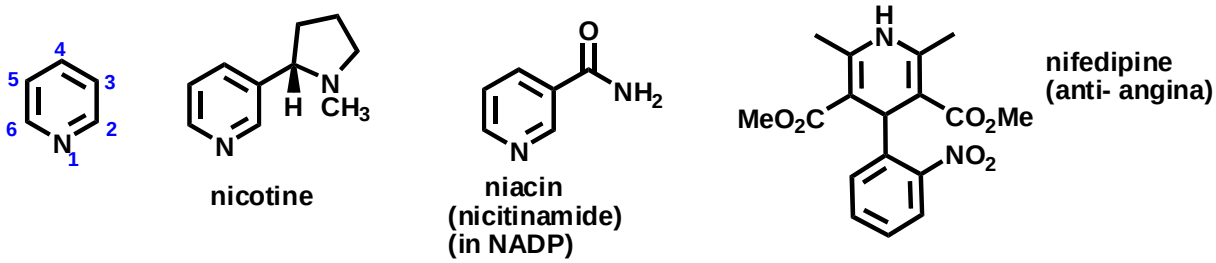
Pyridines

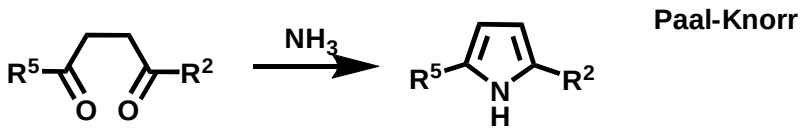
Pyridines are the most commonly encountered π- electron deficient heterocycle. Examples abound.



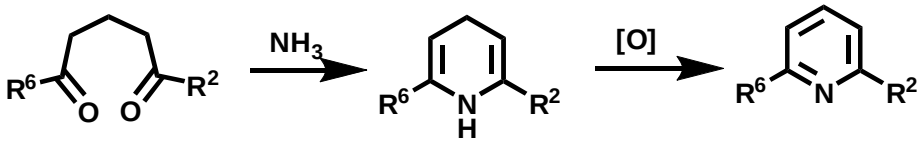
There are *many* classical syntheses of pyridines; only a few can be covered in the time available.

1. **Hantzsch Synthesis**

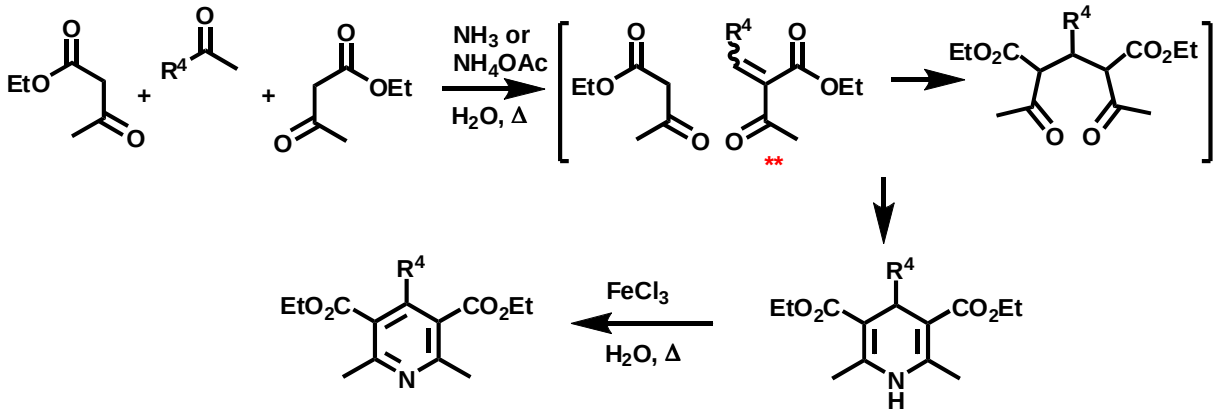
Probably the conceptually simples pyridine synthesis would be a simple extension based on the Paal-Knorr pyrrole synthesis. In other words….



the shouldn't a 1,5-dicarbonyl do….



