Concept of Chemistry for Engineering
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Lecture 77
Synthesis of a drug molecule

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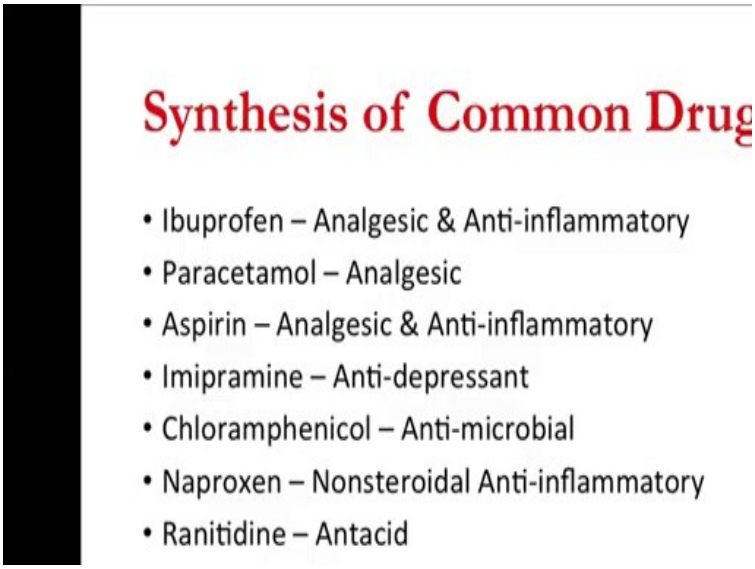

Hello everyone today we will discuss Synthesis of common pharmaceuticals or medicine or drug molecule, I am sure all of us are familiar with many drug molecules. We are talking about pharmaceuticals. These are life-saving polymers or life-saving material. Many pharmaceuticals are available which are prepared in organic chemistry levels.

Similarly, there are many metal containing medicine which can be also life-saving but today we will mainly look at some of the molecules which can be prepared very easily by using our organic chemistry knowledge which we have acquired and read. Let us look at some of the most famous one.

All of us are familiar with paracetamol, Ibuprofen, Aspirin, naproxen, Ranitidine these are very simple organic molecules and these are prepared by using sometime one step to up to six or seven step synthesis. From readily available starting material, as you all know ibuprofen is analyzing that essentially means that it is a painkiller and also it is anti-inflammatory.

We look at in a moment their synthesis, paracetamol on the other hand is analgesic used almost for every purpose, every little bit pain there are people who use it quite a lot sometimes they end up abusing, so please do not use the medicine unless it is prescribed by doctor, do not take over the counter medicine whenever you feel that something is wrong with you.

You can take any of these medicines or I will say no medicine one should take without prescription or without the need which is justified by the doctor, aspirin, once again heavily used I would say abused maybe to a greater extent, it is an analgesic as well as anti-inflammatory all these are available over the counter that means without prescription from doctor you can get it but that does not mean that for every little cause or every little pain you should start using medicine.

It is a very bad habit which would usually lead to lesser potency in your body, lesser drug resistance or lesser disease resistance in your body so please do not once again take the medicine without prescription, there is Imipramine which is anti-depressant again these are the medicine one should not take without consulting the doctor.

I think in India we need to do better in terms of sale of the medicine. Sometimes lot of medicines are available without proper prescription which need to be stopped and all of us being educated we should try our best to tell people that consuming medicine without proper reason is something not desirable at all.

Chloramphenicol; it is an antimicrobial we will see in a moment how one can (())(4:35) this molecule quite interestingly naproxen which is in a set will also see how to prepare it very-very simple. Finally, we will see the synthesis of Ranitidine which is an antacid.

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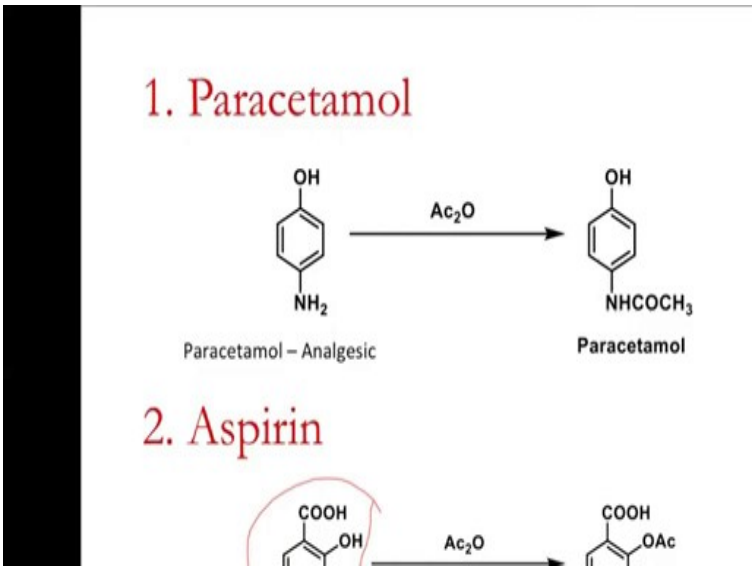

