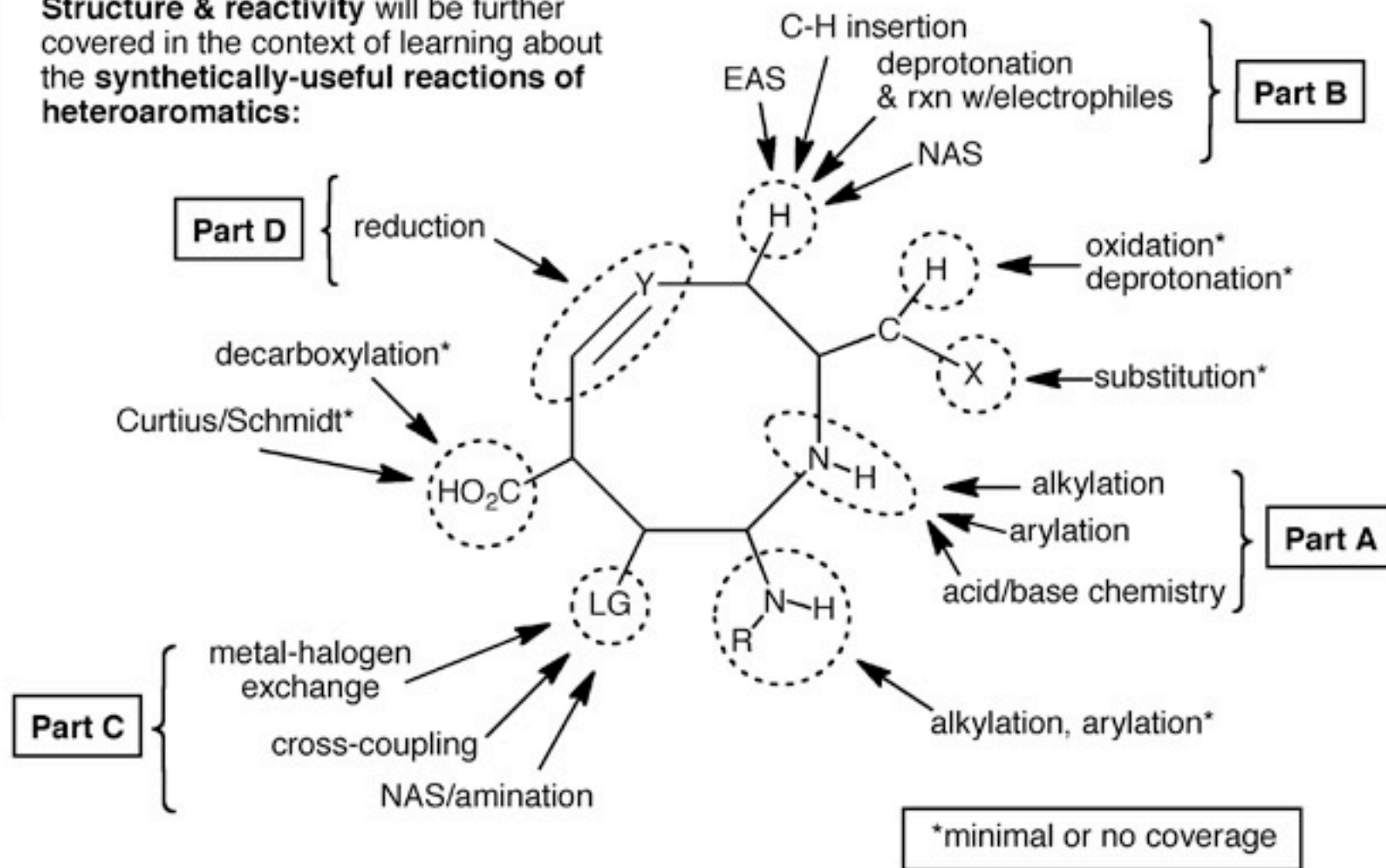


Toolbox, Part 3: Reactions of Heteroaromatic Compounds

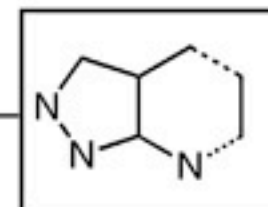


Structure & reactivity will be further covered in the context of learning about the **synthetically-useful reactions of heteroaromatics**:



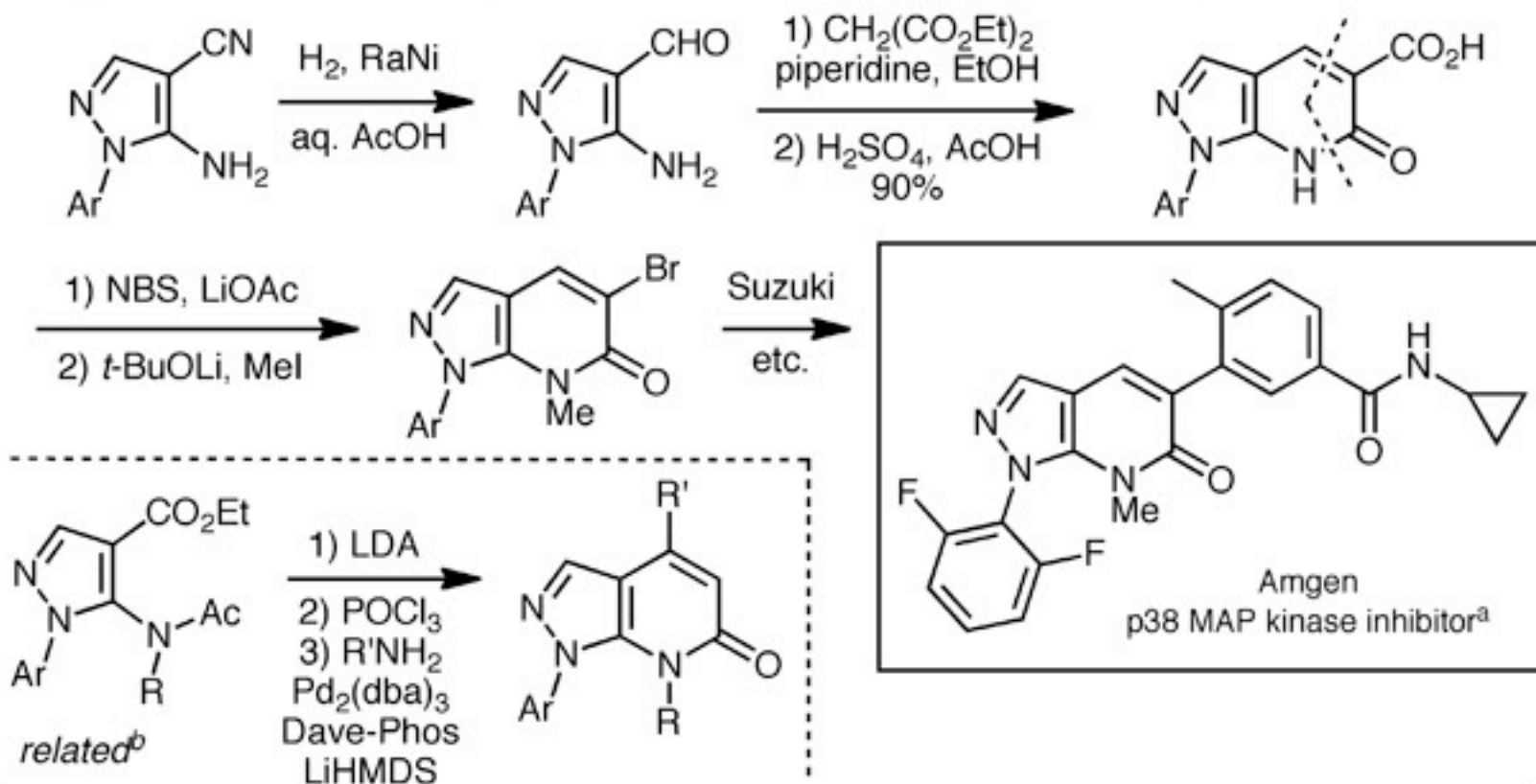
Heteroaromatics Fused to Another Heterocycle

Category #1 - Without Bridgehead Nitrogen



Pyrazole + pyridinone = pyrazolo[3,4-*b*]pyridinone

Amgen's Process route to a p38 MAP kinase inhibitor: Related to AICA cyclocondensation



