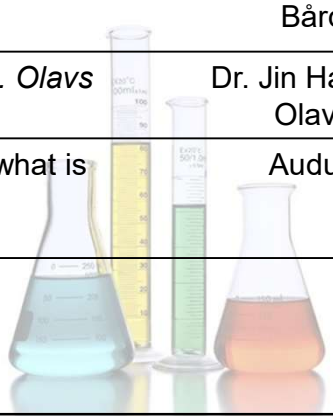
In today's seminar

Topics	By who
Cake and coffee	
Introduction to the seminar series	Audun
Tutorial: *Formalities in experimental protocols*	Bård
Presentation: *How and why we make radioactive drugs at St. Olavs*	Dr. Jin Han, St. Olavs
Closing summary, idea session for new topics and a look at what is planned for the next seminar	Audun



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How do we communicate with you?

- Seminars are announced through Outlook invites
  - Supervisors: Invite all your students once and I'll send out the invites every month.
- Webpage for Organic Chemistry Section
- FB groups or other communication channels for each research group.

Seminar - Why, what and how?

Why?

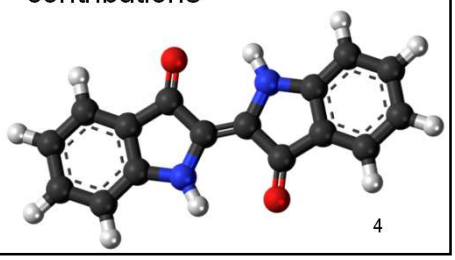
- Arena to bring everyone together!
  - We are 40+ organic chemists at the department
- Different chemistry but similar challenges
- Sense of belonging
  - You might not need it, but someone else might

What?

- Sharing of chemistry
- Guest lectures
- Practice your presentation before a conference
- Laboratory techniques, hacks and bodges
- Short tutorials
- Kringle (cake 🎂), coffee and talking to colleagues

How?

- One meeting every month
- Interesting topics needed
  - Do you have a chemistry skill you can share?
  - Topic requests
- Baking of cakes
- Attendance and contributions



Formalities in experimental protocols

Key point

- Other scientist should be able **to reproduce** your experiment and the analysis.
- The experimental part should be a **condensed type of reading**, but with complete sentences: nones and verbs.
- If the same protocol is used on closely related analogues shorten the text.
  - Use a “General method” or refer to another experiment
- **Harmonise your style** on reporting: abbreviating or not; reporting of compound data, etc.

Materials and Methods

- Origin of chemicals
- Analytical methods and equipment.

The solvents and reagents used in the project were purchased from VWR and Merck. 4-Chloro-7*H*-pyrrolo[2,3-*d*] pyrimidine was obtained from 1 Click Chem, while compound **7** was prepared as preaviusly described [8]. Silica-gel chromatography was performed using silica-gel 60A purchased from VWR with a pore size 40-63 um. Solvents were dried on a Braun MB SPS-800 Solvent Purification System and stored over molecular sieves (4 Å) for 24 h prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded using a Bruker Advance III HD NMR spectrometer from Nanaobay electronics with a Smartprobe 5 mm probe head, operating at 400 MHz or 600 MHz, and carbon spectra at 100 MHz or 150 MHz, respectively. Samples were mainly analyzed in DMSO-d_6 or chloroform-*d* where specified. ^{1}H and ^{13}C NNR chemical shifts are in ppm relative to the DMSO-d_5 solvent peak at 2.50 ppm and DMSO-d_6 39.5 ppm, respectively. High resolution mass spectroscopy (HRMS) was performed using a WaterTM's Synapt G2-S Q-TOF instrument. Samples were ionized by Electrospray Ionization (ESI/70eV) and analyzed using an Atmospheric Solids Analysis Probe (ASAP). Calculated exact mass and spectra processing was done by WatersTM Software (Masslynx V4.1 SCN871).