Let us look at Paracetamol synthesis first; once again paracetamol is an analgesic and painkiller basically, you take paracetamol quite often I believe, it is one of the most used medicine, synthesis is easier I would say it takes the four amino phenol which is one of the cheapest molecule you can get in organic laboratory, you react it with acetic anhydride to give paracetamol.

One step synthesis, simplest synthesis anyone almost anyone should be able to synthesize without even knowledge of organic chemistry one can synthesize this paracetamol. It can be prepared in metric ton scale, it has been prepared in huge scale in industry, things are nice, simple, a synthesis which is easier or better than this is difficult to imagine.

Of course, there are many different approaches one can think of including the availability of the starting material, till how to deal with the side product if anything is forming, I think this method that is outlined here is unbeatable, this is the one which is used most often. Let us then look at our next molecule which is aspirin; this is ortho-hydroxy benzoic acid also known as salicylic acid.

Now the salicylic acid is once again one of the very cheap organic molecules, you can find in any organic laboratory, it is not a surprise that therefore by using this salicylic acid acidic anhydride treatment gives you aspirin and this is the method which is used industrially. I would say there is no need really to look for an alternative method to prepare this molecule, it works

beautifully and these reactions are quite powerful to prepare this simple drug that is aspirin, aspirin is analgesic as well as anti-inflammatory.

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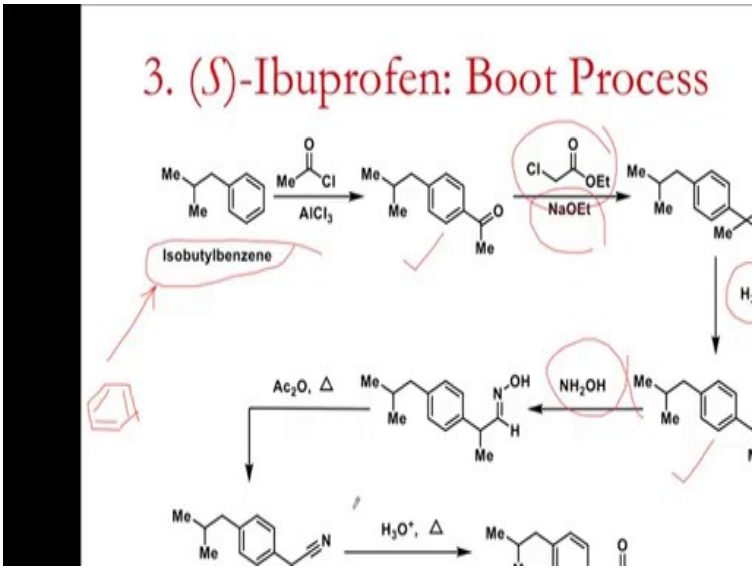

Let us look at this not so simple molecule, ibuprofen; ibuprofen synthesis is known till since I guess 1960's this is one of the heavily used molecules, as you know ibuprofen for its analgesic as well as anti-inflammatory role. Ibuprofen synthesis has been done by 6 steps in industry starting from 1960's this is the famous boot process.

The starting material although I am showing here isobutyl benzene but you can prepare it from benzene, simple benzene you can start with and do a Friedel-craft reaction, Friedel-craft alkylation reaction you can do with benzene by using propylene you take benzene reacted to propylene in presence of aluminum fluoride to get the Friedel-craft alkylated product that is isobutyl benzene.

Now, this is very cheap to prepare, what you do next step is the Friedel-craft acylation, Friedel-craft alkylation followed by Friedel-craft acylation, once again by using aluminium trichloride you do this reaction, okay double Friedel-craft reaction or a product with an alkyl as well as acyl. Subsequently you react it with this ethyl chloroacetate in presence of a base sodium ethoxide.

