



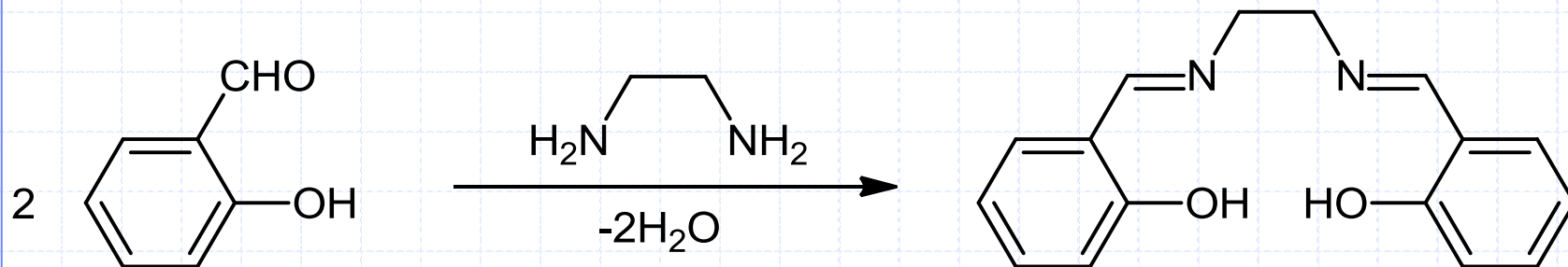
Katedra za farmacevtsko kemijo

Sinteza mimetika encima SOD

1. stopnja: H_2 salen



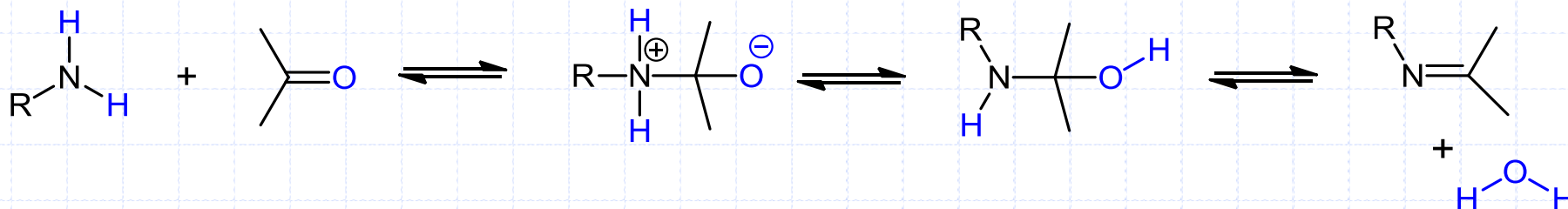
Sinteza N,N' -bis(saliciliden)etilendiamina



- ◆ Predlagajte orositveni reagent za detekcijo poteka reakcije in za selektivno detekcijo salicilaldehida.
- ◆ Kateri tip reakcije poteče med etilendiaminom in salicilalhidom?
- ◆ Zakaj uporabljamo brezvodni etanol in ne 96%?

Mehanizem reakcije

- ◆ Alkilamino-de-okso-bisubstitucija (IUPAC ime reakcije)
- ◆ Tvorba **imina** (Schiff-ove baze) iz amina in aldehida
- ◆ Poteče nukleofilna adicija amina na karbonilno skupino aldehida s sledečim prenosom protona iz dušika na kisik do nastanka nestabilnega **karbinolamina** ali **hemiaminala**. Pri primarnem aminu se odcepi voda (eliminacija) in nastane **imin**.
- ◆ Reakcija je v celoti reverzibilna. Ravnotežje pomaknemo na stran produktov tako, da odstranjujemo vodo z azeotropno destilacijo, molekularnimi siti ali TiCl_4 .



Postopki za odvajanje vode

Sušilna sredstva: Na_2SO_4 , MgSO_4 , CaCl_2 , ...

