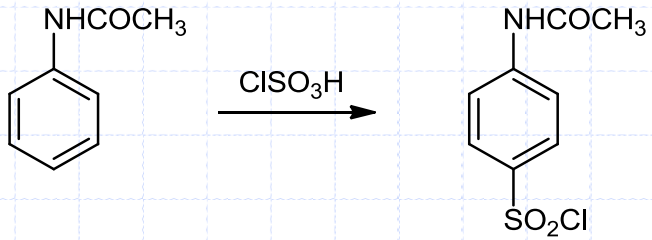
Univerza v Ljubljani
Fakulteta za farmacijo

Katedra za farmacevtsko kemijo

Sulfametoksazol

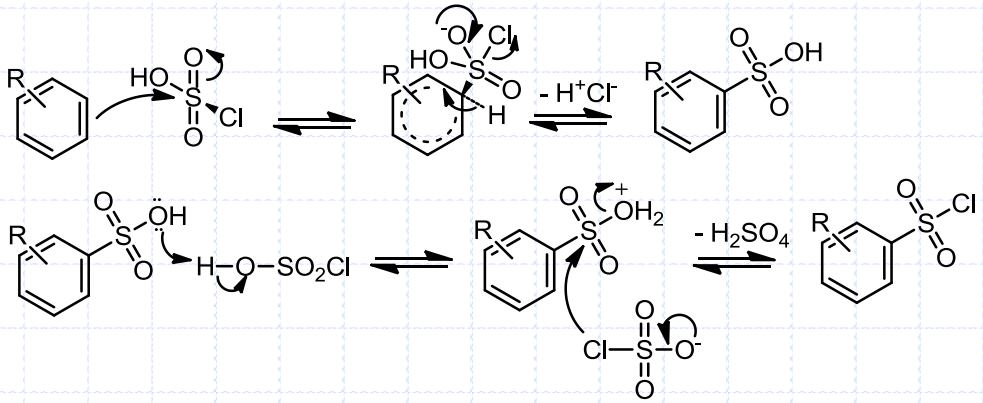
8. vaja

1. Stopnja – elektrofilna aromatska substitucija (SEAr)

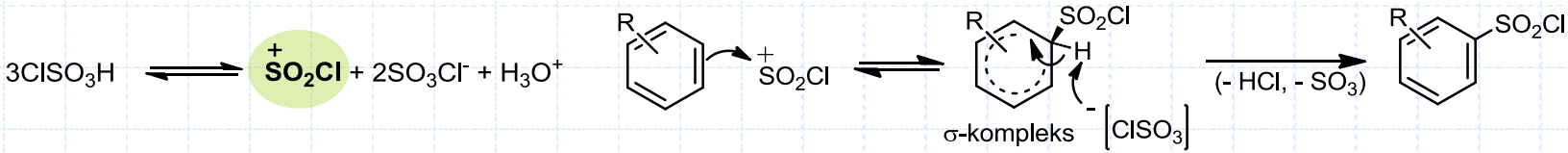


Predpostavljenih je več mehanizmov reakcije:

- preko sulfonske kisline



- preko elektrofila SO_2Cl^+



Cremlyn, RJ. Chlorosulfonic acid: a versatile reagent. Cambridge: The Royal Society of Chemistry, 2002: 7-22.

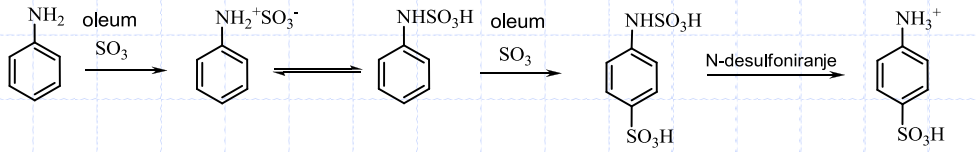
1. Stopnja - vprašanja

- Zakaj nizka temperatura na začetku?
- Zakaj rabimo vsaj dvakratni prebitek klorsulfonske kisline?
- Možni stranski produkti?
- Zakaj reakcijsko zmes zlijemo na zmes ledu in vode?
- Zakaj klorsulfonsko kislino nevtraliziramo s trdnim $NaHCO_3$ ali Na_2CO_3? Napišite reakcijo klorsulfonske kisline z vodo.
- Zakaj smo se pri sintezi sulfametoksazola odločili za uporabo acetanilida in ne anilina?

