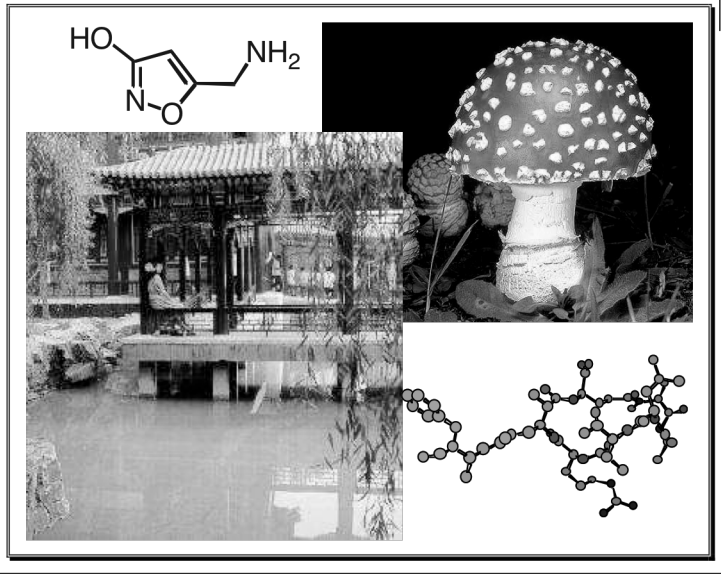
II. Special Topics

Possible Topics:
- heterocyclic chemistry
- pericyclic chemistry [Woodward-Hoffmann Rules]
- medicinal chemistry
- organometallic chemistry
- combinatorial chemistry
- microwave chemistry

IIA. HETEROCYCLIC CHEMISTRY



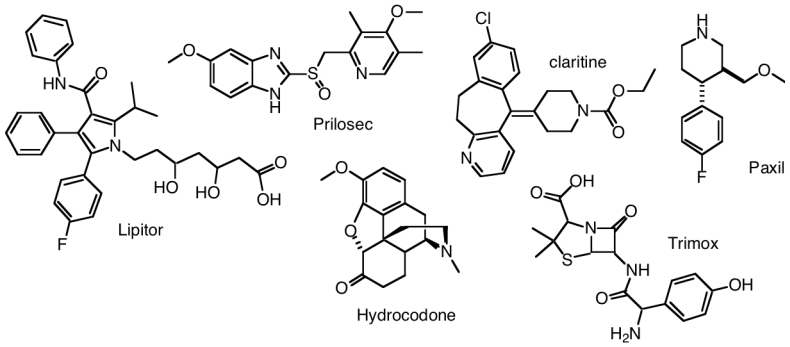
Introduction

Classification

If the ring system is made up of carbons and at least one other element, the compound can be considered as **heterocyclic**. About **50%** of all known organic compounds are heterocyclic. About **55%** of organic chemistry publications are dedicated to this field.

Uses of heterocyclic compounds

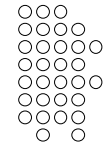
• Pharmaceuticals (13 of the top 20 prescription pharmaceuticals in 1999)



- Agrochemicals
- Veterinary products
- Dyes and pigments, fluorescent agents
- Antioxidants and food additives
- Corrosion inhibitors
- Intermediates in organic synthesis
- Biological functions (pKa, metal binding, hydrogen bonding, hydrophilicity,
- Fire retardant
- Photographic materials
- Organic conductors

cf.: - Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in life and society*; Wiley: Chichester, 1997.

Aromaticity

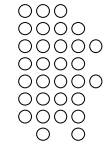


Quantitative measurement of aromaticity from heats of combustion and hydrogenation:

	combustion (kcal/mol)	hydrogenation (kcal/mol)
benzene	36-37	36
pyridine	23-43	
thiophene	24-31	29
furan	16-23	22
pyrrole	14-31	
pyrazine		8-24
pyridazine		12
pyrimidine		8

see also: Katritzky, A. R.; Jug, K.; Oniciu, D. C., "Quantitative measures of aromaticity for mono-, bi, and tricyclic penta- and hexaatomic heteroaromatic ring systems and their interrelationships." *Chem. Rev.* **2001**, *101*, 1421-1449.

Nomenclature



The widely used **Hantzsch-Widman** nomenclature system specifies the ring size and the nature, type, and position of the heteroatom(s).

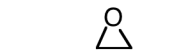
Prefixes for heteroatoms in decreasing order of priority:

Heteroatom	Symbol (Valence)	Prefix
Oxygen	O (II)	Oxa
Sulfur	S (II)	Thia
Selenium	Se (II)	Selena
Tellurium	Te (II)	Tellura
Nitrogen	N (III)	Aza
Phosphorus	P (III)	Phospha
Arsenic	As (III)	Arsa
Antimony	Sb (III)	Stiba
Bismuth	Bi (III)	Bisma
Silicon	Si (IV)	Sila
Germanium	Ge (IV)	Germa

Tin	Sn (IV)	Stanna
Lead	Pb (IV)	Plumba
Boron	B (III)	Bora
Mercury	Hg (II)	Mercura

Stems used to indicate the size of the ring and the level of unsaturation in heteromonocyclic systems:

Ring size	Unsaturation	Saturation
3	-irene	-Irane
4	-ete	-etane
5	-ole	-olane
6, for O, S, Se, Te, Bi, Hg preceding the stem	-ine	-ane
6, for N, Si, Ge, Sn, Pb preceding the stem	-ine	-inane
6, for B, P, As, Sb preceding the stem	-inine	-inane
7	-epine	-epane
8	-ocine	-ocane
9	-onine	-onane
10	-ecine	-ecane



