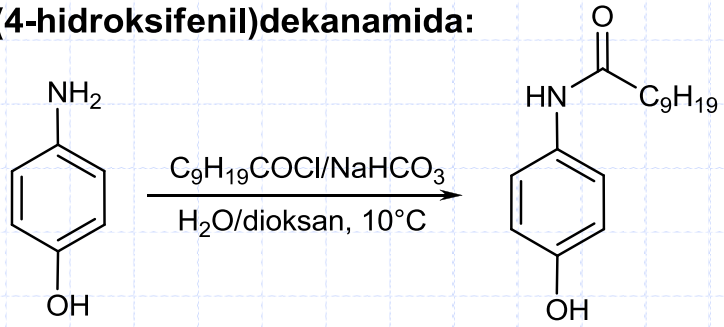
Univerza v Ljubljani
Fakulteta za farmacijo

Katedra za farmacevtsko kemijo

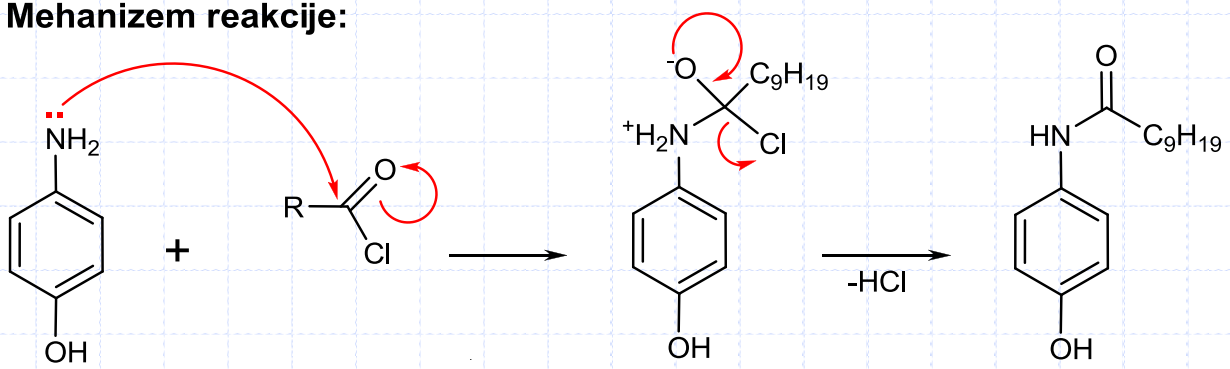
Sinteza homologov paracetamola

Sinteza *N*-(4-hidroksifenil)dekanamida

Sinteza N-(4-hidroksifenil)dekanamida:



Mehanizem reakcije:

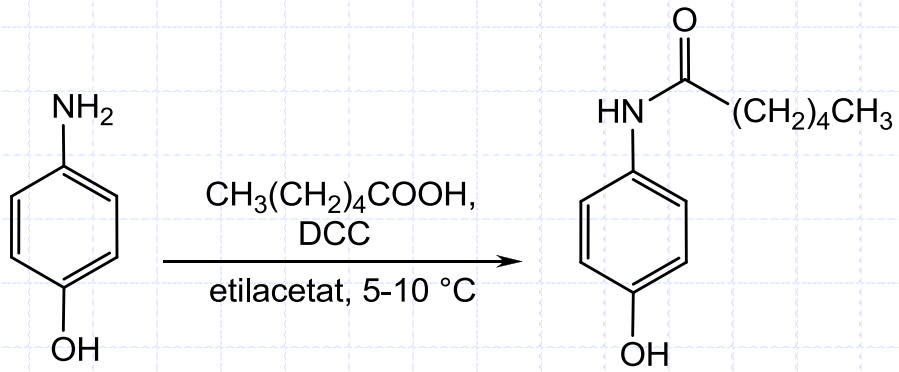


Vprašanja:

1. Zakaj uporabimo zmes voda/dioksan?
2. Predlagajte orositveni reagent za detekcijo poteka reakcije.
3. Zakaj dodamo $NaHCO_3$? Zakaj pri reakciji 4-aminofenola z acetanhidridom nismo uporabili $NaHCO_3$?
4. Zakaj se reakcijska zmes peni?
5. Zakaj izvajamo reakcijo pri znižani temperaturi?
6. Zakaj dodajamo dekanoil klorid postopno?

