Lecture 4: General Reactivity - III

Baran

Tuesday, April 5th, 2011

Background music: Grieg, Piano Concerto (suites 1 & 2)

Syntheses discussed:

- 8-azaergoline ring system (Doll, J. Org. Chem. 1999, 64, 1372)
- Singulair (montelukast sodium) (Merck, BMCL 1992, 1141 and 1995, 283)

Reading assignment: HC chapters 4, 10, 12, 16, 20; Li chapters 8.3.2 and 8.4; Schlosser handout

Partial list of concepts/transforms discussed:

Nucleophilic attack on hydrogen (metallation of heterocycles)
Reaction of heterocycles with radicals and electron deficient species
Minisci reaction
Ciamician–Dennstedt rearrangement
Effect of heterocycles on their substituents:
- By electron withdrawal
- By electron donation

Problems of the day:

1. ![Chemical structure](image)
   
   245 °C, Ph2O

2. ![Chemical structure](image)
   
   H2O/AzOH, cat. AgNO3, (NH4)2S2O8 (1.5 equiv)

3. ![Chemical structure](image)
   
   Chloroform, base
   
   Heterocycle with 2 chlorines (46%)
   
   Heterocycle with 1 chlorine (32%)

4. Propose a synthesis of the following compound from a pyridine-based s.m.

5. ![Chemical structure](image)
   
   1. nBuLi
   
   2. Mel
   
   ?
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Heterocyclic Chemistry

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**Meso-octamethylcalix[4]pyrrole**

- Cl₂C₄CO₂Na (15 equiv) in DME, 26-65%


- **Calix[4]pyridine**

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**EGFR Irreversible Inhibitor**

- F

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**Fmoc-NH₂**

- NH₂

- CH₂OCH₂CH₂OH

- i. AcOH, 98%

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**Final:**

8 steps (3 pots)
55% overall yield