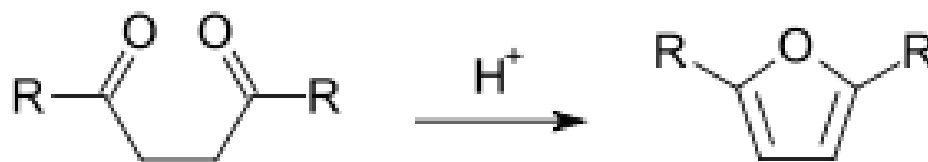


Paal-Knorr Synthesis

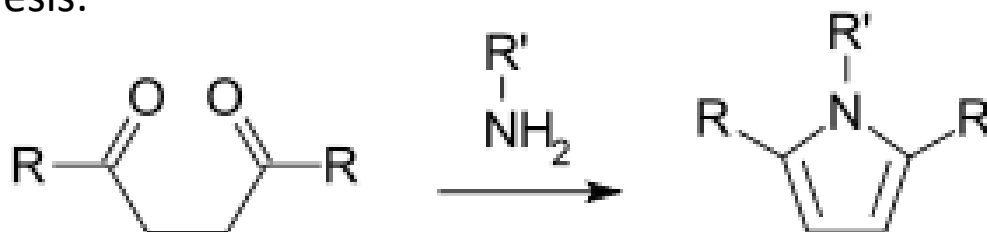
Liangleiming

20161025

Furan Synthesis:



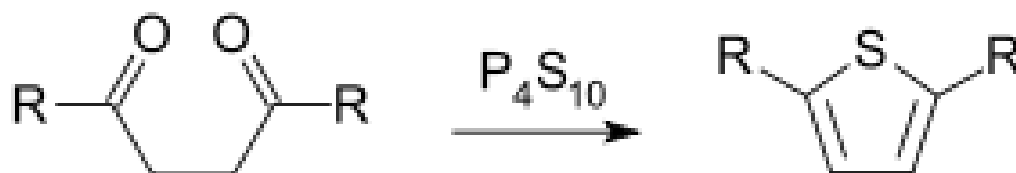
Pyrrole Synthesis:



Pyrazole Synthesis:

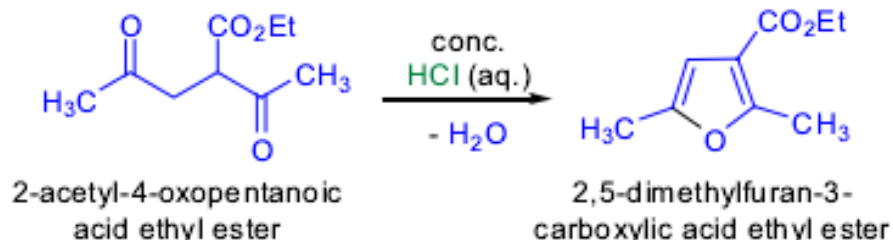
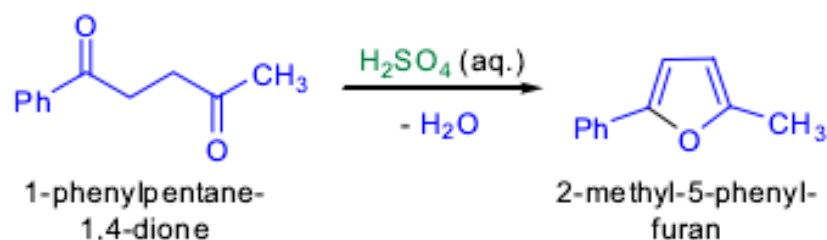


Thiophene Synthesis:



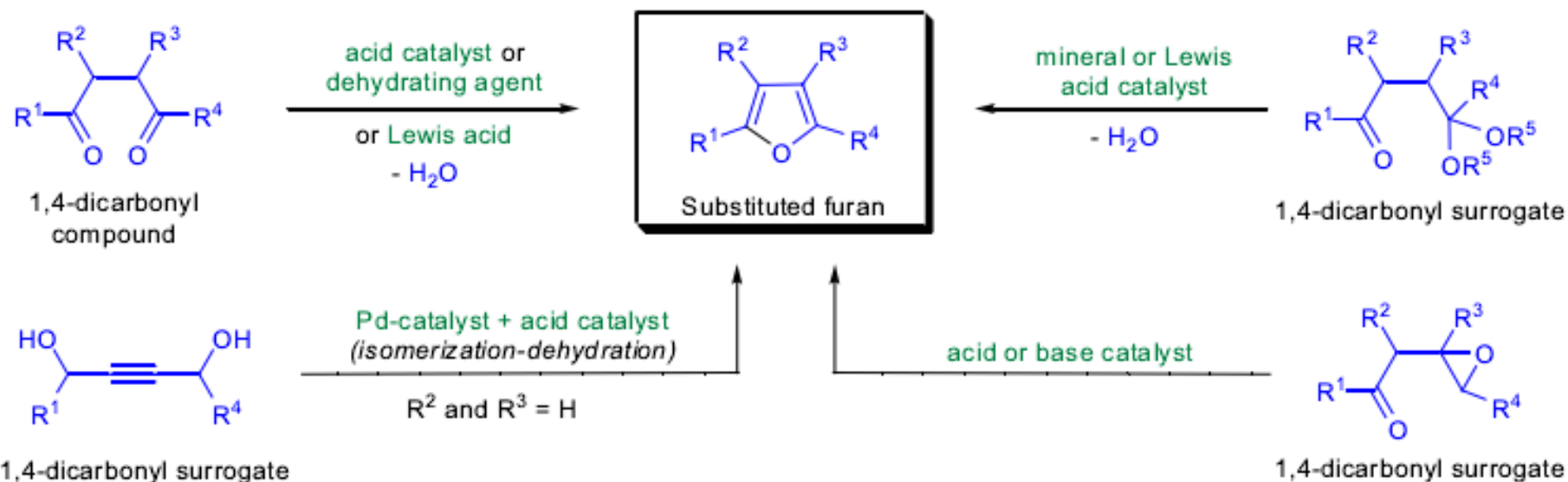
Furan Synthesis

Paal & Knorr (1884):