Oxa + irane = oxirane

Aza + iridine = aziridine

Aza + irine = azirine

Oxa + aza + iridine = oxaziridine

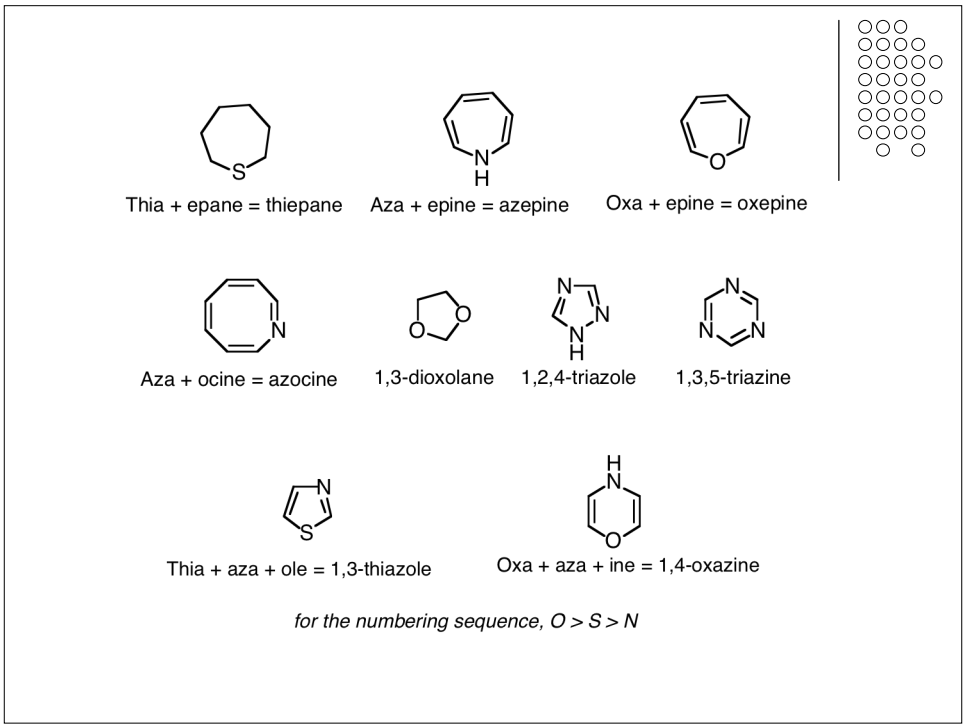
Aza + etidine = azetidine

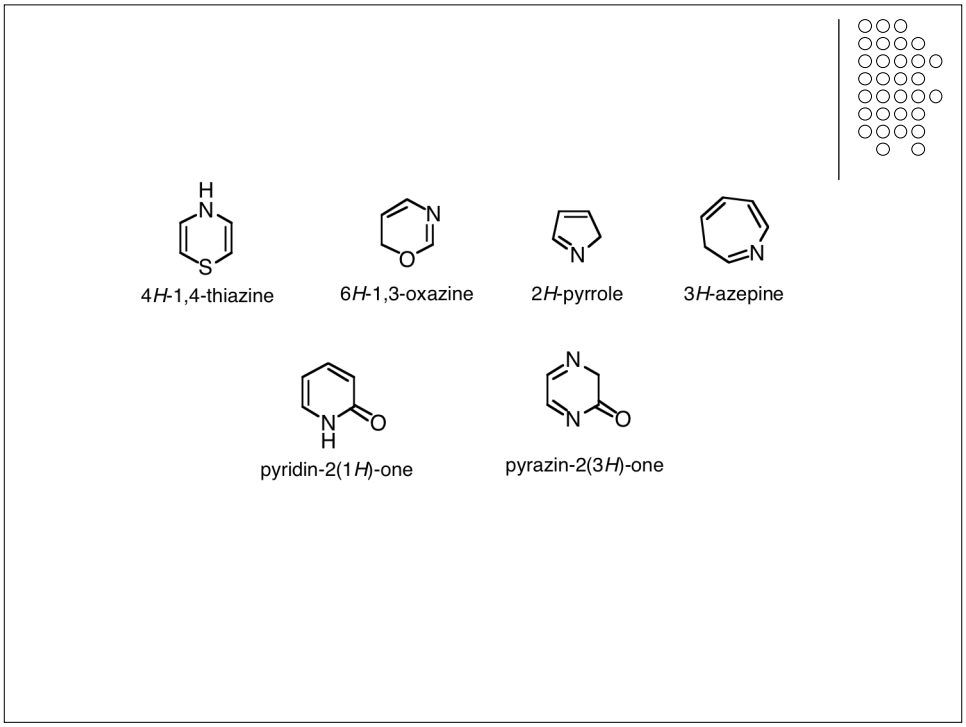
Aza + ete = azete

Thia + etane = thietane

Phospha + ole = phosphole

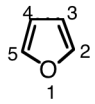
Note: the stem –irine is used for three-membered nitrogen-containing unsaturated heteromonocycles, and the stems –iridine, -etidine, and –olidine, are used for nitrogen-containing saturated 3-, 4-, and 5-membered heteromonocycles, respectively. Trivial names such as pyrrole, pyrazole, imidazole, pyridine, pyridazine, pyrimidine, etc. are preferred over the systematic names.

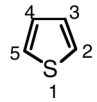

Thia + epane = thiepane
Aza + epine = azepine
Oxa + epine = oxepine
Aza + ocine = azocine
1,3-dioxolane
1,2,4-triazole
1,3,5-triazine
Thia + aza + ole = 1,3-thiazole
Oxa + aza + ine = 1,4-oxazine
for the numbering sequence, O > S > N

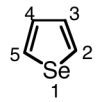

4H-1,4-thiazine
6H-1,3-oxazine
2H-pyrrole
3H-azepine
pyridin-2(1H)-one
pyrazin-2(3H)-one

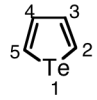
Trivial names:

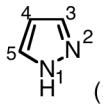

Pyrrole

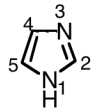

Furan

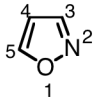

Thiophene

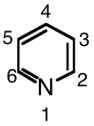

Selenophene

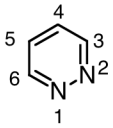

Tellurophene

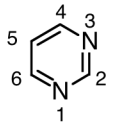

Pyrazole
(1*H*-isomer)

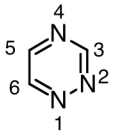

Imidazole
(1*H*-isomer)

