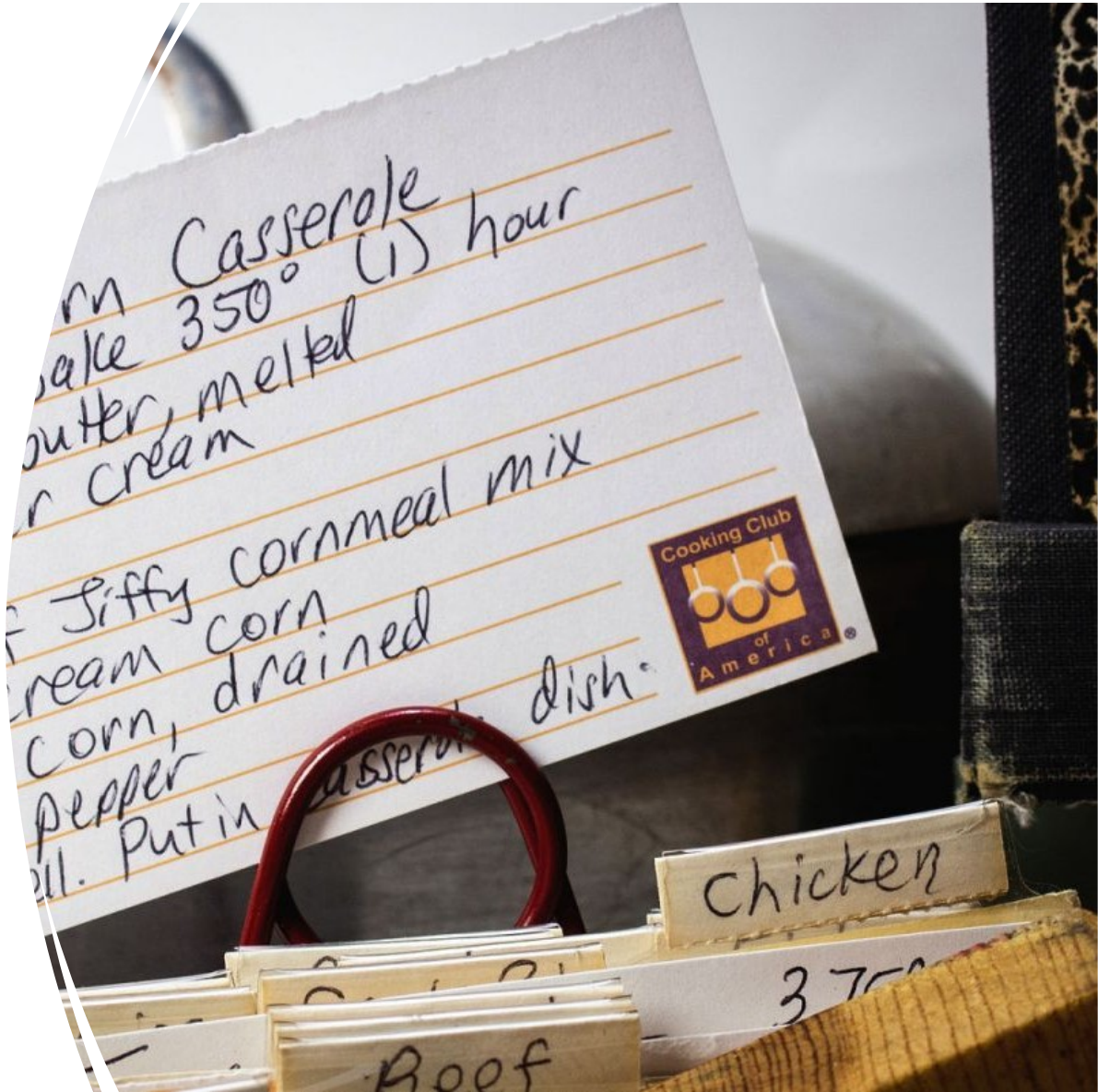
Experimental protocols in organic chemistry

Key point

- A chemists should be able **to reproduce** your experiment and the analysis.

- The experimental part is a **condensed type of reading**, but with complete sentences.
- **Harmonise your style**: abbreviating or not; weights; compound data, etc.



Materials and Methods

Origin of chemicals (suppliers)
Analytical methods and equipment.

The solvents used were from Merck. 1-Phenylethanone was purchased from VWR, while 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine was obtained from 1ClickChem. Compound **7** was previously prepared [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). IR absorption spectra were recorded using a Bruker ALPHA FTIR spectrometer equipped with a universal transmission sampling module. Melting points (mp.)were determined using a Stuart Scientific SMP3 melting point apparatus. Purity analyses of compounds **4** and **5** were performed by high-performance liquid chromatography (HPLC) using an Agilent Infinity…..

