



**SEMMELWEIS
UNIVERSITY**



**PETER PAZMANY
CATHOLIC UNIVERSITY**



Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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WORLD OF MOLECULES

(Molekulák Világa)

A case study on the design of chemical reaction.

(Esettanulmány egy kémiai reakció megtervezéséről)

Compiled by dr. Péter Mátyus
with contribution by dr. Gábor Krajsovszky
Formatted by dr. Balázs Balogh





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Rolf Huisgen

Born 1920 (Gerolsheim/Eifel)

PhD Student of Heinrich Wieland

Faculty Positions

University of Tübingen (1949-1952)

University of Munich (1952 – present)

He studied chemistry in Bonn and Munich, receiving his doctorate in 1943 for a dissertation on a strychnine alkaloid, supervised by the Nobel prize winner Heinrich Wieland. Huisgen published over 580 scientific papers. In Germany alone, 16 of his students became full professors.



Mechanism of 1,3-Dipolar Cycloadditions

Pericyclic reactions - take place via cyclic transition state

In one step - concerted reaction

synchronous

asynchronous

stereospecific and regioselective

In two steps – non concerted reaction

stereo- and regioselective

Regiochemistry depends on

interactions of relevant HOMO-LUMO orbitals

„large-large”, „small-small” interactions (coefficients)

Further depends on

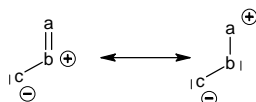
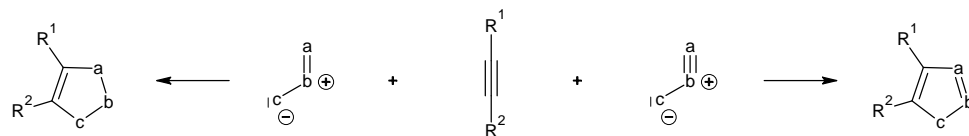
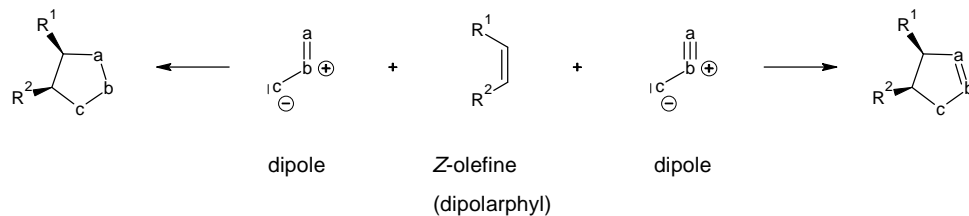
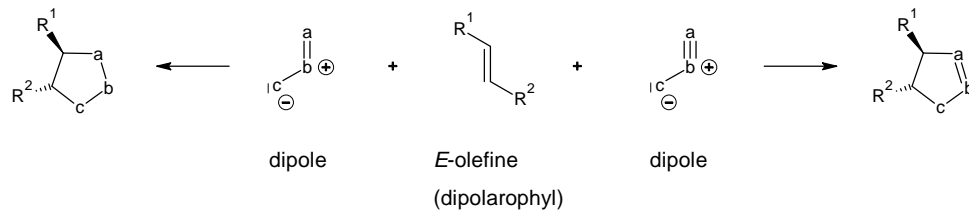
charge of atoms

sterical hinderance

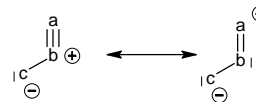
solvent



1,3-Dipolar Cycloadditions



a	b	c	a	b	c
C	N	C	N	N	C
C	N	N	N	N	N
C	N	O	N	N	O

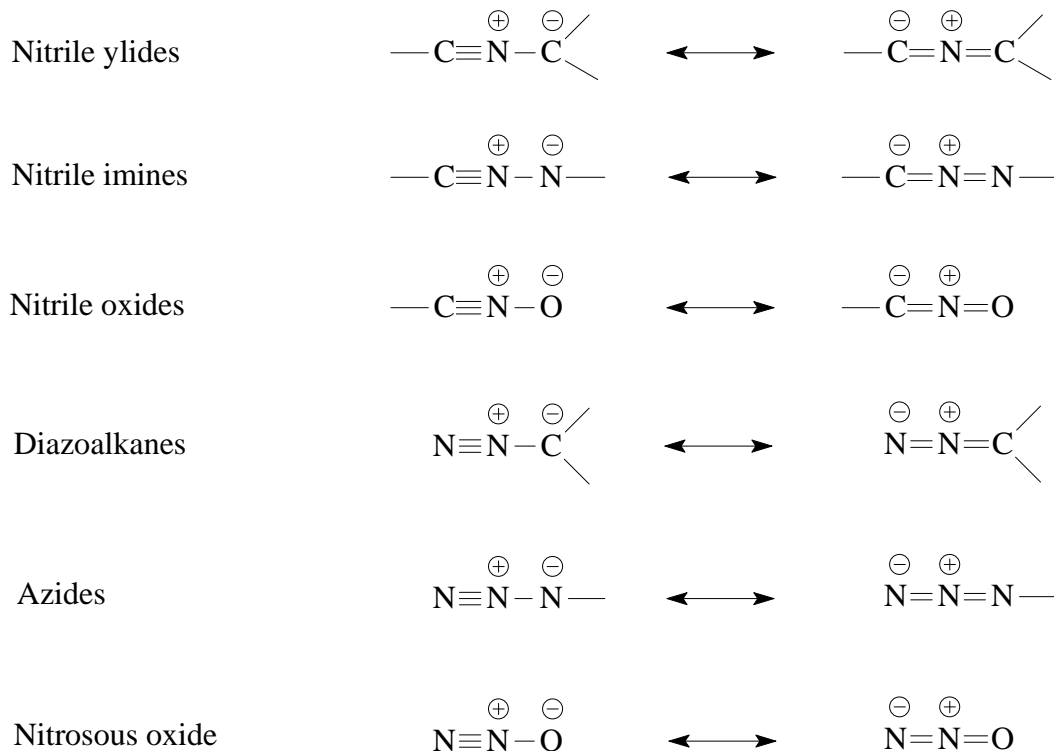


R. Huisgen, *Angew. Chem.* **75**, 604-637. 742-754. (1963)



Classification of 1,3-Dipoles Containing Carbon, Nitrogen, Oxygen and Sulphur Centres

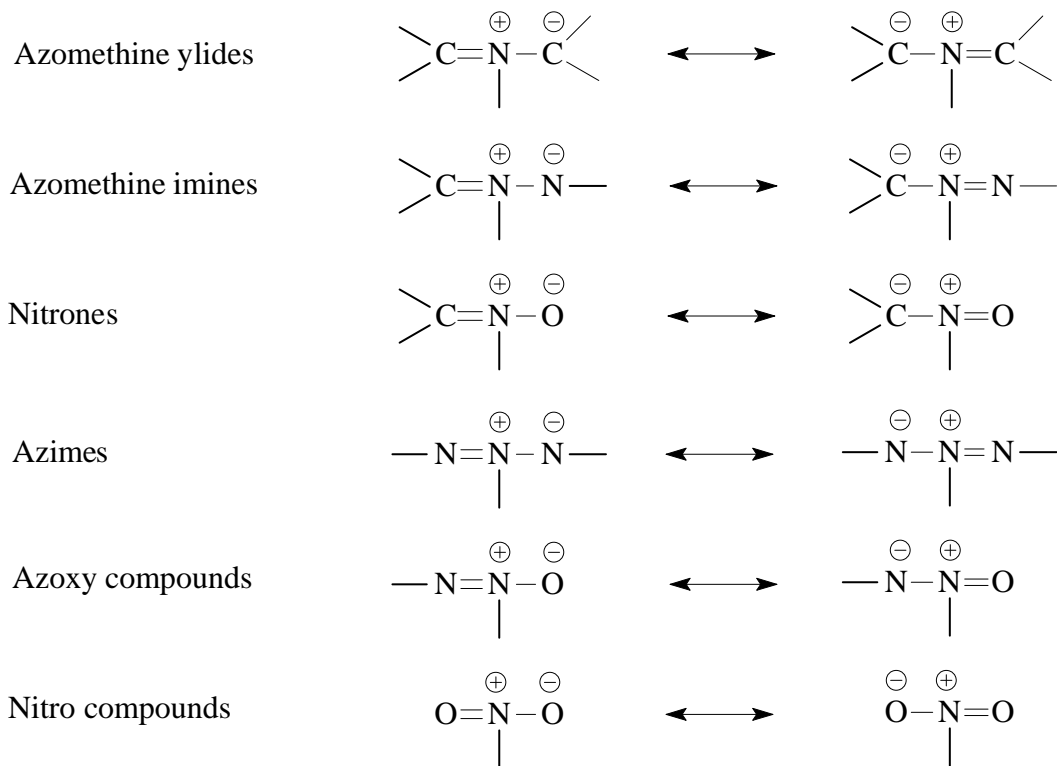
Propargyl-Allenyl Type





Classification of 1,3-Dipoles

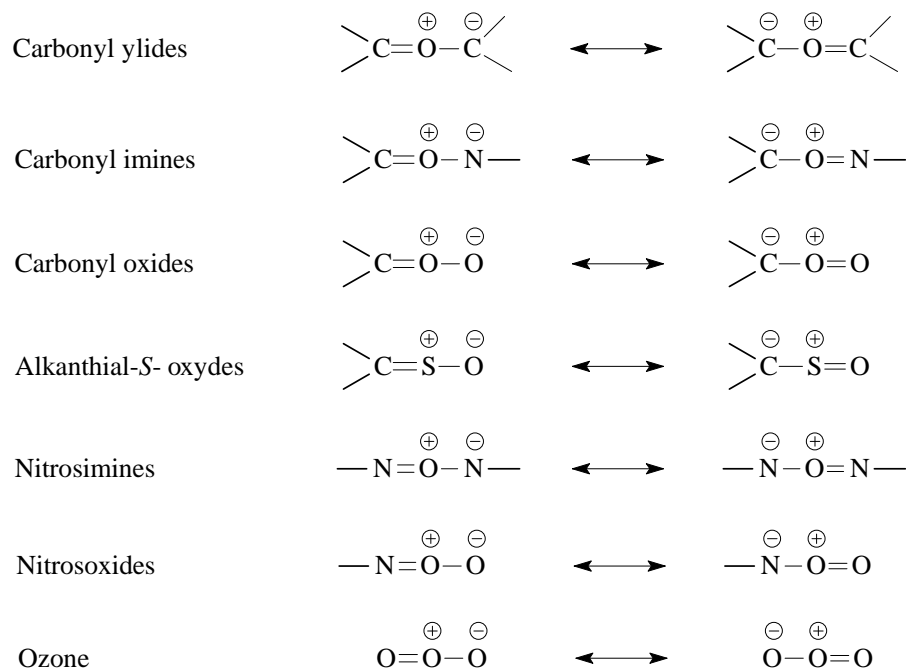
Allyl Type I.





