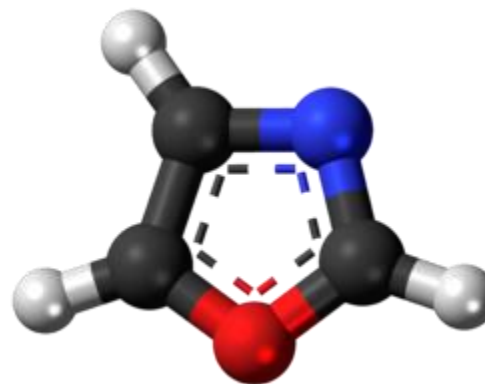


Summary and Synthetic Examples of Azoles



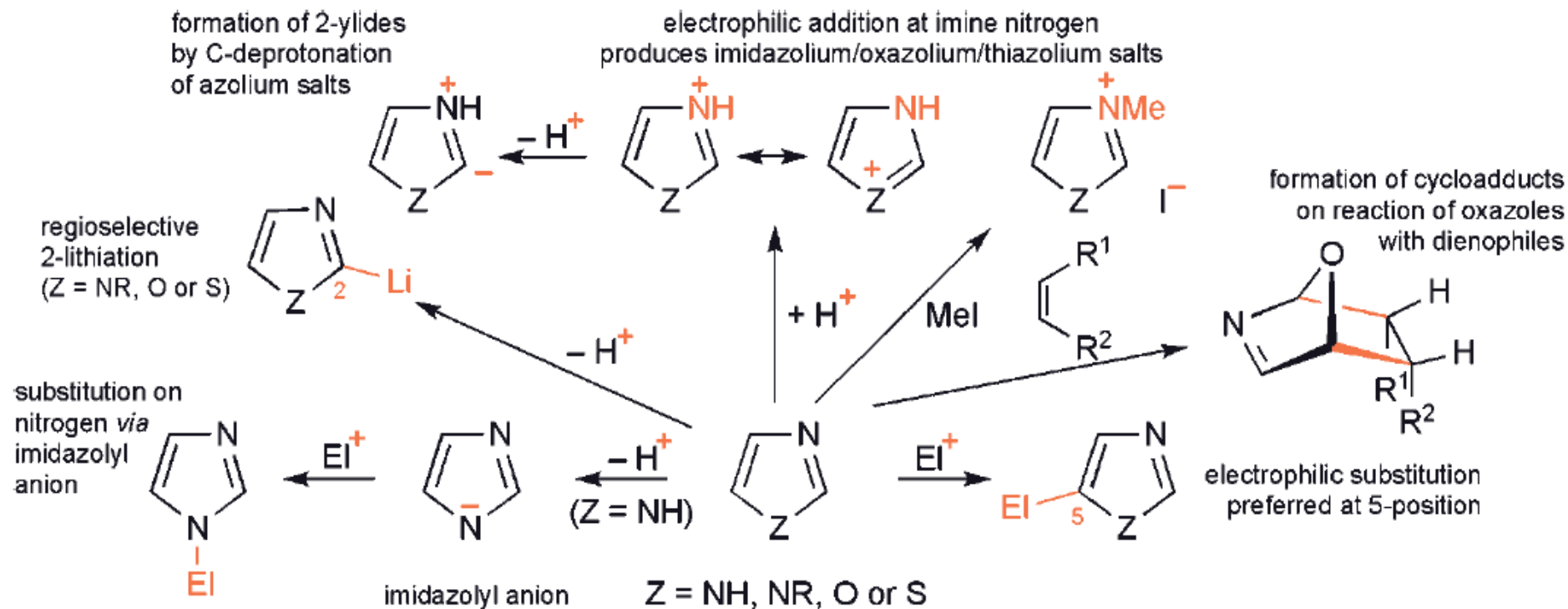
Instructor: Dr. Tanatorn Khotavivattana

