Experimental Synthetic Organic Chemistry

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I. Philosophy

A. Number of reactions per day: ≥ 2 Think(carefully) before do

B. Progress: daily

C. Solutions: weekly

D. Free time

1. Set up another reaction
2. clean glassware
3. Complete miscellaneous menial chores 杂事
4. Read

E. Caution vs. Speed

1. Cut corners when appropriate 走捷径
2. Know what corners have been cut
3. Slow down when necessary

II. Planning the Experiment:

A. Multiple/Parallel reactions.

1. Unrelated reactions: overlap (juggle) when possible
2. Related reactions: run in parallel

B. Scale

1. TLC: 50-100 μg
2. Small Preparative: 0.5-10 mg
3. Preparative: 10 mg- 1.0 g
4. Macroscale: >1.0 g

C. Scale-up

1. ≤ 3-5 fold
2. Avoid large scale prep—even literature preps—on first attempt.

Rule 1: Never change the reaction conditions substantially on an important scale-up.

- Assume that a change in conditions will cause complete failure of the reaction and ascertain whether the quantity of substrate is expendable.

Rule 2: Minimize scale within reason.

- Microscale is faster (vide infra) and consumes less material.
- Microscale allows you to work at the front of the synthesis longer.

Rule 3: You're not making progress if you're not working at the front of the synthesis.

- Bringing up staring materials is *not* making progress.

III. Starting the Reaction

A. Vessel

1. Round-bottom pipettes w/stir flea: 50 μg -≥ 2.0 mg
2. Kimble vials w /stir flea: up to ≥ 1g
   a. (Kimble Science Products: 1-609-794-5561)
   b. 2 mL, part # 150852
   c. 5 mL, part # 150855
   d. 10 mL, part # 1508510
3. Round-bottom flasks: only when necessary.

B. Covers

1. RB pipettes / Kimble vials: septa or NMR caps.
2. Flasks: septa or gas adapter.
3. Sealed tube reactions:
   a. Kimble vials w / NMR cap.
   b. RB flask w / gas adapter.
   c. Sealed NMR tube or 1/4" tubing.
   d. "bomb" w / Teflon joint.

Rule 4: Septa are moisture and oxygen permeable and are consumed by many corrosive chemicals.

C. Inert atmosphere

1. None, N_2, Ar
2. Dynamic vs. static
3. Closed or open system (Caution: use shields when running a reaction in a closed vessel.)

D. Sample/Reagent Purity:

1. Valuable Substrates: caution is advised
2. Inexpensive /easy preps: "purified prior to use" is overkill at times.
   a. shortpath distillation w / airgun is fast.
   b. Filtering through alumina plug.
3. Synthetic intermediates: always purify "Garbage in, garbage out.")
4. Solvent drying:
   a. Ether: Na/benzophenone.
   b. Note: LAH is not great and CaH_2 stinks
   c. Dry molecular sieves
   d. Hydrocarbons: Na/benzophenone/tetarglyme.
   e. P_2O_5

E. Sample/Reagent measurements:

1. Solids:
   a. ≥5 mg directly on balance.
   b. ≤5 mg (or when high precision is necessary) by stock solution. (Using 10 mg and discarding 90 mg of a commercially available reagent is *not* very wastergul.)
2. Liquids/solutions:

a. μL pipettes: 2-250 μL

b. *Costly* μL syringes: 5-100 μL

c. Gas-tight syringes: 100 μL-20 mL

d. Disposable (sort of) syringes: 100 μL-50 mL

e. Dropping funnels 滴液漏斗

f. Motor driven syringes

IV. Monitoring the Reaction

Rule 5: ***Always*** **monitor reactions from start to finish.**

A. Which reactions:

1. Brand new reactions
2. reactions you personally have done before
3. Literature procedures
4. Formation of transiently stable reactive intermediates!
5. *i.e.* all reactions.

B. When:

1. Before last reagent is added.
2. Immediately after last reagent is added.
3. No later than 2 minutes after start.
4. Every time the total reaction time triples.
5. Right before you work up the reaction.
6. Immediately after completion of the workup; immediately before purification.

C. How:

1. Through a low gauge needle, gas adapter or T-joint. 玉米管
2. Through opened joint under positive nitrogen flow.
3. Via quenched aliquots.