Classification of 1,3-Dipoles

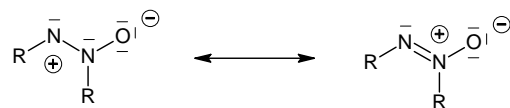
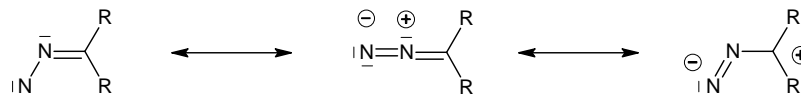
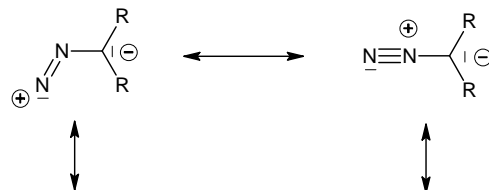
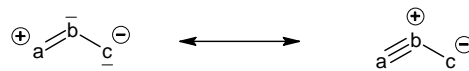
Allyl Type II.



R. Huisgen, *J. Org. Chem.* **41**, 403. (1976)



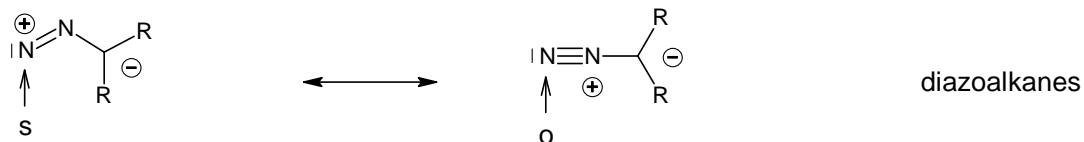
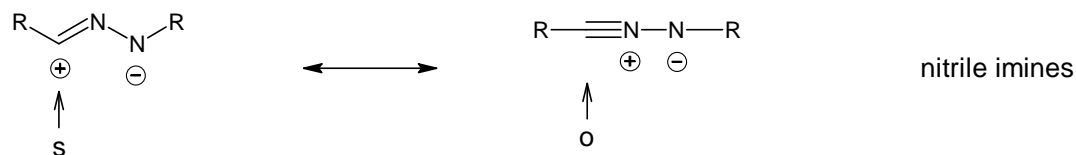
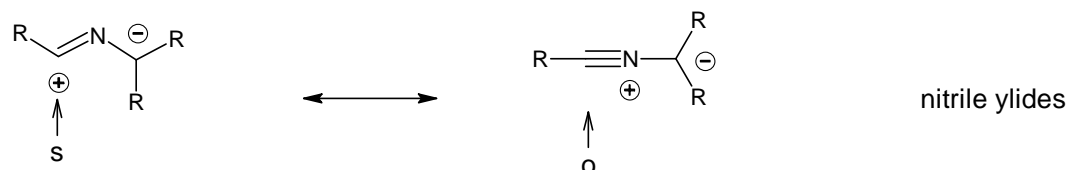
Mesomer Forms of Several Dipoles



azoxy compound



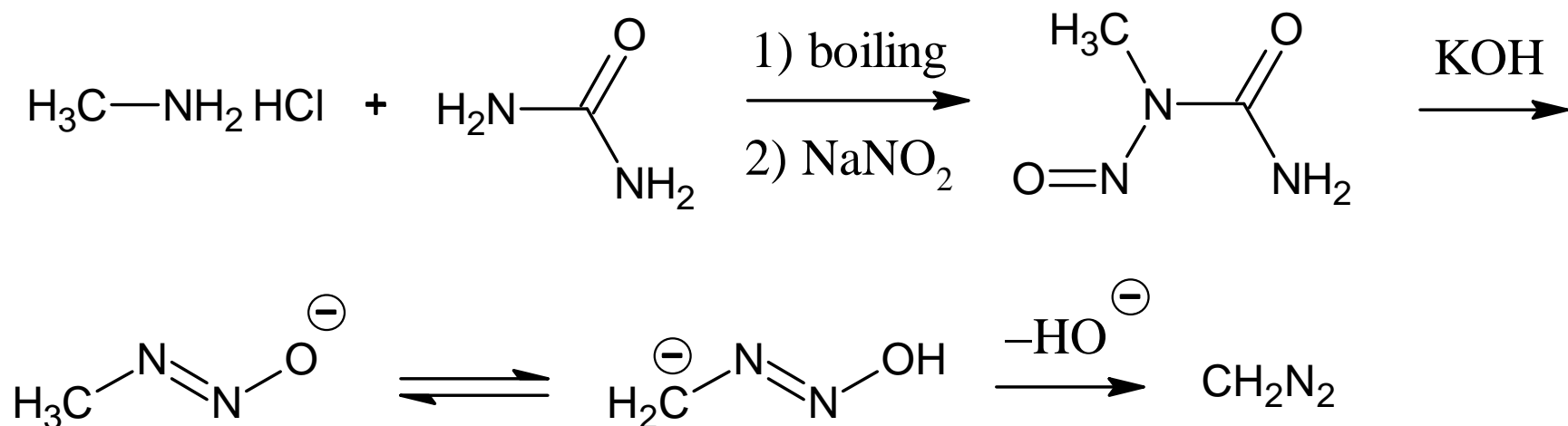
Sextett and Octett Configurations of Dipoles



o: octett configuration around the appropriate atom
s: sextett configuration around the appropriate atom

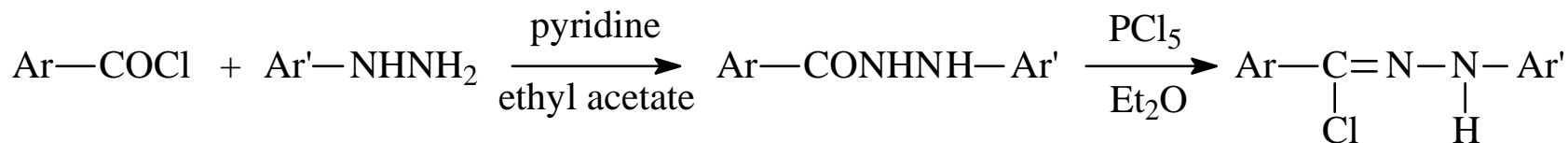
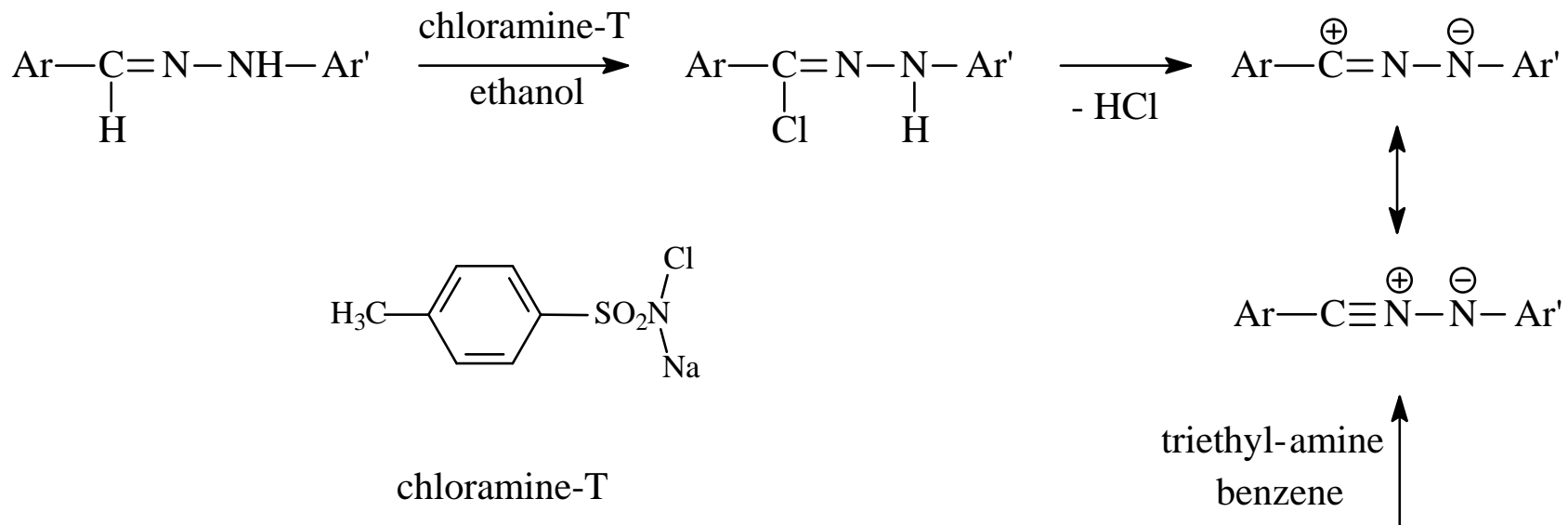


