

Definitions:

Mesoionic compounds are "five membered heterocycles which cannot be satisfactorily represented by any one covalent or dipolar structure, but only has hybrids of polar structures...they possess a sextet of electrons."

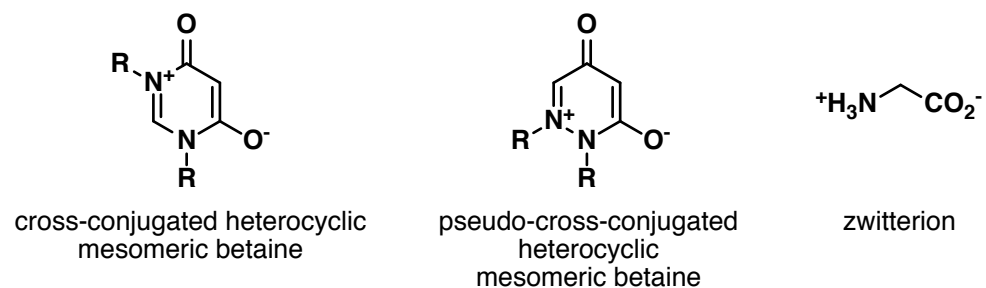
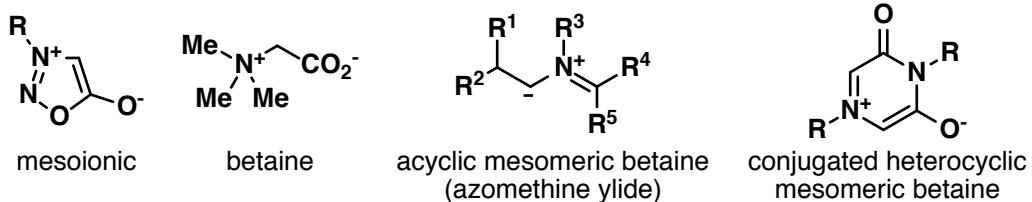
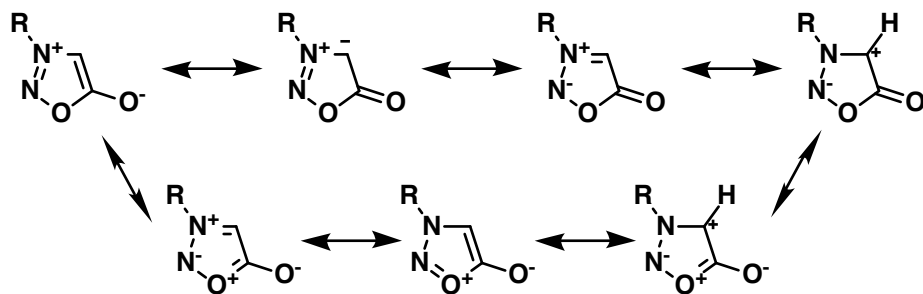
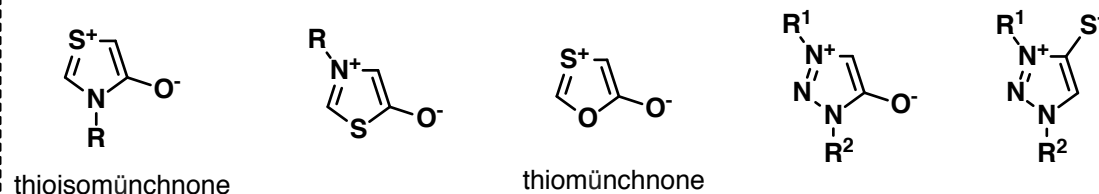
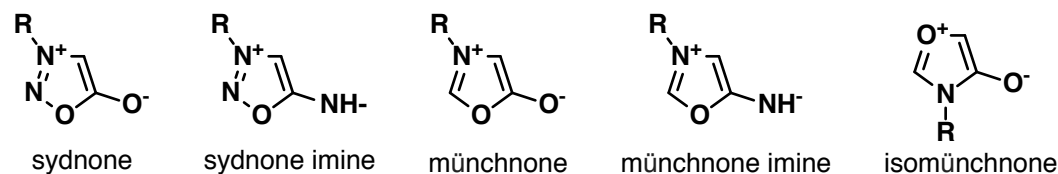
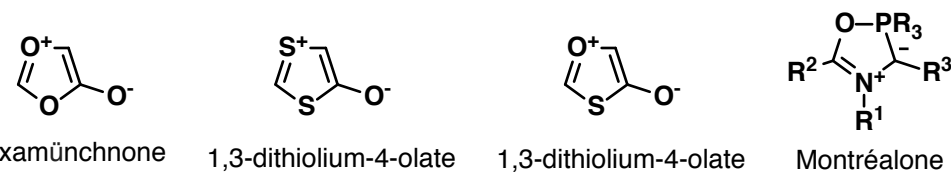
– Ollis and Stanforth, *Tetrahedron*, **1985**, 41, 2239

Betaines are compounds that bear a positively charged cationic functional group (such as a quaternary ammonium group) and a negatively charged functional group (such as a carboxylate).

Mesomeric betaines are neutral conjugated molecules which can be represented by dipolar structures in which both the positive and negative charges are delocalized within the π -system

- acyclic (1,3- and 1,5-dipoles)
- conjugated heterocyclic mesomeric betaines
- cross-conjugated heterocyclic mesomeric betaines
- pseudo-cross-conjugated heterocyclic mesomeric betaines

Zwitterionic compounds are neutral molecules with both positive and negative charges (amino acids).

**Resonance structures of a syndnone (mesoionic):****Examples of mesoionic compounds:****Other common mesoionic compounds:****Outline:**

- Syndnones: synthesis and reactions
- Münchnones: synthesis and reactions
- Isomünchnones: synthesis and reactions
- Assorted mesoionic compounds

Some of the key figures in the chemistry of mesoionic compounds:**Topics not covered in great detail or at all:**

- Mesoionic carbene ligands
- Related mesomeric betaine compounds



Kenneth Turnbull



Masami Kawase

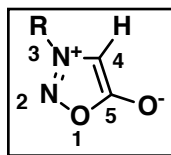
Gordon Gribble
(Gianatassio,
2014)Rolf Huisgen
(Hafensteiner,
2004)

Manfred Regitz

Albert Padwa
(Krawczuk,
2009)

Bruce Arndtsen

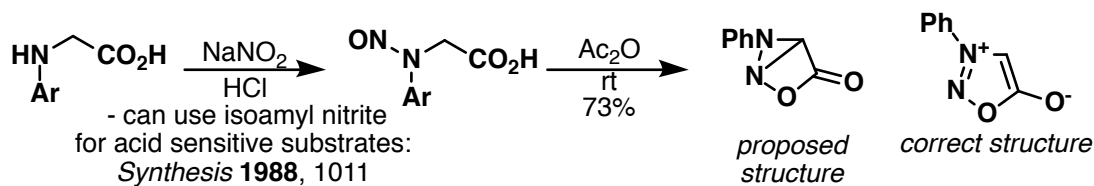
Sydrones



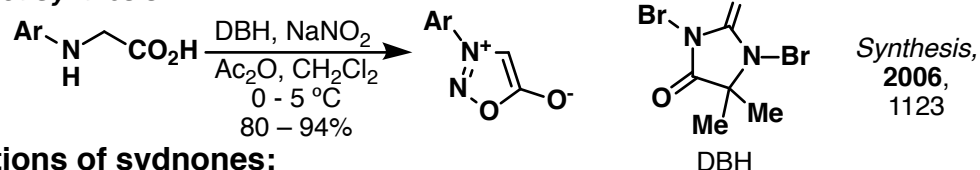
- often crystalline solids (can be purified by recrystallization)
- typically stable at room temperature
- conc. acid or heat can result in decomposition via decarboxylation to hydrazine derivatives; relatively stable to hydrolysis
- C4 $pK_a = 18 - 20$
- discovered in Sydney, Australia

Synthesis of sydrones:

