

Bent and Twisted Amides

Synthesis, Spectroscopy, Reactivity, Utility

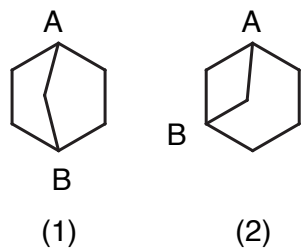
Reviews:

Chem Rev 83, 549 (1983) H.K. Hall Jr., Ali El-Shekeil

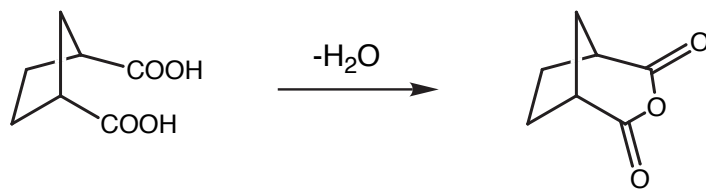
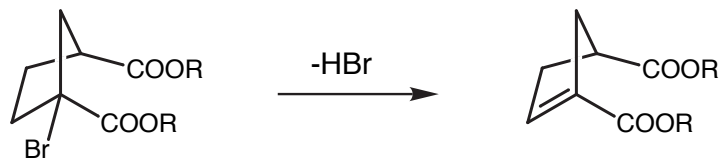
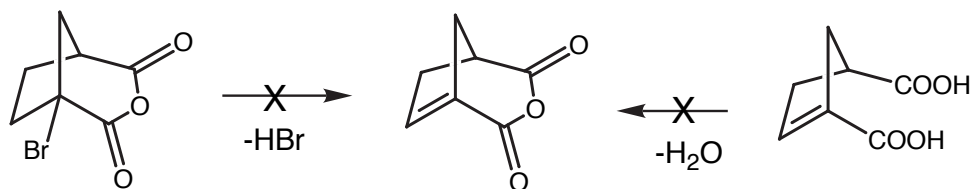
Structure and Reactivity J.F. Liebman, A. Greenberg eds.
CH 4 Twisted Bridgehead Bicyclic Lactams, A. Greenberg

J.K. Lynch Group Meeting 4/30/91

Bredt's Rule



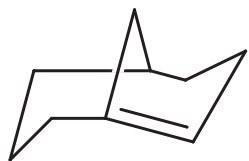
" in systems of the camphane and pinane series and related compounds (1) and (2), the branching points A and B of the carbon bridges (bridgeheads) cannot be involved in a carbon double bond."



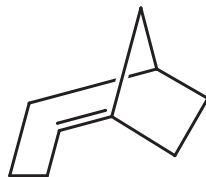
Justus Lieb. Ann. Chem. 437,1(1924) J. Bredt, H. Thouet, J. Schmitz
 ACIEE 12, 464 (1973) G. Koebrich (review)

Bredt's Rule- Strained Bridgehead Olefins

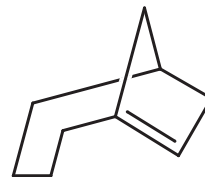
Isolated Bridgehead Olefins



[3.3.1]

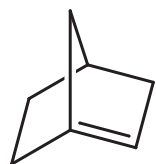


[4.2.1]

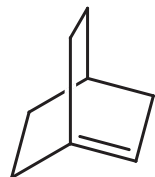


[4.2.1]

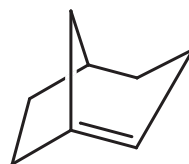
Detected by Trapping



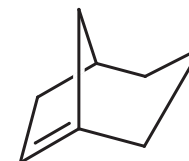
[2.2.1]



[2.2.2]



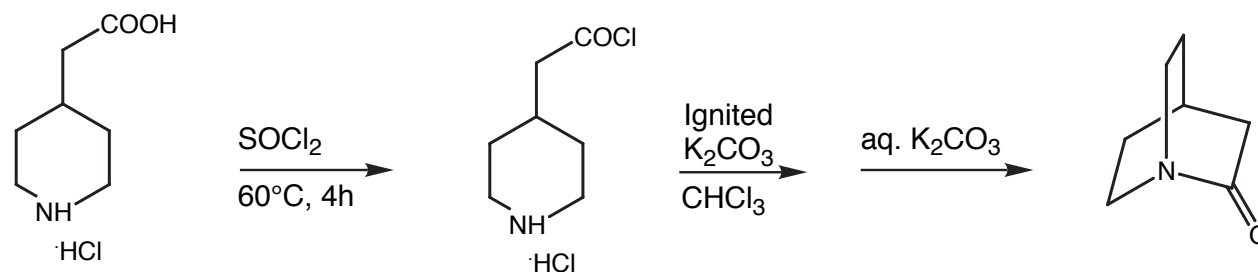
[3.2.1]