Synthesis of Diazomethane





Synthesis of Nitrilimines

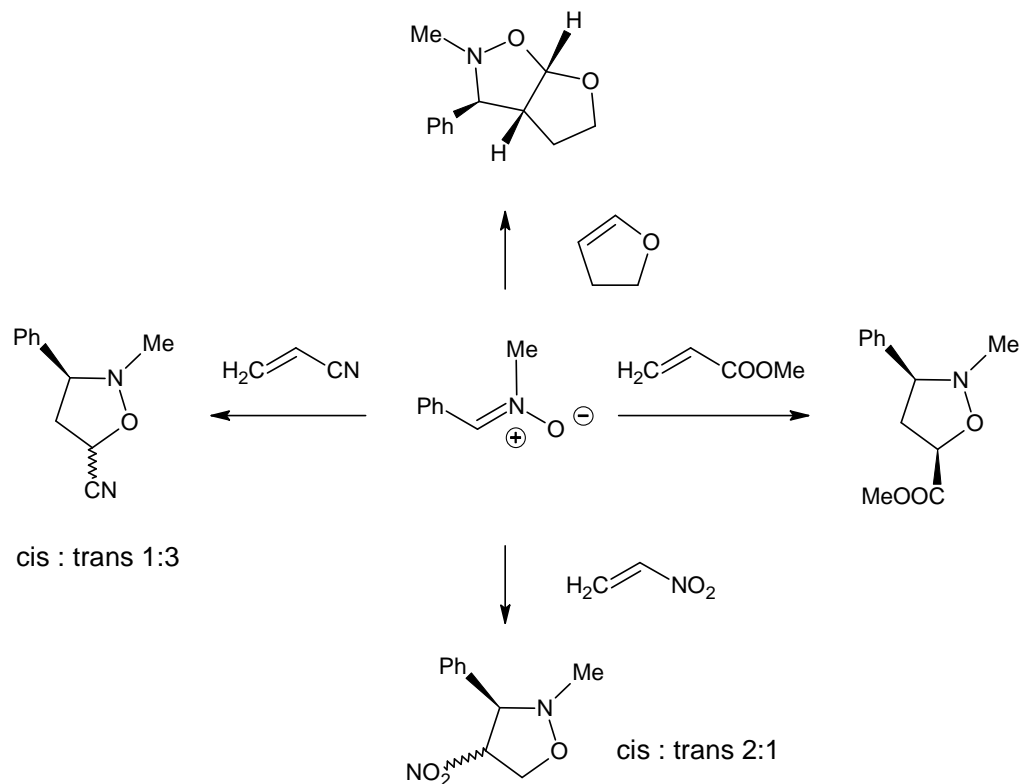


K.M. Lokanatha Rai, A. Hassner, *Synthetic Communications* **19**, 2799. (1989)

R. Huisgen, M. Seidel, G. Wallbillich, H. Knupfer, *Tetrahedron* **17**, 3. (1962)

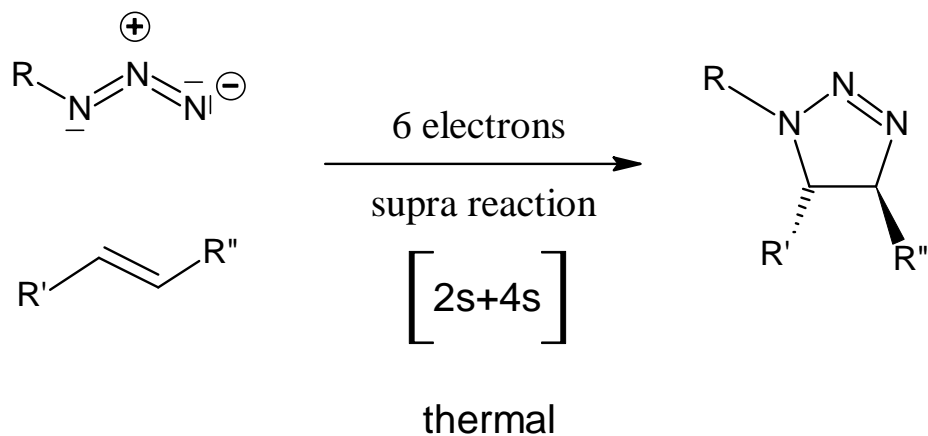
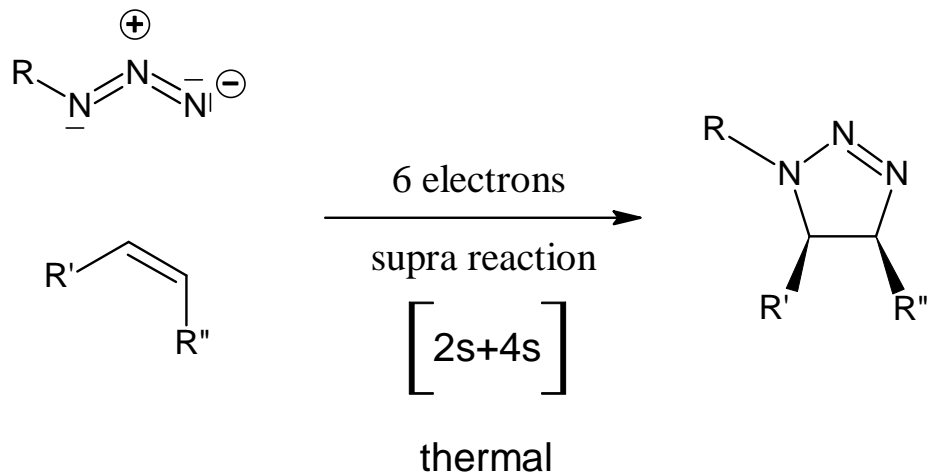


Regio- and Stereoselectivity of 1,3-Dipolar Cycloadditions





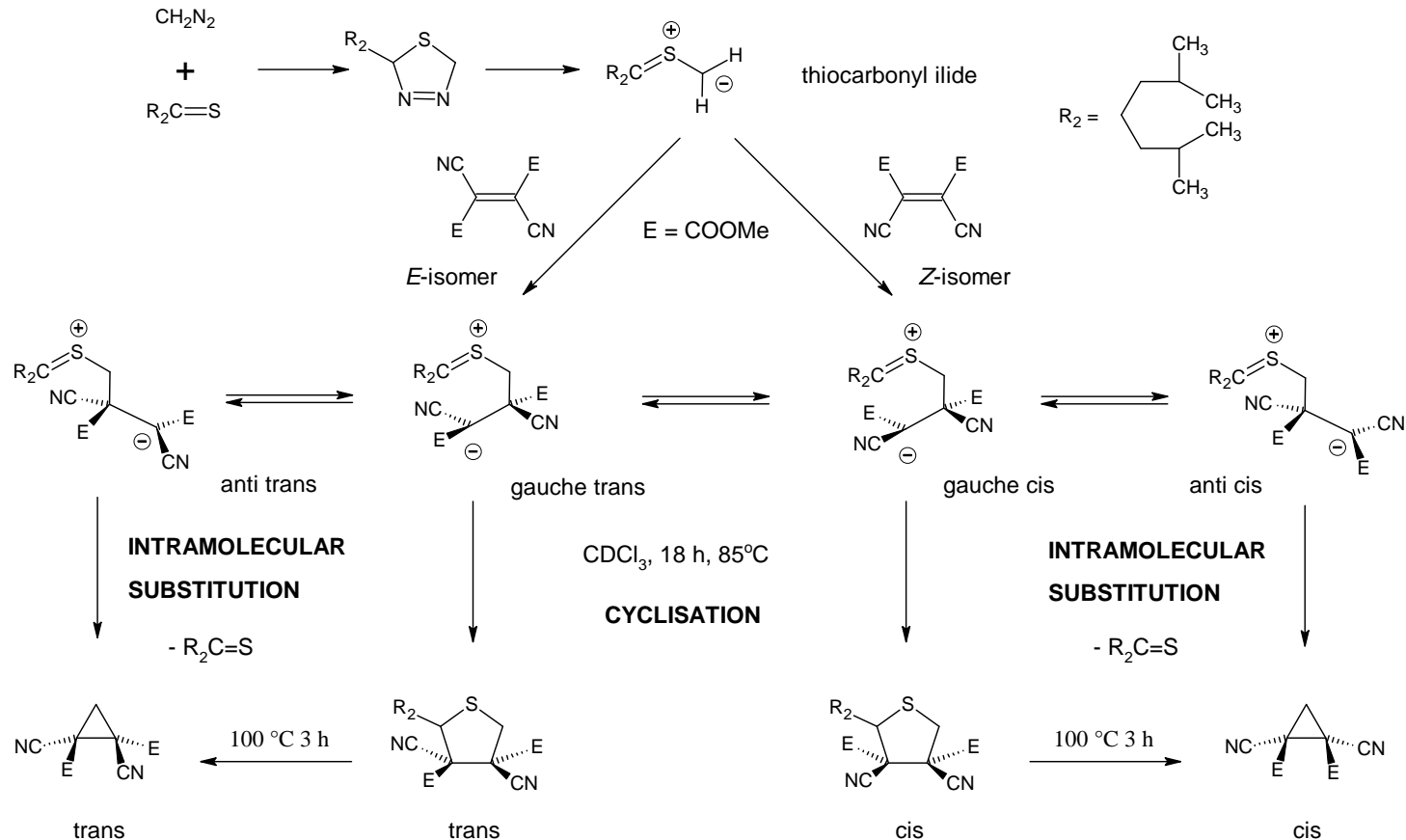
One Step Mechanism





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Two Step Mechanism R. Huisgen et al, *Tetrahedron* **61**, 6143. (2005)



from *E* trans/cis: 64/36 (26%/15%) thiolane
trans/cis: 57/43 (27%/20%) c-propane