E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

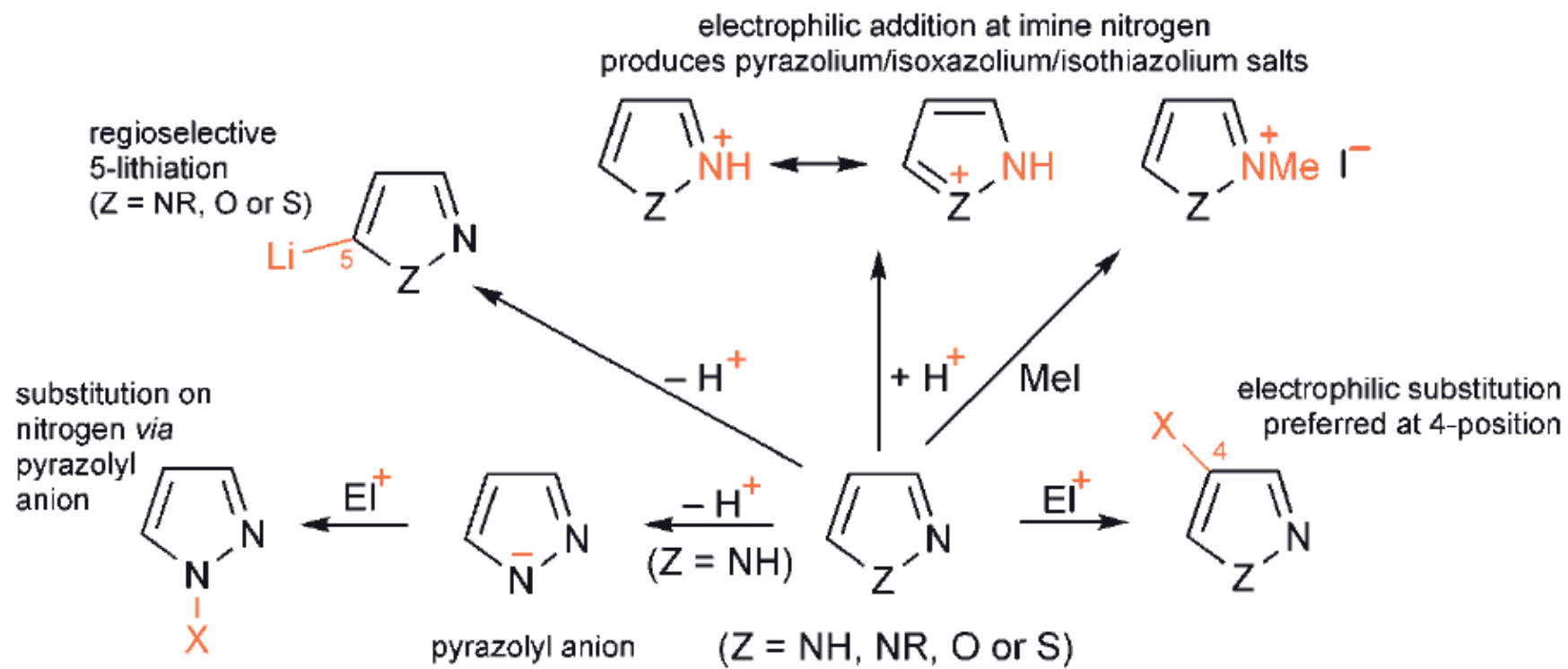
Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