First reported synthesis

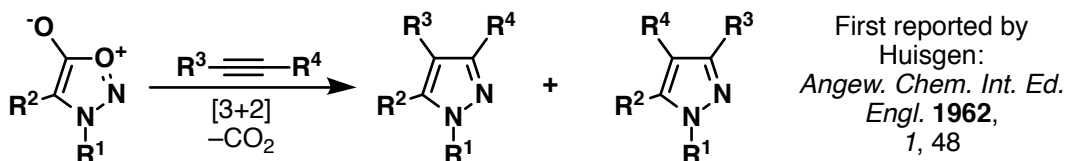
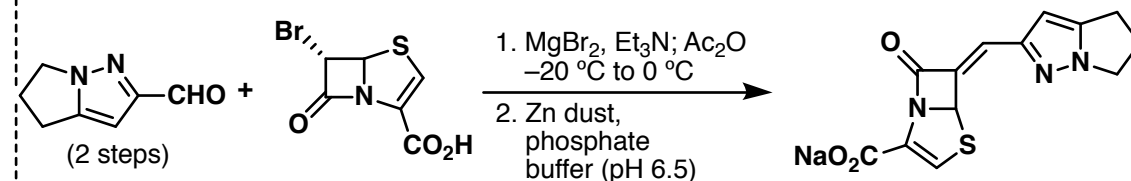
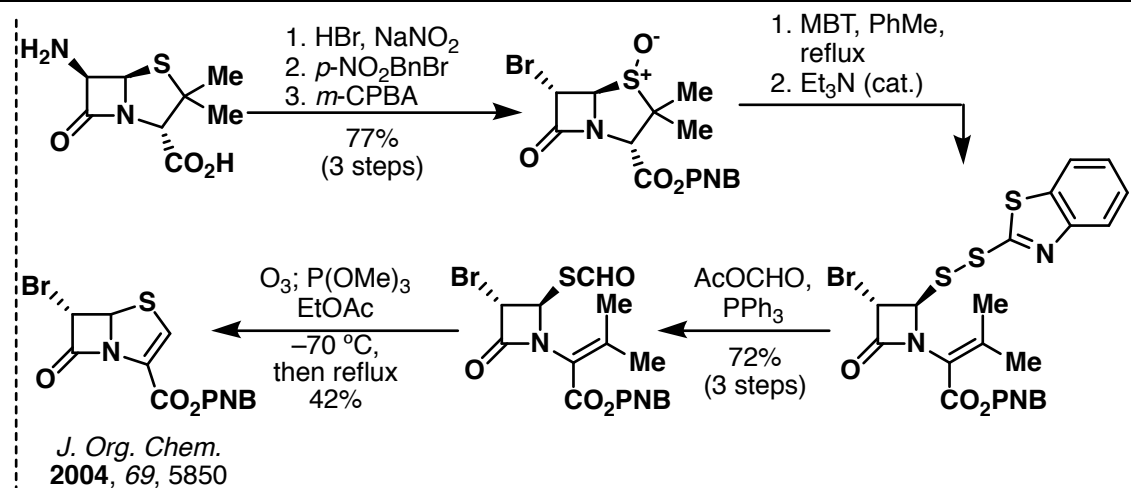
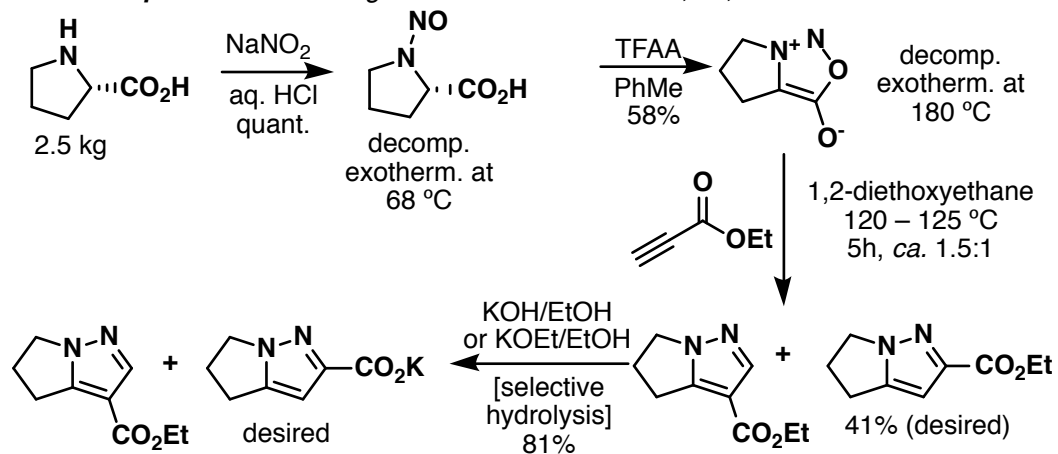
Earl, J. C.; Mackney, A. W. *J. Chem. Soc.* **1935**, 899.

One-pot Synthesis

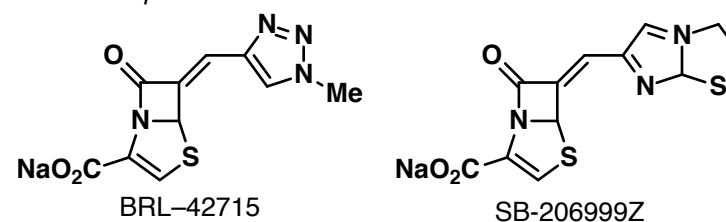


Reactions of sydrones:

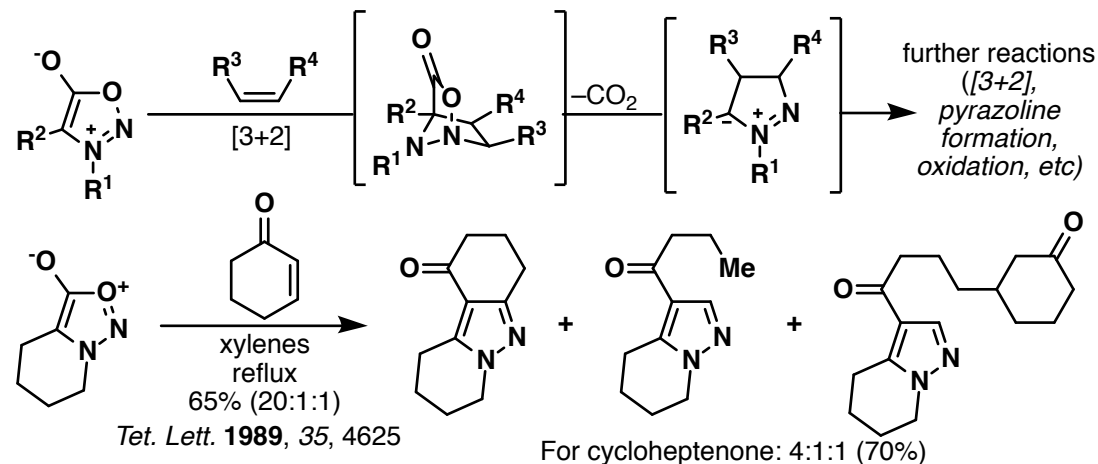
Pyrazole Synthesis (Cycloadditions with Alkynes)

For discussion on regiochemistry of sydnone cycloadditions, see: *Tetrahedron*, **2010**, 66, 553Sydrones on process scale: *Org. Process Res. Dev.* **2006**, 10, 712.

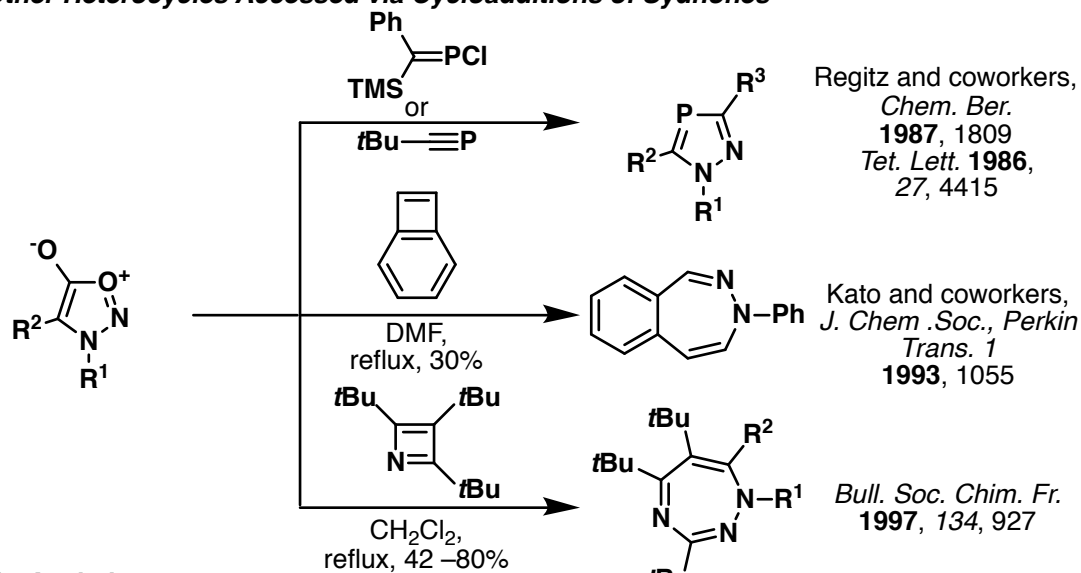
Related compounds:



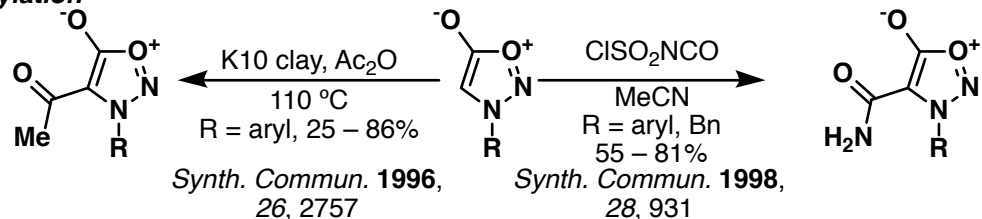
Cycloadditions with Alkenes



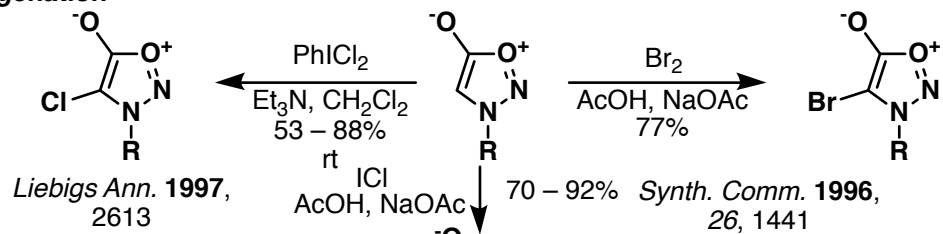
Other Heterocycles Accessed via Cycloadditions of Sydnones



