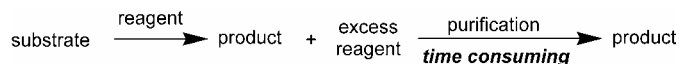


Organic synthesis in drug discovery

- Lecture 1: Solid phase synthesis techniques
 - Introduction – what is it?
 - Resins and linkers
 - Protecting groups
 - Building blocks
 - Example: solid-phase peptide synthesis (SPPS)
- Lecture 2: Solution phase techniques for high throughput synthesis!
 - Scavenger resins
 - “Fluorous” synthesis

Solution Phase Synthesis: Scavenger Resins

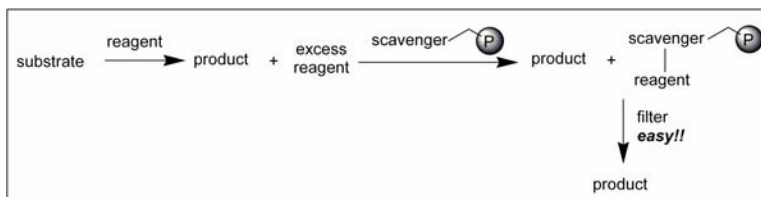
- Traditional solution phase synthesis (Chem 333, 335):



- Solid phase synthesis (last lecture):

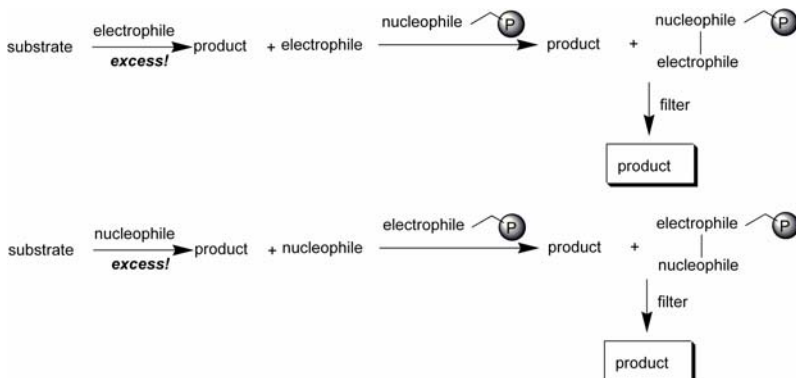


- Solution phase synthesis with scavenger resins (this lecture):



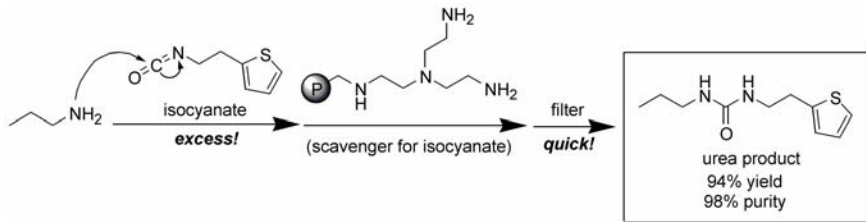
Solution Phase Synthesis: Scavenger Resins

- We'll consider two strategies in using scavenger resins
- The issue is whether the reagent is electrophilic or nucleophilic
 - If the reagent is electrophilic, use a nucleophilic scavenger!
 - If the reagent is nucleophilic, use an electrophilic scavenger!



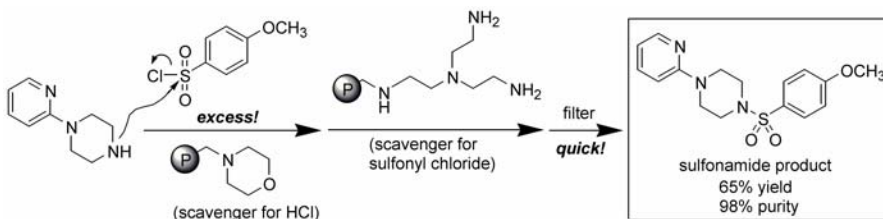
Solution Phase Synthesis: Scavenger Resins

- Electrophiles scavenged by a nucleophilic resin:
 - Example 1: urea synthesis



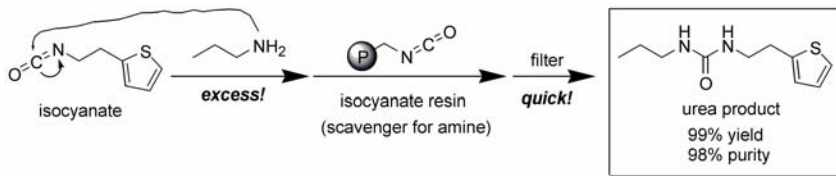
Solution Phase Synthesis: Scavenger Resins