So, you deprotonate it and attack it on the ketone to get this epoxide intermediate which then one can hydrolyze to get this branched aldehyde. One can think of preparing this branch aldehyde by

many other methods such as if you have an olefin is there branch hydroformylation one can do let us not get into the other possible routes by which you can synthesize this intermediate, this is I think it is quite an interesting method to prepare it.

You prepare this intermediate by this method and no metal, metal 3 so far and you then use this hydroxyl amine to give the aldoxime which upon treatment with acetic anhydride heating condition gives you the corresponding cyano intermediate. So in the ibuprofen then we can synthesize this ibuprofen in the boot process by following this excellent procedure which is 6 steps and gives the product in excellent quality.

Now if we are looking at, so this ibuprofen can be synthesized from the three steps starting from simple benzene, this is known as the boot process that is known since 1960s. It is a very effective process, indeed industrial preparation of ibuprofen started with boot process. But in the next slide you will see a modified version of this where we find that ibuprofen can be synthesized only in three steps as opposed to the six steps that you have seen in the last slide.

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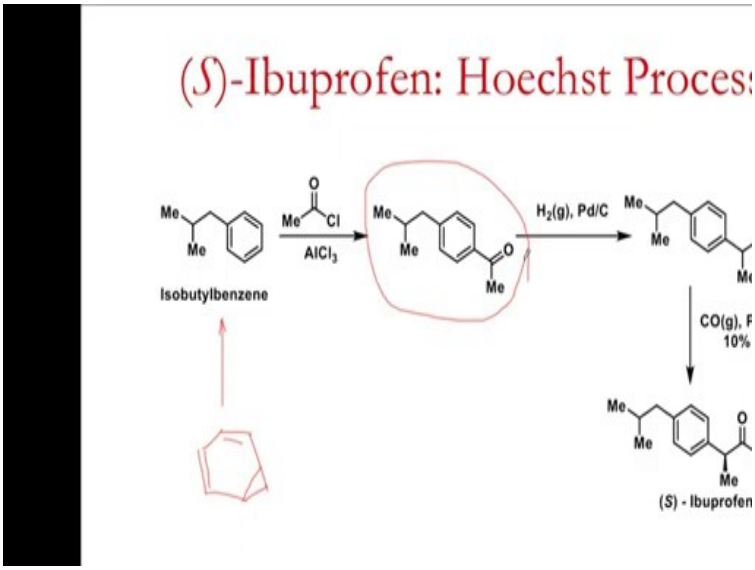

Once again here also we start with benzene, the simplest possible starting material. We take benzene and we do a Friedel-craft alkylation reaction with propylene to give isobutyl benzene just like in the last case. This Friedel-craft alkylation is followed by Friedel-craft acylation where acyl chloride and aluminum trichloride is reacted with this isobutyl benzene to give this same double Friedel-craft alkylated acylated intermediate.

This is the same intermediate as in boot process, if we take this intermediate now in a little bit different sense where we see that this ketone is reduced to the hydroxyl by using hydrogen gas and palladium on charcoal. It is a very effective method therefore although it is the metal mediated process industrially it is still viable and it has been followed.

Subsequently with this secondary alcohol with 10 percent HCl and CO gas in presence of palladium chloride this triphenylphosphine complex it is oxidatively added CO inserted and then hydrolysis gives you the ibuprofen directly. This is quite amazing synthesis simple synthesis in three steps as opposed to the six steps as you have seen in the boot process. This is (())(14:14) process and it works beautifully. Industrially it has been used quite a lot. Now we have seen this analgesic of this ibuprofen which is used quite a lot in regular life it can be done by utilizing this simple methodology as you see in here.

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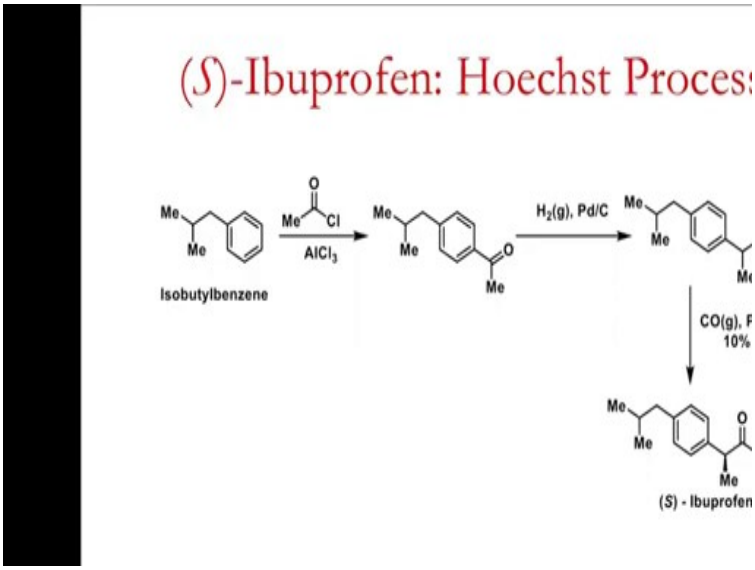

The basic difference between these two process has led to this Hoechst process which is more important and it gives the product in useful yield despite having the metal mediated synthesis.