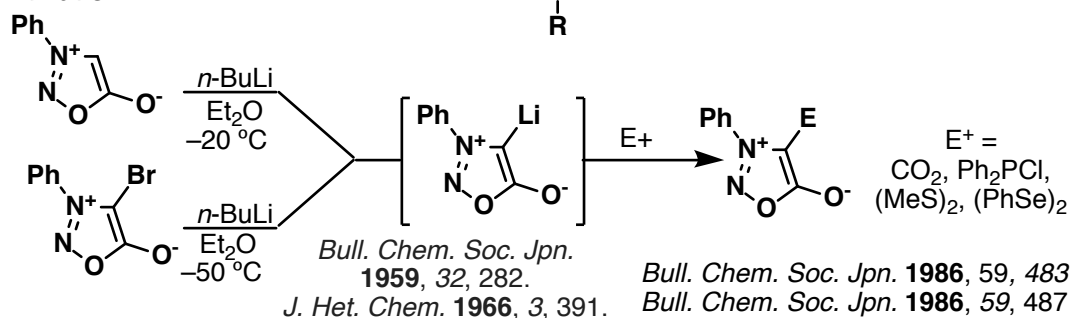
C4 Acylation



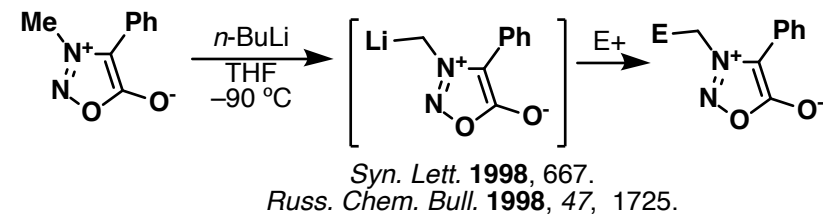
C4 Halogenation



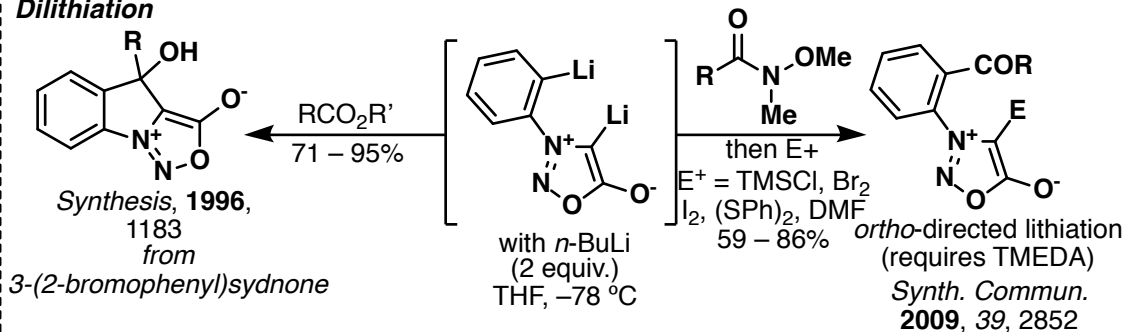
C4 Lithiation



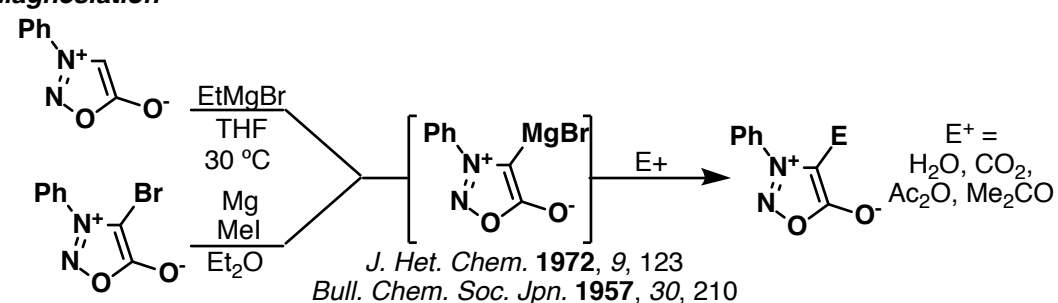
N3 Side Chain Lithiation



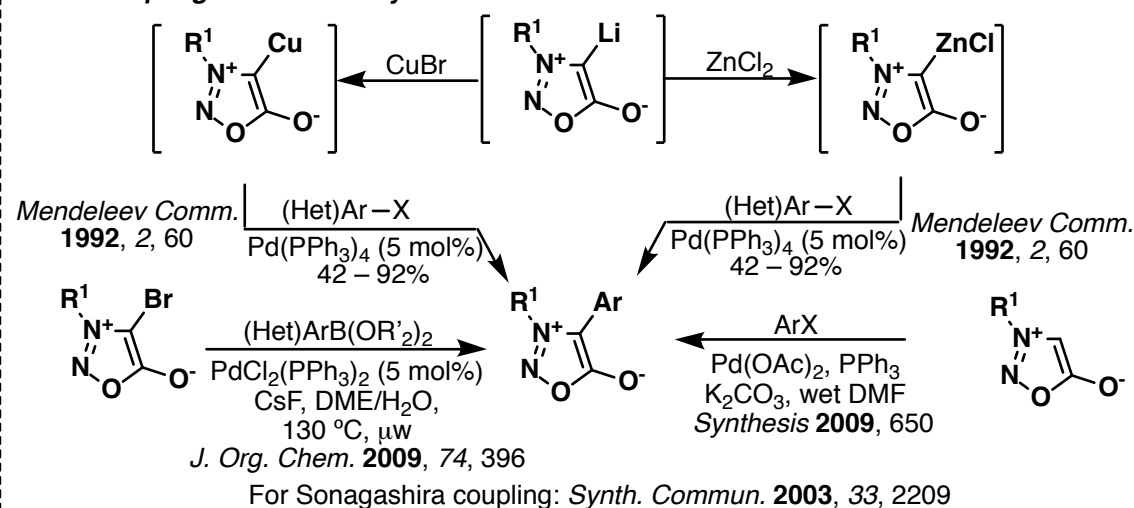
Dilithiation



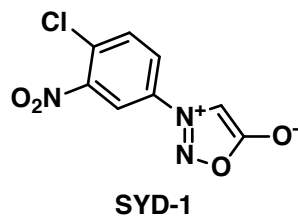
C4 Magnesiumiation



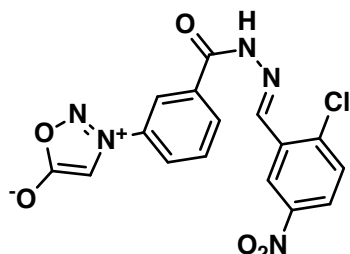
Cross coupling reactions of sydnones



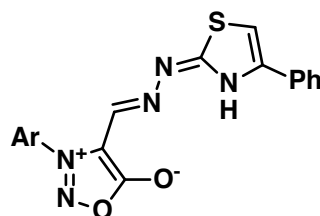
Medicinal Chemistry Investigations of Sydnones



anti-carcinoma
Basic Clin. Pharmacol. Toxicol.
2016, 119, 41

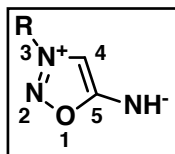


broad-spectrum antibacterial activity
Arch Pharm. Pharm. Med. Chem.
2004, 337, 427



anti-oxidant
Bioorg. Med. Chem.
2004, 12, 4633

Sydnone Imines

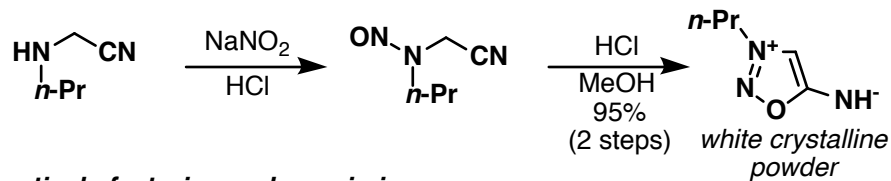


- can be directly lithiated at C4 (Li-halogen exchange fails)
- synthesized by Greco in 1962
- stabilized by N-acylimino groups
- can undergo ring-opening reactions at neutral pH

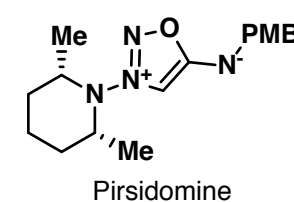
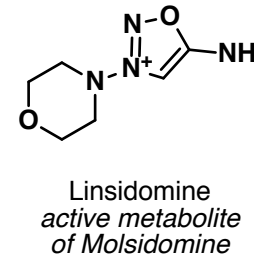
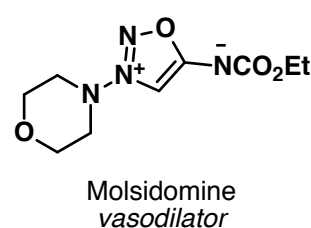
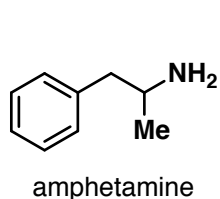
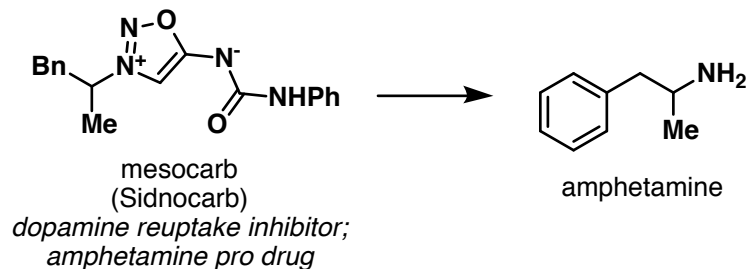
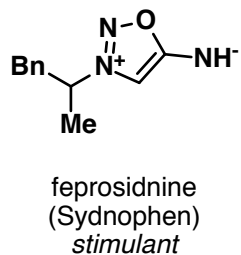
Synthesis of sydnone imines:

First reported successful synthesis

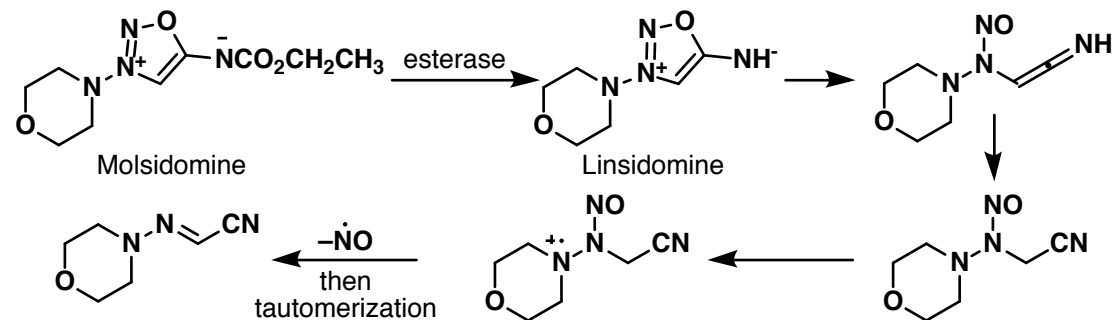
Greco, C. V.; Nyberg, W. H.; Cheng, C. C. *J. Med. Chem.* 1962, 5, 899.