a) R. R. Milburn, *et al. Org. Proc. Res. Dev.* **2011**, *15*, 31-43

b) R. P. Wurz, *et al. Bioorg. Med. Chem. Lett.* **2009**, *19*, 4724-4728

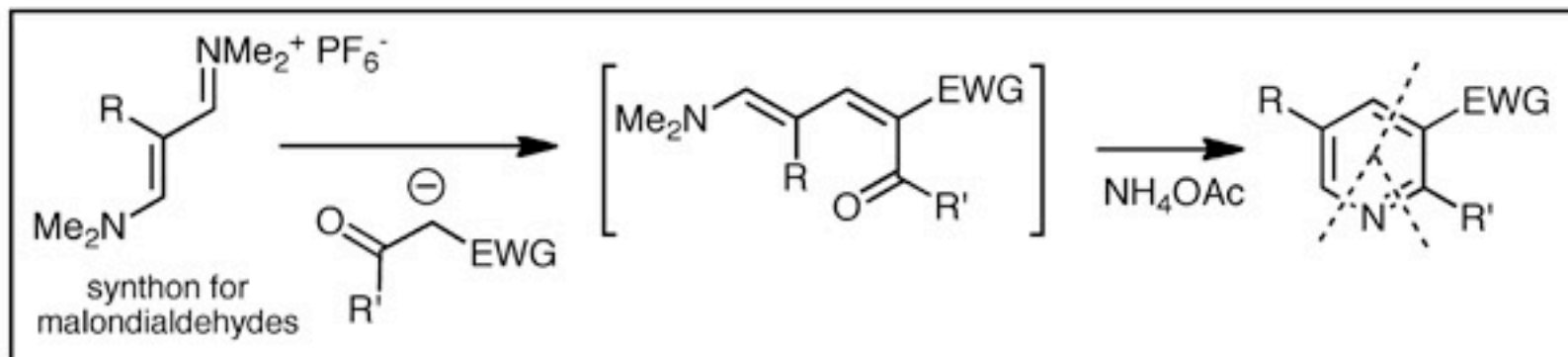
Sample Pages

Heterocyclic Chemistry - A Drug-Oriented Approach

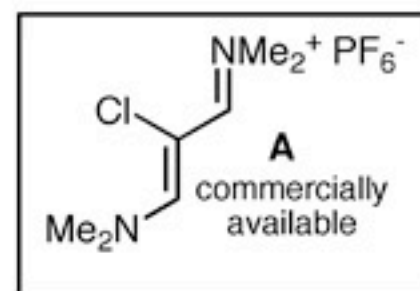
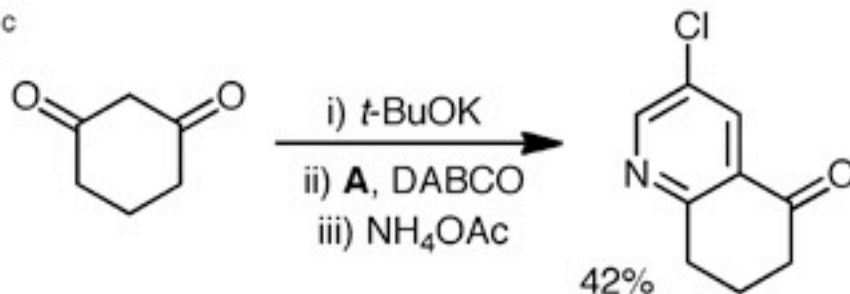
Pyridines: C-C then C-N Bond Formation

Pyridines from the **Merck synthesis**

vinamidinium salts and activated carbonyl compounds



e.g.^c



a) Petrich, *et al.*, *Tetrahedron*, **1995**, *51*, 1575

b) J.-F. Marcoux, E. G. Corley, K. Rossen, P. Pye, J. Wu, M. A. Robbins, I. W. Davies, R. D. Larsen, P. J. Reider *Org. Lett.* **2000**, *2*, 2339-2341

c) J.-F. Marcoux, F.-A. Marcotte, J. Wu, P. G. Dormer, I. W. Davies, D. Hughes, P. J. Reider, *J. Org. Chem.* **2001**, *66*, 4194-4199 and earlier work cited therein