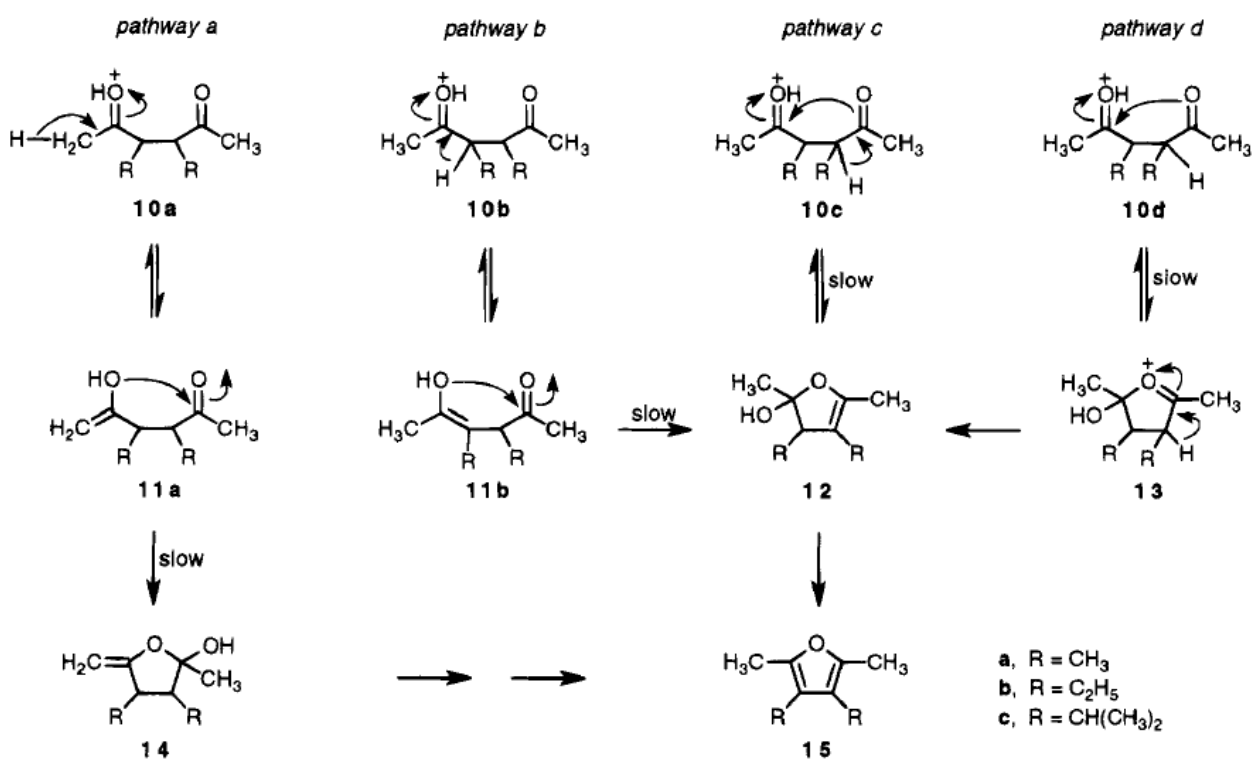
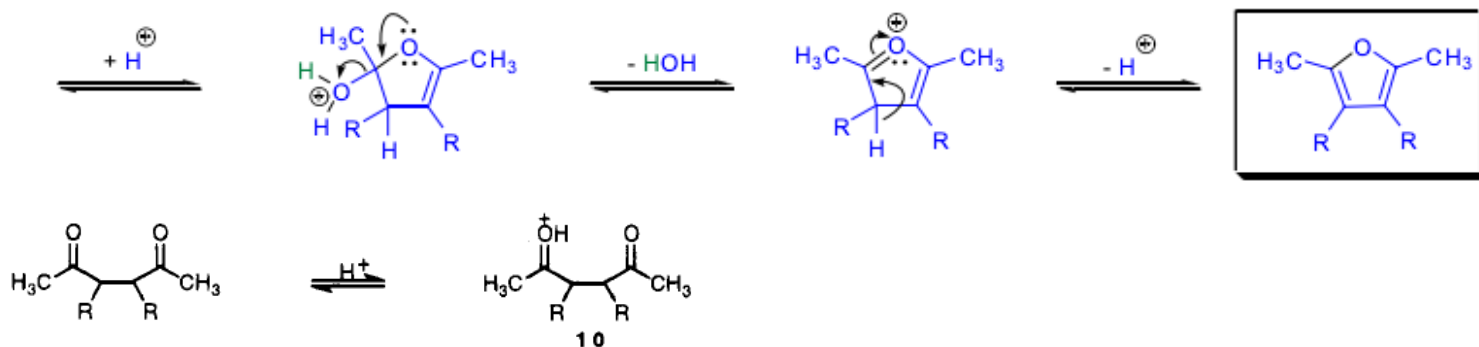
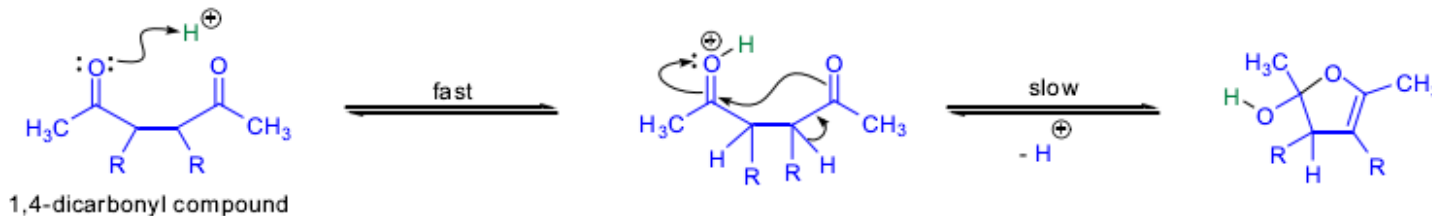
The General Formula:

Paal-Knorr furan synthesis:



$R^1 = H, alkyl, aryl$; $R^{2-3} = H, alkyl, aryl, CO_2-alkyl, CO_2-aryl$; $R^4 = H, alkyl, aryl$; $R^5 = CH_3, C_2H_5$; **acid catalyst**: HCl, H_2SO_4 , PPA, $p-TsOH$, $(COOH)_2$, Amberlyst 15; **Lewis acid**: $ZnBr_2$, $ZnCl_2$, $BF_3 \cdot Et_2O$; **dehydrating agent**: P_2O_5 , Ac_2O