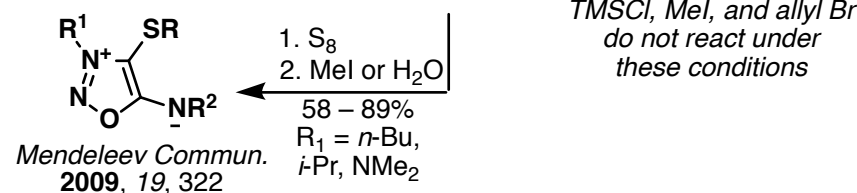
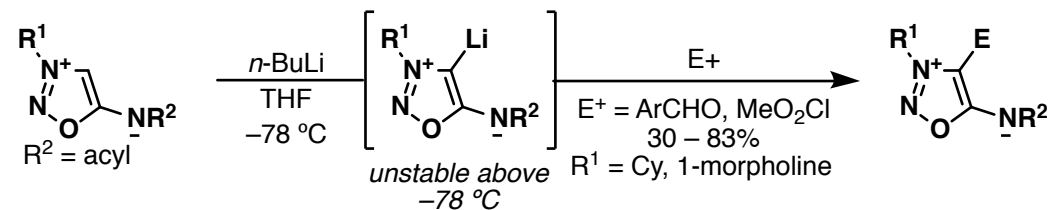
Pharmaceuticals featuring sydnone imines



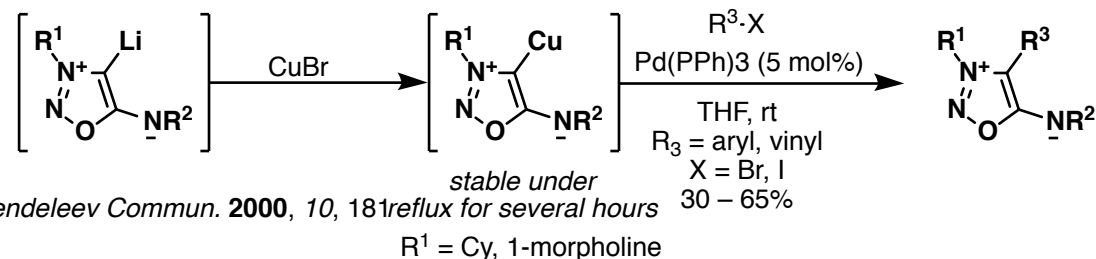
Activation mechanism of Molsidomine (NO release)



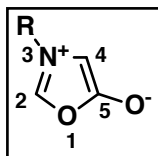
C4 Lithiation (Sydnone imines)



Cross Coupling of Sydnone imines



Münchnone (See Gordon W. Gribble, Gianatassio, 2014 for more examples)

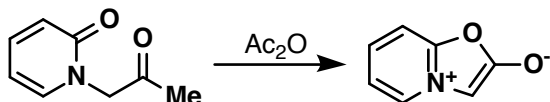


- hydrolysis prone; often generated *in situ*
- C4-electron withdrawing groups stabilize münchnone/enable isolation
- electrophilic at C2
- nucleophilic at C4
- cannot be lithiated at C2/C4

Synthesis and reactions of münchnones

First reported synthesis

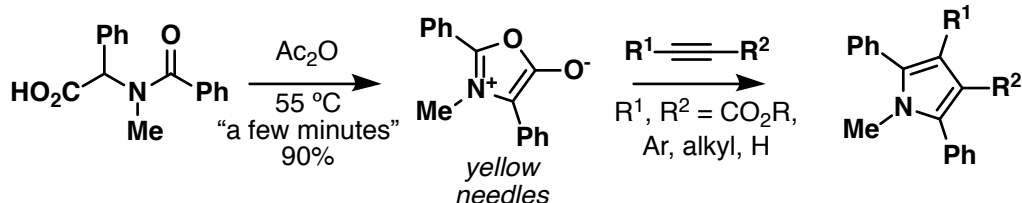
Lawson, A.; Miles, D. H. *Chem. Ind. (London)* **1958**, 461.



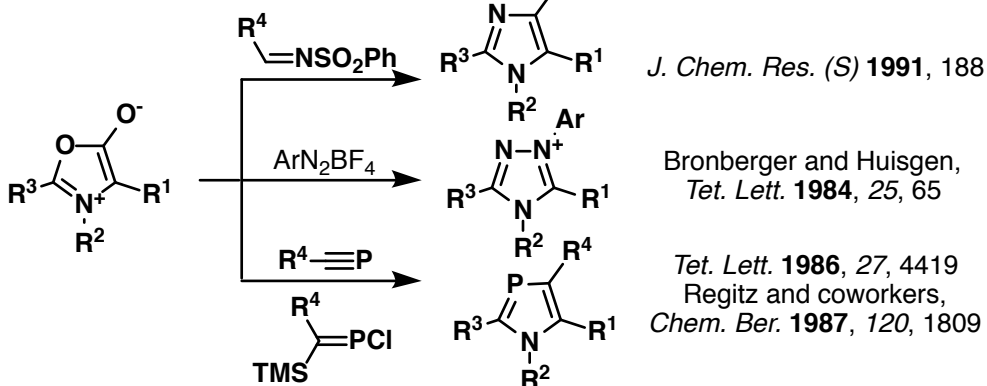
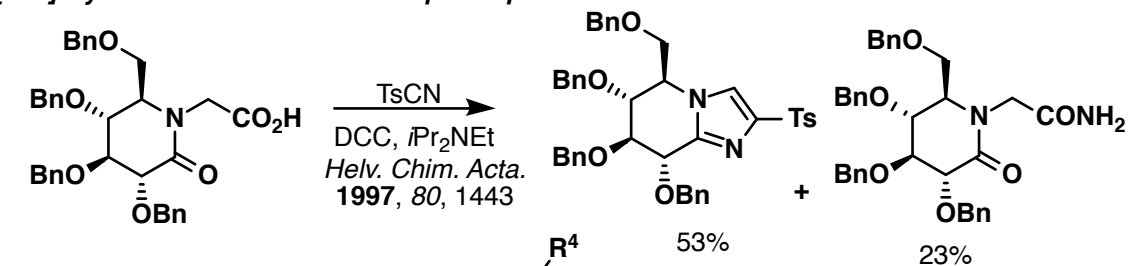
Dehydration with DCC:
J. Org. Chem. **1979**, *44*, 977
Dehydration with EDCI:
Synth. Commun. **1986**, *16*, 357.

Huisgen Pyrrole Synthesis ([3+2] cycloadditions with alkynes)

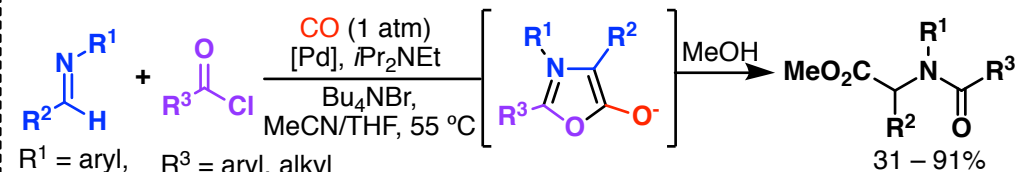
Angew. Chem. Int. Ed. Engl. **1964**, *3*, 136.



[3+2] Cycloadditions with other Dipolarophiles

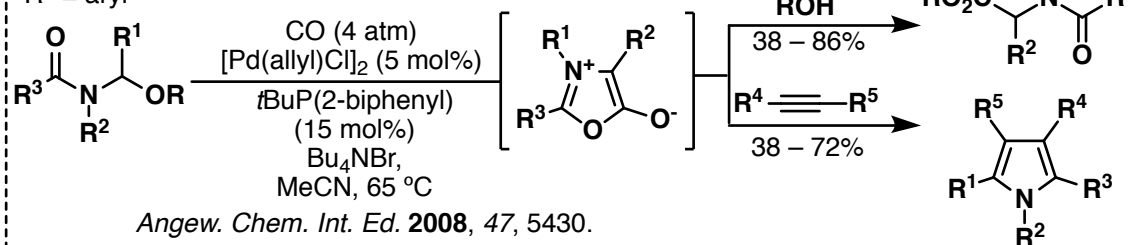


Multicomponent synthesis of münchnones (Palladium-catalyzed)



R¹ = aryl,
alkyl, Bn
R² = aryl
R³ = aryl, alkyl

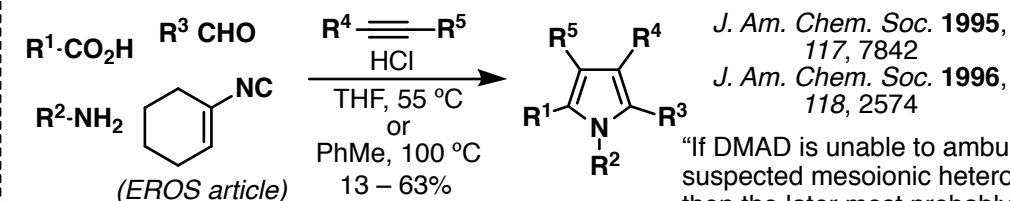
Arndtsen and coworkers, *J. Am. Chem. Soc.* **2003**, *125*, 1474



Angew. Chem. Int. Ed. **2008**, *47*, 5430.