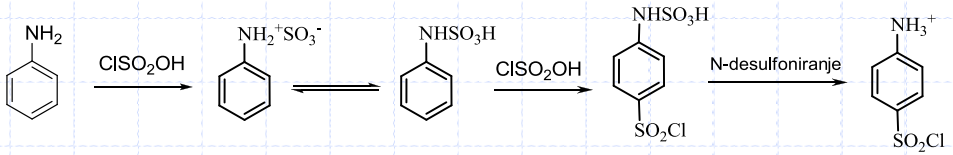
Če aminske skupine ne zaščitimo...

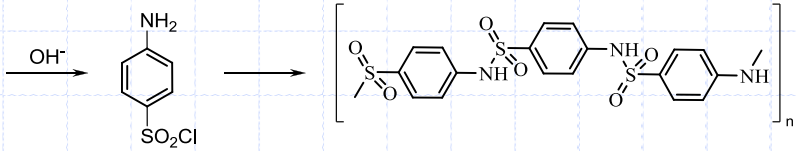
- v kislih pogojih -> protoniranje proste $-NH_2$ skupine, $-NH_3^+$ skupina pa usmerja m- z deaktivacijo!
- Usmerjanje o-/p- zaradi steričnega oviranja
- **Analogija s sintezo sulfanilne kisline**

Sinteza sulfanilne kisline



Analogija (ce ne uporabimo zascitenega anilina)





Oligo/polimeren produkt

Reakcije sulfoniranja, klorsulfoniranja

- Sulfoniranje aromatskega obroča – običajno uporabimo oleum (konc. H_2SO_4 – SO_3)

  Kaj nastopa kot elektrofil?

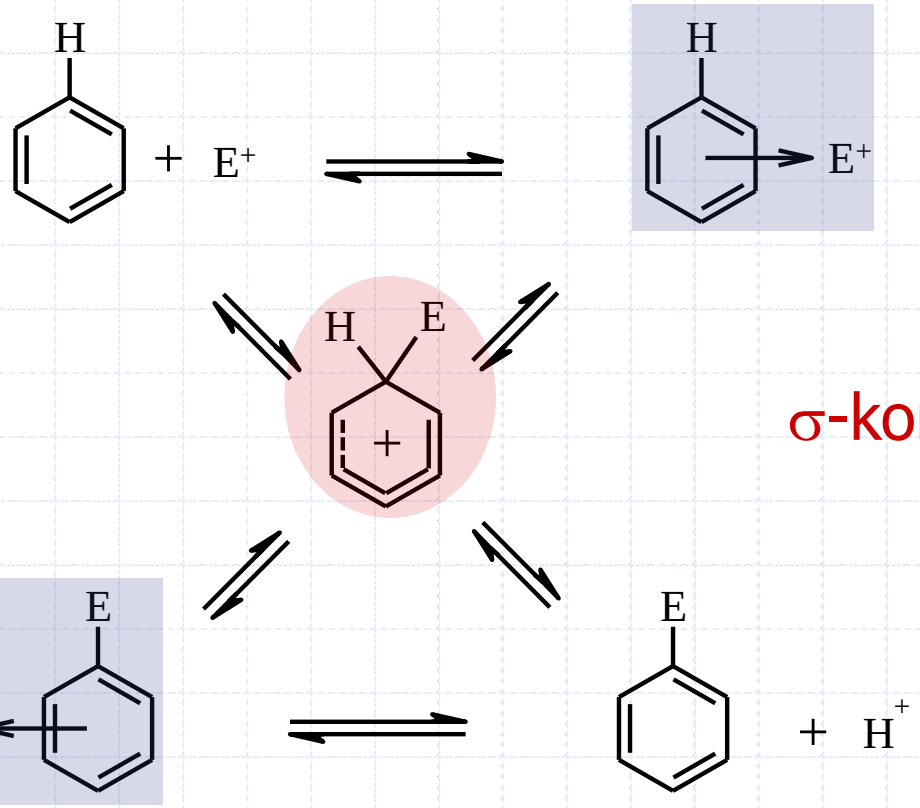
  sulfonsko kislino dobimo tudi, če uporabimo le en ekvivalent klorosulfonske kisline!