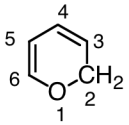

Isoxazole

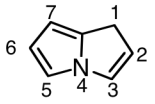

Pyridine

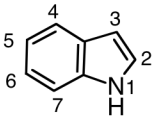

Pyridazine

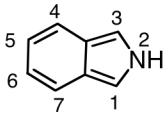

Pyrimidine

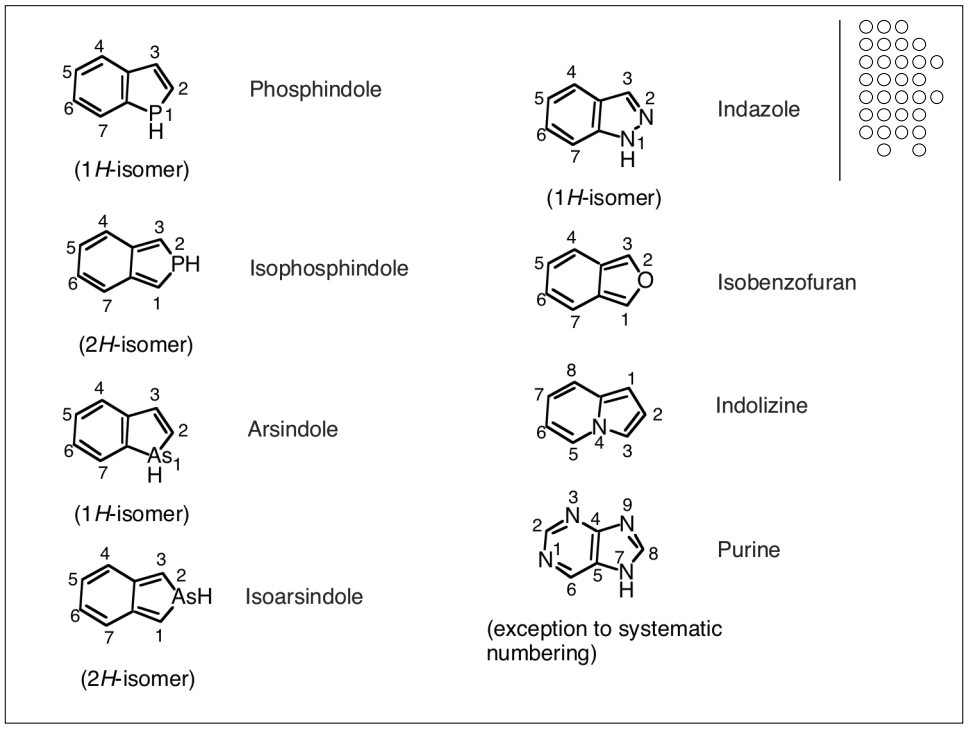

Pyrazine

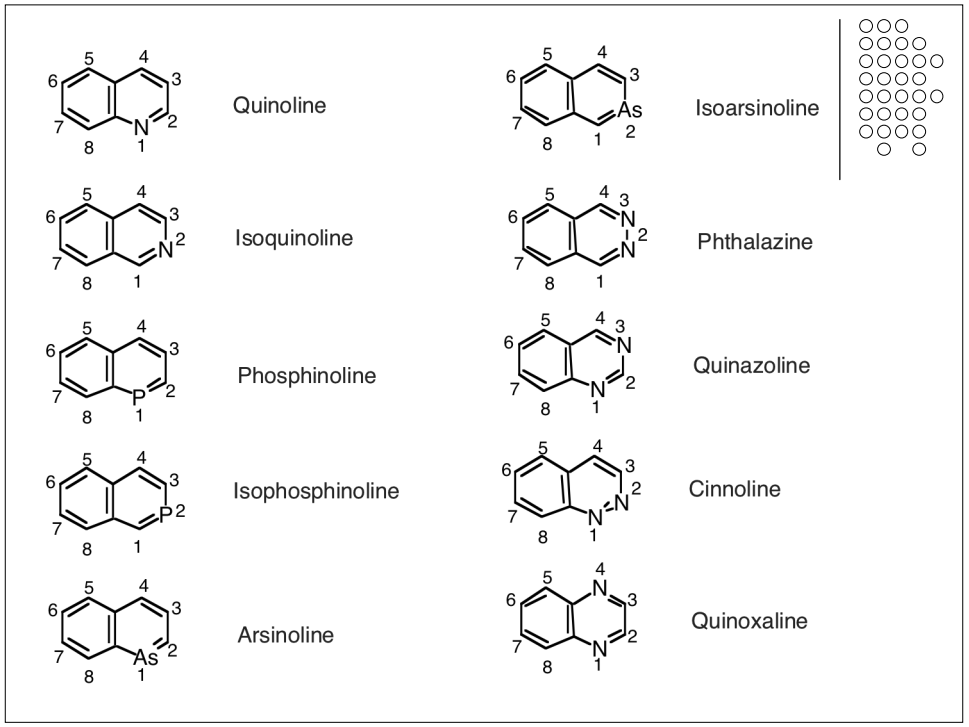

Pyran
(2*H*-isomer)

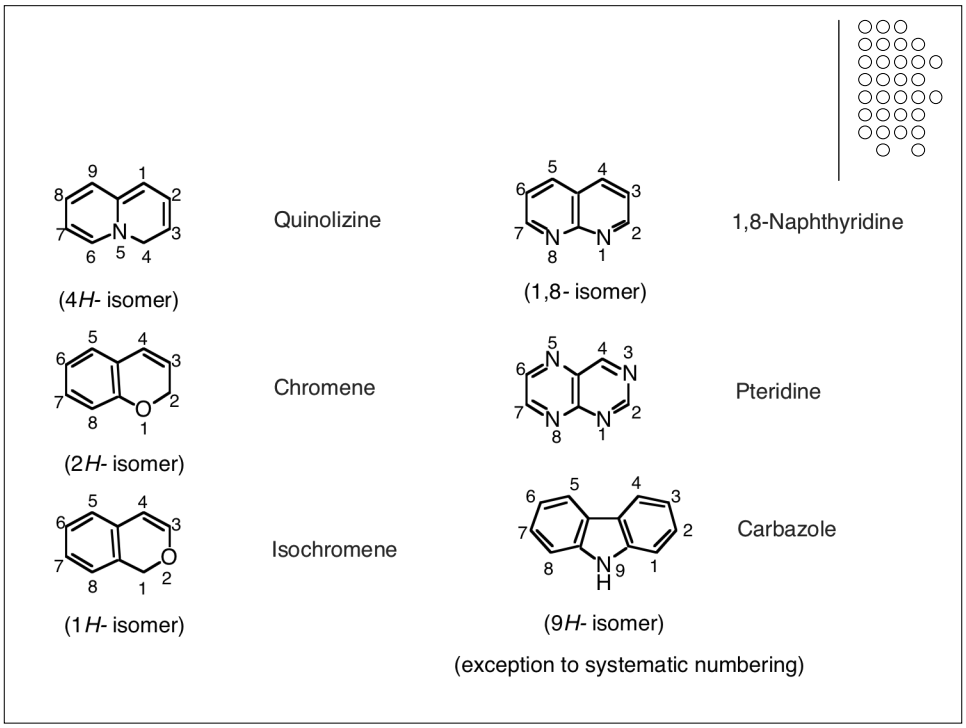

Pyrrolizine
(1*H*-isomer)

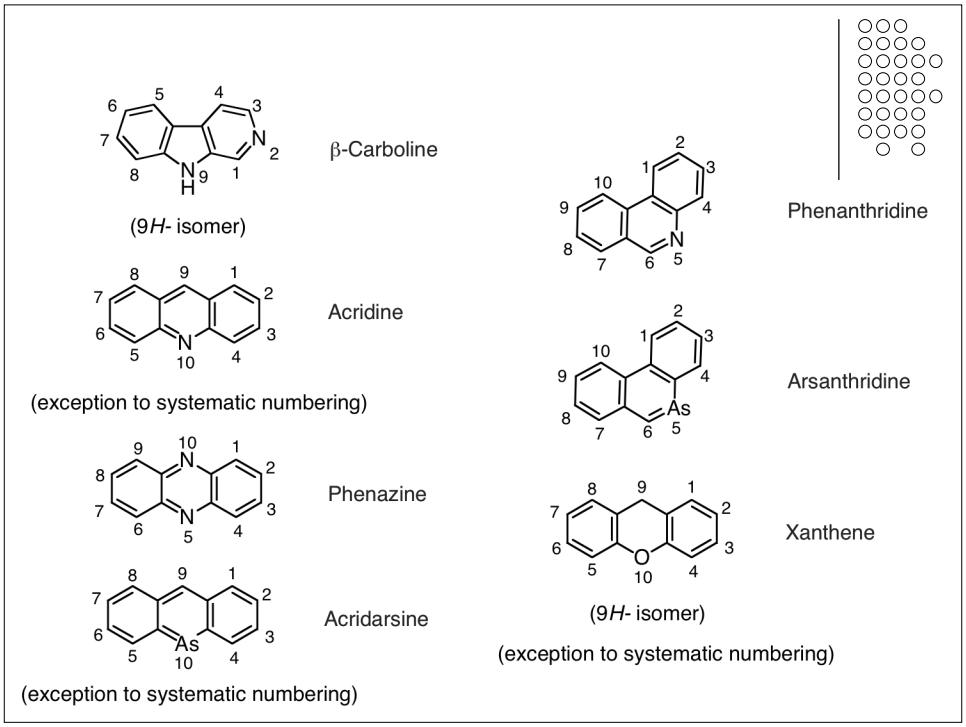

Indole
(1*H*-isomer)

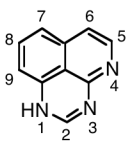

Isoindole
(2*H*-isomer)


Phosphindole
(1H-isomer)
Indazole
(1H-isomer)
Isophosphindole
(2H-isomer)
Isobenzofuran
Arsindole
(1H-isomer)
Indolizine
Isoarsindole
(2H-isomer)
Purine
(exception to systematic numbering)


