

# Heterozyklen Chemie

11.10.2011

Aromatische Heterozyklen:

elektronenarm:



117

$pK_a \approx 5$

elektronenreich



68

(2)



122

kleinsten reaktiv

(1)



90

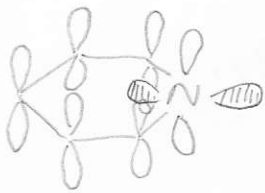
(3)

Stabilisierungsenergie kJ/mol

(Benzol +150 kJ/mol)

Dipolmoment  $\neq$

Elektrophile arom. Substitution



lone pair senkrecht

elektronenarm



lone pair  $\pi$ -möglicht Aromatizität

H elektronenreich



imin



H Enamin

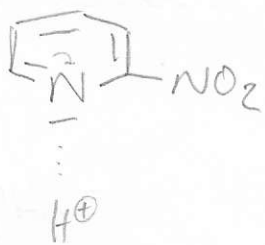
→ gleichmäßige Reaktivität, Enamin zugänglich für Elektrophil



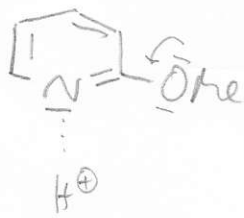
isoelektronisch zu Benzol



isoelektronisch zu Pymol



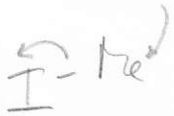
Schwerer  
protonisierbar



leichter  
protonisierbar



elektronische  
Effekte



langsamer zu  
pyridine:

3x



2,6-lutidine

40x



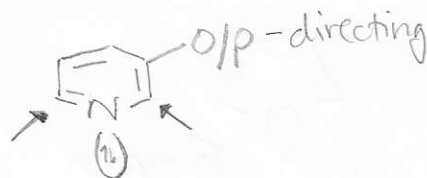
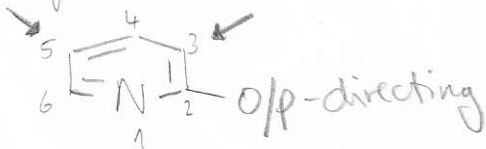
2,6-bis(t-butyl)-  
pyridine

nicht methylierbar

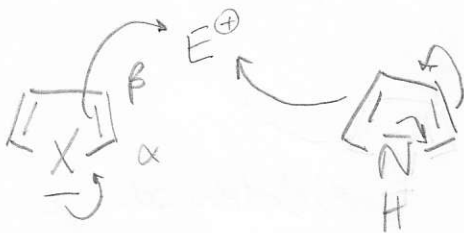
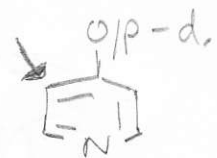
sterische  
Effekte

Substitution: EDG

Grundkörper quasi nicht substituierbar

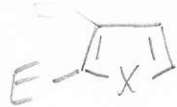
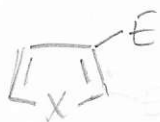


$E^+$  → H-abstr. fähig  
→ nur 1 ortho-Position



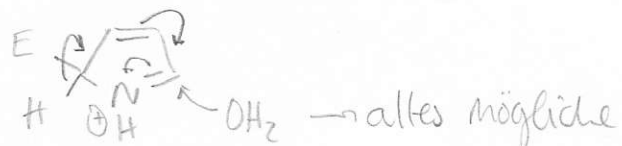
$\beta$ -Produkt

$\alpha$ -Produkt



Pyrrrole > furane > thiofene

$5 \times 10^7 > 1,5 \times 10^2 > 1$



$\text{OH}_2$  → alles mögliche

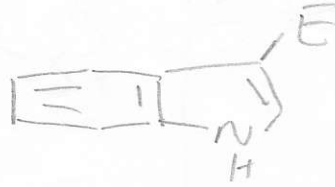
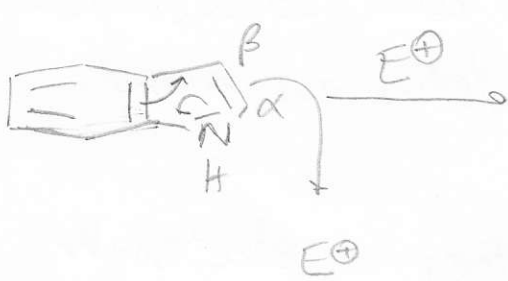


→  $\alpha$ -selektiv



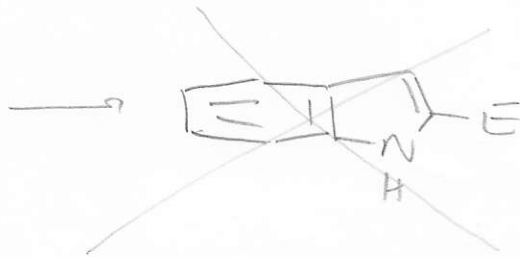
→  $\beta$ -selektiv

modulierbar durch  
sterische Hinderung



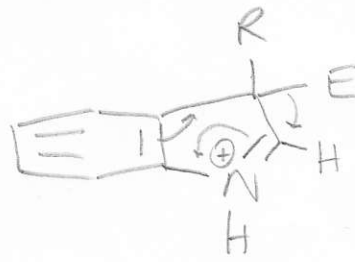
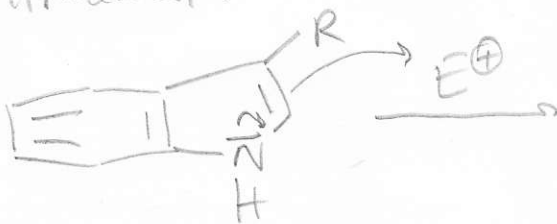
$\beta$ -selektiv

Intermediat:



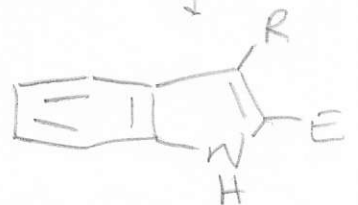
Aromat am  
leben halten

Intermediat:

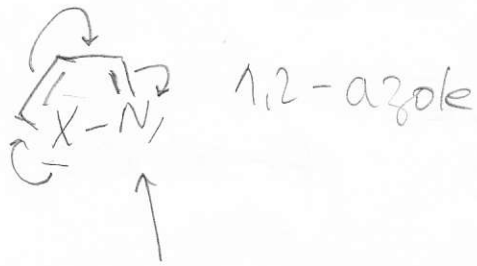
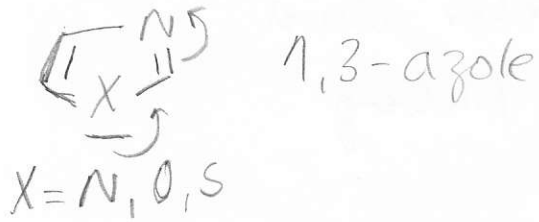


Orthoquinonoides  
Intermediat

1,5-shift



# 2 Heteroatome: 1,2- & 1,3-azole



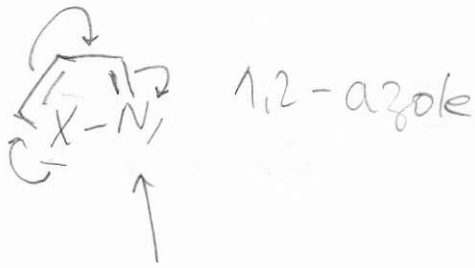
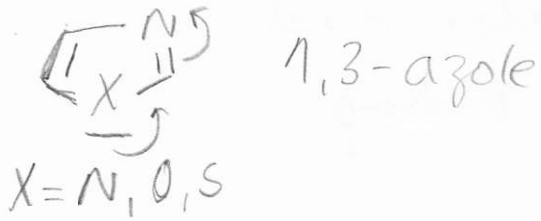
Senke: Elektronendichte hin verschiebbar



keine Senke: negative Ladung auf Kohlest.

Wesentlich reaktiver in elektrophiler arom. Substitution

## 2 Heteroatome: 1,2- & 1,3-azole



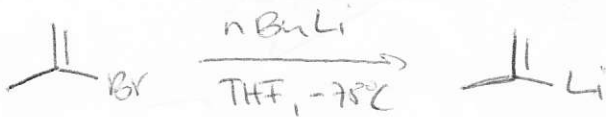
Senke: Elektronen-  
dichte hin verschiebbar



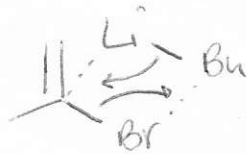
keine Senke: negative  
Ladung auf Kohlenst.

Wesentlich reaktiver in elektrophiler  
arom. Substitution

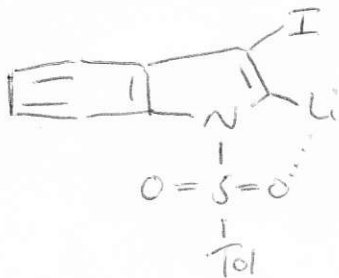
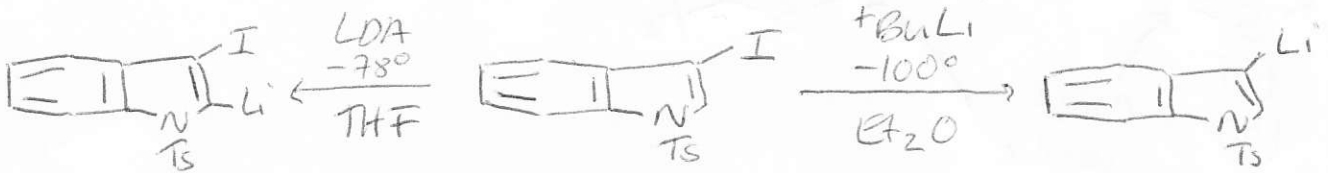
Organometallic derivatives:



transition state:



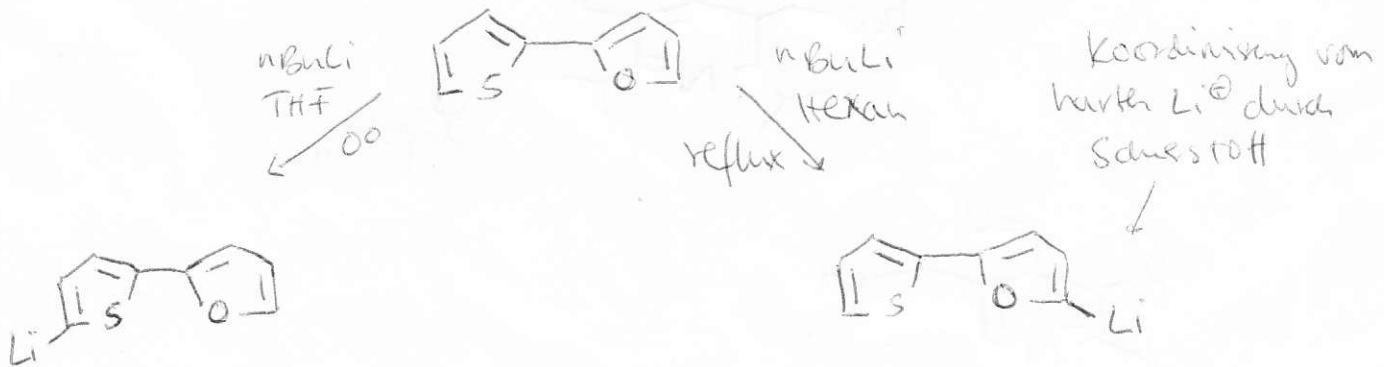
base: *t*-BuLi, sec-BuLi, LDA



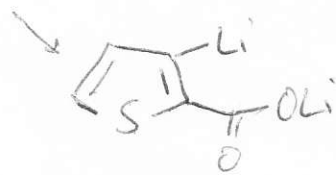
Wie ortho-Metallierung



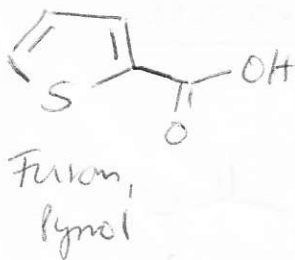
Thiophen Furan



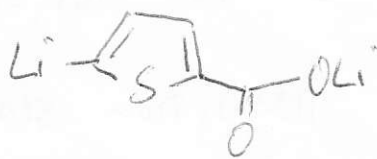
Koordination von  
BuLi durch  
Carboxylat



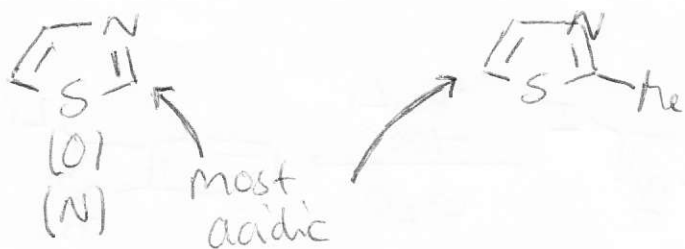
Zug <sup>n</sup>BuLi  
THF  
00



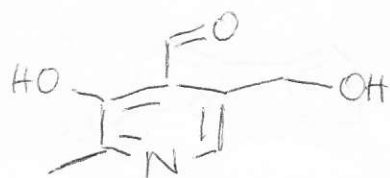
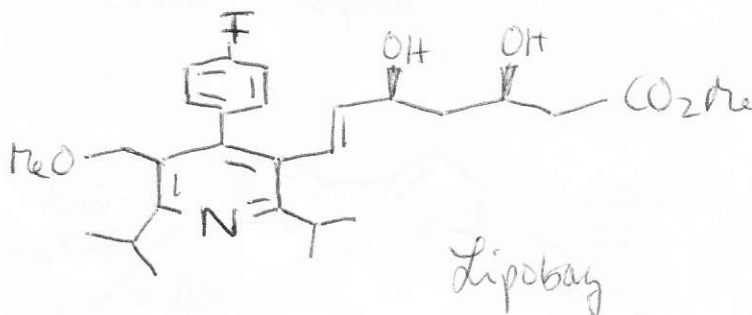
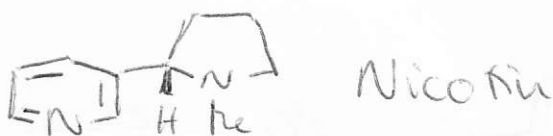
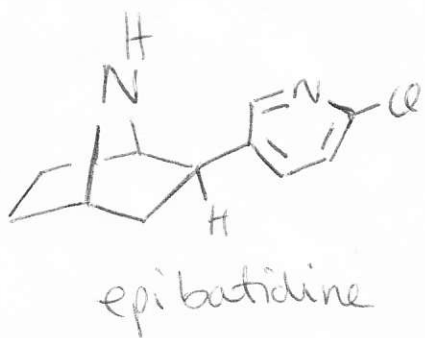
Zug LiOA  
-78 → 0°



1,3azoles:



Pyridin - Heterocyklen:



Pyridoxal  
→ Vitamin B6

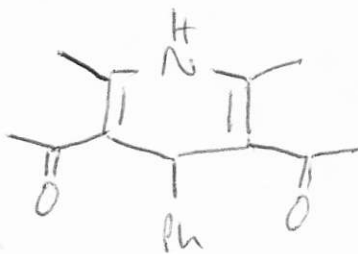
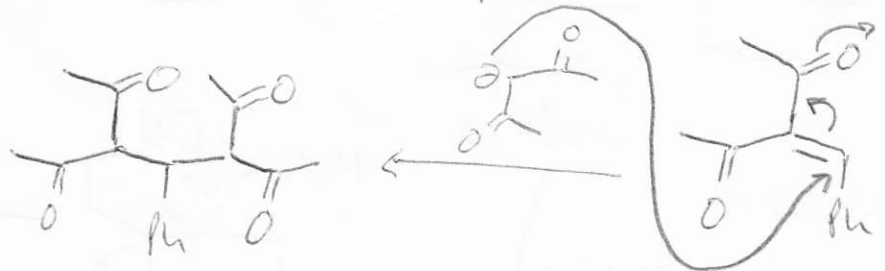
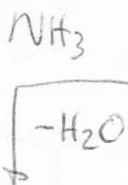
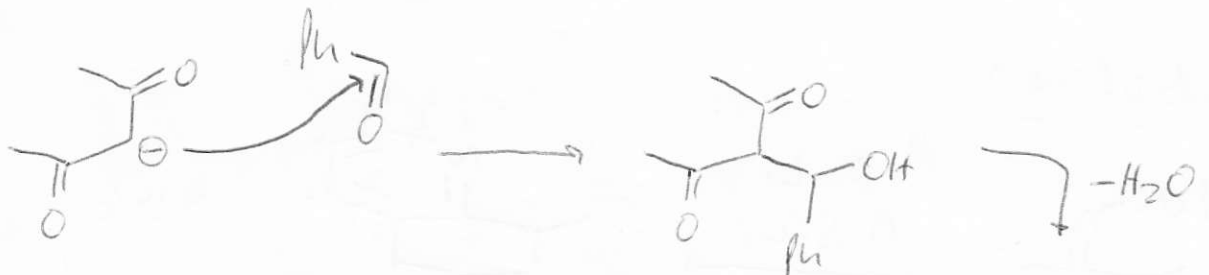
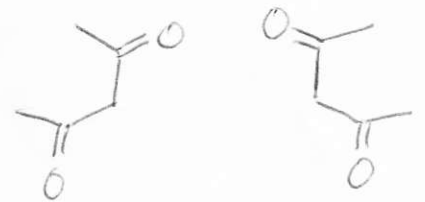


# Darstellung von Pyridinen

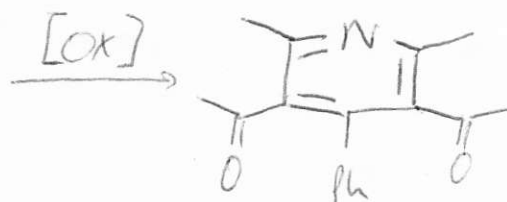
- 1) Hantzsche Pyridin Synth.
- 2) Kröhnke
- 3) Guareschi-Thorpe
- 4) Bohlmann-Ratz
- 5) Cycloadditionsreaktionen zur Darstellung von Pyridinen (Dale Boger)

## Hantzsche Pyridin-Synthese

building blocks: 1,3-dicarbonyl



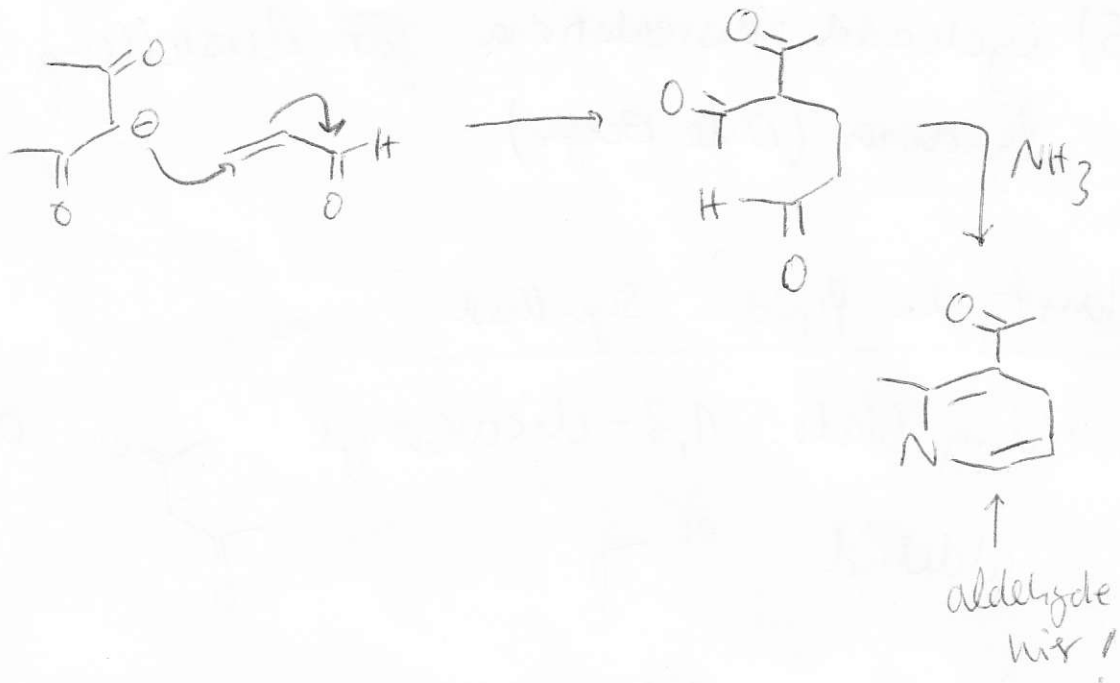
Dihydropyridin



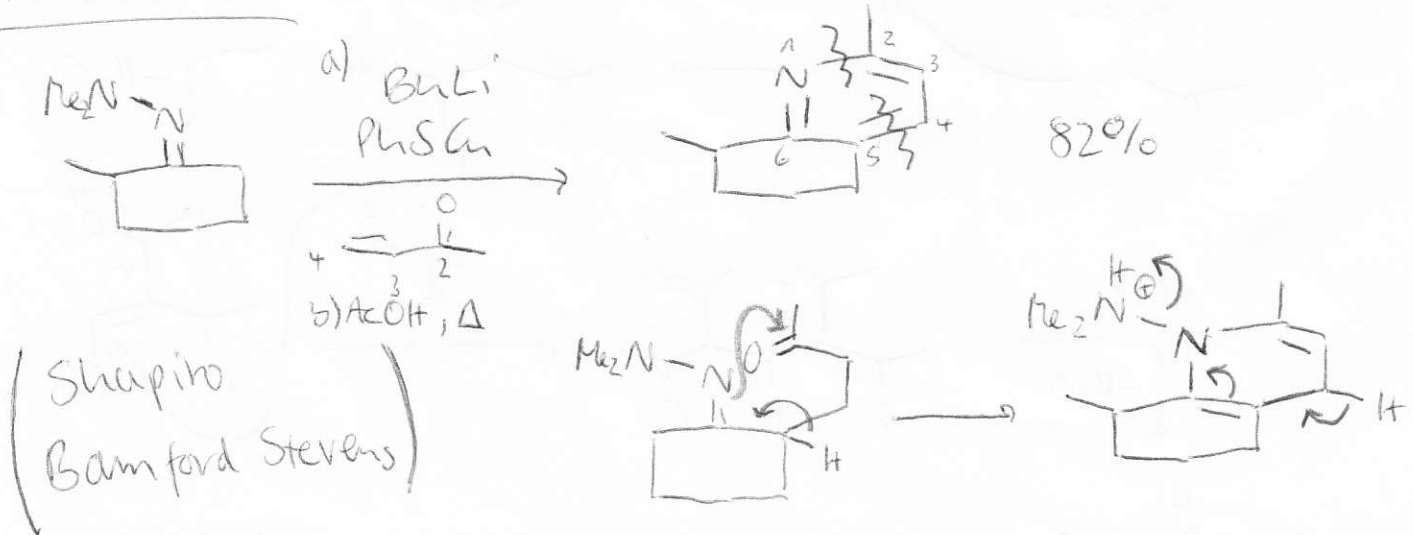
Nachteil =  
Symmetrisch

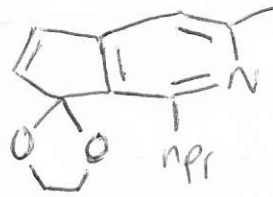
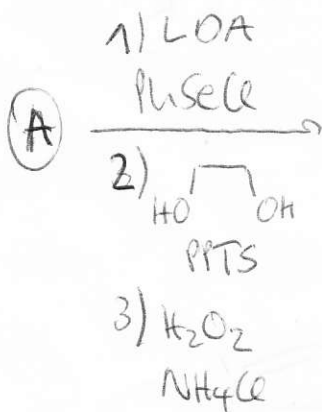
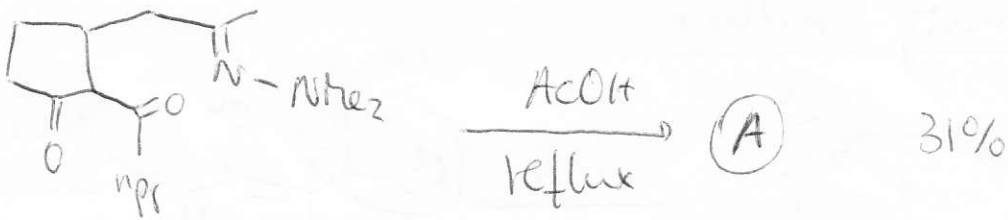
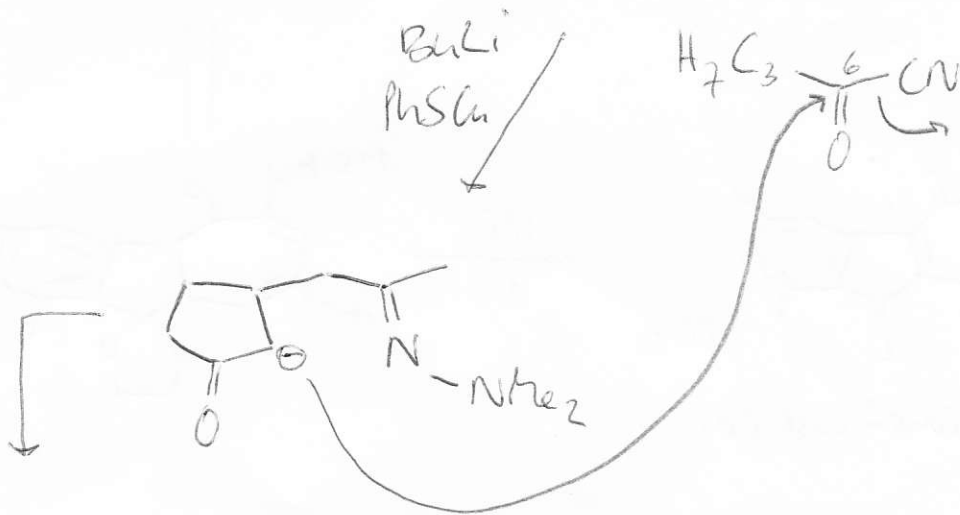
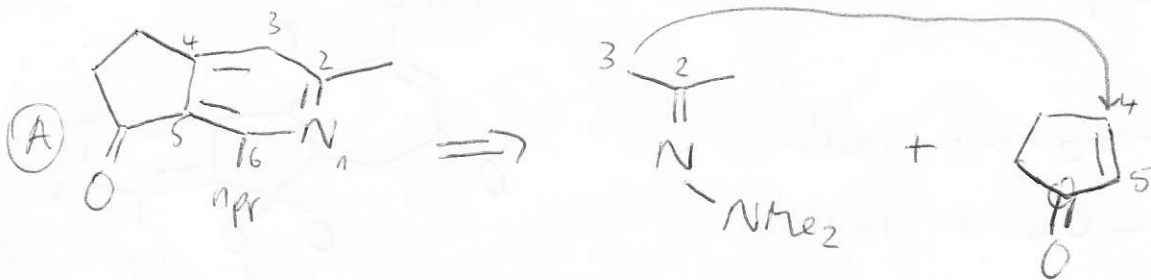
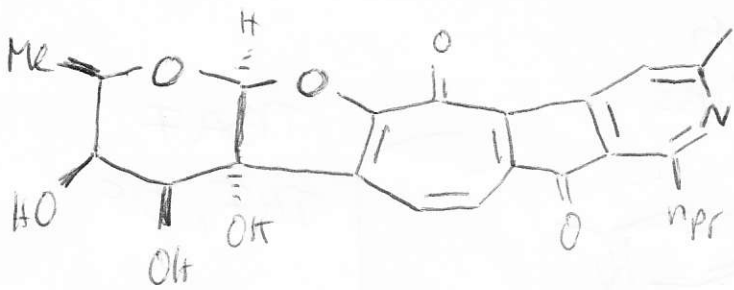
Limitierung: - Symmetrie: 1,3-Dicarbonyl kann nicht unterschiedlich substituiert sein  
 - Rest am Aldehyd variabel  
 -  $\text{NH}_2\text{OH}$  statt  $\text{NH}_3$  spart Oxidation

$\alpha,\beta$ -ungesättigtes Aldehyd:



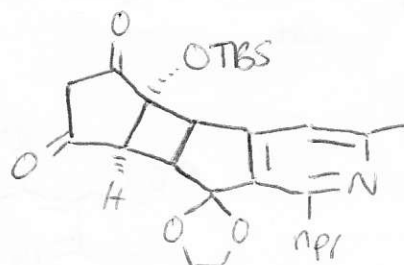
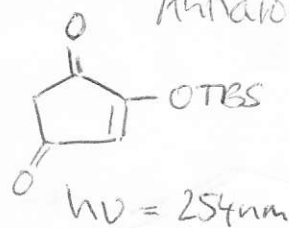
Rubrolone:



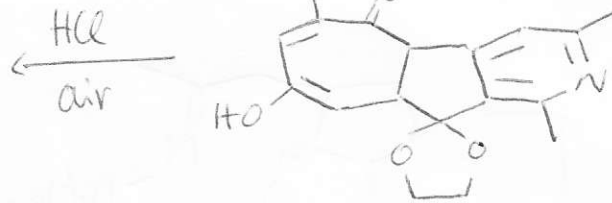
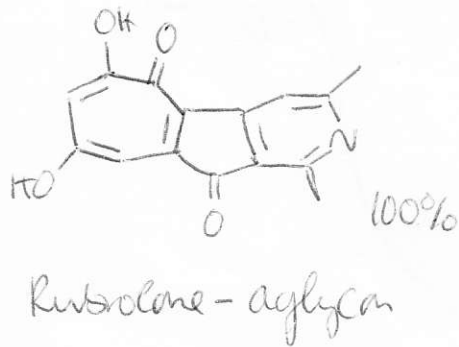
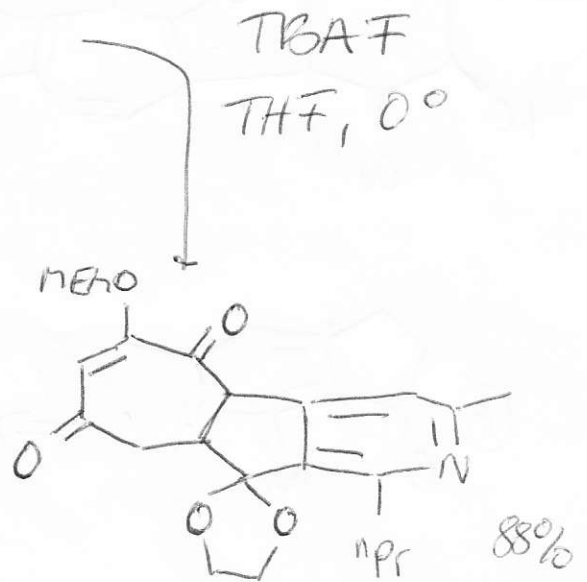
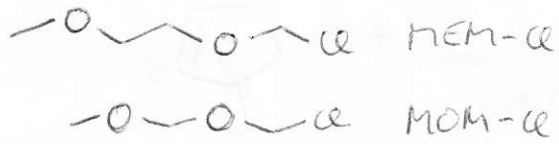
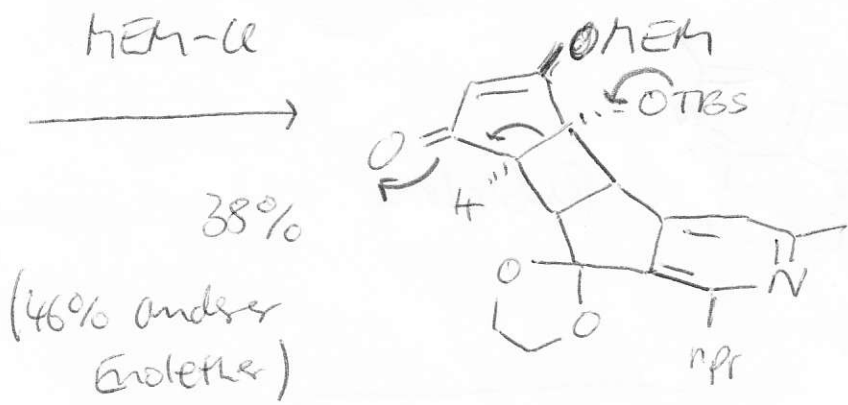


Cyclopentenone

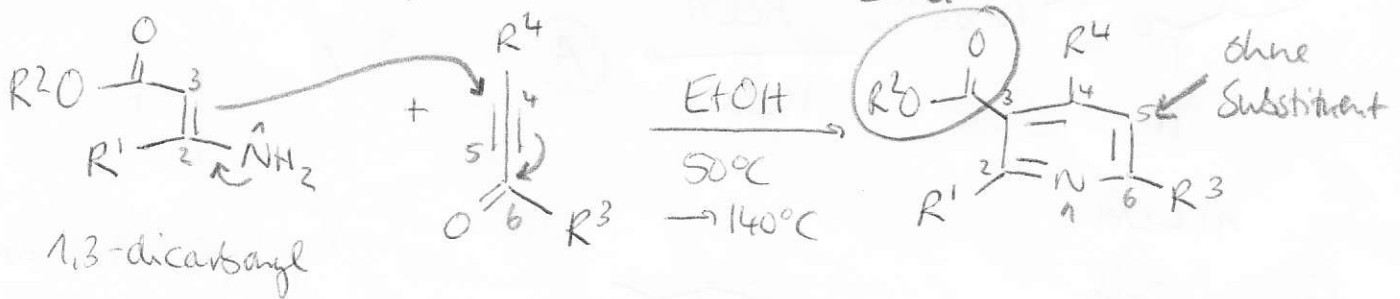
Antiaromatisch → nicht haltbar!



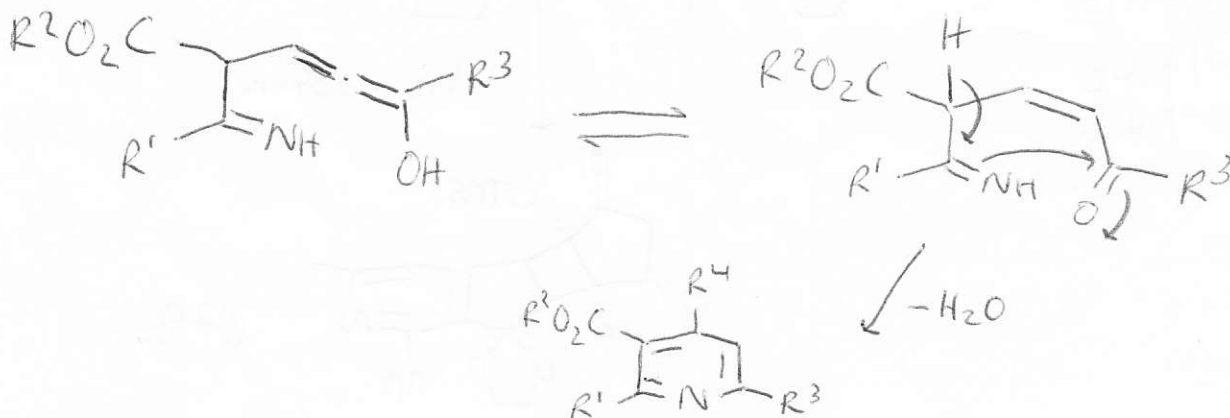
67%



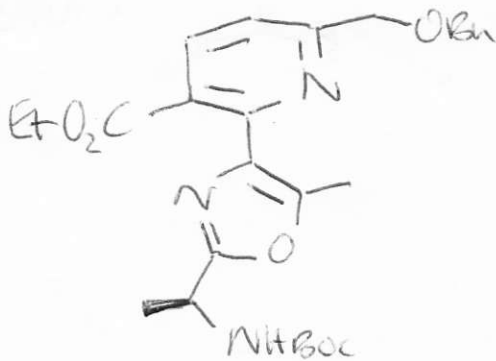
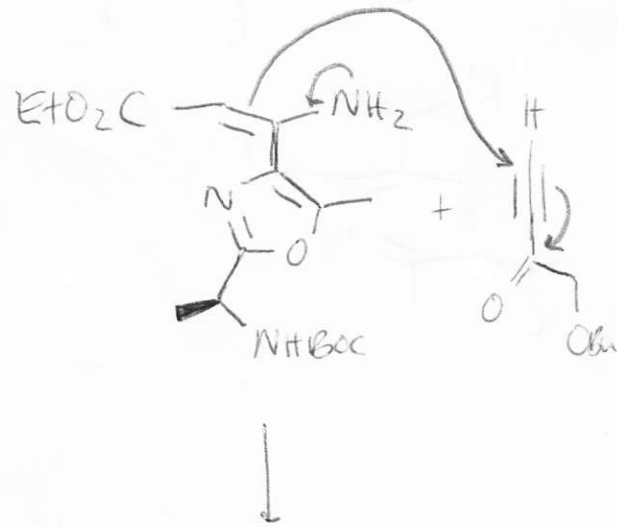
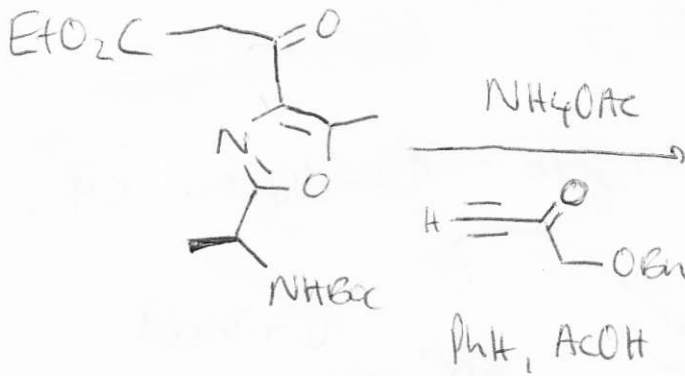
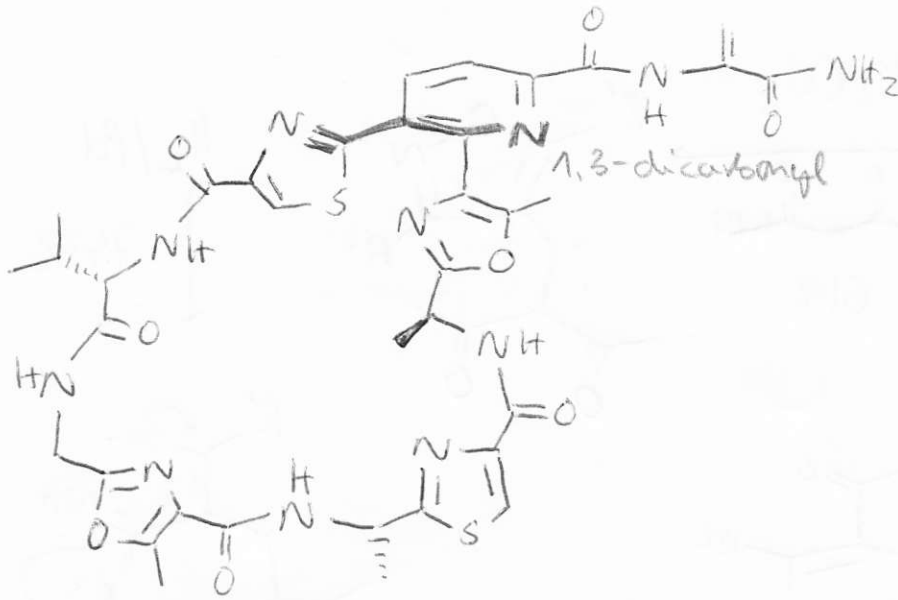
Bohlmann-Rhatsz Synthese:



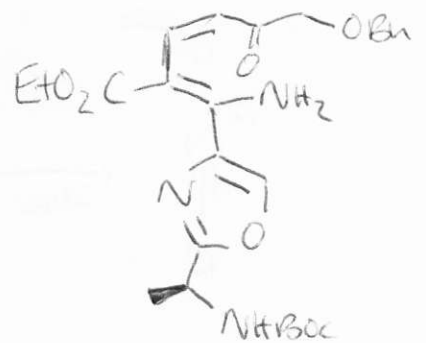
Mechanismus:



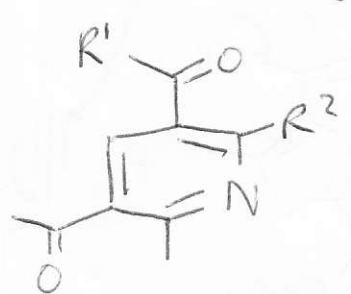
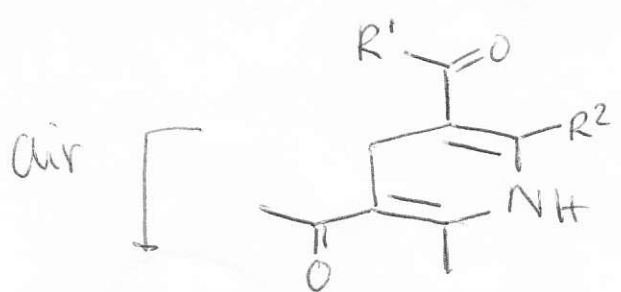
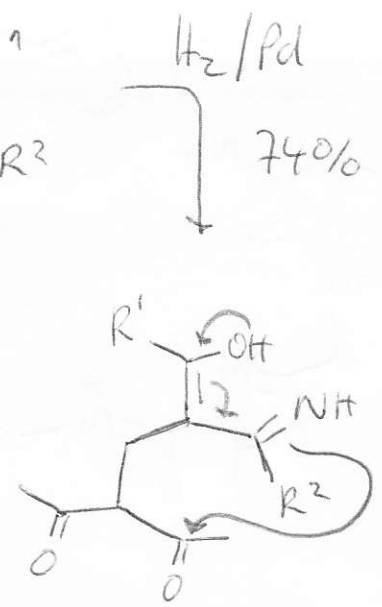
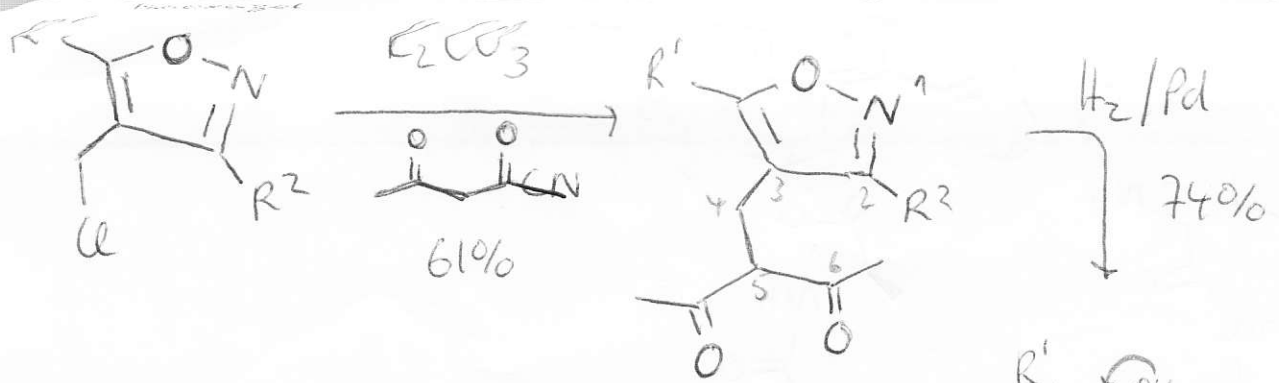
# Primothioin



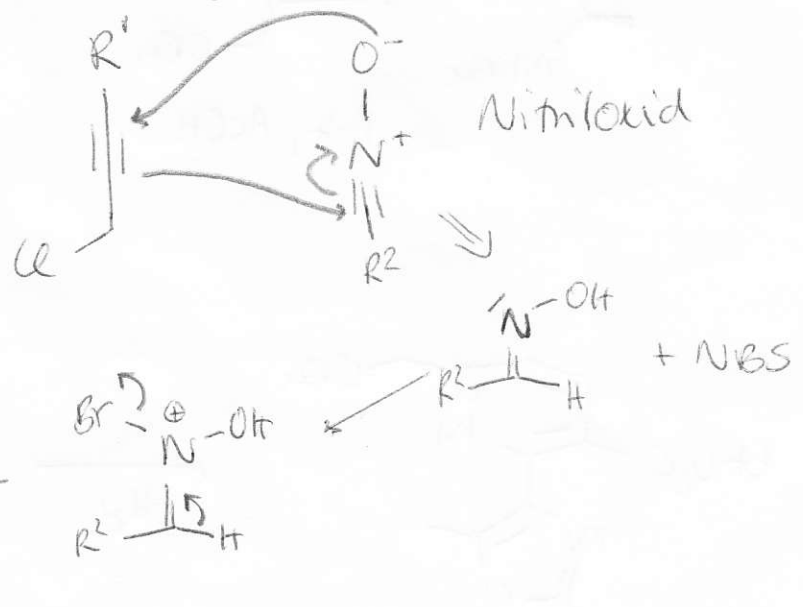
$-\text{H}_2\text{O}$



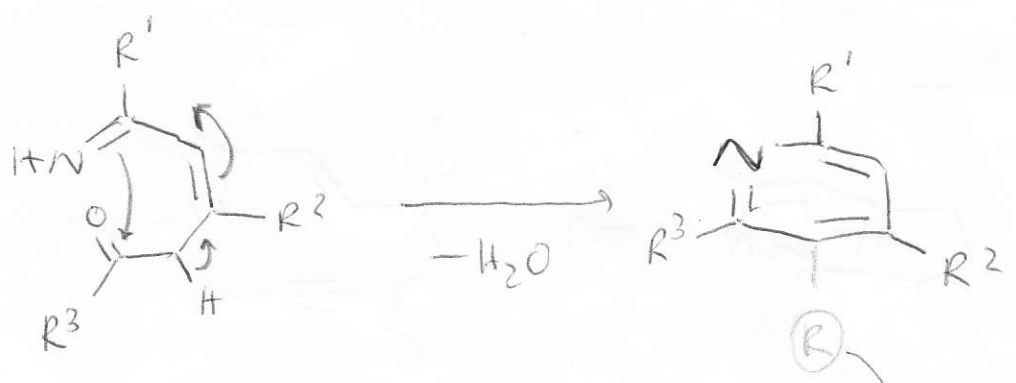
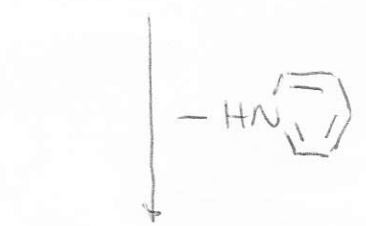
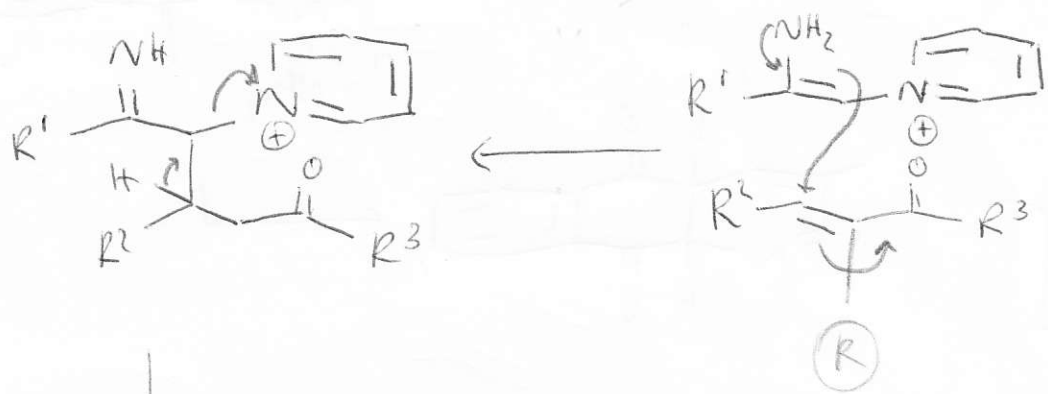
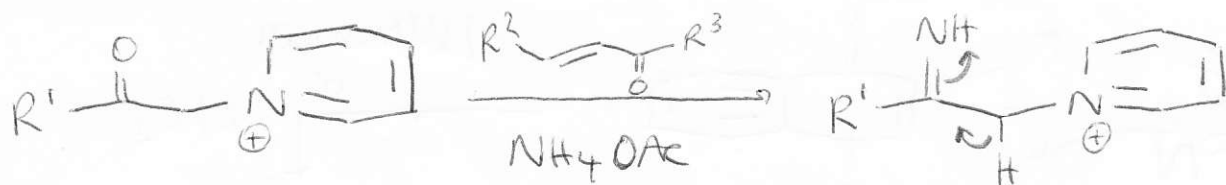
1,3-dipolar cycloaddition of isoxazoles



Isoxazole: 1,3-dipolar CA

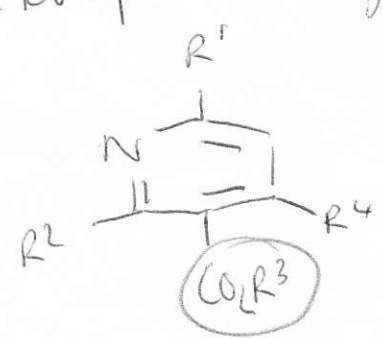


# Kröhnke-Synthese:

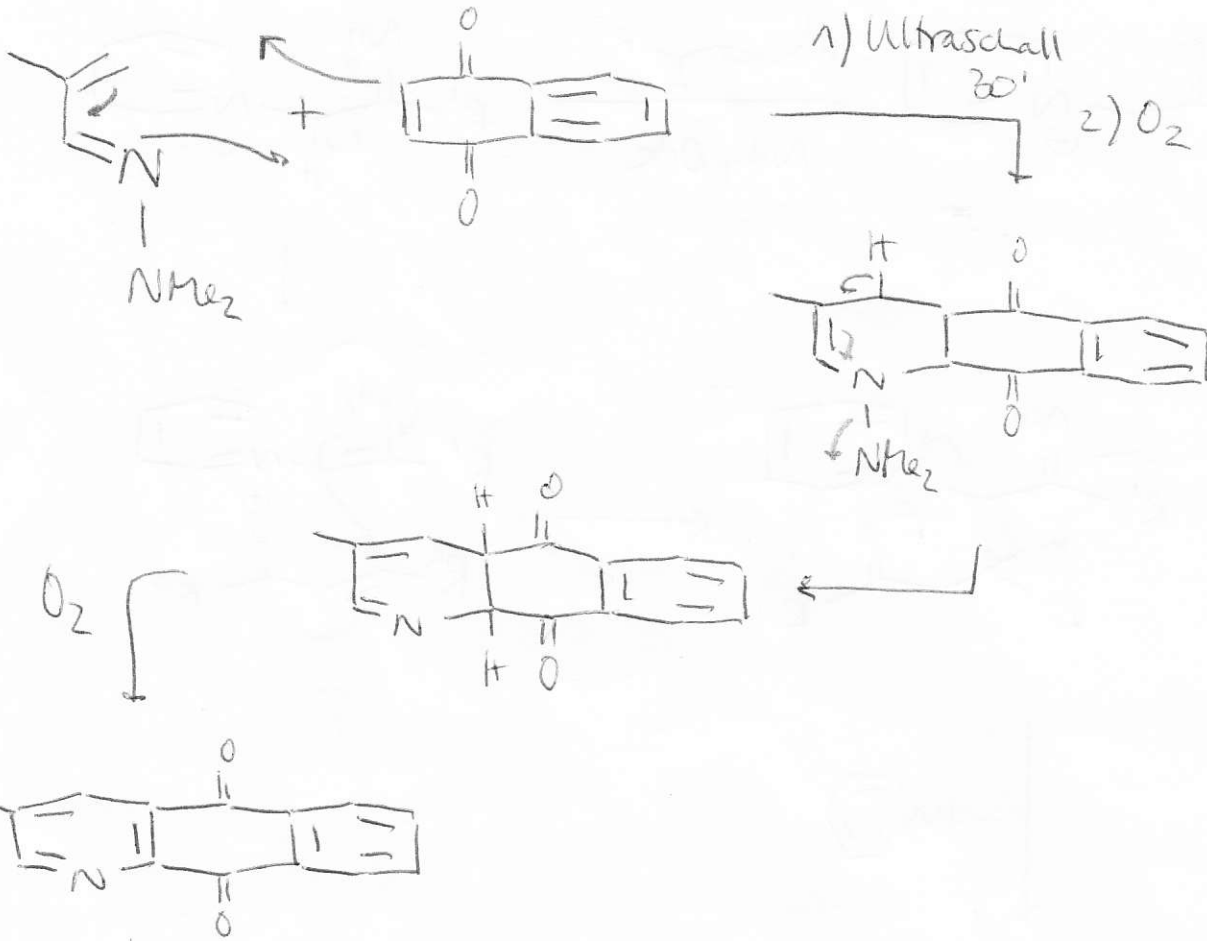


nur gut mit Alkyl, Aryl  
↓  
keine EWG!

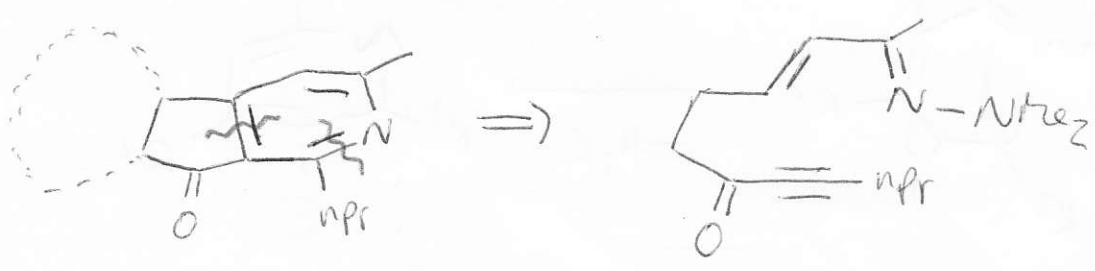
→ komplementär zur Bohlmann-Rathz



Cycloadditionsreaktionen: Dale Beger, Chem. Rev. 1986, 86, 781-793

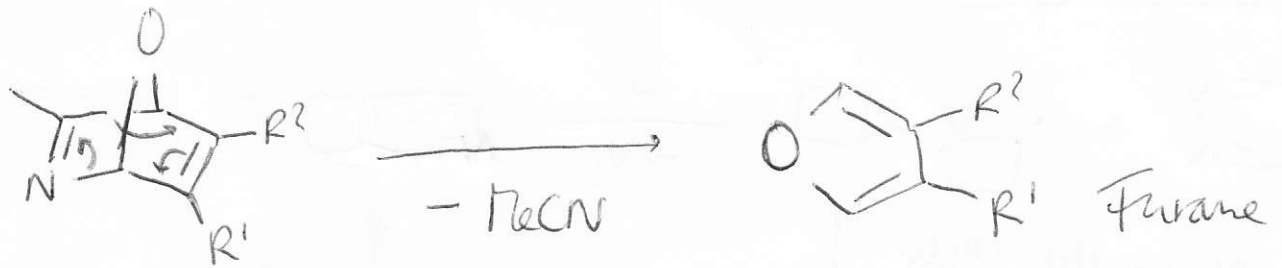
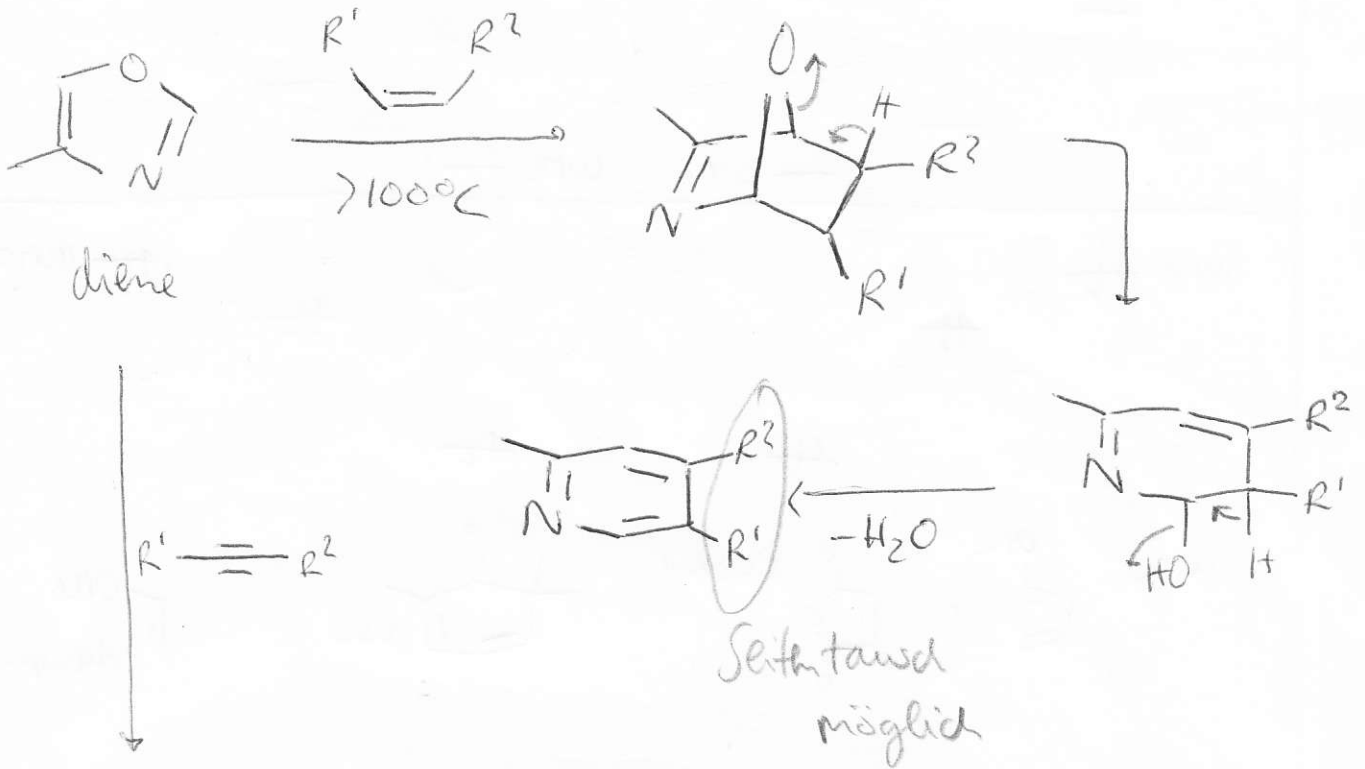


Retrolyse:

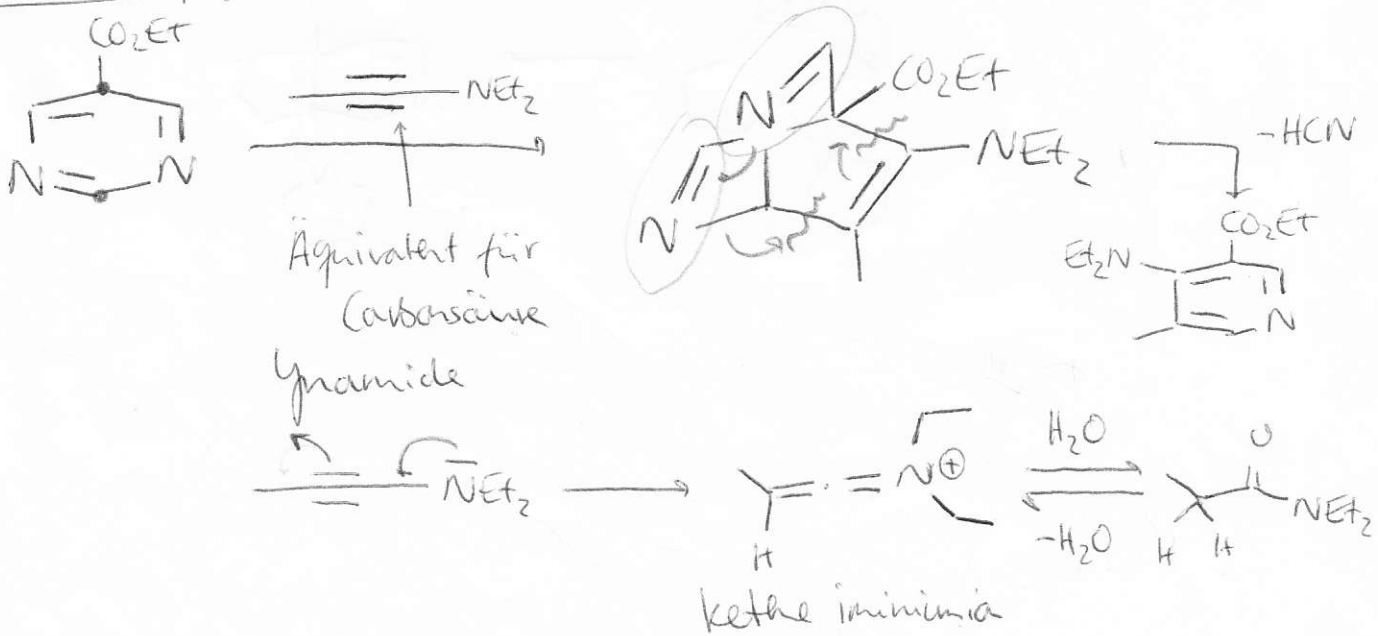


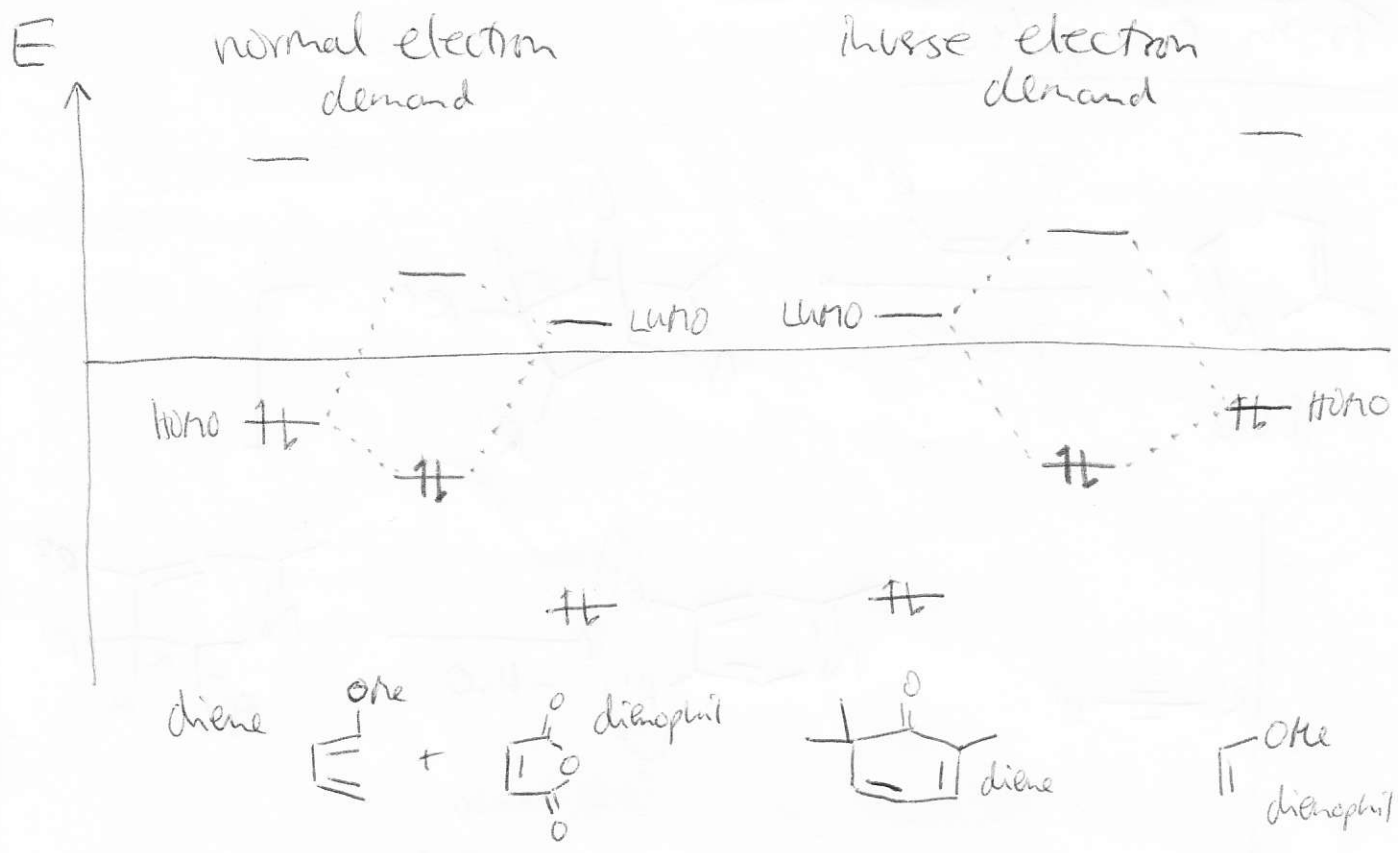


# From oxazoles:

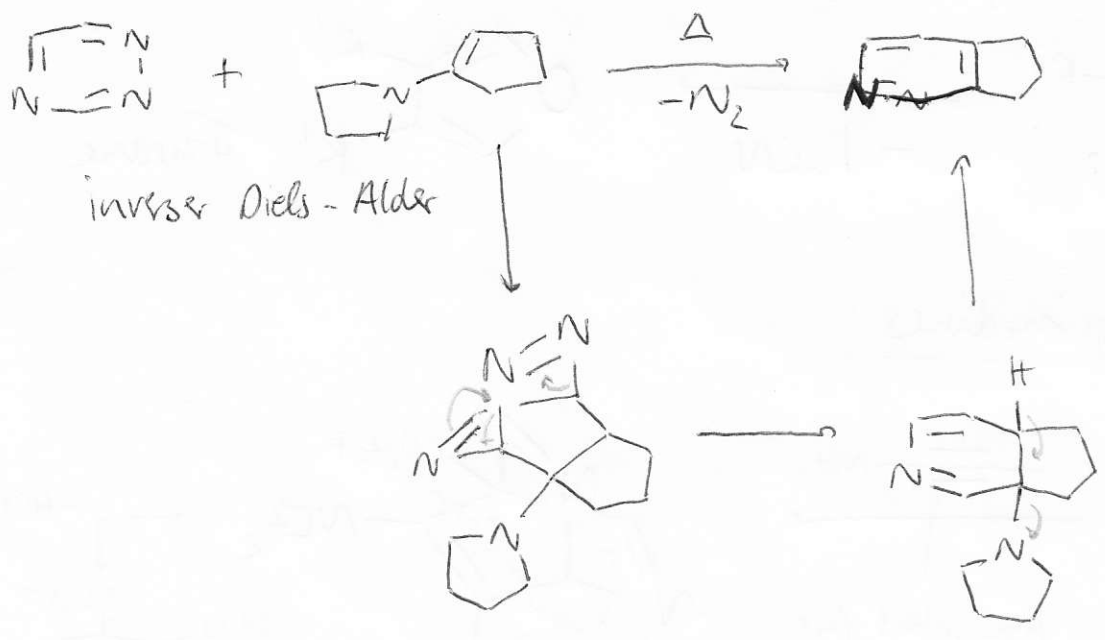


# From pyrimidines:



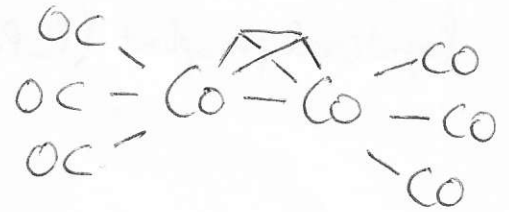
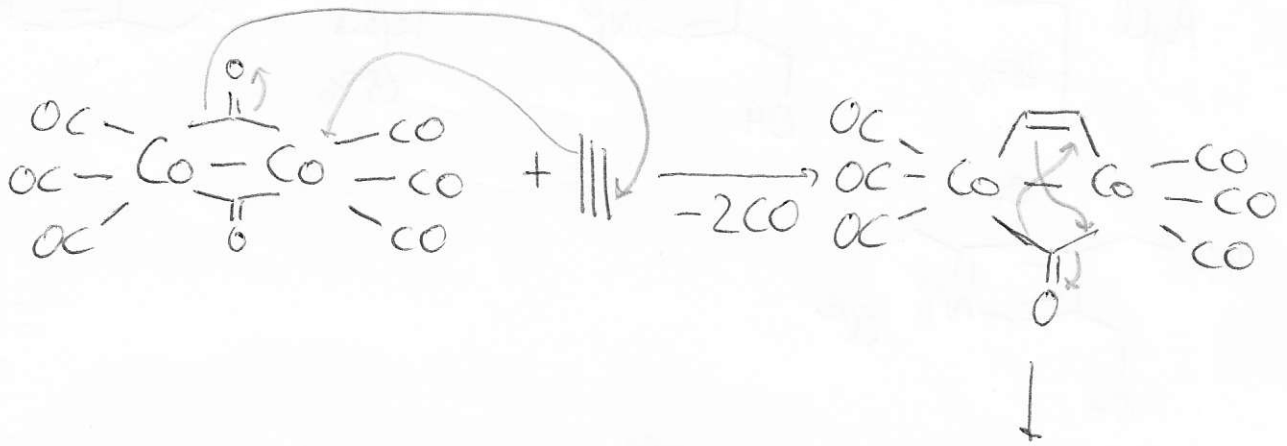
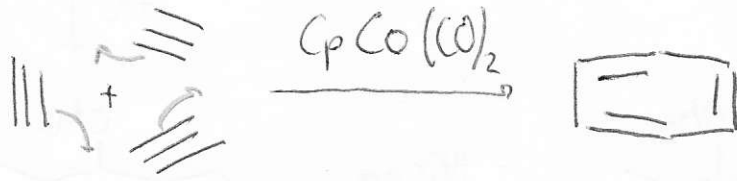


1,2,4-Triazolen

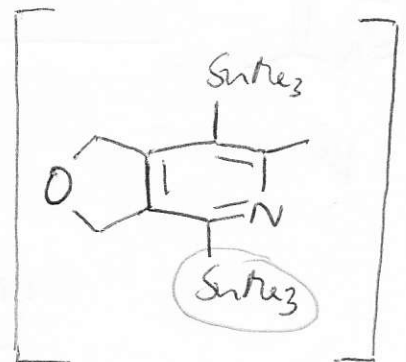
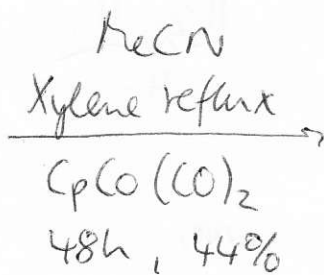
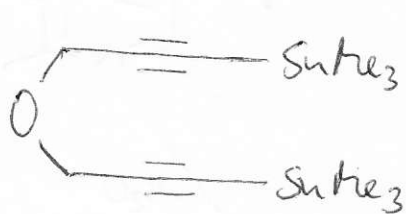
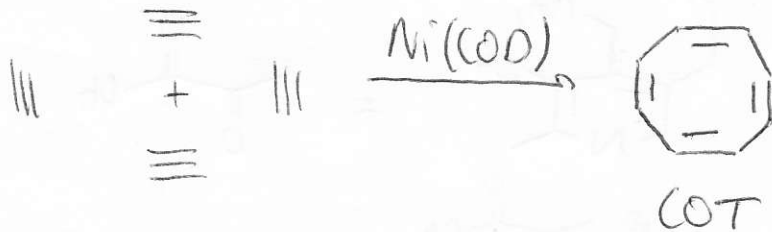


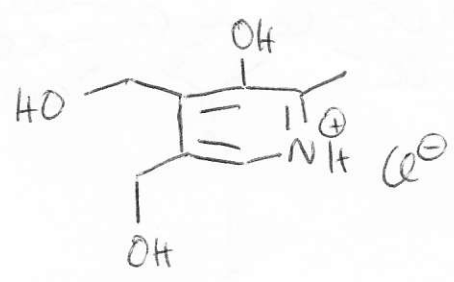
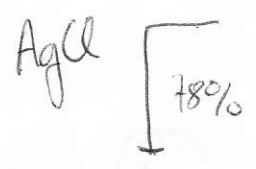
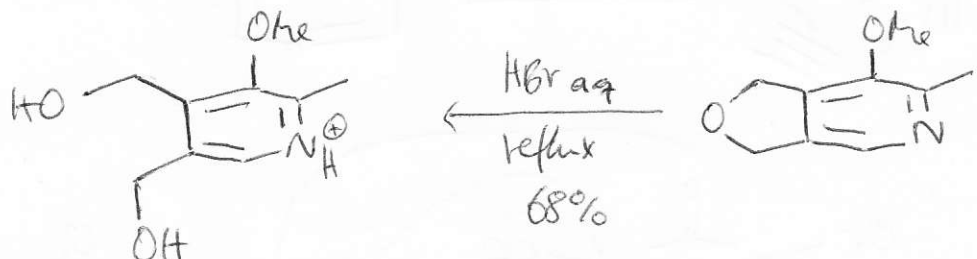
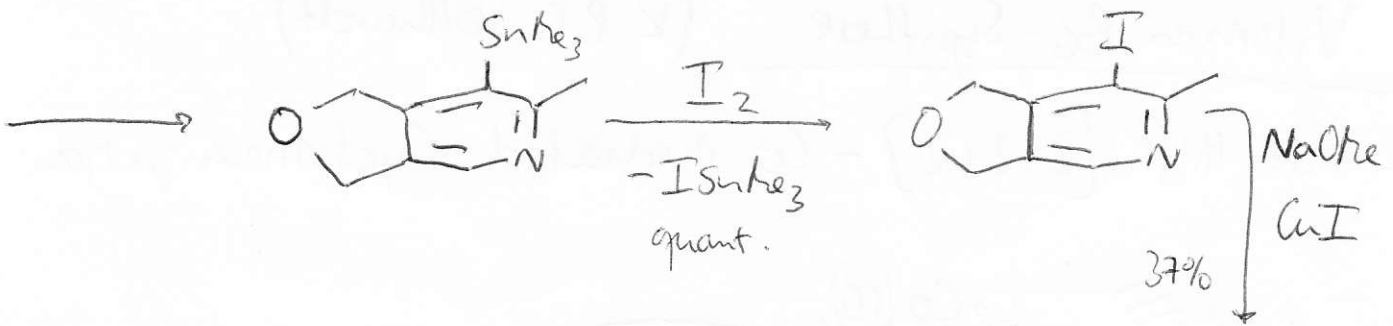
# Vitamin B6-Synthese (K.P.C. Vollhardt)

mit Hilfe [2+2+2] - Co mediated Cyclotrimerization

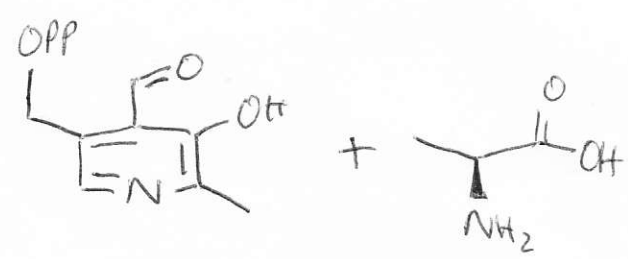


Reppe:

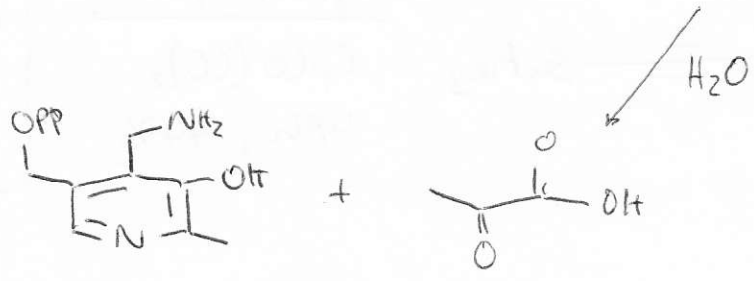
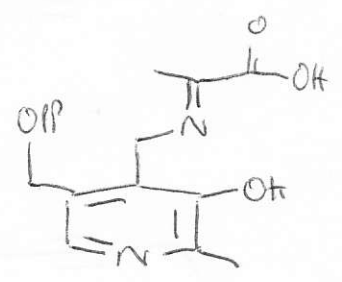
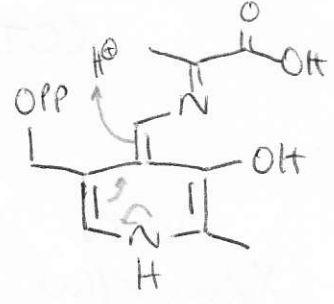
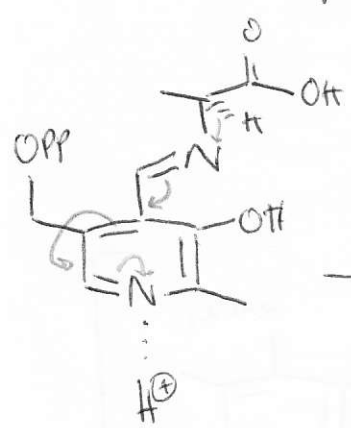
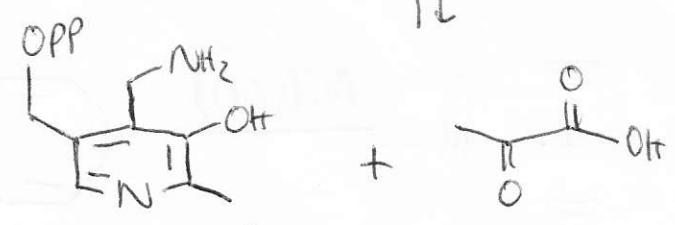




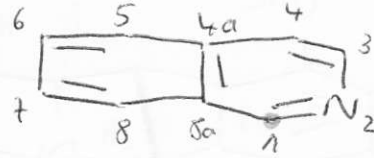
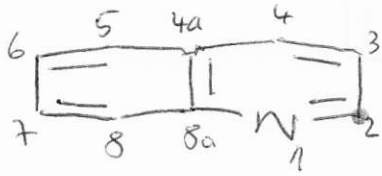
Pyridoxal phosphat (PLP):



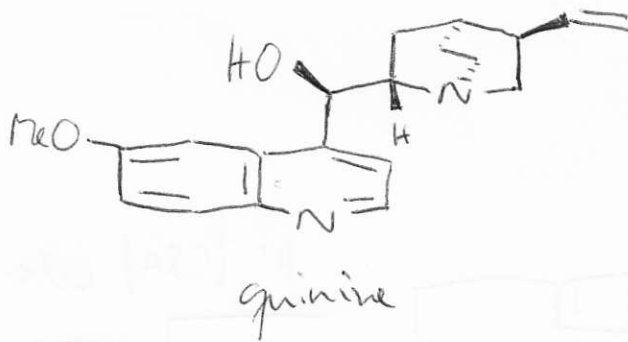
Pyridoxamin



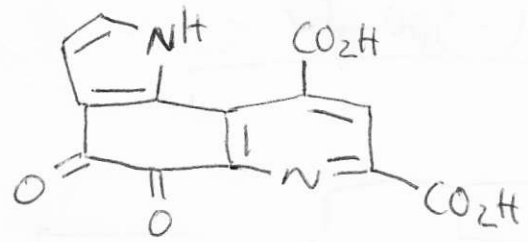
# Quinolines / Isoquinolines



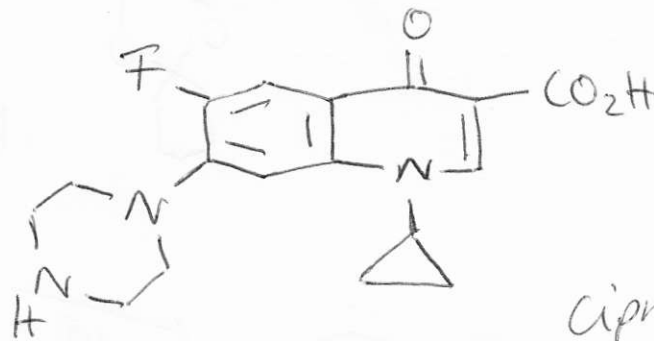
- $pK_a = 4,9 - 5,4$
- elektrophile aromatische Substitution  $\rightarrow$  schlecht (seide elektronenarm)
- nucl. Substitution  $\rightarrow$  Imid-Kohlstoff (Analog Pyridin)
- De-novo Synthese bei Quinolone ausgehend von Anilin, bei Isoquinoline von Benzylamin