- Klorosulfoniranje – vsaj 2 ekvivalenta $ClSO_3H$, povišana temperatura (skupine na Ar, ki deaktivirajo)

- Kateri so možni stranski produkti pri klorosulfoniranju acetanilida?

1. Stopnja - SEAr

- elektrofilna aromatska substitucija



Usmerjanje - S_EAr

o,p/aktivacija	$-O^{(-)}$	$-NH_2$
	$-OH$	$-NR_2$
	$-OR$	$-NHCOCH_3$
	$-OC_6H_5$	$-R$
	$-OCOCH_3$	$-C_6H_5$
o,p/deaktivacija	$-F$	$-I$
	$-Cl$	$-CH_2Cl$
	$-Br$	$-CH{=}CHNO_2$
m/deaktivacija	$-NO_2$	$-CO_2H$
	$-NR_3^{(+)}$	$-CO_2R$
	$-PR_3^{(+)}$	$-CONH_2$
	$-SR_2^{(+)}$	$-CHO$
	$-SO_3H$	$-COR$
	$-SO_2R$	$-CN$

Usmerjanje - SEAr

Summary of directing and activating effects

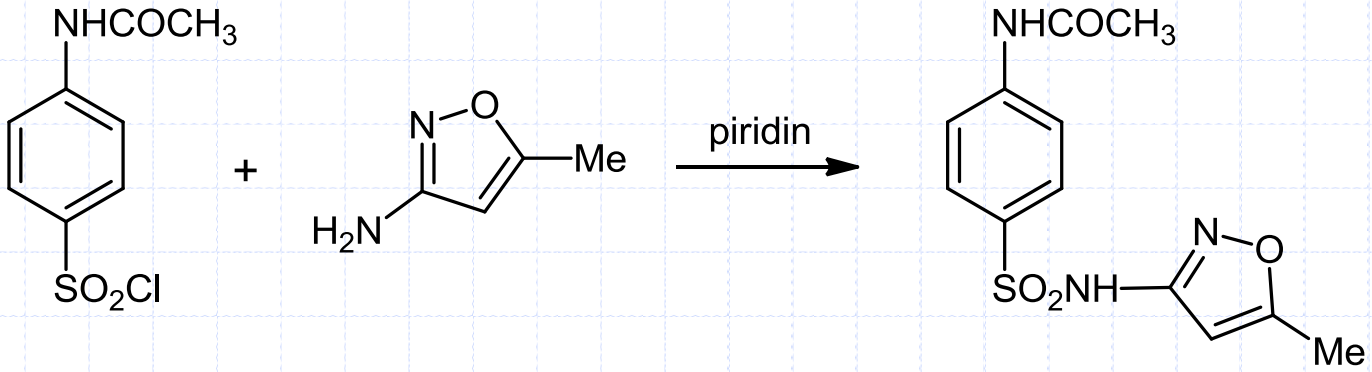
Now we can summarize the stage we have reached in terms of *activation* and *direction*.