Quinoline
Isoarsinoline
Isoquinoline
Phthalazine
Phosphinoline
Quinazoline
Isophosphinoline
Cinnoline
Arsinoline
Quinoxaline

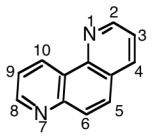

Quinolizine
(4H- isomer)
1,8-Naphthyridine
(1,8- isomer)
Chromene
(2H- isomer)
Pteridine
Isochromene
(1H- isomer)
Carbazole
(9H- isomer)
(exception to systematic numbering)


β-Carboline
(9H- isomer)
Phenanthridine
Acridine
(exception to systematic numbering)
Arsanthridine
Phenazine
Acridarsine
(exception to systematic numbering)
Xanthene
(9H- isomer)
(exception to systematic numbering)



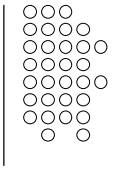
Perimidine

(1*H*-isomer)



Phenanthroline

(1,7-isomer)



Fusion nomenclature system:

Benzothiazole = Benzene + Thiazole

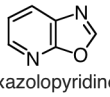
Benzimidazole = Benzene + Imidazole

Thienopyridine

Base component: Pyridine

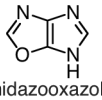
Furopyrrole

Base component: Pyrrole



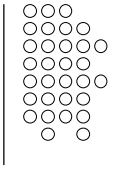
Oxazolopyridine

Base component: Pyridine



Imidazooxazole

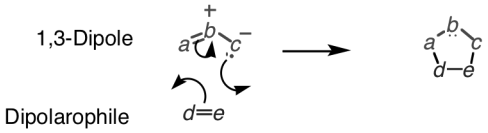
Base component: Oxazole

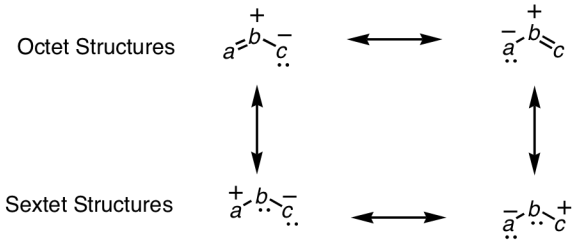


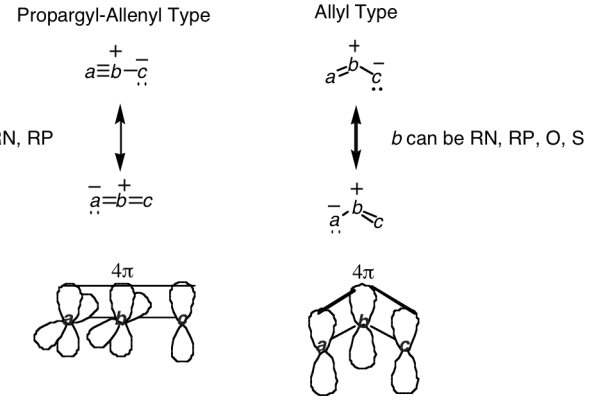
For more detailed discussions, see: Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer: Berlin, 1998; Vol. I.

Classifications of 1,3-dipoles

Huisgen (1960) [1,*3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: 1984; 2002].





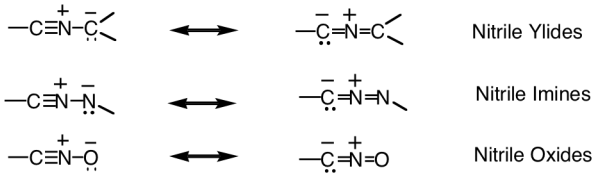


By restricting the permutation to second-row elements, one obtains six 1,3-dipoles of the propargyl-allenyl type and twelve of the allyl type.

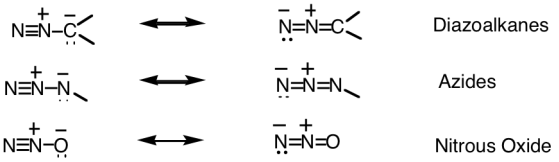
Classification of 1,3-Dipoles Consisting of Carbon, Nitrogen, and Oxygen Centers