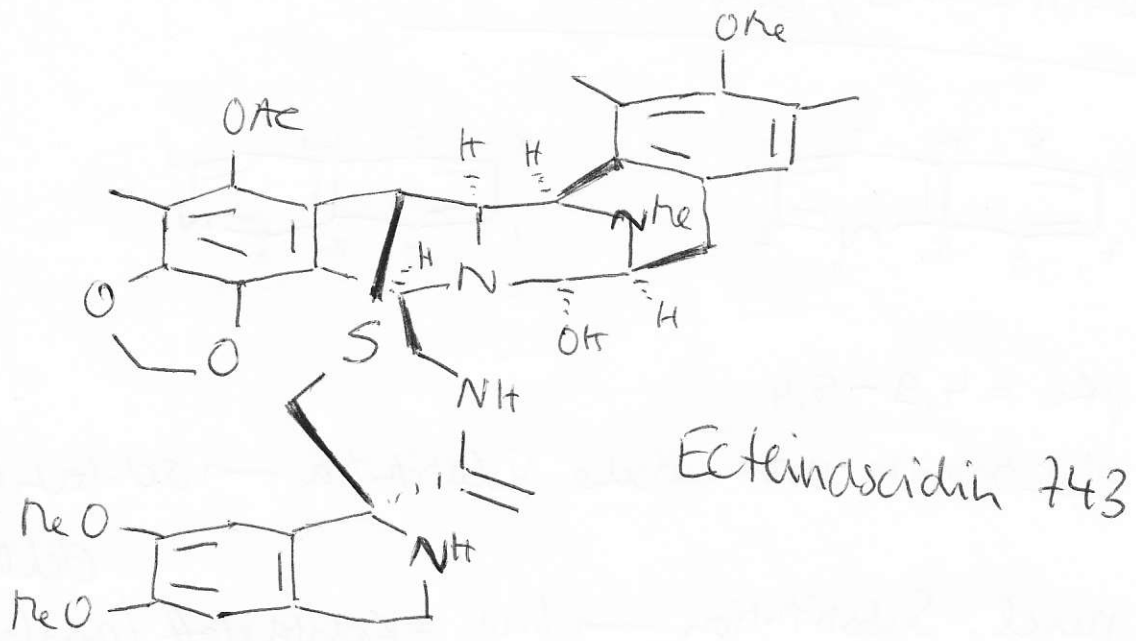
quinine



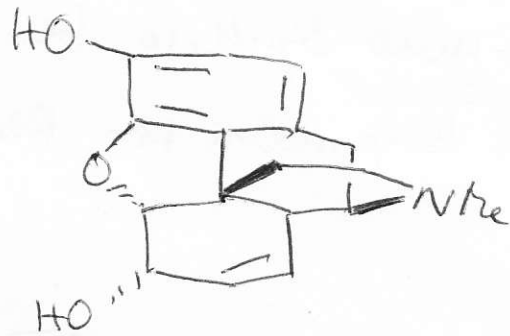
methoxatin



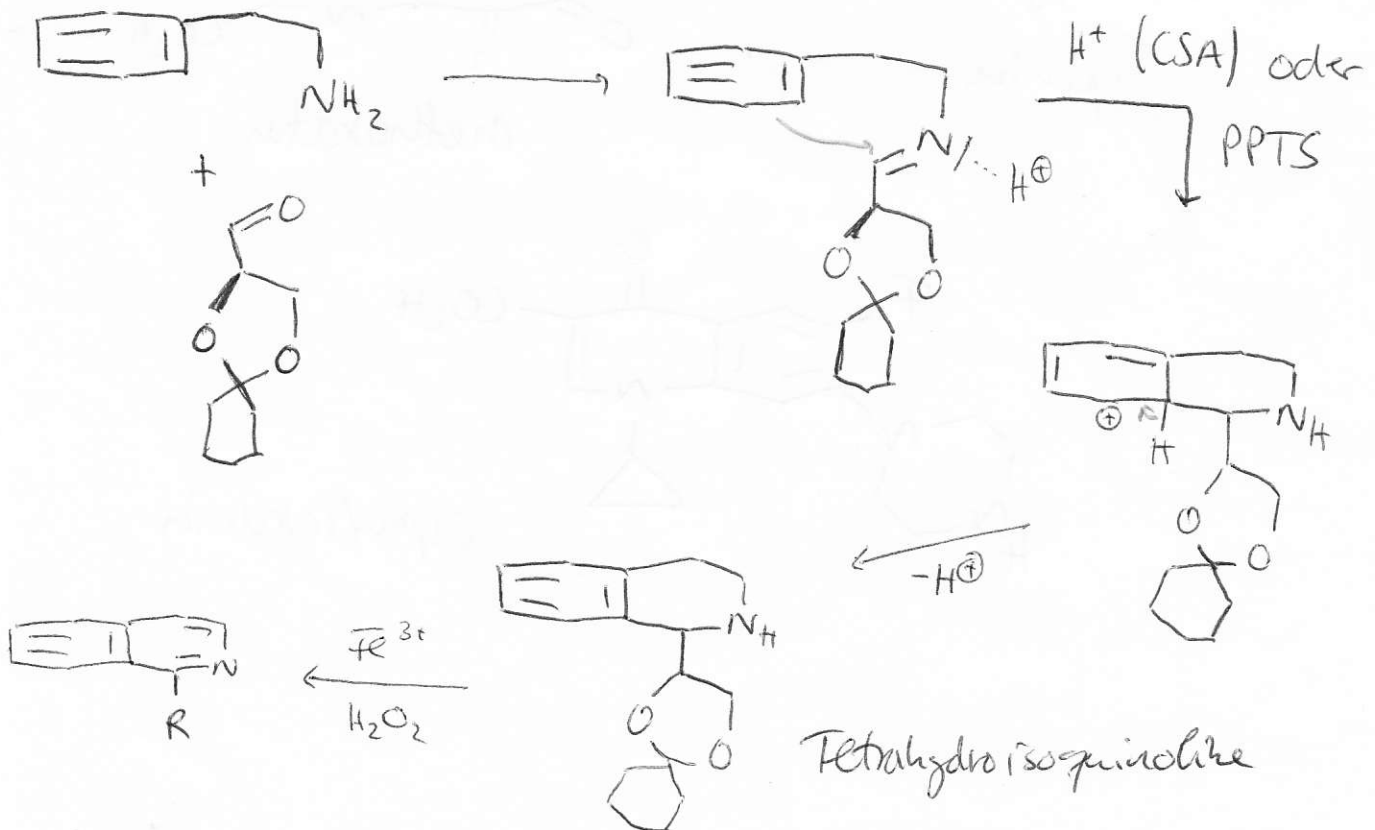
ciprofloxacin



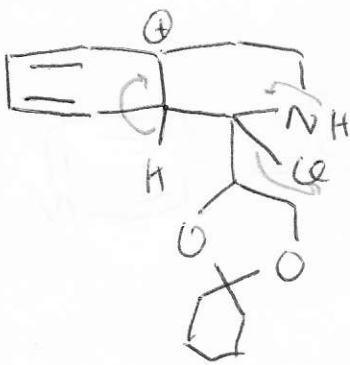
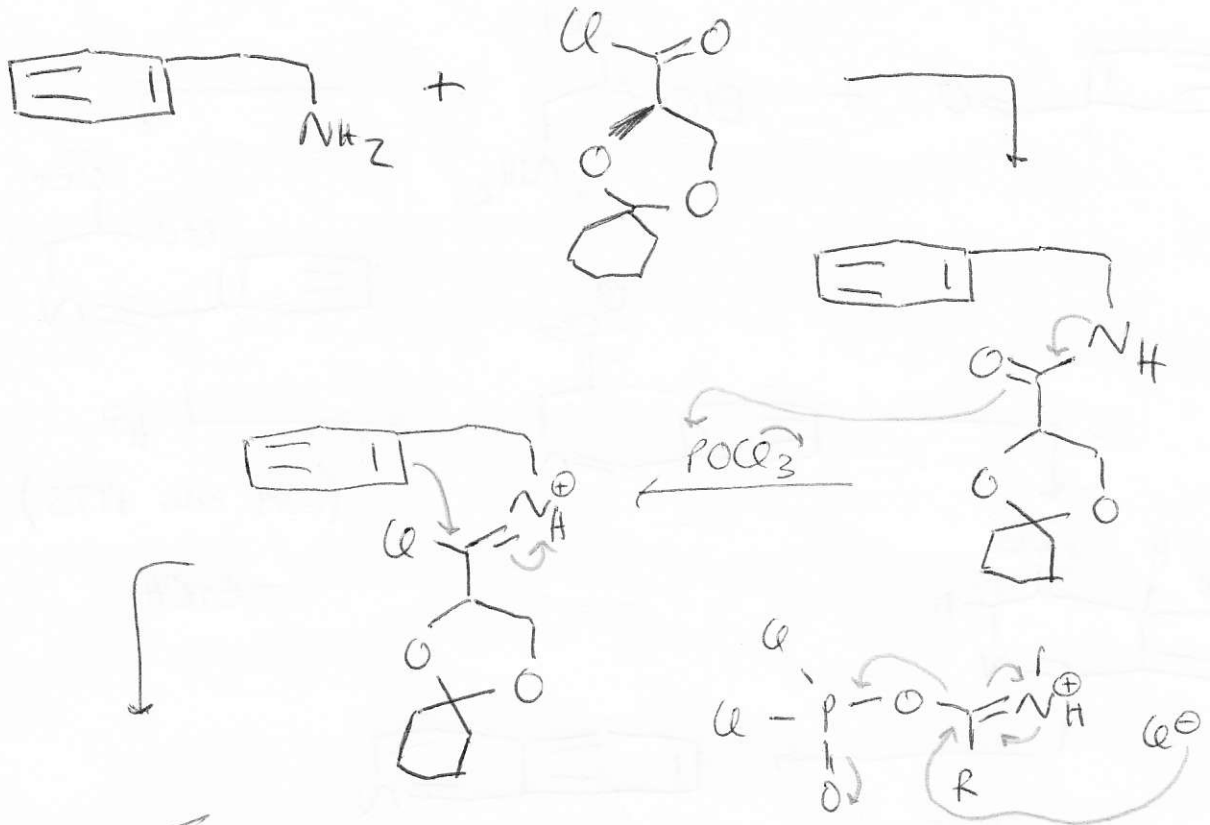
Morphine



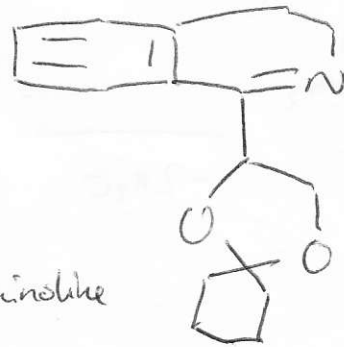
Pictet-Spengler



# Bischler-Napieralski



Dihydroisoquinoline

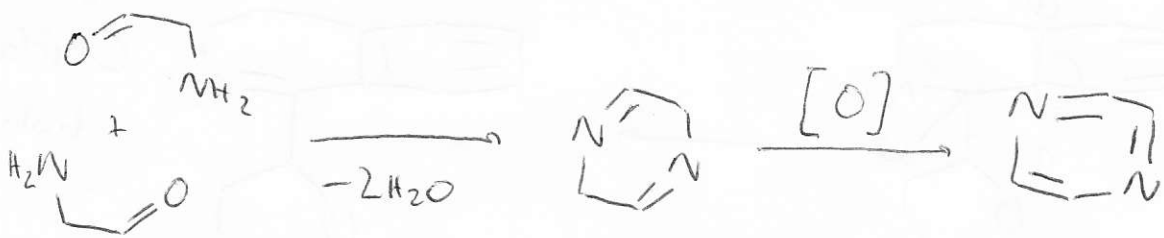
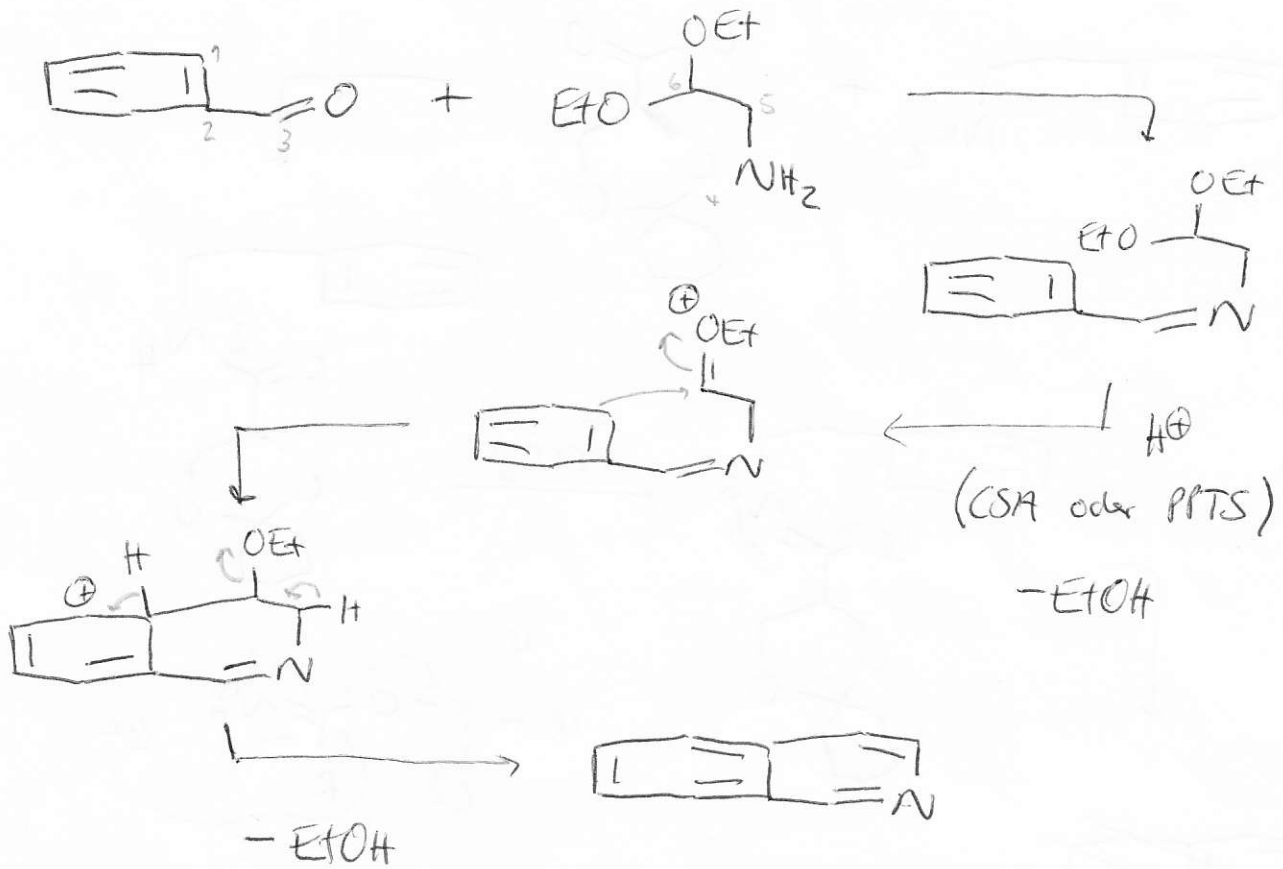


eine Oxidationsst. höher!

Pd/C oder DDQ



# Pomeranz-Fritsch

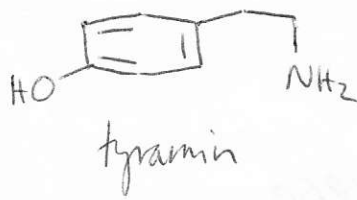




# Biosynthese der Isochinolinalkaloide

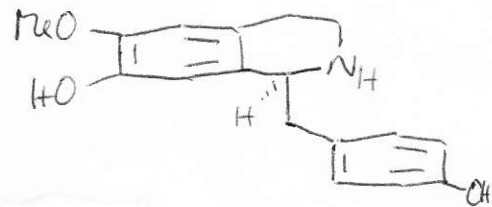
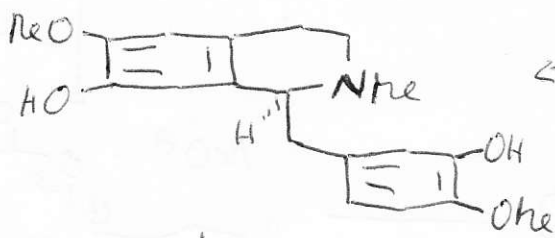
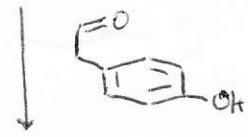
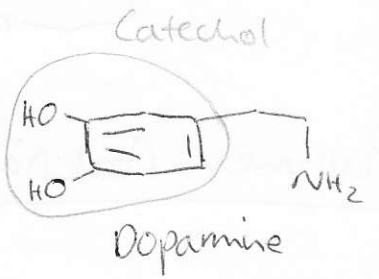
Tyrosin  
oder  
Manglalamin

PLP



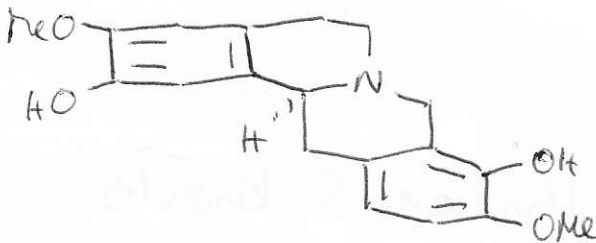
Hydroxylase

Ferrihydro-  
pterin  
O<sub>2</sub>



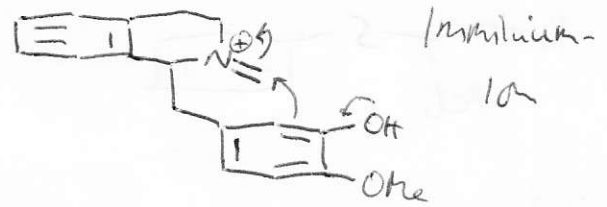
Coclaurine

[OX]

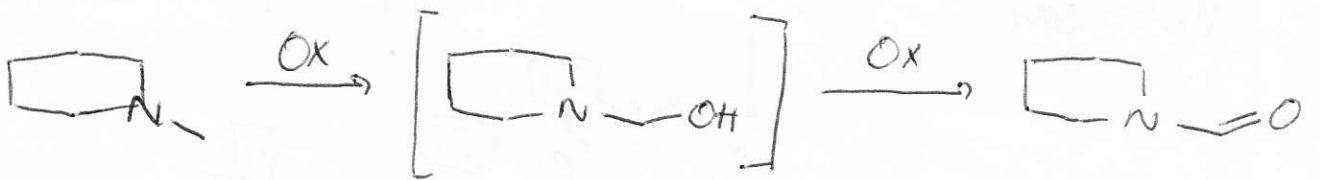


Scotinine

na:

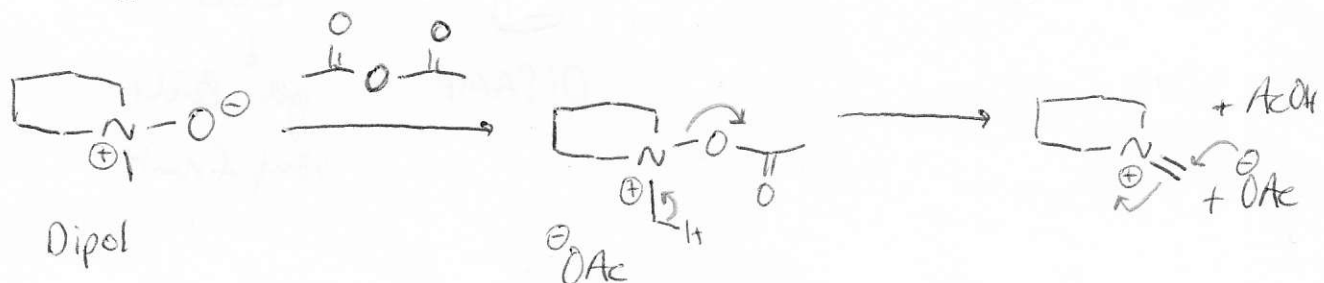


## 1) Polonovski Reaktion



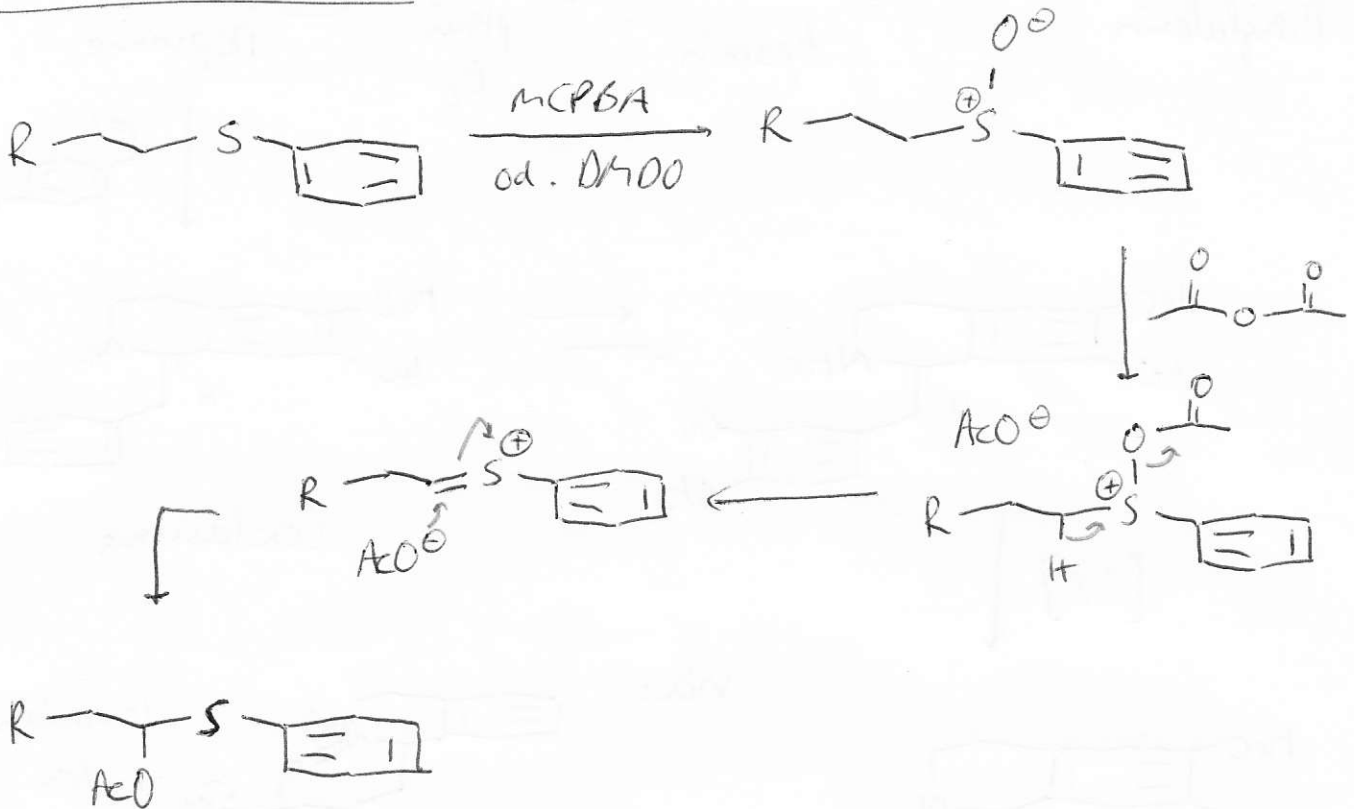
H<sub>2</sub>O<sub>2</sub> od.  
Oxone od.  
OMDO

instabil



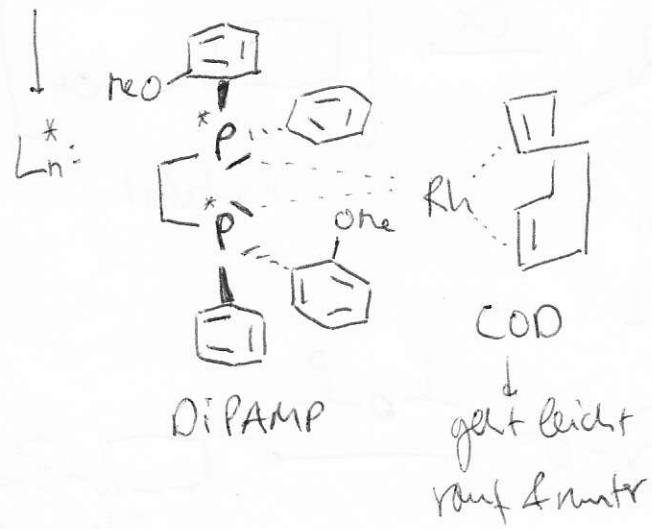
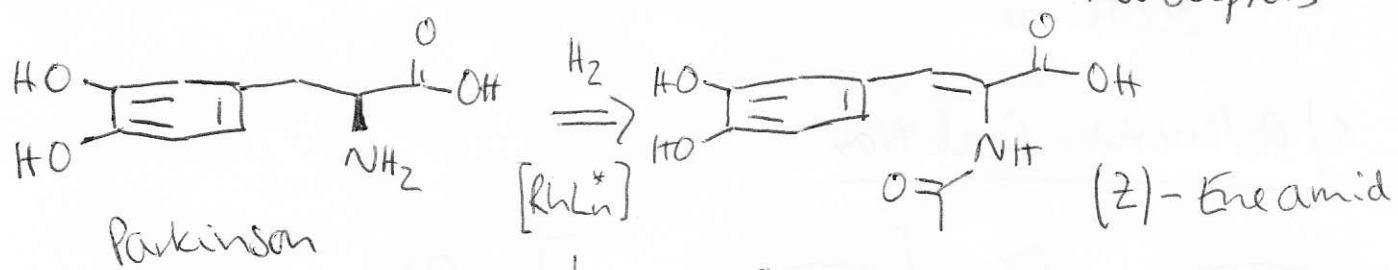


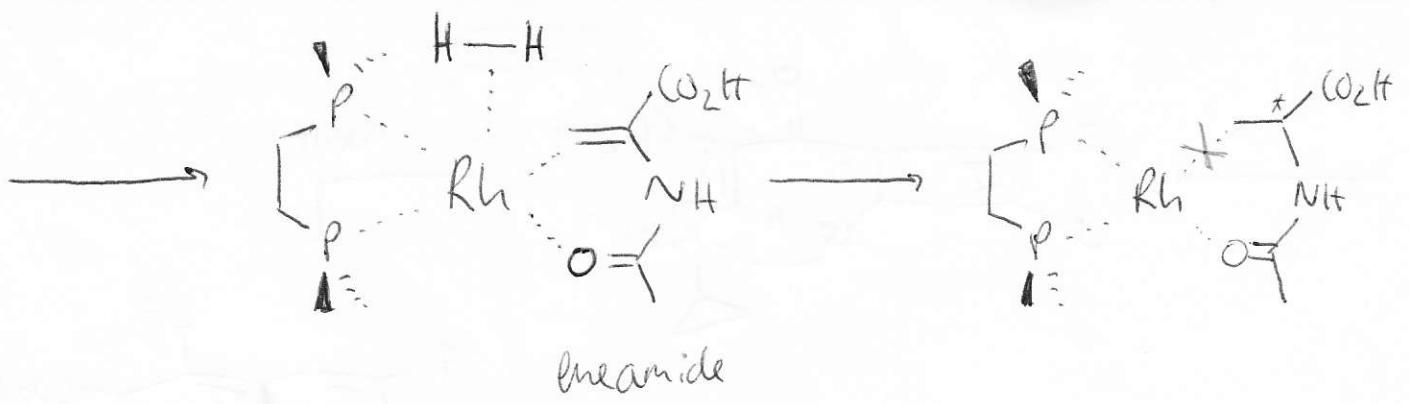
Prüfung - Reaktion:



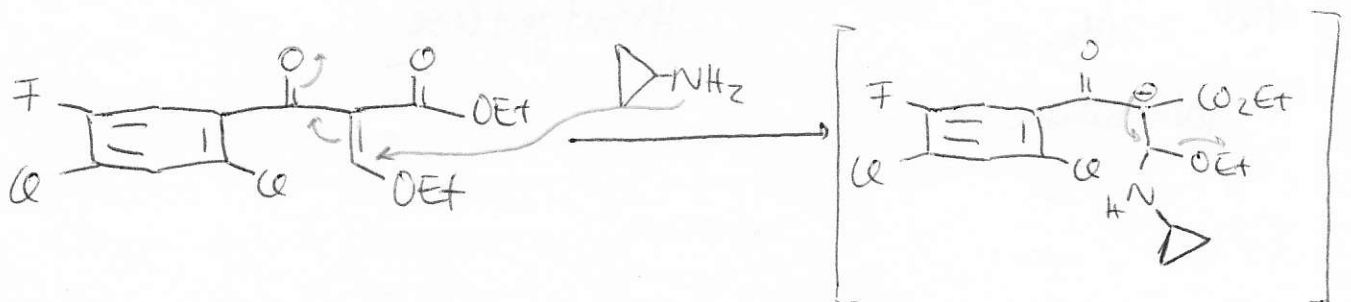
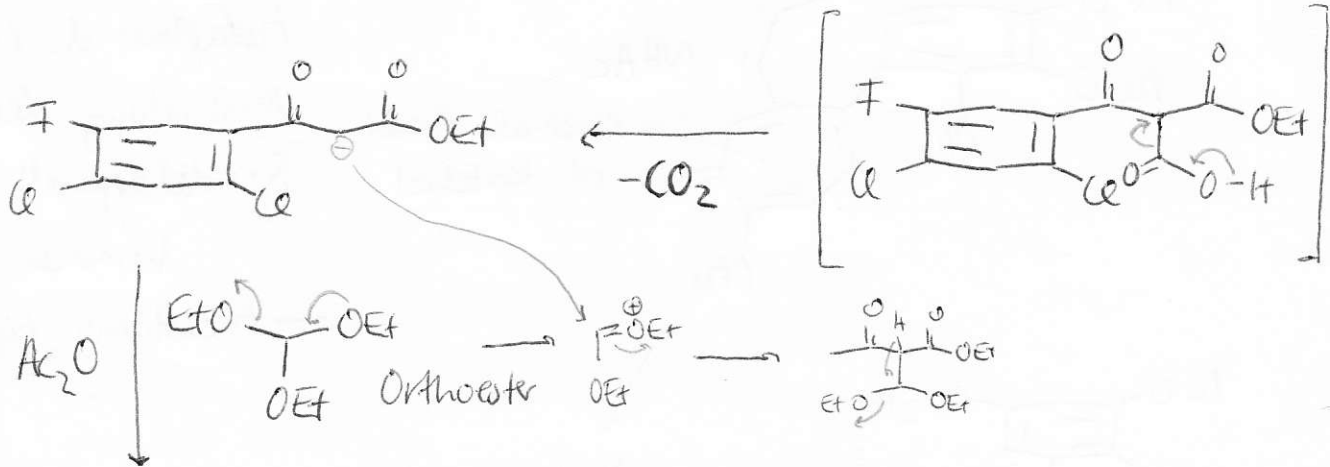
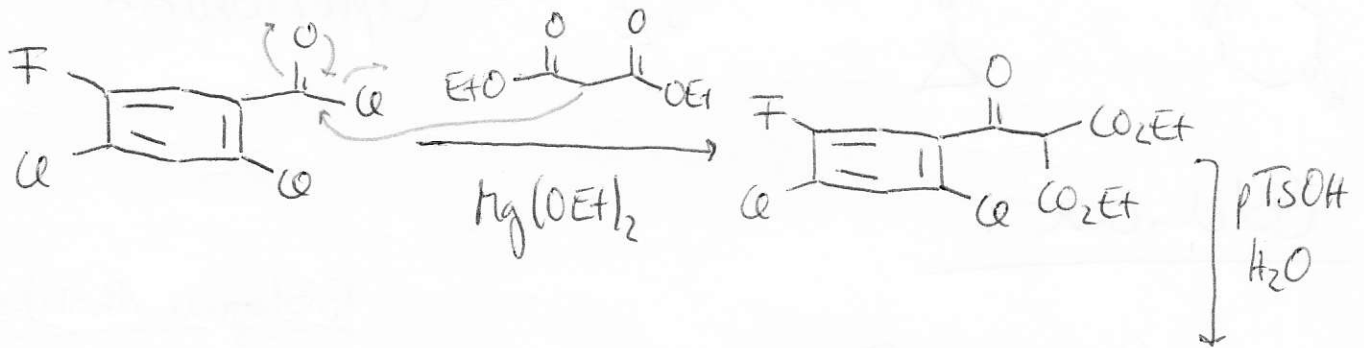
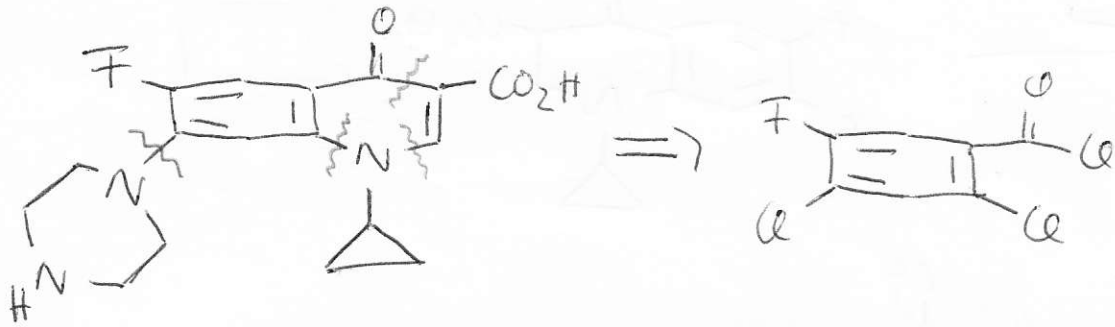
2) L-DOPA - Monsanto (2001) William S. Knowles

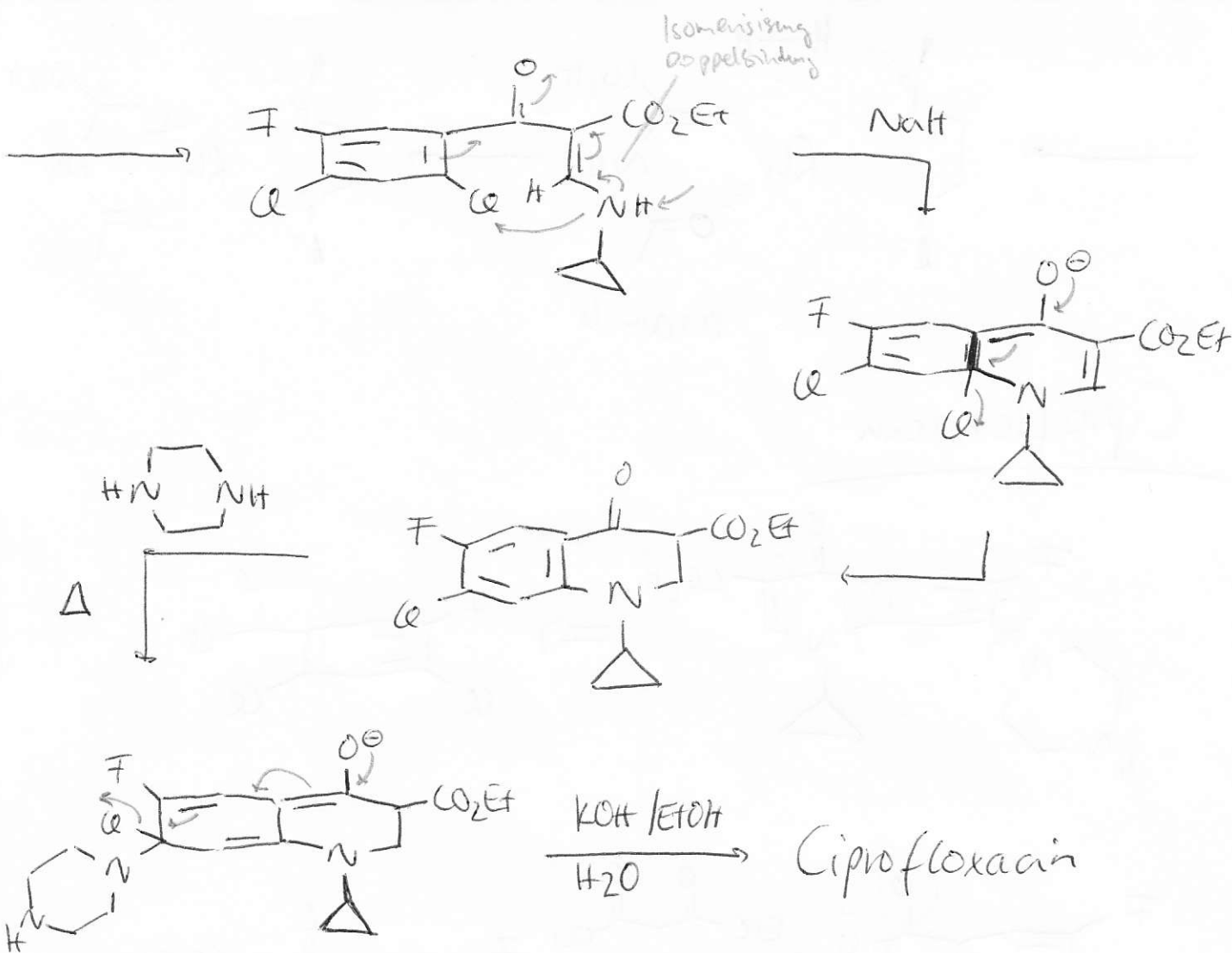
Nobelpreis





## Ciprofloxacin:



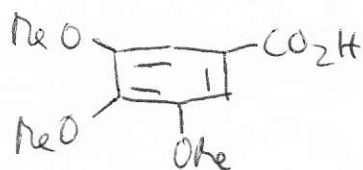
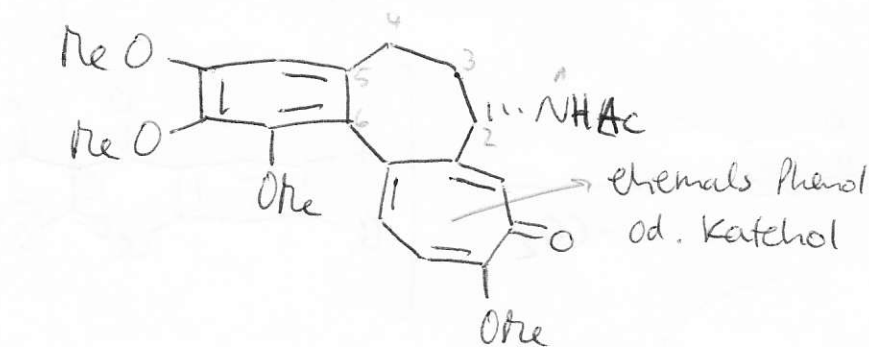


## Colchicine:

### Biologische Aktivität:

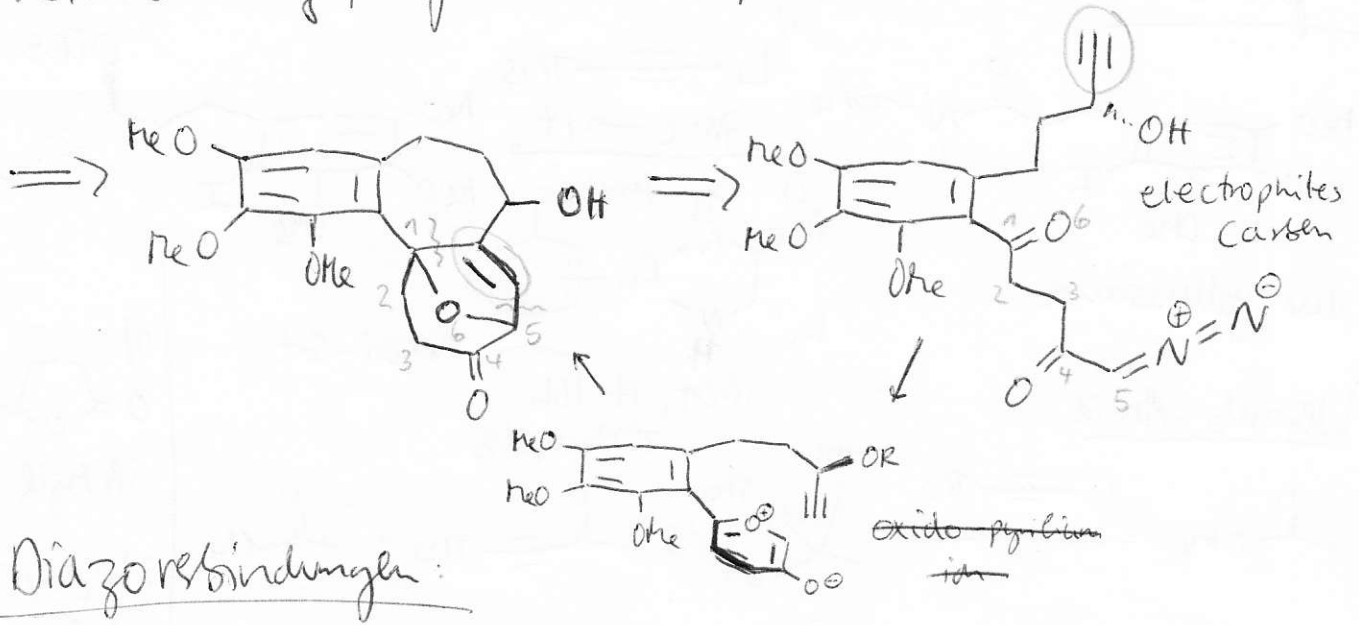
Metaphase d. Mitose  
 Ausbildung des  
 Spindelapparats zu  
 hemmen