For mechanistic analysis of these reactions,
see *Chem. Eur. J.* **2016**, *22*, 15945

Multicomponent synthesis of münchnones (via Ugi Reaction)

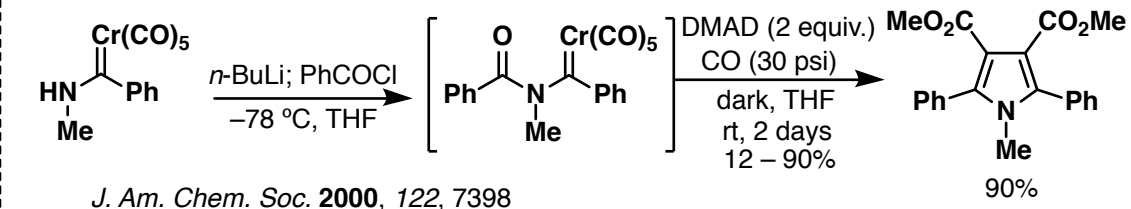


J. Am. Chem. Soc. **1995**,
117, 7842

J. Am. Chem. Soc. **1996**,
118, 2574

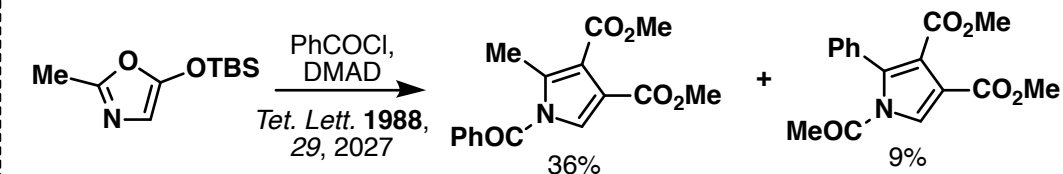
“If DMAD is unable to ambush a suspected mesoionic heterocycle, then the later most probably has not been generated!” –Gordon Gribble

From acylamino chromium carbene complexes



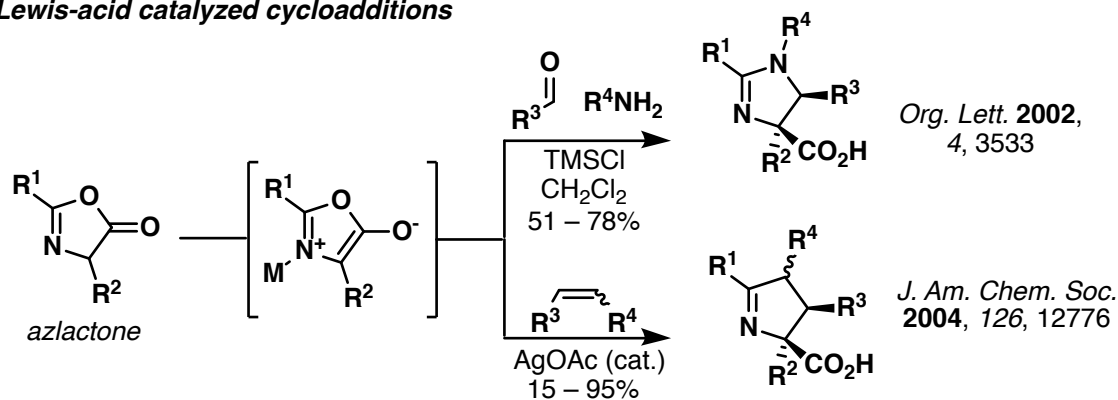
J. Am. Chem. Soc. **2000**, *122*, 7398

Ring chain tautomerization



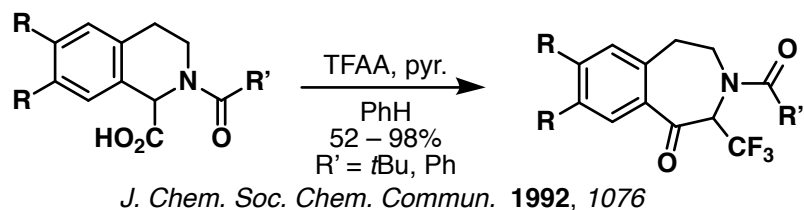
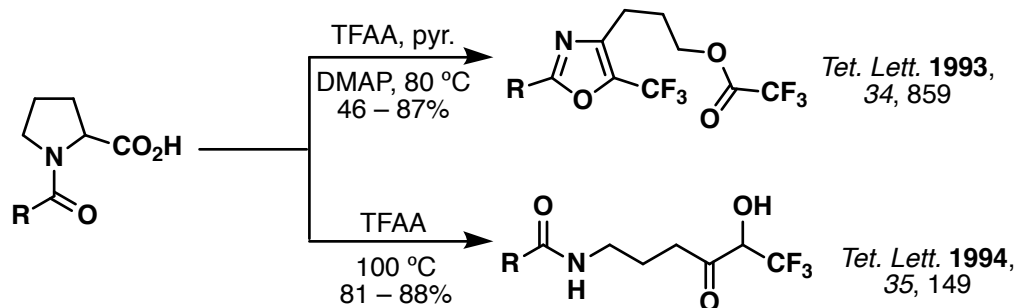
Tet. Lett. **1988**,
29, 2027

Lewis-acid catalyzed cycloadditions

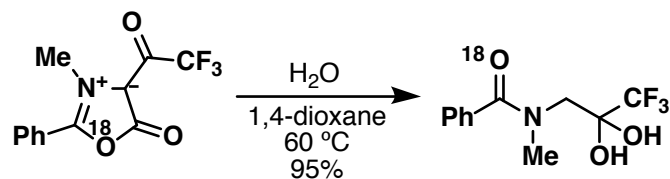


For Au-catalyzed enantioselective [3+2] cycloaddition see:
Toste and coworkers, *J. Am. Chem. Soc.* **2007**, 129, 12638

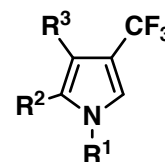
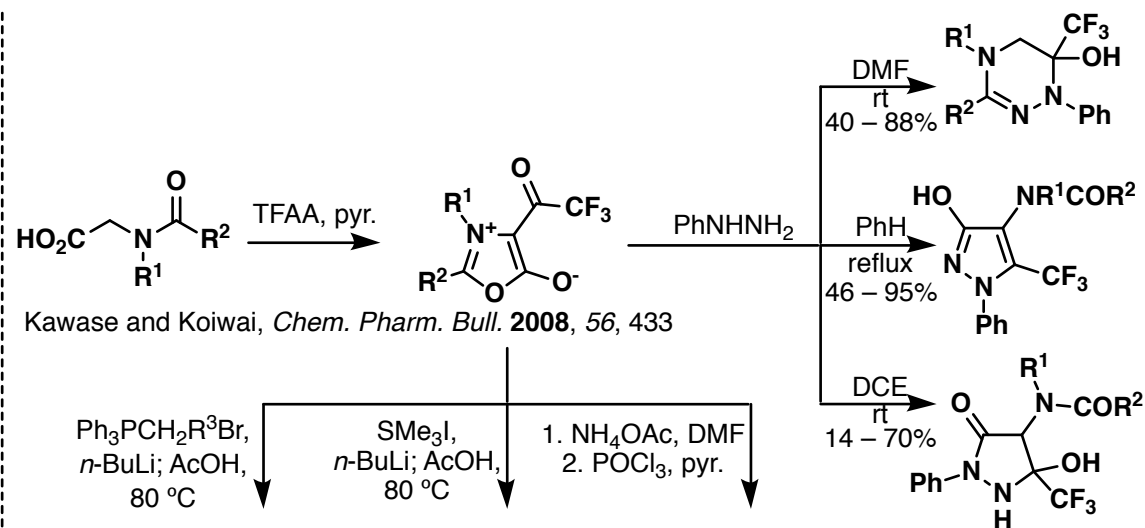
Münchnones As Nucleophiles



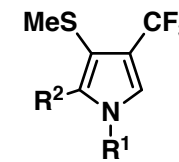
Münchnones As Electrophiles: Reactions of C4 trifluoroacylated münchnones



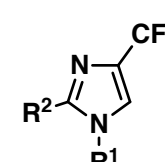
Kawase and coworkers,
Tet. Lett. **1998**, 39, 6189



Kawase and coworkers,
Org. Lett. **2010**,
12, 4776

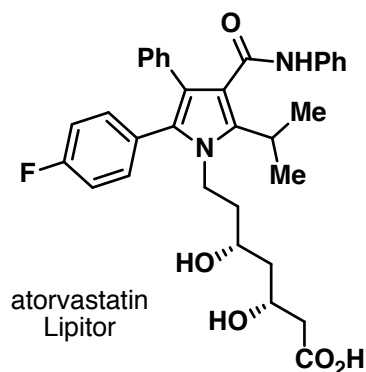


Kawase and coworkers,
Tet. Lett. **2012**,
53, 2782

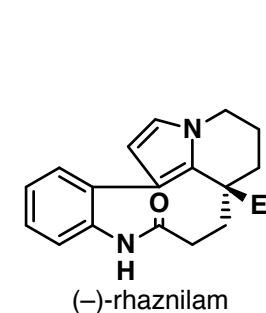


Kawase and coworkers,
Chem. Pharm. Bull.
2001, 49, 461

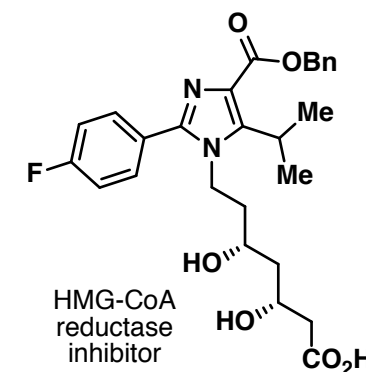
Complex structures synthesized via münchnones



Lopchuk and Gribble,
Tet. Lett. **2015**, 56, 3208.