Propargyl-Allenyl Type

Nitrillium Betaines

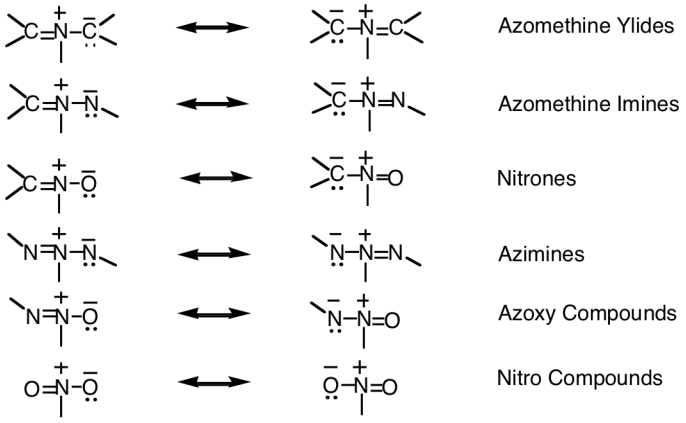


Diazonium Betaines

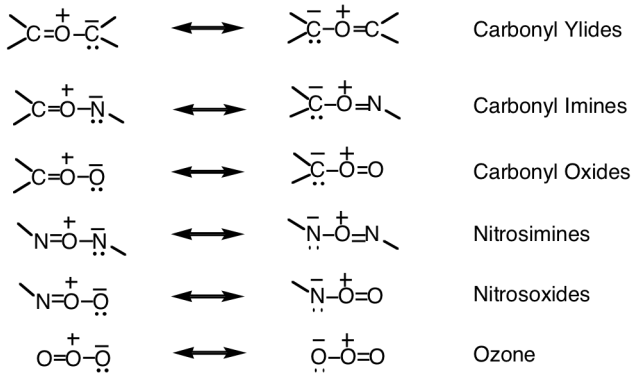


Allyl Type

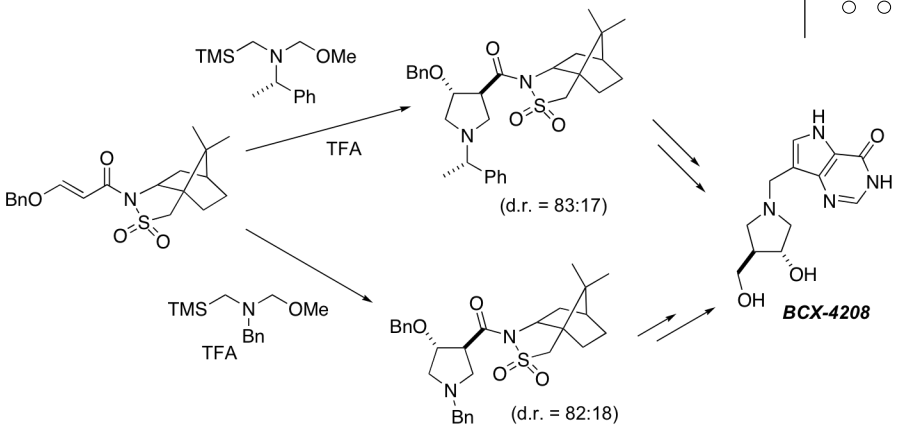
Nitrogen Function as Middle Center

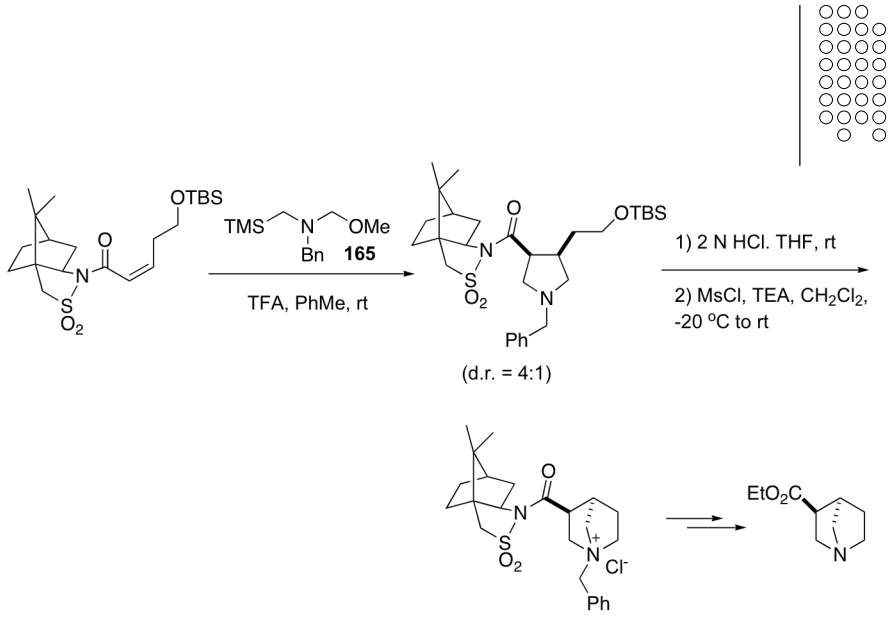


Oxygen Atom as Middle Center

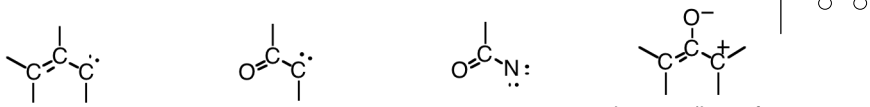


Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J., "Asymmetric synthesis of active pharmaceutical ingredients." *Chem. Rev.* **2006**, *106*, 2734-2793.



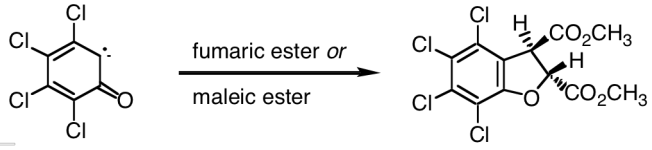


1,3-Dipoles without octet stabilization include:

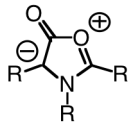


vinylcarbene ketocarbene ketonitrene intermediate of Favorskii rearrangement

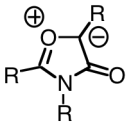
However, reactions with these derivatives are generally non-concerted:



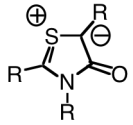
Many 1,3-dipoles, such as azomethine ylides and carbonyl ylides shown below, can be found as a substructure of reactive heterocycles:



münchnone



isomünchnone



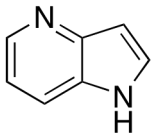
thioisomünchnone

For further info, see: - Karlsson, S.; Högberg, H.-E., "1,3-Dipolar cycloaddition for the construction of enantiomerically pure heterocycles. A review." *Org. Prep. Proc. Int.* **2001**, *33*, 103-172.

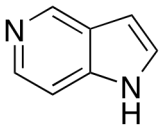
The Heterocyclic Chemistry of Azaindoles

- Structural and electronic properties:

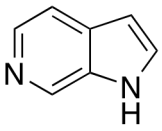
• Azaindoles, or more correctly pyrrolopyridines, are π-deficient heterocycles, related to pyridine & pyrrole but with a broader variation of pKa's:



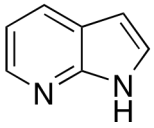
4-azaindole
*1*H-pyrrolo[3,2-*b*]pyridine
pKa = 6.94



5-azaindole
1*H*-pyrrolo[3,2-*c*]pyridine
pKa = 8.26



6-azaindole
1*H*-pyrrolo[2,3-*c*]pyridine
pKa = 7.95



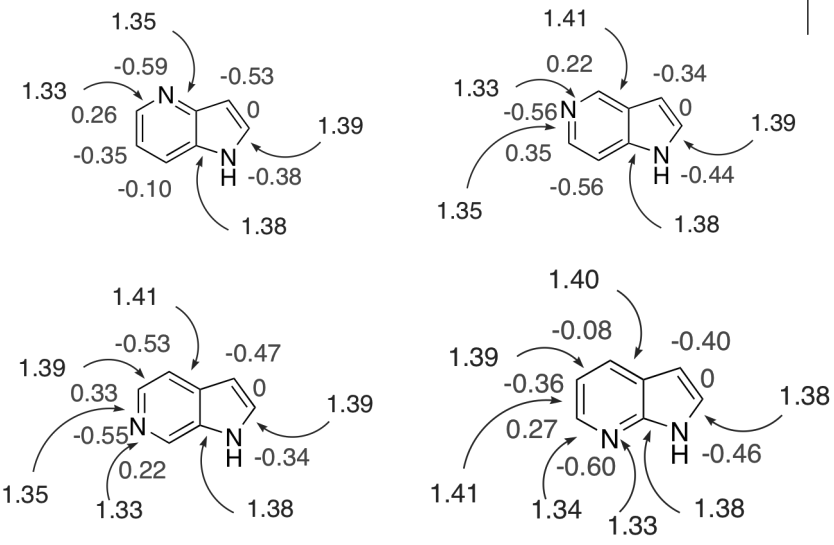
7-azaindole
1*H*-pyrrolo[2,3-*b*]pyridine
pKa = 4.59

• These different pKa's illustrate the push-pull interactions between the two parent rings; for 5- and 6-azaindoles, this is reminiscent of 4-aminopyridine (pKa 9.1), and for 4- and 7-azaindoles, 2-aminopyridine (pKa 7.2) could be used as a comparison.

