O'Malley

Pyridine Synthesis: Cliff Notes

Group Meeting
6/9/2004

Note: Due to time constraints, this is not an exhaustive exploration of the myriad ways to create substituted pyridines. This summary focuses on ring-construction reactions, rather than functionalization of existing pyridine rings. Quinolines and Isoquinolines can be considered substituted pyridines; however they possess their own rich chemistry and deserve their own summary. This review summarizes their chemistry only insofar as it pertains to pyridine chemistry in general.

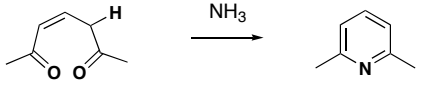
General approaches to pyridine rings:

Most synthses of pyridine rings rely upon one of two approaches: the condensation of carbonyl compounds or cycloaddition reactions. There are exceptions, such as ring expansion from 5-membered rings, but these approaches are generally low-yielding, narrow in applicability, or both.

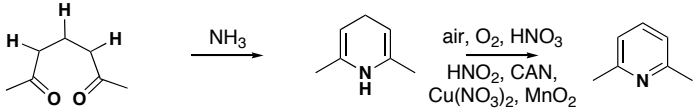
Condensation approaches to pyridines:

1. Condensation of 1,5-dicarbonyls

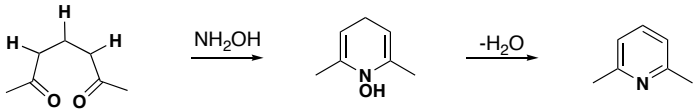
Condensation of 2,3-ene-1,5-diones with ammonia is the simplest approach, but offers relatively little simplification:



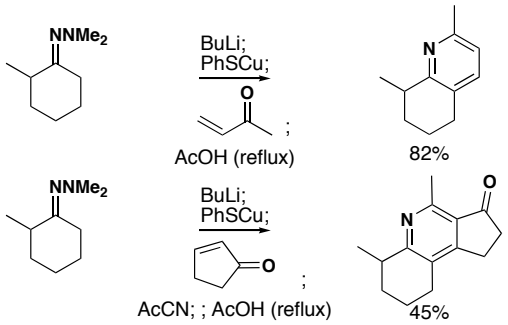
A somewhat simpler approach relies on condensation of 1,5 diones followed by oxidation



The oxidation step can be avoided by using hydroxylamine instead of ammonia

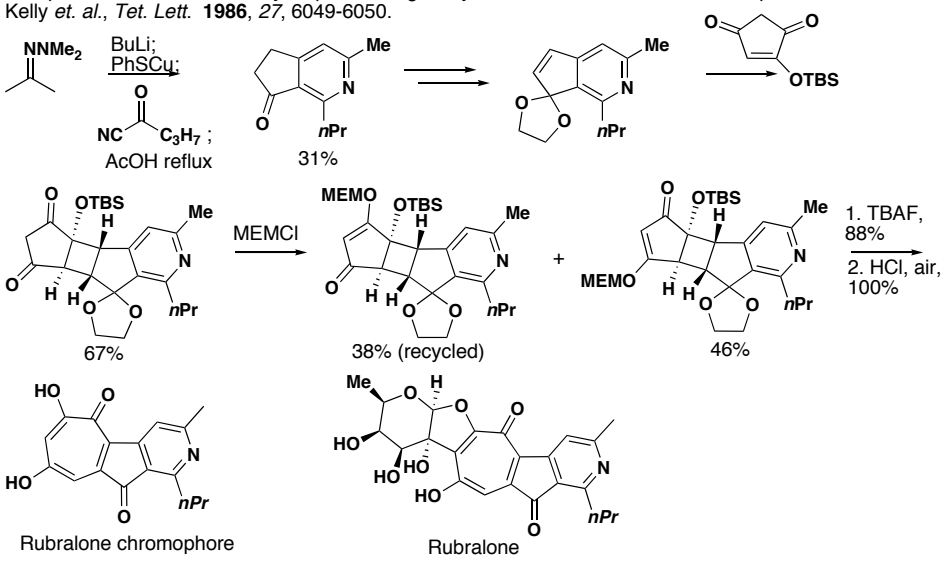


Several variations on these themes have been developed, such as the use of dimethyl hydrazones Kelly and Liu, *JACS*, **1985**, *107*, 4998-4999.