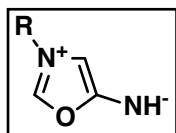


Tokuyama and coworkers,
Tetrahedron **2015**, 71, 3619



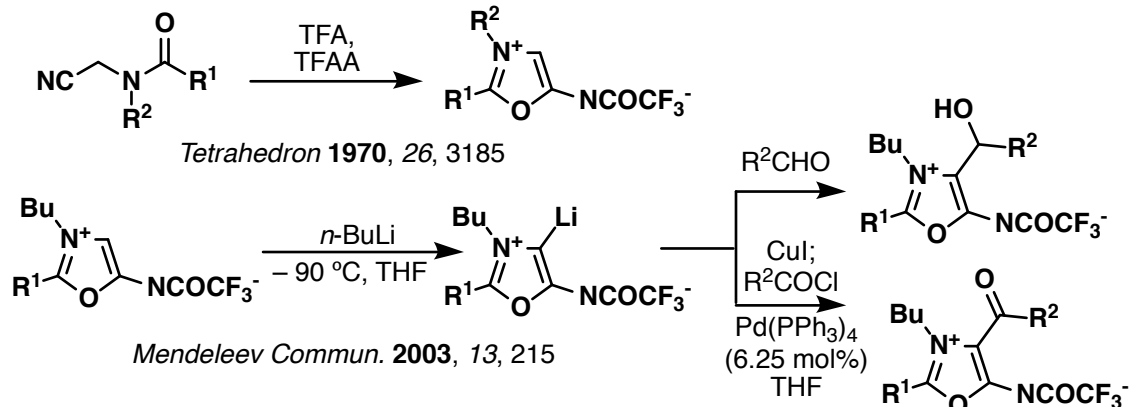
U.S. Pat. Appl. 0239857 A1, 2005
Also see: *OPRD*, **2008**, 12, 1183

Münchnone imine

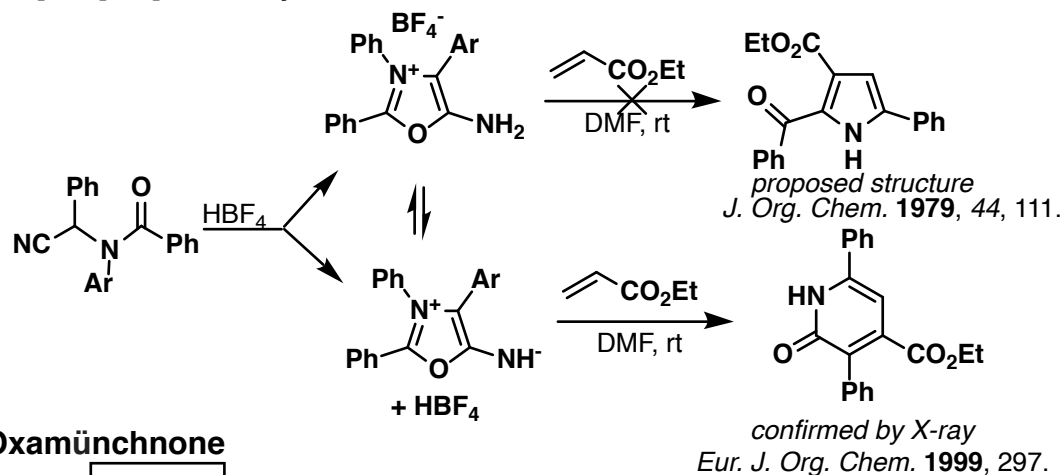


- synthesized by Gotz and Zale in 1970
- can be lithiated unlike the parent münchone

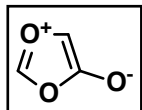
Synthesis and reactions of münchnone imines



[4+2] vs. [3+2] Reactivity

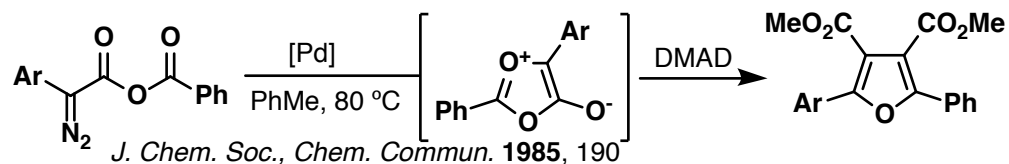


Oxamünchnone

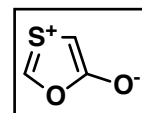


- synthesized by Burk in 1980
- Hamaguchi and Nagai indicated utility of oxamünchones for cycloaddition chemistry (furan synthesis)
- form stable adducts with olefin cycloaddition partners

Synthesis and reactions of oxamünchnone

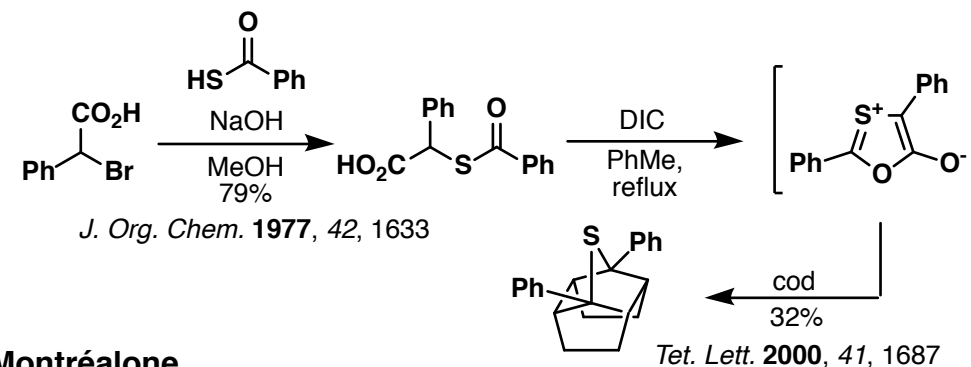


Thiomünchnone

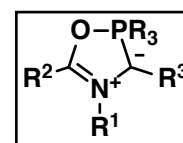


- synthesized by Potts in 1977
- reports of reactions with thiomünchones are incredibly limited

Synthesis and reactions of thiomünchones

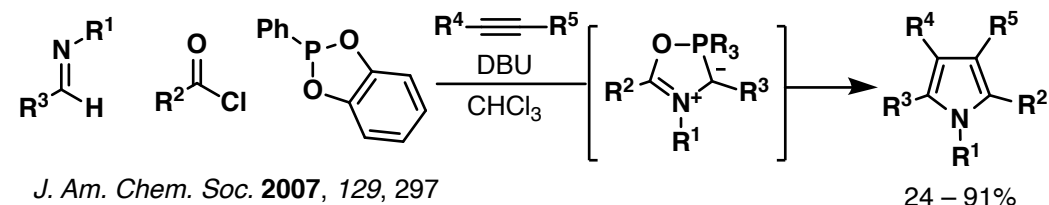


Montréalone

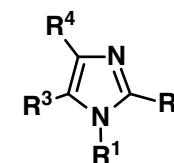


- synthesized by Arndtsen in 2007
- bulky PR₃ unit allows for highly regioselective cycloaddition compared to münchone/offers opportunity for asymmetric cycloadditions

Synthesis of Montréalone

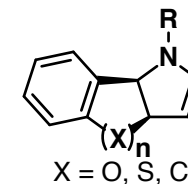


For computational analysis of 1,3-dipolar cycloadditions of münchone derivatives:
J. Am. Chem. Soc. **2013**, *135*, 17349



Synthesis of imidazoles from Montréalone

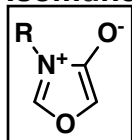
J. Org. Chem. **2015**, *80*, 2709



Enantioselective synthesis of pyrrolines with a chiral BINOL-derived phosphite from Montréalone

Org. Lett. **2014**, *16*, 1056

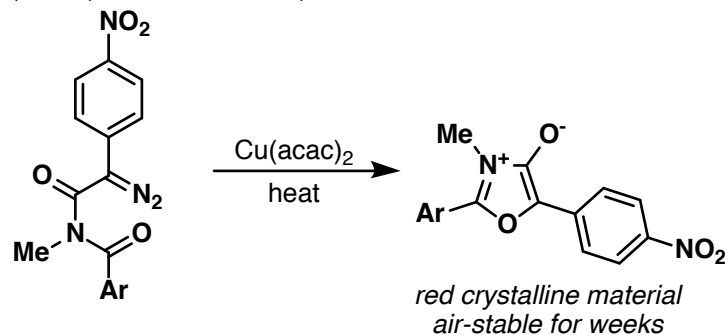
Isomünchnone



- synthesized and isolated by Iyata in 1974
- typically not isolable/stable (EWG stabilizes)
- primarily used in cycloaddition chemistry