Molekularna sita: 0,3 ali 0,4 nm

Kislina: H_2SO_4 (večkrat katalizator in sušilno sredstvo hkrati)

Azeotropna destilacija (Dean-Starkova past)

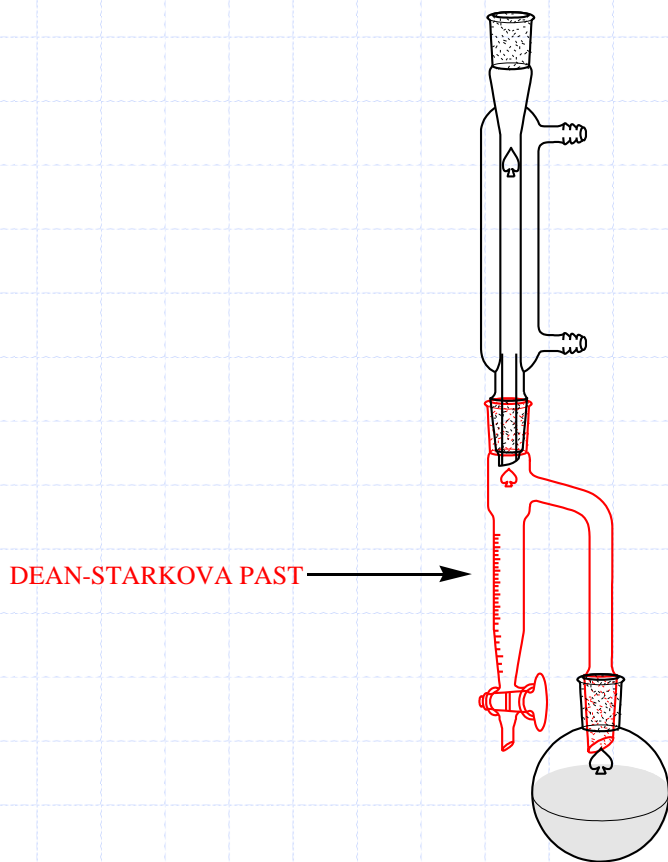
◆ Benzen/ H_2O – 9% vode v azeotropni zmesi, $T_v(\text{benzen})=80^\circ\text{C}$,
 $T_v(\text{az.})=69^\circ\text{C}$

◆ Toluen/ H_2O – 20% vode v az. zmesi, $T_v(\text{az.})=84,2^\circ\text{C}$

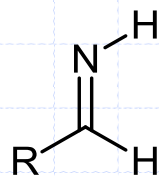
◆ CCl_4 / H_2O – 4% vode v az. zmesi, $T_v(\text{az.})=66^\circ\text{C}$

- Kaj so azeotropne zmesi?
- Homogena, heterogena azeotropna destilacija?
- Pozitivni, negativni azeotropi?

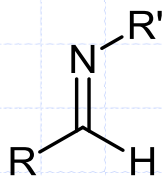
Dean-Starkova past



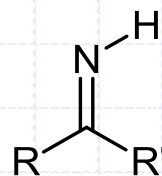
Imini - nomenklatura



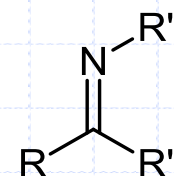
primarni aldimin



sekundarni aldimin

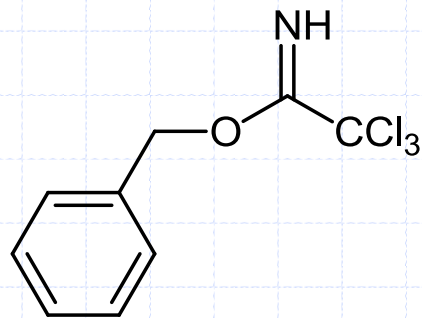


primarni ketimin



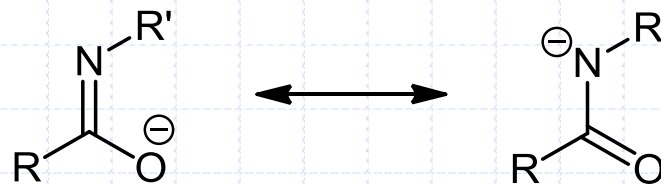
sekundarni ketimin

Starejši izraz: Schiff-ova baza



Benzil-trikloro-acetimidat

Imidati ali imino etri so imini s kisikom povezanim z ogljikom.



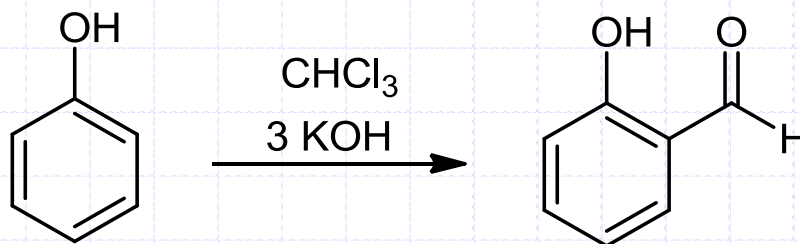
amidat

Amidati so amidni enolati.