This is absolutely feasible. Furthermore, as you might expect, the 1,5-dicarbonyls are readily accessible by Michael reaction chemistry (1,4-, conjugate additions). The one- pot version of this, where the unsaturated carbonyl is prepared, the Michael reaction occurs, and the pyridine formation is accomplished, is quite common. It is called the **Hantzsch synthesis.**

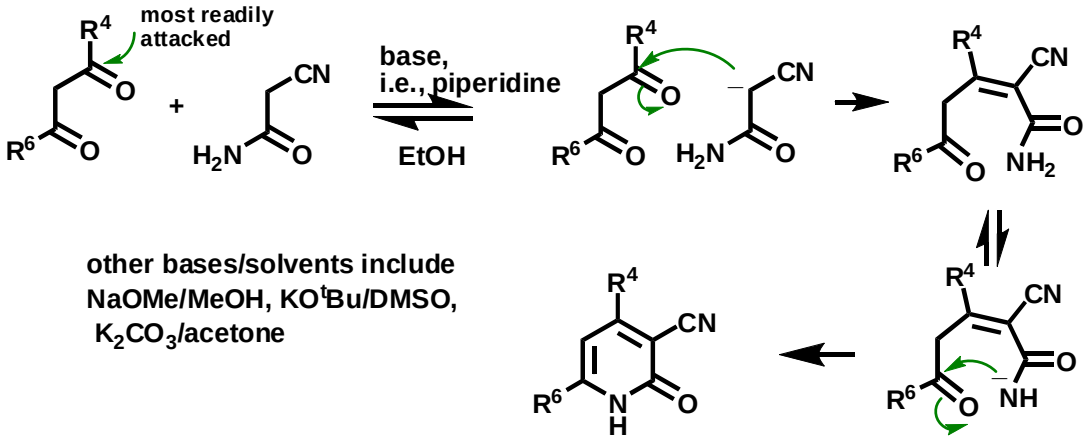


It's rather forceful conditions, but the ester groups can be decarboxylated.

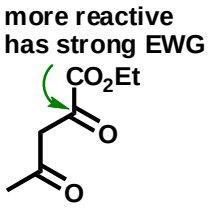
The shown example is a symmetric case, but unsymmetrical ones can be done by doing the aldol condensation (here called a Knoevenagel) first, discretely, and then putting that compound (**) into a separate reaction doing the subsequent steps.

2. **Guareschi Synthesis**

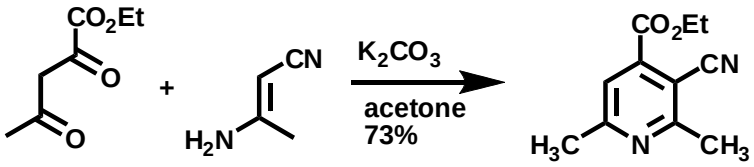
A closely related synthesis a cyanoacetamide and a β-diketone, or alternatively the enamine of a β-keto nitrile. In these cases one of the ketone functions of the β-diketone is the most readily subject to nucleophilic attack. This is called the **Guareschi synthesis.**



The two ketone carbonyls are normally widely different in reactivity to give pyridine formation without regiochemical mixtures of products. Otherwise, symmetric diketones ($R^4 = R^6$) are used.



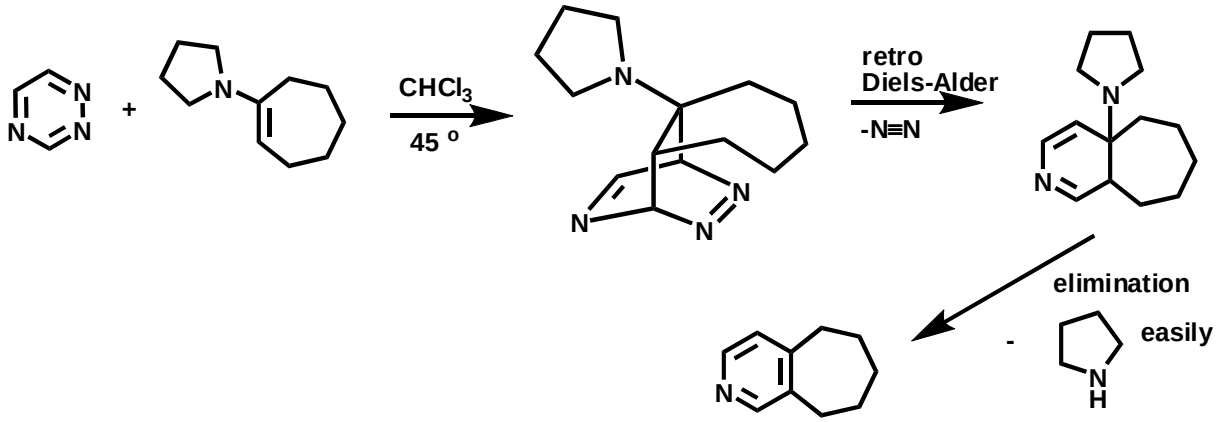
The following is an example of the modification of Guareschi that employ the enamine of a β- keto ester.