→ Microtubuli-Polymerisation

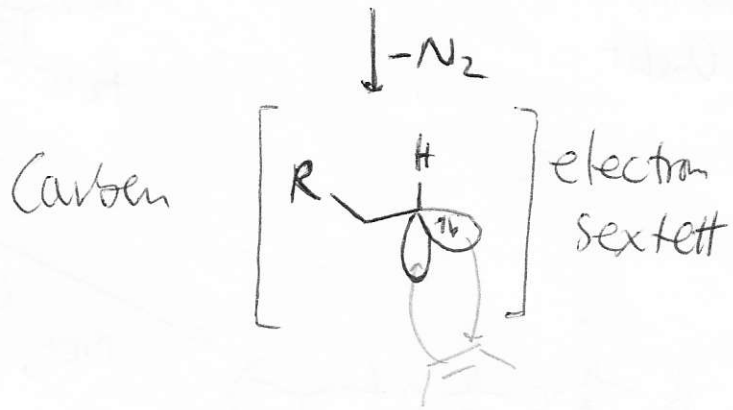
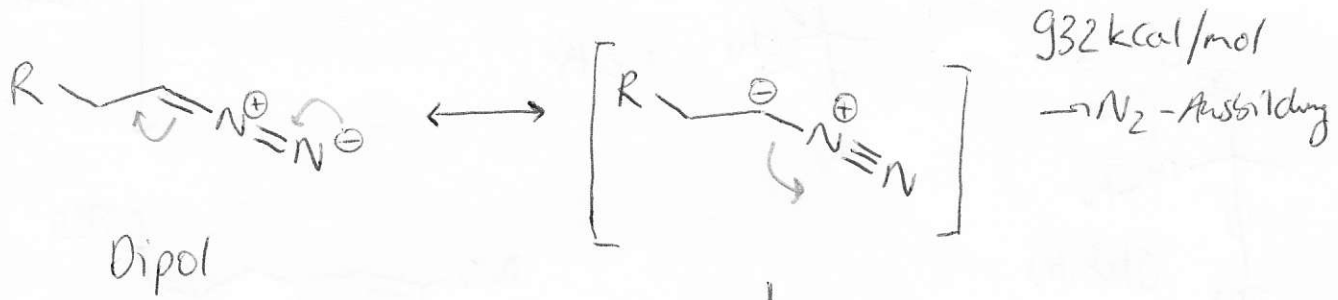


Galbussäure

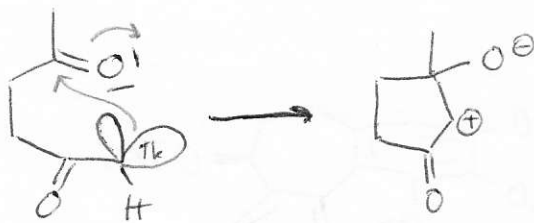
Herbstzeitlose



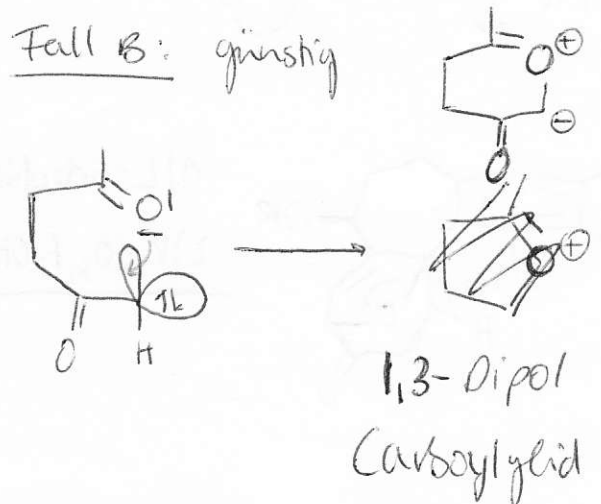
Diazoreaktionen:



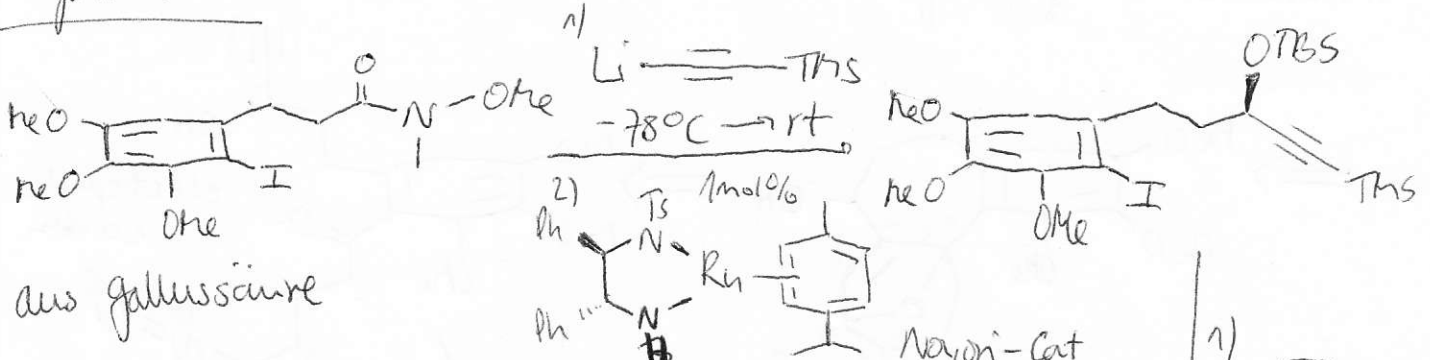
Fall A: ungünstig



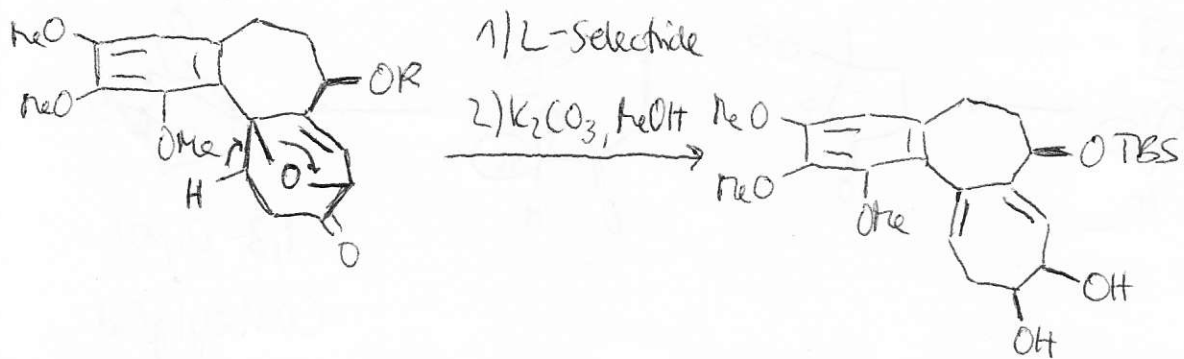
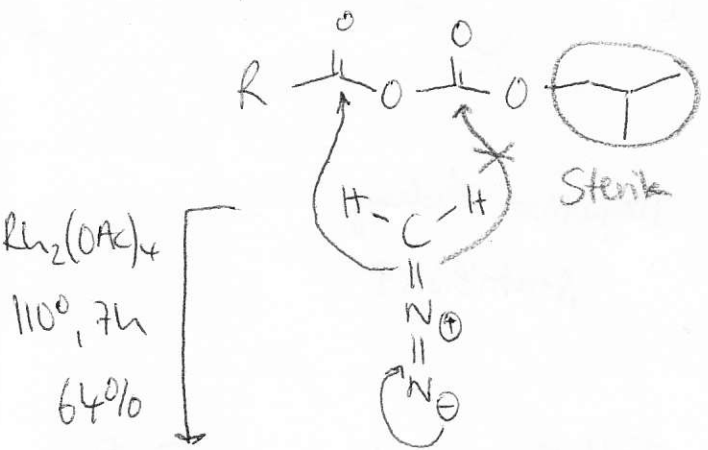
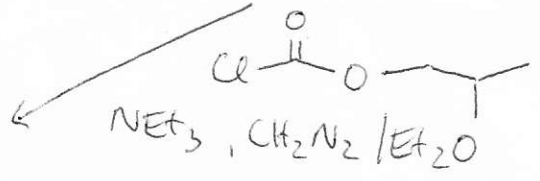
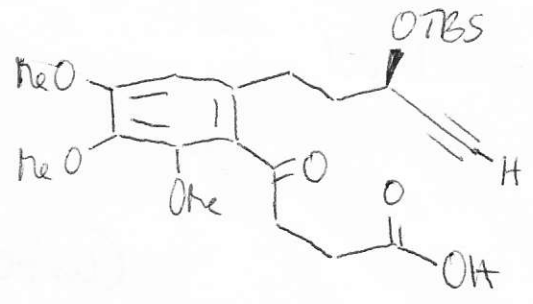
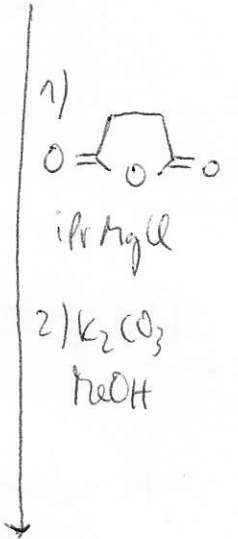
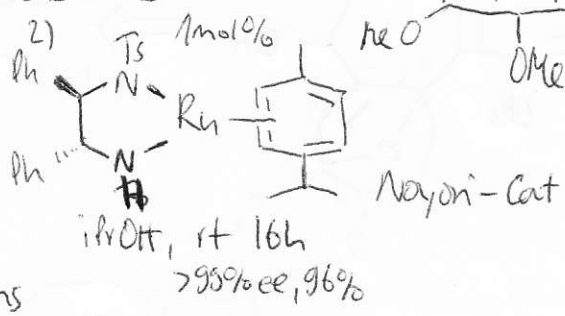
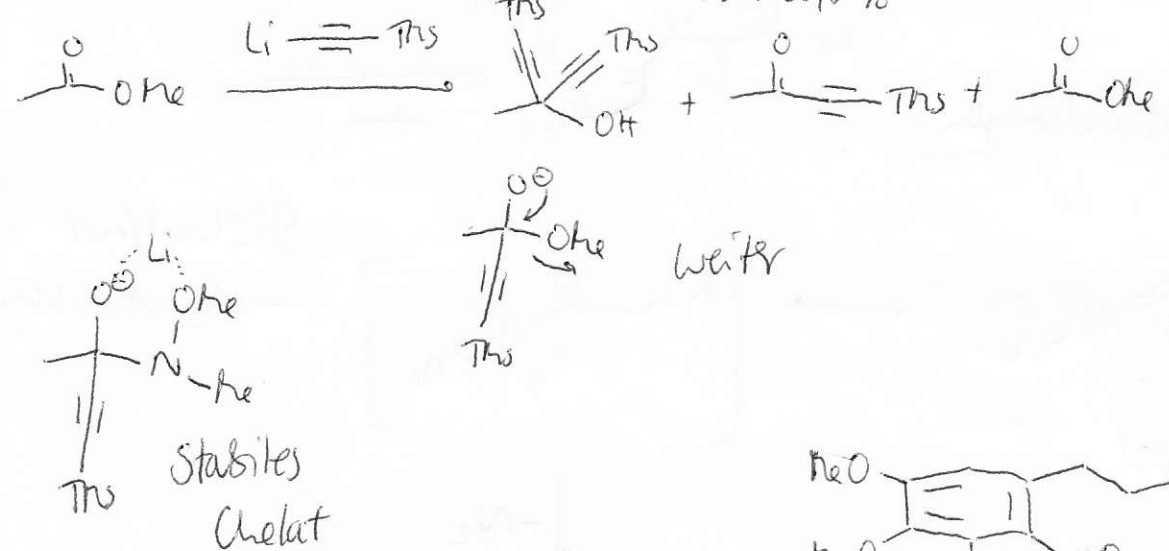
Fall B: günstig



Synthese:



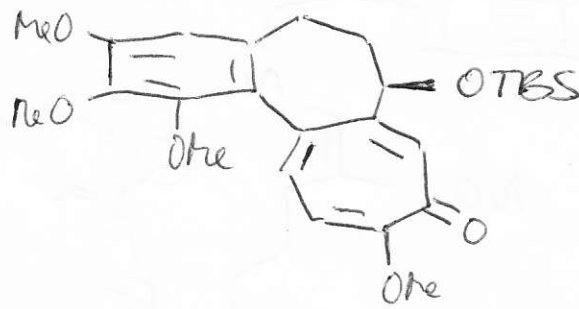
Weinreb-Amid:



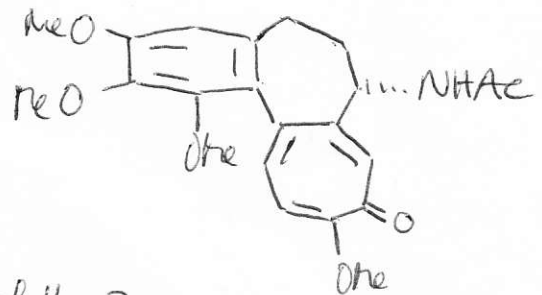
1) DMSO, TFAA

NET<sub>3</sub>

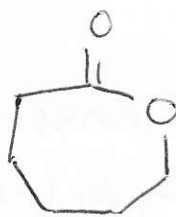
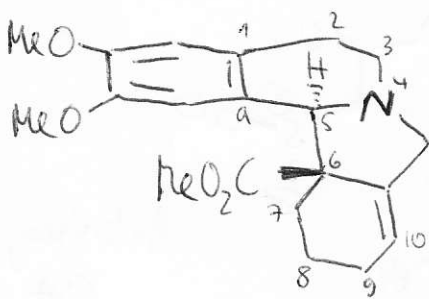
2) CH<sub>2</sub>N<sub>2</sub>



- 1) HF, Pyr
- 2) HCl, Pyr
- 3) DMSO, NaN<sub>3</sub>
- 4) Pd/H<sub>2</sub>
- 5) Ac<sub>2</sub>O, Pyr



Jamntine: A. Padwa, Org. Lett. 2002, 4, 715-717

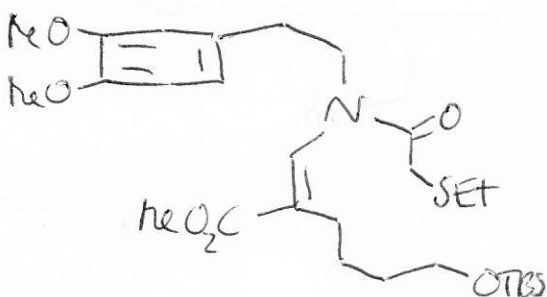
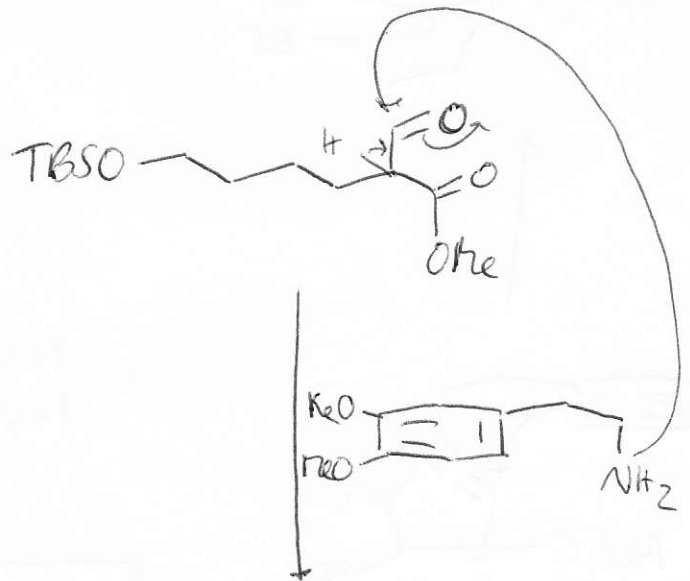
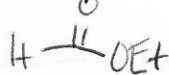


1) H<sup>+</sup>, MeOH

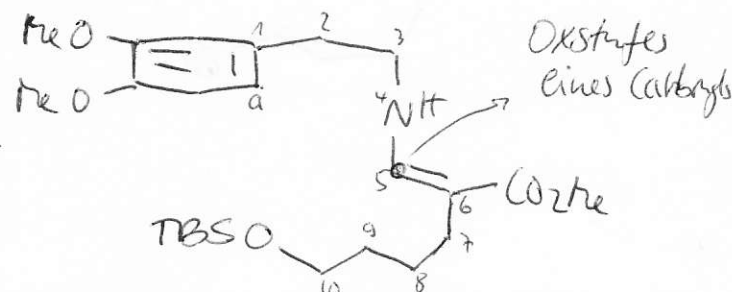
2) TBSCl, DMAP

CH<sub>2</sub>Cl<sub>2</sub>

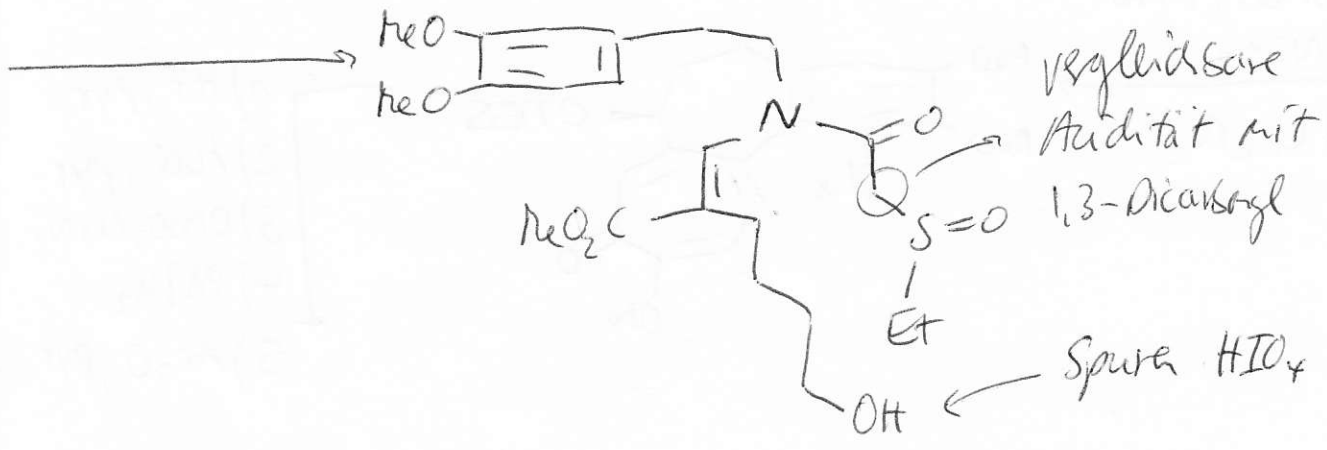
3) LDA



ETS  
base

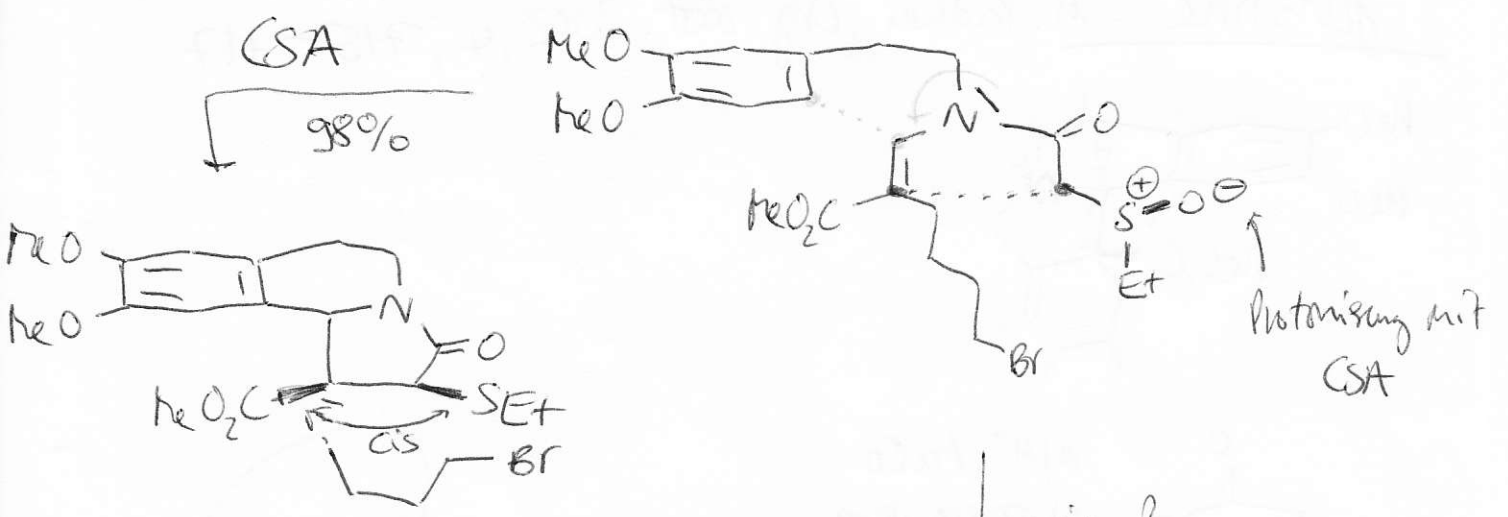


1) NaIO<sub>4</sub>

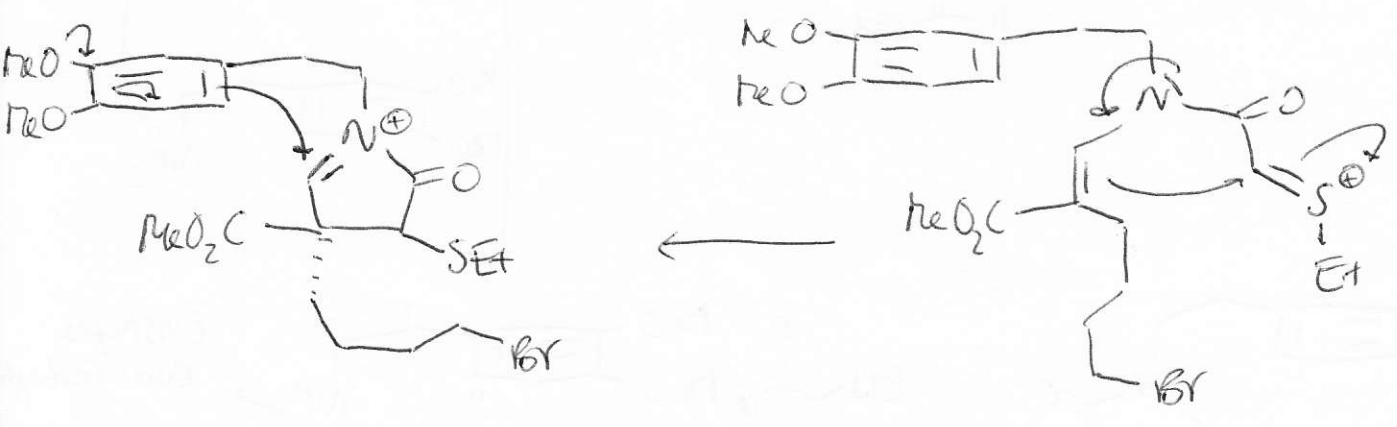


1) CBr<sub>4</sub>, PPh<sub>3</sub> (Zeq) → reduziert  
Sulfoxid  
2) NaIO<sub>4</sub>

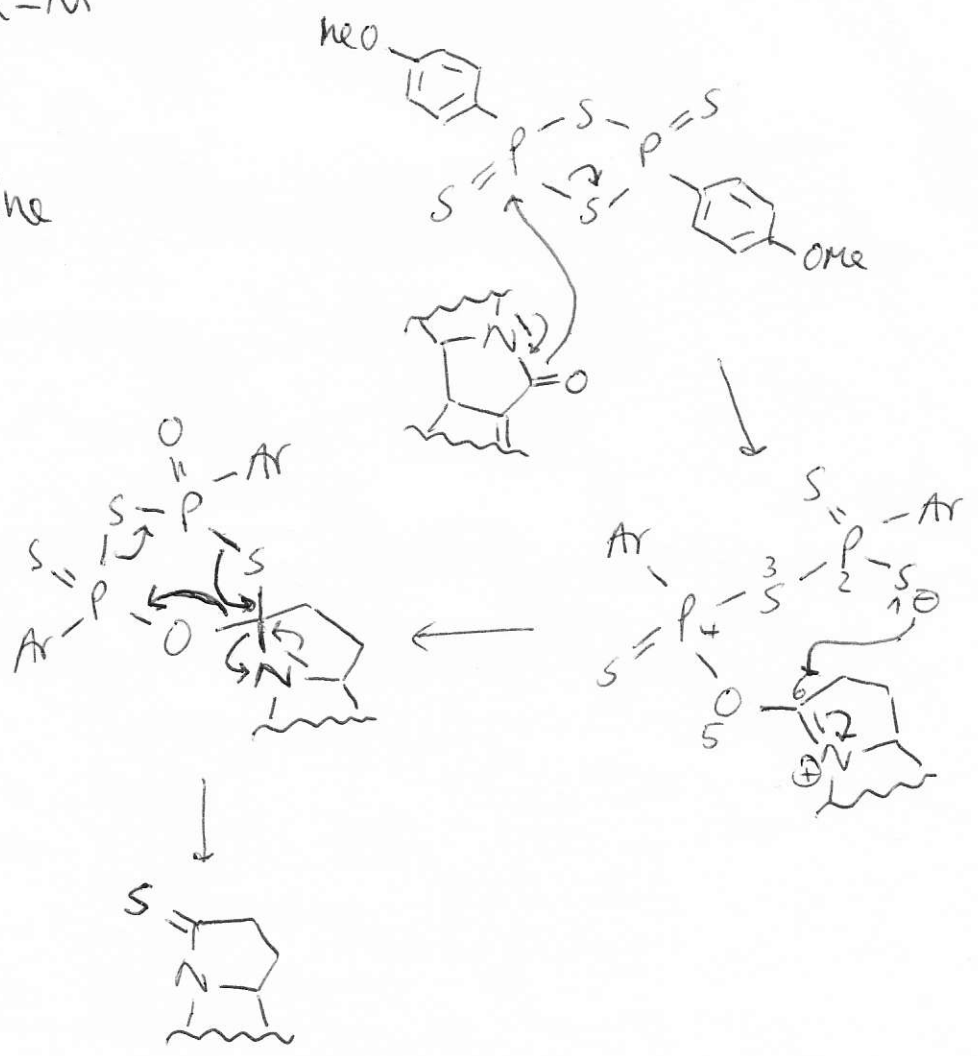
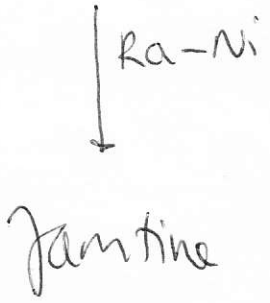
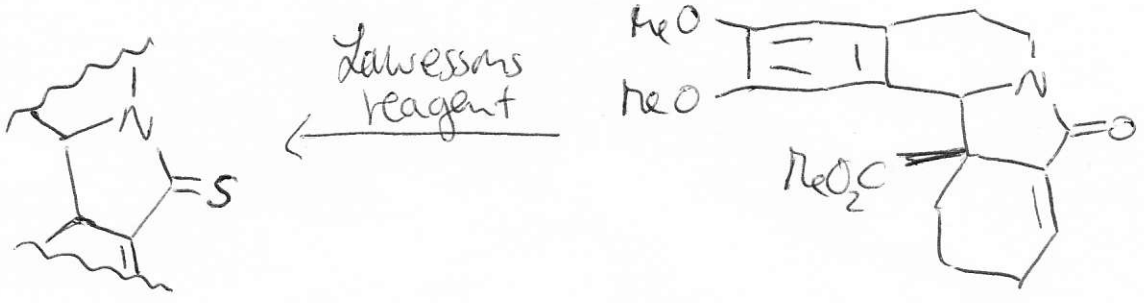
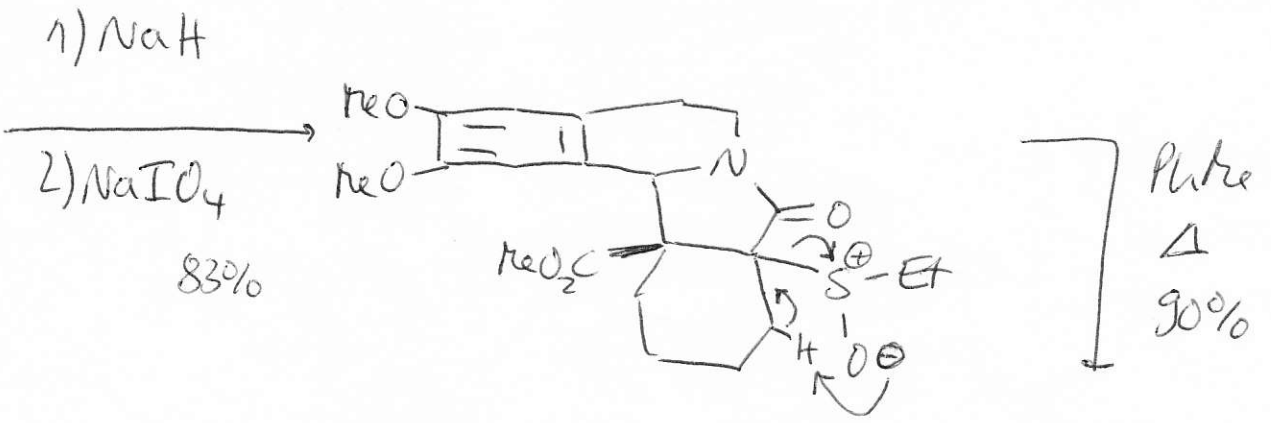
CSA  
98%



wie immer  
Umpolung des 1,3-Dicarbonyls





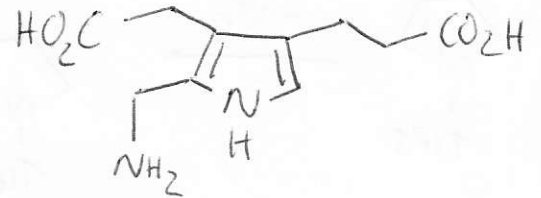
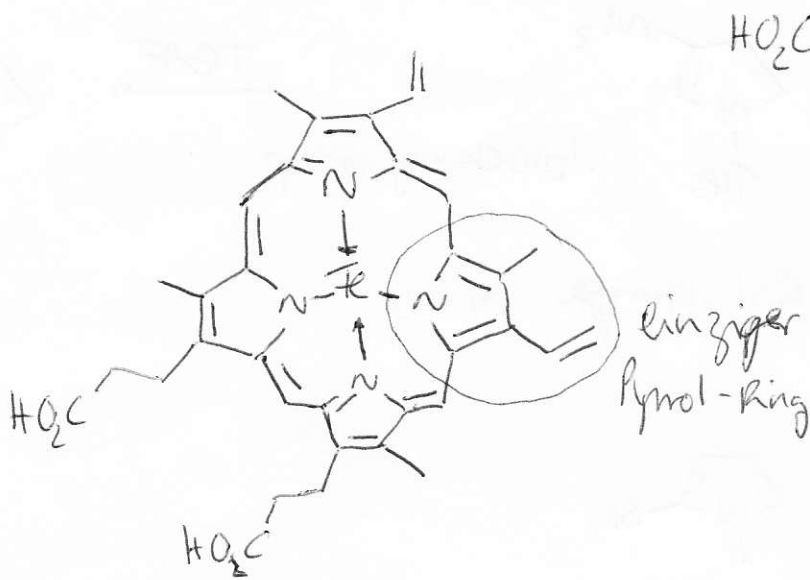


# 5-membered Heterocycles

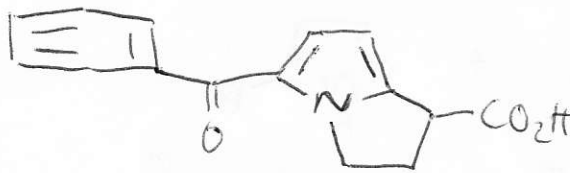
Pyroles : pyrrol  $\rightarrow$  griech. rot (HCl-exposure)

$\rightarrow$  Natur : Porphyrin (Cobalamin, Haem, Chlorophyll)

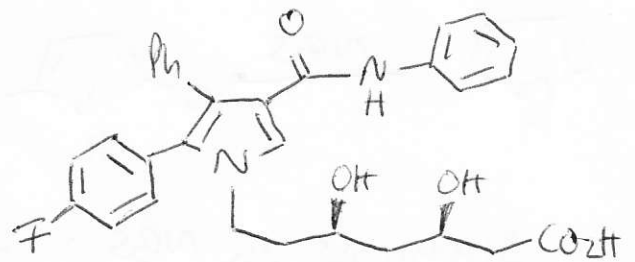
$\rightarrow$  Baustein : porphobilinogen



$\rightarrow$  Pharma :



Ketorolac : Painkiller



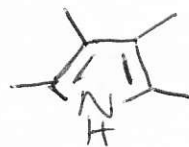
Atorvastatin :

Cholesterinblocker



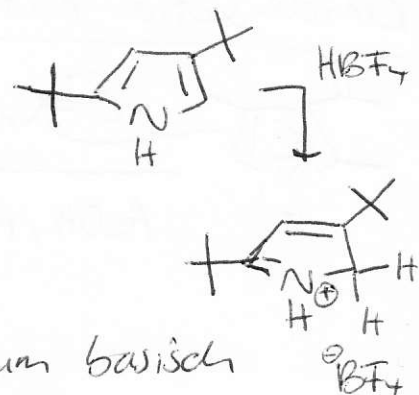
$\text{pK}_a = -3.8$

$\rightarrow$  1/5000 in 1M HCl

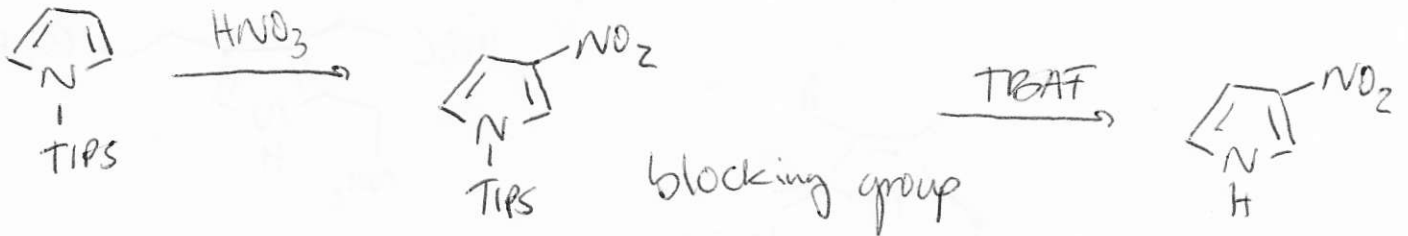
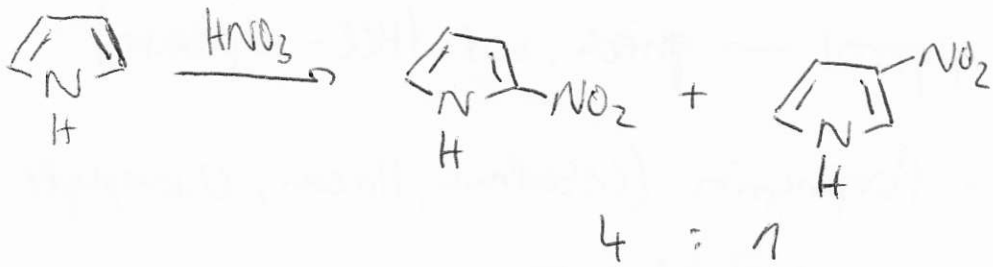


$\text{pK}_a = +3.7 \rightarrow$  complete protonation

$\text{C} = 0.1 \text{ M}$  (bez. Pyrrol) protoniert  $\Rightarrow$  kaum basisch



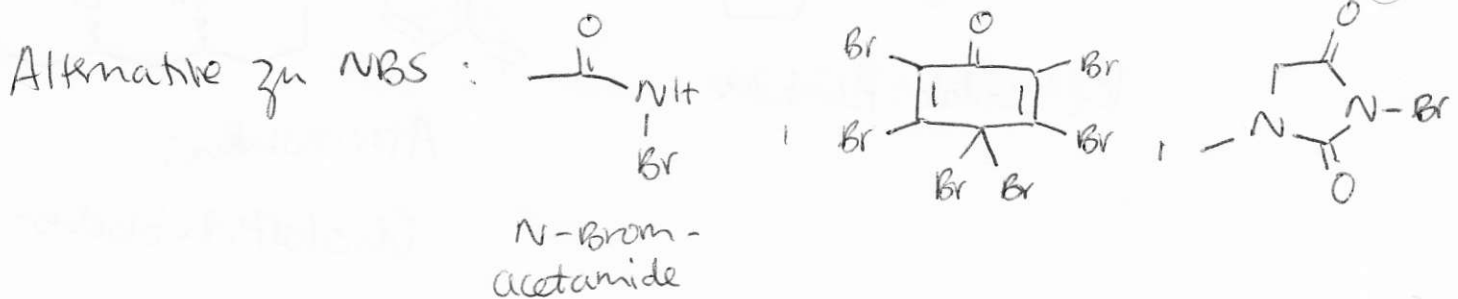
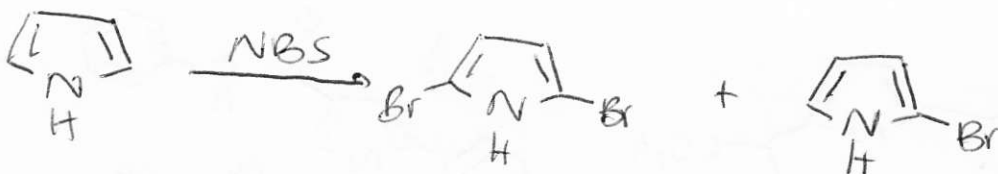
## Nitrierung:



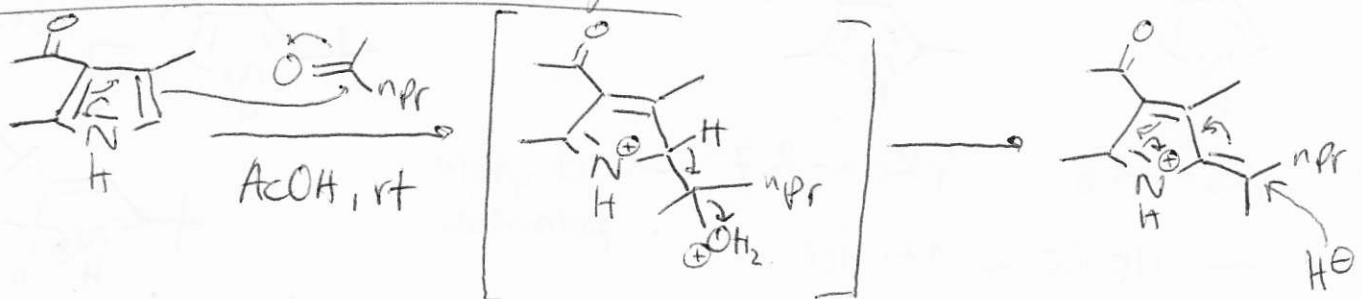
## Sulfonierung: milde Bedingungen py \cdot SO\_3