- **Avoid:** Solvent and reagents were from VWR, Merck and 1ClickChem.

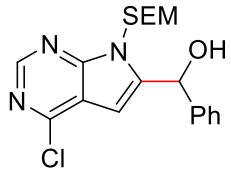
General procedure: to shorten the text

If the same protocol is used 3 or more times on closely related analogues shorten the text: use a "General method chapter"

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 for each compound.

Then you only state what is different!

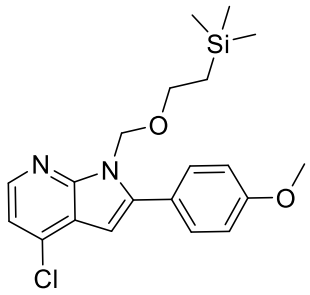


3a

(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 viscous 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.

Purification

- Include sufficient details to allow for later use



Column:

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

Crystallization:

The crude product (1.02 g) was recrystallized from refluxing 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…

The accuracy of our most important instrument

- Weighting

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 by volumetric means) were examined by the above methods and the 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

This is why we state yield and mg in whole numbers
E.g: 10 mg (xx mmol, 11%)

Weight and mol

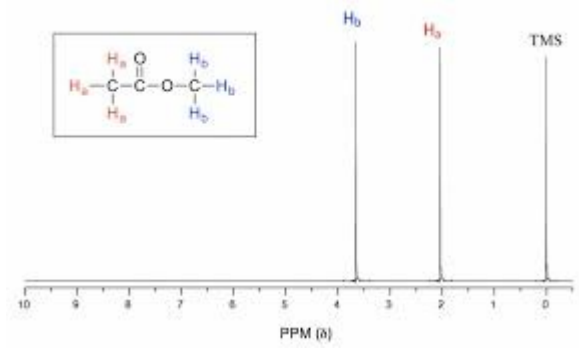


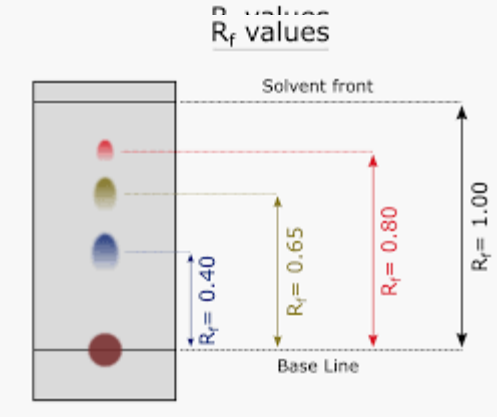
- Include weight and mol of all reagents.
- Number of equivalents (equiv.) is useful for the reader.
- Aim to use 3 digits: 356 mg, 1.36 g
  - Below one gram, use mg
  - Use whole numbers for mg: 5 mg
- Report the amount of product in this order: weight (mol, %).

This gave 345 mg (0.345 mmol, 89%) of a white solid.

Which analysis to include for known compounds!

- The physical state of the product: oil, solid and the colour.
  - “This gave 33 mg (0.066 mmol, 90%) of a yellow oil.”
- Melting points for solids/crystals.
  - “This gave 33 mg (0.066 mmol, 90%) of a grey solid, *mp.* 140-160 °C (*lit.* [Ref] 155-158 °C)”
- R_f value if the compound is isolated by column chromatography
  - “Purification was by silica-gel column chromatography (*n*-pentane/EtOAc, 4:1, R_f: 0.23). This gave..”
- Optical rotation (in the same solvent and same concentration)
  - $[\alpha]_D^{20} = +45.3$ (c 0.84, $CHCl_3$), *lit.* [Ref] $[\alpha]_D^{20} = +50.0$ (c 1.00, $CHCl_3$)
- **^{1}H NMR** (in the same solvent as previously reported)
  - Make a statement like: The ^{1}H NMR confirms with that reported. (Ref)
- ^{13}C NMR spectra if this has not been reported by others.
- HPLC purity data might be required (samples for biology)
- Chiral analysis might be requires (asymmetric synthesis/resolution work)





Analysis required on new structures

- The physical state of the product: oil, solid and the colour.
- Melting point
- ^{1}H NMR
- **^{13}C NMR**
- **IR**
- **High resolution mass data**

- ^{19}F NMR (if applicable)
- Additional 2D experiments (if needed)
- Optical rotation data (if applicable)
- HPLC data (if applicable)
- X-ray (if needed)
- Elemental analysis (if needed)



^{1}H NMR

Include details of magnetic field strength and solvent.
Two desimals for ^{1}H NMR shift
One desimal for coupling constants (*J*, italic)
State the number of protons from each signal
Multiplets are reported as an intervals

- ^{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);

Careful:

- You must carefully **check Mnova**: it can be wrong
- 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 dynamic phenomenon.