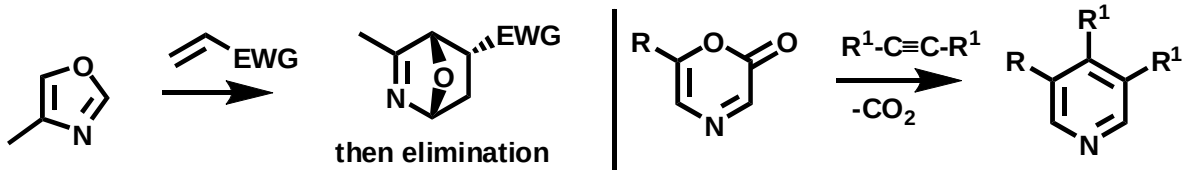
3. **By Cycloaddition Chemistry**

Six pyridine is a six membered ring system, there are several approaches to it that employ Diels-Alder chemistry to prepare the system. Some need a subsequent elimination, or a subsequent retro- Diels-Alder (or both) to form the pyridine. One example will be shown

If one has a 1,2,4-triazene, it can participate in Diels-Alder chemistry, particularly inverse electron demand versions (i.e., electron poor diene); in this case the electron rich dienophile is an enamine. The product then undergoes elimination of the amine to give the pyridine. This is a bit unfair, in that you've seen no triazine chemistry to this point. These can be substituted at the 3-,5-, and 6- positions.

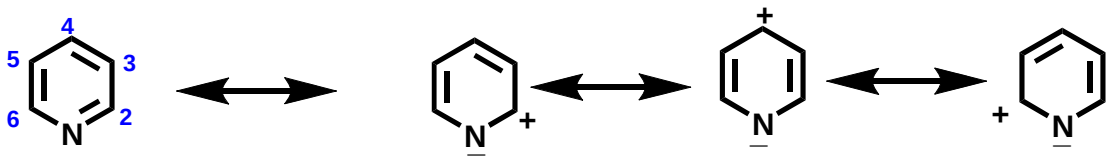


It is certainly not the only type of Diels-Alder process employed, i.e., ….



Reactions of Pyridines

Since pyridines are electron deficient species, it is possible to do nucleophilic attack reactions on carbon atoms. For the expected reasons, C-2, C-4, and C-6 are the sites susceptible to nucleophilic attack.

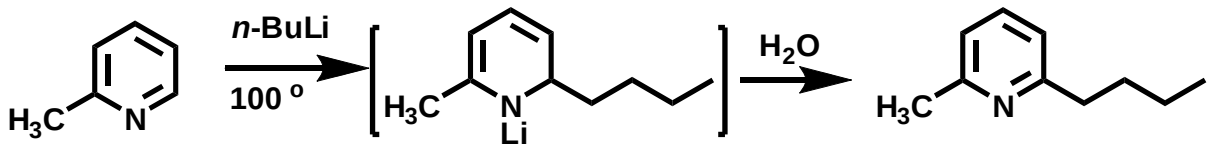


If the nucleophile is sufficiently reactive, it may attack the unactivated pyridine itself, but it must be pretty reactive. The immediate product is a 'reduced' pyridine; how the product gets back to a pyridine depends upon the case. It may be..

-due to spontaneous loss of H_2 from the dihydropyridine

-due to spontaneously loss of H_2 from the anion of the dihydrpyridine

-due to oxidation by air (O_2) after workup



This only works for the most reactive nucleophiles, such as:

RLi, RMgBr, $NaNH_2$ (this is the least reactive nucleophile I've seen, called the Chichibabin reaction)

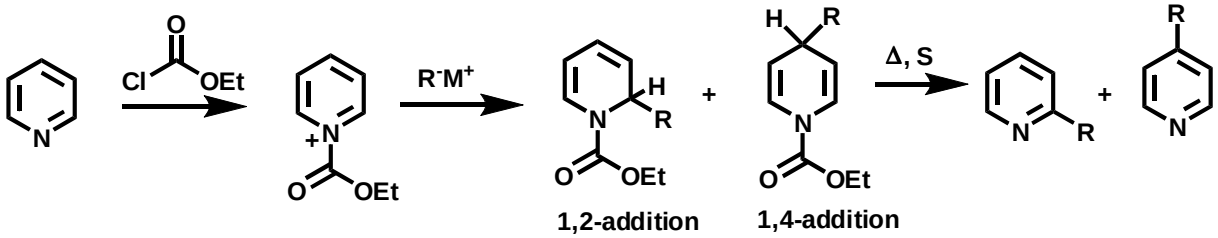
The pK_a limits is ≥ 35 under reasonable conditions

Note: I have seen a report of KOH at 300 °C

Regiochemistry is normally at C-2 (or C-5); it's reasonable that coordination of the metal counterion to the N lone pair has a role in this.