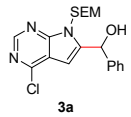
General procedure: to shorten the text

- If you have 3 or more similar experiments

General procedure A: directed lithiation without additives.

Under an N_2 atmosphere 4-chloro-7-((2-(trimethylsilyl)-ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (500 mg, 1.83 mmol) was dissolved in dry THF (4 mL) and cooled down to -78 °C. Then, LDA (2 M in THF/*n*-hexane/ethylbenzene, 1.47 mL, 2.93 mmol, 1.6 equiv) was added dropwise over 30 min by cannulation. This was followed by drop wise addition of the ketone/aldehyde (2.19 mmol, 1.2 equiv.) dissolved in THF (2 mL). After another 60 min, the reaction mixture was quenched with saturated NH_4Cl solution (0.5 mL) and stirred until ambient temperature was reached. The mixture was concentrated and added CH_2Cl_2 (25 mL) and water (30 mL). After phase separation, the water phase was extracted with more CH_2Cl_2 (2 × 20 mL) and washed with brine (20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica-gel flash chromatography as specified.

Then you only state what is different!

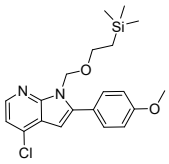


3a

(4-Chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)(phenyl)methanol (3a)

Compound **1** (650 mg, 2.28 mmol) and benzaldehyde (0.291 mL, 2.74 mmol) were reacted as described in general procedure B. The reaction time was 1 h. Purification by silica-gel chromatography (gradient from *n*-pentane/acetone/MeOH, 90:10:2 to 85:15:2:, TLC: *n*-pentane/acetone/MeOH, 90:10:2, R_f = 0.21), gave 835 mg (2.14 mmol, 93%) of a thick, oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.43 – 7.34 (m, 5H), 6.39 (d, *J* = 5.5 Hz, 1H), 6.27 (d, *J* = 0.9 Hz, 1H), 6.05 (d, *J* = 5.5 Hz, 1H), for N-CH_2-O an AB-system: δ_A= 5.77, δ_B = 5.56, J_{AB} =11.0 Hz, 3.50 – 3.37 (m, 2H), 0.83 – 0.70 (m, 2H), -0.11 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 152.5, 150.7, 150.3, 146.4, 141.5, 128.3 (2C), 127.9, 126.9 (2C), 115.9, 98.1, 70.7, 67.6, 65.5, 17.0, -1.47 (3C); IR (neat, cm^{-1}): 3483 (br, w), 3057 (w), 2950 (m), 2896 (w), 1557 (s), 1455 (s), 1252 (s), 1163 (s), 834 (s), 763 (s); HRMS (ES+, m/z): found 390.1407, calcd for $C_{19}H_{25}ClN_3O_2Si$, $[M+H]^+$, 390.1404.

Alternatively, reference to another experiment



4-Chloro-2-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (14b)

The compound was made as described for **14a** starting with 4-chloro-2-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**7**) (1.00 g, 2.44 mmol) and 4-methoxyphenylboronic acid (440 mg, 2.93 mmol). The reaction time was 30 min at 100 °C. The product was purified by silica-gel column chromatography (n-hexane/EtOAc, 4:1, R_f = 0.40) to give a yellow oil, 650 mg (1.67 mmol, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 5.2 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.61(s, 1H), 5.63 (s, 2H), 3.84 (s, 3H), 3.74 (t, J = 8.3 Hz, 2H), 0.97 (t, J = 8.3 Hz, 2H), -0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.2, 142.8 (2C), 134.9, 130.7 (2C), 123.9, 119.9, 116.9, 114.2 (2C), 98.2, 70.9, 66.5, 55.3, 18.0, -1.4 (3C); IR (neat, cm^{-1}): 2951 (w), 2837 (w), 1613 (w), 1498 (m), 1246 (s), 1075 (m), 832 (s), 695 (w); HRMS (APCI/ASAP, m/z): found 389.1445, calcd. for $C_{20}H_{26}N_2O_2SiCl$, $[M+H]^+$, 389.1452.