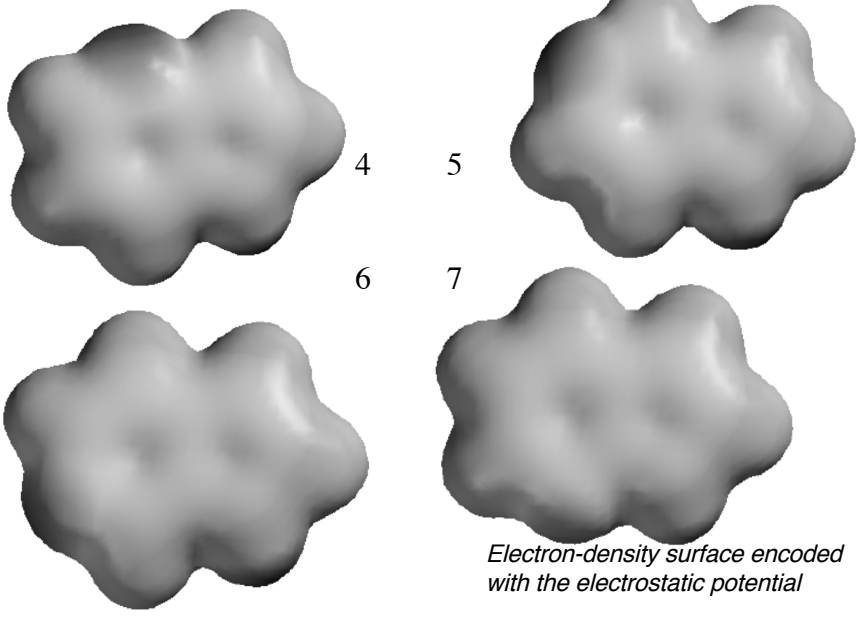
• The azaindole skeleton is only present in nature as fused polycyclic derivatives, such as the variolins.

• Structural and electronic properties (cont):

• The following electrostatic charges and bond distances were calculated at the DFT/BLY3P/6-31G* level:

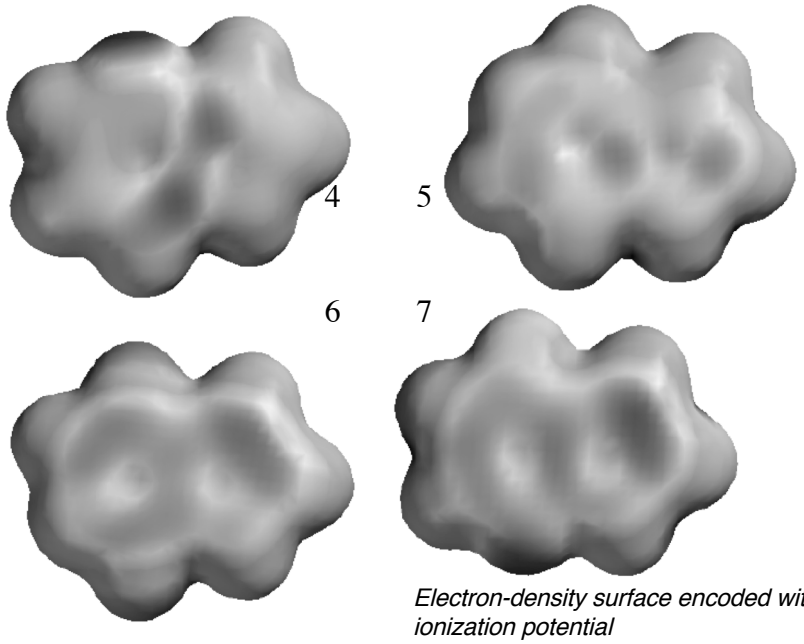


• Structural and electronic properties (cont):



Electron-density surface encoded with the electrostatic potential

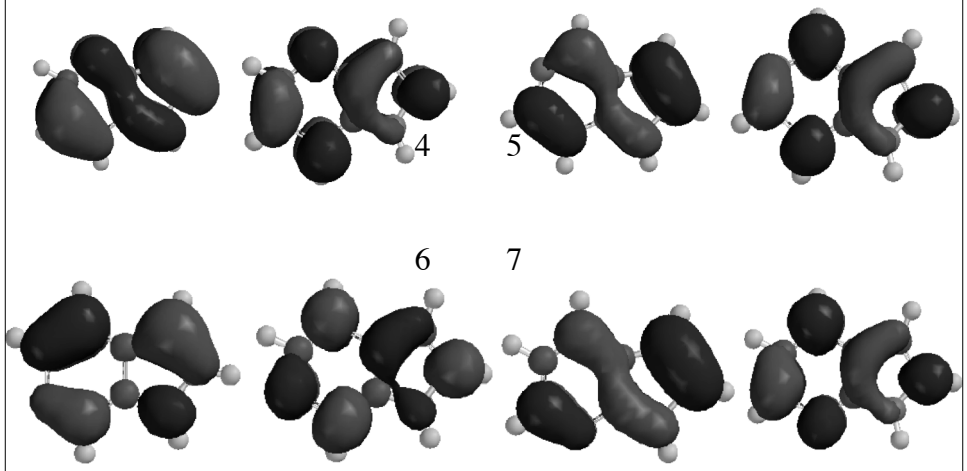
• Structural and electronic properties (cont):



Electron-density surface encoded with the ionization potential

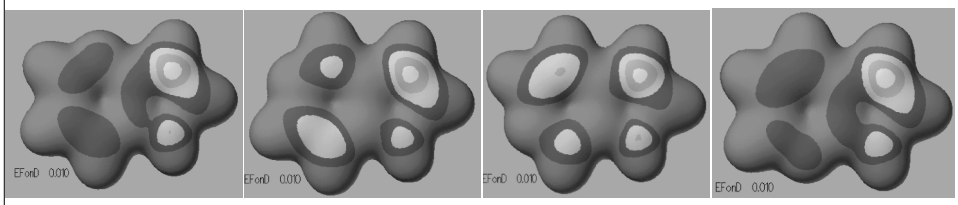
• Structural and electronic properties (cont):

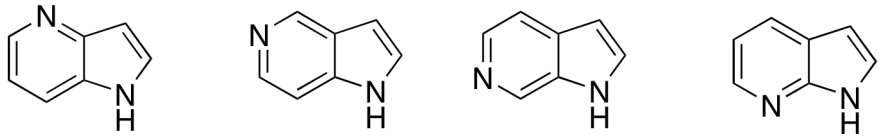
• HOMO and LUMO as calculated at the DFT/BLY3P/6-31G* level:



• Structural and electronic properties (cont):

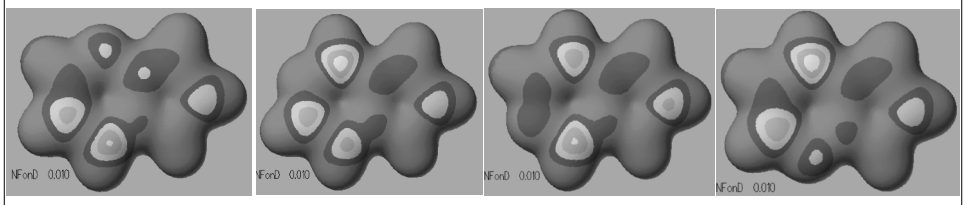
• The **electrophilic frontier density** measures the susceptibility of the substrate to attack by an electrophile. It reveals reactive sites based on the electron distribution of a set of active orbitals near the HOMO. It is especially useful for large molecules where several orbitals may have energies nearly equal to the HOMO [K. Fukui, et. al., J. Chem. Phys., 11, 1433-1442 (1953)]. The susceptibility to an electrophilic attack is generated by a MOPAC/PM3 wavefunction for the chemical sample, at a geometry determined by performing an optimize geometry calculation in MOPAC using PM3 parameters.