<http://en.wikipedia.org/wiki/Imine>

Salicilaldehid

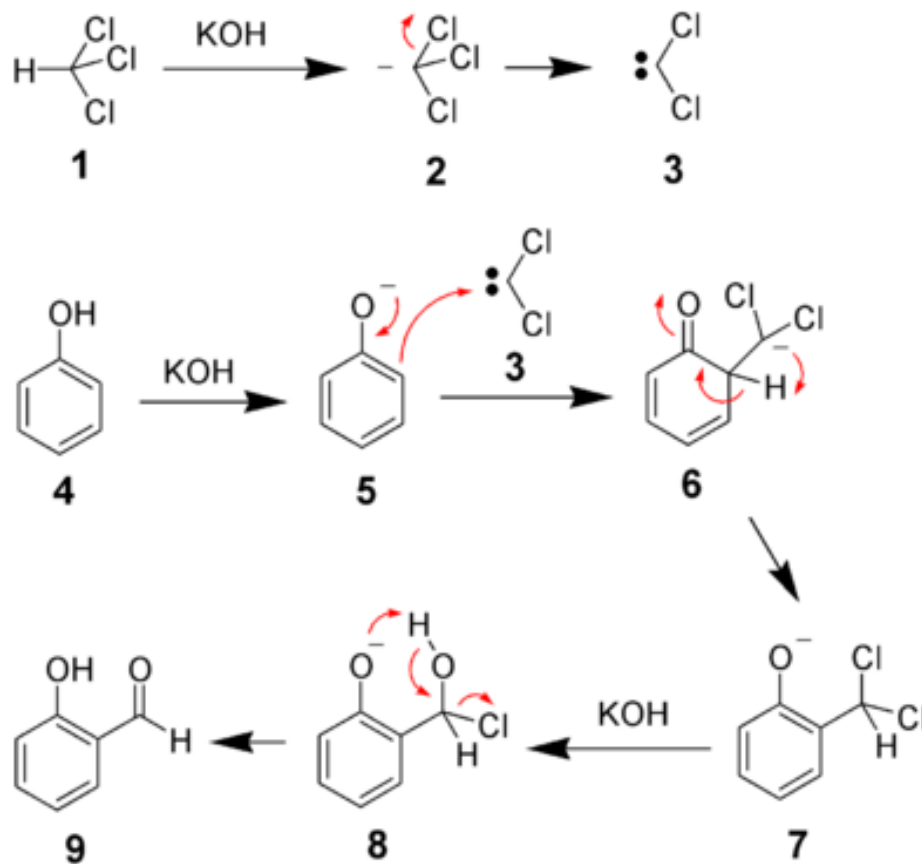
Sinteza (Reimer-Tiemann-ova reakcija):



Kakšen je mehanizem reakcije?

<http://en.wikipedia.org/wiki/Salicylaldehyde>

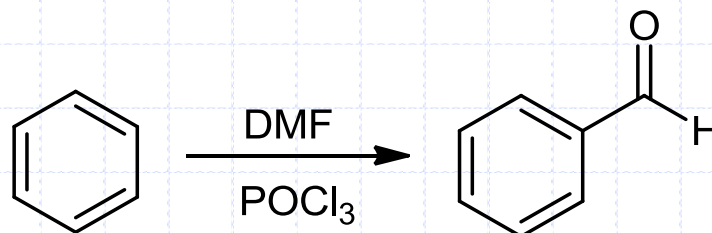
Mehanizem Reimer-Tiemann-ove reakcije



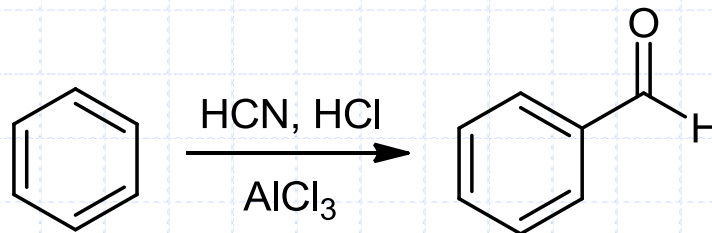
Kloroform (**1**) reagira z močno bazo do kloroform karboaniona (**2**), ki hitro vstopa v alfa-eliminacijo in daje **diklorokarben (3)**.
Diklorokarben reagira s fenolatom (**5**) na orto-poziciji do diklorometil substituiranega fenola (**7**).
Po alkalni hidrolizi se tvori želeni produkt (**9**).