D. Thin layer chromatography (TLC):

1. Developing chamber Kodak Developing Jar
   房间, 室室

2. Plates: normally silica on glass from Merck

3. Solvent system

   a. EtOAc/hexane: become familiar with standard pair.

   b. Others:

   (1) tight separations

   (2) very low polarity: Et_2O/hexane

   (3) High polarity: methanol or acetone additives

   (4) Amines: 0.5% ~~HOAc~~ ? Et_3N

   (5) Acids: 0.5% HOAc

4. Visualization

   a. By sight

   b. UV

   c. "Jones Spray"; CrO_3(53 g)/H_2SO_4(46 mL) /H_2O (100 mL)

   d. I_2, Vanillin, phosphomolybdic acid

5. Caution:

   a. Warming in capillary

   b. Decomposition on plate

6. Notebook Record:

   a. Full scale drawing with accurate shading

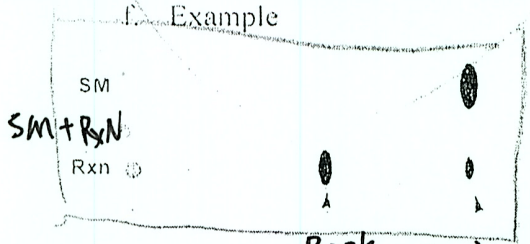
   b. Note solvent system and stain

   c. Note UV with dotted line

   d. Note any color oddities

   e. Purified sample numbers.

   f. Example



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E. Other Methods

1. Gas chromatography
2. NMR or other spectroscopy
3. ReactIR

Rule 6: **Work up a reaction when it is finished.**

V. The Workup:

A. Round-bottom flask-scale reactions: tedious, cumbersome, glassware-intensive.

B. KimbleVials/round-bottom pipettes.

1. Add water and shake.
2. Eliminate emulsions, suspensions, and gels with centrifuge.
3. Remove organic layer with pipette.
4. Filter directly through plug of Na_2SO_4 into *tared* pear-shaped flask.
5. Rotavap and pump to dryness (rotary evaporator will not remove all solvent).
6. Clean reaction vessel / stir flea concurrently with step 5.
7. Observe, smell, and weigh sample.

Rule 7: **Keep tract of mass balance through purification.**

Rule 8: **Do not let crude reaction products stand on your bench-top or in the freezer unnecessary.**

Rule 9: **Skip those costly, time consuming, and typically useless crude NMR spectra.**

- If the reaction appears to have proceeded smoothly, you will isolate a purified sample.
- The presence of potentially interesting by-products will be detected by TLC and their structures will only be determined after purification.

- A decision on whether to purify should not be based on a crude NMR spectrum.
- -Crude NMR spectra *are* meaningful when (1) you know *exactly* what you are looking for, or (2) instability to purification has already been determined or suspected.

-Caution: Rule 9 will be contentious among some advisors.

VI. Purification:

Rule 10: Take every opportunity to purify your products during the developmental stages of a synthesis.

-Garbage in, garbage out.

-One pot, multiple step sequences as well as multiple-pot reactions without intermediate purification are developed after the initial successes have been achieved using pure materials in a step-wise manner.

A. Flash chromatography:

W. C. Still et al. J. Org. Chem. 1978, 43, 2923.

1. Scale: 10 mg->20g
2. When? Whenever possible. (Scale ups w/o chromatography come later.)
3. Choosing a column size:
   a. see reference
   b. Increase length or diameter for improved resolution.
4. Solvent:
   a. 0.30-0.35 Rf; no lower than 0.25.
   b. You should have a good idea from the *extensive* TLC used to follow the reaction!
   c. Bad guesses can be costly.
5. Packing:

a. Under pressure.

b. Do not release pressure rapidly until gas and hot solvent are eluted.

6. Loading:

a. Place narrow band of a solution (not suspension or sludge) at top of column.

b. Rinse walls and elute several times quickly to avoid band broadening).

c. Add solvent without disturbing the surface.

d. Save a small sample of the crude product to compare to the eluent (50 μg) or for crude NMR analysis after-the-react (0.5-1.0 mg; vide infra)

7. Elution:

a. 2.0"/min (pre-set at packing stage)

b. Keep eluting until all of the materials are off the column.