Intramolecular substitution takes place in the case of sterical hinderance

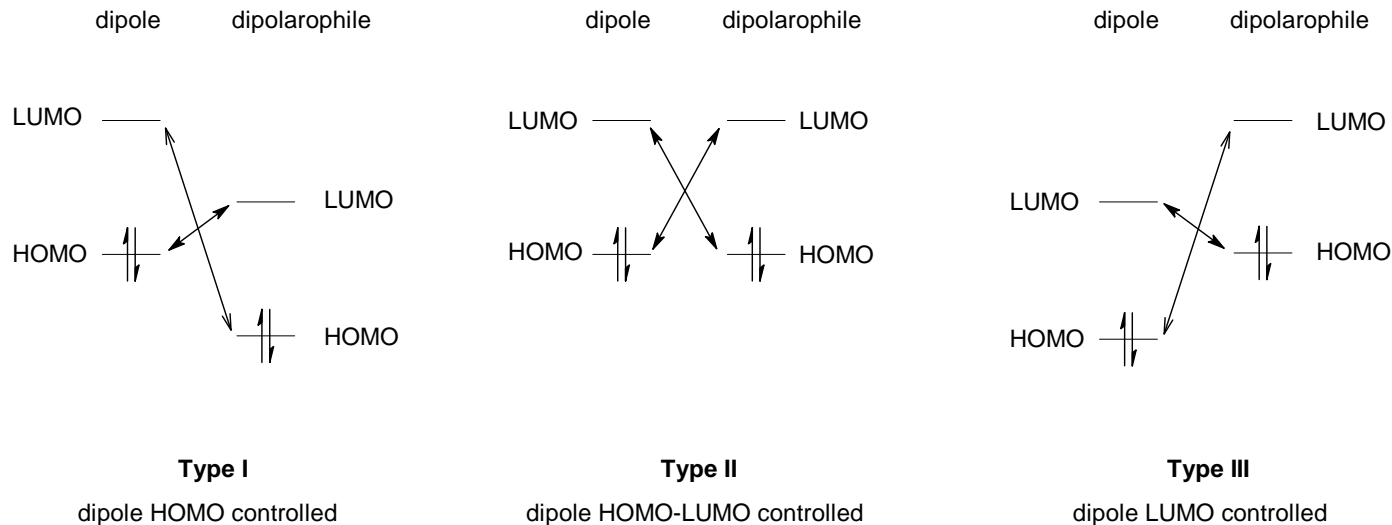
from *Z* trans/cis: 63/37 (24%/14%) thiolane
trans/cis: 55/45 (26%/21%) c-propane





Type of Dipolar Cycloadditions

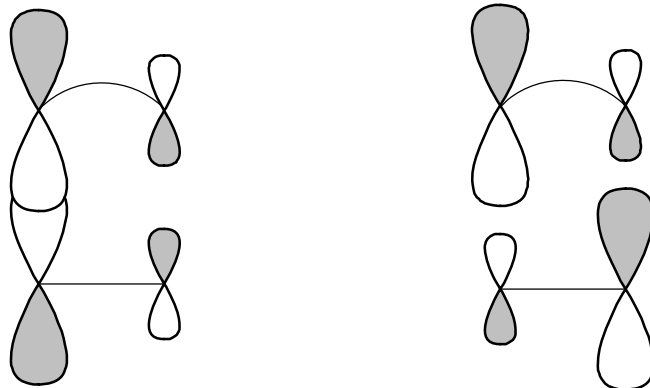
HOMO-LUMO Interactions



K.N. Houk, *J. Am. Chem. Soc.* **95**, 7287-7315. (1973)



Overlapping of Orbitals



Large-large

Small-small

Large-small

Small-large

Interactions





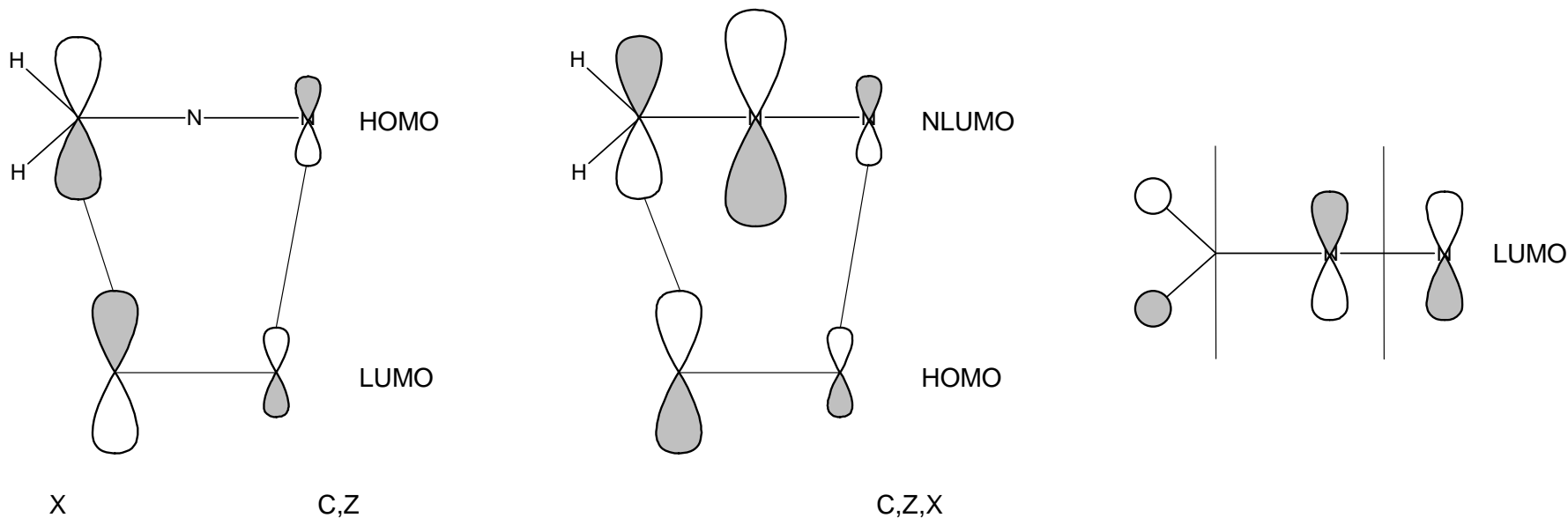
Prediction the Regioselectivity of a Cycloaddition

1. Estimate the energies of the HOMO and the LUMO of both components.
2. Identify which HOMO/LUMO pair is closer in energy.
3. Using this HOMO/LUMO pair, estimate the relative sizes of the coefficients of the atomic orbitals on the atoms at which bonding is to take place.
4. Match up the larger coefficient on one component with the larger on the other.