Reactivities of 1,3-Azoles; Summary



Typical reactions of 1,3-azoles

Reactivities of 1,2-Azoles; Summary

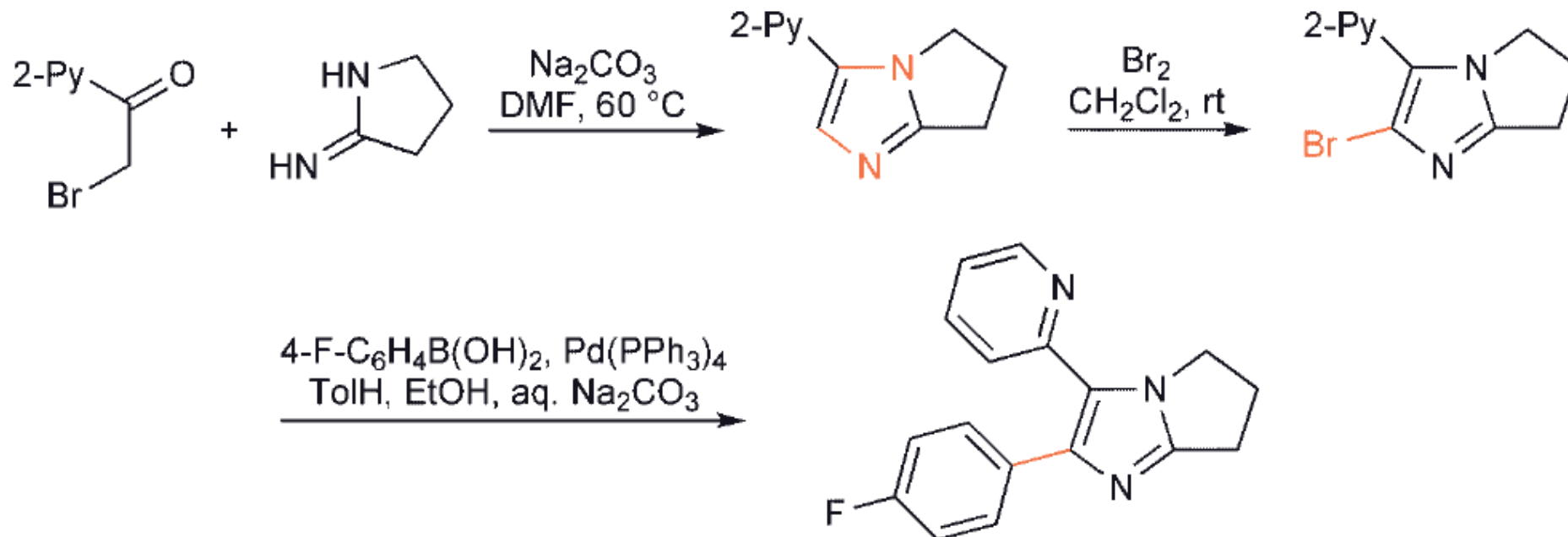


Typical reactions of 1,2-azoles

Notable Synthesis

Inhibitor of Transforming Growth Factor β 1, Type 1 Receptor

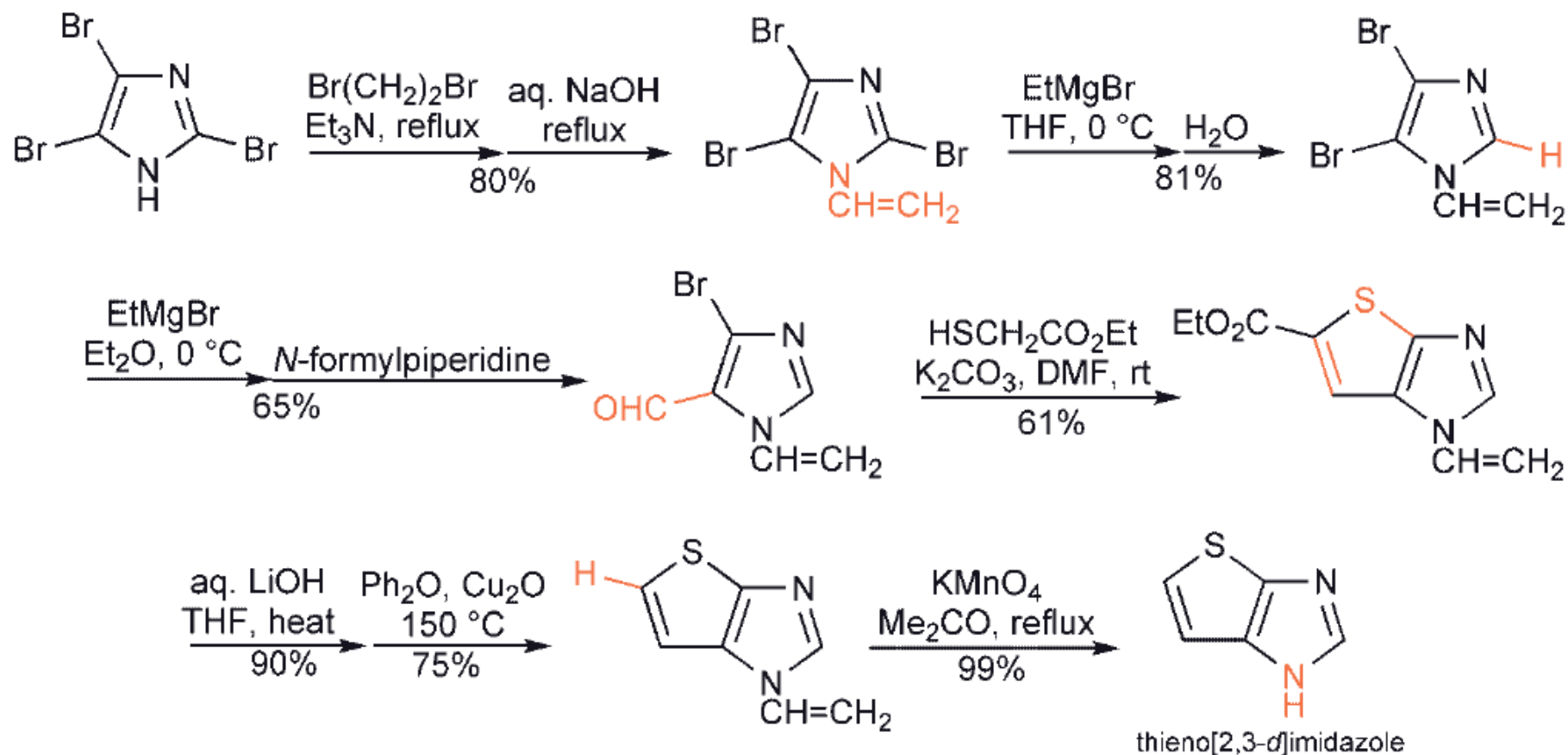
This sequence illustrates the interaction of an amidine and a 2-bromo-ketone with subsequent ring halogenation and palladium-catalysed coupling