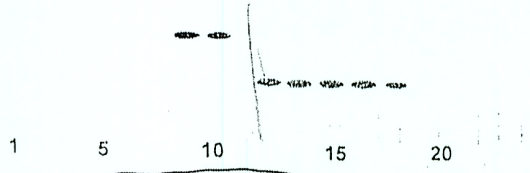
c. Changes in solvent to elute polar fractions require proper Rf determination in advance.

8. Monitoring by TLC:

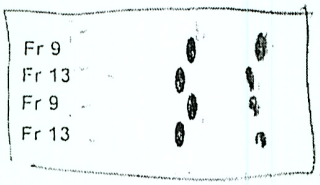
a. TLC plate on its side

b. Pipette, not capillary

c. Example



d. If purity is critical, check beginning and end of tail by full TLC or as follows:



9. Sample collection: No mixed fractions when characterization is critical.
10. Cleanup:
    a. Balance delayed cleanup versus premature disposal of silica.
    b. If possible, clean up column and test tubes during solvent removal.

B. Pipette Flash Chromatograph:
1. Scale: 0.5-10mg
2. 1.5" flash column in 5" pipette.
3. SolventL set Rf at 0.3 and then cut EtOAc concentration by 2.
4. Elute with a pipette bulb and monitor as above.

C. Preparative TLC:
1. Harsher than flash chromatography.
2. Can be useful for compounds that "streak"

D. MPLC/HPLC:
1. Micro scale: follow small quantities by UV
2. Macroscale: Prep 500 is very solvent intensive.

E. Recrystallization:
1. Scale: 100 mg-1 ton.
2. Highest possible purity.
3. A reflux condenser eliminates mixed solvent composition drift.

F. Distillation:
1. Prep GC: <500 mg
2. Bulb-to-bulb: 100 mg-5 g
3. Fractional / Short Path: ≥ 1.0 gm
4. Note: Volatile compounds are not easily handled on the microscale.
5. Partial Vacuum:
    a. aspirator: uncontrollable pressures.
    b. Manostat: J. Chem. Educ. 1989, 66, 181.

DME:

c. Vane Pump

VII. Characterization / Purity Determination:

A. ^{1}H NMR spectroscopy

1. Requires < 1.0 mg.
2. Don't use high field spectrometers unnecessarily.

B. ^{13}C NMR spectroscopy:

1. Excellent purity check
2. Needs ≥ 10 mg. (Can be deferred to a scale-up)

C. Heteronuclear NMR spectroscopy: ^{2}H, ^{11}B, ^{19}F others

D. IR:

1. Most under utilized physical measurement
2. 15 min determination of functional groups

E. MS:

1. Highly dependent on users interpretive skills
2. High resolution MS may no longer substitute for elemental analysis.

F. Elemental Analysis:

1. Destructive, costly, painful method of indirectly checking purity.
2. Inferior to ^{13}C NMR for most instances.
3. Minimal use in modern day organic chemistry (although central to organometallic chemistry still.)
4. Still required by some stubborn, knuckle-headed editors.

Rule 11: Make sure you collect the analytical data necessary to humor thesis committee members, advisors, and journal editors.

* Your primary concern in the early stages is to determine how well the reaction worked and if the final product is pure. Be careful to stay focused on the problem rather than spend all of your time collecting analytical data on compounds that may never appear in print.

- Missing data can be collected on a second or third preparation of the compound if necessary, but be sure to get it!

VIII. **Notebook Documentation:**

A. detailed experimental includes:

1. Reagent/substrate physical properties: MW's, densities.
2. Weights and or volumes of reagents/substrate.
3. JACS-style experimental.
4. Weight and color of the crude product.
5. Annotated TLC data including:
   a. Picture of TLC plate (see above).
   b. Correction of pure isolated fractions with corresponding TLC spots.
6. Details of purification.
7. Purified weight and percent yield.
8. Reference to spectra for each compound isolated.

B. Literature procedures include:

1. All of the above.
2. Literature reference.

C. Repeated procedure includes

1. Clear reference to previously detailed experimental (notebook/pg number).
2. Changes to procedure.
3. TLC data and spectra numbers

Rule 12: Keep a notebook that can be accessed by a third party.

IX. **Sample Storage and Disposal**

A. Consult the authorities on proper waste disposal.