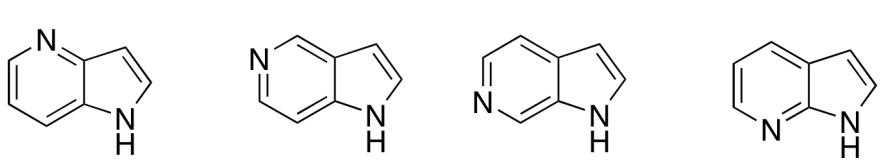




• Structural and electronic properties (cont):

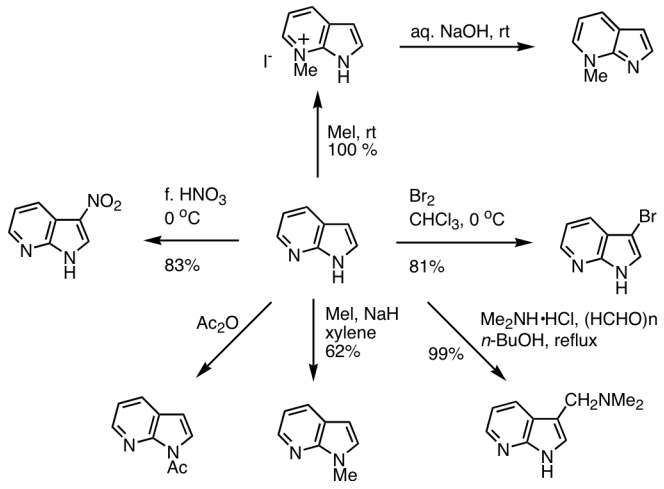
• The **nucleophilic frontier density** measures the susceptibility of the substrate to attack by a nucleophile. It reveals reactive sites based on the electron distribution of a set of active orbitals near the LUMO. It is especially useful for large molecules where several orbitals may have energies nearly equal to the LUMO.





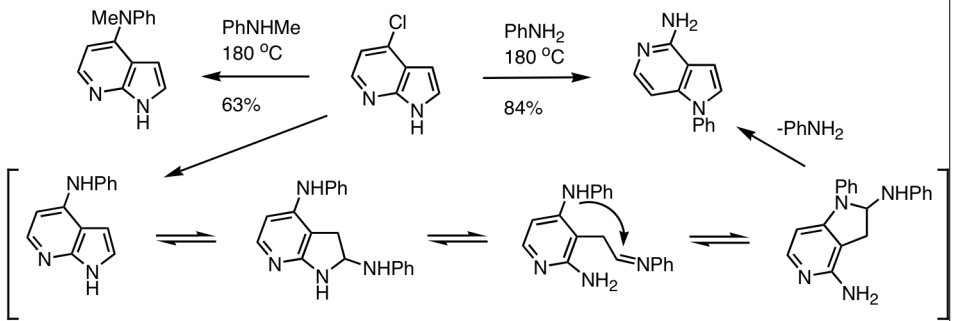
• Chemical properties of azaindoles

• Reactions with electrophilic reagents take place with substitution at C-3 or by addition to the pyridine nitrogen. All azaindoles are much more stable to acid than indoles, no doubt due to the diversion of protonation to the pyridine nitrogen, but the reactivity toward electrophilic attack at C-3 is only slightly lower than in indoles. Alkylation under neutral conditions results in quaternization of the pyridine nitrogen, and alkylation with sodium salts allows N-1 alkylation. Acylation under mild conditions also occurs at N-1. For 7-azaindole, electrophilic substitution can be summarized as follows:



• Chemical properties of azaindoles

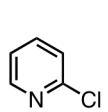
• Nucleophilic displacement of halogen alpha- and gamma- to the pyridine nitrogen can be carried our under vigorous conditions or long reaction times. Reaction of 4-chloro-7-azaindole with a secondary amine results in normal substitution of the halogen but reaction with primary amines gives 5-azaindole rearrangement products by the sequence shown below:



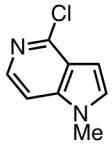
• Chemical properties of azaindoles

• The reactivity of 4-chloro-1-methyl-5-azaindole toward nucleophilic substitution of chlorine by piperidine can be compared with that of some related systems: it is significantly less reactive than the most closely related bicyclic systems, probably due to increased electron density in the six-membered ring resulting from donation from N-1 (*J. Org. Chem.* **1982**, *47*, 1500; *Bull. Soc. Chim. Fr.* **1973**, *10*, 511).

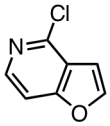
Relative rates for nucleophilic displacement with piperidine in $MeO(CH_2)_2OH$ at 100 °C:



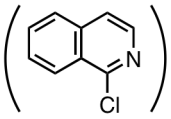
1



0.58



11



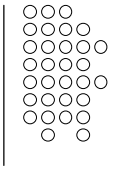
340
(with EtO^- relative to 2-chloropyridine)

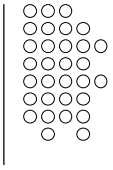
• Metalations of azaindoles

Tetrahedron **1997**, *53*, 3637

- Metalations of azaindoles

L'Heureux, A.; Thibault, C.; Ruel, R. "Synthesis of functionalized 7-azaindoles via directed ortho-metalations." Tetrahedron Letters **2004**, *45*, 2317-2319.

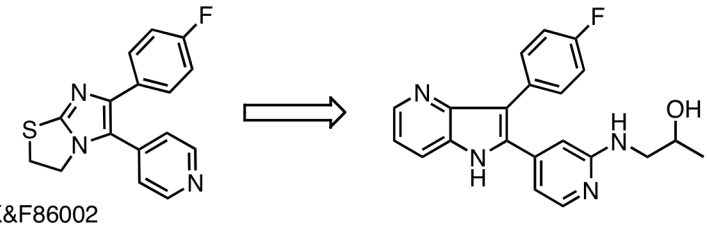




Syntheses of Azaindoles

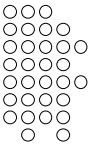
The earliest synthesis of this heterocycle dates back to 1943 (*Chem. Ber.* **1943**, *76*, 128). To date, the most common synthetic approaches include the Madelung-type cyclization, a Reissert-type procedure, the Leimgruber-Batcho reaction, a Lorenz-type cyclization, and Pd-catalyzed reactions starting from iodoaminopyridines.

Trejo, A.; Arzeno, H.; Browner, M.; Chanda, S.; Cheng, S.; Comer, D. D.; Dalrymple, S. A.; Dunten, P.; Lafargue, J.; Lovejoy, B.; Freire-Moar, J.; Lim, J.; McIntosh, J.; Miller, J.; Papp, E.; Reuter, D.; Roberts, R.; Sanpablo, F.; Saunders, J.; Song, K.; Villasenor, A.; Warren, S. D.; Welch, M.; Weller, P.; Whiteley, P. E.; Zeng, L.; Goldstein, D. M. "Design and synthesis of 4-azaindoles as inhibitors of P38 MAP kinase." Journal of Medicinal Chemistry 2003, 46, 4702-4713.



SK&F86002

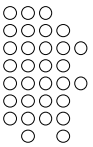
Use of the Bartoli reaction: Zhang, Z.; Yang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T., "A General Method for the Preparation of 4- and 6-Azaindoles." *J. Org. Chem.* **2002**, *67*, 2345-2347. Larger substituents ortho to the nitro group produced higher yields, and a halogen atom at the alpha- or 4-position of the pyridine is also highly beneficial for this reaction:



4- and 6-azaindoles were prepared, but this protocol should also work for 5- and 7-azaindoles from the appropriate nitropyridines

Regioselective functionalization by the use of the N-oxides of azaindoles: Synthesis 1992, 661.