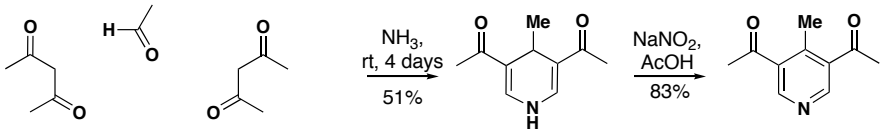
Yields were generally acceptable for enone procedure, low for acyl cyanide procedure. Reaction requires extended time.

This procedure served as a key step in an elegant synthesis of the Rubrolone chromophore Kelly *et. al.*, *Tet. Lett.* **1986**, *27*, 6049-6050.



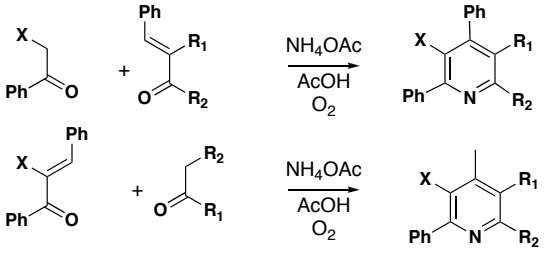
2. Hantzsch Synthesis

Condensation of an aldehyde, two equivalents of a 1,3-dicarbonyl, and ammonia yields symmetrical pyridines.



Modifications have been made to allow for synthesis of asymmetric pyridines, by performing one or more of the condensation steps prior to the reaction.

Robinson *et. al. J. Het. Chem.* **1998**, *35*, 65.



procedures have also been developed using enamine esters and enones

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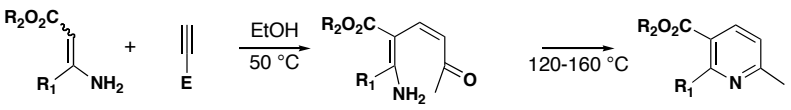
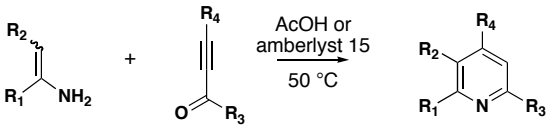
3. Bohlmann-Rahtz Synthesis



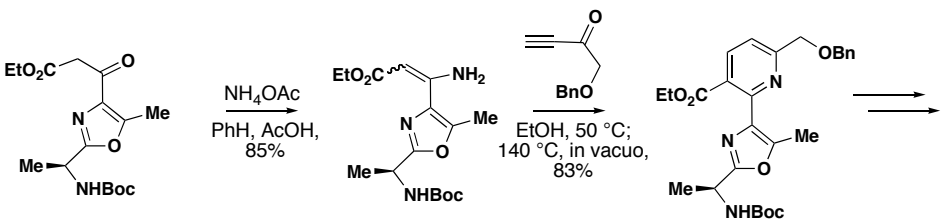
High temperatures in the dehydration step can be avoided by performing the condensation under acidic conditions. Bagley *et. al. Synlett*, **2001**, 1149-1151.

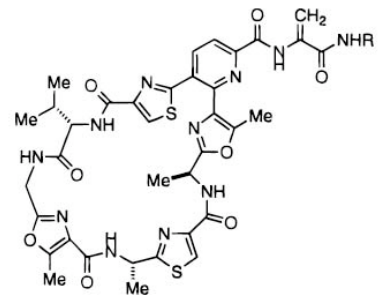


yields 65-95% for R_1= Me or 2-furyl, R_2= EtO_2C or $tBuO_2C$ R_3= Me or CO_2Et, R_4= Alkyl, Ph, H, or TMS

use of amberlyst 15 improved yields for R_2= $tBuO_2C$ and R_4 = Ph

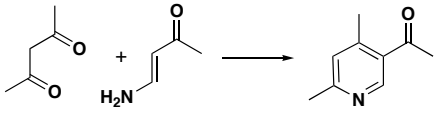
The Bohlmann-Rahtz procedure served as a key step in the synthesis of the thiopeptide promothiocin A
Moody *et. al. JACS*, **2000**, *122*, 3301-3313