Ostale metode za formiliranje aromatskega obroča

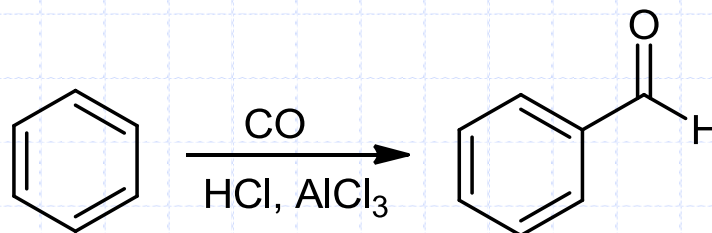
Vilsmeier–Haack-ova reakcija:



Gattermann-ova reakcija:

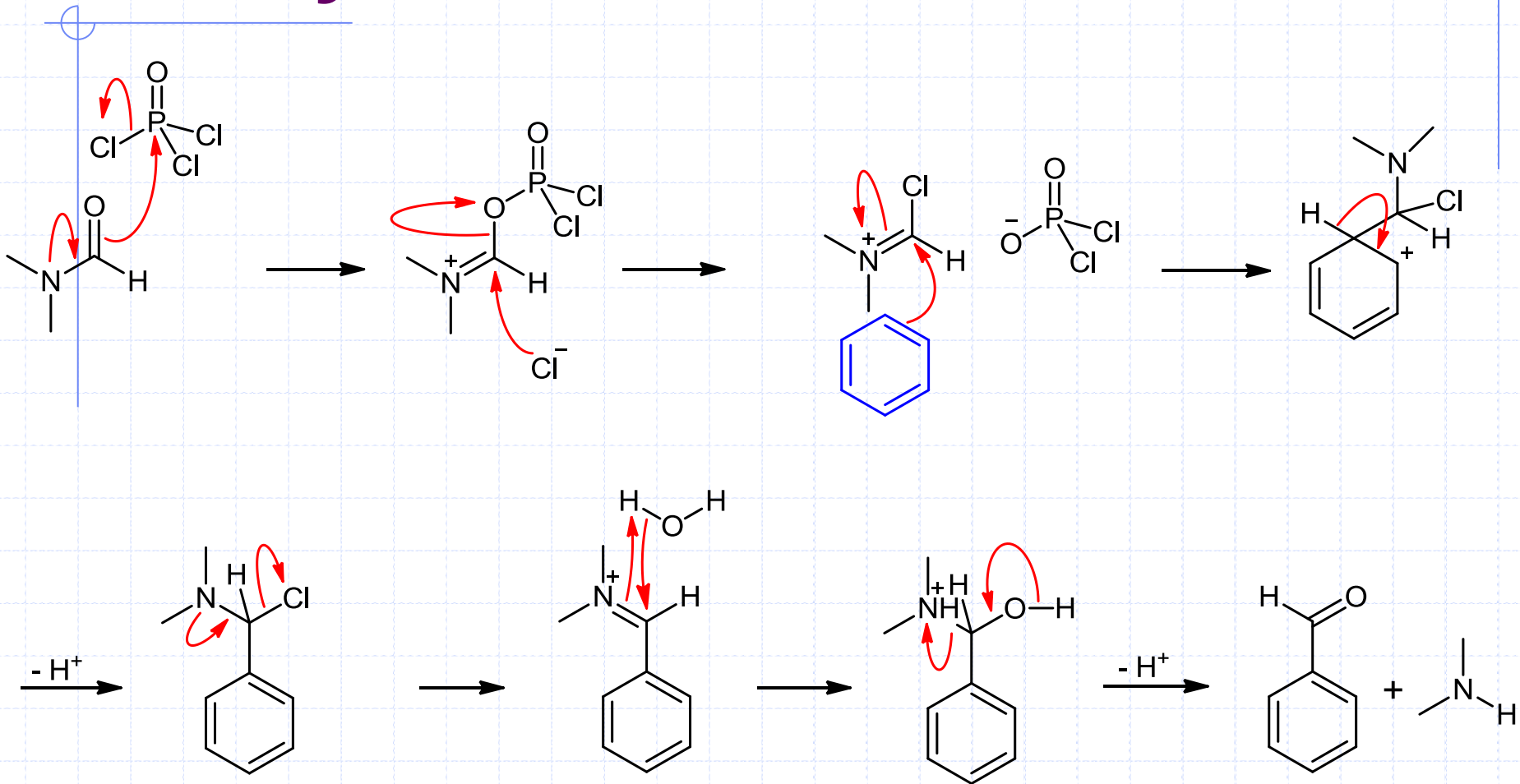


Gattermann-Koch-ova reakcija:

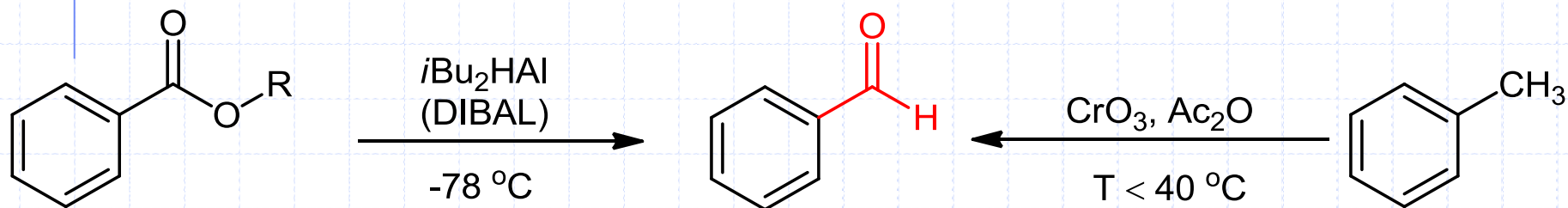


Name reactions: a collection of detailed reaction mechanisms

Mehanizam Vilsmeier–Haack-ove reakcije:

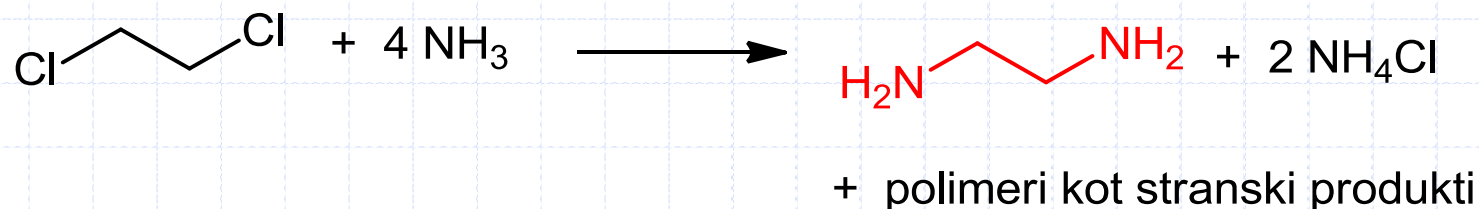


Alternativne metode za sintezo (derivatov) benzaldehida