Synthesis of isomünchnones

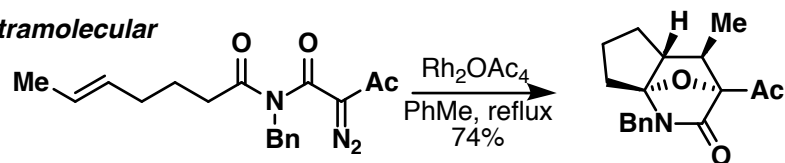
Initial Synthesis and Isolation

Hamaguchi, M.; Iyata, T. *Tet. Lett.* **1974**, 4475

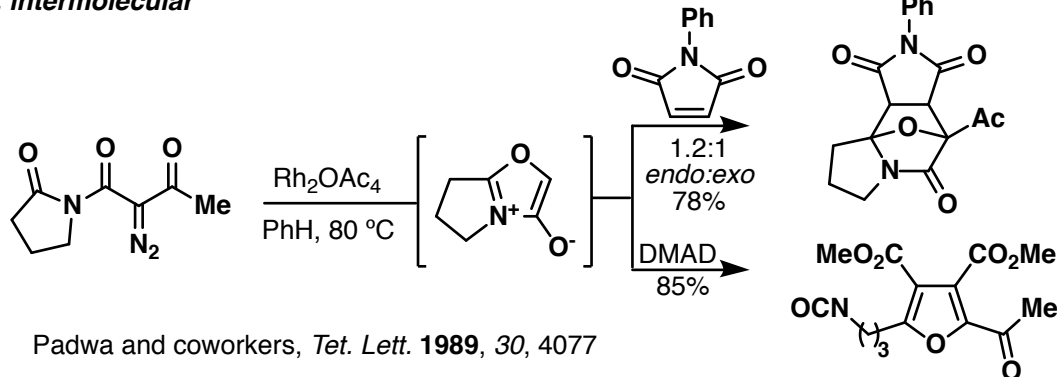
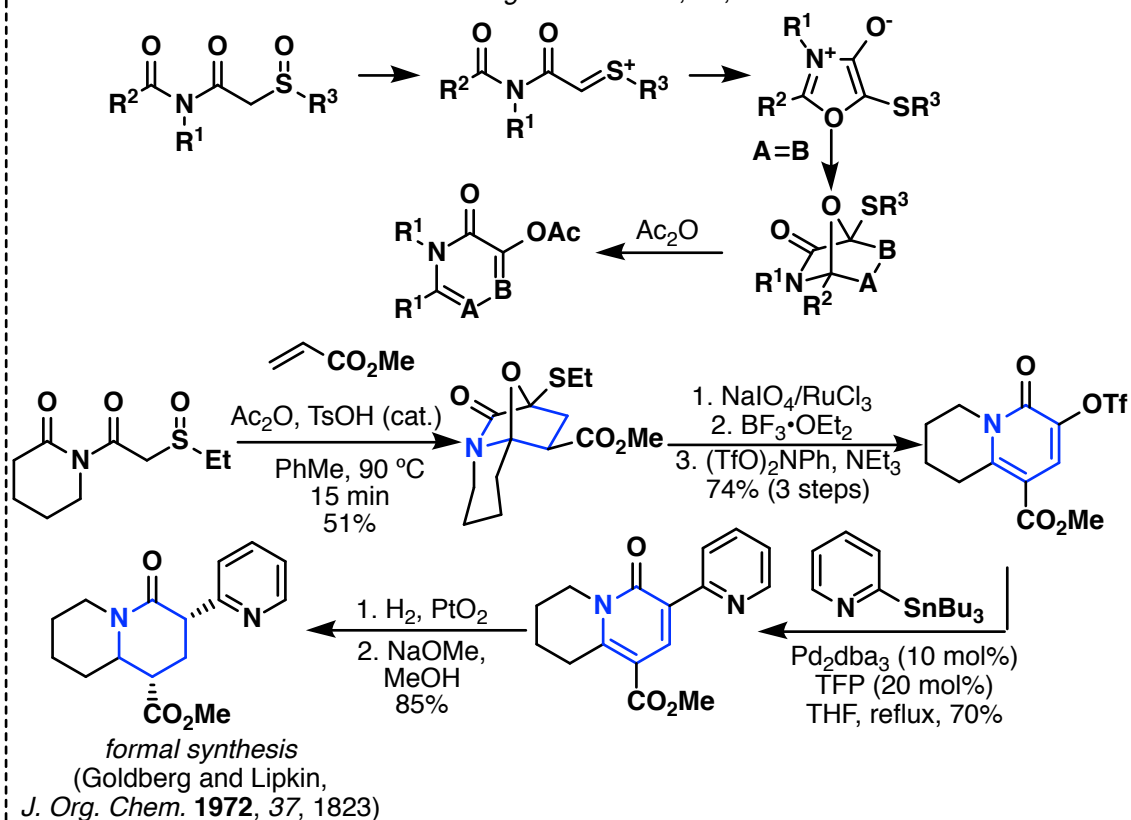
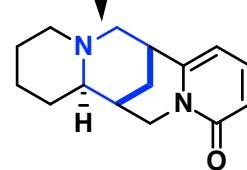
Reactions of isomünchnones

[3+2] Cycloadditions

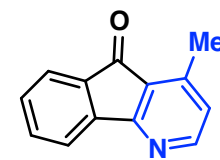
i. Intramolecular

Maier and Evertz, *Tet. Lett.* **1988**, 29, 1988

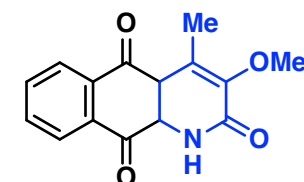
ii. intermolecular

Padwa and coworkers, *Tet. Lett.* **1989**, 30, 4077Imidosulfoxides as isomünchnone precursors via Pummerer
Rearrangement/Deprotonation *J. Org. Chem.* **2000**, 65, 2368formal synthesis
(Goldberg and Lipkin,
J. Org. Chem. **1972**, 37, 1823)Strategy was applied to other alkaloids
in same publication:

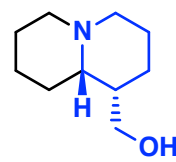
(±)-anagryine



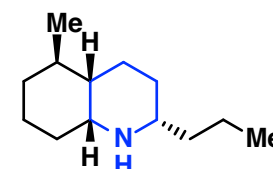
onychine



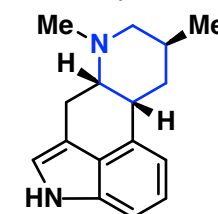
dielsiquinone



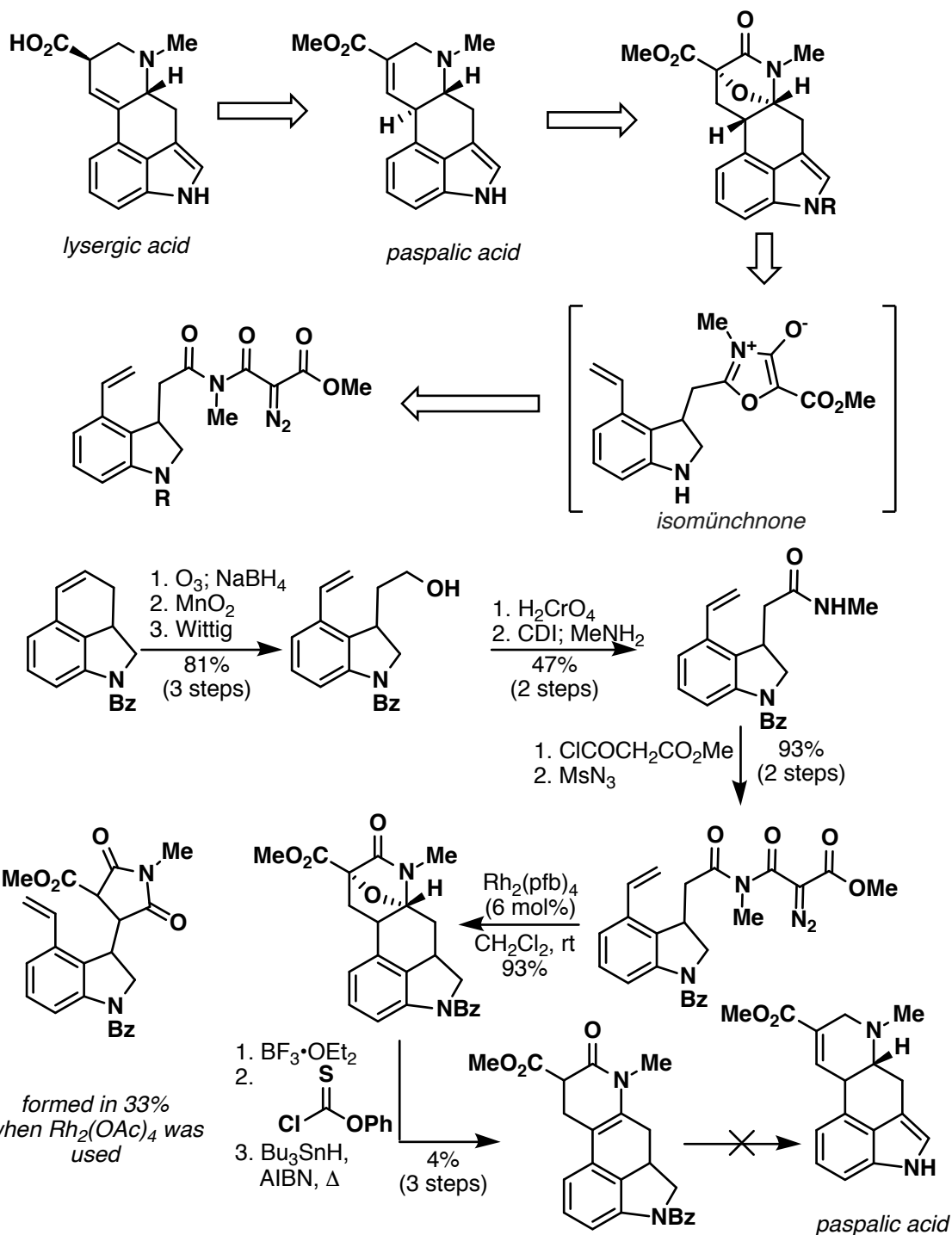
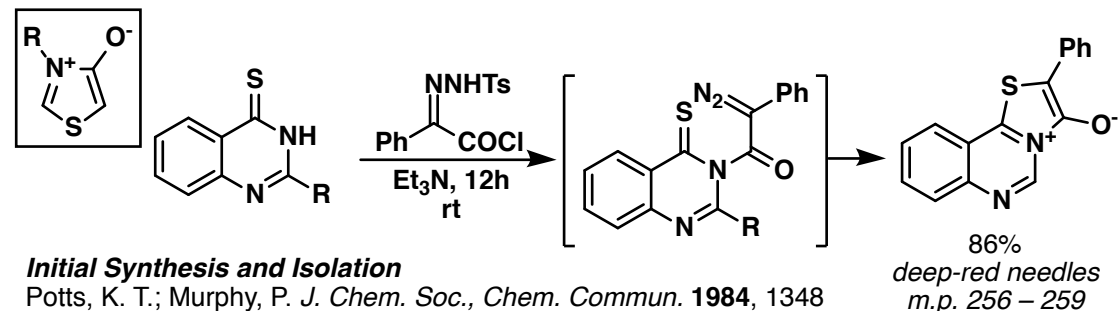
(±)-lupinine