Alternatively, it is possible to employ a wider range of nucleophiles by:

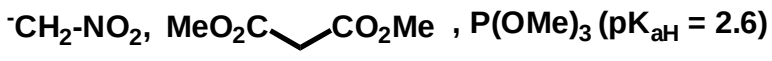
A. Quaternizing the nitrogen atom of pyriidine, preferably with something that can ultimately be removed.



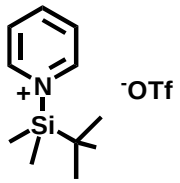
Pyridinium is now more reactive, but reactions often give mixtures if one position isn't blocked.

Organometallics such as R-Li or R-MgBr give mostly 1,2- addition products
Organometallics such as R-Li + CuI give almost entirely 1,4- addition products

Now, nucleophiles associated with lower pK_a's (≤ 10) can be used, and give almost entirely the 1,4-addition products. Examples of these nucleophiles include:

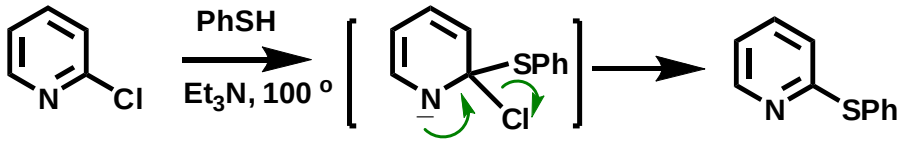


Another alternative is with TBDMS substituted pyridinium ion; due to the steric hindrance present from this group, 1,4-addition is the norm.



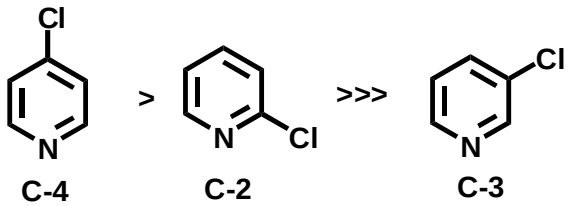
B. Put a leaving group on the pyridine, usually being Cl, but it can be F, Br, NO_2, SO_2OR, or OCH_3

Now the reaction is an addition-elimination type, and nucleophiles with pK_{aH} 's down to 6.

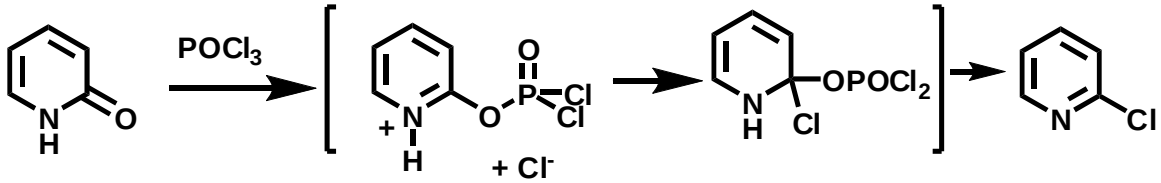


Examples of nucleophiles include MeO^-, NH_3, PhLi, and Ph-CH^-CN

The reactivity is different, depending upon the location of the Cl atom on the pyridine. In order of reactivity, it is

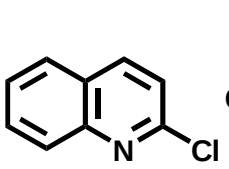


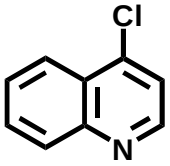
The C-2 chloropyridine is prepared from the pyridine, by $POCl_3$



This reactivity can be extended to quinolones and isoquinolines.

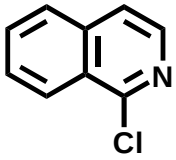
In quinolones, the C-2 and C-4 chloro substituted compounds are directly analogous.



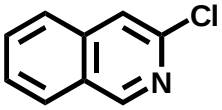


directly analogous reactivity

In isoquinolines, the C-1 chloro substituted case is directly analogous, whereas the C-3 chloro isomer isn't quite as reactive. The valence bond argument supports this, in that the negative charge is not as effectively delocalized onto the electronegative N atom in this latter case.