Reference to protocols

- If a method/protocol is taken from a paper highlight if this is for the same compound or for an analogue.

- The compound was prepared as described by Hoff *et al.* (Ref) .
- or
- The compound was prepared using the protocol described for the corresponding benzyl derivative (Ref) .

What accuracy to expect from:

- Weighting
- Analytical methods

Table 3 Error in Weighing as a Function of Scale[a]

Actual weight (mg)	Observed weight (mg)	Maximum observed error (%)
100	99.4–101.5	1.5
50	48.8–50.8	2.4
20	19.5–20.4	2.5
10	9.7–10.5	5.0
5	4.9–5.4	8.0
3	2.4–3.2	20.0

[a] The data reported represent an average of six individual experiments.

On the Practical Limits of Determining Isolated Product Yields and Ratios of Stereoisomers: Reflections, Analysis, and Redemption[1]

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Abstract: This paper examines the limits of accuracy in reporting isolated product yields (i.e., recovery of total mass from chromatography or extractions) as well as ratios of isomers determined by HPLC, GC, or NMR methods. Attention is directed to the magnitude of errors encountered in the HPLC or GC measurements of such ratios when these measurements are conducted without accurate calibrations or determinations of response factors for the particular isomers. Accurately defined mixtures of compounds (prepared

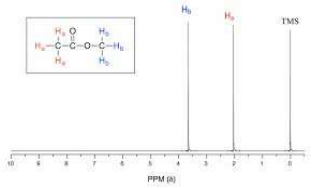
reactions >95%. Such large values were rarely found in the older literature and are all but absent in *Organic Syntheses*, a journal that only publishes procedures that have been independently reproduced. The reporting of selectivity parameters, diastereomer or enantiomer ratios appears to follow a similar trend. Discussion of these trends is often a topic of casual conversations at conferences where professionals within the synthetic community readily re-

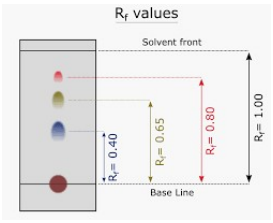
Wernerova et al. Synlett (2010) 2701–2707

Weight and mol

- Include weight and mol of all reagents.
- Number of equivalents can also be useful.
- Well below one gram, use mg
- Aim to use 3 digits: 356 mg, 1.36 g
- (If the uncertainty is large on small weights, this can be changed to e.g. 4 mg)
- Report the amount of product in weight, mol and %.
- E.g: This gave 345 mg (0.345 mmol, 89%) of a white solid.

Analysis to include!





- **For known compounds:**
  - ^{1}H NMR (in the same solvent)
  - The physical state of the product: oil, solid and the colour.
  - Melting points for solids.
  - R_f values if compounds are isolated by column chromatography
  - Optical rotation (in the same solvent and same concentration)
  - Make a statement like: The ^{1}H NMR confirms with that reported. (Ref)
  - If carbon spectra has not been reported, you report this as well.

Analysis required on new structures

- ^{1}H NMR
- ^{13}C NMR
- ^{19}F NMR (if applicable)
- Additional 2D experiments (if needed)
- Melting point
- Optical rotation data (if applicable)
- HPLC data (if applicable)
- IR
- High resolution mass data
- X-ray (if needed)
- Elemental analysis (if needed)

Purification

- Include sufficient details:

Column:

The product was purified by silica-gel column chromatography (*n*-hexane/EtOAc, 4:1, R_f = 0.40) to give a yellow oil, 650 mg (1.67 mmol, 68%).