Sinteza *N*-(4-hidroksifenil)heksanamida

Sinteza *N*-4(hidroksifenil)heksanamida:



Kakšen je mehanizem reakcije?

Vprašanja:

1. Zakaj mešamo heksanojsko kislino in DCC pred dodatkom 4-aminofenola 30 min?
2. Zakaj reakcijo izvajamo pri znižani temperaturi?
3. Zakaj spiramo reakcijsko zmes z nasičeno raztopino $NaHCO_3$?
4. Zakaj spiramo reakcijsko zmes z vodo?
5. Zakaj spiramo reakcijsko zmes z 1M HCl?
6. Zakaj speremo reakcijsko zmes z nasičeno raztopino NaCl?
7. Zakaj je reakcija manj selektivna? Kako bi optimirali pogoje?

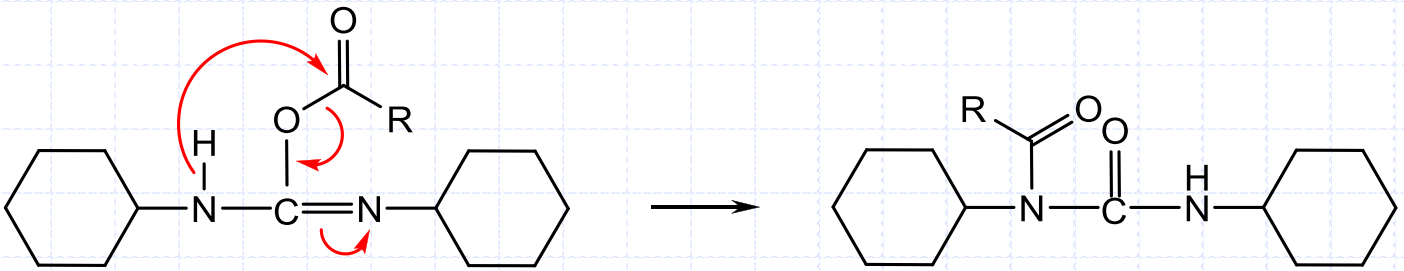
Možni stranski produkti

1. PRI OBEH SINTEZNIH POSTOPKIH:

- ***O*-aciliran produkt**
- ***N*,*O*-diaciliran produkt**

2. PRI UPORABI DCC:

- **produkt O->N intramolekularne migracije acilne skupine**



aktiviran ester

N-acilsečnina

Tankoplastna kromatografija homologov paracetamola

1. Vzorce homologov paracetamola raztopimo v MeOH
2. TLC razvijamo v dveh MF:

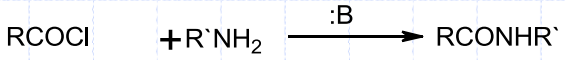
- EtOAc
- CH_2Cl_2 / MeOH = 9 / 1

Komentarji v poročilih: ***primerjava metod N-aciliranja*** (izkoristki, čistost produkta, enostavnost izvedbe, toksičnost reagentov), ***vpliv števila CH_2 skupin*** na lipofilni karakter homologov paracetamola