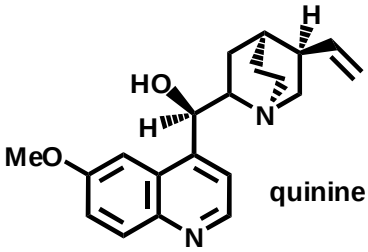
C-1
directly analogous



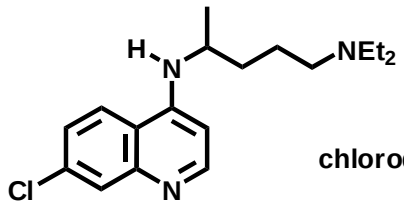
C-3
not as reactive

Quinoline and Isoquinolines

Quinolines and isoquinolines are simply the benzo- fused homologues of pyridine. They are chemically very analogous. Quinolines are particularly important as antimalarial drugs.

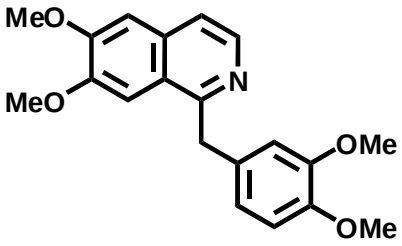


quinine

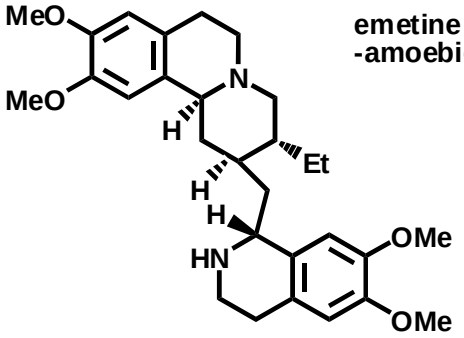


chloroquine

Isoquinolines are more widely encountered, usually as the reduced, 1,2,3,4-tetrahedorisoquinoline nucleus.



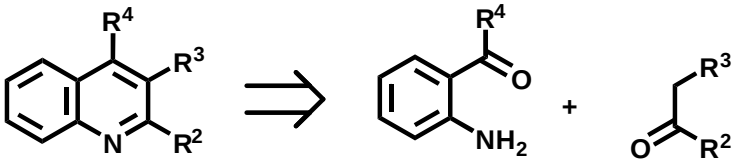
papaverine
opium alkaloid
-anti spasmotic



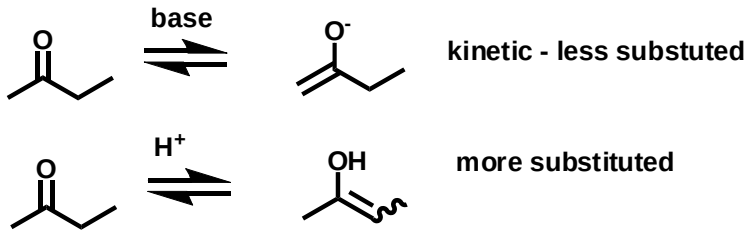
emetine
-amoebicide

Quinolines synthesis

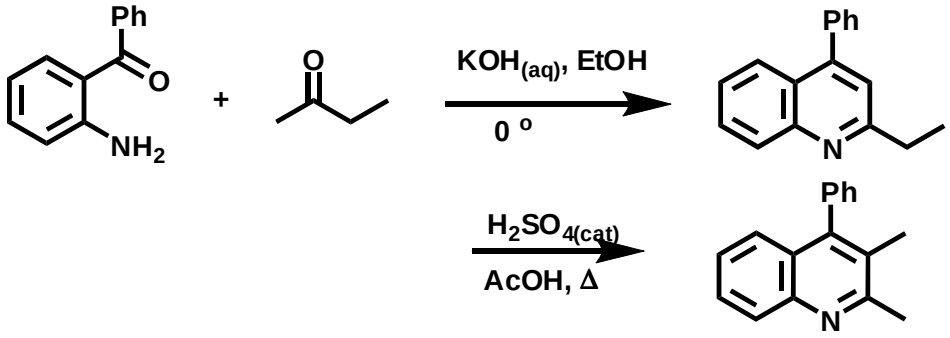
The most common quinoline synthesis is a combination that looks like an aldol condensation and a imine formation reaction. It is called the **Friedländer synthesis**, and can be either acid or base catalyzed.