Electronic effect	Example	Activation	Direction
donation by conjugation	$-NR_2$, $-OR$	very activating	*ortho*, *para* only
donation by inductive effect	alkyl	activating	mostly *ortho*, *para* but some *meta*
donation by conjugation *and* withdrawal by inductive effect	F, Cl, Br, and I	deactivating	*ortho* and (mostly) *para*
withdrawal by inductive effect	$-CF_3$, $-NR_3^{\ddagger}$	deactivating	*meta* only
withdrawal by conjugation	$-NO_2$, $-CN$, $-COR$, $-SO_3R$	very deactivating	*meta* only

Clayden J et al. Organic chemistry, Oxford University press, 2001

2. Stopnja – mehanizem podoben S_N2

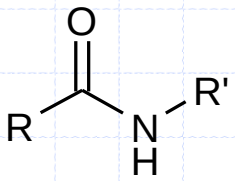
- Nukleofilna substitucija

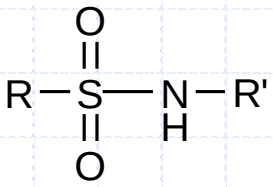


- Kakšna je vloga piridina pri tej reakciji?

- Podobna reakcija je osnova t.i. Hinsbergovega testa – ločevanje med primarnimi, sekundarnimi in terciarnimi amini.

Karboksamidi / sulfonamidi





- Oboji so amfoterni. Sulfonamidi so bolj kisli (pKa=6-8) – Zakaj? Prosti proton odcepimo z NaOH in tudi karbonati (K_2CO_3), pri karboksamidih z Na,K-hidridi in alkoksidi.
- Sulfonamidi so bistveno manj reaktivni; hidroliza le v konc. HCl ali 30% HBr ob refluksu, v bazičnem sploh ne poteče.

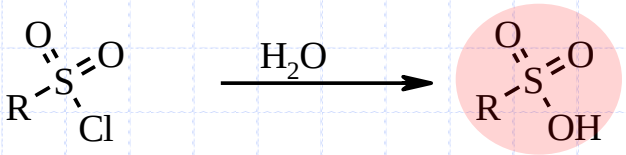
Sulfonil kloridi

- Manj reaktivni od ustreznih karboksilnih analogov – Zakaj?
- Slabo topni v vodi
- Večinoma trdni (kloridi karboksilnih kislin so večinoma tekoči)

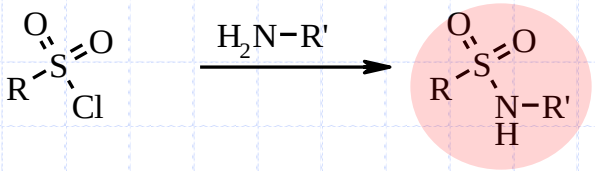
Pretvorbe sulfonilkloridov

- Redukcija do tiolov

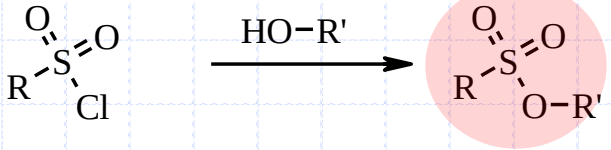
- Hidroliza do sulfonske kisline



- Reakcija z amini - sulfonamidi



- Reakcija z alkoholi - sulfonati



Nomenklatura

- Sulfonska ksl
- Sulfinska ksl
- Sulfenska ksl

- Sulfonil
- Sulfonamid
- Sulfamoil

- Sulfanilamid
- Sulfanil

- Sulfon
- Sulfin (sulfoksid)
- Sulfen (sulfidi, tioetri)

- Zamenjava O/S; predpona tio-

- Sultam, Sulton

- Sultan?