Interactions Between Molecule Orbitals of Diazomethane and Substituted Olefins

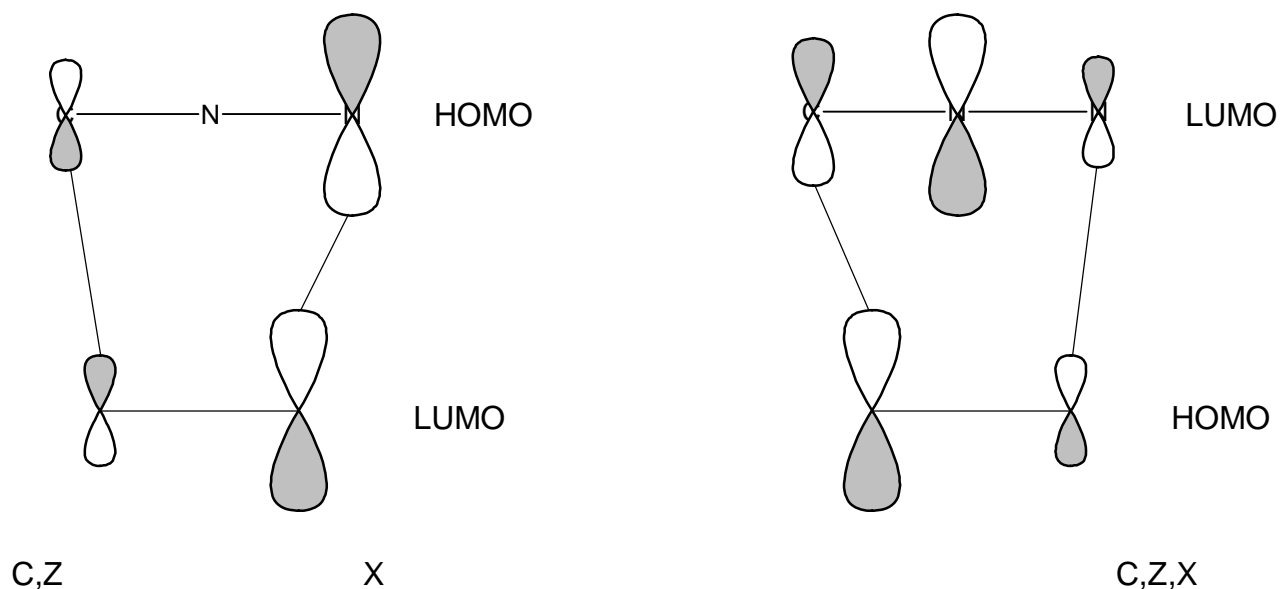
Diazomethane





Interactions Between Molecule Orbitals of Nitrilimines and Substituted Olefins

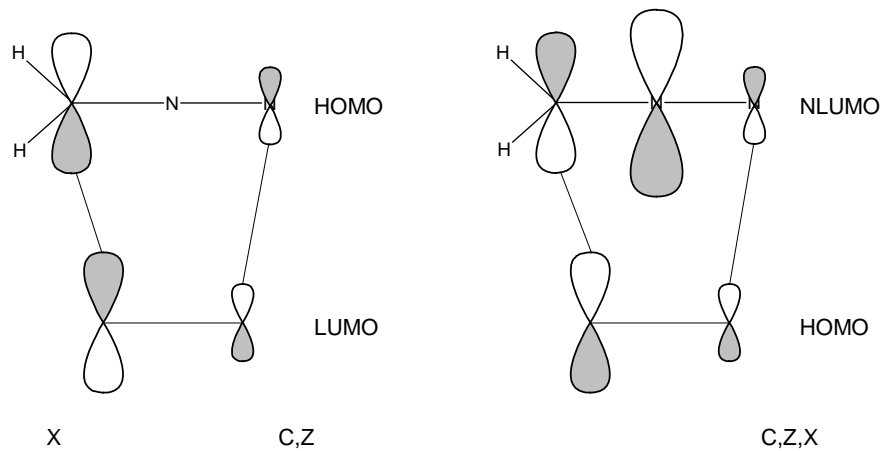
Nitrilimines



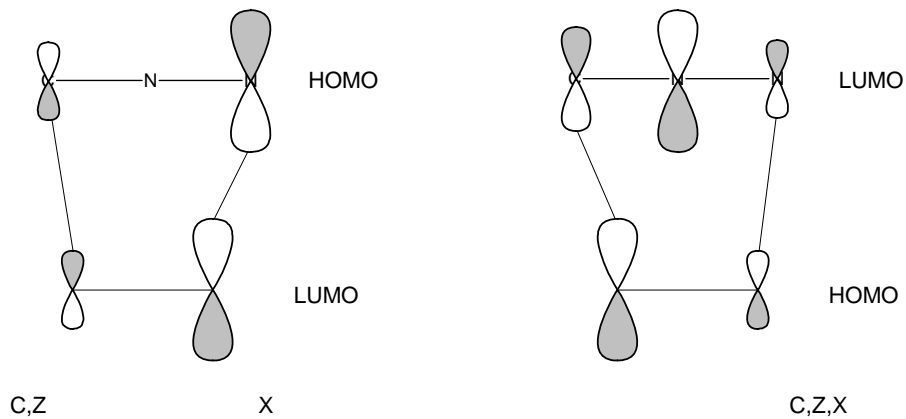


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Diazomethane

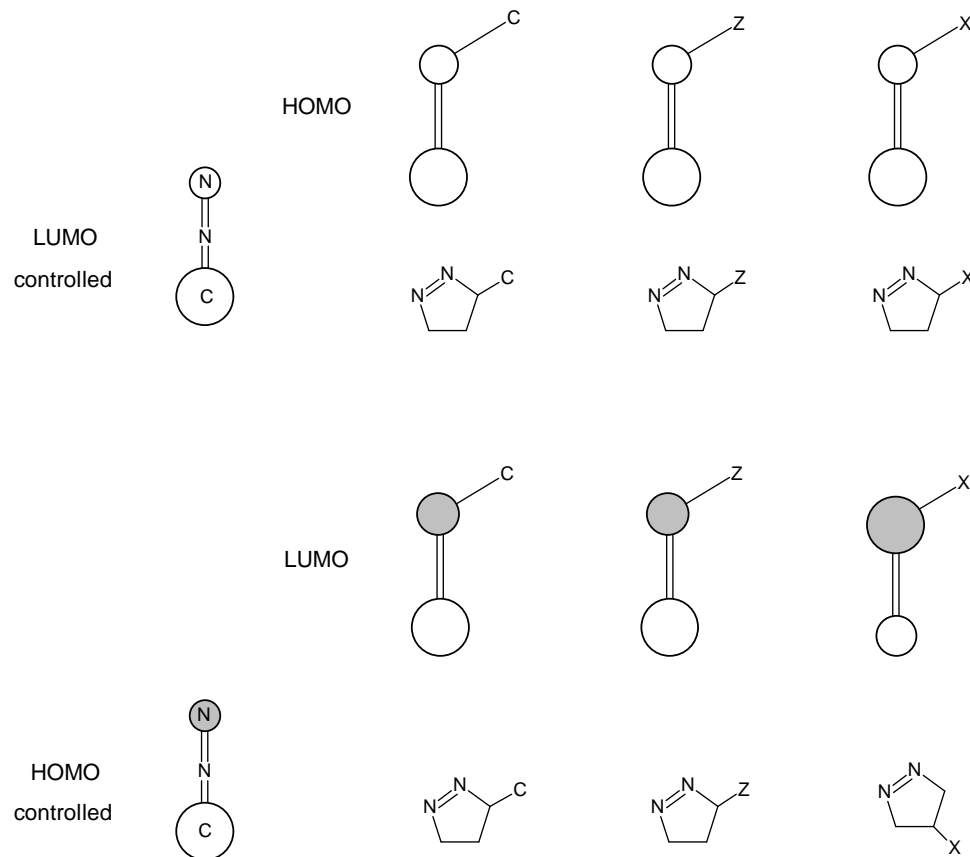


Nitrilimines



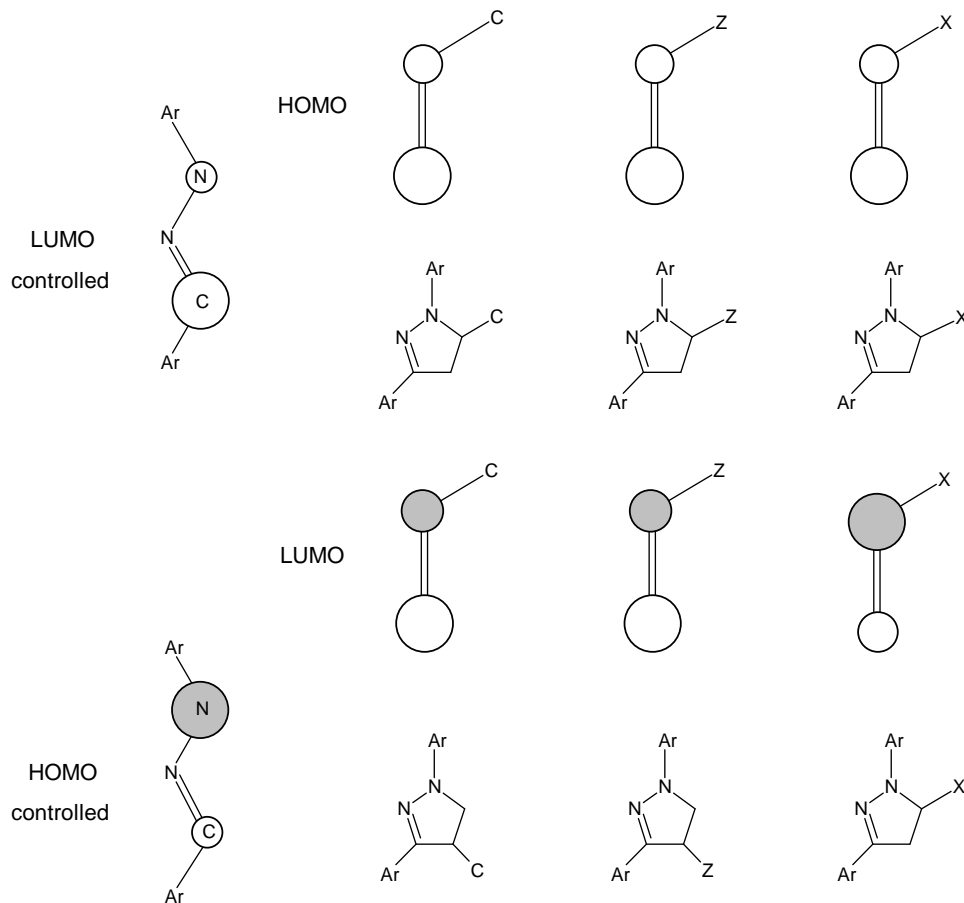


Formation of Possible Regioisomers of Monosubstituted Pyrazoles



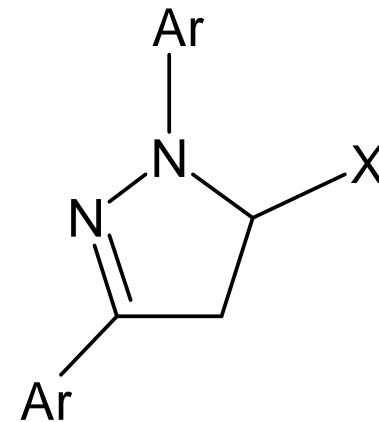
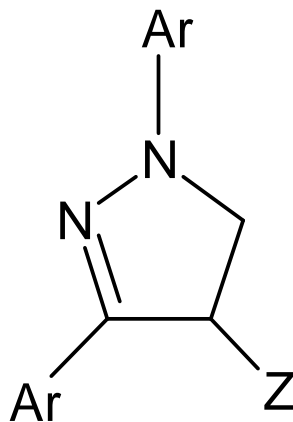
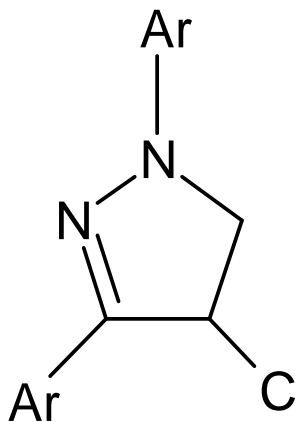
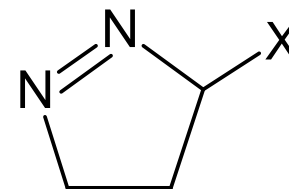
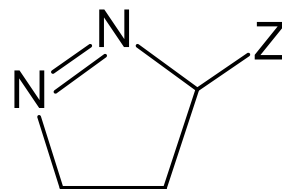
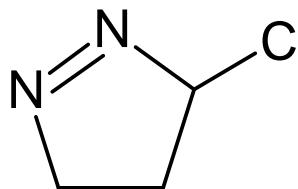