It is not established with certainty which order these two processes occur in, but my bet would be that the aldol is first under basic conditions, and the imine formation is first under acidic conditions.
For the regiochemistry of reaction with unsymmetric ketones, recall basic enolate/enol chemistry…



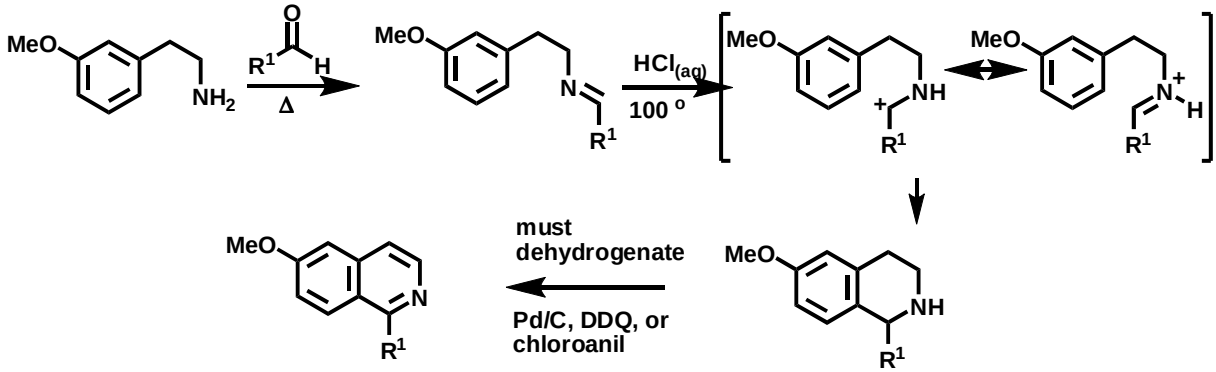
And therefore:



It is reasonable to expect problems when R^4 is alkyl, as there is then a site for competing enolization. As a result, many, many of the Friedländer examples have R^4 = H or aryl, and the few examples with R^4 = alkyl have an acidic β-keto ester as the ketone partner.
Note: We will not cover these reactions, but for an electrophilic substitution alternative in quinolone synthesis, see the **Combes synthesis** or **Skraup synthesis.**

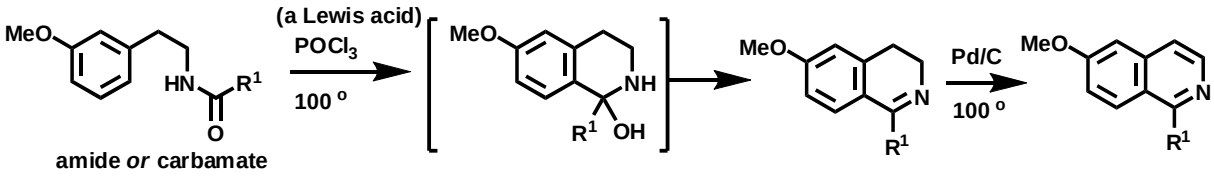
Isoquinoline Synthesis

The most common synthesis of the isoquinoline nucleus is based on Frielde-Crafts type chemistry, but using an imine (instead of an acid chloride). There is a separate dehydrogenation step to get the fully aromatic system. This is called the **Pictet-Spengler synthesis.**



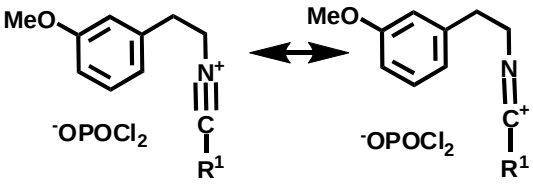
There is a drawback to the Pictet-Spengler. The iminium ion is pretty stabilized as cations go, and consequently is not *that* reactive. As a result, and electron donating group, and a strong one, must be present on the carbocycle for this reaction to proceed.

There is, however, a simple modification of this process which helps out with this problem. This involves working with an amide instead of an imine.