Crystallization: The crude product (1.02 g) was recrystallized from acetonitrile (50 mL). After 18 h at rt the formed solid was isolated by filtration and washed with *n*-pentane (50 mL). After drying this gave…

Analytical data

Melting point:

This gave 345 mg (0.114 mmol, 85%) of a green solid, *mp.* 140-160 °C (*lit.* Ref 155-158 °C)

Optical rotation

- Use the same solvent and concentration as the reference
- $[\alpha]_D^{20} = +45.3$ (*c* 0.84, $CHCl_3$), *lit.* Ref $[\alpha]_D^{20} = +50.0$ (c 1.00)

Proton spectra:

- If the compound is known from before: run ^{1}H NMR in the same solvent

Proton spectra

- Include details of field strength and solvent.
- Two digits for shift
- One digit for coupling constants
- State the number of protons from each signal
- Multiplets are reported as an interval
- (the identity of each signal might also be specified)

- ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.43 – 7.34 (m, 5H), 6.39 (d, J = 5.5 Hz, 1H), 6.27 (d, J = 0.9 Hz, 1H), 6.05 (d, J = 5.5 Hz, 1H), for N-CH_2-O an AB-system: δ_A= 5.77, δ_B = 5.56, J_{AB} =11.0 Hz, 3.50 – 3.37 (m, 2H), 0.83 – 0.70 (m, 2H), -0.11 (s, 9H);

- NB: You must carefully check MNova
- NB: do not be too creative: if you and your supervisor do not understand the splitting pattern: multiplet
- Count the protons, list those protons not seen due to exchange or other phenomenon.

^{13}C NMR

- Include details of field strength and solvent.
- One digits for shift; unless two shift are too close to be separated
- State the number of carbons for each signal with more than one C.
- (the identity of each signal might also be specified)

- ^{13}C NMR (151 MHz, DMSO-d_6) δ 152.5, 150.7, 150.3, 146.4, 141.5, 128.3 (2C), 127.9, 126.9 (2C), 115.9, 98.1, 70.7, 67.6, 65.5, 17.0, -1.47 (3C);

- Do not forget the C-F fluorine couplings

IR data

- Include the most relevant absorptions for functional groups and the strongest signal.
- It could be nice to identify the different absorptions (not done here)

- IR (neat, cm^{-1}): 2951 (w), 2837 (w), 1613 (w), 1498 (m), 1246 (s), 1075 (m), 832 (s), 695 (w);

Mass spectra

- Do not calculate exact mass yourself but rely on Dr Gonzales!!
- State the ionization/MS method used
- State what is found mass
- State the formula, ion type and calculated mass.
- Typical error: molecular formula miss one proton.
- Check that the MS is not than 0.010 off.

- HRMS (APCI/ASAP, m/z): found 389.1445, calcd. for $C_{20}H_{26}N_2O_2SiCl$, $[M+H]^+$, 389.1452.
- HRMS (ES+, m/z): found 390.1407, calcd. for $C_{19}H_{25}ClN_3O_2Si$, $[M+H]^+$, 390.1404.

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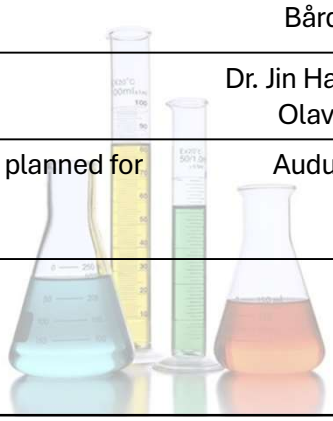

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Closing summary

11th seminar: 25th September, 11.00-12.00

- *«Synthia» - A Retrosynthesis tool by Merck. Lecture and retrosynthesis workshop*
- Seminar times can be found on the Organic Chemistry Group webpage: ntnu.edu/chemistry/research/organic

12th seminar: 30th October, 11.00-12.00

- Round of 5-minute updates from the research groups

Any ideas for topics for upcoming seminars?

Thank you very much for joining!

Suggestions:

- ~~How drying of solvents works~~
- ~~Story of insane lab efficiency from Germany~~
- ~~Formalism when writing experimental sections~~
- ~~Radioactive chemistry~~
- ~~MS and HPLC refreshers~~
- ~~How to work efficiently in MNova~~