[3.2.1]

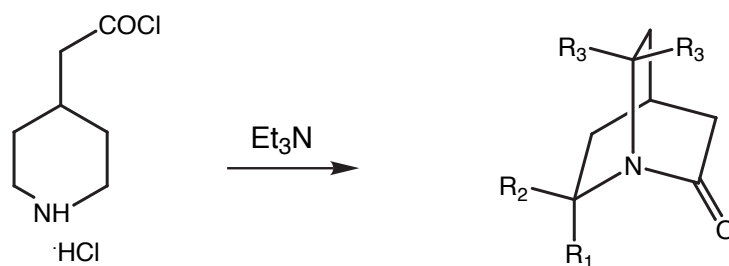
Chem. Rev. 83, 549 (1983) H.K. Hall Jr., S. El-Skekeil

Synthesis of Bridgehead Bicyclic Lactams



$\text{C}_7\text{H}_{11}\text{ON}$
 Cal N 11.20
 Found N 11.61

J.Gen.Chem.USSR (Eng.Trans) 27, 83 (1957)
 L.N. Yakhontov, M.V. Rubsitov

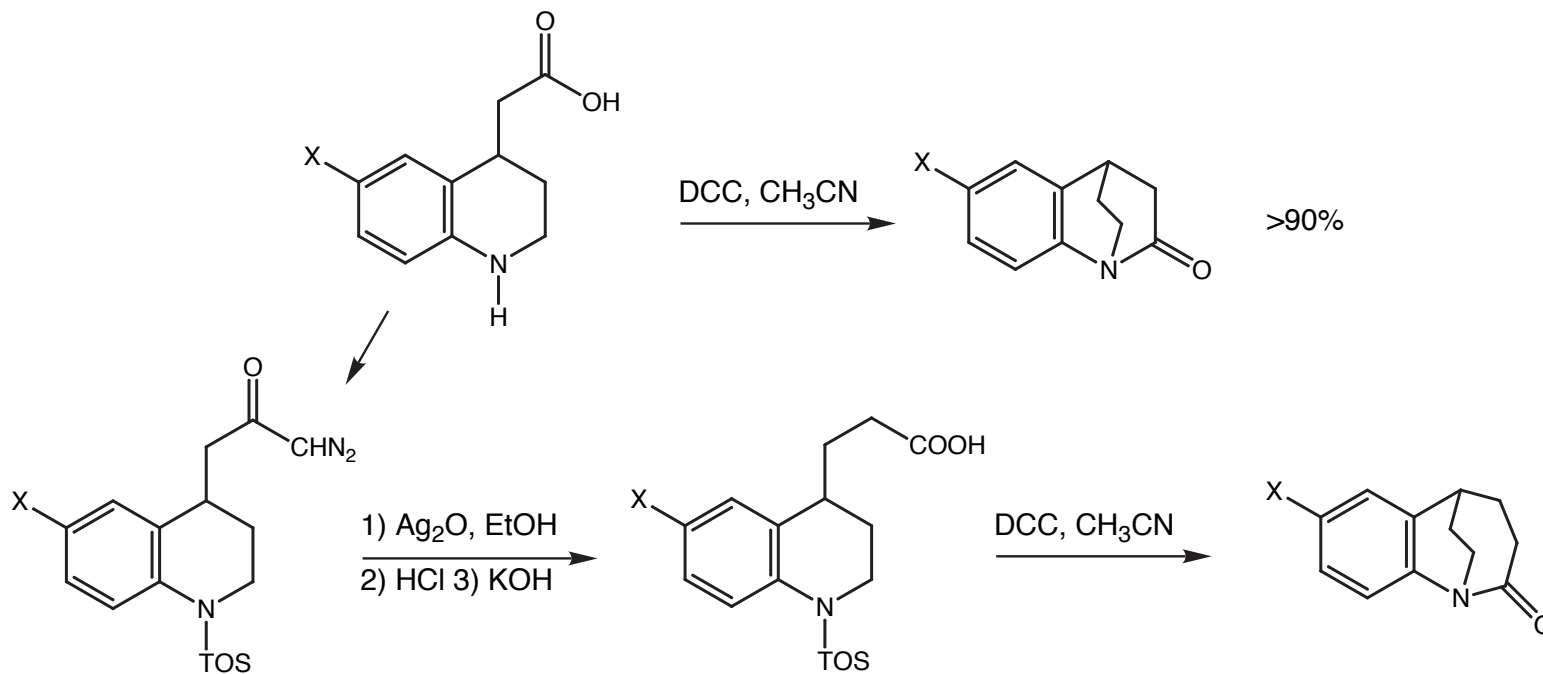


$\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$
 $\text{R}_1=\text{R}_2=\text{H}, \text{R}_3=\text{CH}_3$ Note: $\text{pK}_a=5.33$
 $\text{R}_1=\text{H}, \text{R}_2=\text{R}_3=\text{CH}_3$
 $\text{R}_1=\text{R}_3=\text{CH}_3, \text{R}_2=\text{H}$
 $\text{R}_1=\text{R}_2=\text{R}_3=\text{CH}_3$

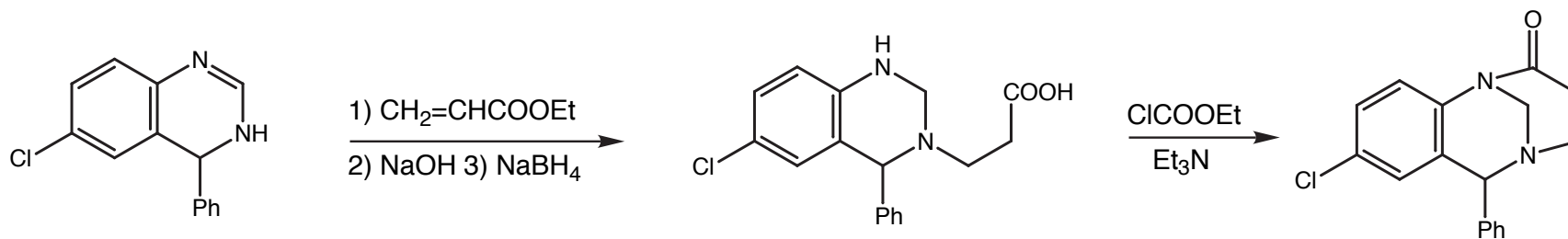
Structure and Reactivity CH4, p140 A.Greenberg