Mechanism:



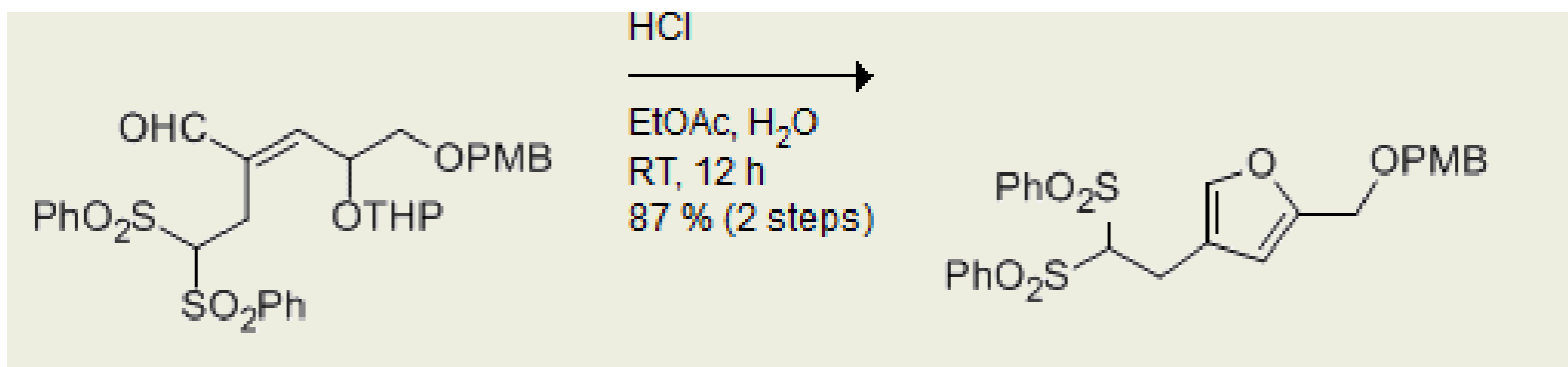
Amarnath, V. et al. *J. Org. Chem.* 1995,60, 301-307

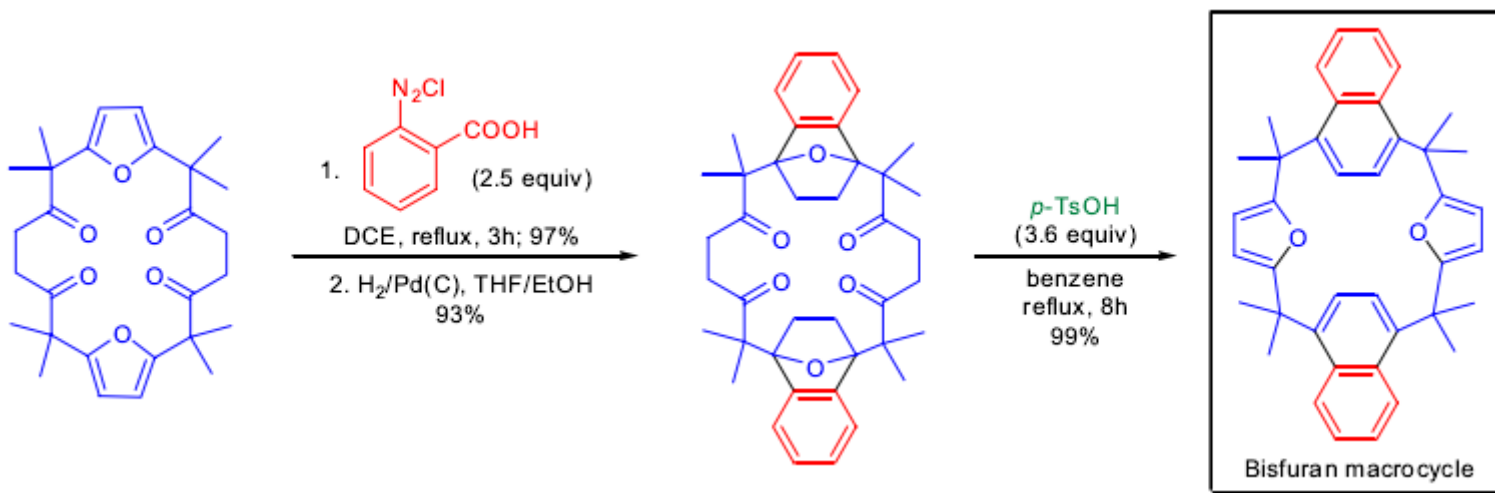
The General Features:

- 1) virtually any 1,4-dicarbonyl compound (mainly aldehydes and ketones) or their surrogates are suitable substrates;
- 2) the dehydration is affected by strong mineral acids such as hydrochloric acid or sulfuric acid, but often Lewis acids and dehydrating agents (e.g., phosphorous pentoxide, acetic anhydride, etc.) can be used;
- 3) the yields are usually moderate to good.

The two major drawbacks of the reaction are the relative difficulty to obtain the 1,4-dicarbonyl substrates, and the sensitivity of many functionalities to acidic conditions.

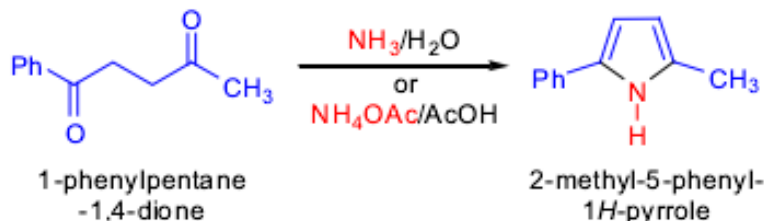
Synthetic Applications:



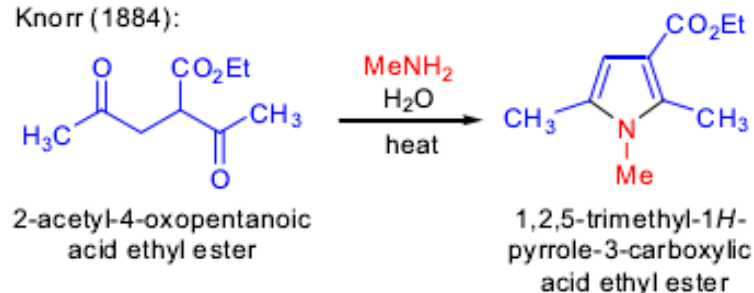


Pyrrole Synthesis

Paal (1884):

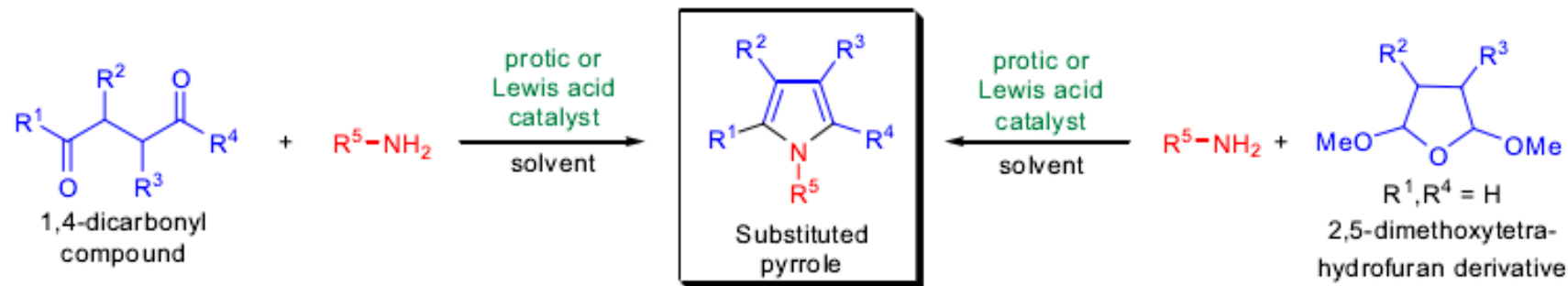


Knorr (1884):