Notable Synthesis

Thieno[2,3-d]imidazole

The synthesis of thieno[2,3-d]imidazole illustrates again the **selectivity in halogen–metal exchange processes** in imidazoles. In this sequence a vinyl was used as *N*-protecting group, and it includes a nucleophilic displacement of bromine from the 4-position, activated by the 5-aldehyde



Homework #1

1.1) Suggest structures for the halo-compounds formed in the following ways:

(i) 1-methylimidazole with excess Br_2 in $\text{AcOH} \rightarrow \text{C}_4\text{H}_3\text{Br}_3\text{N}_2$ (ii) then this with EtMgBr followed by water $\rightarrow \text{C}_4\text{H}_4\text{Br}_2\text{N}_2$ (iii) and this in turn with $n\text{-BuLi}$, then $(\text{MeO})_2\text{CO}$ gave $\text{C}_6\text{H}_7\text{BrN}_2\text{O}_2$

1.2) Draw structures for the intermediates and final products that are formed when:

(i) 4-phenyloxazole is heated with but-1-yn-3-one $\rightarrow \text{C}_6\text{H}_6\text{O}_2$; (ii) 5-ethoxyoxazole is heated with dimethyl acetylenedicarboxylate $\rightarrow \text{C}_{10}\text{H}_{12}\text{O}_6$

1.3) Deduce structures for the 1,3-azoles that are produced from the following reactant combinations: (i) 1-chlorobutan-2-one and thiourea; (ii) thiobenzamide and chloroacetaldehyde; (iii) thioformamide and ethyl bromoacetate

1.4) What imidazoles would be formed from the following reactant combination:

(i) $\text{MeN}\equiv\text{C}/n\text{-BuLi}$ and $\text{PhC}\equiv\text{N}$; (ii) 2-amino-1,2-diphenylethanone and $\text{H}_2\text{NC}\equiv\text{N}$?

Homework #2

2.1) Draw structures for the products obtained by reacting 3,5-dimethylisoxazole with NaNH_2 , then: (i) $n\text{-PrBr}$; (ii) CO_2 ; or (iii) PhCO_2Me

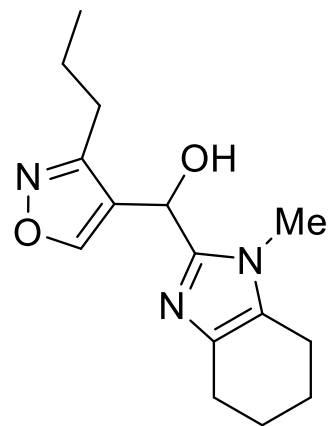
2.2) Deduce structures for the products formed in the following sequence: pyrazole/ $\text{Me}_2\text{NSO}_2\text{Cl}/\text{Et}_3\text{N} \rightarrow \text{C}_5\text{H}_9\text{N}_3\text{O}_2\text{S}$, then this with $n\text{-BuLi}/ -70^\circ\text{C}$, then $\text{TMSCl} \rightarrow \text{C}_8\text{H}_{17}\text{N}_3\text{O}_2\text{SSi}$, then this with $\text{PhCH=O}/\text{CsF} \rightarrow \text{C}_{12}\text{H}_{15}\text{N}_3\text{SO}_3$ (fluoride is a good nucleophile to attack silicon – deprotection of silyl group)

2.3) Draw the structures of the products that would be formed from the reaction of BnNHNH_2 with $\text{MeCOCH}_2\text{COCO}_2\text{Me}$

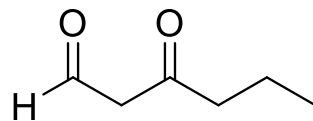
2.4) Draw the structures of the two products that are formed when hydroxylamine reacts with $\text{PhCOCH}_2\text{CH=O}$; suggest an unambiguous route for the preparation of 5-phenylisoxazole

Homework #3

Suggest a synthesis route for the following compound



from



and