Tet. 21, 2257, (1965) V.H. Pracejus, M. Kehlen, H. Kehlen, H. Matschiner

Synthesis-Active Ester

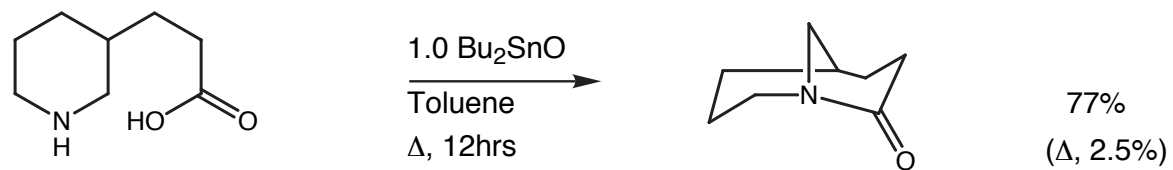


JOC 51, 2676 (1986) R. S. Brown, V. Somayaji

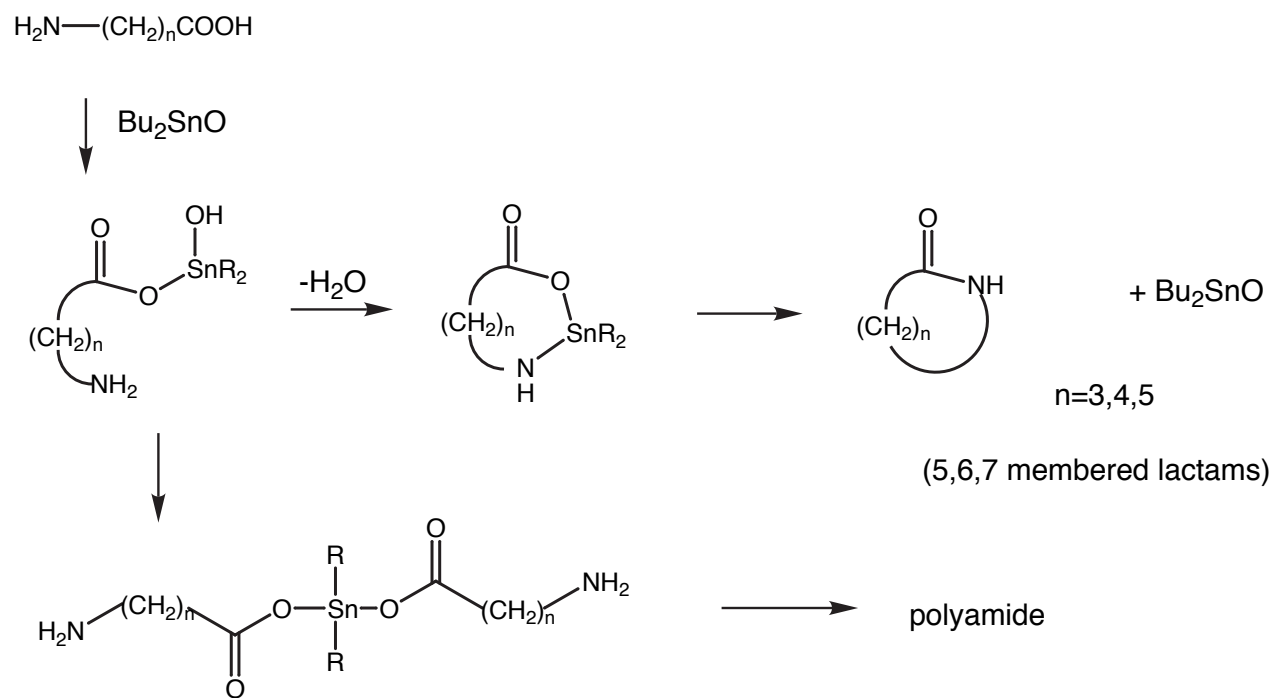