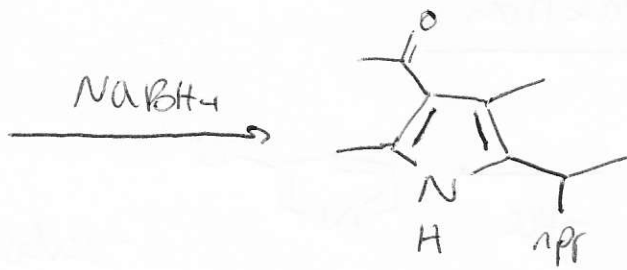


## Bromierung: muss rechtzeitig gestoppt werden

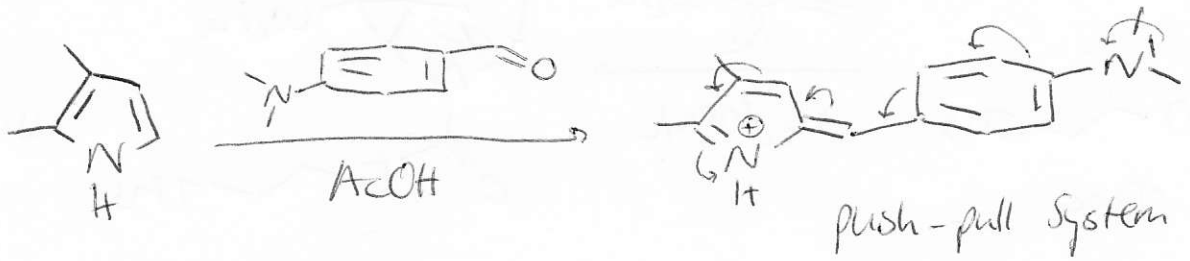


## Kondensation mit Carbonsyl:

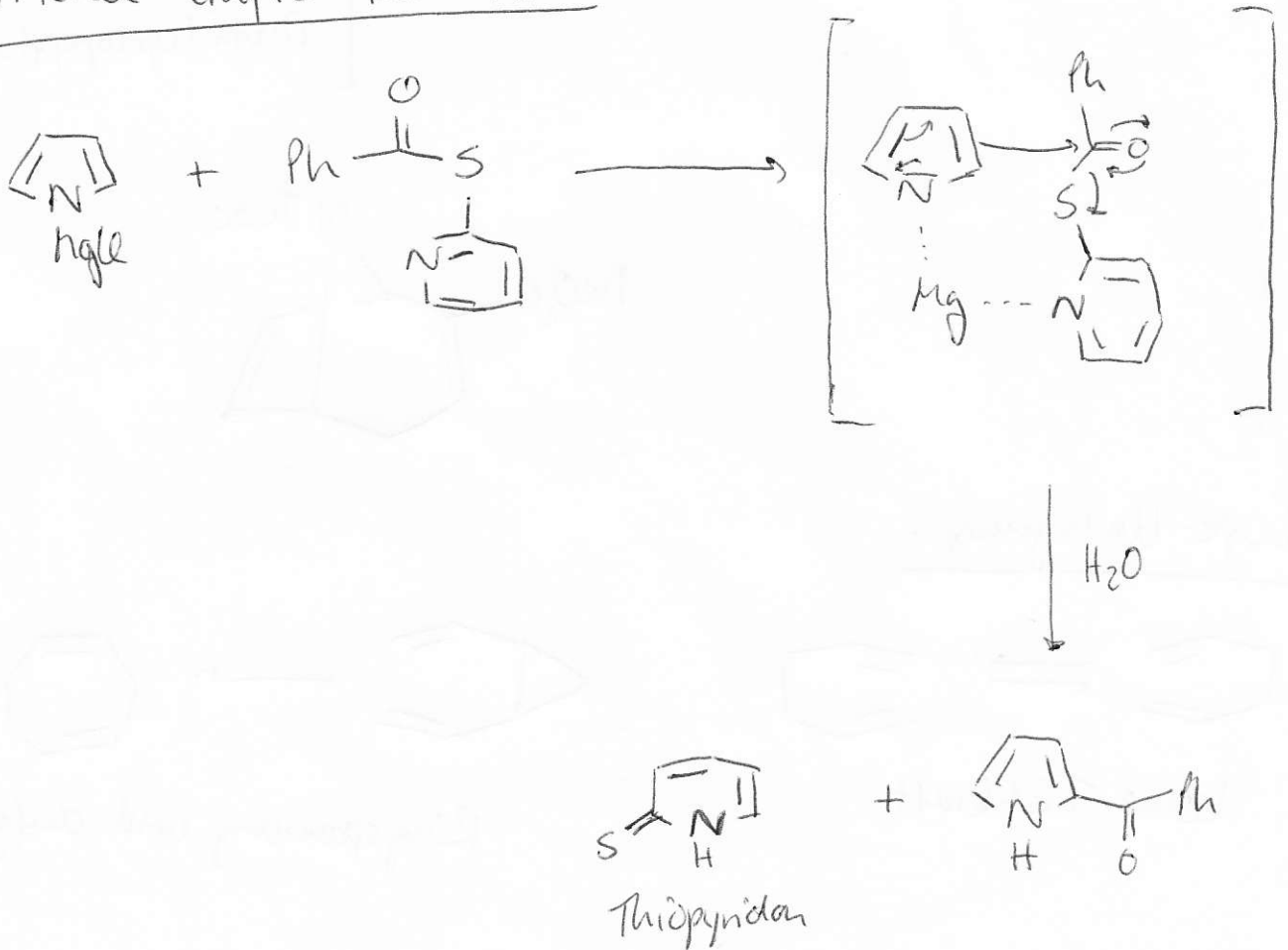




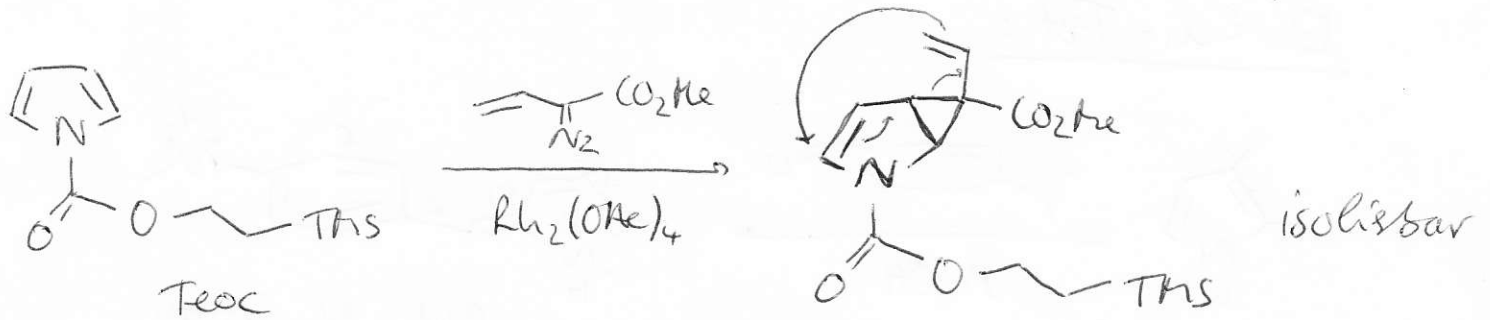
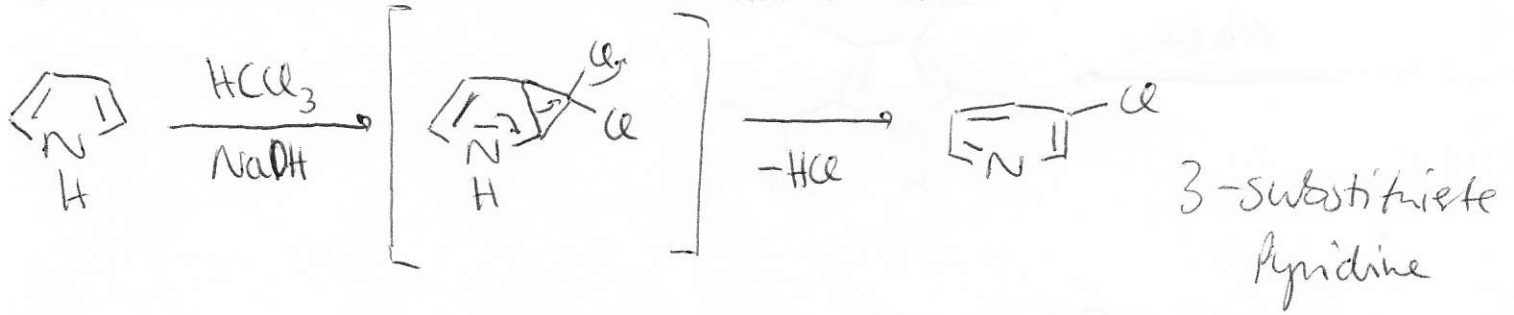
Ehrlich-Test:



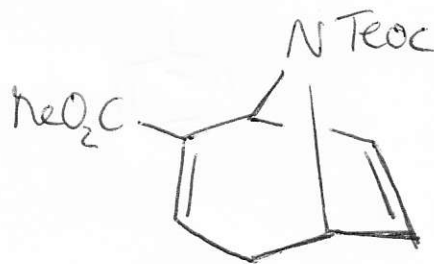
Friedel-Crafts-Reaktion:



# Camician - Denmark - Reaktion:



$\Delta$   
Diving cyclopropyluml.



# Cope-Umlagerung:



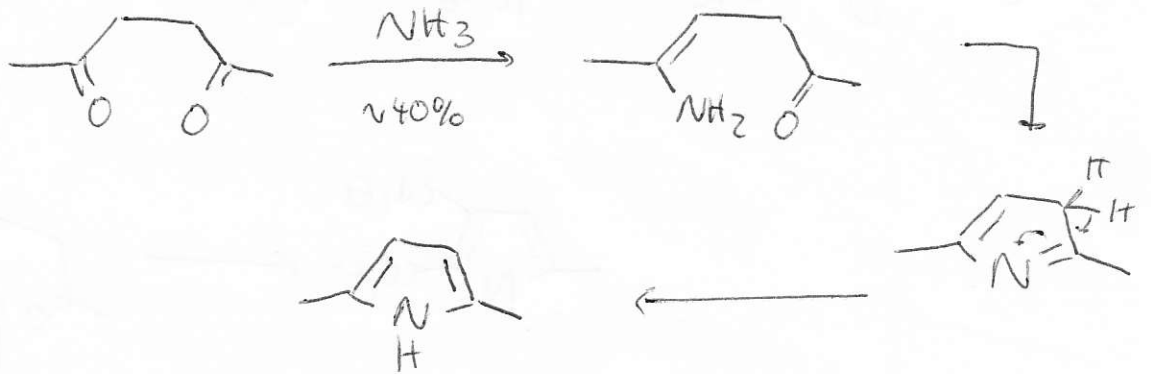
keine Triebkraft



Ringspannung wird aufgegeben

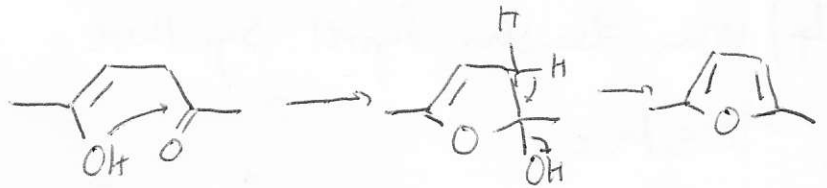
# Synthesen:

## 1) Paal-Knorr:

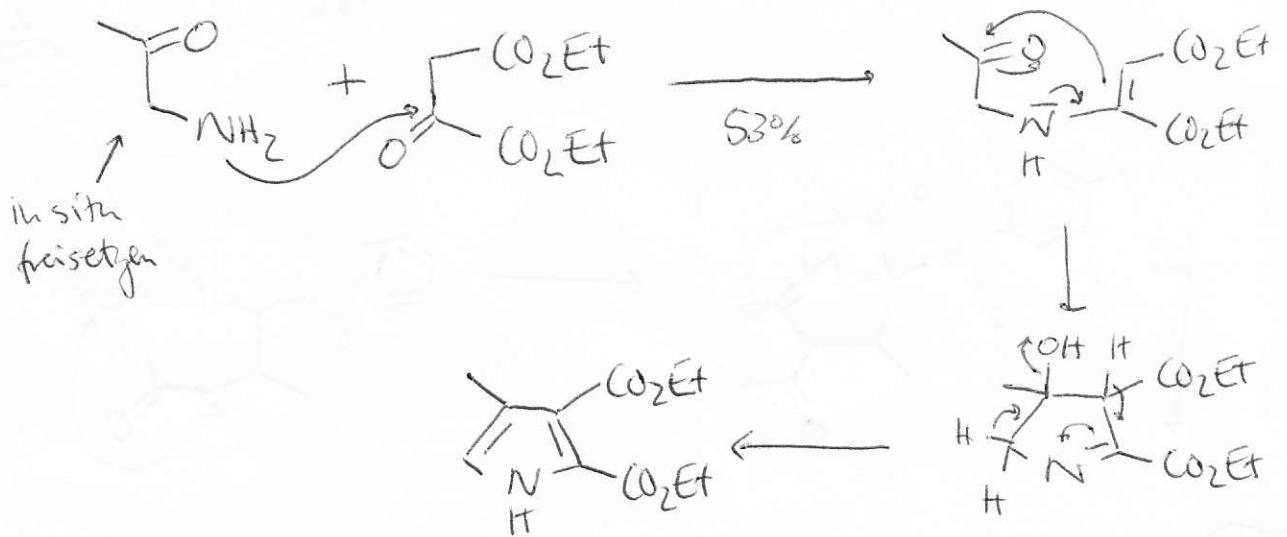


2,5-disubstituierte Pyrrole

## 1,4-Dicarbonyl:

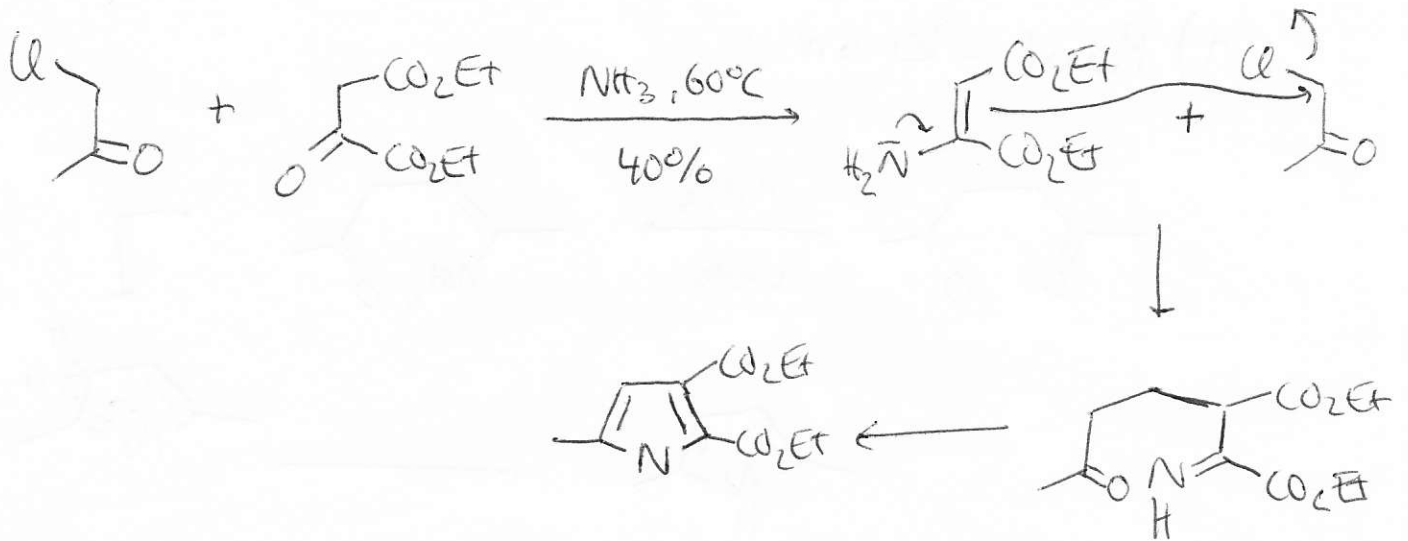


## 2) Knorr:



trisubstituiertes Pyrrol (2 EWG)

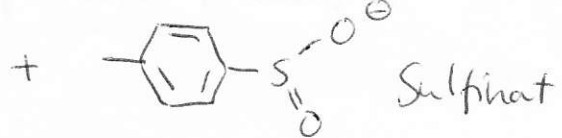
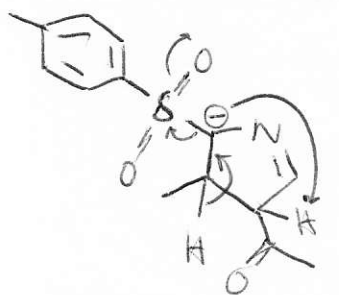
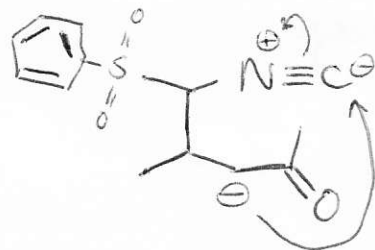
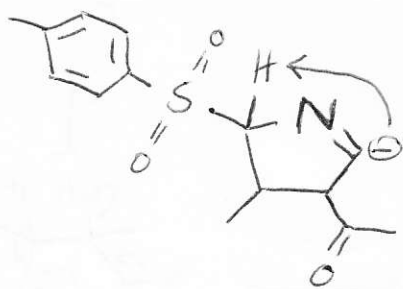
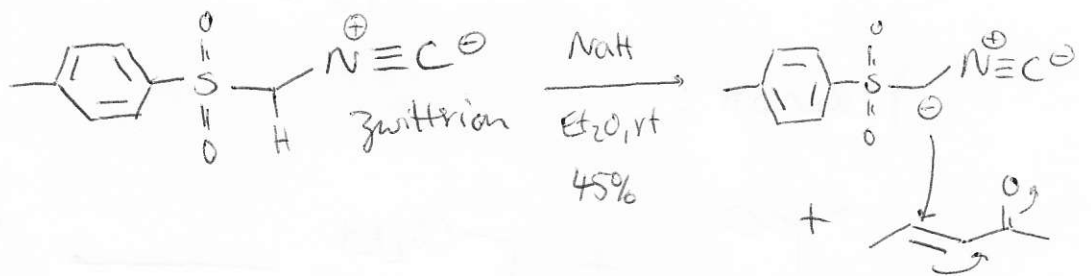
### 3) Hantzschsche Pyridin-Syn.: :



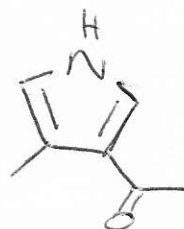
andere Position frei als bei Knorr

### 4) Van Leusen Pyridin-Synthese:

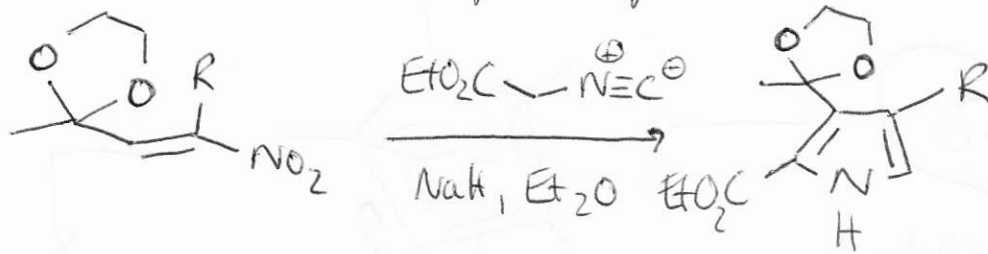
Tosmic:



3,4-substituierte  
Pyridole

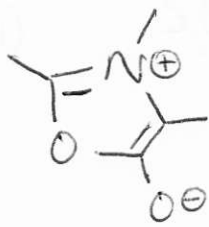


# 5) Barton-Zard Pyridol-Synthese:



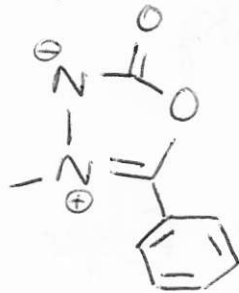
2,3,4-Substituierte Pyridole

# 6) Huisgen Pyridol-Synthese:

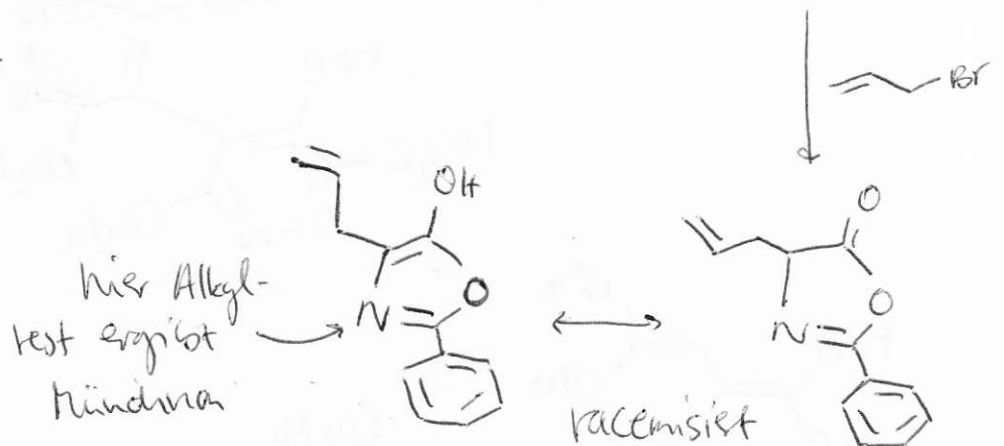
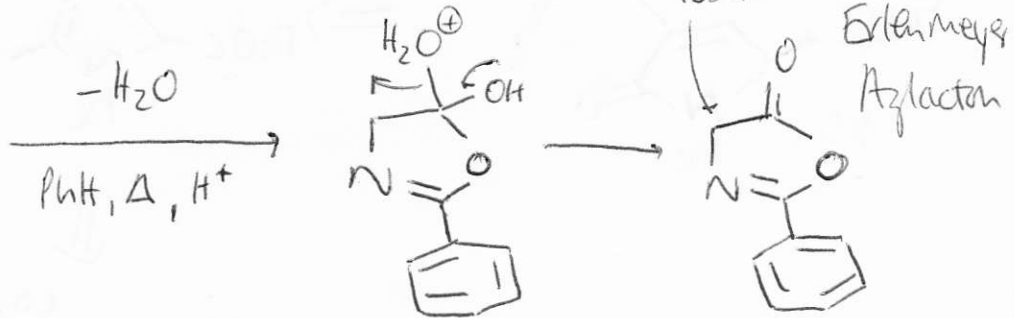


Münchnon  
Azomethinylid

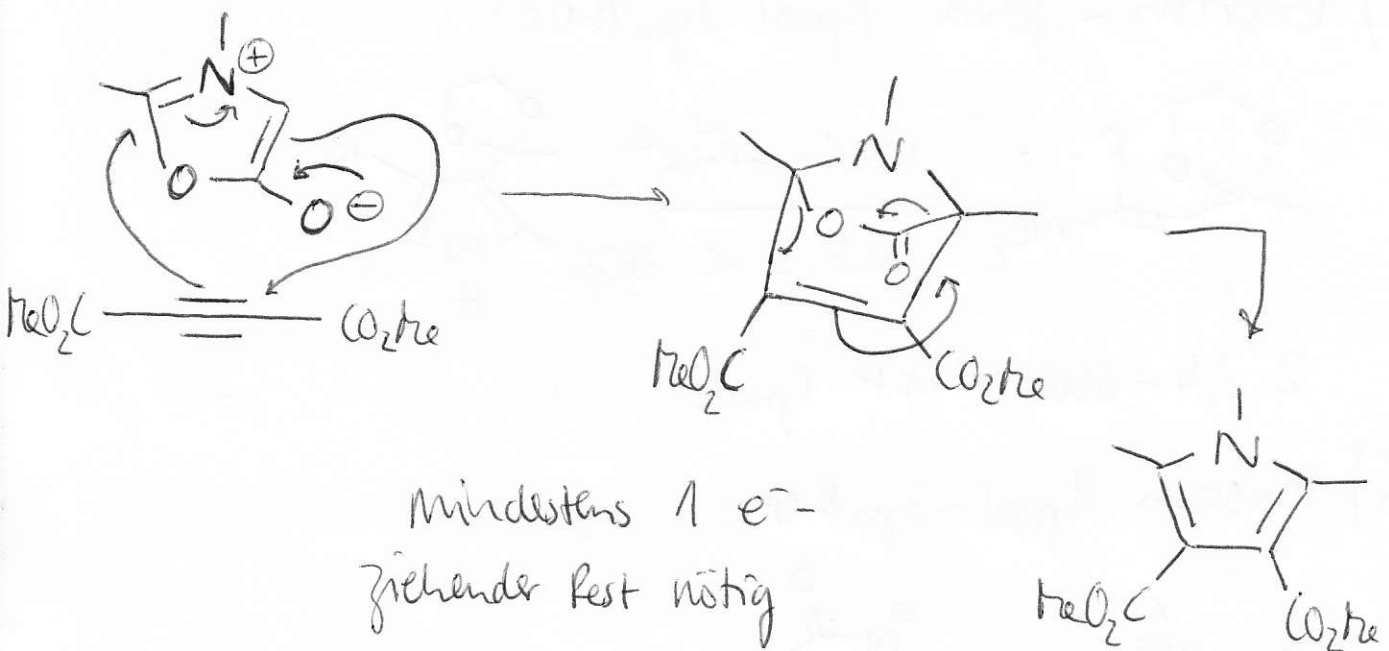
Darstellung:



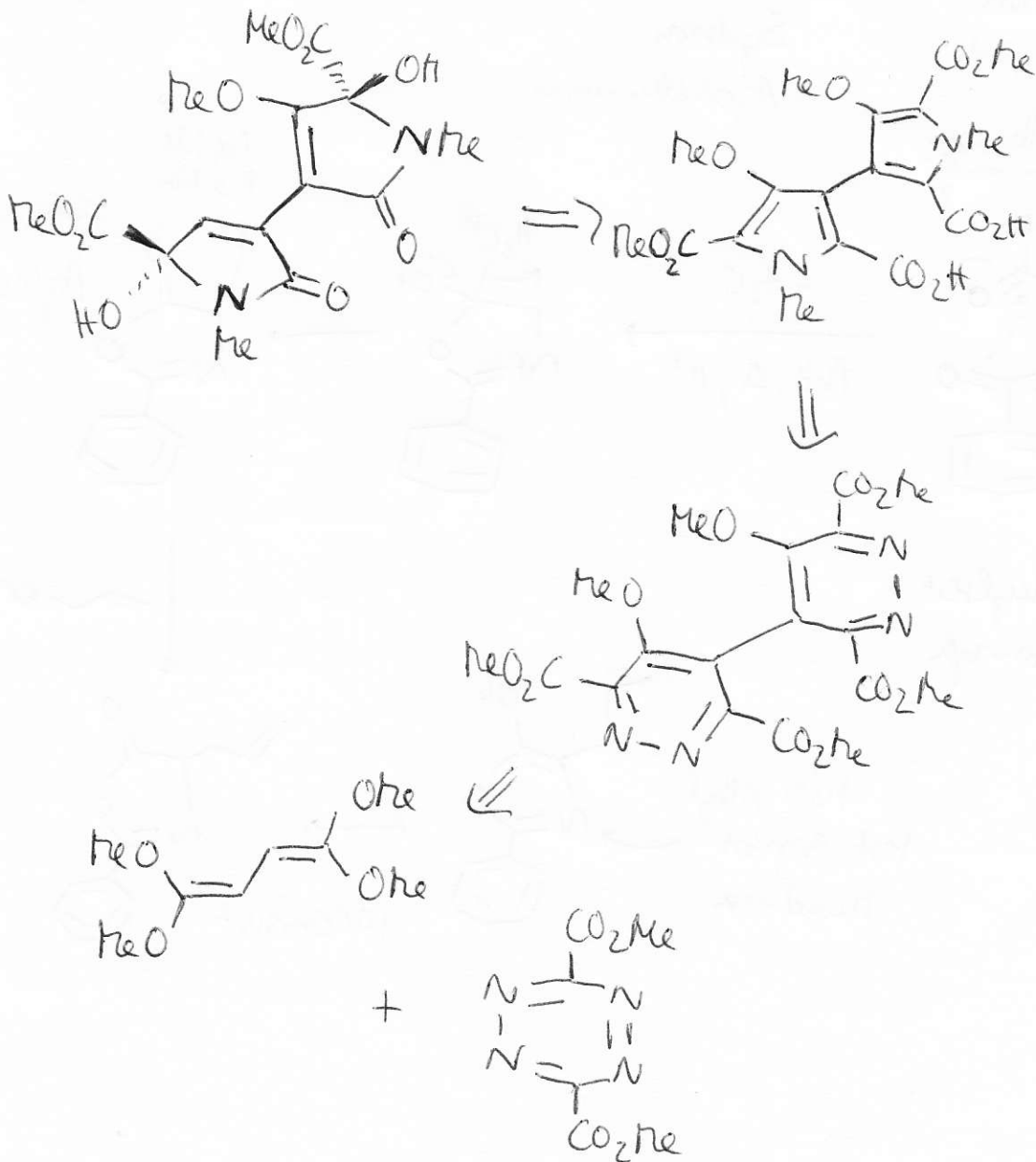
Sydnon  
Azomethinimin



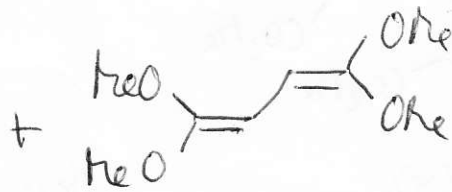
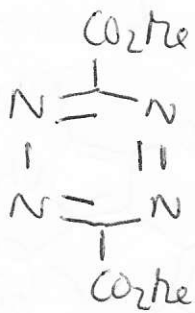




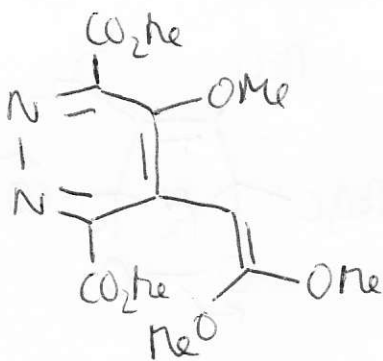
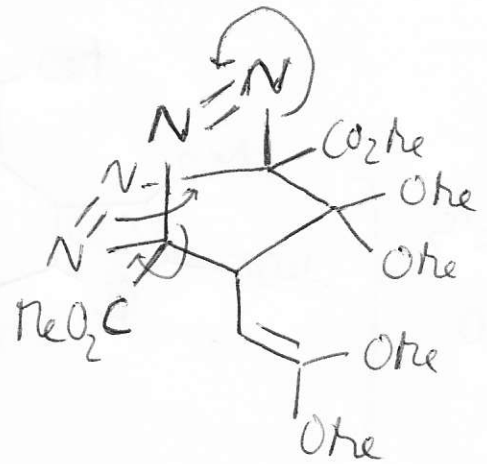
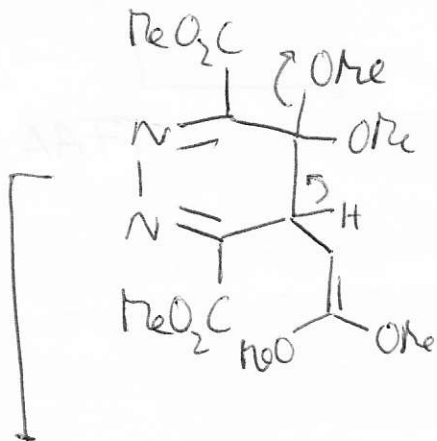
## Isochrysohemidin: Dale Boger



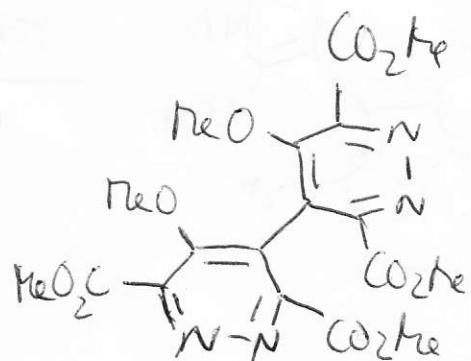
# Synthesis:



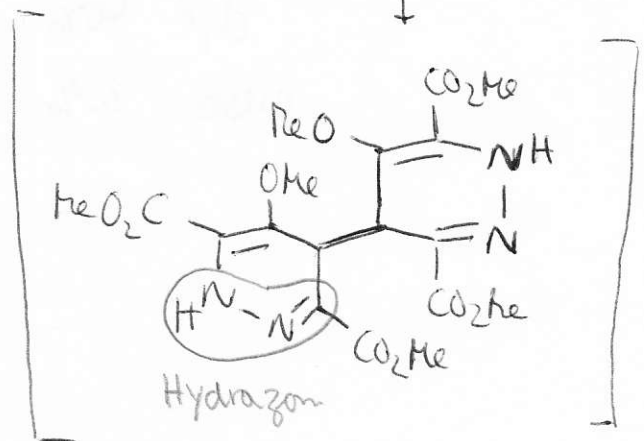
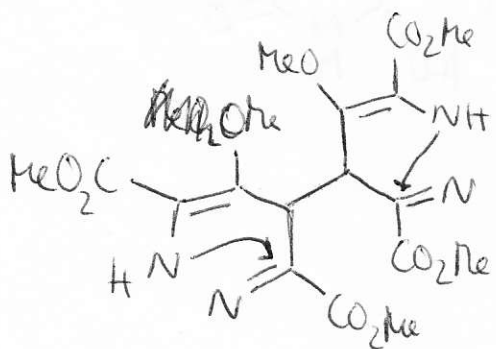
CHCl<sub>3</sub>  
60°C  
5d  
inverse  
DA



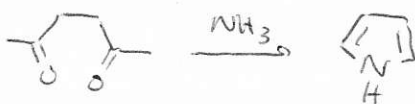
x2

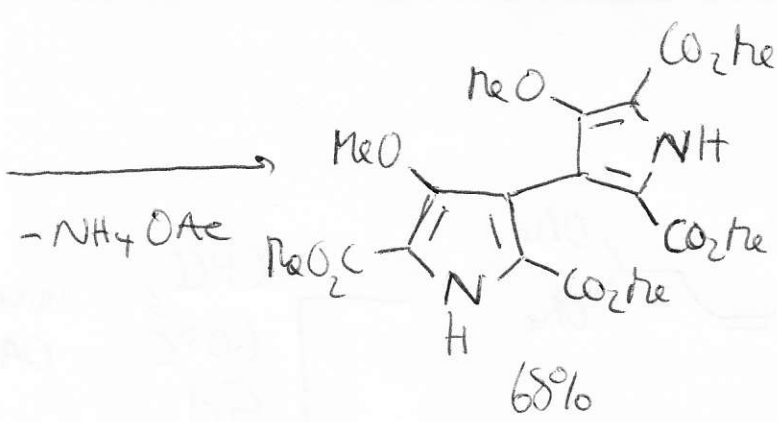


22°C  
24h  
Zn, AcOH



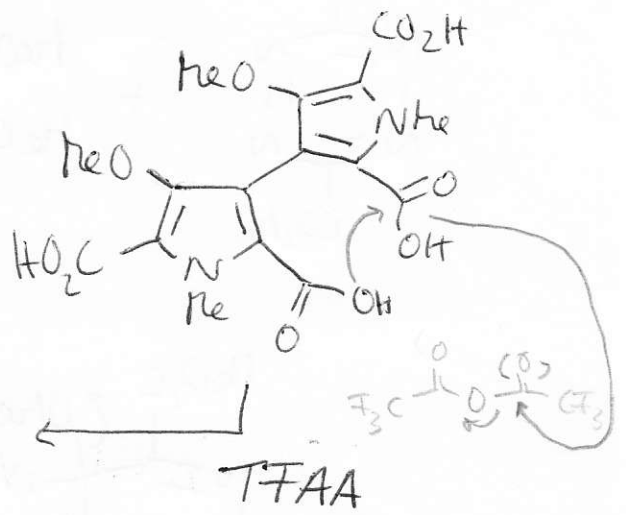
1,4-Dicarbonyl:



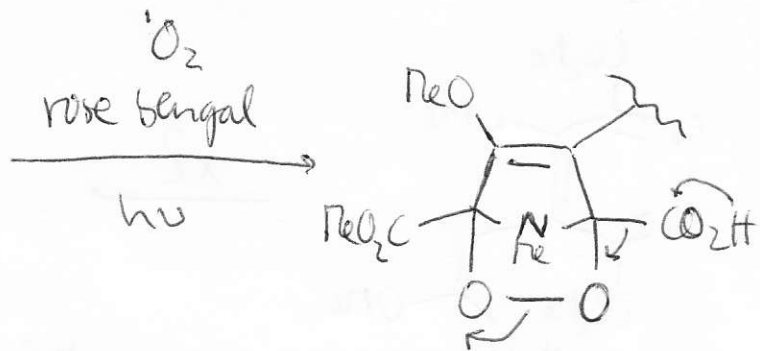
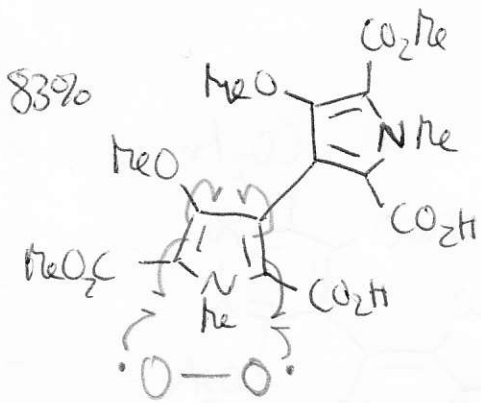
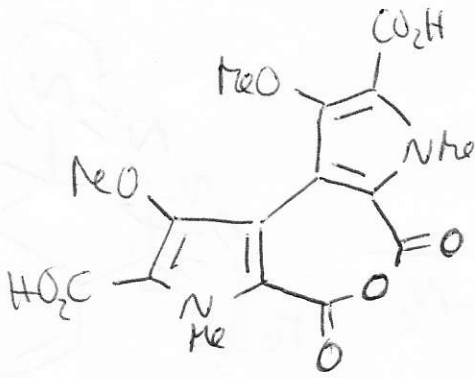


