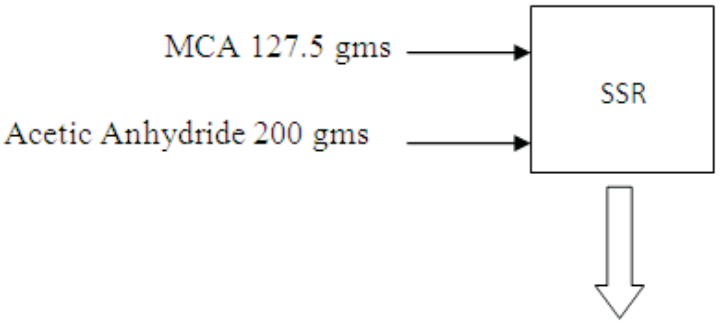
Formula Weight = 446.47688
Molecular Formula = $C_{20}H_{22}N_4O_6S$

Febental

A new methodwas adopted for synthesis of febantel.

IstStage Acylation

Acylation is carried out by using Acetic Anhydride



N (3-Cloro Phenyl Acetamide) 169.5 gms

Un-reacted Acetic Anhydride 98 gms

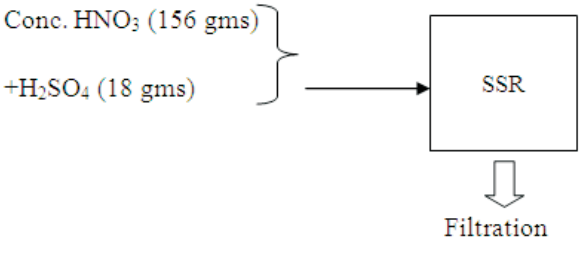
Acetic acid 60 gms

Input Output

MCA+ Acetic Anhydride 327.5 gms → Product + Acetic Acid and un-Reacted Acetic anhydride 327.5 gms

Material was not isolated and nitration carried out in the same reactor.
Reactions were carried without CTC.

Nitration



Solid Product

1) N(5-Chloro-2-nitrophenyl) Acetamide

193.5 gms

Mother Liquor

2) N (5-Chloro-4-niro Phenyl) Acetamide = 17 gms

3) N (3-Chloro-2-niro Phenyl) Acetamide = 4 gms

4) Acetic acid, Acetic anhydride

= 60 gms + 98 gms

Input		Output	
Step 1 (327.5 gms) HNO_3 (156 gms) H_2SO_4(18.00 gms)	Total Weight501.50	1) 193.5 gms 2) 17.00 gms 3) 4.00 gms Acetic Acid, Acetic anhydride = 60 gms + 98 gms Un reacted H_2SO_4 + HNO_3 129 gms.	Total Weight501.50

ML is collected and sent for recovery Sodium acetate after neutralization.
Out of product 1,2 & 3

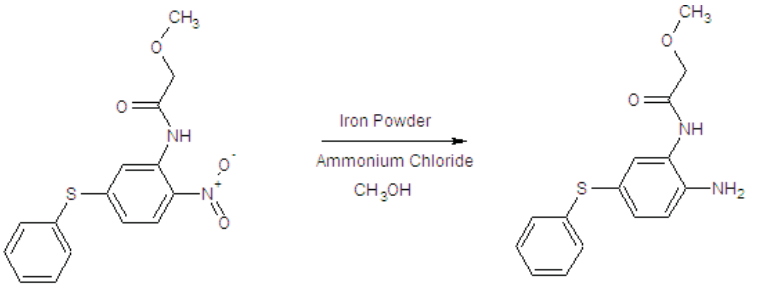
Only 1) N (5-Chloro-2-nitrophenyl) Acetamide is the useful isomer and its weight is only upto 193.5. Other isomers are water soluble and get washed along with water.
Water used for washing is 200 x 3 = 600 ML sent to ETP.
Theoretical yield
127.57 gms ⟶ 214.60 gms
Practical yield = 193.50 gms
% Practical yield = 193.50 x 100 / 214.60 = 90.16 %
There are losses due to solvent used CTC. Nitro compound is explosive hence solvent distillation is not possible or it is dangerous. Also the reaction is highly vigorous, highly exothermic and it was carried out in chilled condition at 0-5 ^{0}C. Astemperature rises unwanted products rises. Acetanilide 2 & 3 are formed. Formation of these compounds ultimately leads to the yield loss.

To avoid this reaction is carried out only in presence of Acetic anhydride in excess and solvent CTC is avoided , reaction becomes less vigorous due to slow heat exchange , we are getting 90.00% useful Acetanilide 1 as a major product and Acetanilide 2 and 3 are 8.00% and 2.00% respectively. Yield improved by 25.00% and environmental impacts are reduced by 75.00%.
For example, in initial process wrong isomers were 40.0% and in improved process wrong isomers or the unwanted isomers are only 10.005 %
Environmental impact reduction = (40-10)/40x100
= 30x100/40
= 75.00%

By this way low boiling carcinogenic solvent Carbon tetrachloride (CTC) is avoided which was not distillable. At this stage 100.00% CTC conservation and environmental impact was nullified.

Reduction

Change of raw materials and process for Reduction.