Formation of Possible Regioisomers of Trisubstituted Pyrazoles



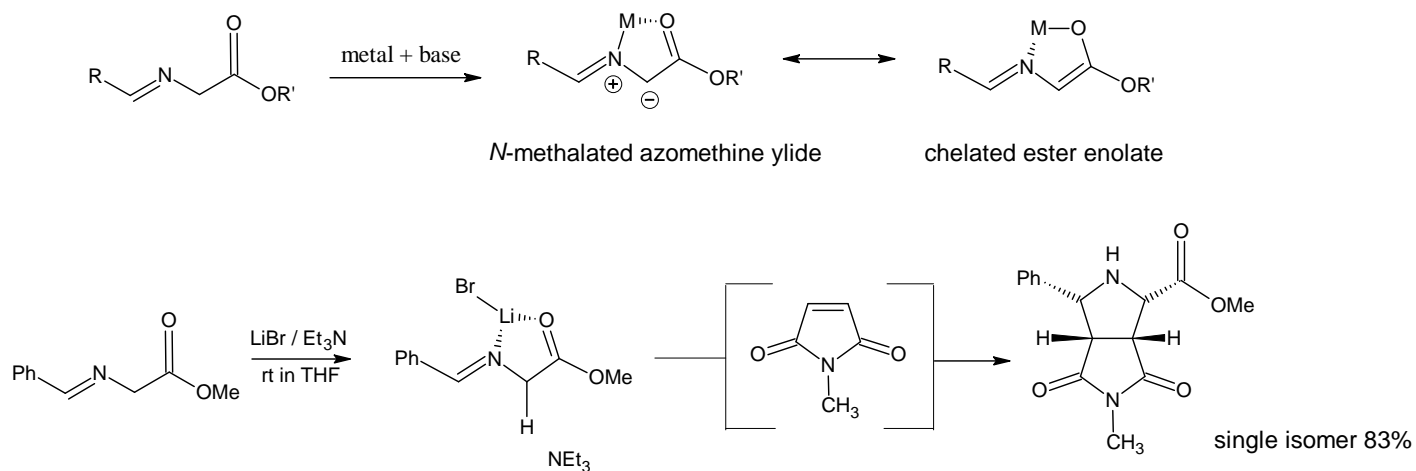


World of Molecules: Design of chemical reaction





Metal-Assisted Stereocontrol of 1,3-Dipolar Cycloaddition Reactions

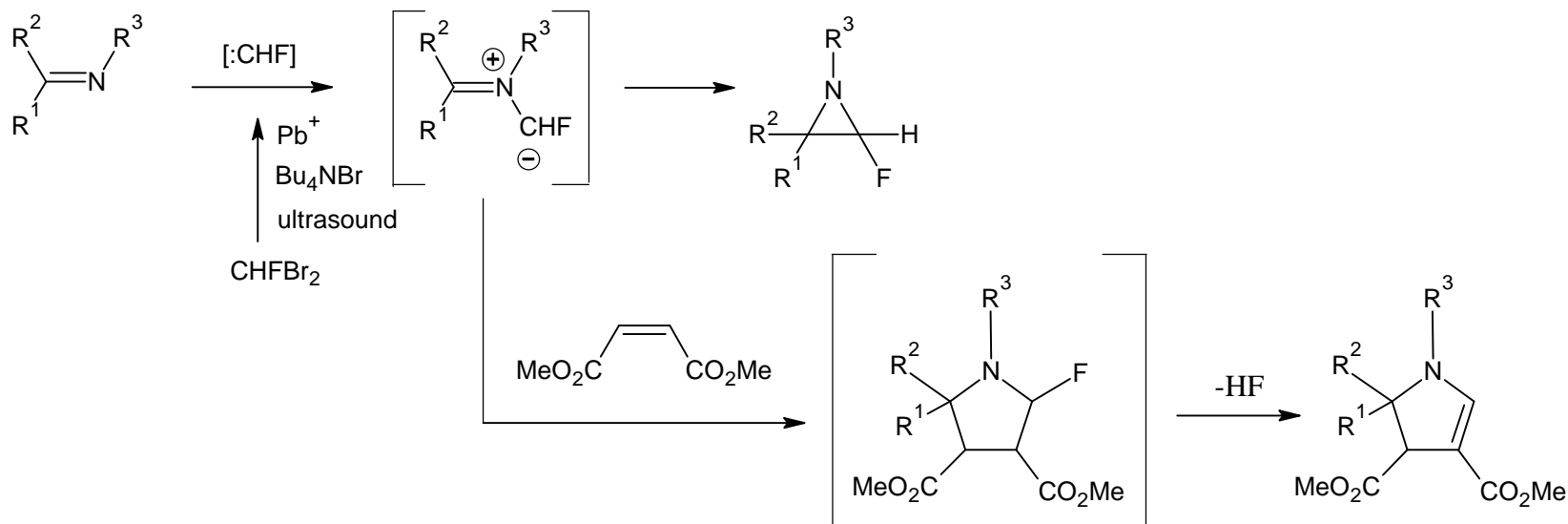


S. Kanemasa, *Synlett* 9, 1371, 1374. (2002)



Generation of Azomethine Ylides from Fluorocarbenes

1,3-Cyclisation and 1,3-Dipolar Cycloaddition

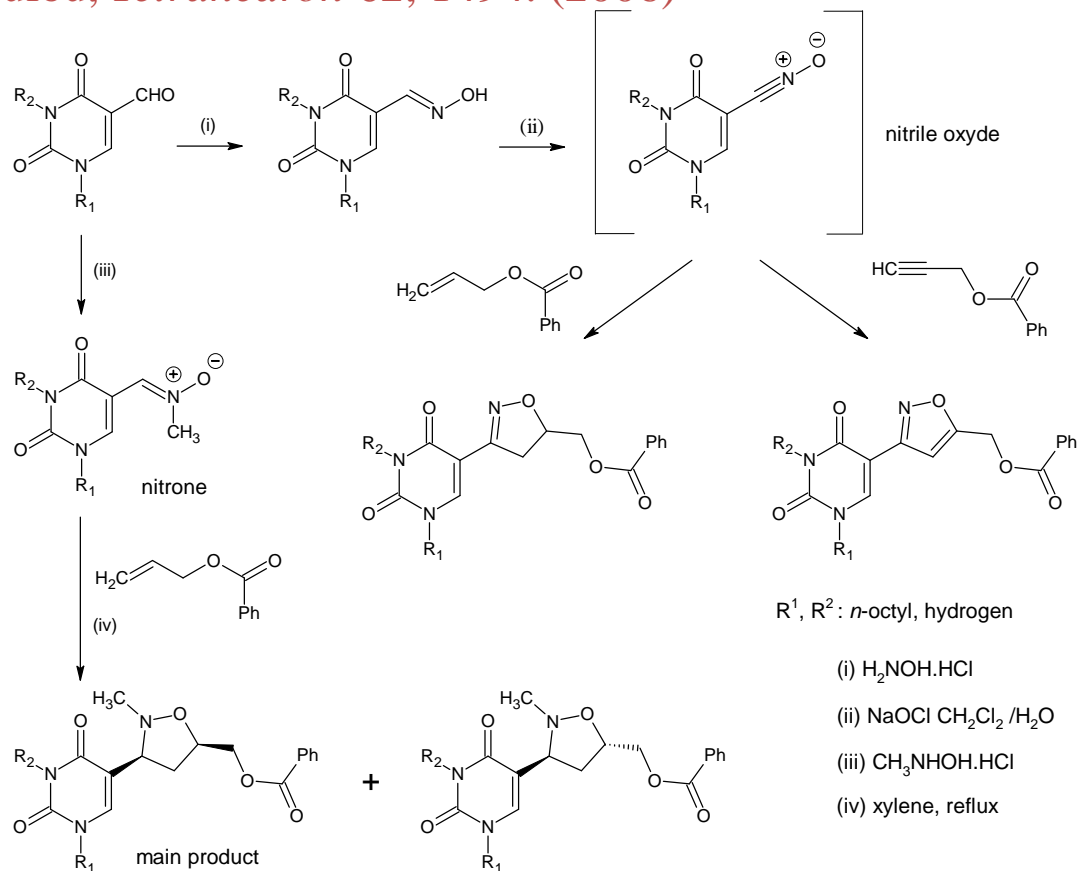


A.S. Konev, *Tetrahedron Letters* **46**, 8337. (2005)

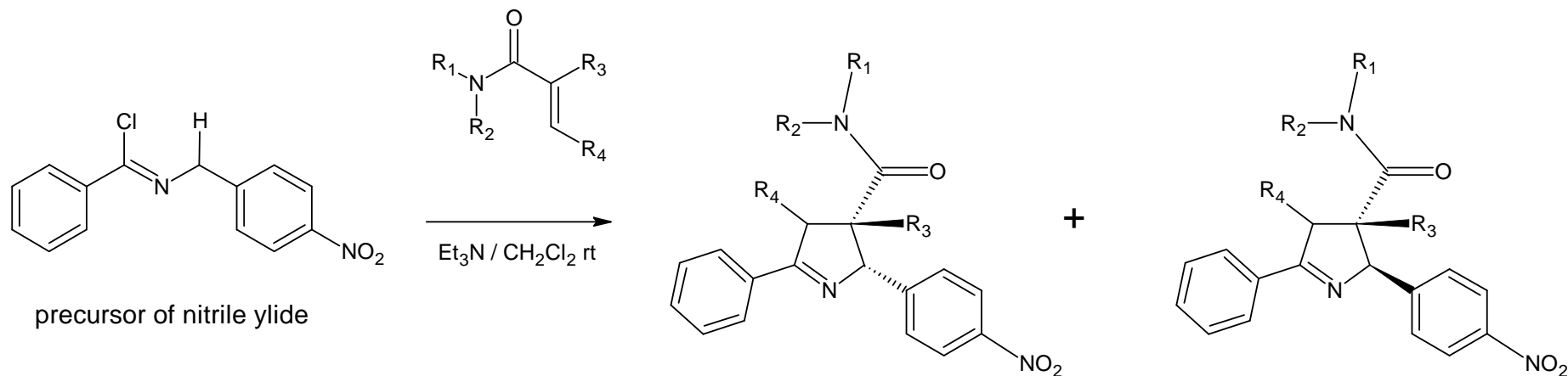


Synthesis of Isoxazoline and Isoxazolidine

E.C. Argyropoulou, *Tetrahedron* **62**, 1494. (2006)