- Electrophiles scavenged by a nucleophilic resin:
 - Example 2: sulfonamide synthesis



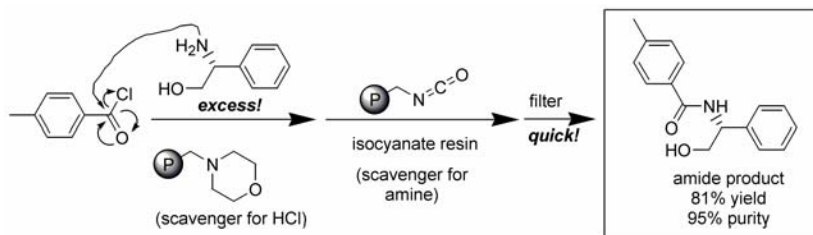
Solution Phase Synthesis: Scavenger Resins

- Or... alternatively
- Nucleophiles scavenged by an electrophilic resin:
 - Example 1: urea synthesis



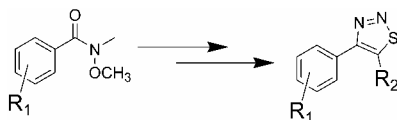
Solution Phase Synthesis: Scavenger Resins

- Nucleophiles scavenged by an electrophilic resin:
 - Example 2: amide synthesis



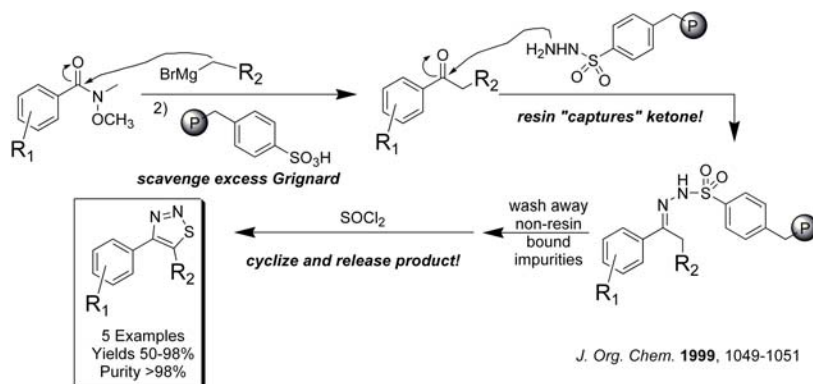
Solution Phase Synthesis: Scavenger Resins

- Cool example: "capture and release" with scavenger resins
 - Making 1,2,3-thiadiazoles (drug-like heterocycle scaffold)



Solution Phase Synthesis: Scavenger Resins

- Cool example: "capture and release" with scavenger resins
 - Making 1,2,3-thiadiazoles (drug-like heterocycle scaffold)

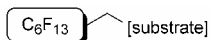


Solution Phase Synthesis: Scavenger Resins

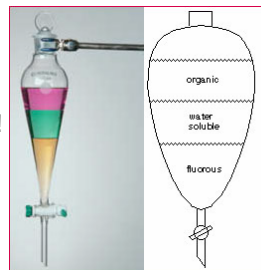
- References:
 - *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886.
(contains the examples that were showed here)
 - *Accounts of Chemical Research* **1999**, *32*, 18-26.
 - (more comprehensive review)

Solution Phase Synthesis: Fluorous technology

- What do we mean by "fluorous"?
 - A molecule with long tag containing many fluorine atoms – e.g.:

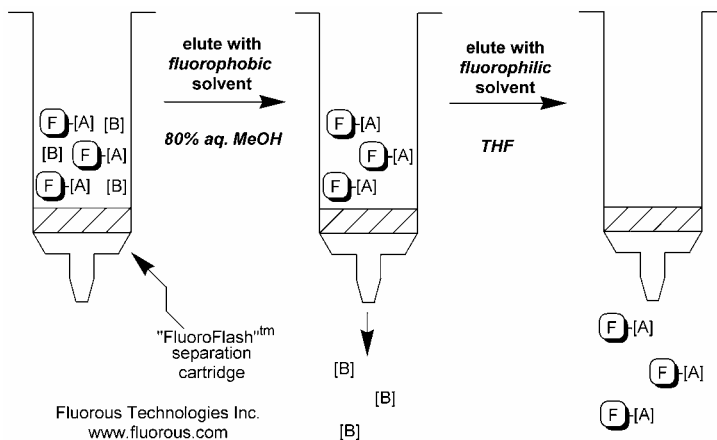


- What is special about fluorous molecules?
 - They have very weird chemical properties!
 - e.g. They can be extracted using "fluorous solvents"
 - Anything "non-fluorous" doesn't get extracted into fluorous solvent!