Sample Pages

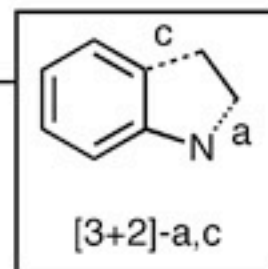
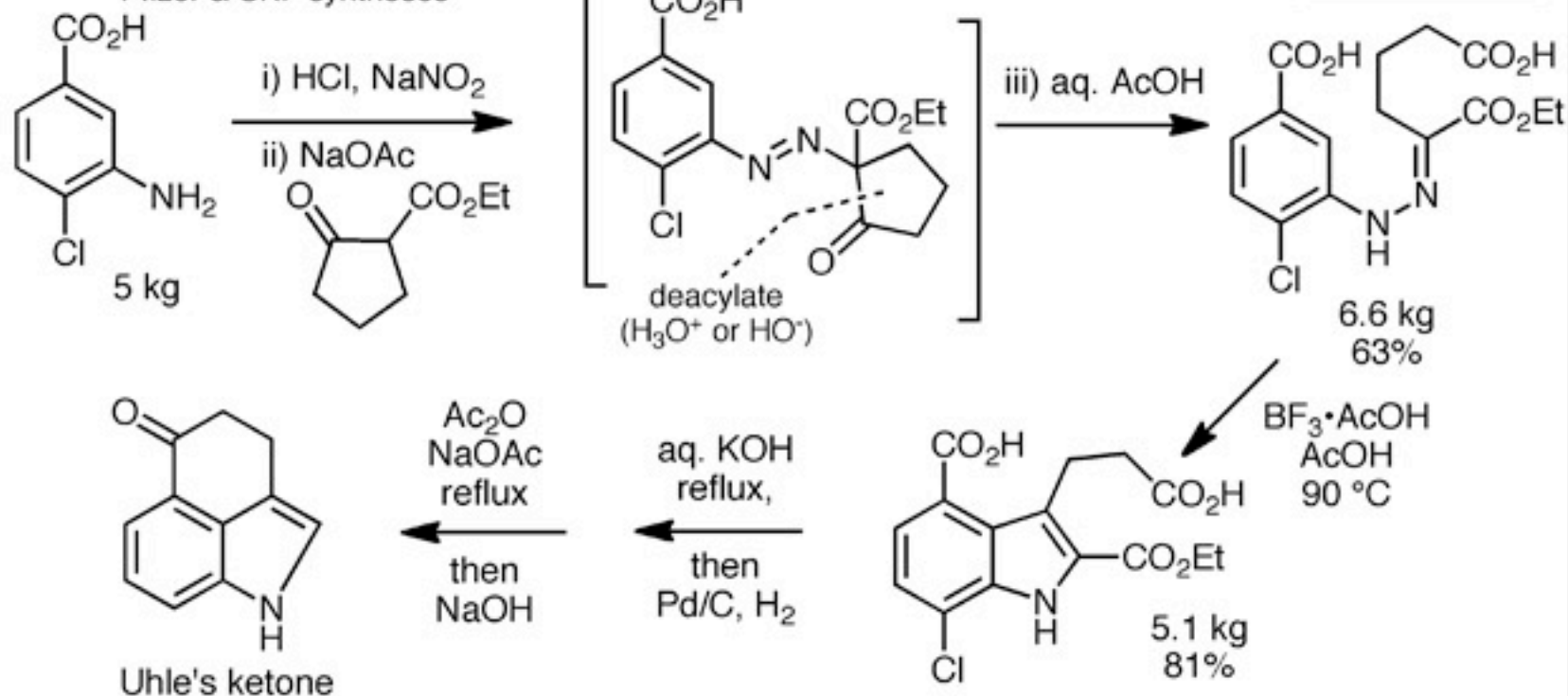
Heterocyclic Chemistry - A Drug-Oriented Approach

[3+2] Routes to Indoles

1. The Fischer Indole Synthesis, continued

Uhle's ketone: **Japp-Klingemann** reaction for the hydrazone synthesis

Pfizer & SKF syntheses



- R. E. Bowman, T. G. Goodburn, A. A. Reynolds *J. Chem. Soc. Perkin I*, **1972**, 1121-1123
- See also: M. D. Meyer, L. I. Kruse, *J. Org. Chem.* **1984**, 49, 3195-3199
- Process chemistry route to 5-methoxyindole-2-carboxylic acid featuring J-K reaction:
Y. Bessard *Org. Proc. Res. Dev.* **1998**, 2, 214-220