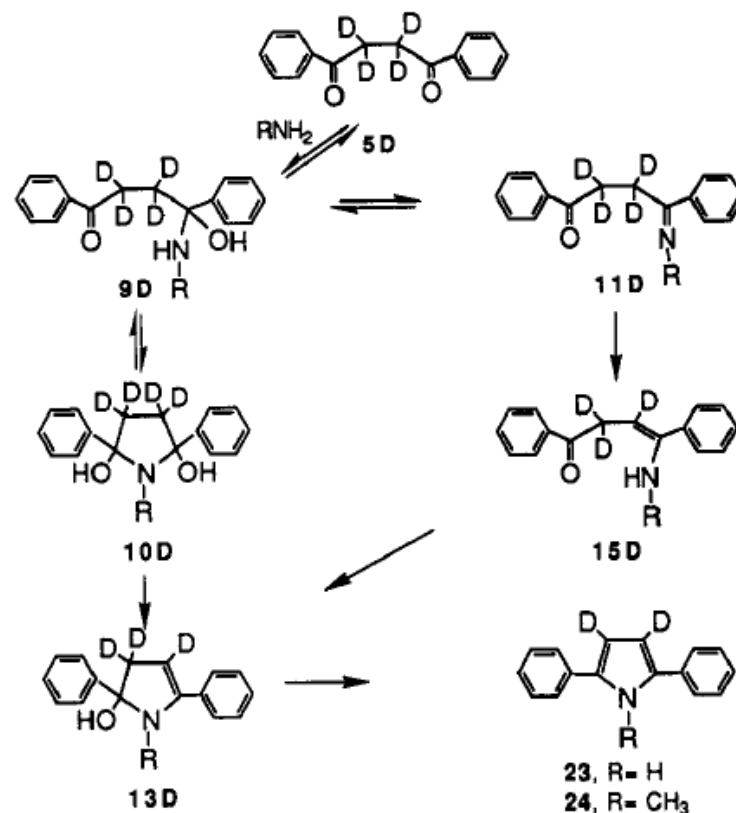
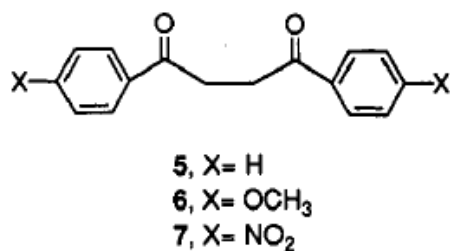
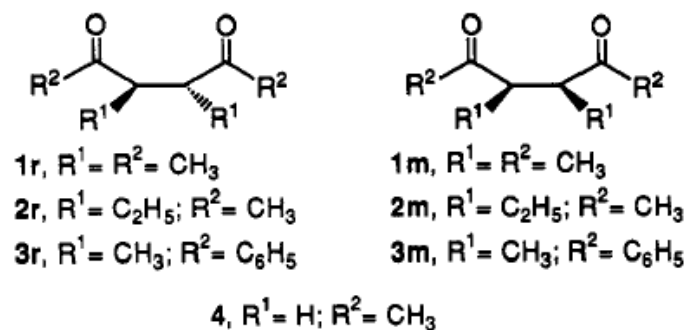
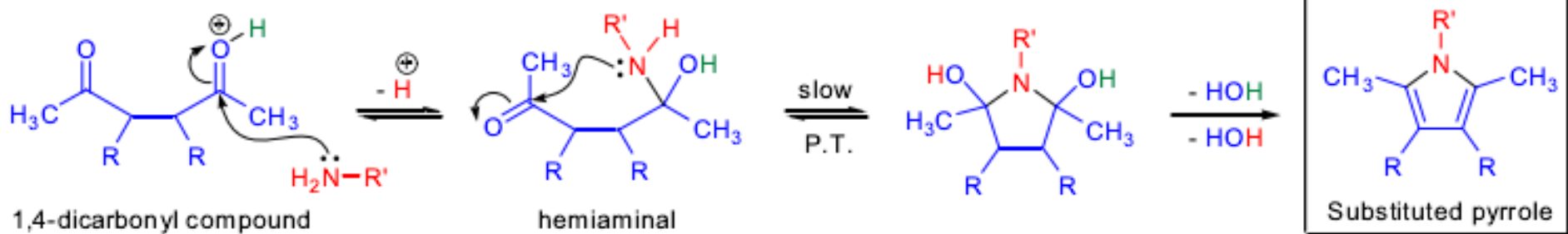
The General Formula:

Paal-Knorr pyrrole synthesis:



$R^1 = H, \text{ alkyl, aryl}; R^{2-3} = H, \text{ alkyl, aryl, CO}_2\text{-alkyl, CO}_2\text{-aryl}; R^4 = H, \text{ alkyl, aryl}; R^5 = H, 1^\circ, 2^\circ \text{ or } 3^\circ \text{ alkyl, aryl, heteroaryl, NR}_2, \text{NHR, NH}_2, \text{OH};$ **ammonia precursors:** $NH_4OAc, (NH_4)_2CO_3$; **catalyst:** zeolite, $Al_2O_3, p\text{-TSOH, CSA, zirconium phosphate, Ti(Oi-Pr)}_4, \text{microwave};$ **solvent:** MeOH, EtOH, $H_2O, \text{toluene, DMF, ionic liquid}$

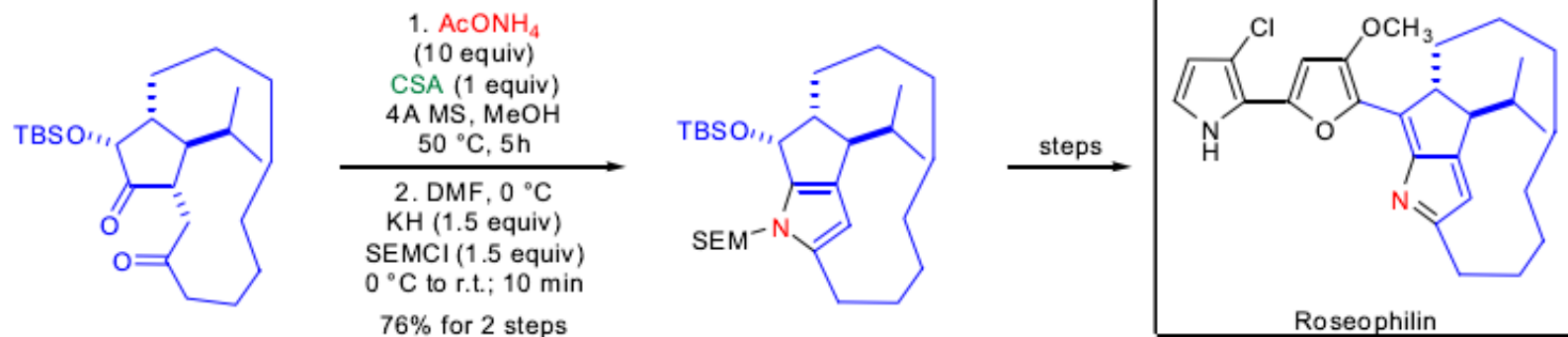
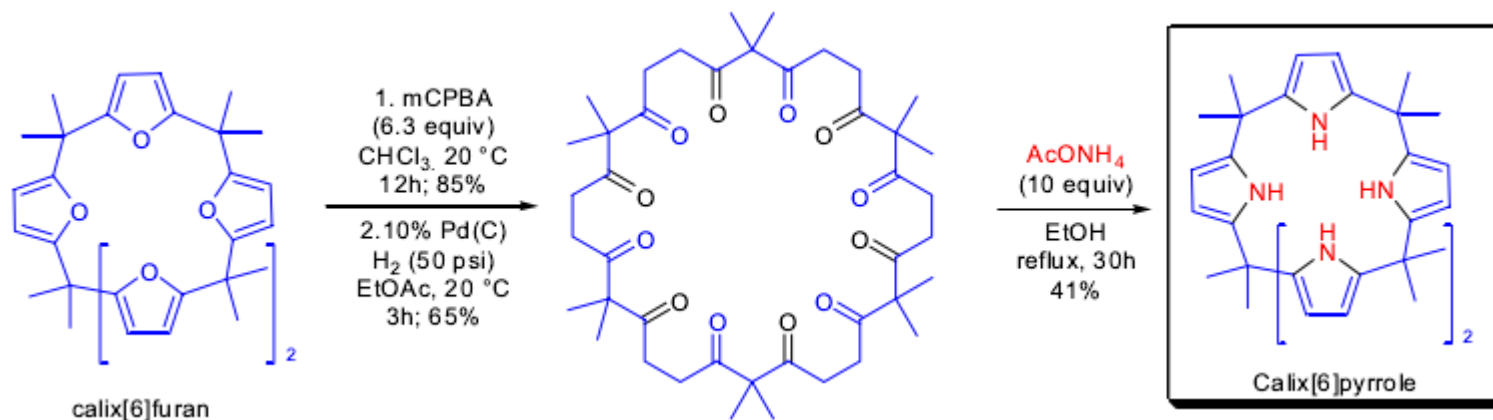
Mechanism:



The General Features:

- 1) practically any 1,4-dicarbonyl compound (mainly 1,4-diketones) or their surrogates are good substrates for the reaction;
- 2) 1,4-dialdehydes or keto aldehydes are used less often mainly because of their relative instability and the lack of general methods for their preparation;
- 3) the structure of the amine component can be varied widely, since ammonia, aliphatic primary amines, both electron-rich and electron-poor aromatic amines, and heterocyclic amines (e.g., aminopyridines, aminothoazoles, etc.) can be used;
- 4) α,ω -diamines afford dipyrrolyl derivatives tethered via their nitrogen atoms;
- 5) ammonia can be introduced either as a concentrated aqueous solution, as ammonium acetate in an alcohol solvent or ammonium carbonate in DMF at high temperature;
- 6) the relatively basic alkylamines do not react if the acidity of the reaction medium is below pH 5.5, while aromatic amines usually undergo cyclization only when $\text{pH} < 8.2$ and the highest yields are observed between pH 4.5 and 5.5;
- 7) besides protic acids, certain Lewis acids such as $\text{Ti}(\text{O}i\text{-Pr})_4$, as well as layered zirconium phosphate also catalyze the reaction;
- 8) the solvent of choice depends on the type of amine used, and it can range from polar protic to dipolar aprotic all the way to nonpolar solvents;
- 9) yields range from good to excellent and occasionally can be close to quantitative.

Synthetic Applications:

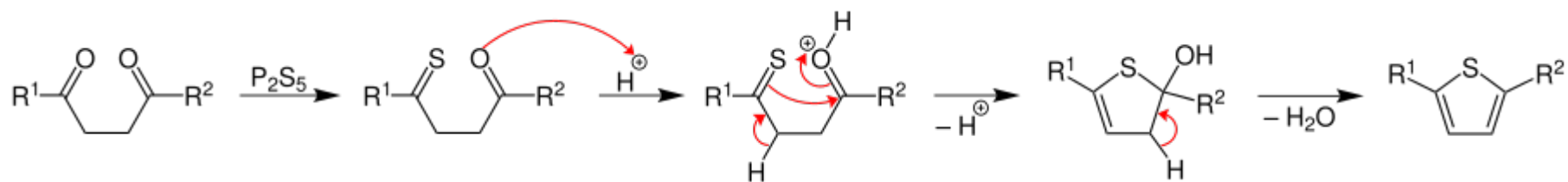


Pyrazole Synthesis



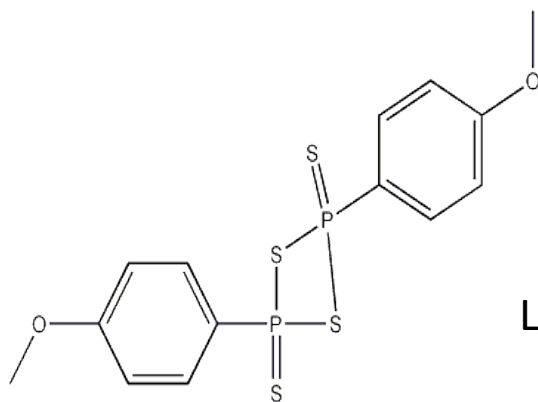
a synthesis of pyrazoles from 1,3-dicarbonyls and hydrazines, hydrazides, or semibicarbazides. This synthesis occurs via a condensation mechanism similar to the Paal-Knorr, however if a substituted hydrazine is used, it results in a mixture of regioisomers where the substituted heteroatom is either next to the R¹ substituent or the R³ substituent.

Thiophene Synthesis



Synthesis of a thiophene requires a sulfurizing agent which is typically a sufficient dehydrator, such as phosphorus pentasulfide, Lawesson's reagent, or hydrogen sulfide.

Campaigne, E.; Foye, W. O. *J. Org. Chem.* 1952, 17 (10): 1405–1412



Lawesson's reagent