1) NaH, MeI  
 DMF  
 2) LiOH

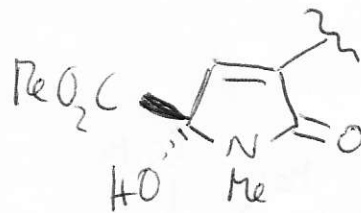
98%



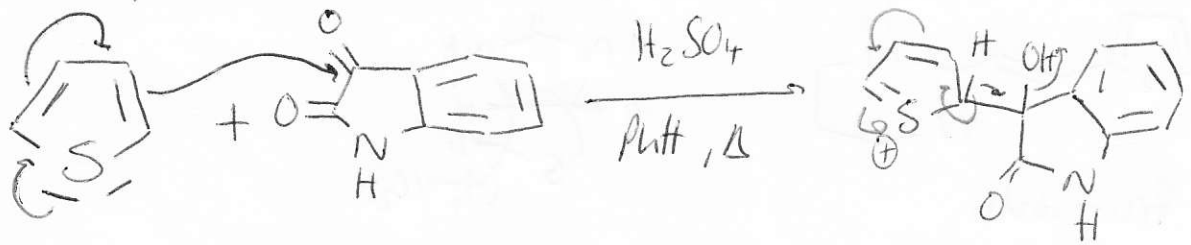
1)  $CH_2N_2$   
 2)  $H_2O$



d,l 40%  
 meso 30%



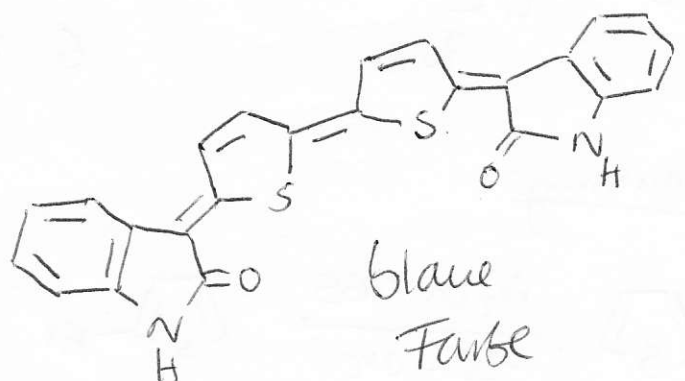
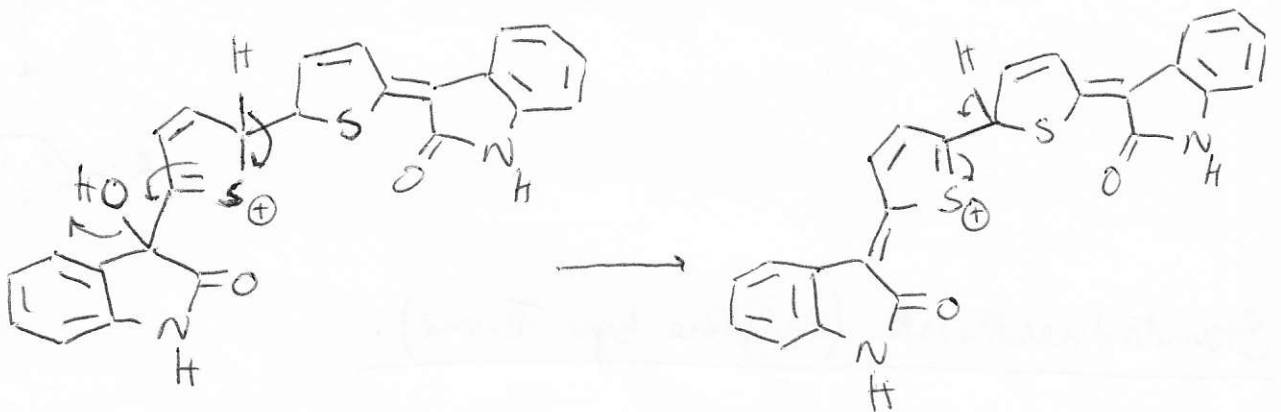
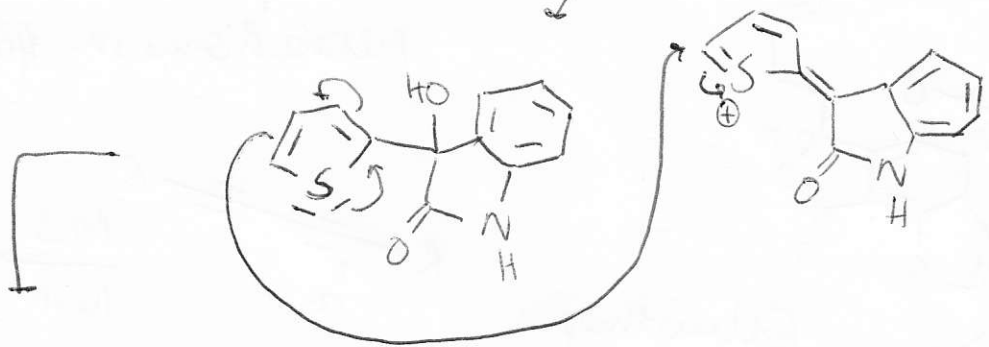
# Thiophene



historischer Benzol-Nachweise  
 → Thiophen-Kontaminationen

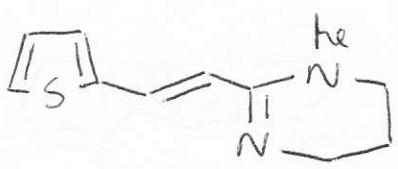
Retro-  
 matrisierung

↓ -H<sub>2</sub>O

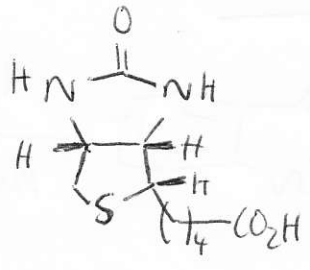


blaue  
 Farbe

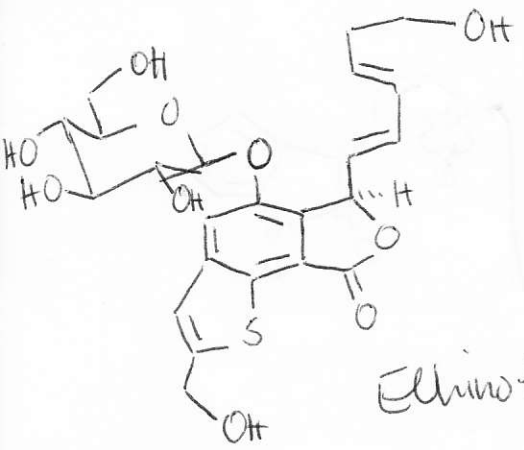
- Naturstoffe / Pharmazentika:



Berberin  
Chemotherapeutika

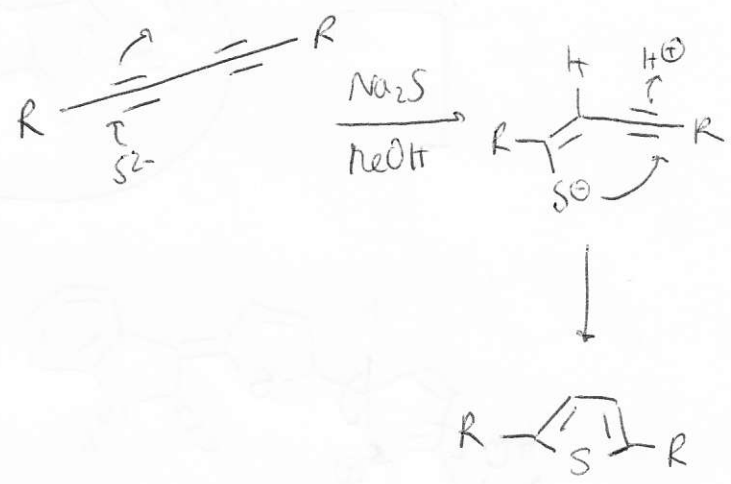


Biotin



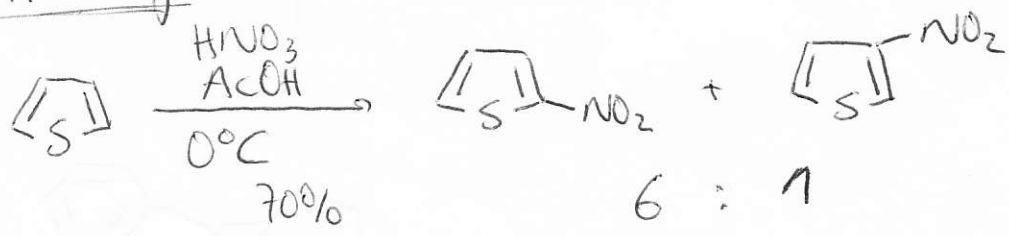
Ellinoglycyrrhizin

Thiophene im Sekundär-  
metabolismus von Pflanzen:

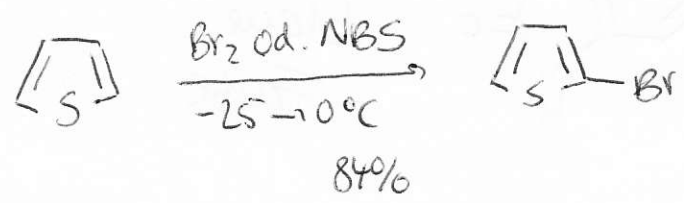


- Standardreaktivitäten (Thiophene bzw. Furane):

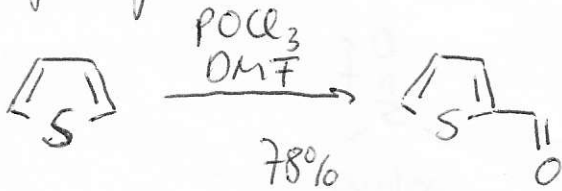
Nitrierung:



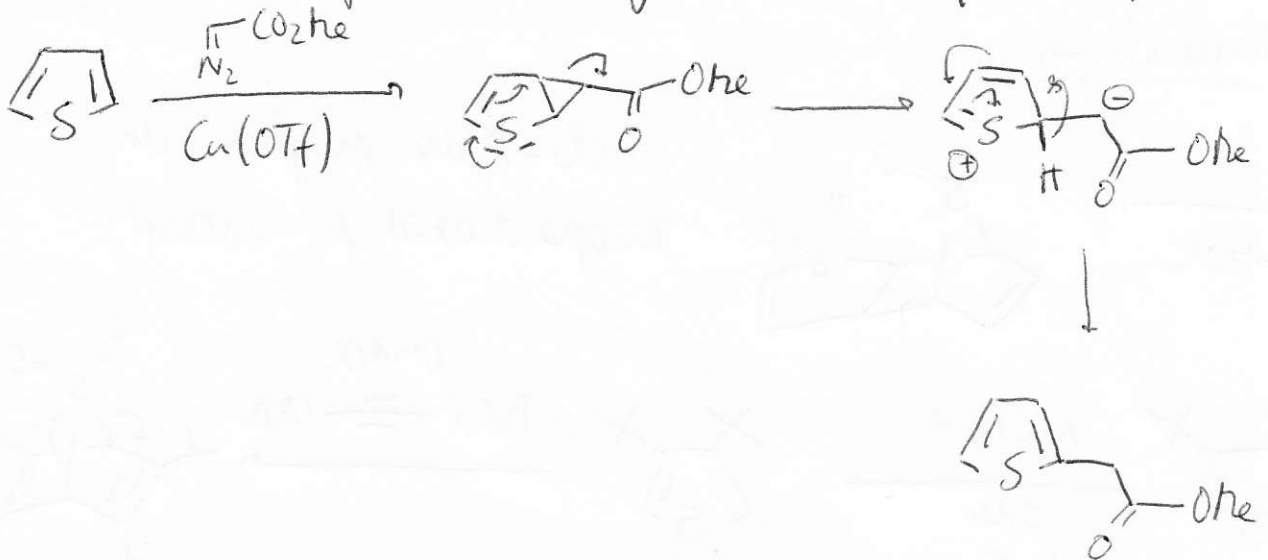
Bromierung:



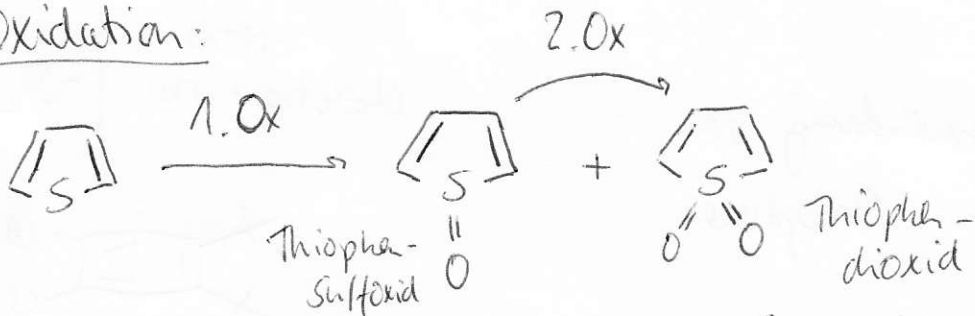
Acylierung: Vielsmeier-Hack Formylierung



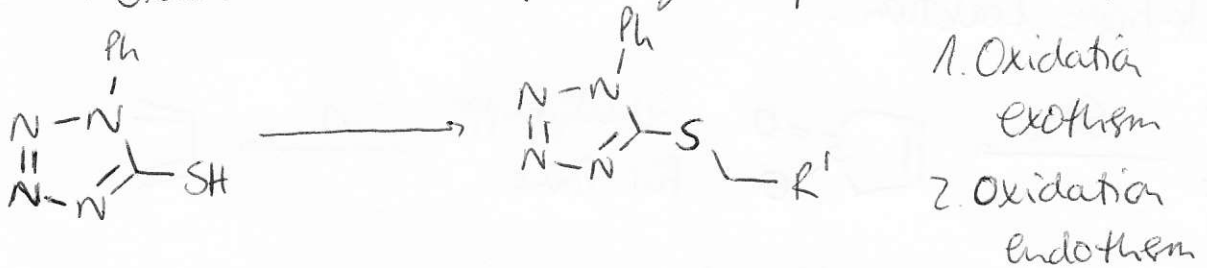
Carbene: beim Pyridol Beeinflussung über Stickstoff (Boc etc.)



Oxidation:

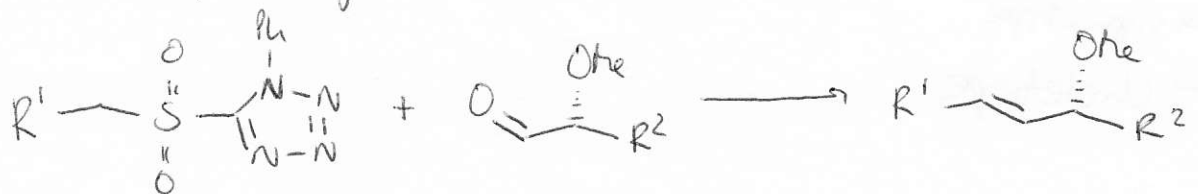


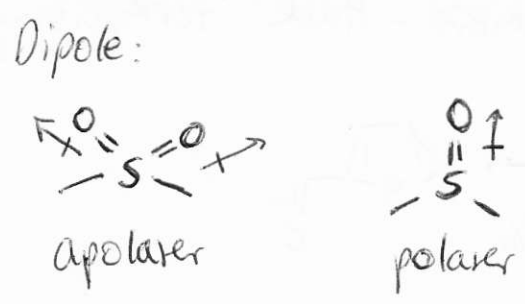
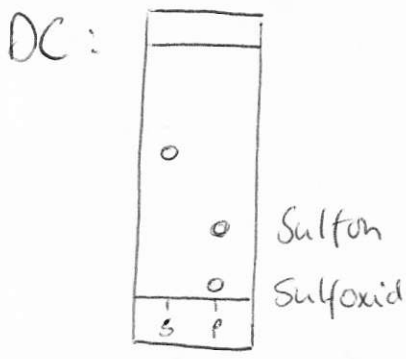
→ Oxidation von Sulfiden zu Sulfoxiden & Sulfonen



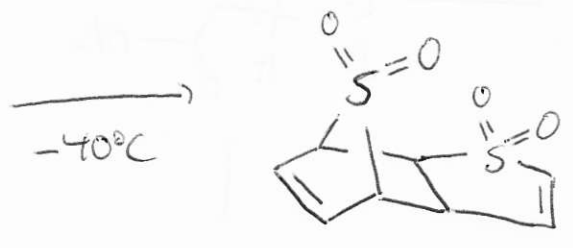
Julia Kociensky: Aldehyd + Sulfon

→ Olefinierung

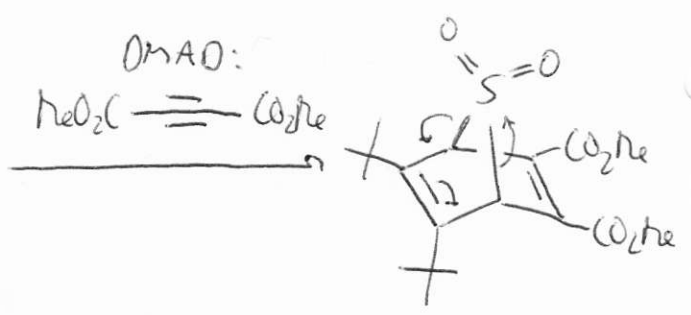
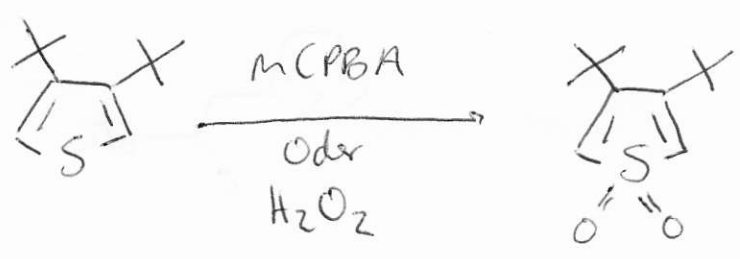




Dimensionierung:

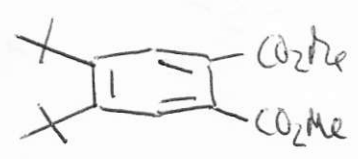


Diels-Alder möglich, da  
Triophendioxid so instabil

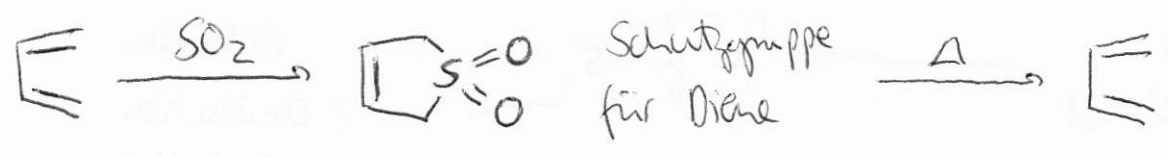


Anwendung von  
Triophenen

retro -  
Chetetrope rxn  $\downarrow$  -SO<sub>2</sub>



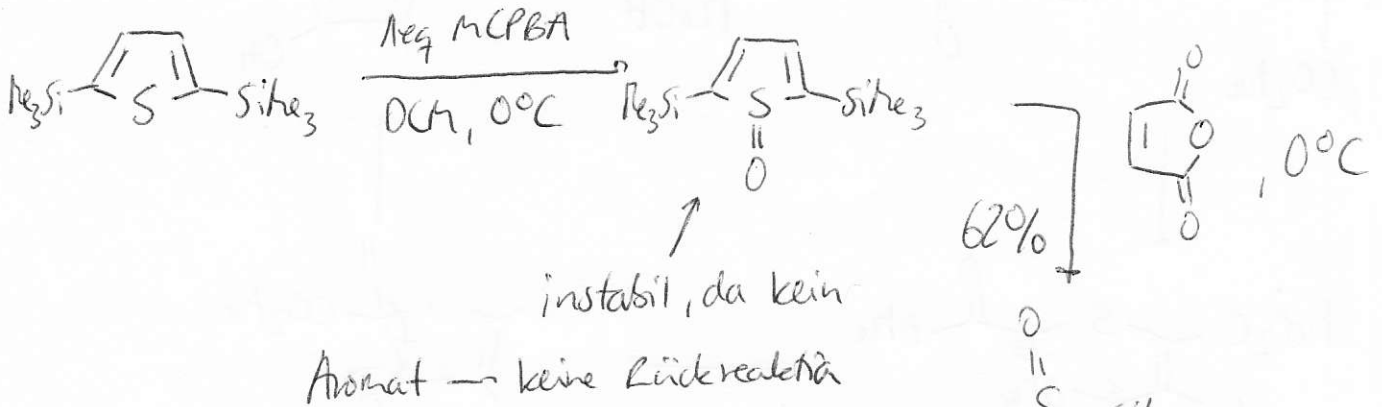
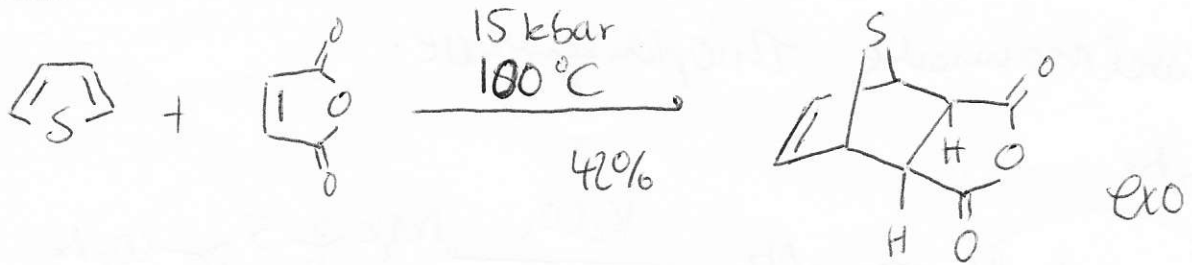
Chetetrope Reaktion:



Woodward-Hoffman kontrollierte Reaktionen:

- elektrocyclische
- sigmatrope
- chetetrope

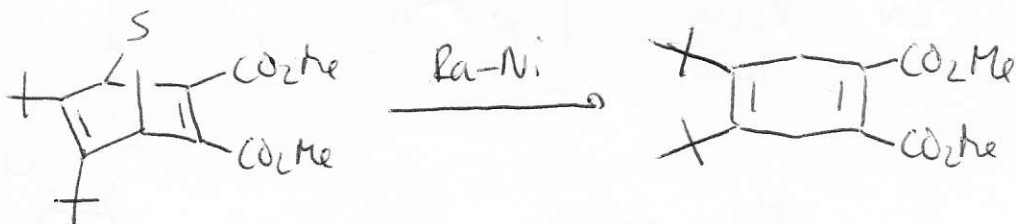
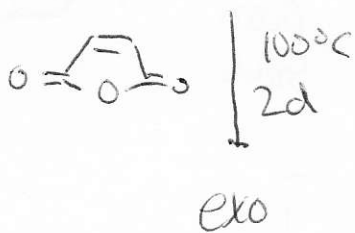
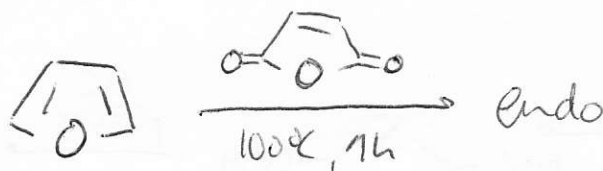
# Diels Alder mit Thiophen:



↑ instabil, da kein

Aromat → keine Rückreaktion

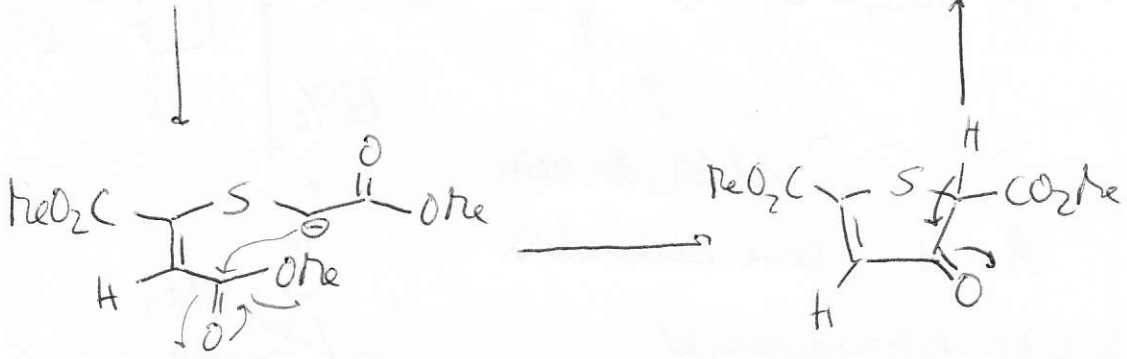
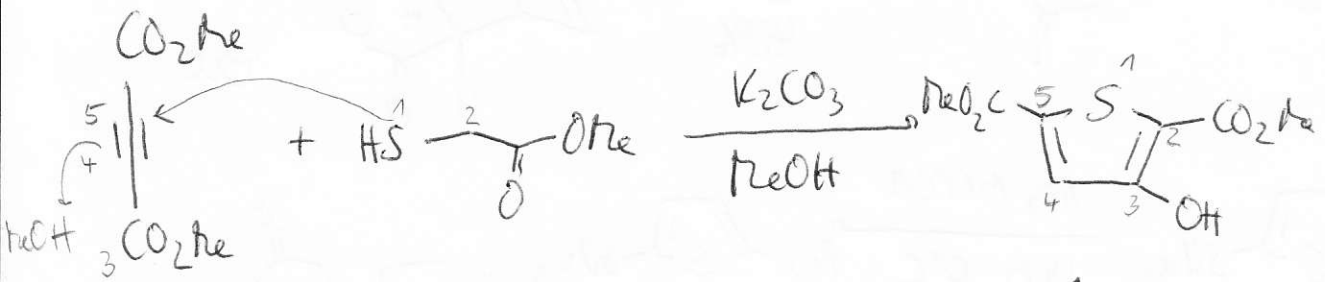
→ exo-Produkt thermodynamisch bevorzugt, sein 1. Beispiel über Rückreaktion einstellbar



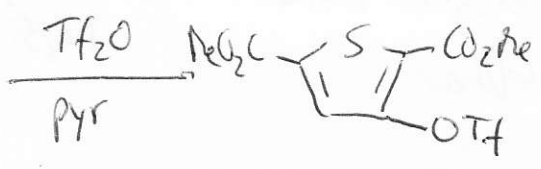


# Thiophensynthesen:

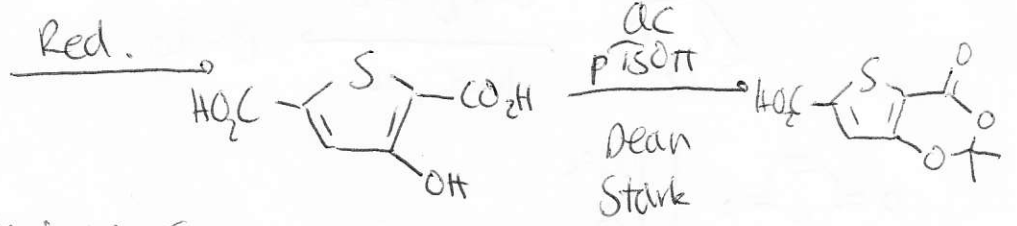
## 1) Fieser-Mannische Thiophensynthese:



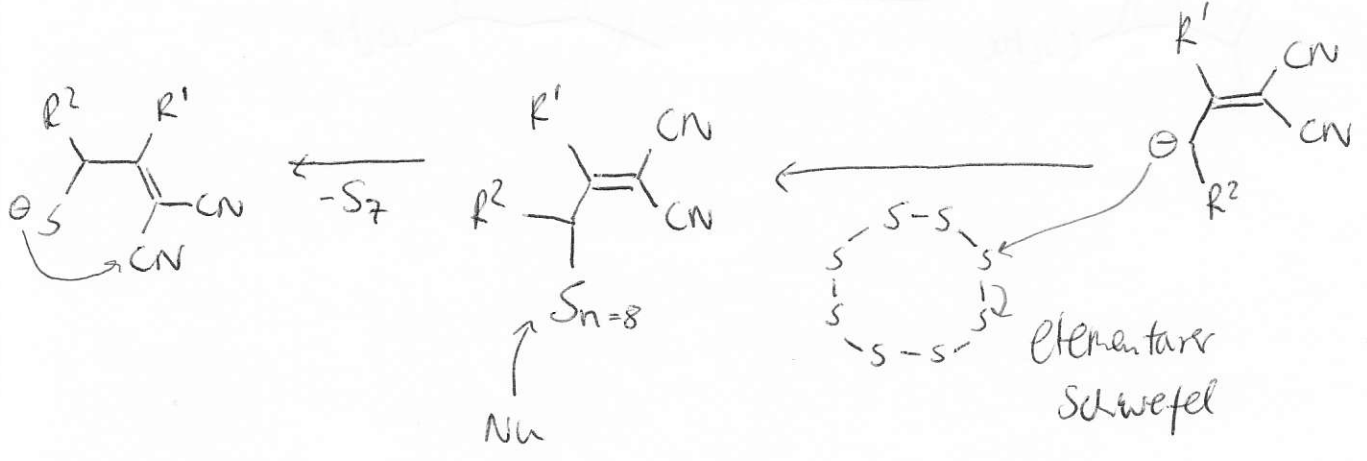
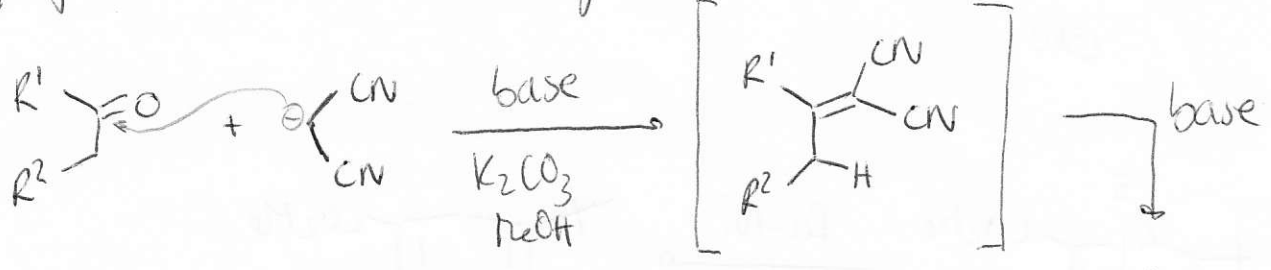
→ Anwendung:

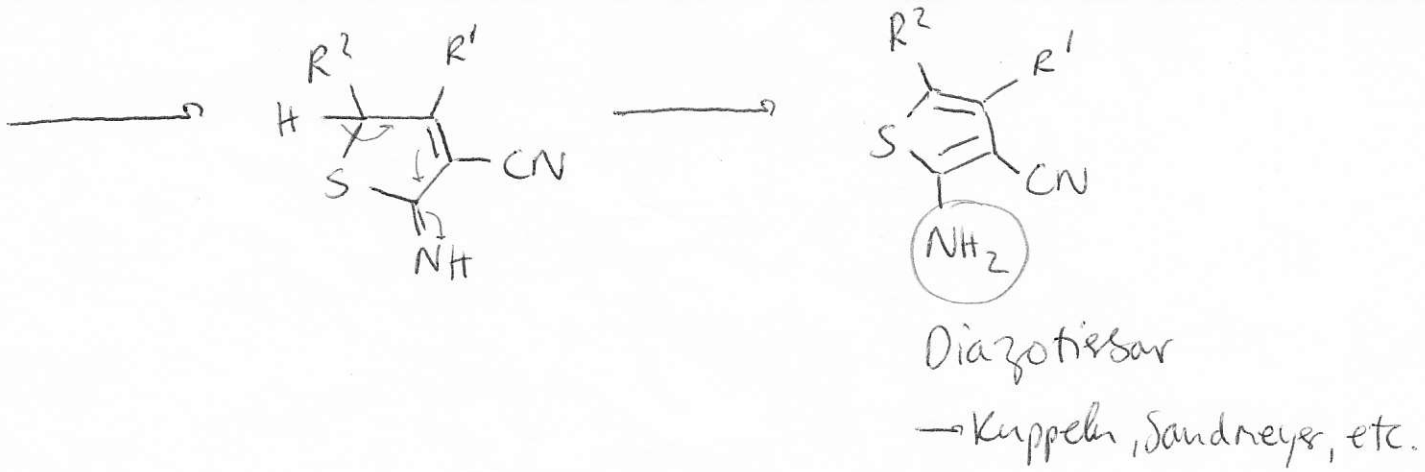


Suzuki, Stille etc. Hede

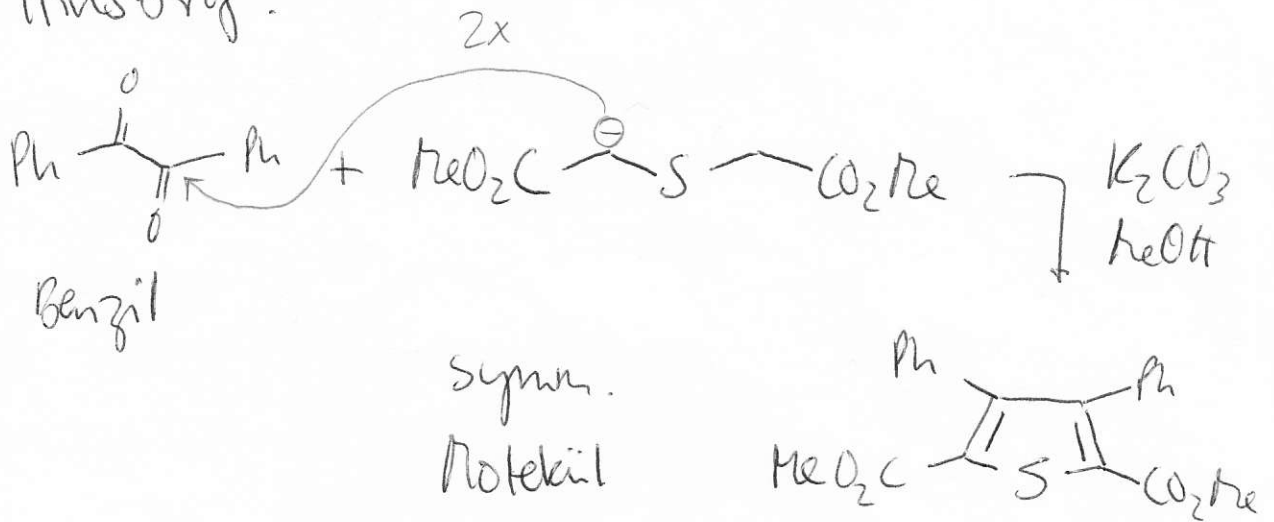


## 2) Gewald - Aminothiophen Synthese:

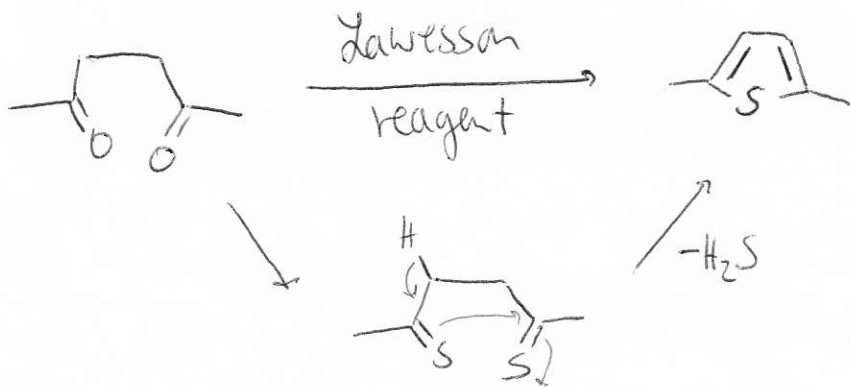




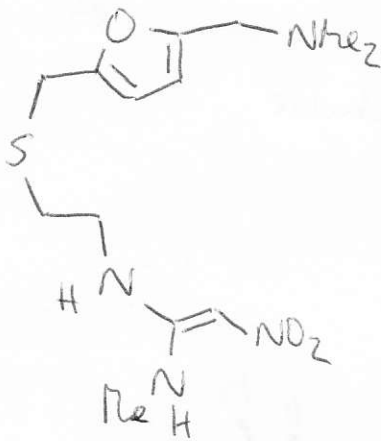
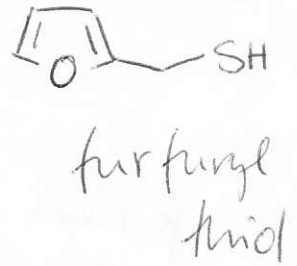
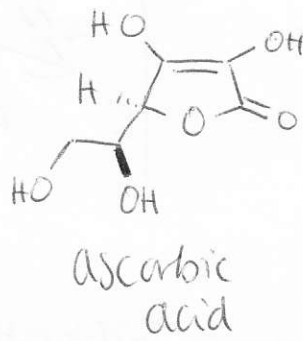
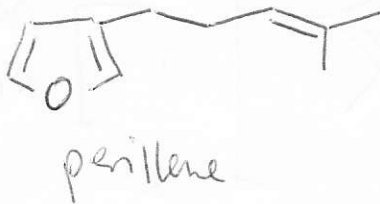
3) Hinsberg:



4) Paal-Knorr:



# Furane:

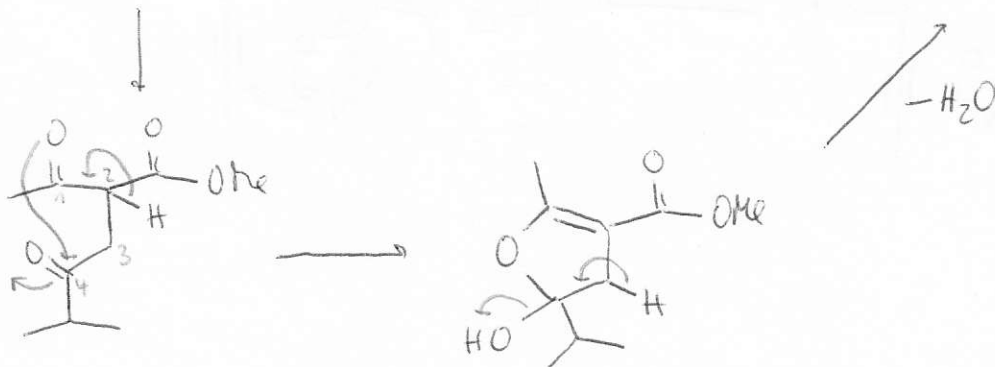
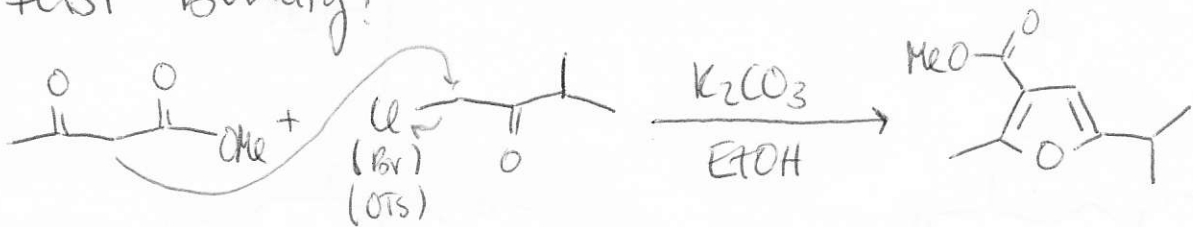


Zantac, ranitidine  
 → Protonenpumpenhemmer gegen  
 Magengeschwür, von Omeprazol abgelöst

→ in Naturstoffen hauptsächlich in Terpenen

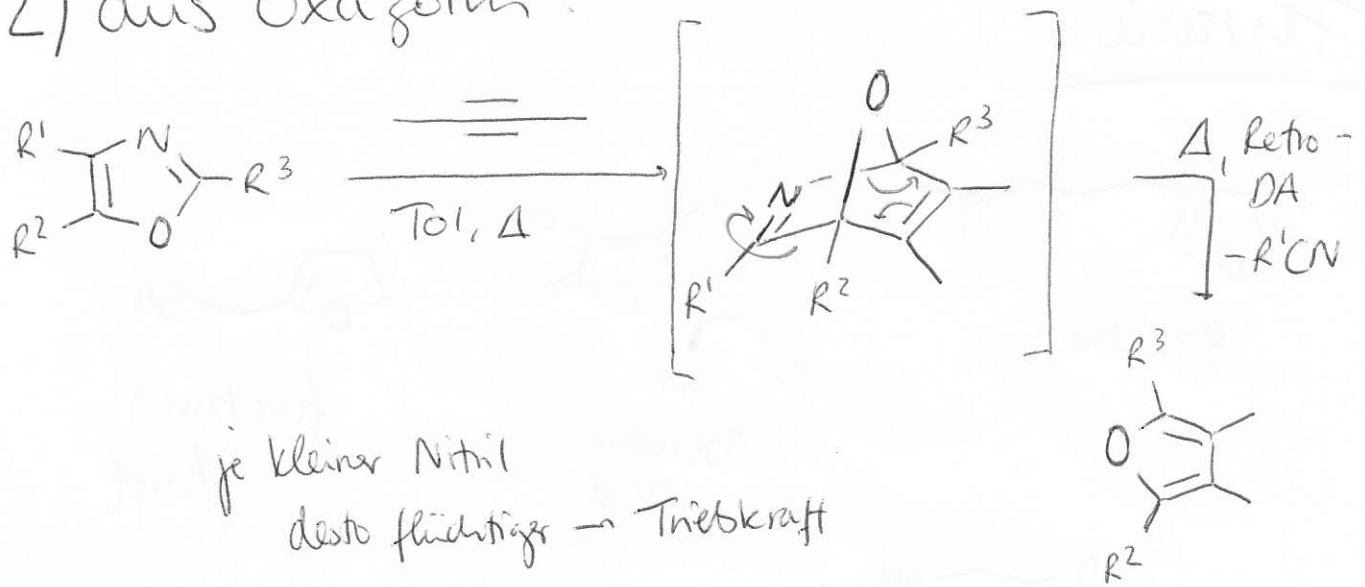
## Synthesen:

### 1) Feist-Benary:



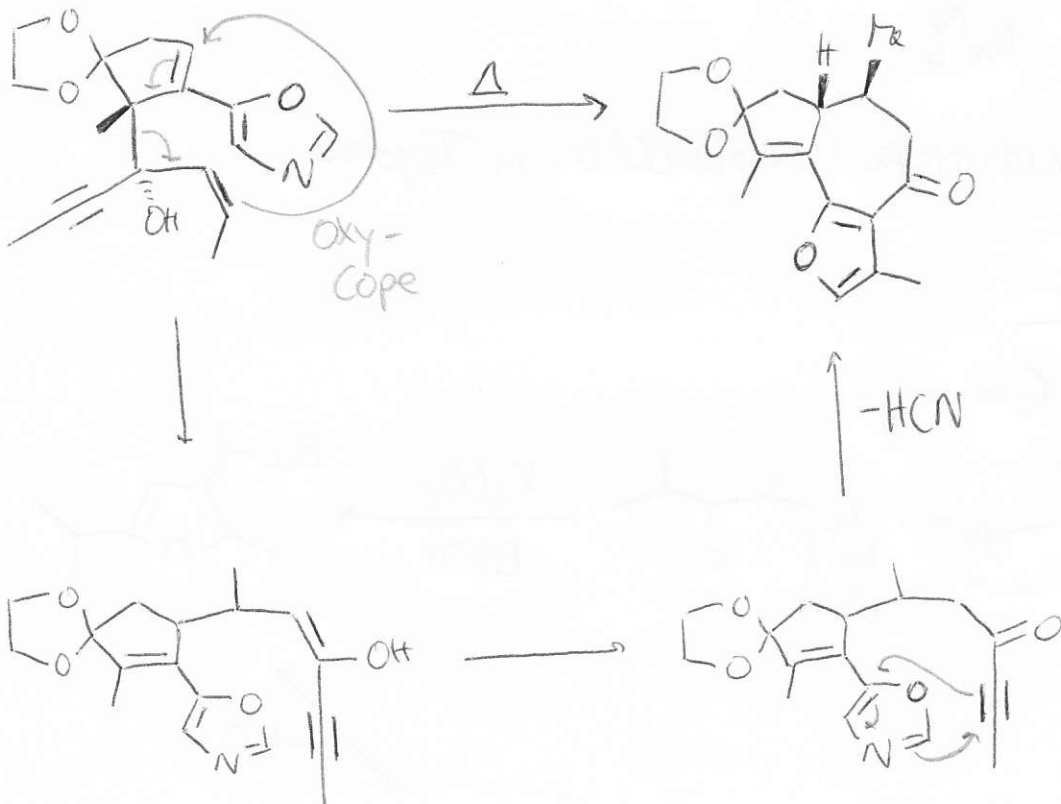
1,4-Diketone aromatisieren  
 immer zum Furan

2) aus Oxazolen:

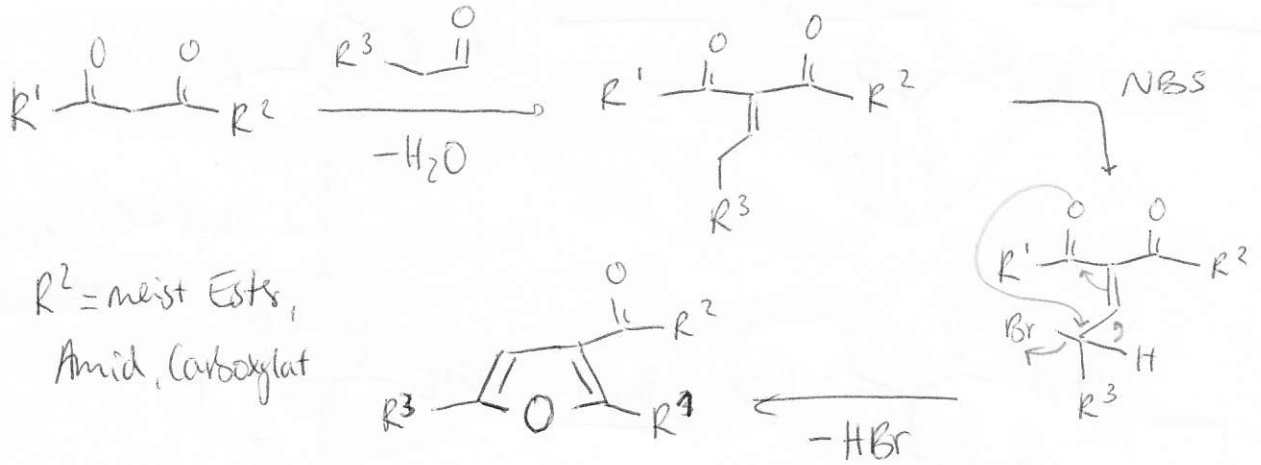


Limitierung: Symm. Alkin  $\rightarrow$  intramolekular

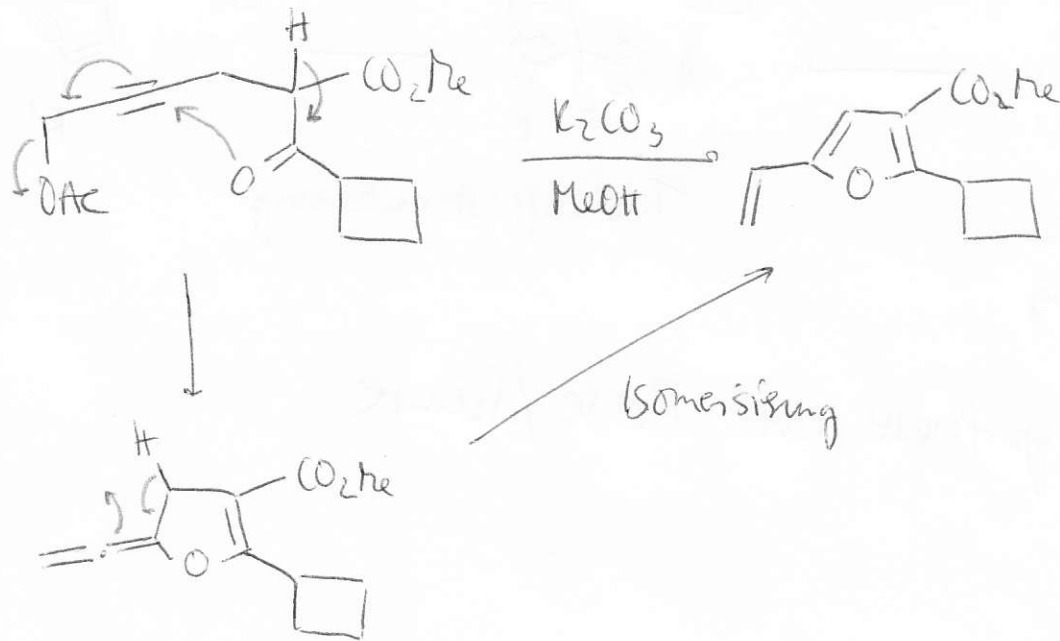
Beispiel:



3) JOC 1978, 4596

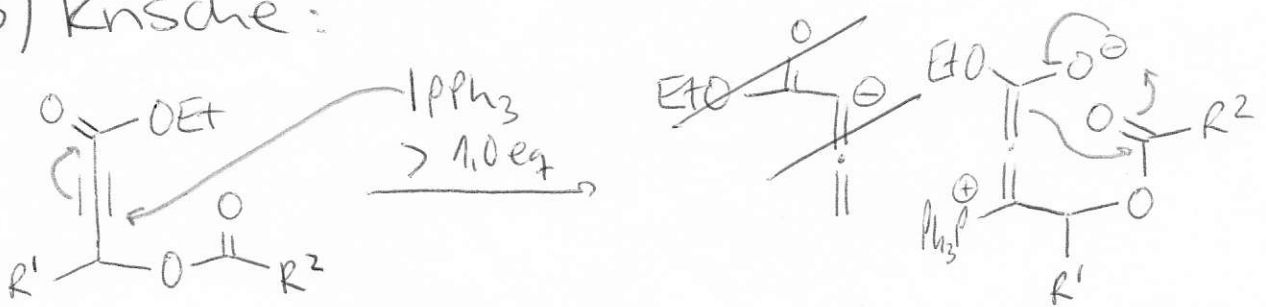


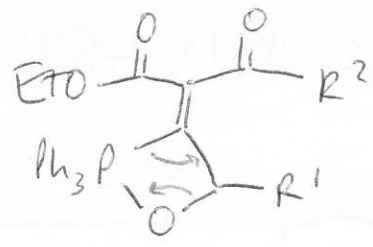
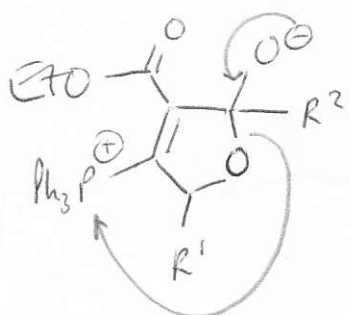
4) SN2'-Reaktion



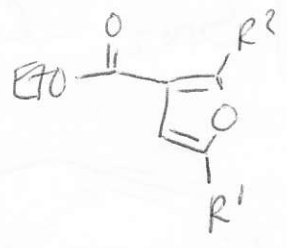
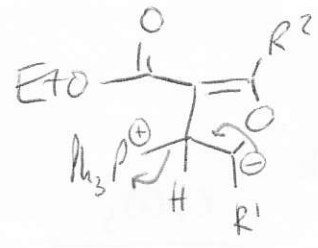
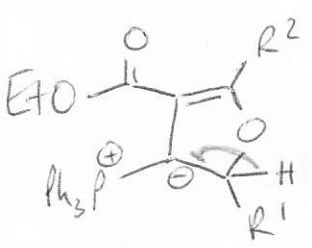
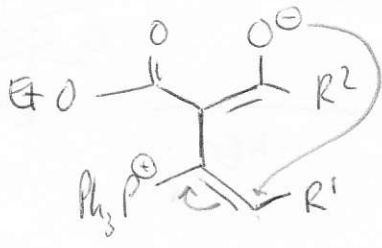
SN2' an Propagylen ergibt ein Allen.

5) Knische:





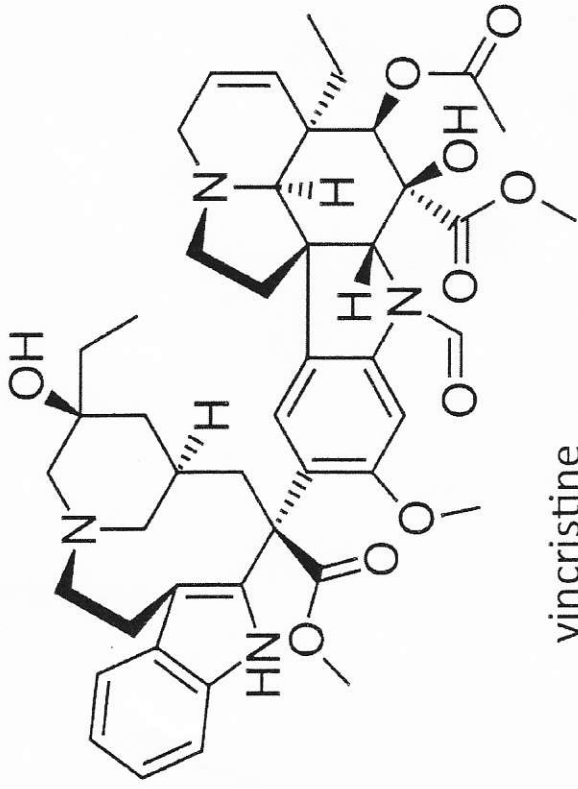
↓ - Ph<sub>3</sub>P=O 1,0 eq  
verbraucht



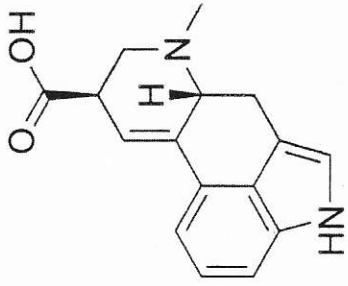
normales Ylid  
→ Triebkraft = keine  
Ladungstrennung

Triebkraft: Aromatisierung

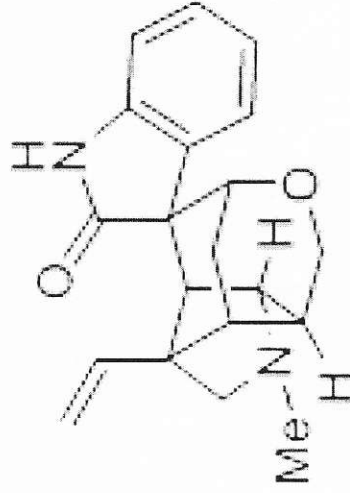
⇒ Synthese ohne Base/Säure



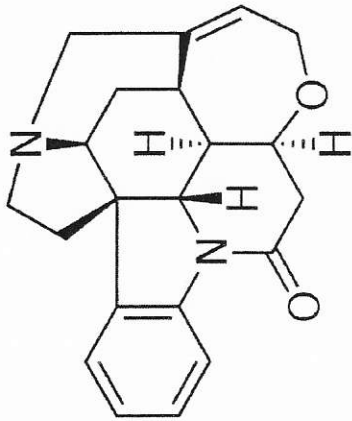
vincristine



Lysergic acid



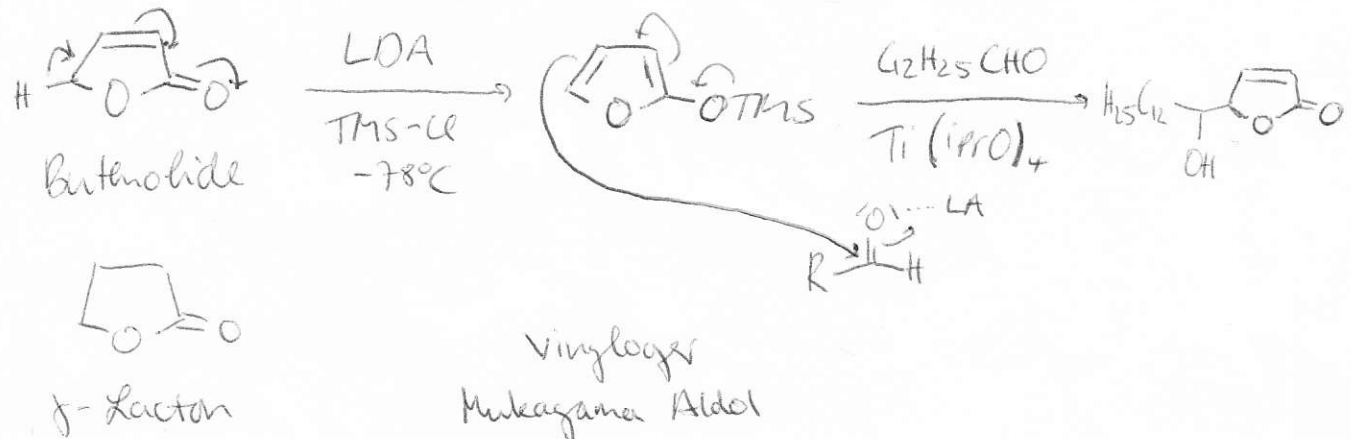
gelsemine



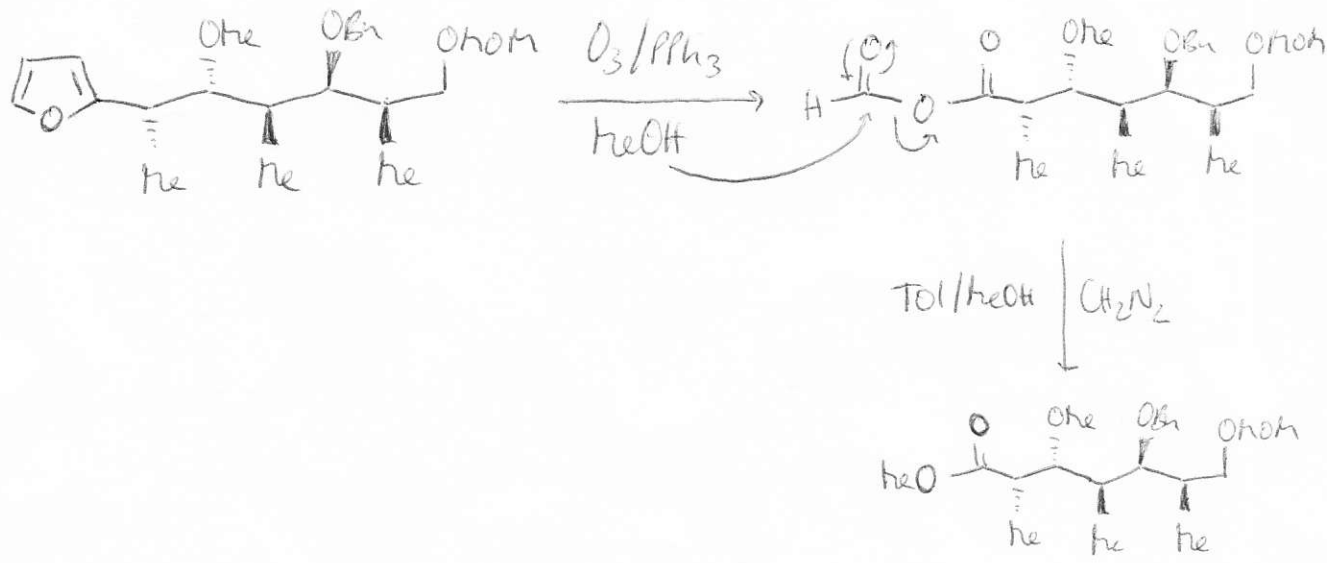
strychnine

Furane:

Casiraghi:

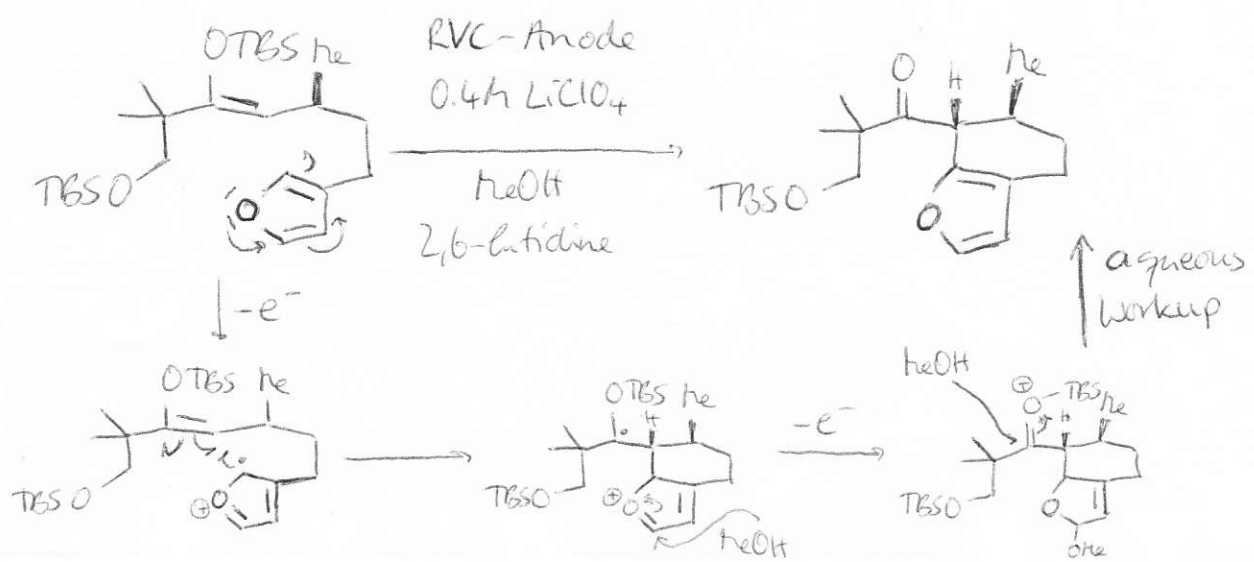


Furane als Ester-Schutzgruppe:



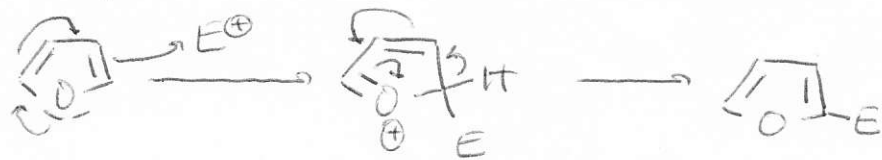
Oxidative C-C-Knüpfung (elektrochemisch):

Quinacastephin-Synthese: D. Trauner et al., JACS 2005





Electrophile Substitution:



# Indole:

Häufigster Heterocyclus in Natur

→ größte Naturstoffklasse: Indolalkaloide

Darstellung aus Kohle/Teer-Destillation

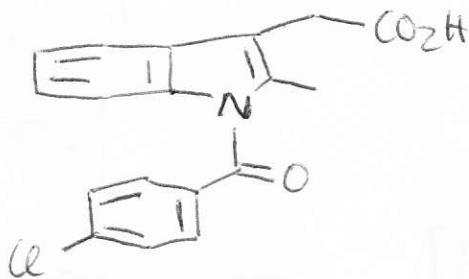
größttechnische Darstellung aus: C#CC1=CN=C1

## Pharmazeutika:

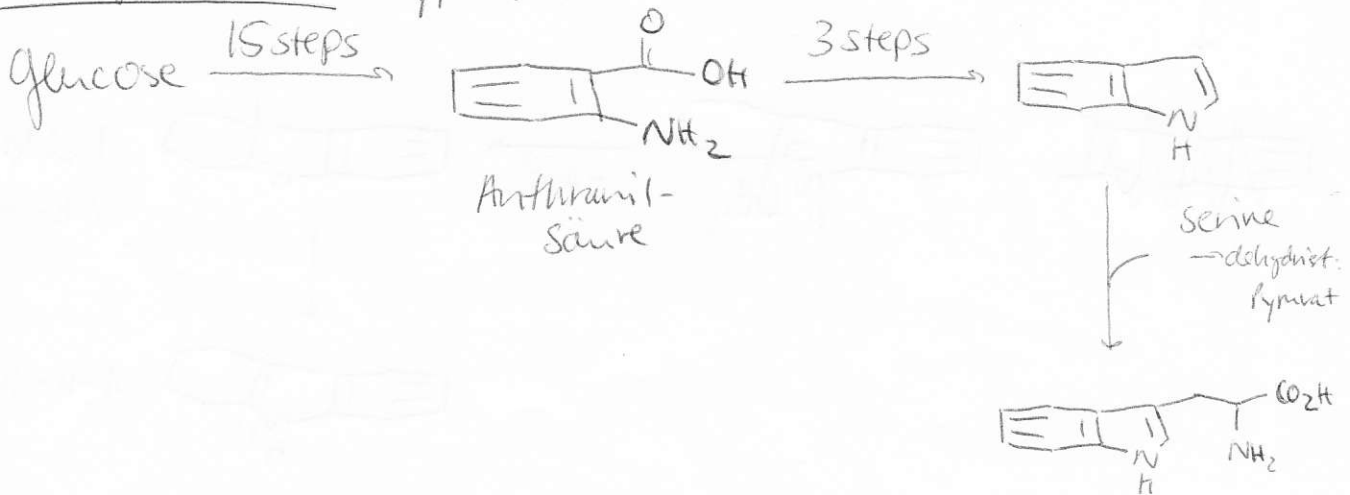
Sumatriptan (Migräne):



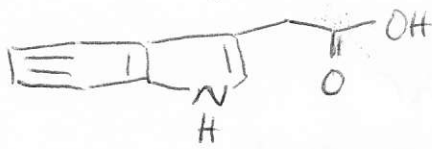
Indomethacin (rheumatische Arthritis):



## Biosynthese: Tryptophan



Indol-3-essigsäure:



Pflanzenwachstumshormon

Serotonin:



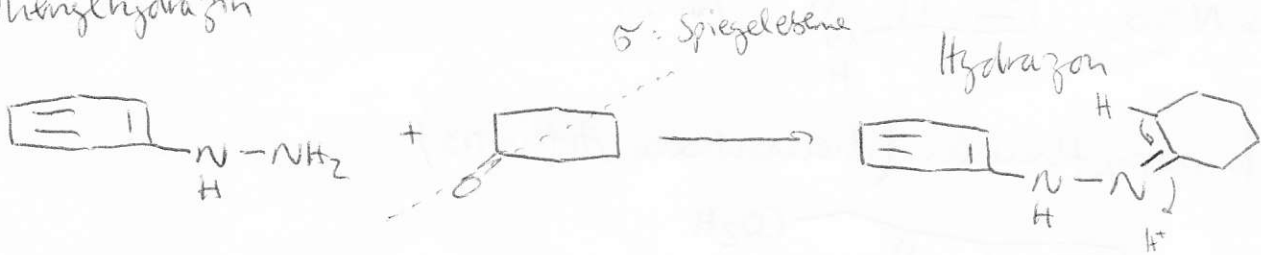
Melatonin:



Synthesen:

1) Fischer-Indol Synthese:

Methylhydrazin



Hydrazon

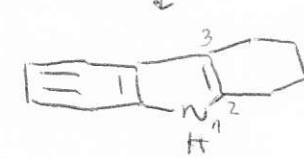
[3,3]

EtOH/H<sup>+</sup>

Eranin

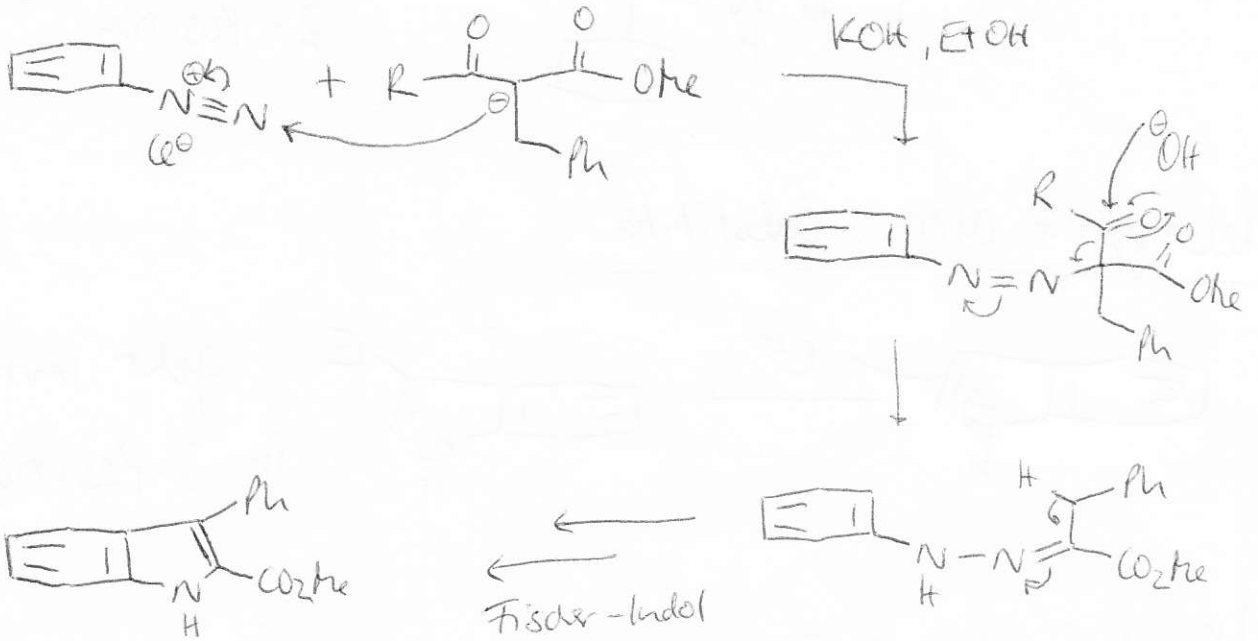
Indolemine  
3-H-indole

1-H-indole



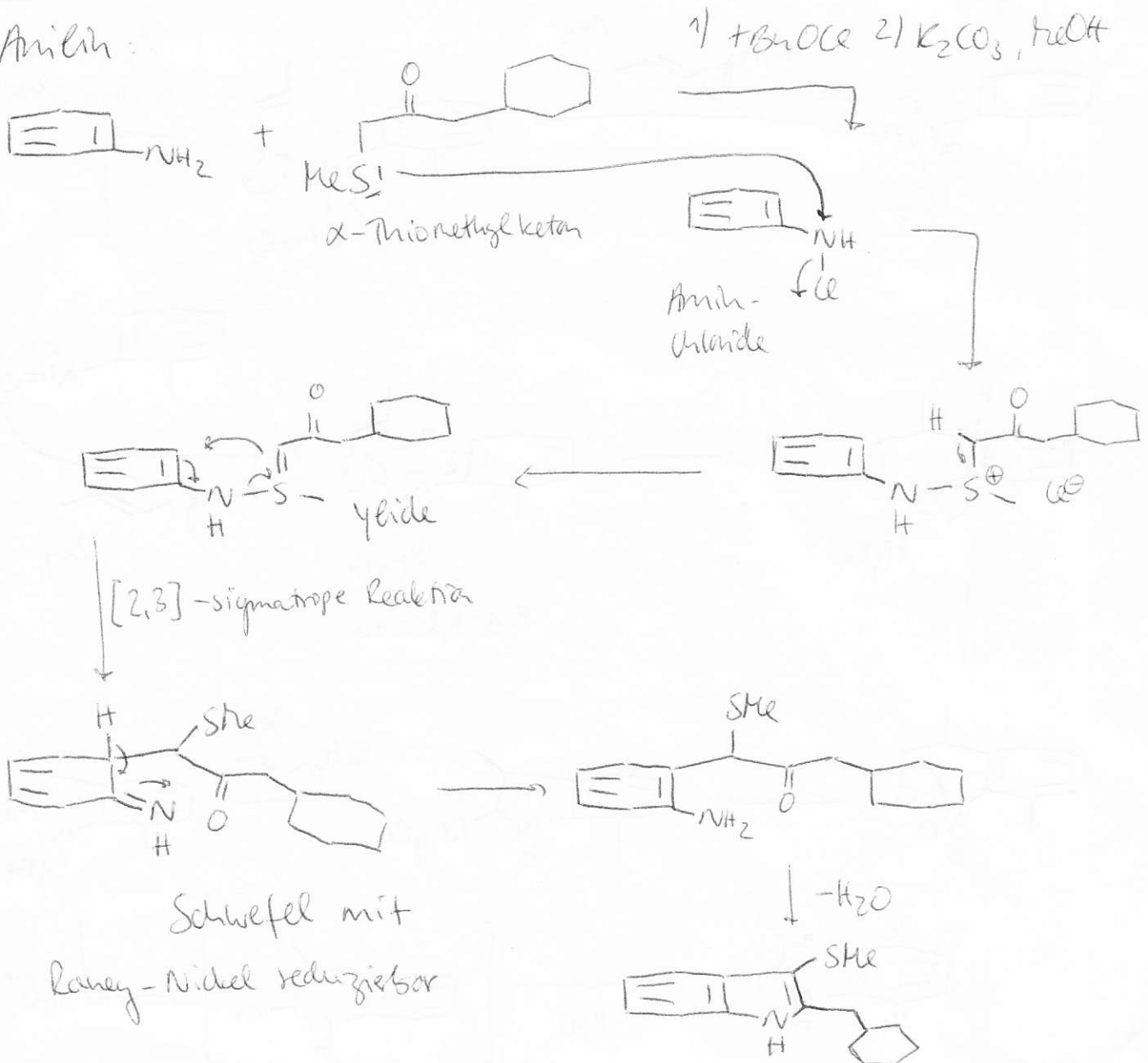
## 2) Fopp-Klingemann Reaktion:

Diazonium-Salz:

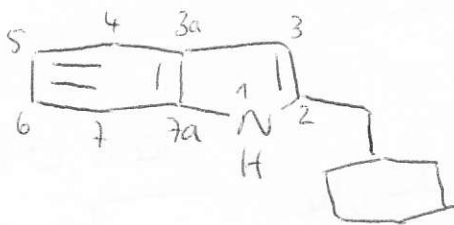


## 3) Gassmann-Indol Synthese:

Anilin:

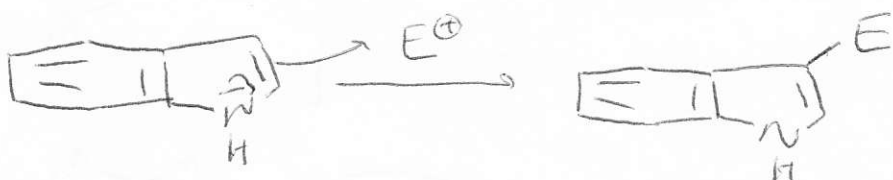


Ka/Ni →



Substituent an 2-Position

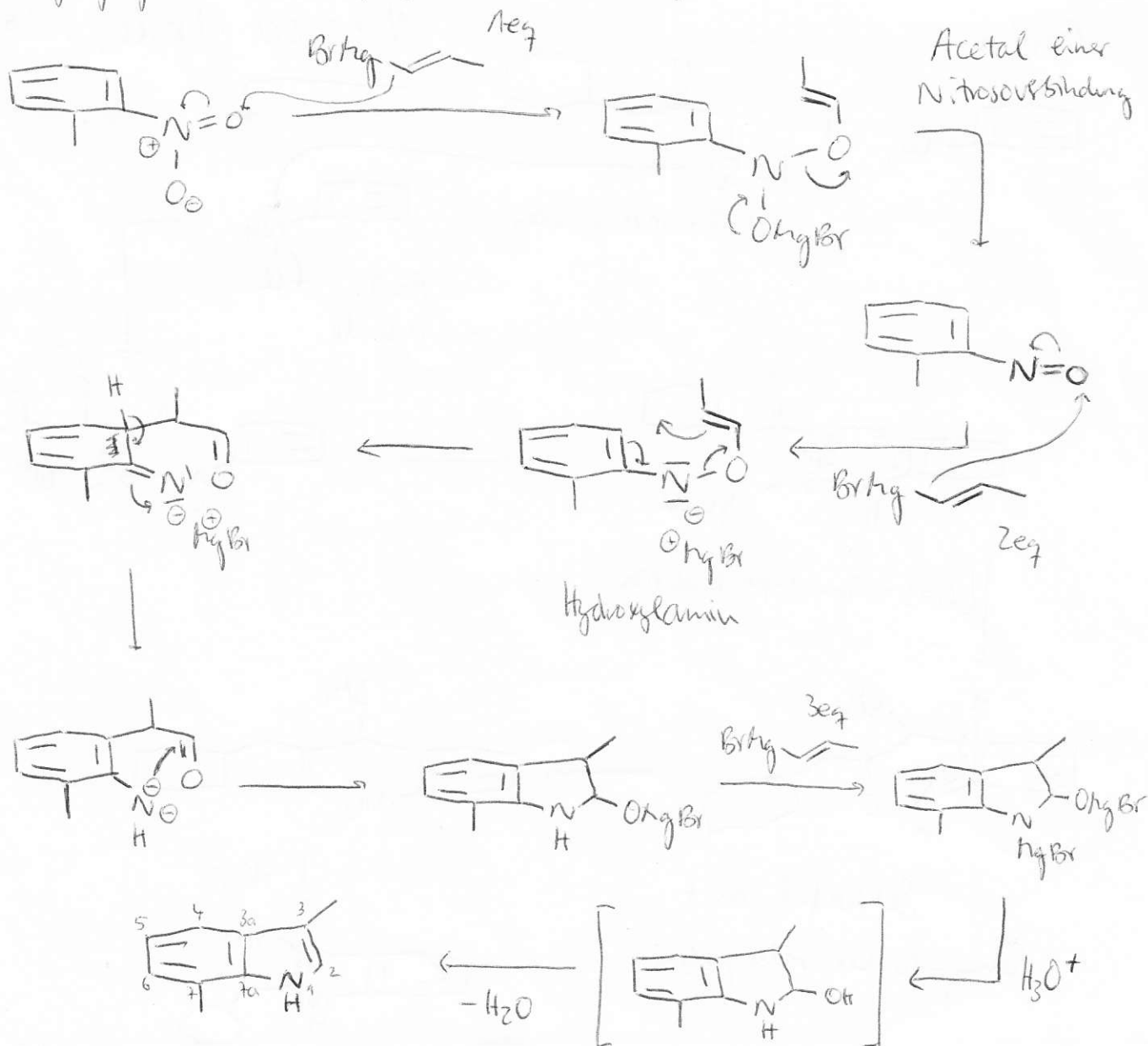
elektrophile arom. Substitution:



geht immer in 3-Position!

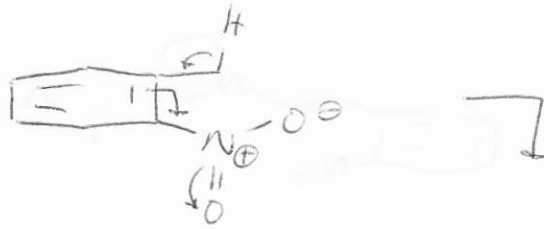
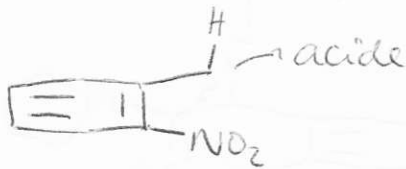
#### 4) Bartoli-Indol Synthese

Vinylnitril: keine  $\beta$ -Hydrid Eliminierung

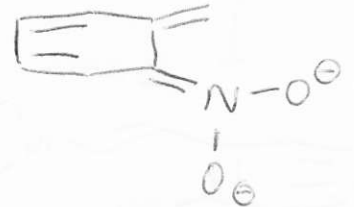


→ Indole mit Substituenten in 3er & 7er Position

Ortho-Nitro-Verschiebungen



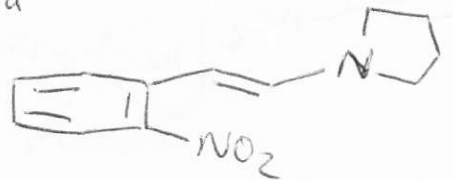
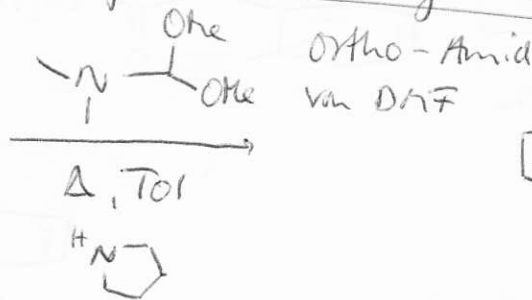
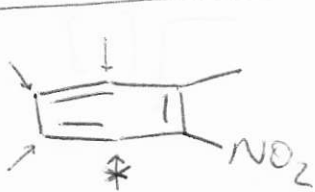
Nitrogruppe als Schutzgruppe für Indol-Stickstoff



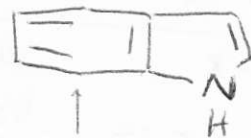
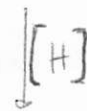
Reduktionsmethoden: Ra-Ni, Pd/C/H<sub>2</sub>, SnI<sub>2</sub>, Zn/EtOAc, In/NH<sub>4</sub>Cl, etc.