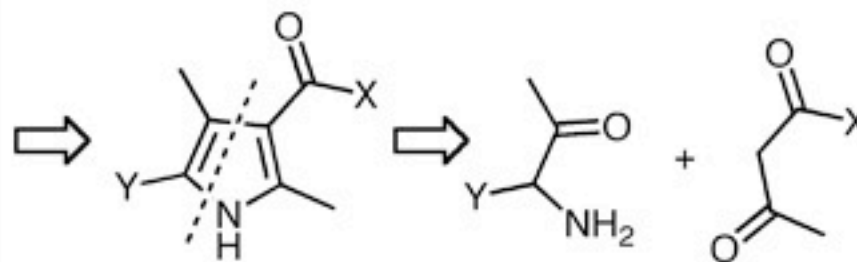
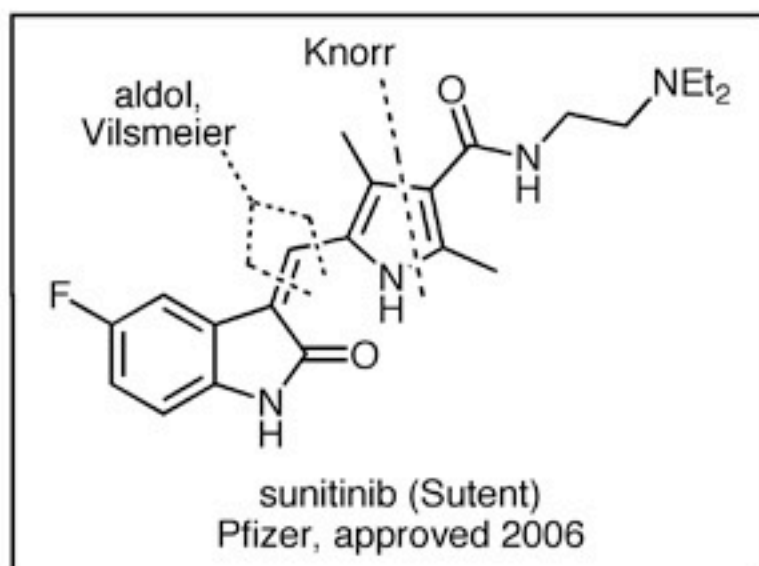
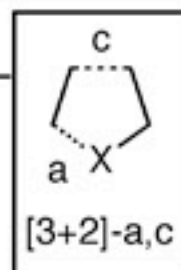
Sample Pages

Heterocyclic Chemistry - A Drug-Oriented Approach

[3+2]-a,c Routes to 5-Membered Ring Heteroaromatics (1 heteroatom)

2. The Knorr Synthesis of pyrroles, continued

Application to the protein kinase inhibitor **sunitinib** (Pfizer)

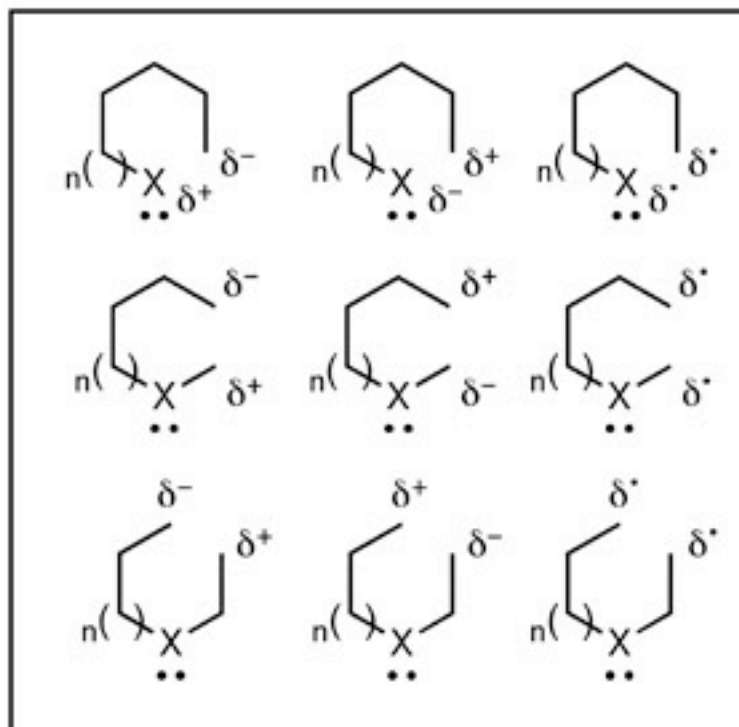
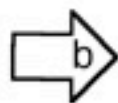
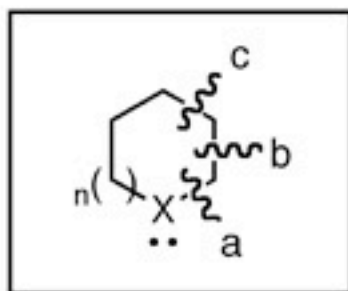


M. Pettersson in "Modern Drug Synthesis," J. J. Li and D. S. Johnson, Eds., Wiley, **2010**, Ch. 7
J. M. Manley, M. J. Kalman, B. G. Conway, C. C. Ball, J. L. Havens, R. Vaidyanathan,
J. Org. Chem. **2003**, *68*, 6447-6450

General synthetic strategies and retrosynthetic analysis

Nonaromatic Heterocycles

electronic retrosynthetic analysis



Sample Pages

Heterocyclic Chemistry - A Drug-Oriented Approach