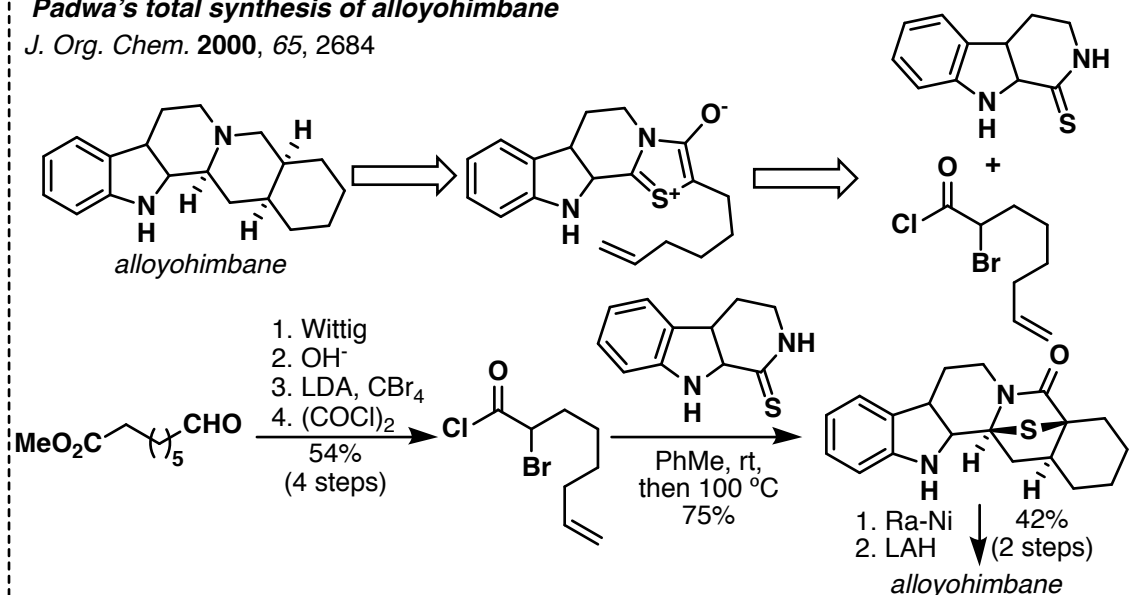
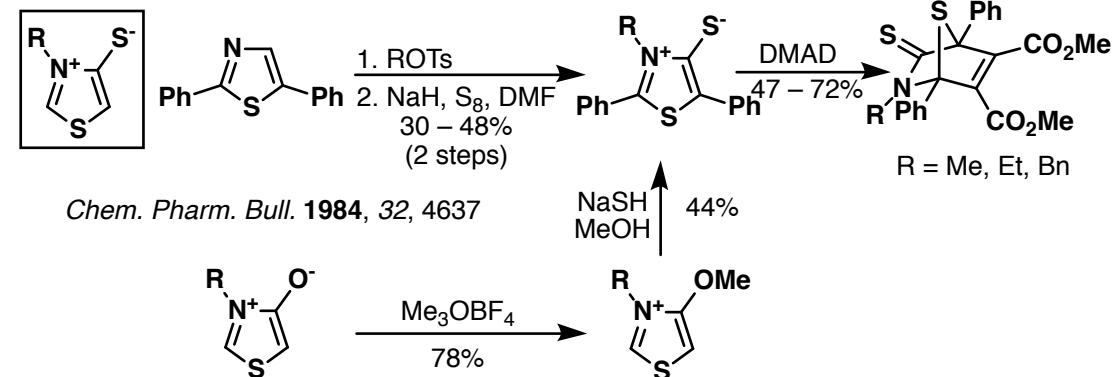
(±)-pumiliotoxin C



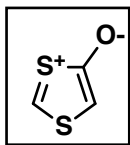
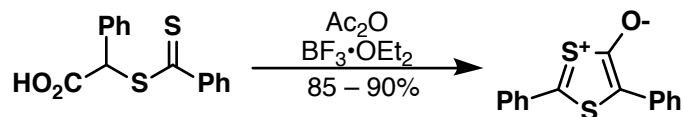
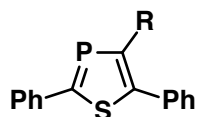
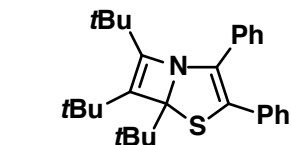
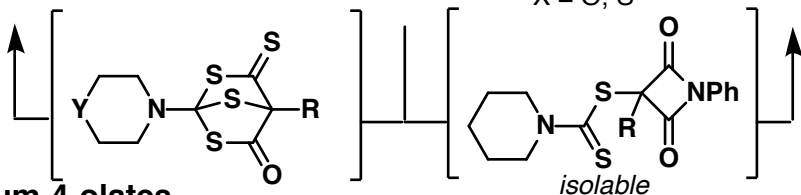
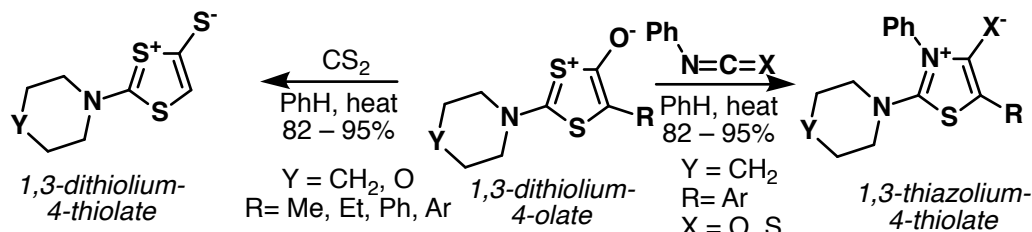
(±)-costaclavin

Padwa's Approach to Lysergic Acid*J. Org. Chem.* **1995**, *60*, 2704**Thioisomünchnone****Initial Synthesis and Isolation**Potts, K. T.; Murphy, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1348

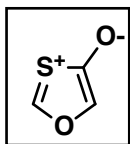
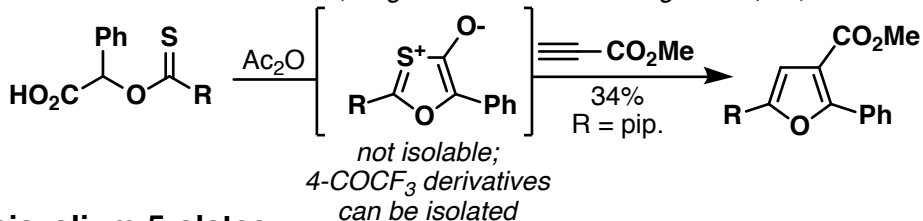
For preparation via diazothioamides with Rh, see:

Padwa and coworkers, *Heterocycles*, **1993**, 35, 367.**Padwa's total synthesis of allooyhimbane***J. Org. Chem.* **2000**, *65*, 2684**1,3-thiazolium-4-thiolate**

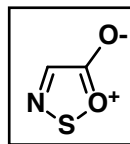
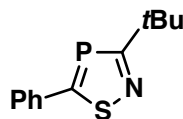
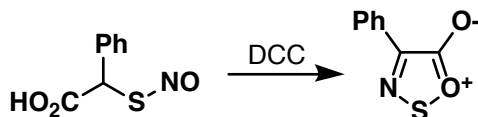
1,3-dithiolium-4-olates

**Synthesis**Gotthardt and Christl, *Tet. Lett.* **1968**, 4743**Heterocycles synthesized from 1,3-dithiolium-4-olates***Chem. Ber.* **1987**, 120, 1809*Bull. Soc. Chim. Fr.* **1997**, 134, 927**Interconversion of mesoionic compounds**Souizi and Robert, *Synthesis*, **1982**, 1059Souizi and coworkers, *J. Chem. Soc., Chem. Commun.* **1993**, 998.

1,3-oxathiolium-4-olates

**Synthesis**Gotthardt and coworkers, *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 422

1,3,2-oxathiazolium-5-olates

**Synthesis**Gotthardt, *Chem. Ber.* **1972**, 105, 188*Chem. Ber.* **1987**, 120, 1809**Key References:**

The Chemistry of Heterocyclic Compounds, Volume 60: Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A (edited by David C. Palmer)

The Chemistry of Heterocyclic Compounds, Volume 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products (Edited by Albert Padwa)

Metalation of Azoles and Related Five-Membered Ring Heterocycles (Topics in Heterocyclic Chemistry) (Edited by Gordon W. Gribble)