JOC 34, 183 (1969) M. Denzer, H. Ott

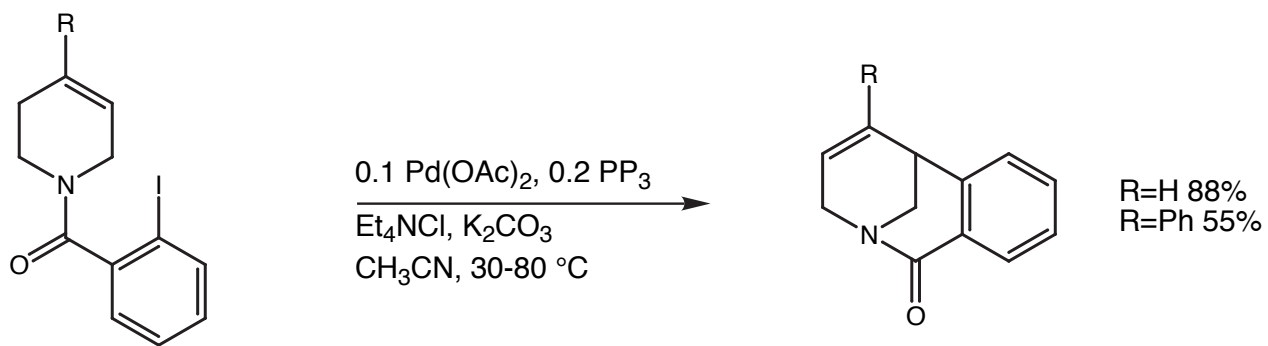
Synthesis- DibutylTinOxide



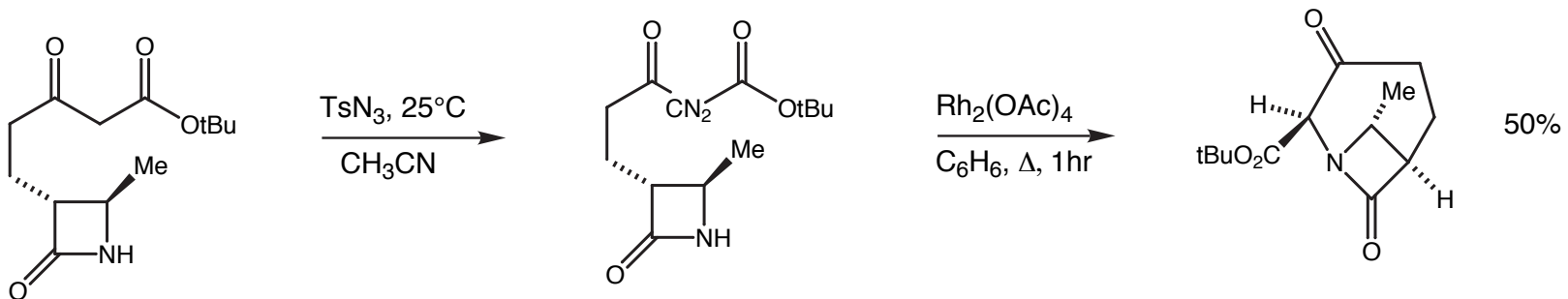
JACS 105, 7130(1983) K. Steliou, M. Poupart
 Helv. 70, 1981(1987) R. Brehm, D. Ohnhaus, H. Gerlach