Synthesis of Pyrroles

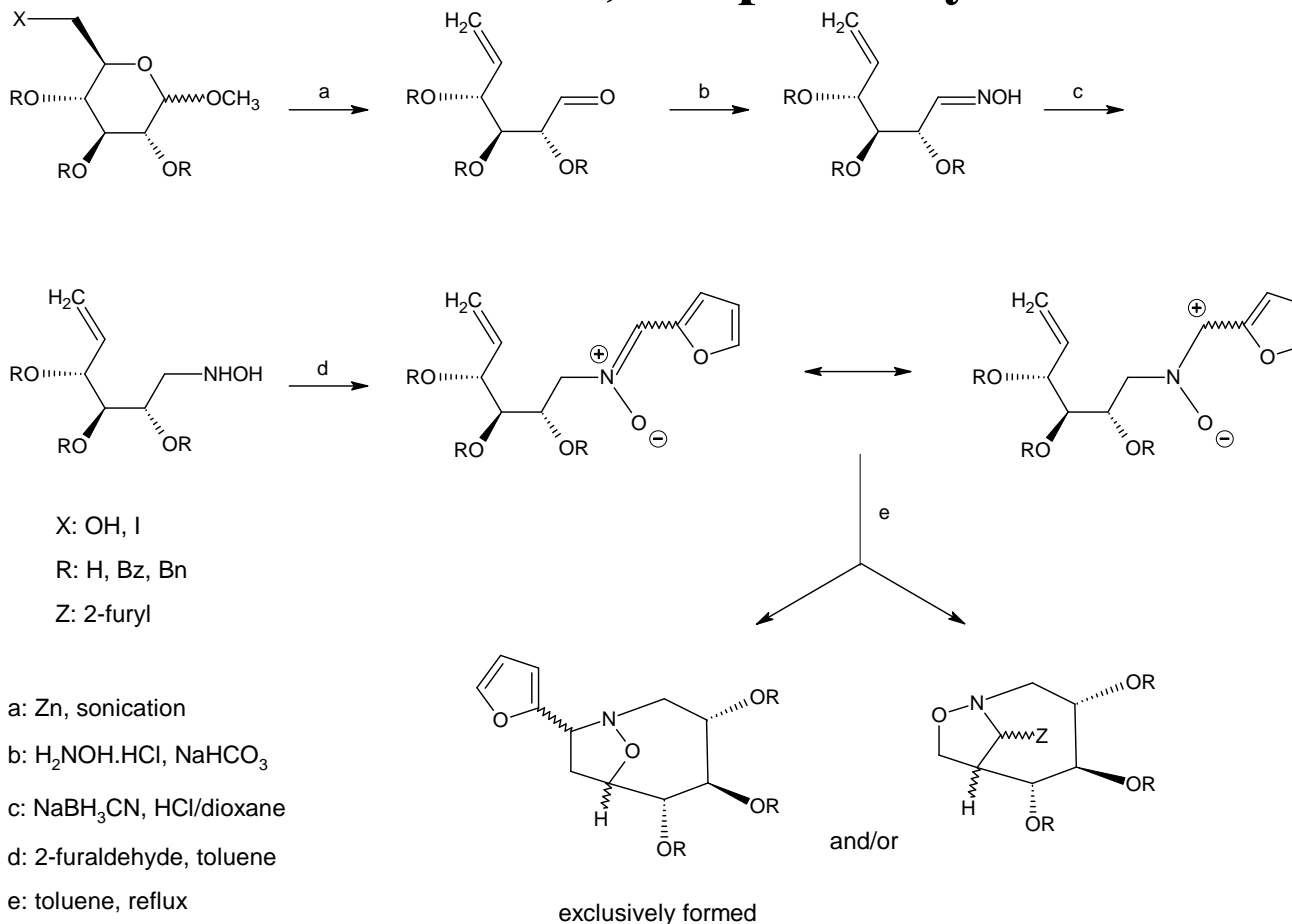


R ¹	R ²	R ³	R ⁴	yield	ratio
4-CH ₃ OC ₆ H ₄ CH ₂	4-BrC ₆ H ₄	H	H	72	65/35
CH ₃	CH ₃	H	H	73	60/40
H	H	CH ₃	H	45	21/79

C.L. Yoo, *Tetrahedron Letters* **47**, 477. (2006)



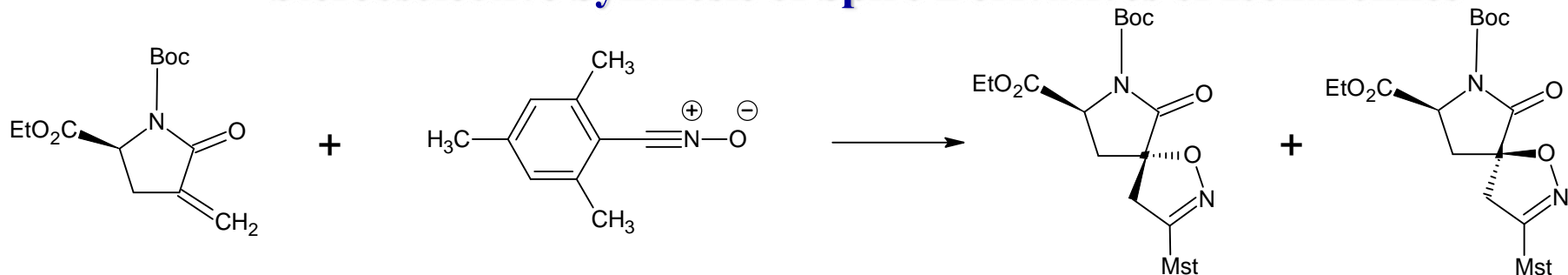
Intramolecular 1,3-Dipolar Cycloaddition



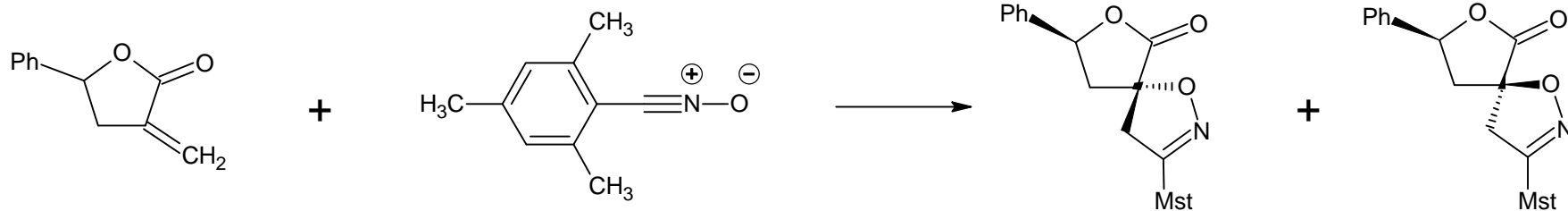
L. Kovács, *Tetrahedron* **61**, 6816. (2005)



Stereoselective Synthesis of Spiro Derivatives of Isoxazolines



67 : 33

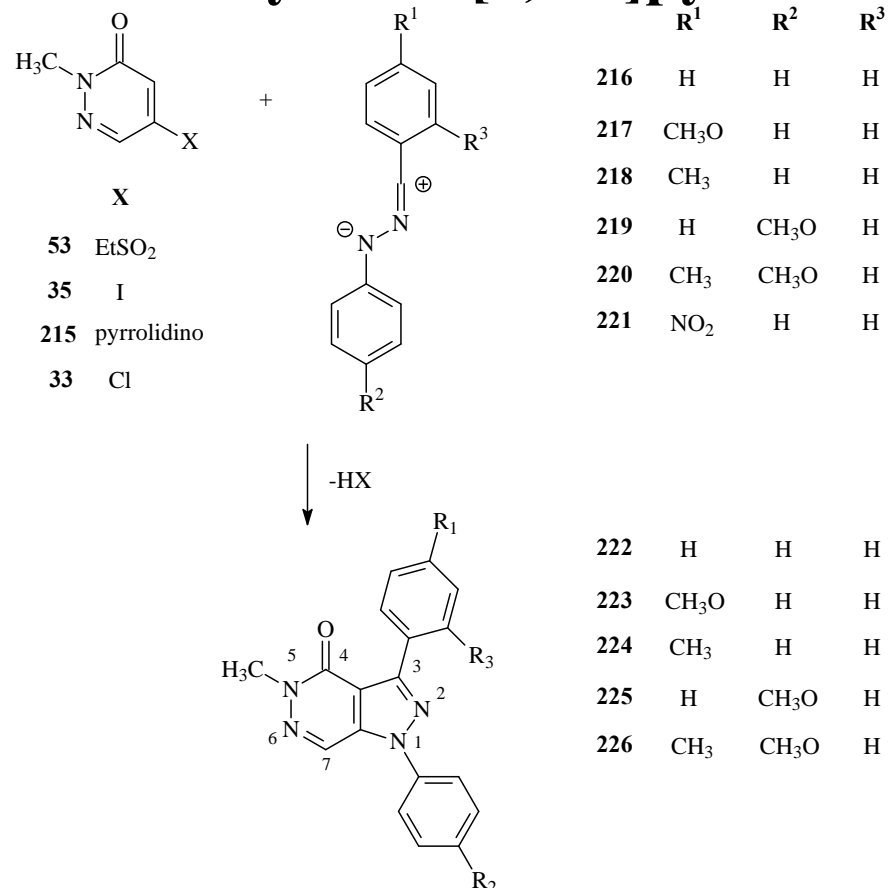


90 : 10

L. Fisera, *J. Heterocyclic Chem.* **37**, 553. (2000)



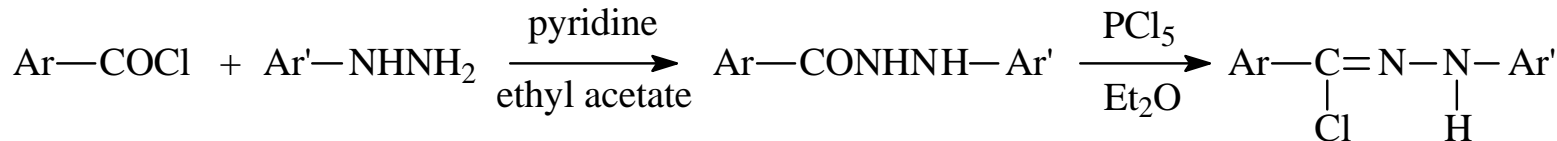
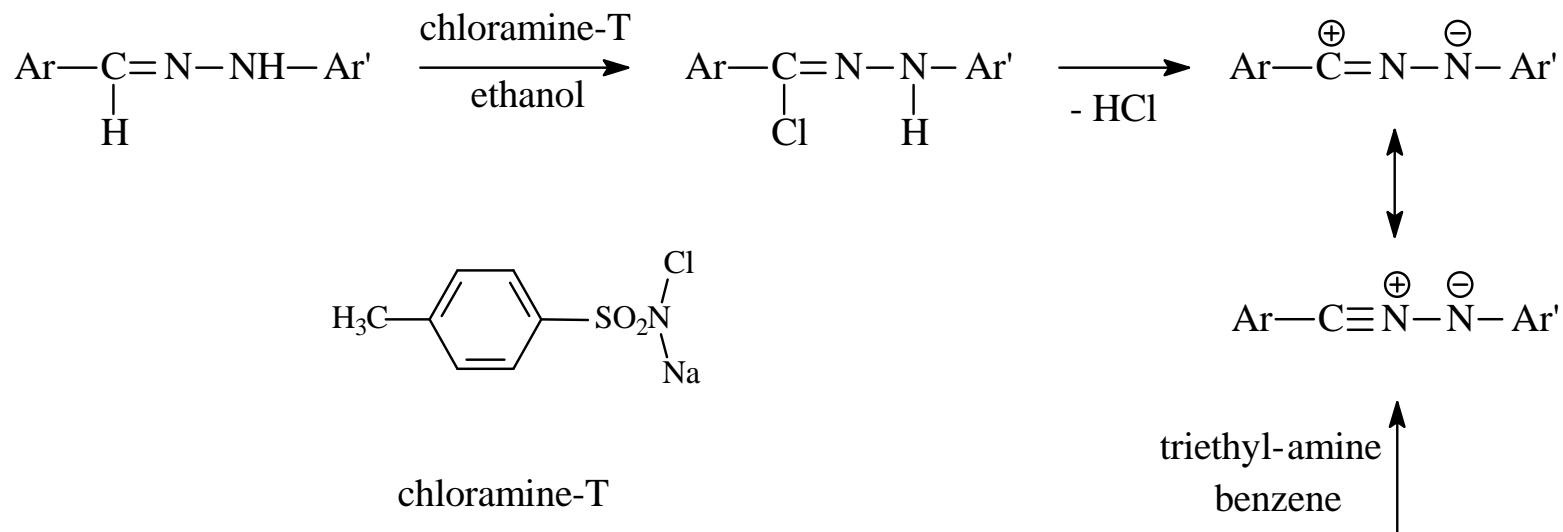
Synthesis of Pyrazolo[3,4-*d*]pyridazines