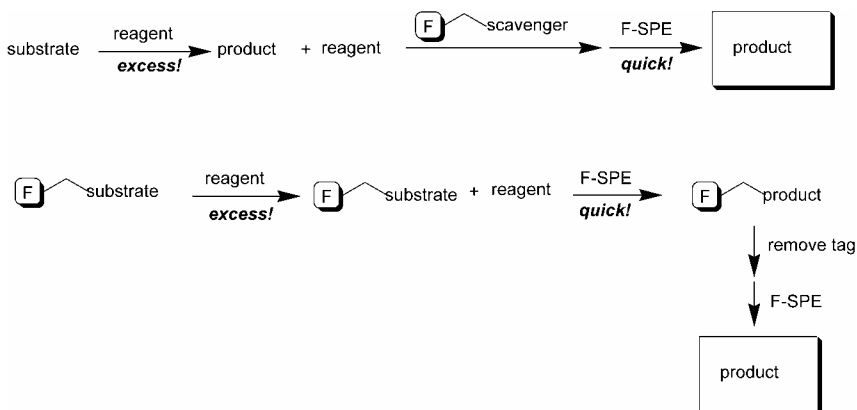
Solution Phase Synthesis: Fluorous technology

- A newer/quicker separation strategy
"Fluorous solid phase extraction" (F-SPE)



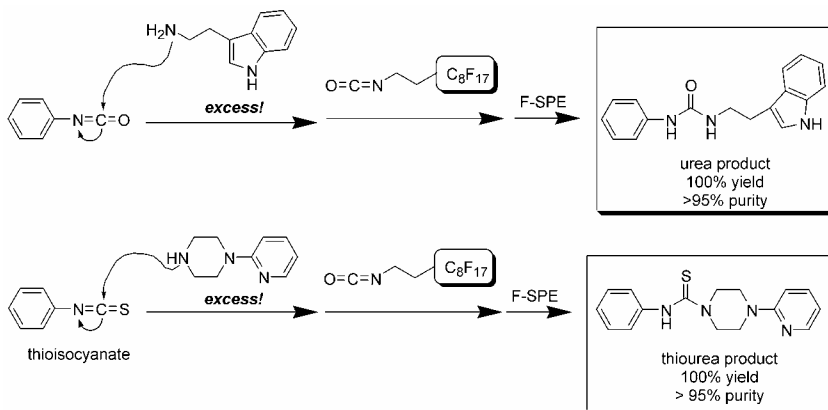
Solution Phase Synthesis: Fluorous technology

- Two fluorous scavenger strategies we'll quickly look at:



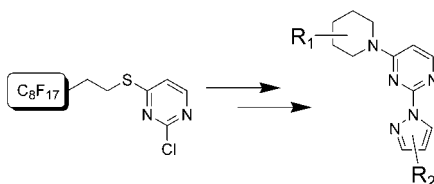
Solution Phase Synthesis: Fluorous technology

- Nucleophiles scavenged by an electrophilic fluorous scavenger
 - Examples: urea and thiourea synthesis



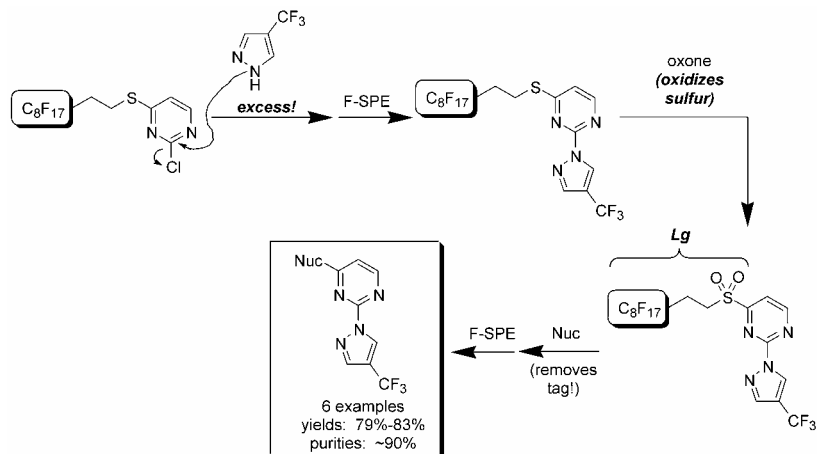
Solution Phase Synthesis: Fluorous technology

- Fluorous tagged substrates: Multi-step synthesis
 - Example: disubstituted pyrimidines (drug-like scaffold!)