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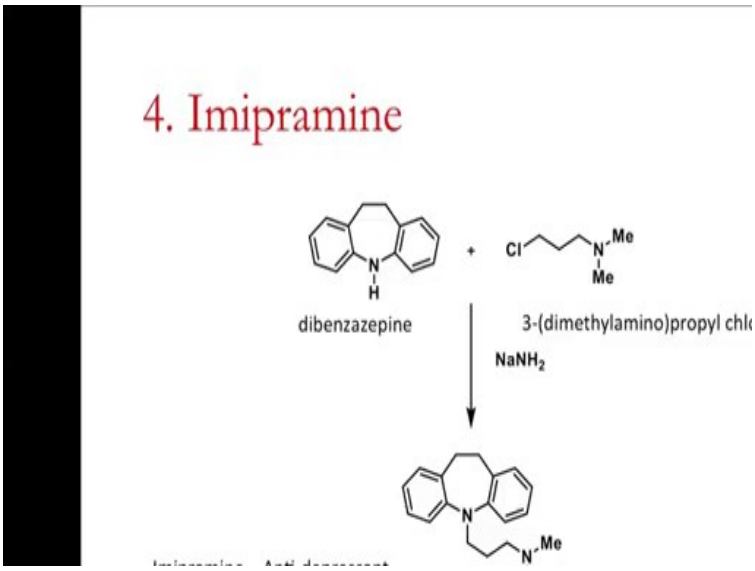

Let us look at yet another powerful pharmaceuticals known as imipramine, it is antidepressant and it is used quite often. It is one of the best-selling antidepressant for some time imipramine is synthesized from dibenzazepine as you see this tricyclic ring containing organic molecule it is reacted with 3 dimethyl amino propyl chloride as you see on the right hand side, it is a simple nucleophilic substitution reaction gives you imipramine in right one step.

It in one step only which is fantastic, imipramine which is an antidepressant can be synthesized from these two reagents by using these 3 dimethyl amino propyl chloride and NH2 to keep this product.

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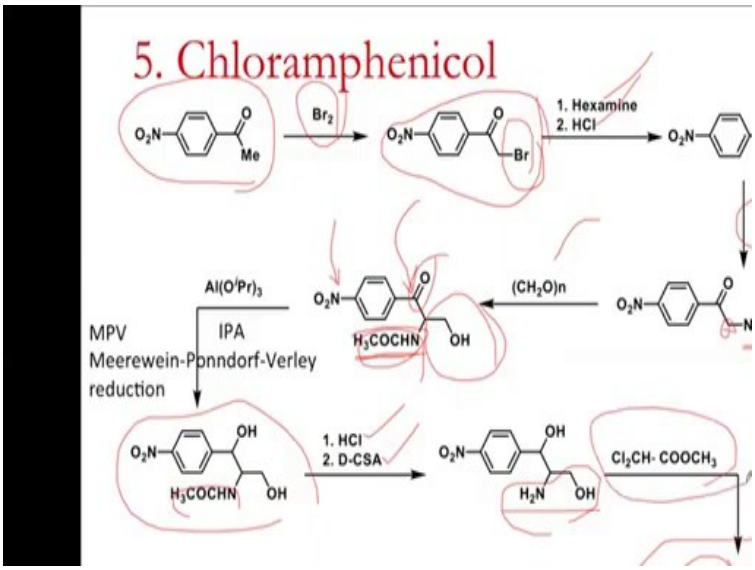

Now here is yet another exciting drug molecule known as Chloramphenicol, Chloramphenicol synthesis is a marvel in synthetic chemistry domain, it is started with a simple material such as this 4 nitro acetophenone one phenicol is a famous anti-microbial which is used quite a lot as you can see in here. Chloramphenicol has this CCL2 (())(16:46) which is important and this is a little bit complex molecule compared to what we have seen previously.