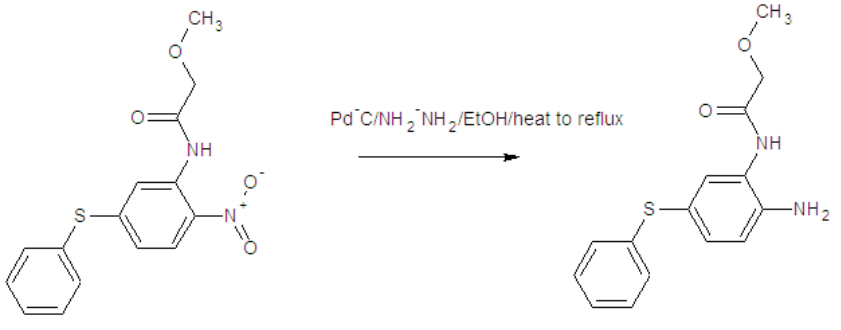


2-methoxy-*N*-[2-nitro-5-(phenylsulfanyl)phenyl]acetamide
Molecular Formula = $C_{15}H_{14}N_2O_4S$
Formula Weight = 318.34766

N-[2-amino-5-(phenylsulfanyl)phenyl]-2-methoxyacetamide
Molecular Formula = $C_{15}H_{16}N_2O_2S$
Formula Weight = 288.36474

Reduction of -NO2 group is carried out in presence of Fe/NH4Cl/NaCl and methanol as solvent.

Reduction of – NO_2 group is easily possible but it create nuisance of waste disposal. Large excess of iron powder and NH4Cl required to complete reaction because reaction do not complete by using stoichiometric amount of iron and ammonium hydrochloride salt so for 1 kilograms, stage of 5th product requires half kg iron powder and after complete reduction iron get oxidized to Ferrous oxide and weight gained by residue due to water, NaCl, NH4Cl, which are large excess in quantity.
So to avoided this, reduction is carried out



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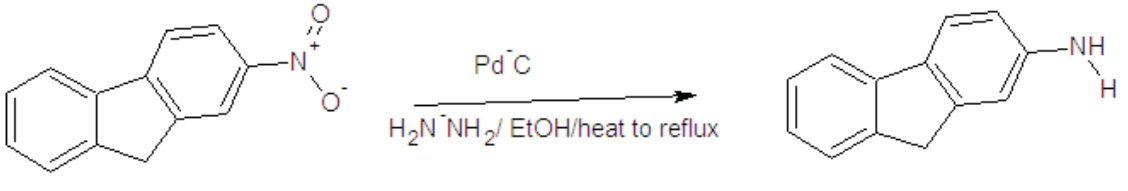
This reduction was done for the following substrate molecule.



Catalyst is removed by filtration and it can be recycled.

Thus the nuisance of residue is minimized up to 100%.Pd metal can be recovered after long use of catalyst and can be recycled for production of same catalyst and heavy metal can be prevented to get discharged in waste.

Use of new catalyst H_2N-$NH_2/FeCl_3/C$

Again to avoid the use of Pd being a heavy metal in the process we tried H_2N-$NH_2/FeCl_3/C$ as catalyst and reactions are carried out we got better results and again less troublesome $FeCl_3$ residue was obtained in the process. This is very minor as compared to the old iron/ ammonium chloride method. Next to this we are trying to get very neat & clear technology by using Rany nickel catalyst. But there is one possibility. That the carbonyl group present in methoxyanilide may get hydrogenated up to some extent and create impurity in the final product.

So far this reaction can be carried out by just bubbling H_2 in the Alcoholic solution of Step-5th product. At reflux temperature at atmospheric pressure to avoid the hydrogenation of the carbonyl group.

Impact on environment

Comparison between old and new process is done to make the process easy and environmentally friendly.While doing all these things it becomes automatically Ecofriendly. Our aim was to make the process cleaner for the production of above said product by doing R&D to minimize Environmental load factor. Weight of raw materials solvents, catalyst used for the production of the unit mass of the product. The weight of the finished product is subtracted from the sum and the difference is divided by the weight of the finished product.

$$\text{E.L.F.(Environmental Load Factor)} = \frac{\text{Input-output}}{\text{Output}}$$

As suggested the smaller the E.L.F. better is the process from ecological point of view .It also suggest minimum use of additives because additives also become waste at some point.

Waste ratio was used by us and it is achieved very successfully.

$$\text{Waste-Ratio(\%)} = \frac{\text{Waste}}{\text{total output}} X100$$

Following table shows the real impact of the old & new technology.

Step. No.	Old method Impact on resources & Environment	New method Impact on resources & Environment	Deviation in Yield	Deviation in any physical or chemical properties of the product	Remark
I Acylation	CTC solvent saved. Low, Carcinogenic boiling solvent.	Without solvent, less wrong isomers are generated	Improved by 29.00%	No change in M.P. & physicochemical properties. M.P. 118-119'C	Solvent elimination & yield improvement.

VI Thiourea complex	Methanol Solvent is used for crystallization	Methanol and energy saved which Is required for distillation of H2O	No change in yield Handlin g loss is avoided	No change in M.P. and physicochemic al properties. M.P. 129-130'C	Solvent elimination and yield is saved due to less handling up to 10.00%
IIX Reduction	Using NH4Cl/NaCl/Meth anol	Reduction using NH2-NH2/FeCl3 or by Hydrogenation using Rany nickel. Residue will not be produced.	No product is lost in the residue.	No change in physicochemic al properties , and product in the methanol solvent taken for condensation with the adduct	Residue nuisance is reduced up to 100%

CONCLUSION:

In the stage of nitration product loss due to solvent and vigorous nature of the reaction is avoided by elimination of solvent. Isomer formation is also reduced up to remarkable level.

In the step of adduct formation use of solvent is eliminated & due to this product loss by extra filtration and handling is reduced. Reduction becomes very clean and easy by bubbling of H2 in the presence of rani Ni thus the overall production was cleaner production by change of rawmaterial and reaction route.

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