Rewiring Chemistry: Algorithmic Discovery and Experimental Validation of One-Pot Reactions in the Network of Organic Chemistry

Chris M. Gothard, Siowling Soh, Nosheen A. Gothard, Bartlomiej Kowalczyk, Yanhu Wei, Bilge Baytekin, and Bartosz A. Grzybowski

James Johnson
Current Literature 12/1/12
Wipf Group

DOI: 10.1002/anie.201202155
Chemistry of the future

- Atom Economy
- Step Economy
- Redox Economy
- Eintopf Reactions
  - One-pot synthesis
- Man vs. Machine
The PASE ideology

• Pot, Atom, and Step Economy
  – Reduce amount of solvents used in workup, purification, cleaning, contamination.
  – Idea to create greener chemistry to reduce environmental impact and cost.

• Annual Cost of Goods for production of pharmaceuticals $200 billion (2008)

• NIH annual budget ~31 billion
MCR as a “one-pot” synthesis

• Multi Component Reactions (MCR) have been around for over 140 years and can be used to readily access complex molecules from a series of simple precursors.

• Have been used extensively in drug discovery

• Products can also act as building blocks for further synthetic modifications.
Januvia a one pot approach


Hiyashi
Chematica

• Chemical Network
  – Seven million compounds linked by numerous chemical reactions
  – 86,000 chemical constraints
• Based on the Beilstein Database (BD) now known as Reaxys ca. 2009
Goals

• the algorithm on a par with the detailed synthetic knowledge of experienced organic chemists (including stereoselective syntheses)
iChemist: The Five Laws

• (1) If at least one reagent used in a reaction step is water sensitive, all other reactions in the sequence have to be performed in water-free environment.

• (2) If the reagent(s) used in one reaction step is oxidizing, no reducing reagents can be used concurrently in order to avoid redox reaction between reagents.

• (3) If the reagents used in any given reaction step are acidic, basic reagents cannot be concurrently present in order to avoid acid-base reaction between them.

• (4) If the reagents used in one reaction step contains hydride source, reagents containing proton source cannot be concurrently present.

• (5) The functional groups in the reagents must be compatible between reaction steps.
Synthesis of Quinoline derivatives

(i) POCl₃, 90°C, 6h
(ii) N₂ evaporation
(iii) Et₃N, THF-Water
80% lit

80% step-wise
77% one-pot

(i) POCl₃, 90°C, 4h
(ii) N₂ evaporation

80% step-wise
91% one pot

(i) POCl₃, 90°C, 4h
(ii) N₂ evaporation

(i) Cs₂CO₃ (aq)
(ii) phenylboronic acid, Pd(PPh₃)₄
dioxane.

88% lit

59% over 3 steps
95% one pot

(i) Cs₂CO₃ (aq), rt
(iv) Pd(PPh₃)₄,
phenylacetylene
water-dioxane
80 °C, 24 h

84% lit

35% lit

28% stepwise 2 steps
43% one pot

(i) POCl₃, 90°C, 3h
(ii) N₂ evaporation

(iii) POCl₃, 80°C, 4h
(iv) N₂

Ph

NH

EtO

EtO

EtO

88% lit

3 steps*
91% one pot

70% lit

77% one-pot

80% lit

3 steps
91% one pot

80% lit

59% over 3 steps
95% one pot

77% one-pot
Thiophene derivatives

(i) PhB(OH)$_2$, NaCO$_3$ (aq), Pd(PPh$_3$)$_4$, PhMe, EtOH

(ii) AcOH

75% step-wise 80% one pot

(i) Mg, THF reflux 2h

(ii) NiCl$_2$(dppp) 3 bromothiophene reflux, 1h

59% lit

81% lit

41% stepwise 3 steps 60% one pot

(i) Mg, THF reflux 2h

(ii) NiCl$_2$(dppp) 3 bromothiophene reflux, 1h

59% lit

81% lit

48% stepwise 2 steps 83% one pot

(iv) I$_2$, PhI(OAc)$_2$

59% lit

48% stepwise 2 steps 83% one pot

(v) NiCl$_2$(dppp)

reflux, 1h.

31% stepwise 3 steps 65% one pot

30min, 0°C
Two one-pot reactions to Ezetimibe

Problems with the program
Parallel optimization of synthesis and cost

• Cost analysis for optimization
  – Algorithm starts with the target and works backwards to the reactants. Then in a recursive manner the algorithm returns results for each level of reactants and products.
  – This process is based on a cost benefit analysis of the reactants (commercially available vs synthetically available)

• Compounds that are chemically similar will benefit from collective optimization.

Chemical Warfare

• Large scope of reactions available to produce a large number of compounds
• Some compounds have been used in chemical warfare and through the use of this program can teach a layperson how to produce them.
• Identifying through reactants screening which precursors are the right ones to regulate.
Nerve Agents

- G series (1930s)
  - Named after the Germans who made them.
  - Inhibit acetylcholine esterase
  - Suicide binder

- V series (1960s)
  - Originally discovered in attempts to make better insecticides.
  - VX $LD_{50}$ 10mg through skin contact
  - Cholinesterase inhibitor
Synthesis of VX
Conclusions

• Algorithm cannot recognize all possible incompatibilities of reactants
• Algorithm built off existing chemistry and is not discovering new chemistry
• By making this chemistry available to everyone are we threatened by what they can and will make.