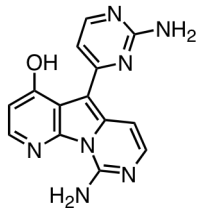
Direct functionalization at the 6-position of 7-azaindoles is rare, but halogenation is facile using its N-oxide via a Reissert-Henze salt. HMDS probably traps the HBr resulting from the acylation at N-1. While other organic bases form ammonium salts with may serve as proton donors (and thus lead to unreacted, protonated pyridine N-oxide), HMDS generates ammonia and TMS-Br.

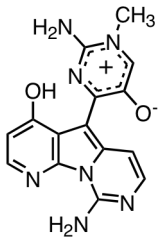


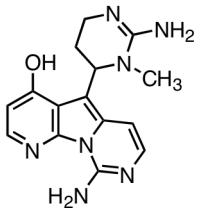
Synthesis of variolin B

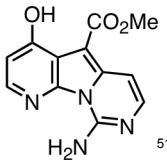
- Ahaidar, A.; Fernandez, D.; Perez, O.; Danelon, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. "Synthesis of variolin B." Tetrahedron Letters 2003, 44, 6191-6194.

Variolins A-D; marine heterocycles isolated from an antarctic sponge that show antiviral and antiproliferative activities. Variolin D is inactive.



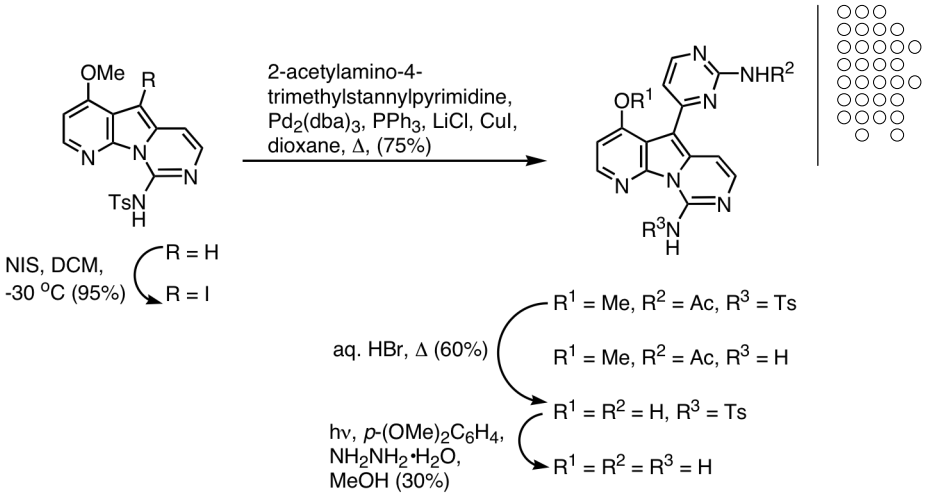






51

A lithium-carboxylate was used as an N-protective group as described by Katritzky for indole-2-lithiation



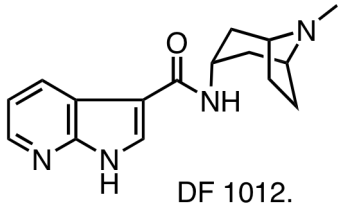
A reductive photolysis of the tosyl group was accomplished using a high pressure Hg lamp with a pyrex filter, and with hydrazine as a reducing agent.

A process synthesis of a 7-azaindole

- Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. "A practical synthesis of 7-azaindolylcarboxy-endo-tropanamide (DF 1012)." Organic Process Research & Development 2003, 7, 209-213.

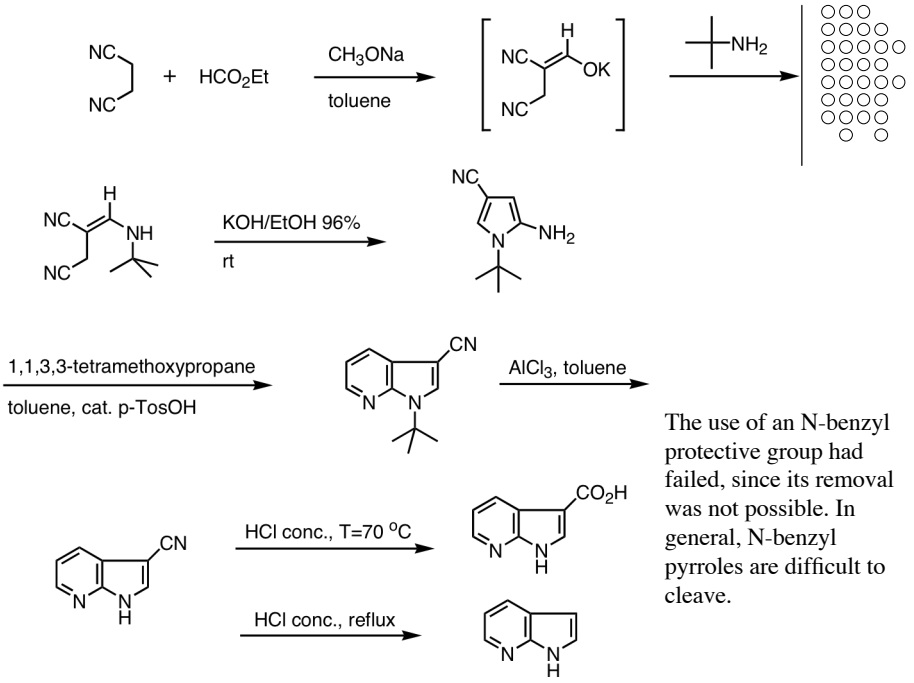
DF 1012 is a drug candidate in a new class of non-narcotic antitussive compounds, and was prepared for phase II clinical trials.

The synthetic route is based on an unusual deprotection step of a t-butylated intermediate, and can also be regarded as a convenient way to produce the expensive parent 7-azaindole.



DF 1012.

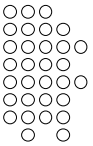
54



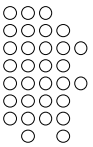
The use of an N-benzyl protective group had failed, since its removal was not possible. In general, N-benzyl pyrroles are difficult to cleave.

- Nazare, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. "A flexible, palladium-catalyzed indole and azaindole synthesis by direct annulation of chloroanilines and chloroaminopyridines with ketones." Angewandte Chemie, International Edition 2004, 43, 4526-4528.

- An example of the Batcho-Leimgruber procedure: Sanderson, P. E. J.; Stanton, M. G.; Dorsey, B. D.; Lyle, T. A.; McDonough, C.; Sanders, W. M.; Savage, K. L.; Naylor-Olsen, A. M.; Krueger, J. A.; Lewis, S. D.; Lucas, B. J.; Lynch, J. J.; Yan, Y. "Azaindoles: Moderately basic P1 groups for enhancing the selectivity of thrombin inhibitors." Bioorganic & Medicinal Chemistry Letters 2003, 13, 795-798.



Siu, J.; Baxendale, I. R.; Ley, S. V. "Microwave-assisted Leimgruber-Batcho reaction for the preparation of indoles, azaindoles, and pyrroloquinolines." Organic & Biomolecular Chemistry 2004, 2, 160-167.



- Carbolithiation route to azaindoles

Cottineau, B.; O'Shea, D. F. "Carbolithiation of vinyl pyridines as a route to 7-azaindoles." Tetrahedron Letters 2005, 46, 1935-1938.