Sintezni pristopi za tvorbo amidov

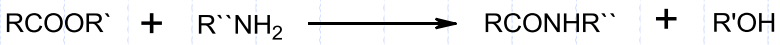
N-aciliranja

1. Kislinski klorid + amin

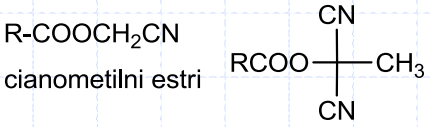


2. Kislinski anhidrid + amin

3. Tvorba amidov z uporabo aktiviranih estrov (aminoliza estrov)

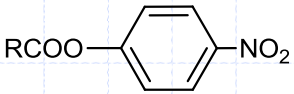


3a. estri s ciano-alkoholi

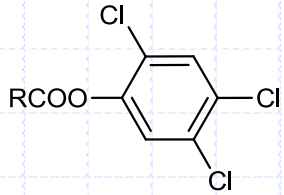


1,1-dicianoetilni estri

3b. arilni estri

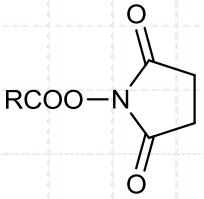


p-nitrofenilni estri



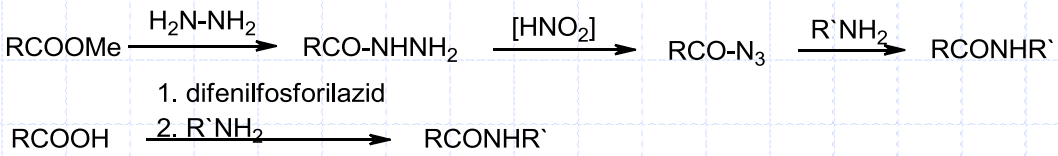
2,4,5-triklorofenilni estri

3c. estri N-hidroksisukcinimida



4. Uporaba `coupling` reagentov (DCC)

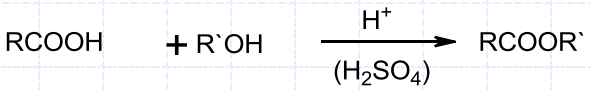
5. Metoda kislinskih azidov



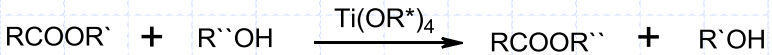
Sintezni pristopi za tvorbo estrov

O-aciliranja

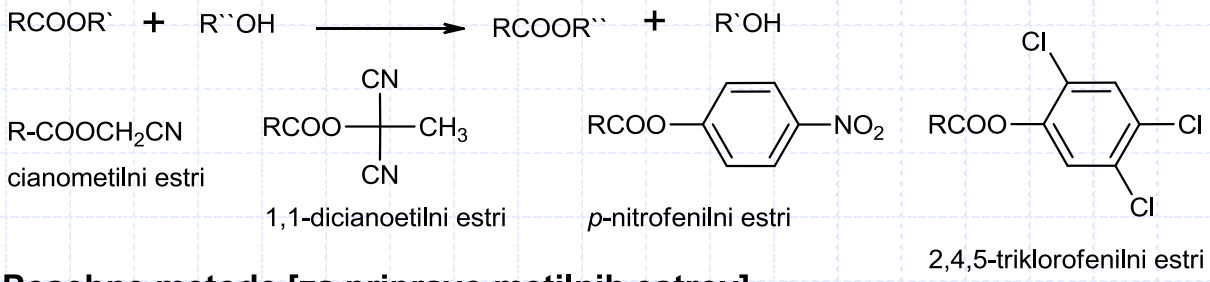
1. Kislinsko katalizirana esterifikacija