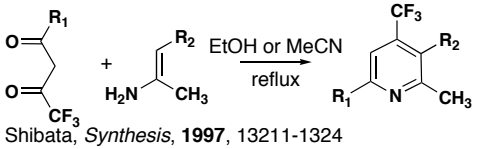




promothiocin A **1** R = H
promothiocin B R = $C(=CH_2)CONHC(=CH_2)CONH_2$

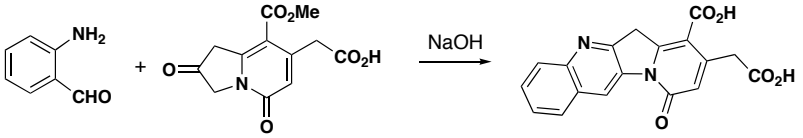
4. Synthesis from 1,3 dicarbonyls and 3-aminoenones



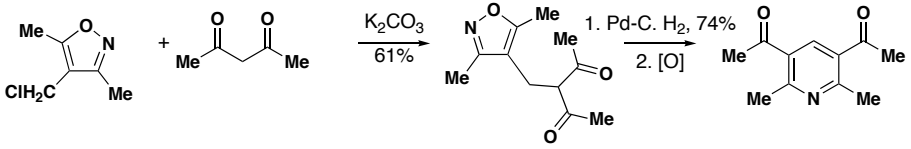


Gives 70-80% yield for R_1= Me or aryl, R_2 = CO_2Et or CN

Shibata, *Synthesis*, **1997**, 13211-1324
When applied to quinolines, this is referred to as the Friedlander condensation. This procedure was used by Danishefsky and Stork in their syntheses of Camptothecin. Danishefsky *et. al. JACS*, **1971**, *93*, 4074

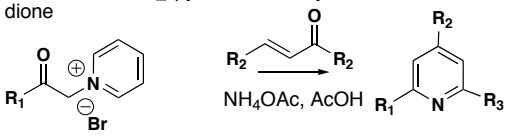


Stork has developed a method of using isoxazoles as masked 3-amino-2-enones
Stork *et. al. JOC*. **1971**, *36*

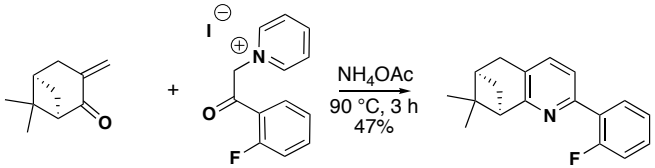


5. Kröhnke annulation

Condensation of -pyridinium methyl ketone salts and eneones that proceeds through a 2,3-ene-1,5-dione

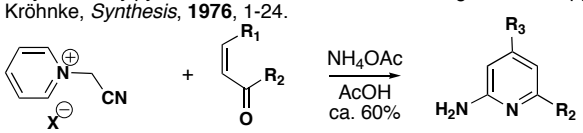


Gives good yields for R= alkyl, aryl, or alkenyl. R_3= COOH gives somewhat lower yields (40-80%).



(Malkov *et. al. Tet. Lett.* **2001**, *42*, 3045-3048)

1-cyanomethylpyridinium salts can also be used to give 2-aminopyridines
Kröhnke, *Synthesis*, **1976**, 1-24.



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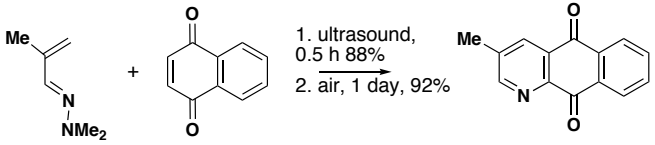
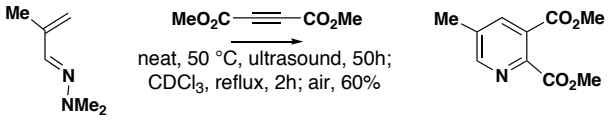
Cycloaddition approaches to pyridines

1. Diels-Alder reactions with 1-azadienes

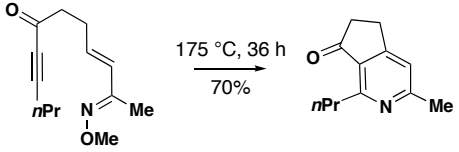
The most straightforeward cycloaddition approach to pyridines involves a Diels-Alder reaction of an 1-azadiene with an alkene or alkyne, followed by subsequent oxidation. However, this route is rarely used, as the Diels-Alder reaction is disfavored on electronic, conformational, and thermodynamic grounds. A modification of this approach uses an electron donating group on the nitrogen, which is subsequently eliminated.





