Automated / Semi-Automated Synthesis of Natural Products and Pharmaceuticals

automation (ə təˈmeɪʃən) n.1. the technique, method, or system of operating or controlling a process by highly automatic means, as by electronic devices, reducing human intervention to a minimum. – The Free Dictionary

Seiko Fujii
Burke Group Literature Seminar
8.17.13
HANDS-OFF CHEMISTRY

Automated new SYNTHESIS TOOLS boost chemists’ efficiency

“We measure the value of automation not by the number of compounds it turns out, but by the diversity of the compounds.”

-Scott Sheehan
(Senior director of discovery research and technology)
November, 2012 issue of C&EN
A Remote-Controlled Medchem Lab: Drug Discovery in the 21st Century

Godfrey, A. G. et al. *Drug Discovery Today*. 2013, [http://dx.doi.org/10.1016/j.drudis.2013.03.001](http://dx.doi.org/10.1016/j.drudis.2013.03.001)
Total Synthesis of Complex Natural Products

Automated synthesis?

Manual synthesis

Person Time * Reproducibility * Safety

Solu8on-­‐Phase	
  Automated	
  Synthesizer

Advantage	
  over	
  solid-­‐phase	
  synthesizers:
• Most	
  reac’ons	
  op’mized	
  for	
  solu’on	
  phase
• Ease	
  in	
  reproducibility	
  from
discovery	
  scale	
  to	
  process

Takahashi Group Strategy:
1. Perform reactions manually
2. Group reactions into automable vs manual
3. Optimize conditions on the synthesizer
   [treat each reaction as individual process]

Advantage over solid-phase synthesizers:
• Most reactions optimized for solution phase
• Ease in reproducibility from
discovery scale to process

Disadvantage to solid-phase synthesizers:
• PURIFICATION method not general
ChemKonzert: Automated Synthesizer

**General automated reaction procedure:** Solvent addition, reagent addition, rxn (cool/heat/stir), aqueous work up, drying with MgSO$_4$, purification by SiO$_2$ plug (or connect to Combi flash)

**Manual procedure:** Reagent addition, Reaction set-up, evaporation of solvent after each run

Semi-Automated Total Synthesis of Spiruchostatin B

spiruchostatin B
histone deacetylase (HDAC) inhibitor

5 steps
Manual purifications

Total Synthesis of (±) Baccatin III (Taxol Precursor) Aided by Automated Synthesizers

- Mitotic inhibitor for cancer treatment
- 200+ groups attempted to synthesize
- 7 syntheses reported

Automated Synthesis of the Key Intermediate

- C-C bond forming reactions [radical cyclization, Shapiro rxn]
- oxidations and reductions [epoxidation, allylic oxidation etc]
- protection and deprotections
- other transformations

12-Step Manual Synthesis of B and D Rings to Complete the Total Synthesis of Baccatin (III)

“One PhD student carried out the entire sequence of the total synthesis from geraniol, through the key intermediate provided via an automated synthesizer”

Unsolved challenge:
uninterrupted multi-step automated synthesis platform?

Continuous Flow Multi-Step Synthesis

Traditional multi-step synthesis:

One flow, multi-step synthesis

Potential to SIMPLIFY and IMPROVE the SYNTHESIS PROCESS

Solution-Based Multi-Step Flow Synthesis

Suited for fast and exothermic rxns
- Enhanced mass and heat transfer
- Excellent mixing
- pH control
- safer to use hazardous reagents

Disadvantages
- Incompatible with solids
- difficult to translate from traditional synthesis
- more parameters to control
- difficult to automate purification

Solid-Phase Flow Chemistry: Immobilized Reagents

- Safer use of hazardous reagents
- Reagents can be recycled
- Aqueous work up and quench can be avoided
- Facile product isolation and separation
- Avoid chromatographic purification, distillation, crystallization

Steven Ley Group Targets for Flow Chemistry

- Spirangien A and B
- O-Methyl Siphonazole
- Grossamidine
- PQS
- Oxomaritidine
- Hennoxazole
- Imidazopyridazine
- Imatinib base
- 5HT1B antagonist
Solid-Phase Flow Chemistry to Alkaloid (±) Oxomaritidine

Solid-Phase Flow Chemistry:
20 mg of Alkaloid Oxomaritidine in 6 h

seven steps, 40% yield
(>90% purity)

Flow Synthesis of Anticancer Drug

Imatinib (Gleevec®)
Tyrosine Kinase inhibitor

Challenges:
1. Insolubility of reagents
2. Precipitation during reaction
3. Purification of intermediates

Flow Synthesis of Imatinib (Gleevec®) Analogues

QuadraSil-SA (SS-SA) sulfonic acid functionalized silica – high surface area
- Catch the intermediate
- Release with NH₃ in MeOH (2M)
- 47% (over 2 steps), >95% purity

Flow Synthesis of Imatinib (Gleevec®)

Flow Synthesis of Imatinib Analogues

Derivatization
R1:
All reduced level of Activity

R2:
Only benzimidazole Substituent retained Activity (75% inhibition)

Future Outlook

ENGINEERING DEVELOPMENT
Develop new technology to translate known reactions for automation

REACTION METHODS DEVELOPMENT
Develop new chemistry compatible with and optimal for automated technology

INTEGRATED EXPLORATION OF CHEMISTRY AND BIOLOGY
Evaluate newly prepared small molecules flowing directly from a reactor into a bioassay

"Using any new technology takes some adjustment, Sheehan acknowledges. "When chemists started to realize that these instruments weren't designed to compete with them, but to augment their capabilities and provide them with more time to focus on judgment-based, value-added activities, they really embraced the idea."