2. Preestrenje (katalizator: Ti-alkoksidi)

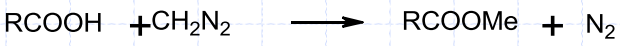


3. Preestrenje z uporabo aktiviranih estrov

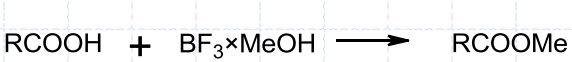


4. Posebne metode [za pripravo metilnih estrov]

a) uporaba diazometana

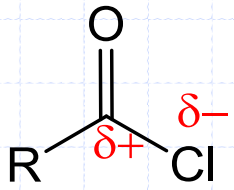


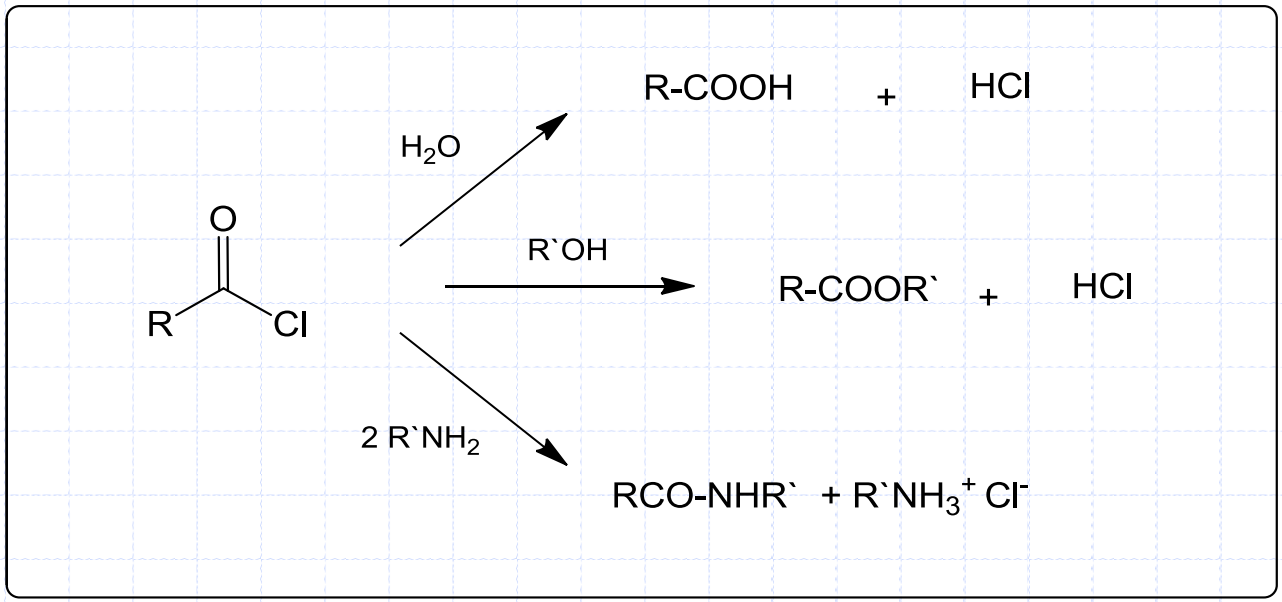
b) uporaba BF_3-metanolnega kompleksa



Lastnosti kislinskih kloridov

1. So dobri eklektrofili (elektronprivlačni efekt Cl atoma)
2. So izredno reaktivni in agresivni (dražijo sluznice zato obvezno delo v digestoriju!)



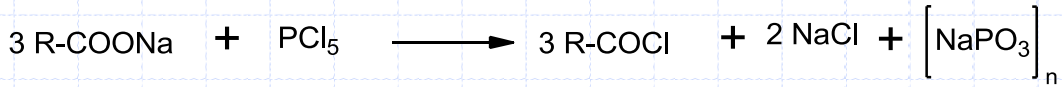


Sinteza kislinskih kloridov

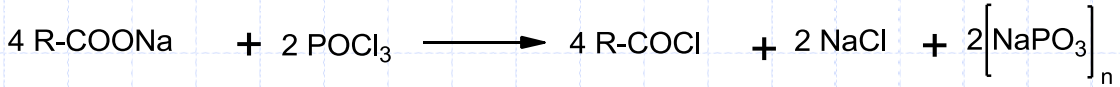
1. Z uporabo ustreznih fosforjevih spojin

a) fosforjev(III) klorid

b) fosforjev(V) klorid



c) fosforil klorid



2. Z uporabo tionil klorida

Ostale kislinske halogenide pripravimo z uporabo kislinskih kloridov ob prisotnosti HBr, HI ali HF. Bromide lahko pripravimio analogno kot kloride z PBr_3.

Sintezna naloga

Iz toluena pripravite p-acetilaminobenzojsko kislino!