Villacampa *et. al. Tetrahedron*, **1994**, *50*, 10047-10054

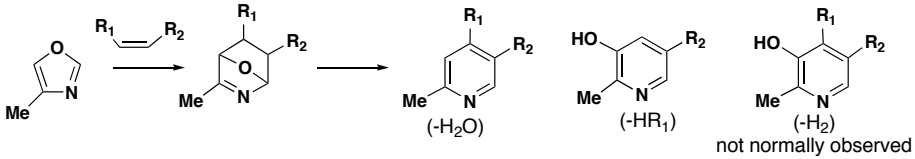
This technique was used by Boger in his approach to the Rubrolone aglycon
Boger *et. al. JACS*, **2000**, *122*, 12169-12173.



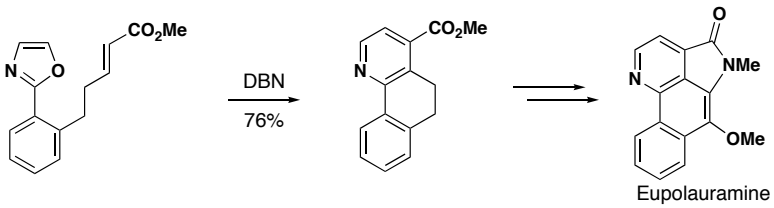
2. Inverse electron demand Diels-Alder approaches

Because of the intransigence of 1-azadienes in [4+2] cycloadditions, the use of a variety of heterocyclic azadienes in an inverse demand Diels-Alder reaction, followed by either extrusion of part of the resulting bicycle in a retro-[4+2] reaction or scission of the resulting bridge has become the favored method for constructing pyridine rings. (Boger, *Chem. Rev.*, **1986**, *86*, 781-793.

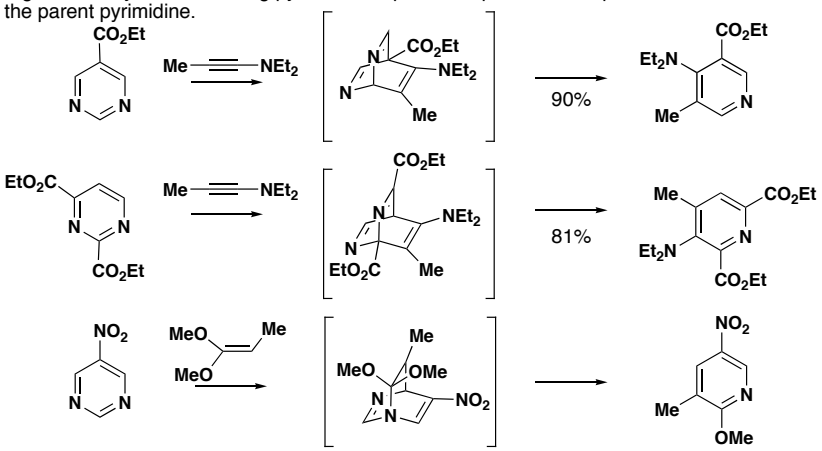
Isozaxoles have been used for this reaction, but fragmentation of the oxo bridge can proceed by several different pathways, complicating the reaction. Also, only isoxazoles with particular substitution patterns undergo cycloaddition in productive yields. This reaction is called the Kondrat'eva synthesis.



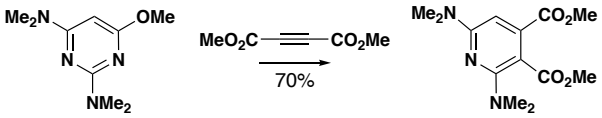
The Kondrat'eva synthesis was used by Weinreb in his synthesis of Eupolauramine.
Weinreb *et. al.*, *JOC*, **1984**, *49*, 4325-4339.



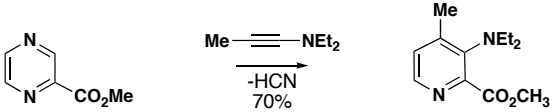
Pyrimidines are also capable of serving as pyrrole precursors in a DA/Retro-DA sequence. The regiochemistry of the resulting pyridine is dependent upon the dienophile and the substitution pattern of the parent pyrimidine.