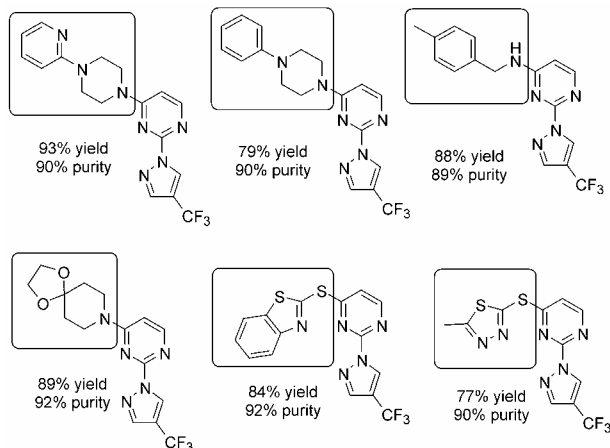
Solution Phase Synthesis: Fluorous technology

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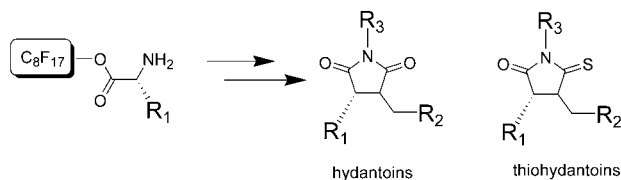
Solution Phase Synthesis: Fluorous technology

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Solution Phase Synthesis: Fluorous technology

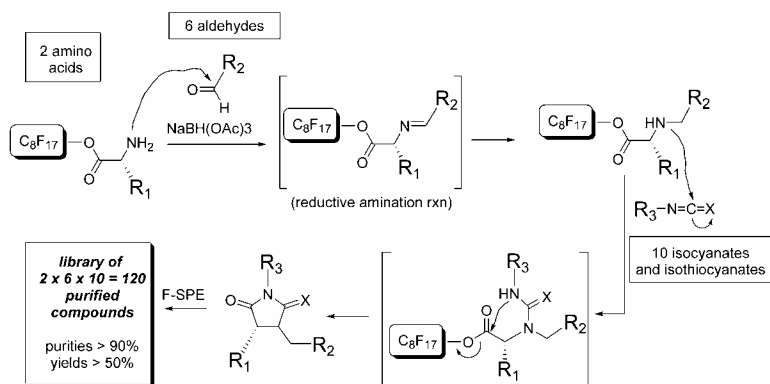
- Fluorous tagged substrates: Multi-step synthesis
 - Last example: trisubstituted hydantoins / thiohydantoins (another drug-like scaffold)



total library of
 $2 \times 6 \times 10 = 120$
 purified
 compounds

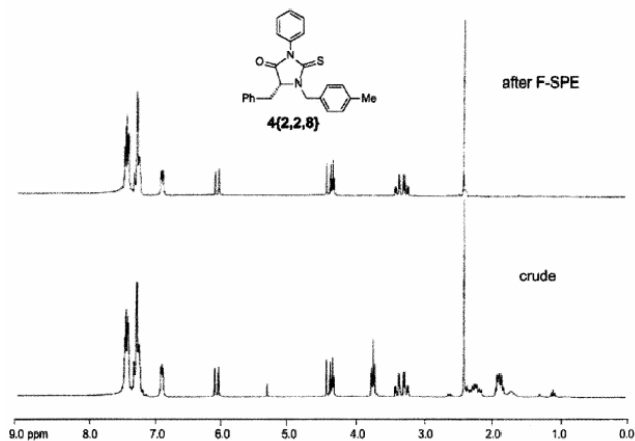
Solution Phase Synthesis: Fluorous technology

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Solution Phase Synthesis: Fluorous technology

- Fluorous tagged substrates: Multi-step synthesis
 - Examples: trisubstituted hydantoin / thiohydantoin



Solution Phase Synthesis: Fluorous technology

- References:

Tetrahedron **2003**, *59*, 4475-4489

(general review containing the examples cited here)

Fluorous technologies, inc. (<http://www.fluorous.com>)