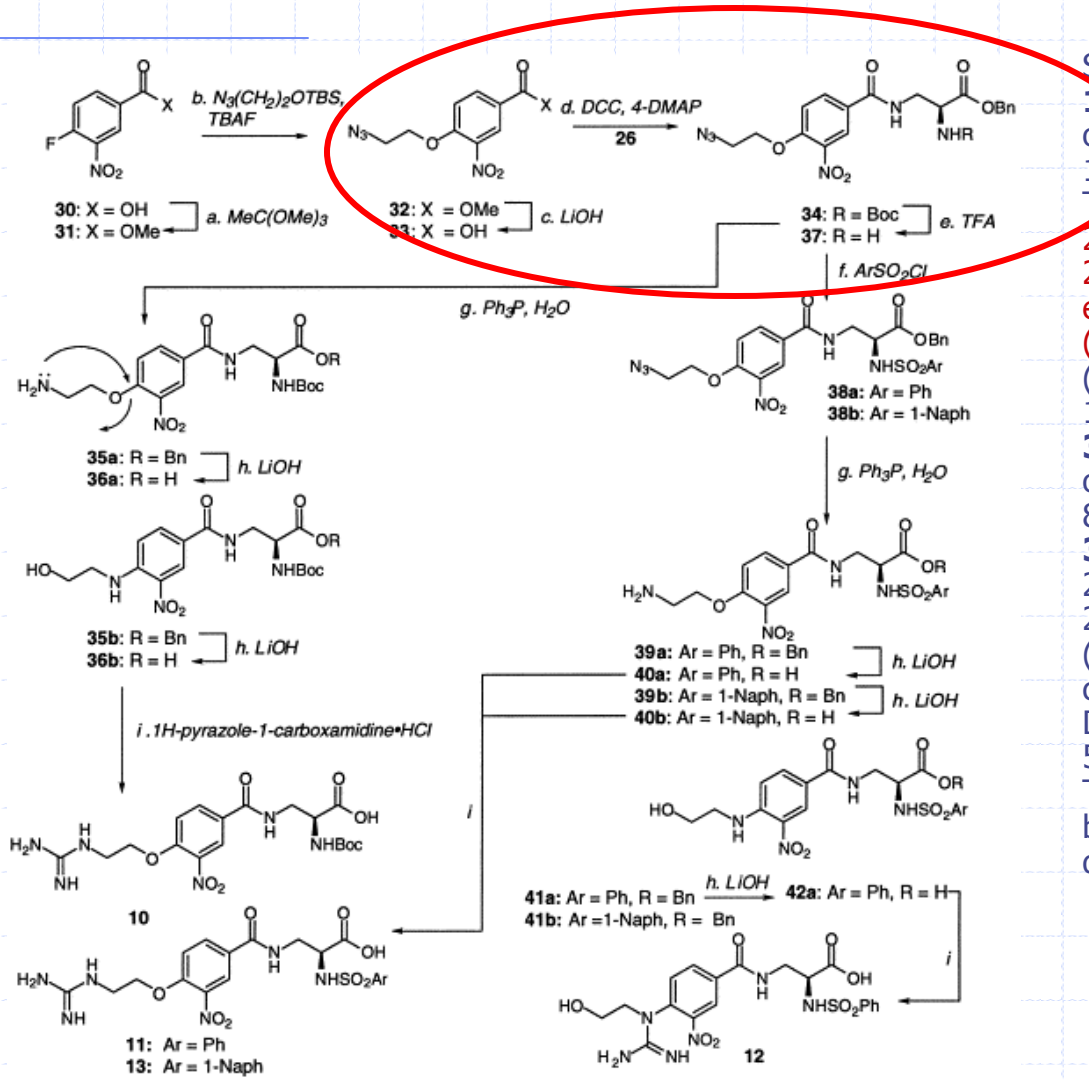
Sintezna naloga

Iz benzena pripravite 3-bromo-4-propilfenol!

Sintezna naloga

Iz 2-nitrotoluena pripravite propil 2-(N-acetilamino)benzoat!

Angleški tekst – predpis



Scheme 2. Synthesis of compounds **10**–**13**. Reagents and conditions: (a) 5.0 equiv of $MeC(OMe)_3$, PhMe, 80 °C, 8 h, 98%; (b) 1.1 equiv of $N_3(CH_2)_2OTBS$, 0.1 equiv of TBAF, 4 Å MS, DMF, 25 °C, 4 h, 73%; (c) 2.0 equiv of $LiOH \cdot H_2O$, dioxane:H_2O (3:1), 25 °C, 4 h 99%; (d) 1.0 equiv of DCC, 0.2 equiv of 4-DMAP, CH_2CL_2, 25 °C, 4 h, 82%; (e) 50% TFA in CH_2Cl_2, 25 °C, 2 h, 84%; (f) 1.1 equiv of $PhSO_2Cl$ or 1-$NaphSO_2Cl$, 1.3 equiv of *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 4 h, **38a** (78%), or **38b** (57%); (g) 2.0 equiv of Ph_3P, 44 equiv of H_2O, THF, 25 °C, 12 h, 80%, ca. 1:1 of **35a**:**35b**; 80%, ca. 1:1 of **39a**:**41a**: 81%, ca. 1:1 of **39b**:**41b**; (h) 2.0 equiv of $LiOH \cdot H_2O$, THF:H_2O (3:1), 25 °C, 4 h, 93–99% for **36ab**, **40ab**, **42a**; (i) 1.1 equiv of 1*H*-pyrazole-1-carboxamidine·HCl, 1.1 equiv of *i*-Pr_2NEt, DMF, 25 °C, 16 h, 13–15% for **10**, **11**, **13**: 50 °C, 16 h, 5% for **12**, after RP-HPLC. TFA=trifluoroacetic acid; TBAF=tetra-*n*-butylammonium fluoride; DCC=1,3-dicyclohexylcarbodiimide.