Pyrimidines with two or three complementary electron donating groups are capable of undergoing normal Diels-Alder reactions with activated dienophiles, although yields are moderate at best.



Pyrazines can also undergo inverse electron demand DA/retro DA cascades to give pyridines, although this is less common.



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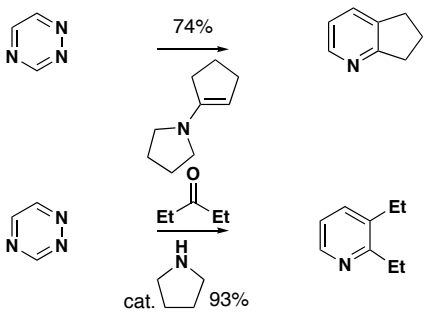
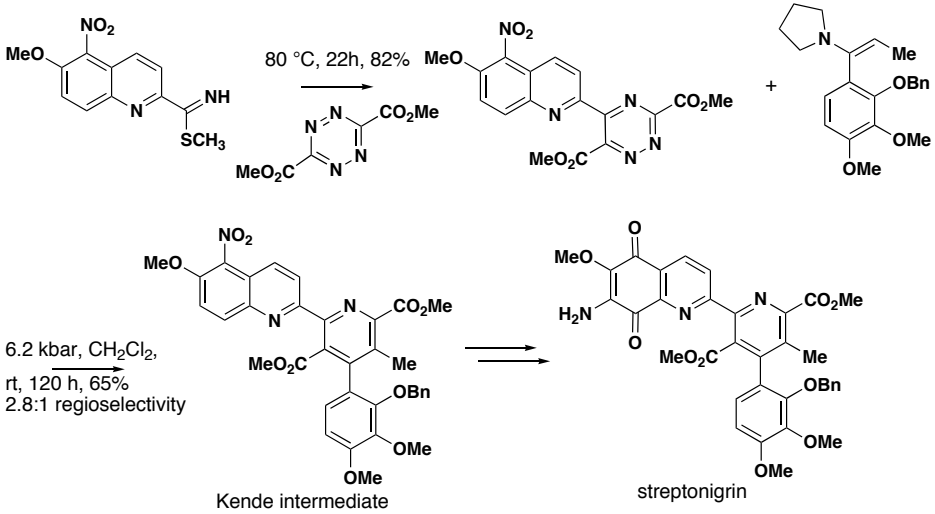
1,2,4-triazenes readily undergo inverse demand Diels-Alder reaction with electron-rich dienophiles with well-defined regioselectivity. This makes them attractive precursors to pyridines, as addition across C-3/C-5 is favored for all dieneophiles, with the exception of some ynamines. The most popular version of this reaction uses a pyrrolidine enamine or a ketone and pyrrolidine as the dienophile; this is called the Boger pyridine synthesis.



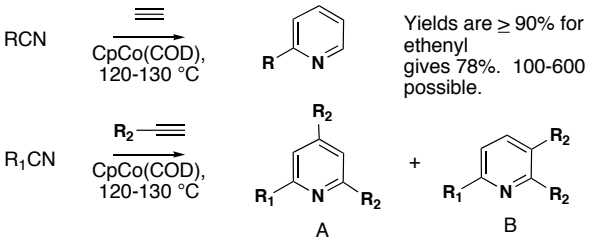
There is a strong preference for the nucleophilic carbon of the dienophile to add to C-3 of the triazine. This is reinforced by electron withdrawing substituents at C-3 or C-3, C-5, and C-6, but can be reversed by electron withdrawing substituents at C-3 or C-3 and C-5. The presence of alkyl groups on the dienophile or the use of a morpholino dienophile can degrade the extent of regioselectivity.

A convenient method for the generation of 1,2,4-triazines is via a Diels-Alder/Retro Diels-Alder sequence involving a 1,2,4,5-tetrazine and a nitrogen-containing dienophile. This strategy was used by Boger in his synthesis of Streptonigrin. (Boger and Panek, *JOC*, **1983**, *48*, 621-623, *JACS*, **1985**, *107*, 5745-5754.