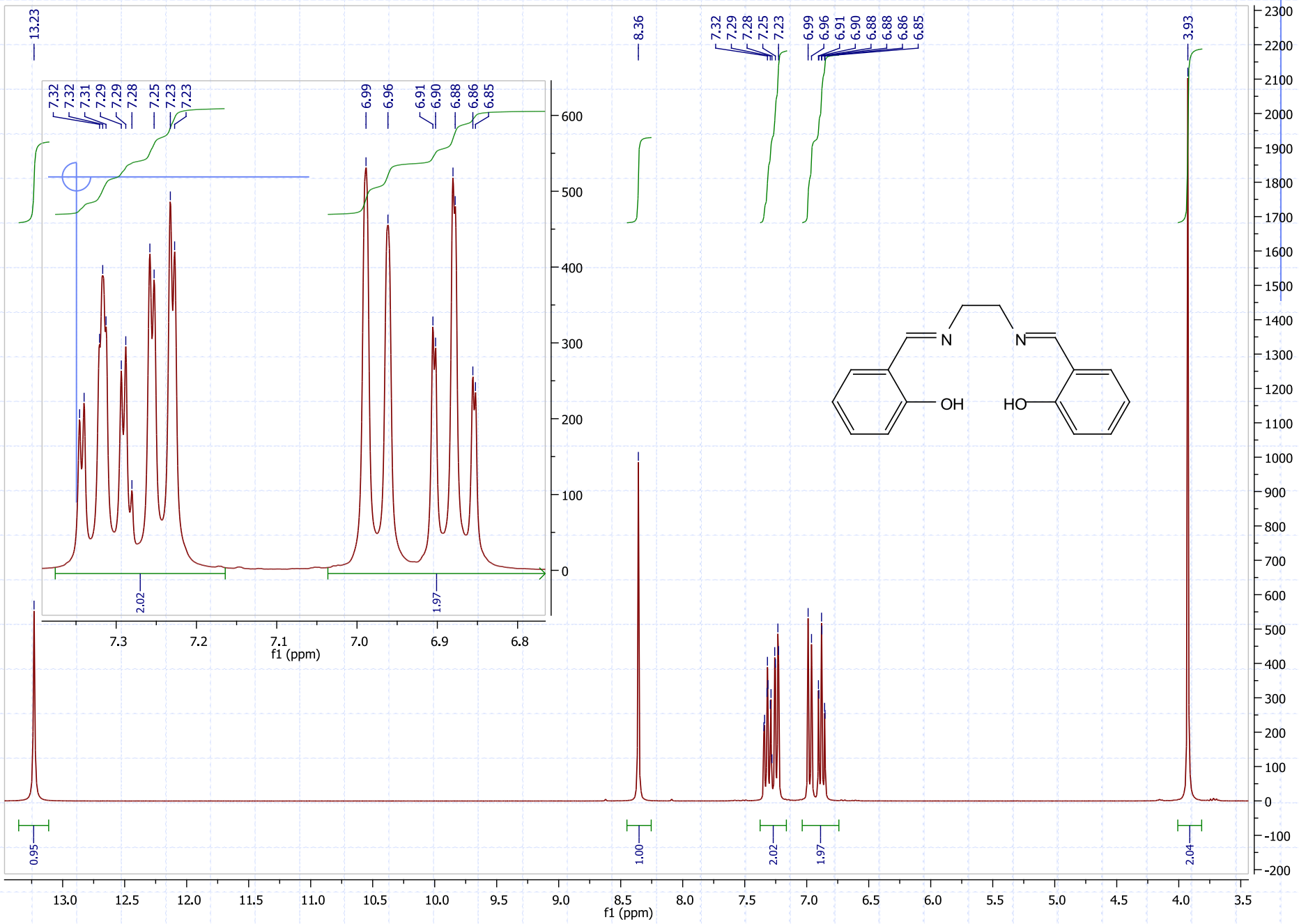


Etilendiamin

Sinteza:



- Derivate tvori s karboksilnimi kislinami, nitrili, CS_2 , aldehidi in ketoni.
- Bifunkcionalen - pogosto tvori heterocikle (npr. imidazolidin)
- Kelator za tvorbo koordinacijskih spojin