Angleški tekst - predpis

Compound 34. To a solution of amine **26** (0.33 g, 1.10 mmol) and acid **33** (0.286 g, 1.10 mmol) in CH_2Cl_2 (30 mL) was added a catalytic amount of 4-DMAP (0.03 g, 0.22 mol) and DCC (0.26 g, 1.1 mol) at room temperature. The reaction mixture was stirred for 4 h at this temperature and the precipated dicyclohexyl urea was then filtered and the filtrate washed successively with water, saturated aqueous $NaHCO_3$-solution and brine. The organic solvent was removed under reduced pressure to give an oil which after purification by flash column chromatography (silica gel, 60% ethyl acetate in hexanes) gave amide **34** as a yellow solid (2.48 g, 82%). R_f=0.28 (silica gel, 60% ethyl acetate in hexanes); IR (KBr): V_{max} 3343, 2977, 2933, 2112, 1738, 1710, 1619, 1531, 1498, 1366, 1333, 1280, 1161, 1084, 1047 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J*=2.0 Hz, 1H, Ar), 7.98 (dd, *J*=2.0, 11.0 Hz, 1H, Ar), 7.40 (bt, 1H, NHCO), 7.39–7.31 (m, 5H, Ph), 7.09 (d, *J*=11.0 Hz, 1H, Ar), 5.67 (d, *J*=8.0 Hz, 1H, $NHCO_2$), 5.21 (s, 2H, CH_2Ph), 4.60–4.50 (bm, 1H, C*H*CH_2), 4.30 (t, *J*=6.0 Hz, 2H, OCH_2), 3.95–3.85 (bm, 1H, CHC*H*H), 3.78–3.70 (bm, superimposed, 1H, CHCH*H*), 3.70 (t, *J*=6.0 Hz, 2H, CH_2N_3), 1.43 (s, 9H, ^{t}Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 164.9, 153.8, 139.8, 135.0, 133.0, 128.7, 128.6, 126.9, 124.6, 114.3, 81.0, 68.8, 67.9, 49.8, 33.8, 28.2, 25.5, 24.8; FAB-HRMS ($M+Cs^+$) calcd 661.1023, found 661.1050.

Compound 37. To a solution of **34** (0.10 g, 0.019 mmol) in CH_2Cl_2 (4 mL) at room temperature was added trifluoroacetic acid (4 mL). The mixture was stirred for 2 h. The solvent was removed in vacuo to give a yellowish oil, which after flash chromatography (silica, 5% methanol in dichloromethane) gave **37** as an oil (0.07 g, 84%). R_f=0.19 (silica, 5% methanol in dichloromethane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J*=2.0 Hz, 1H, Ar), 7.95 (dd, *J*=2.0, 11.0 Hz, 1H, Ar), 7.39–7.29 (m, 5H, Ar), 7.21 (bm, 1H), 7.05 (d, *J*=9.0 Hz, 1H), 5.16 (s, 2H, CH_2Ph), 4.27 (t, *J*=5.0 Hz, 2H, C*H*$_2$OAr), 3.67 (t, *J*=5.0 Hz, 2H, C*H*$_2N_3$), 3.95–3.78 (bm, 1H, C*H*NH_2), 3.65–3.52 (bm, 1H, CHC*H*H), 4.32–4.31 (bm, 1H, CHCH*H*); ^{13}C (125 MHz, $CDCl_3$): δ 164.9, 153.7, 139.2, 135.1, 133.1, 128.6, 128.5, 128.4, 127.0, 124.6, 114.2, 68.7, 67.4, 49.7, 33.8, 25.5; FAB-HRMS ($M+Cs^+$) calcd 561.0499, found 561.0507.

Angleški tekst - predpis

- Za kakšno reakcijo gre pri pretvorbi spojine **32** v **33**?
- Zakaj predpis sinteze spojine **34** navaja spiranje reakcijske zmesi samo z raztopinami $NaHCO_3$ in NaCl, ne pa tudi z 1M HCl?
- Kakšna je vloga 4-DMAP pri tej reakciji?
- Kaj bi se zgodilo s spojino **34** po kat. hidrogeniranju?
- Kakšna reakcija poteče pri sintezi spojine **37**?
- Zakaj menite, da je pri izolaciji te spojine potrebna kolonska kromatografija?