G. Krajsovsky, A. Gaál, N. Haider, P. Mátyus,
Journal of Mol. Struct. (Theochem) **528**, 13. (2000)

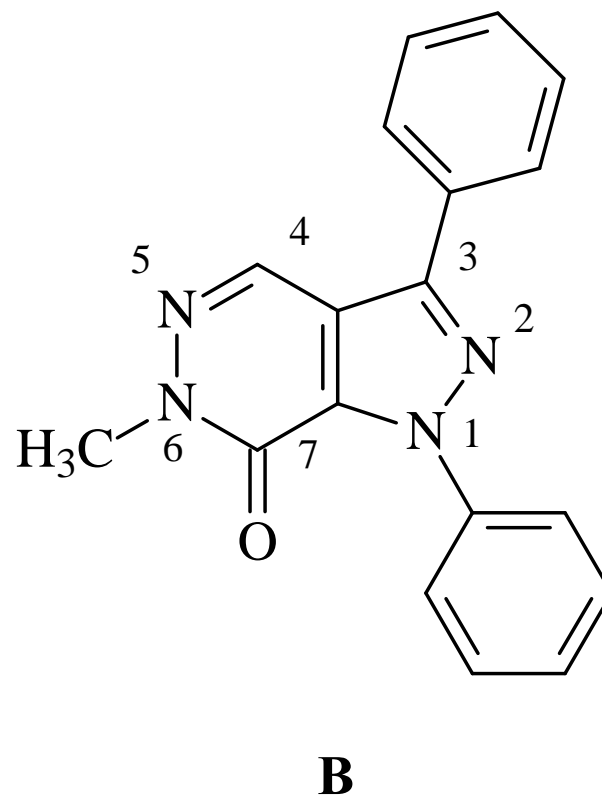
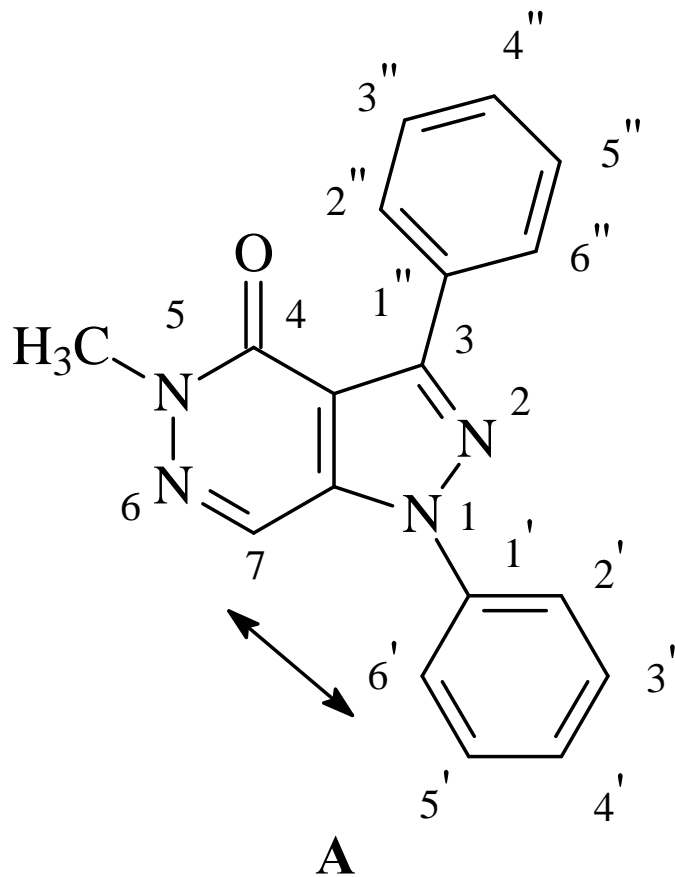


Generation of Nitrile Imines



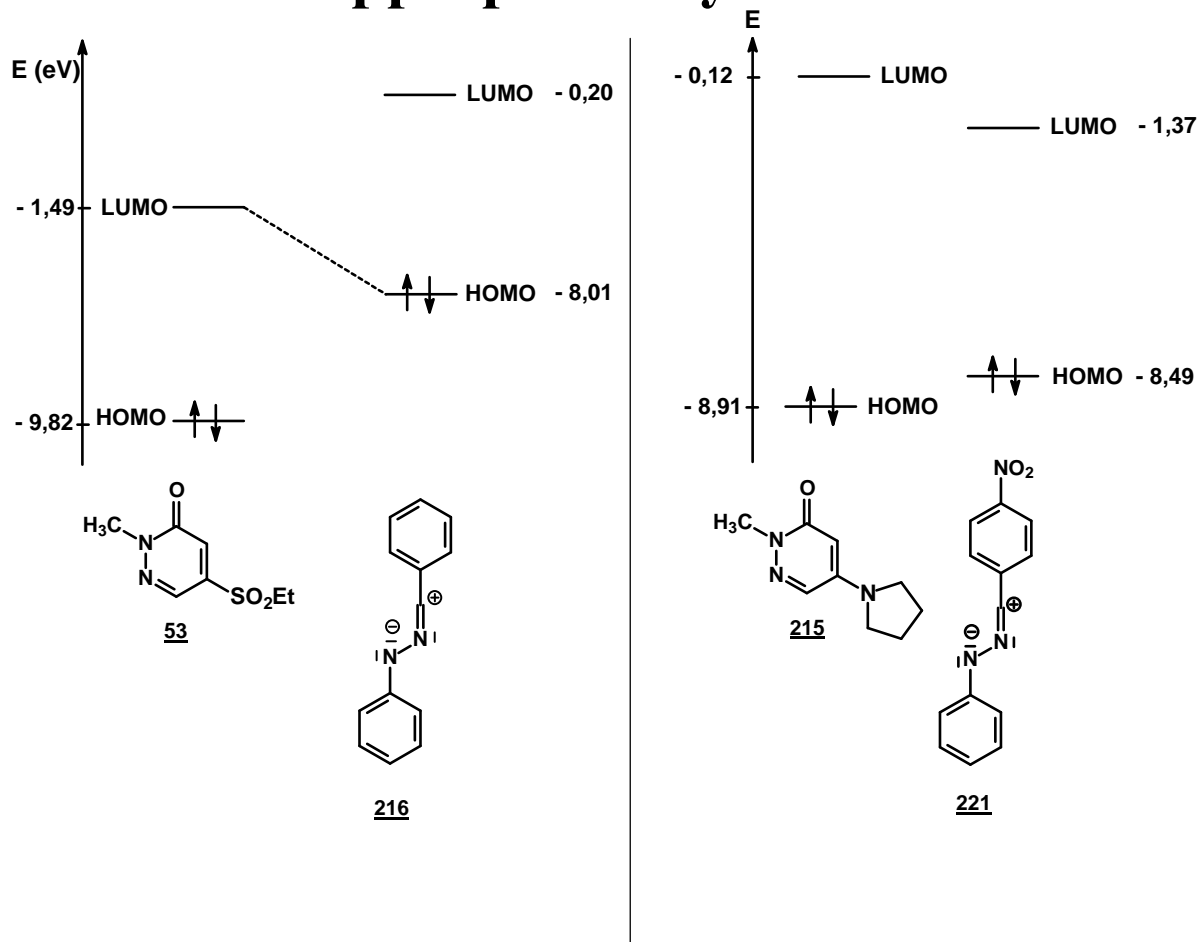


Possible Regioisomers of Pyrazolopyridazines



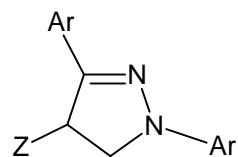
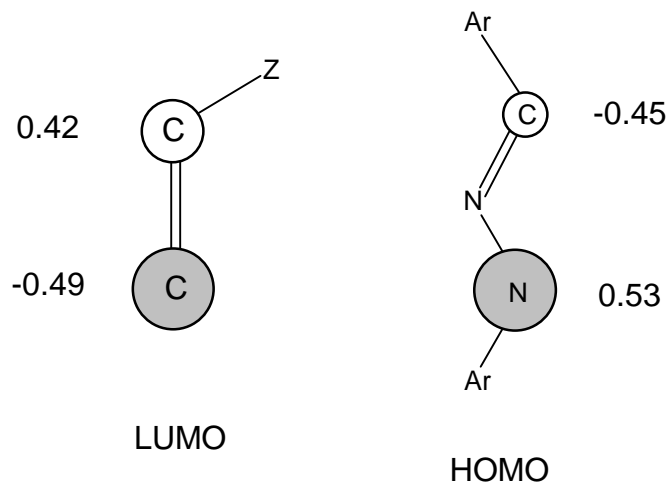


Frontier Orbitals of Appropriate Pyridazinones and Nitrilimines

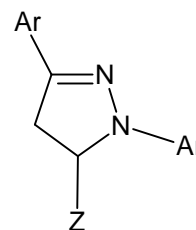




Expected and Obtained Isomers of Pyrazole Derivatives



expected isomer



obtained isomer