EDTA

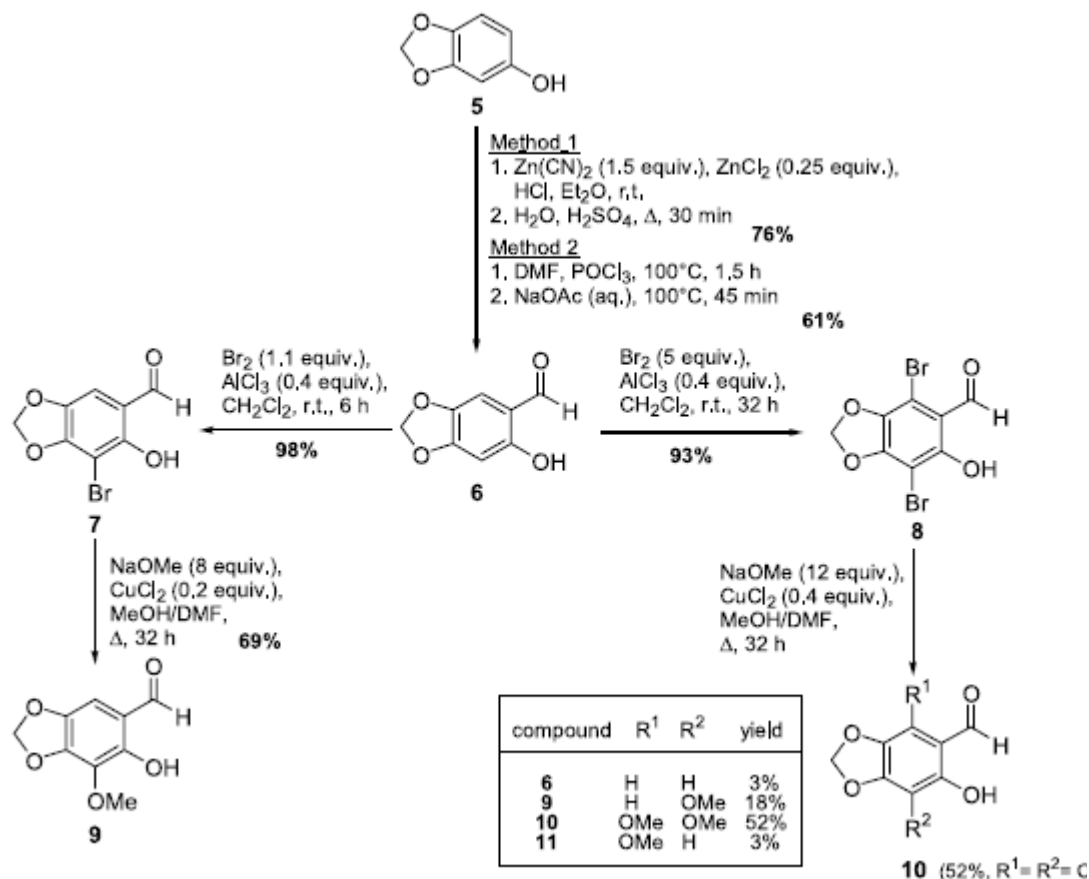
- ◆ Sintetizirajte etilendiamintetraocetno kislino iz:
 - Etilendiamina in kloroocetne kisline
 - Alternativa: Etilendiamina, formaldehida in NaCN

Salicilaldoksim – kelator ionov elementov prehodnih kovin

- ◆ Sintetizirajte salicilaldoksim iz fenola in hidroksilamina.

Angleški tekst - predpis

D. Maes et al. / Tetrahedron 61 (2005) 2505–2511



4.2. Synthetic procedures

4.2.1. 2-Hydroxy-4,5-methylenedioxybenzaldehyde 6. Gattermann procedure. Dry hydrogen chloride was bubbled through a stirred suspension of sesamol **5** (4.14 g; 30 mmol), zinc(II) cyanide (5.28 g, 45 mmol), zinc(II) chloride (1.02 g; 7.5 mmol) and a trace of sodium chloride in 100 ml of diethyl ether. To prevent the in situ formed hydrogen cyanide from escaping, the flask was connected to a condenser, cooled with ice water. After the formation of a green precipitate the solution is additionally treated with dry hydrogen chloride gas for 30 min. The ether was decanted and the precipitate was rinsed thoroughly with ether. The formed iminium salt was dissolved in 75 ml of water. A few drops of concentrated sulfuric acid were added and the resulting mixture was heated to 100 °C for 30 min. The reaction mixture was cooled to room temperature and the formed crystals were filtered off. The crystals were dissolved in dichloromethane and the solution was dried over magnesium sulfate. After filtration and evaporation of the solvent 3.76 g (76%) of pure 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** was obtained.