Sintezne naloge

Saharin-Na^+

Na – sol 4,5-benzizotiazol-3-on-1,1-dioksida

iz: *o*-toluensulfonil klorida

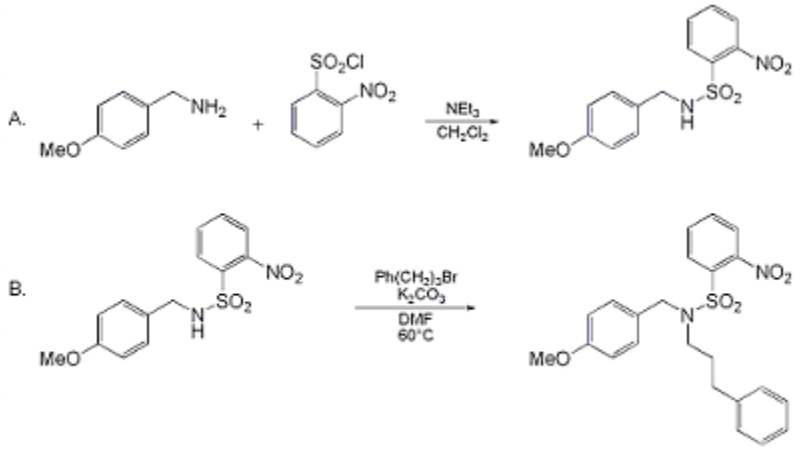
Sintezne naloge

Sultiam

p-(tetrahidro-1,2-tiazin-2-il)benzensulfonamid-*S,S*-dioksid

iz: anilina, 4-klorobutansulfonil klorida

Naloga – angleški predpis



1. **Zakaj hladimo reakcijsko zmes pri reakciji A? Na koliko stopinj (zanima nas najnižja možna temperatura) bo zmes ohlajena, če delamo po postopku A?**
2. **Kakšna je vloga dodatka 1N HCl? Ali bi prebitek 2-nitrobenzensulfonil klorida reagiral s še kakšno skupino, poleg primarne –NH_2?**
3. **Zakaj smo pri drugi reakciji dodali kalijev karbonat?**
4. **Zakaj delamo v brezvodnih pogojih pri sintezni poti B?**
5. **Kakšen produkt (ali produkte) bi lahko pričakovali, če bi v reakcijsko zmes namesto kalijevega karbonata dodali aluminijev bromid?**
6. **Kam se porazdeli DMF po ekstrakciji?**

A. *N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide* . A 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and a rubber septum is charged with 6.81 g (49.6 mmol) of 4-methoxybenzylamine (Note 1), 100 mL of dichloromethane and 6.93 mL (49.6 mmol) of triethylamine. The mixture is stirred and cooled in an ice-water bath while 10.0 g (45.1 mmol) of 2-nitrobenzenesulfonyl chloride is added over a period of 5 min. After 5 min, the ice bath is removed and the reaction mixture is allowed to warm to room temperature, stirred for 15 min, and then quenched with 100 mL of 1N hydrochloric acid (HCl). The aqueous layer is extracted with two 100-mL portions of dichloromethane , and the combined organic extracts are washed with 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 14.2 g (98%) of the crude 2-nitrobenzenesulfonamide . Recrystallization from 500 mL of 1:1 ethyl acetate/hexane gives 13.00-13.15 g (90-91%) of N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide as white crystals.

B. *N-(4-Methoxybenzyl)-N-(3-phenylpropyl)-2-nitrobenzenesulfonamide* . A 200-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen gas inlet, and a rubber septum is charged with 10.0 g (31.0 mmol) of N-(4-Methoxybenzyl)-2-nitrobenzenesulfonamide, 12.9 g (93.1 mmol) of potassium carbonate, and 40 mL of anhydrous dimethylformamide (DMF). To the stirred mixture is added 5.19 mL (34.1 mmol) of 3-phenylpropyl bromide over a period of 5 min and the resulting mixture is heated in a 60°C oil bath for 70 min. The reaction mixture is allowed to cool to room temperature, diluted with 250 mL of water, and extracted with three 250-mL portions of ether. The combined organic extracts are washed with brine (100 mL), dried over magnesium sulfate , filtered, and concentrated under reduced pressure to give a pale yellow liquid. The residue is purified by column chromatography on silica gel to give 13.5 g (99%) of N-(4-Methoxybenzyl)-N-(3-phenylpropyl)-2-nitrobenzenesulfonamide as a viscous pale yellow liquid.