^{1}H NMR

- In some cases, the identity of each signal might also need to be specified.

- ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H, H-2), 7.43 – 7.34 (m, 5H, Ph), 6.39 (d, J = 5.5 Hz, 1H, CH(OH)Ph), 6.27 (d, J = 0.9 Hz, 1H, H-5), 6.05 (d, J = 5.5 Hz, 1H, CH(OH)Ph), 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, O-CH_2), 0.83 – 0.70 (m, 2H, CH_2-Si), -0.11 (s, 9H, $SiMe_3$);

^{13}C NMR

- Include details of field strength and solvent.
- One desimal for shift ^{13}C NMR ; 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);

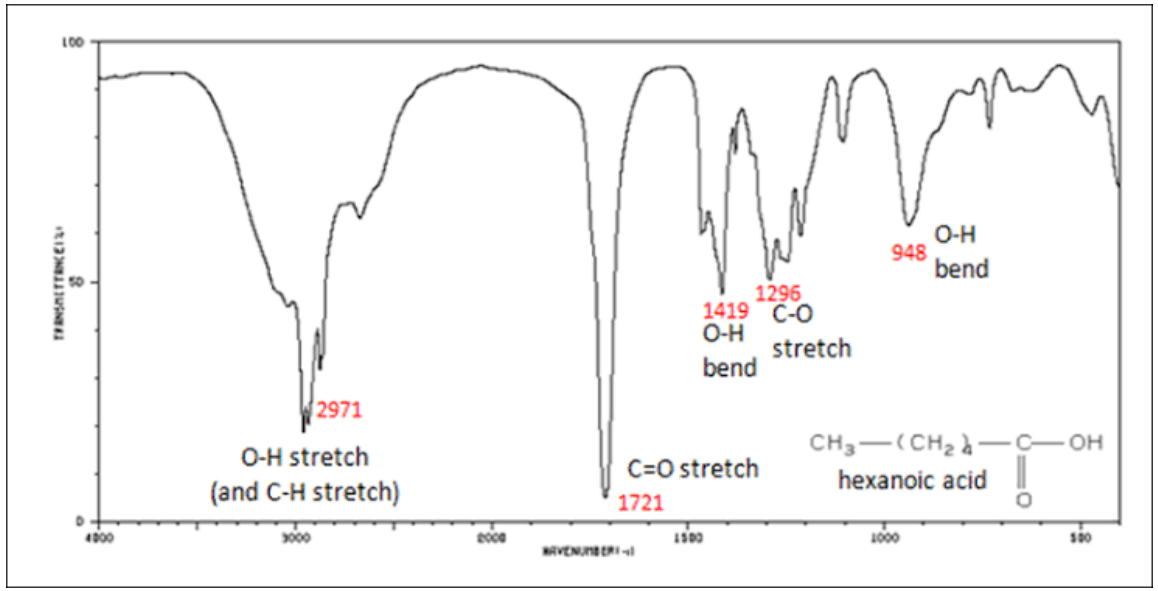
Remember:

- **Count the carbons**
- Do not forget the C-^{19}F couplings (or other nuclei: ^{31}P)

IR data

- Include the most relevant absorptions for functional groups and the strongest signal.
- S = strong, m= medium, w= weak
- It is best to identify the different absorptions

- IR (neat, cm^{-1}): 2971 (s, O-H, C-H), 1721 (s, C=O), 1419 (m, OH), 1296 (m, C-O), 948 (m, O-H).



Mass spectra

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

Purity



- **All purity analysis is like looking through a keyhole.**
  - HPLC: see only UV active compounds
  - NMR: see only 1H, 13C, 19F etc. Moderate sensitivity
  - Melting point deviations might indicate salts/silica
  - GC: only volatile compounds
  - Elemental analysis: universal method (costly)
- **Use multiple methods**

- **HPLC is used for compounds undergoing biological studies.**
- **NMR is often regarded sufficient for intermediates.**
  - **But, it is difficult to state a purity (impurities are unknown, low intensity signals are not seen)**

Different statement can be used.

- The compound appeared pure as judged from ^{1}H NMR and melting point.
- The compound contained small amount of EtOAc.
- ^{1}H NMR indicated that the compound contained 2% of a related impurity.
- If NMR contain multiple signals not accounted for: Compound **1** was isolated in semi-pure form.

Remember to include:

- Protocols and analytical data for side-product.

- **Do not** duplicate elements from the Result and Discussion section
  - Tables
  - Reaction schemes/Figures
- Less important stuff can be placed in Appendix.

End message

- A good experimental section allows another chemist to reproduce your results.

- A great experimental section allows another chemist to reproduce them without asking a single question.