The synthesis is straightforward, simple organic synthesis without any metal mediated process we get this compound. So starting from this 4 nitro acetophenone, we have the bromination reaction rather alpha bromination alpha bromo acetophenone and the para position nitro group which is simple, exciting this alpha bromination happens this activated CH bond get brominated.

And subsequently we have hexamine as well as HCL to do the amination reaction over here and you protect this amine with HCL subsequently acidic anhydride treatment give you an acetyl intermediate to protect the amine and then reacting with formaldehyde gives you this alcohol. This primary alcohol via deprotonation of this carbon center and attacking on the formaldehyde gives you this primary alcohol.

But if you deprotect this in acyle group you will get the amino alcohol which you see in here so the deprotection of this in acetyl will give you amino alcohol that is required for the preparation of chloramphenicol but before doing that you have to do the reduction of this ketone. So this

ketone selective reduction in these cases in presence of nitro as you can see you have a nitro moiety in there and you have a ketone.

So selective reduction of this ketone can be done by this mpv reduction which utilizes aluminum this isopropoxide compound along with isopropyl alcohol which is a sacrificial donor, hydrogen donor, hydride donor actually. So this reduces this is a mild, relatively mild reducing condition to give you the secondary alcohol in presence of nitro this reduction can be occurring to give you this intermediate.

From where if you deprotect this n-acetyl with in presence of HCL and chloroacetic or sulfonic acid you get this amino alcohol intermediate. From there on it is just one more step as you can see here with this simple reagent you can get the chloramphenicol synthesis.

So just to come back again for this chloramphenicol synthesis it is 1, 2, 3, 4, 5, 6, 7; 7 step from a readily available starting material and the simplest possible starting material one can synthesize or one can complete the synthesis of chloramphenicol which is an antimicrobial. You start with nitro acetophenone do the bromination, convert it to amine protect the amine and then react it with formaldehyde and then you get this second, this primary alcohol and the keto group that you have over here selectively you need to reduce it in presence of the nitro group.

So, you use mpv reduction procedure, subsequently remove, you remove the acetyl protection by acid hydrolysis with HCL and camphor sulfonic acid and then you install this final cochcl2 motif to give you the chloramphenicol which is fantastic molecule if you look at for this sort of antimicrobial synthesis, okay. Let us look at the next one.

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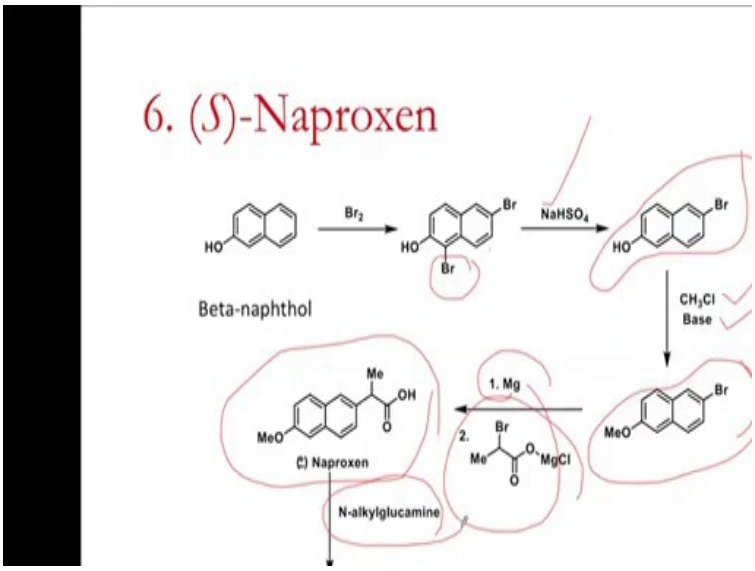

Next one is the naproxen synthesis, it is again another beautiful demonstration of what synthetic chemist can achieve by simple organic chemistry. Beta-naphthal is taken which is one of the cheapest and readily available starting material one can get for this naproxen synthesis. You start with beta-napthal, you brominate it.

Of course, monobromination is not easy to get it is always end up giving dibromination in the position as it is shown in here. This dibromo of course we do not want, one of this bromo that is in here this bromine is removed by NaHSo4 treatment to give you this monobrominated beta-naphthal derivative. Protecting this hydroxyl or since in the naproxen you have methoxy group so you install the methoxy group or you protect the phenol with methyl group OME by using the CH3Cl in presence of a base.