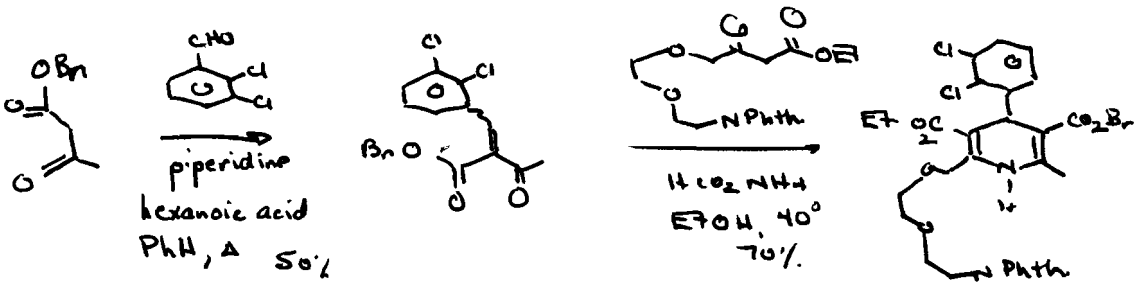


Lewis acid can also be PCl_5, $AlCl_3$, $SOCl_2$, $ZnCl_2$, Al_2O_3, $SiCl_4$

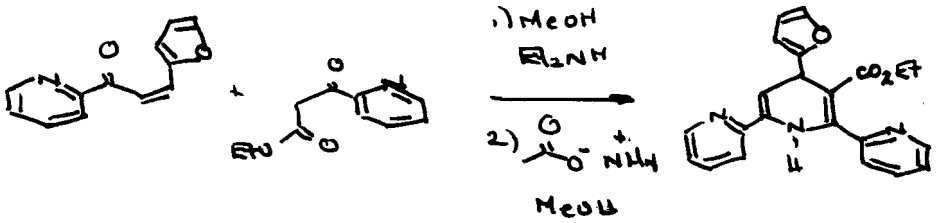
This is better in terms of reactivity, because the carbocationic intermediate formed is more reactive (less stabilized). So, while and EDG on the carbocycle certainly speeds up the reaction, it is *not* absolutely necessary for success. For some reason, it is known by a different name, specifically the **Bischler-Napieralski synthesis.**



Hantzsch Pyridine Synthesis - Examples



Bioorg. Med. Chem. 1997, 5, 749.



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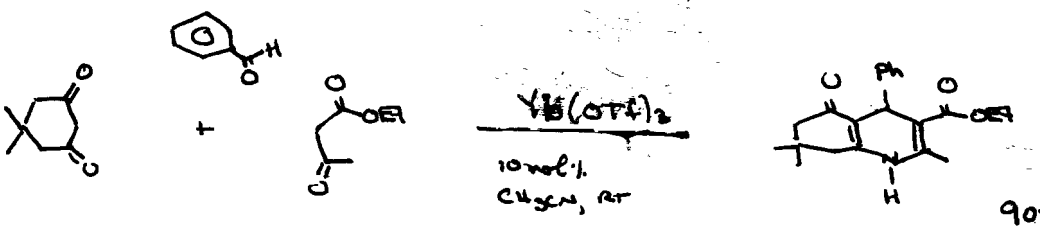
J. Heterocycl. Chem. 2000, 37, 1077.



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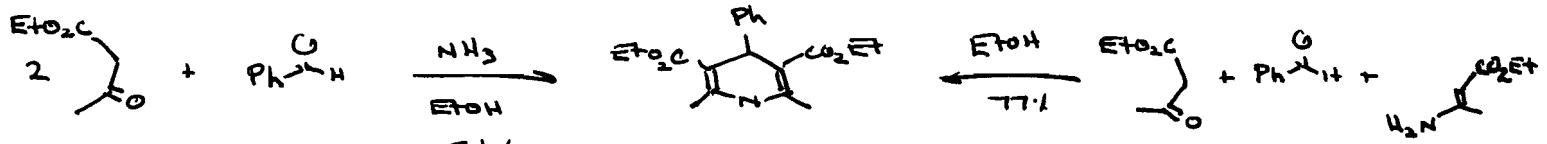
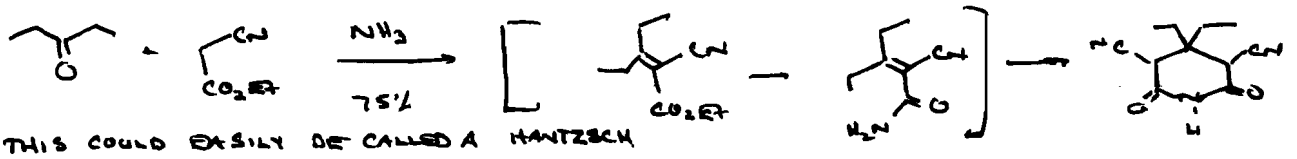
Org. Lett. 2009, 11, 2957

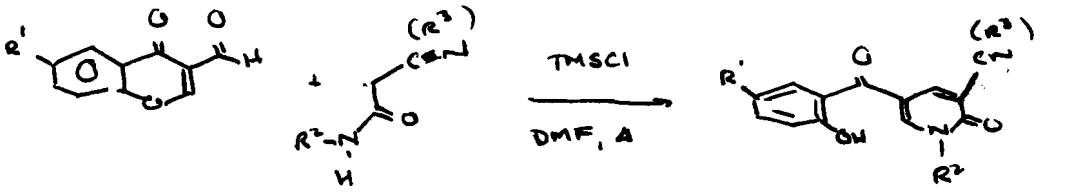


Angew. Chem. Int. Ed. Engl. 1981, 20 762.