Über Acidität leicht funktionalisierbar

5) Bartsch - Leimgruber Indol Synthese:

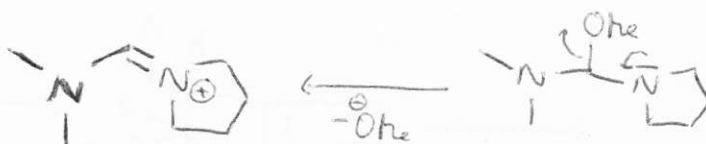
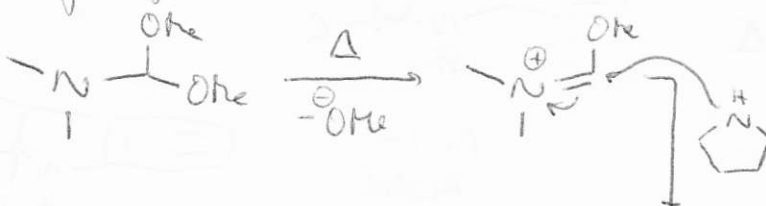


Aromat beliebig substituierbar

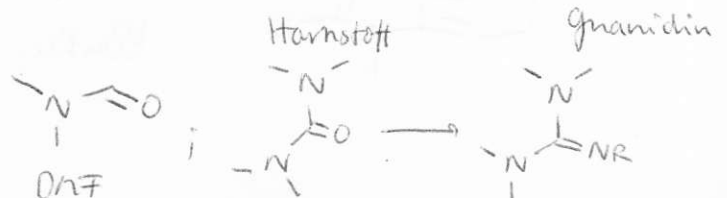


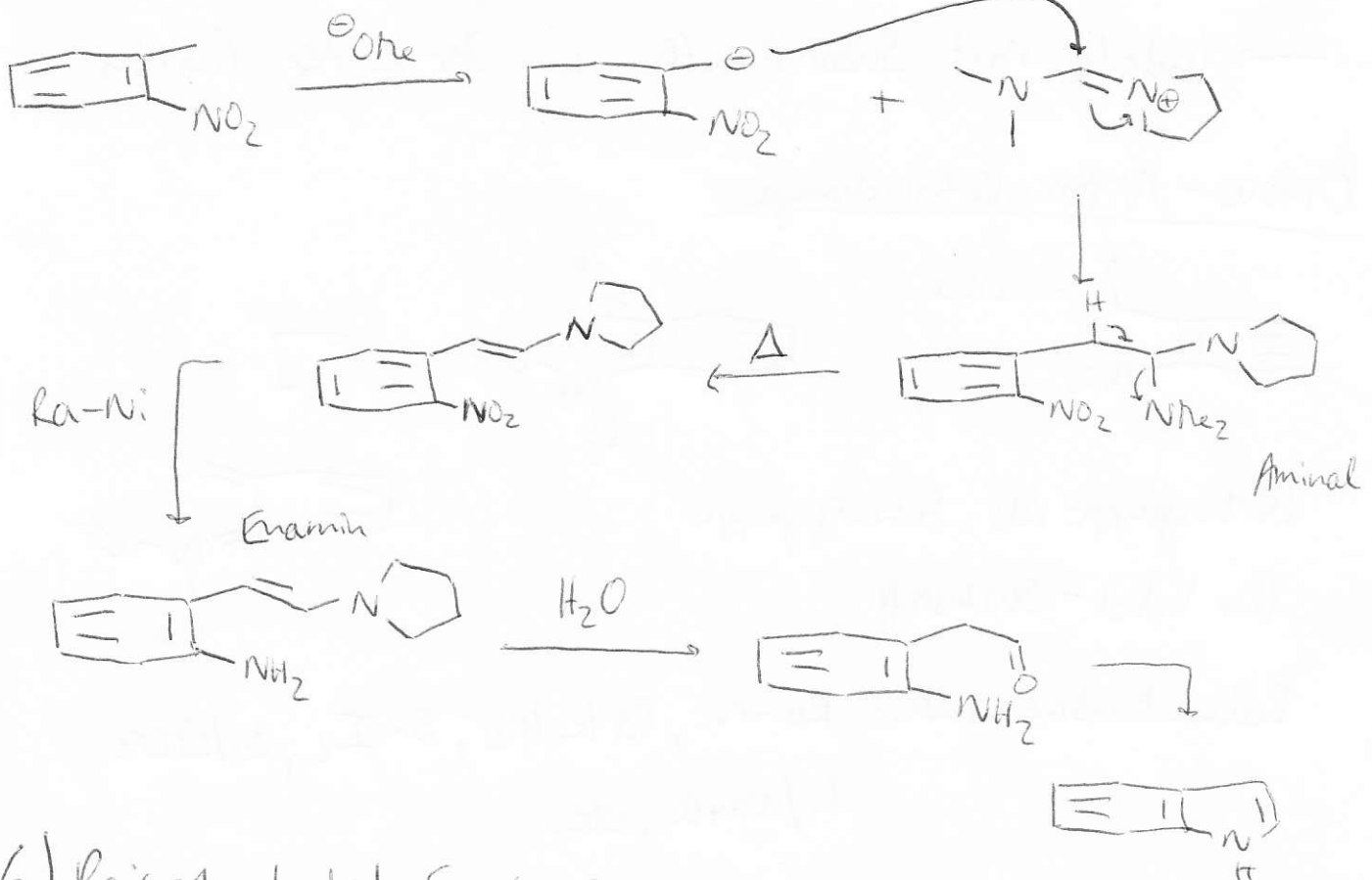
kein Alkylierer

Vorgelagerte Reaktion:

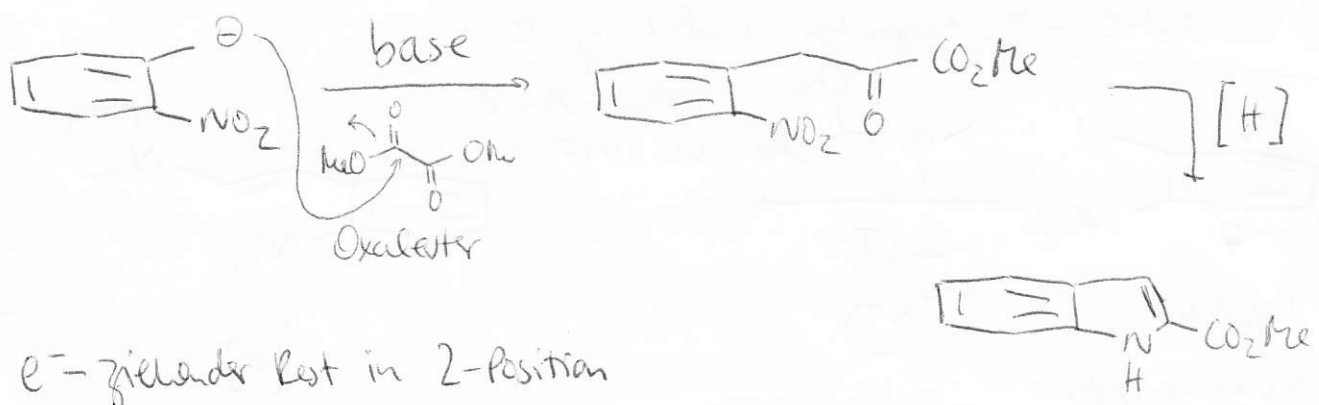


Amidin: Ox-Stufe einer Carbonsäure

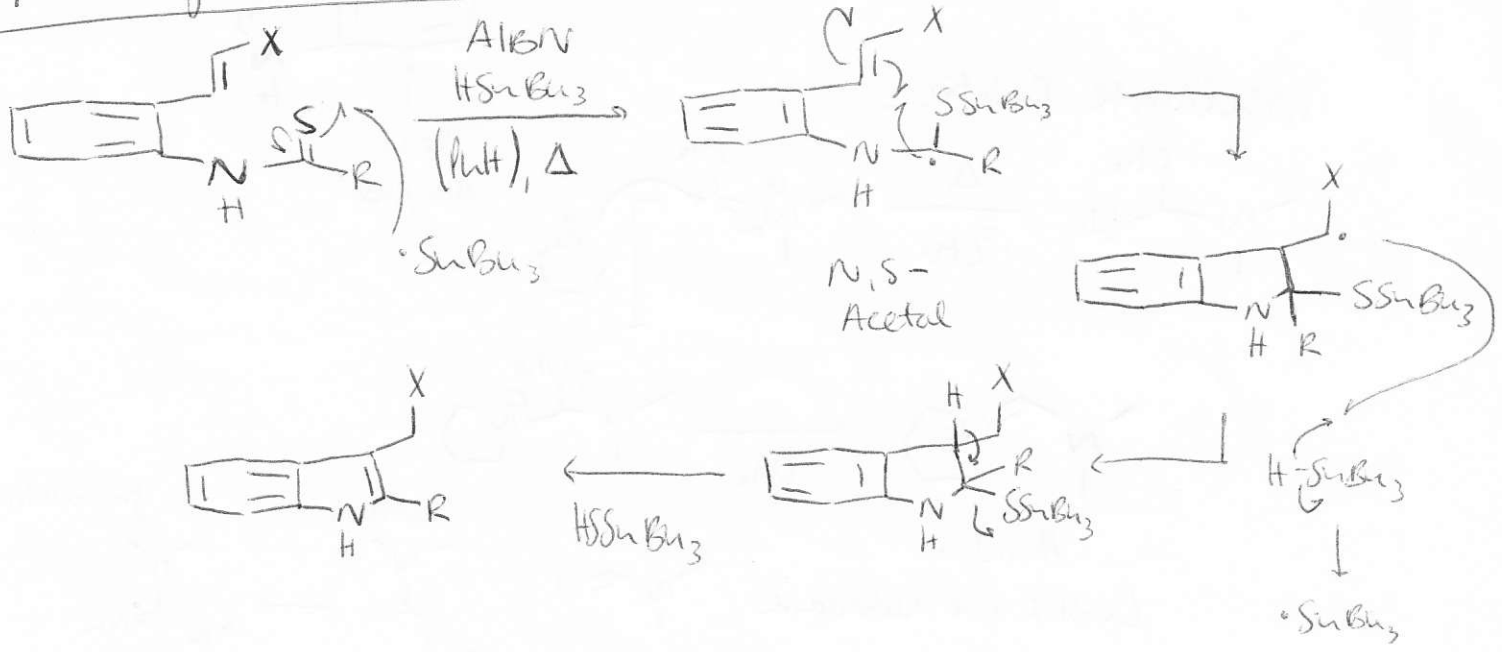




6) Reissert-Indol Synthese:



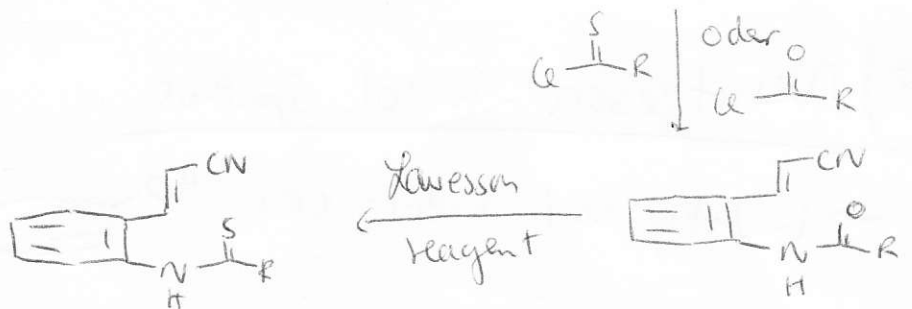
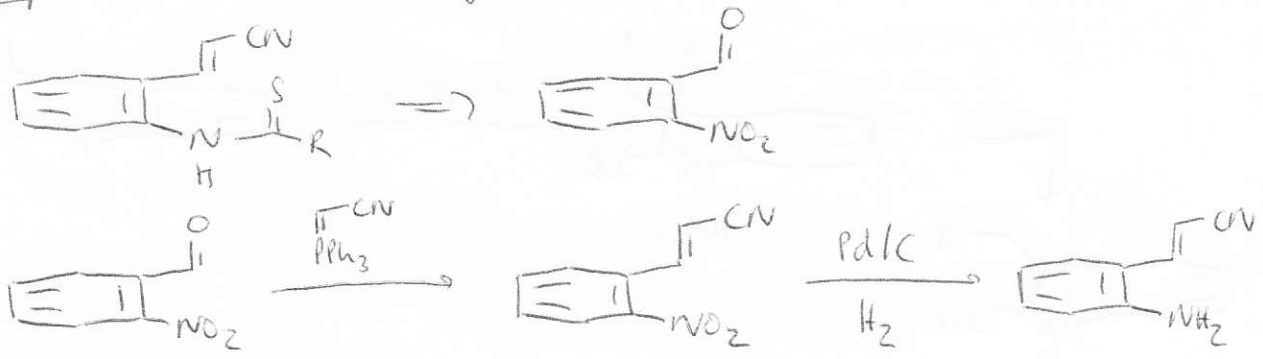
7) Fukuyama-Indol Synthese:



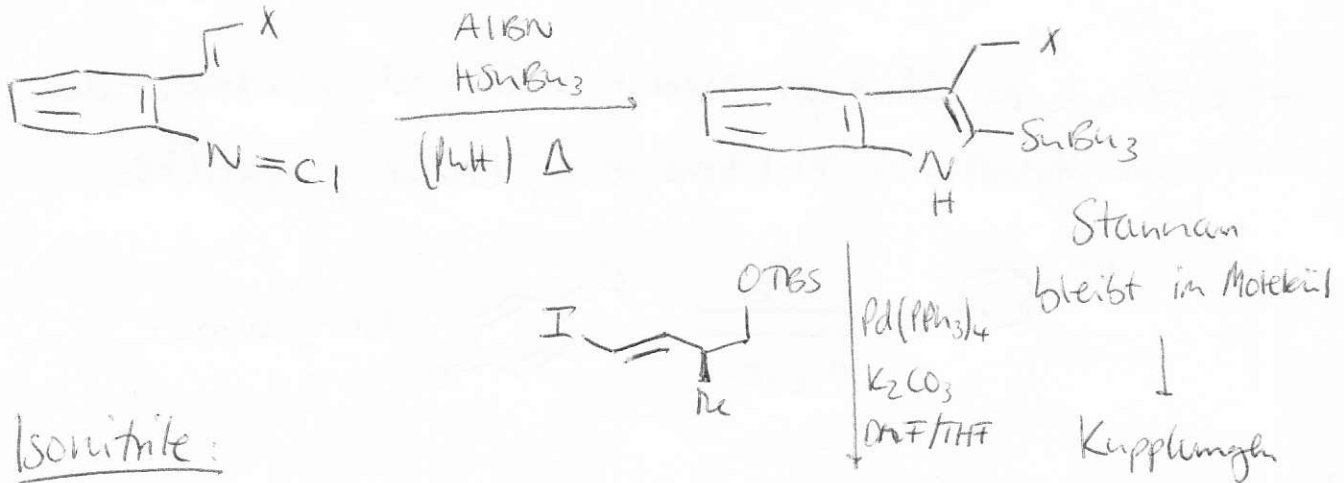
X ist limitiert: muss Radikal stabilisieren können

→ X = EWG (CN, CO<sub>2</sub>Me, CO<sub>2</sub>R)

Synthese der Verbindungen:



Variante mit Isocyanid:



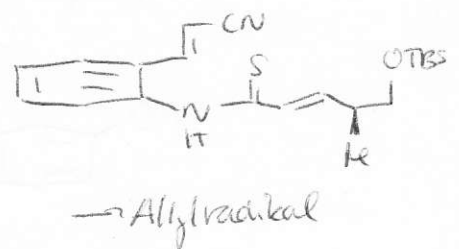
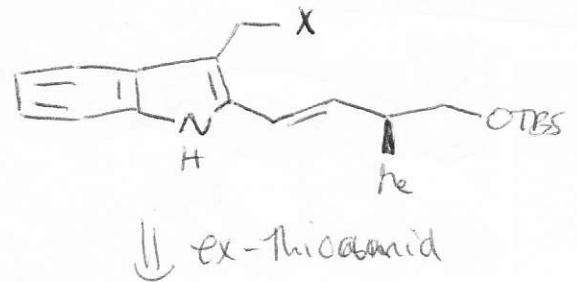
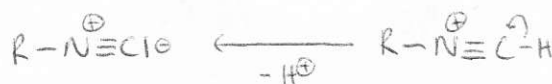
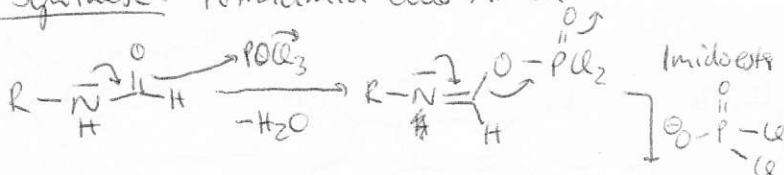
Isocyanide:

R-N=C Carbenoide Form

↓

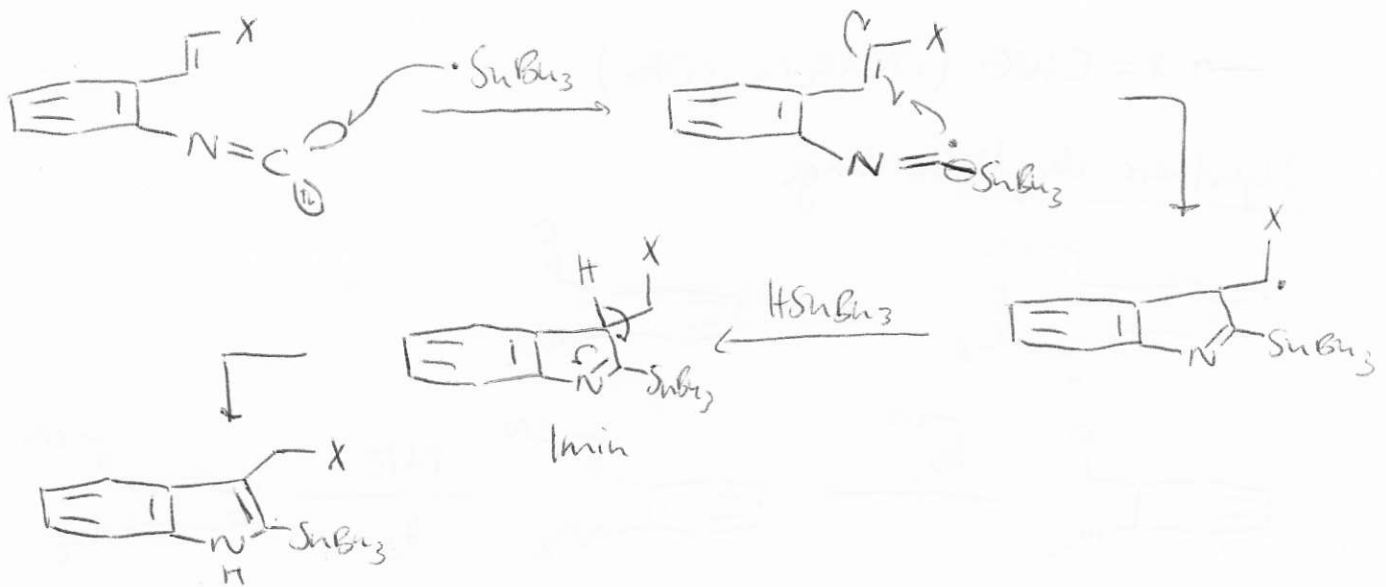
R-N<sup>+</sup>≡C<sup>-</sup>O<sup>-</sup> zwitterionide Form

Synthese: Formamid aus Amin





# Mechanismus:



## 8) Nenitzescu - Indol Synthese

→ wichtig weil Indol-core:   
HO-Indol-core:  $\text{R}^1, \text{R}^2, \text{R}^3$

Funktionalität sämtlicher Neurotransmitter

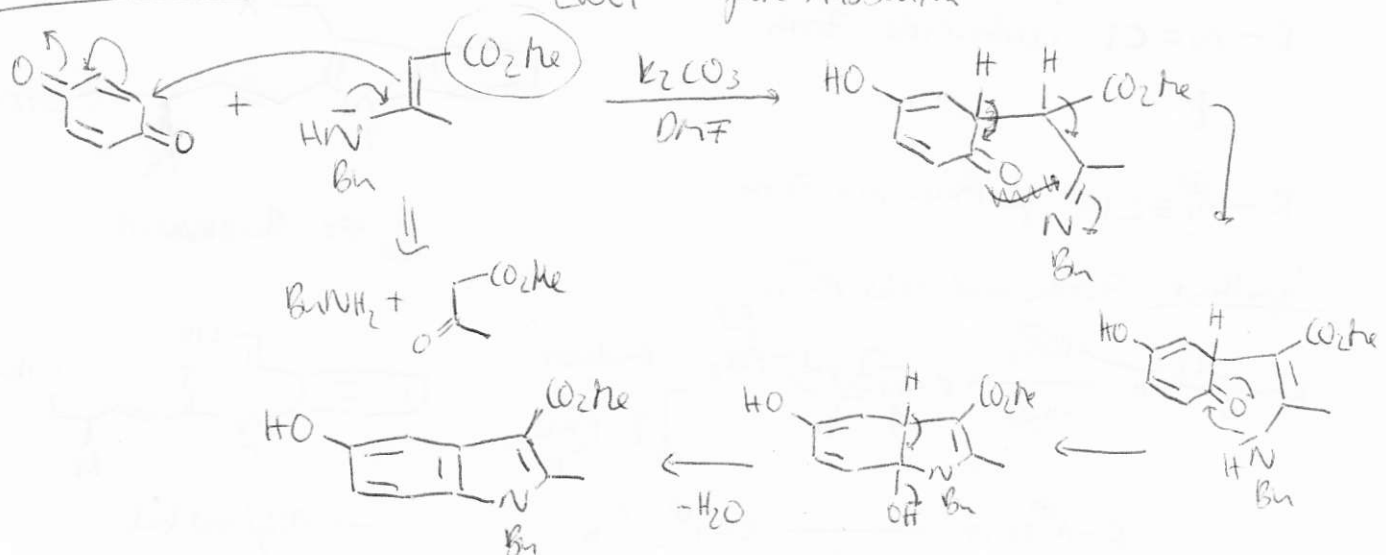
→  $e^-$ -Druck der OH-Gruppe macht Indol noch elektronenreicher

→ para-Hydrochinon: elektronenreich, leicht zu oxidieren

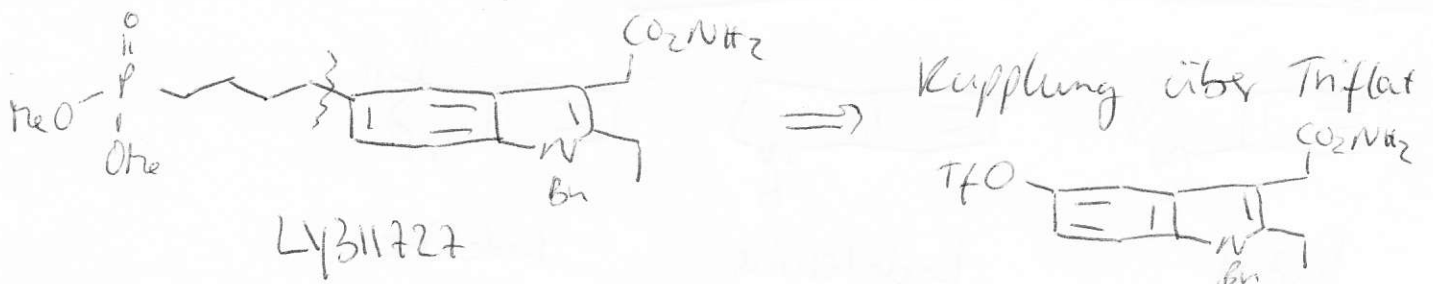


## Mechanismus:

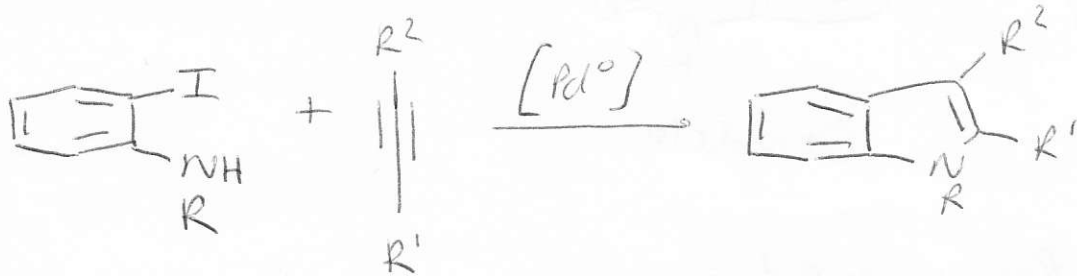
EWG → gute Absenten



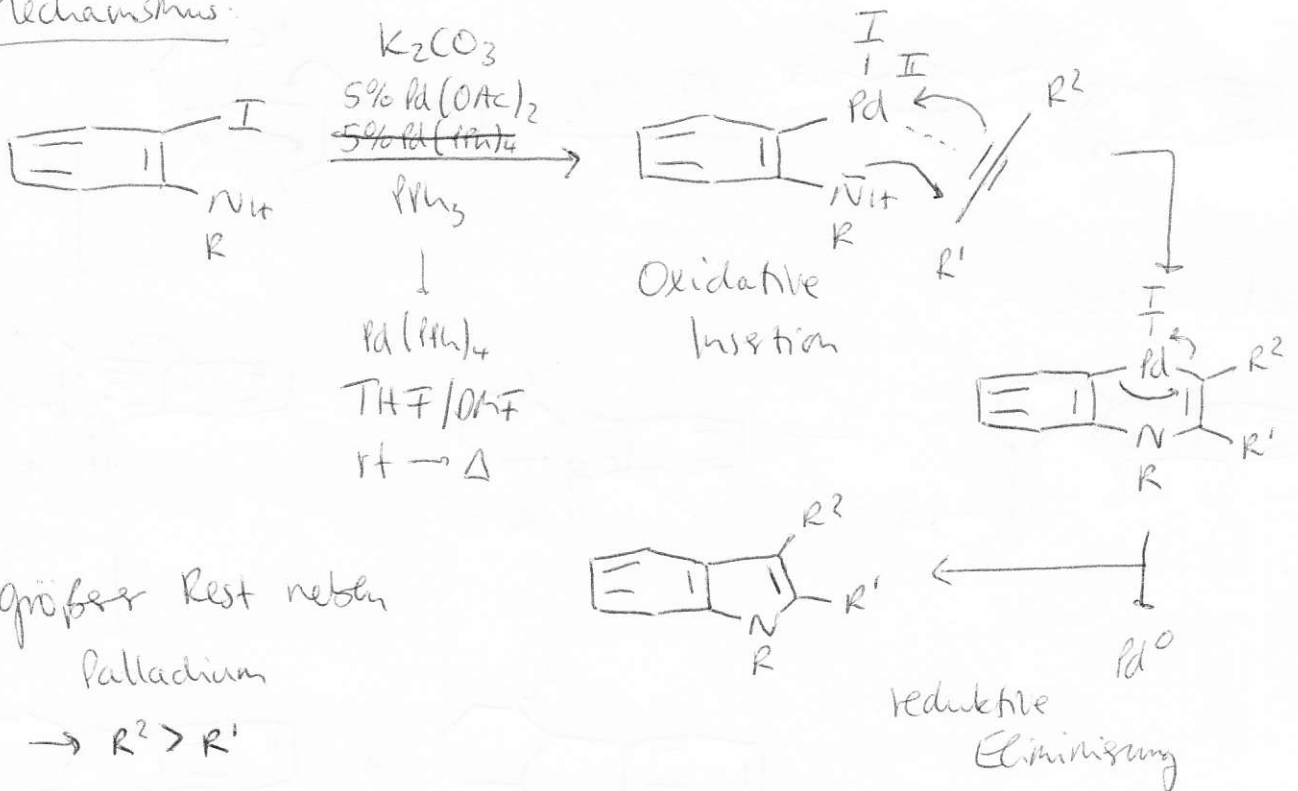
andere Alkylsubstituenten



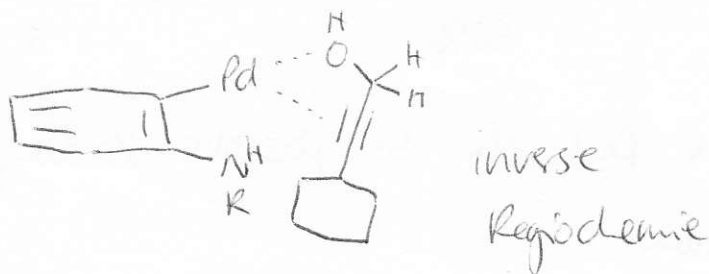
9) Larock-Indol Synthese:



Mechanismus:



Koordinierung über Propargyl-Alkohol:



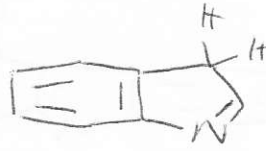
# Indolformen in der Natur:



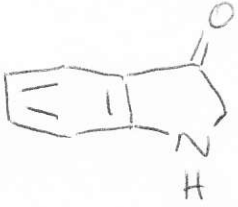
Indol



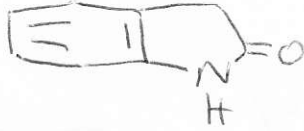
Indolenine



Indoline

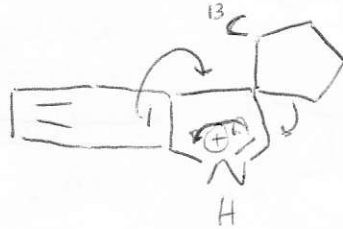
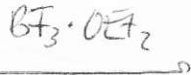
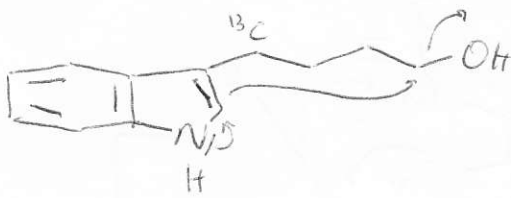


Indoxyl

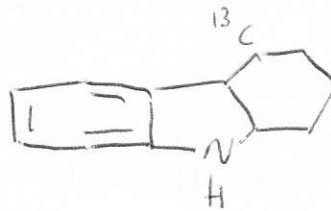
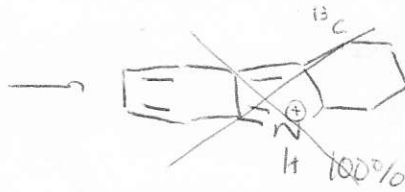


Oxindole

## Plancher-Rearrangement:

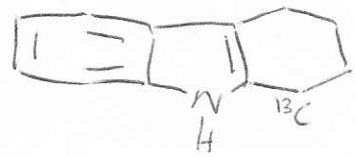


not observed:



50%

+



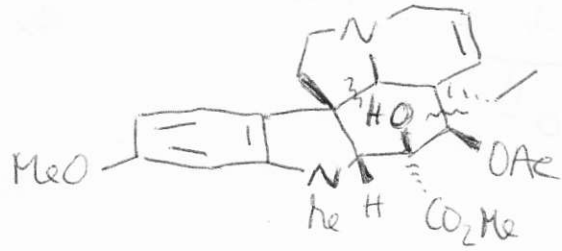
50%

→ es wandert immer der Rest, der die positive Ladung besser stabilisieren kann

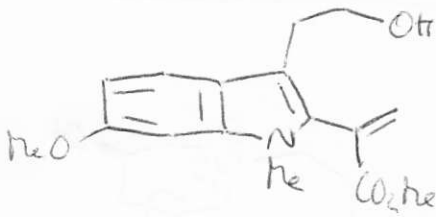
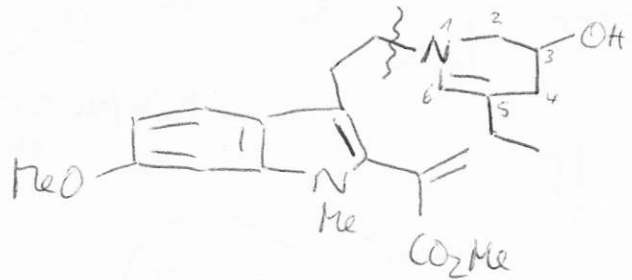
# Vindoline-Synthese: T. Fukuyama et al.

Synlett, 2000, 883

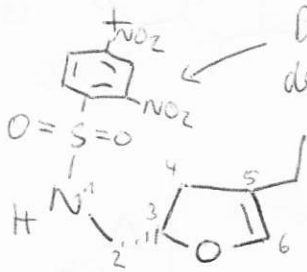
Anti-Tumor activity



DA

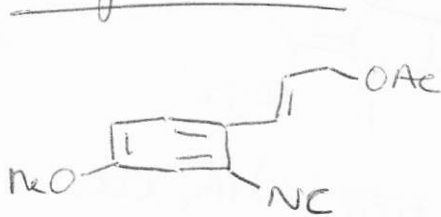


Sn<sub>2</sub>

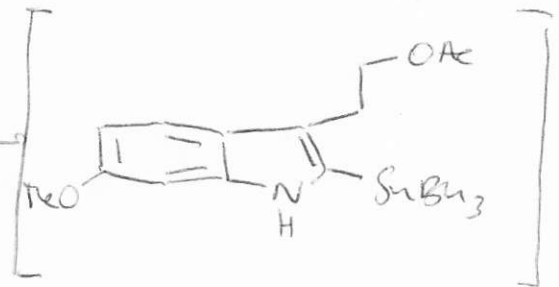


Dinitroverbindung um Acidität des Stickstoffs für Mitsunobu verwenden zu können

## Synthese:



1) Bu<sub>3</sub>SnH  
AIBN  
80°C, MeCN  
~~H<sub>2</sub>~~ I<sub>2</sub>



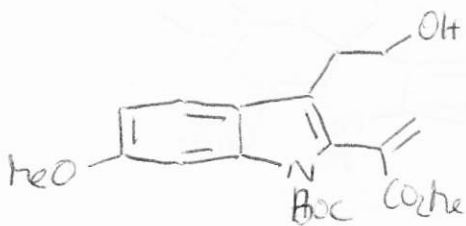
2) Boc<sub>2</sub>O, DMAP

3) K<sub>2</sub>CO<sub>3</sub>, MeOH

4) BuPd(PH<sub>3</sub>)<sub>2</sub>Cl

Ph<sub>3</sub>As, CuI

Bu<sub>3</sub>Sn  $\parallel$  CO<sub>2</sub>Me  
67%

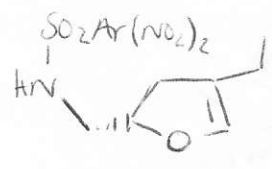


79%

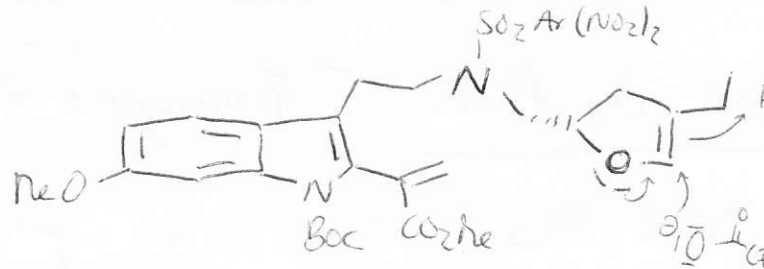


5) DEAD,  $PPH_3$

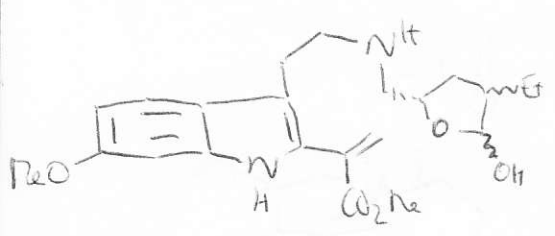
$PhH, rt$



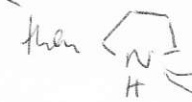
89%



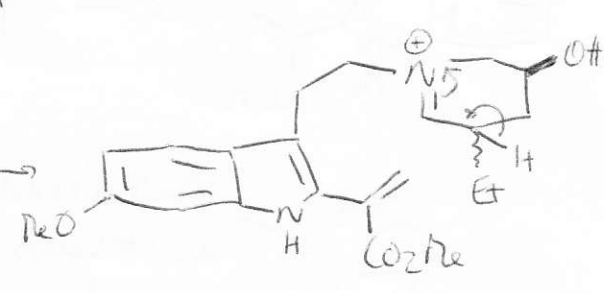
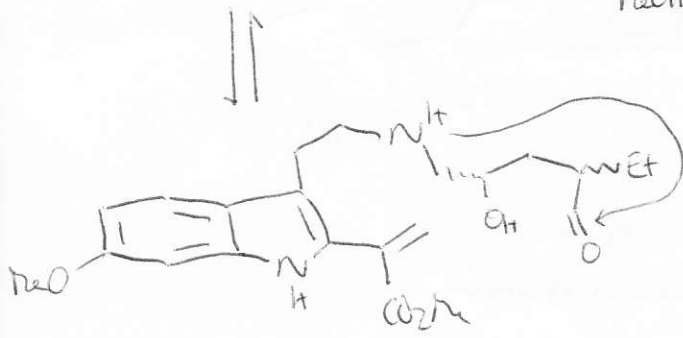
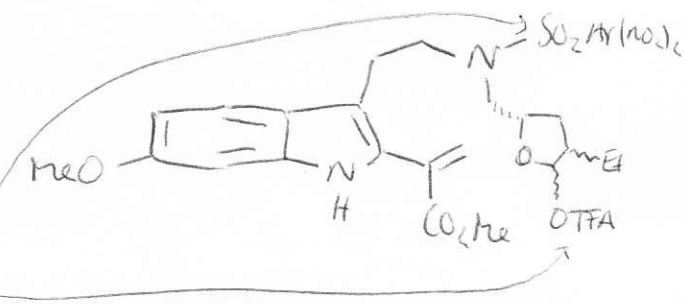
6) TFA, DCM  
 $rt, 15'$



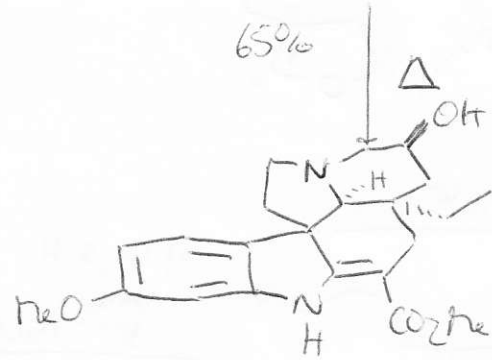
then Rot



$NaOH / MeCN = 5:1$   
 $rt$



Stereochemie definiert  
vom Alkohol

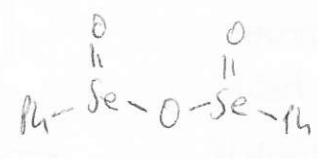
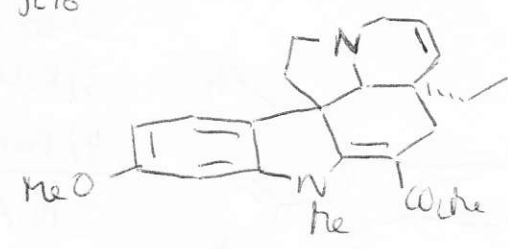


65%

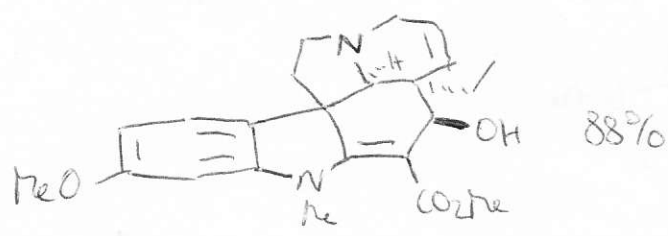
7)  $MeI, KO^+Bu$   
 $THF, rt$

6)  $PPH_3, CCl_4$   
 $MeCN, 70^\circ C$

92%

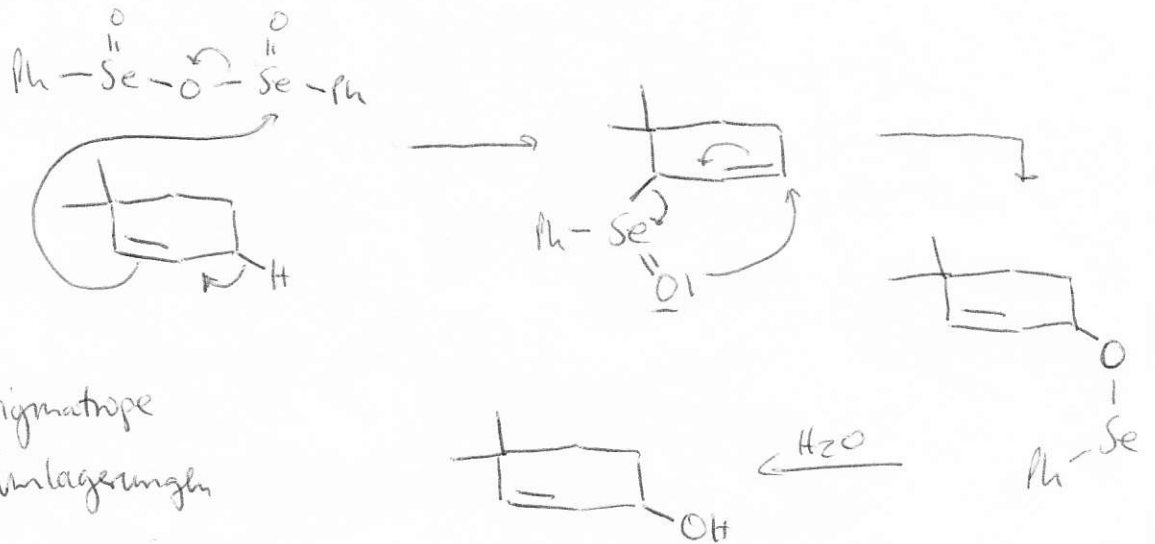


$80^\circ C, PhH$



88%

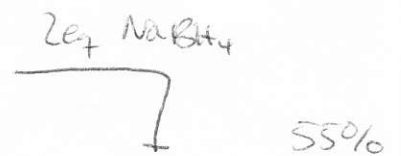
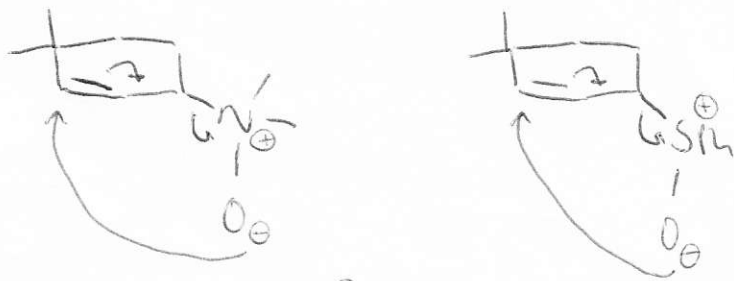
Allylische Oxidation:



→ Analoge Reaktionen: Wittig-Still

Cope-Umlagerung:

Evans-Mieslow:



Oxidation zum N-Oxid geht schneller → 2eq

(-)-Vindoline