So, you have bromo methoxy beta methoxy naphthalene which is again quite useful or quite important intermediate from hair treatment with magnesium and bromo magne bromo this ethyl acetate you get, this beautiful naproxen molecule which is in racemic from by using this n alkyl glucomine you can resolve it to give the s-naproxen, it is a NSID non-steroidal anti-inflammatory drugs which is quite popular and used widely in pharmaceutical world. Once again please do not consume the any of these or any other medicine directly without doctor's permissions or doctor's advice.

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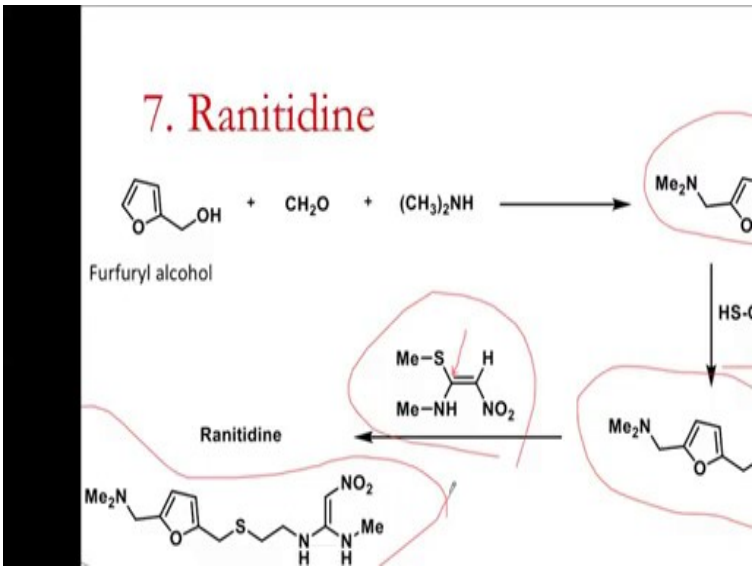

This is the final molecule synthesis for today that is ranitidine, ranitidine is an antacid, it is used widely worldwide. Specifically in our country it has been used quite a lot, it is prepared only in three steps starting with furfuryl alcohol once again it is a very cheap starting material furfuryl alcohol.

Reacting it with formaldehyde and dimethyl amine gives you these 15 disubstituted furan derivatives, 1 5 disubstituted furan derivative and reacting this furan with this amino thiol you get further derived or advanced intermediate which is having a primary amine over there which is nucleophilic enough to attack on this carbon center to give you the complete synthesis of ranitidine.

Once again this is a simple reactions condensation simple reaction in information and attack on the on five position subsequently, a further intermediate synthesis to give you the ranitidine. This completes a very important medicine pharmaceuticals that is available over the counter and it gives you access to the preparation of this molecule in the shortest possible route.

Only in three steps one can synthesize this molecule to give the desired pharmaceuticals. With this I hope you would look for many more synthesis of the simple pharmaceuticals and will be happy to discuss in future regarding this. Thank you very much, see you later.

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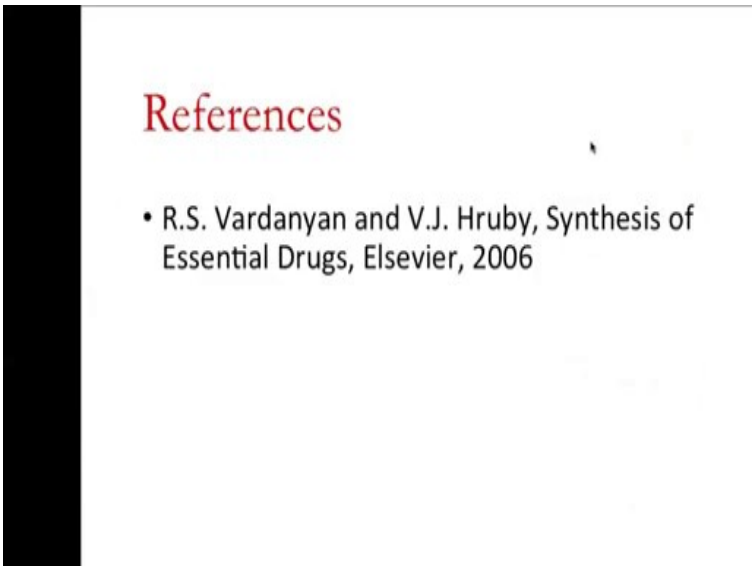

Here is the reference for this work or any of these you can get from the internet as well, here is the reference for all these synthesis.