GUARESCHI-(THORPE) CONDENSATION - EXAMPLES



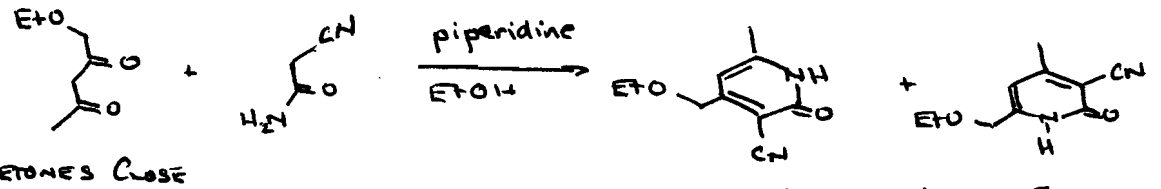
- THIS COULD EASILY BE CALLED A HANTZSCH



VOLOSHYNYUK, D.M.
SYNLETT 2004 2287.

R^3 CAN BE AMIDE, TOO
(SYMMETRICAL DIAMIDE)

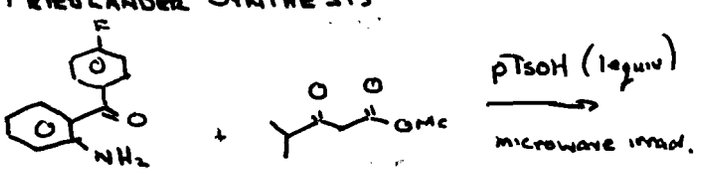
84%



KETONES CLOSE IN REACTIVITY

75 : 15

FRIEDLANDER SYNTHESIS

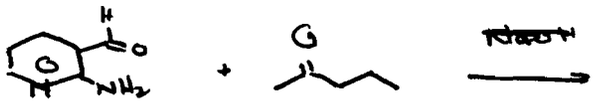


94%.

OBC 2006, 4, 104

WANG, G.W.

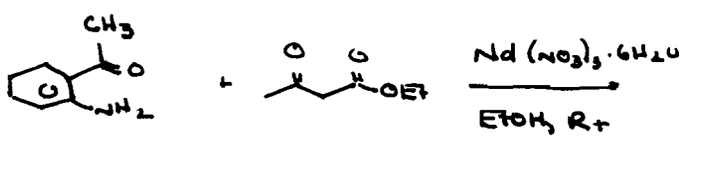
ORG. BIOMOL. CHEM 2006, 4, 104



ⓐ NaOH	35	: 65
ⓑ 5mol% H_2SO_4 + 1equiv	93	: 7 (84%)

EtOH, 65°

J. ORG. CHEM. 2003, 68, 467.



78%.

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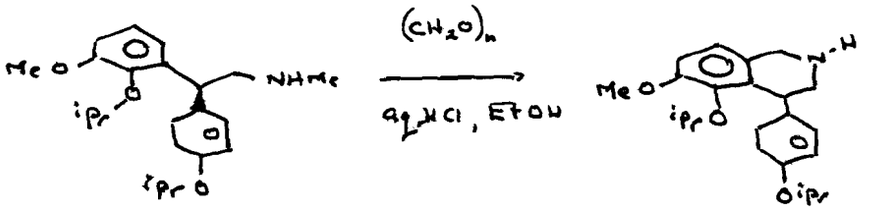

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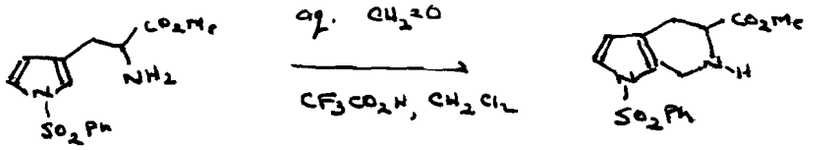

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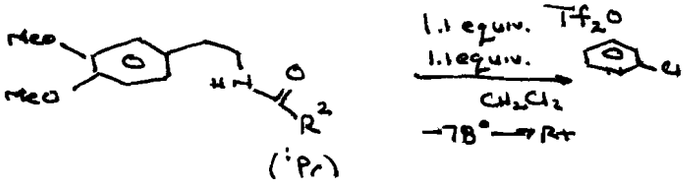

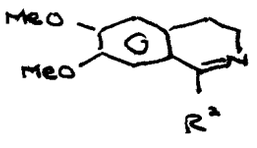

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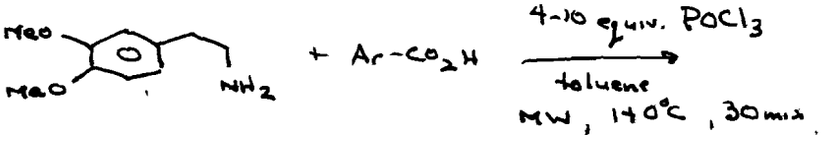

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