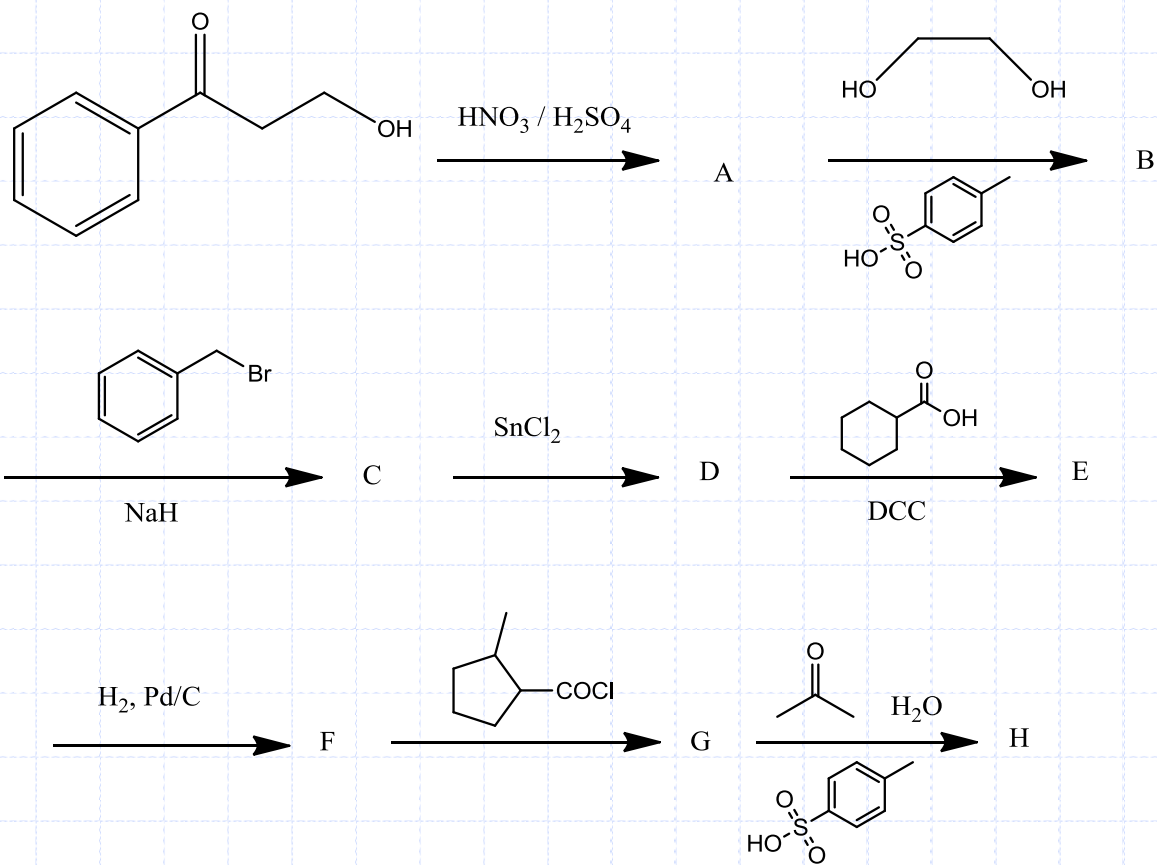
Vilsmeier procedure. Sesamol (4.14 g, 30 mmol) was dissolved in *N,N*-dimethylformamide (24 ml). At 0 °C 16 ml of phosphoroytrichloride was added. The resulting mixture was stirred for 1 h at 100 °C. After cooling, the reaction mixture was poured into 250 ml of a saturated sodium acetate solution and heated for 45 min at 100 °C. The reaction mixture was cooled down again and the precipitate was filtered off. The precipitate was recrystallized from ethanol, giving 3.02 g (61%) of pure 2-hydroxy-4,5-methylenedioxybenzaldehyde **6** as white needles.

Mp (°C): 127 (lit. 125–126¹⁸). IR (KBr, cm⁻¹): 3500 (broad, OH); 1605 (broad, C=O). ¹H NMR (270 MHz, CDCl₃): δ 6.02 (2H, s, OCH₂O); 6.46 (1H, s, 3-CH); 6.85 (1H, s, 6-CH); 9.62 (1H, s, CHO); 11.78 (OH). ¹³C NMR (68 MHz, CDCl₃): δ 98.33 (3-CH); 102.19 (OCH₂O); 109.34 (6-CH); 113.64 (1-C_q); 141.33 (5-C_q); 155.18 (2- or 4-C_q); 161.51 ((2- or 4-C_q); 193.71 (CHO). MS (70 eV,

Angleški tekst - predpis

- ◆ Kakšna je vloga magnezijevega sulfata?
- ◆ Zakaj je pri Vilsmeierjevem postopku bolje uporabiti brezvodni DMF? Kaj se zgodi, če je prisotno voda v topilu? Napišite reakcijo, ki pri tem poteče?
- ◆ Zakaj pri Vilsmeierjevem postopku dodamo nasičeno raztopino natrijevega acetata? Napišite reakcijo, ki pri tem poteče!
- ◆ Navedite vsaj dva orositvena reagenta, s katerima bi lahko detektirali produkt reakcije (spojino **6**)?
- ◆ Narišite produkt reakcije, ki ga dobimo, če spojini **6** dodamo pol ekvivalenta etilendiamina!
- ◆ Kakšna vloga ima AlCl_3 pri pretvorbi spojine **6** v **8**?

Naloga



Naloga za točko