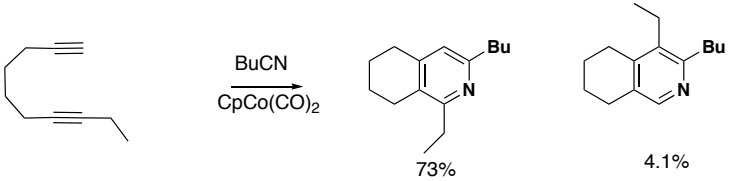


3. Co-catalyzed [2 + 2 + 2] cycloadditions

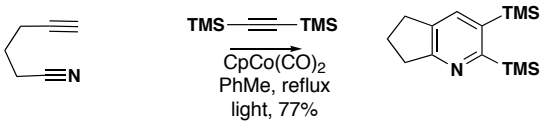
Reaction of excess acetylene with one equivalent of a nitrile and ca. 1 mol % of a cobalt catalyst, such as CpCo(COD), leads to 2-substituted pyridines in good yield under conditions where an initial excess of nitrile is present. However, when unsymmetrical acetylenes are used mixtures of regioisomeric products are often obtained. Electron-poor nitriles do not work in this reaction. Bönneman, *ACIEE*, **1978**, *17*, 505-515



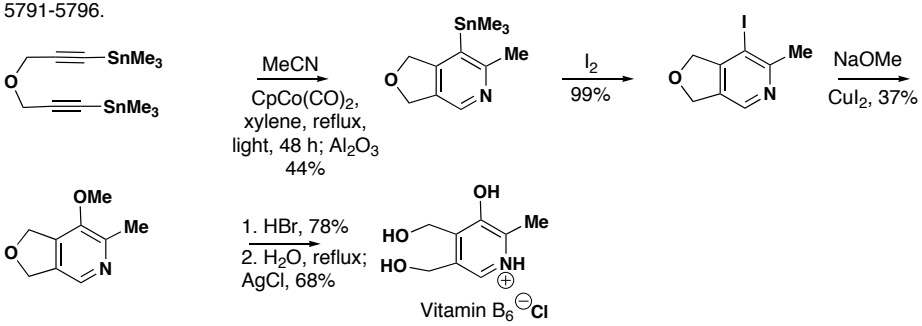
Problems of regioselectivity can be avoided by using diynes and nitriles or alkynyl nitriles and alkynes. The less sterically hindered orientation of the product pyridine is greatly favored under these conditions. Vollhardt, *ACIEE*, **1984**, *23*, 539-556.



Vollhardt *et. al. J. Chem. Soc. Chem. Comm.* **1982**, 133-134.

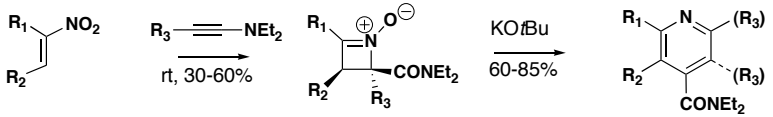


Heteroatoms are tolerated in the linking chain, but N and S can interfere with catalyst turnover. This served as the basis of Vollhardt's synthesis of vitamin B_6. Parnell and Vollhardt, *Tetrahedron*, **1985**, *41*, 5791-5796.



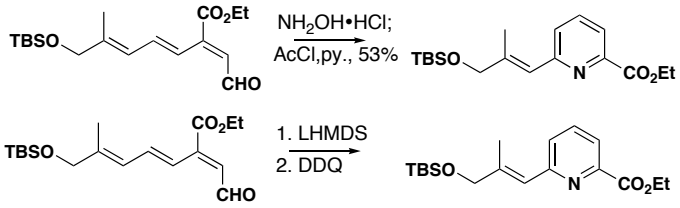
4. Electrocyclization of polyunsaturated imines or oximes

Reinhoudt and co-workers cyclized unsaturated oximes generated from cyclic nitrones to pyridines in moderate yield. (Reinhoudt *et. al., Tetrahedron,* **1989**, *45*, 3131-3138.



R_1= Alkyl or Ph, R_2= Ar, R_3= Ph or alkenyl

Katsumura and co-workers used two distinct electrocyclizations in their approach to the ocular age pigment A2-E. Katsumura *et. al. JOC*, **2001**, *66*, 3099-3110.



How Medicinal Chemists Do It

Lee *et. al. J. Med. Chem.* **2001**, *44*, 2133-2138.