Synthesis- Pd, Rh

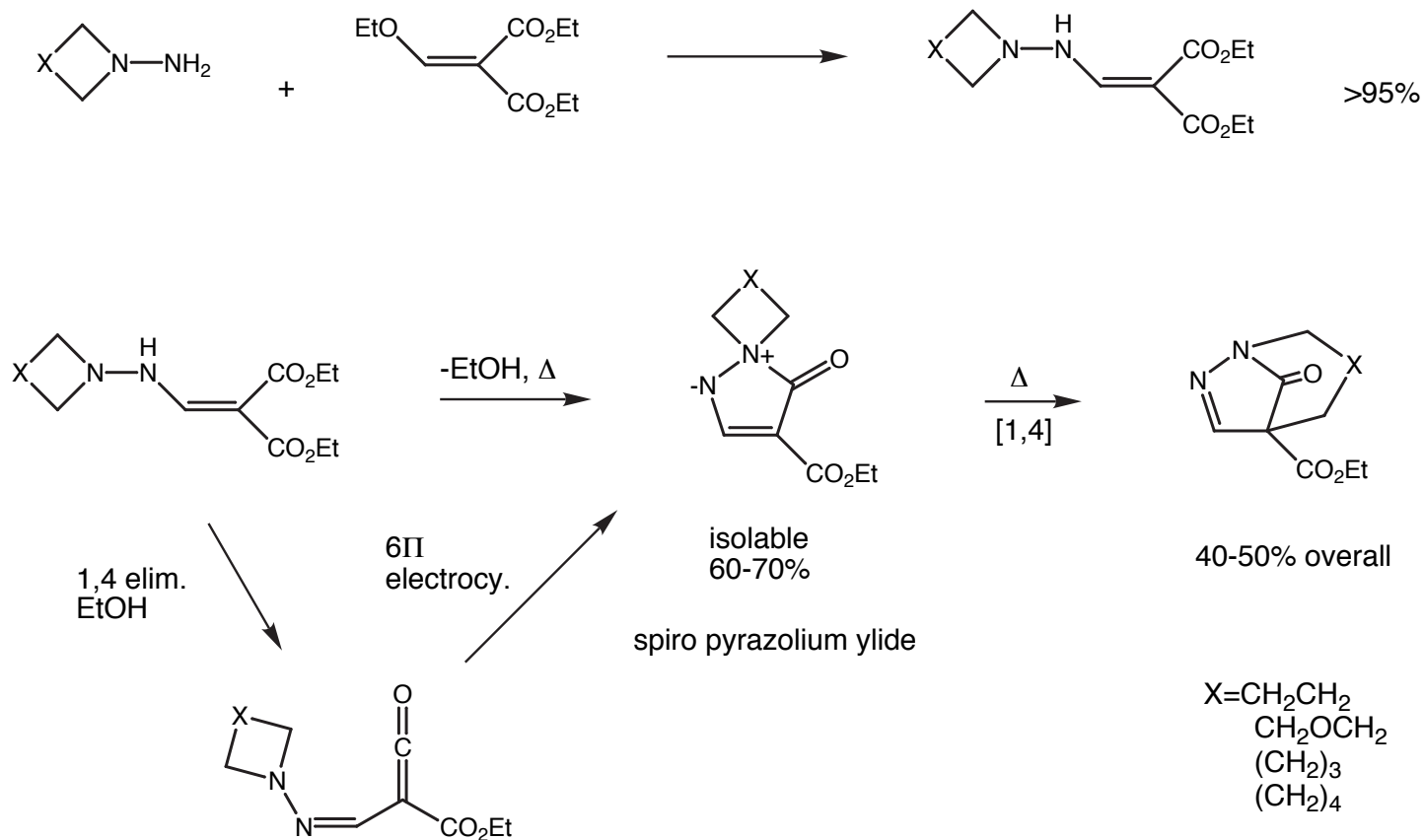


JCS Chem Comm. 1696(1986) R. Grigg, et. al



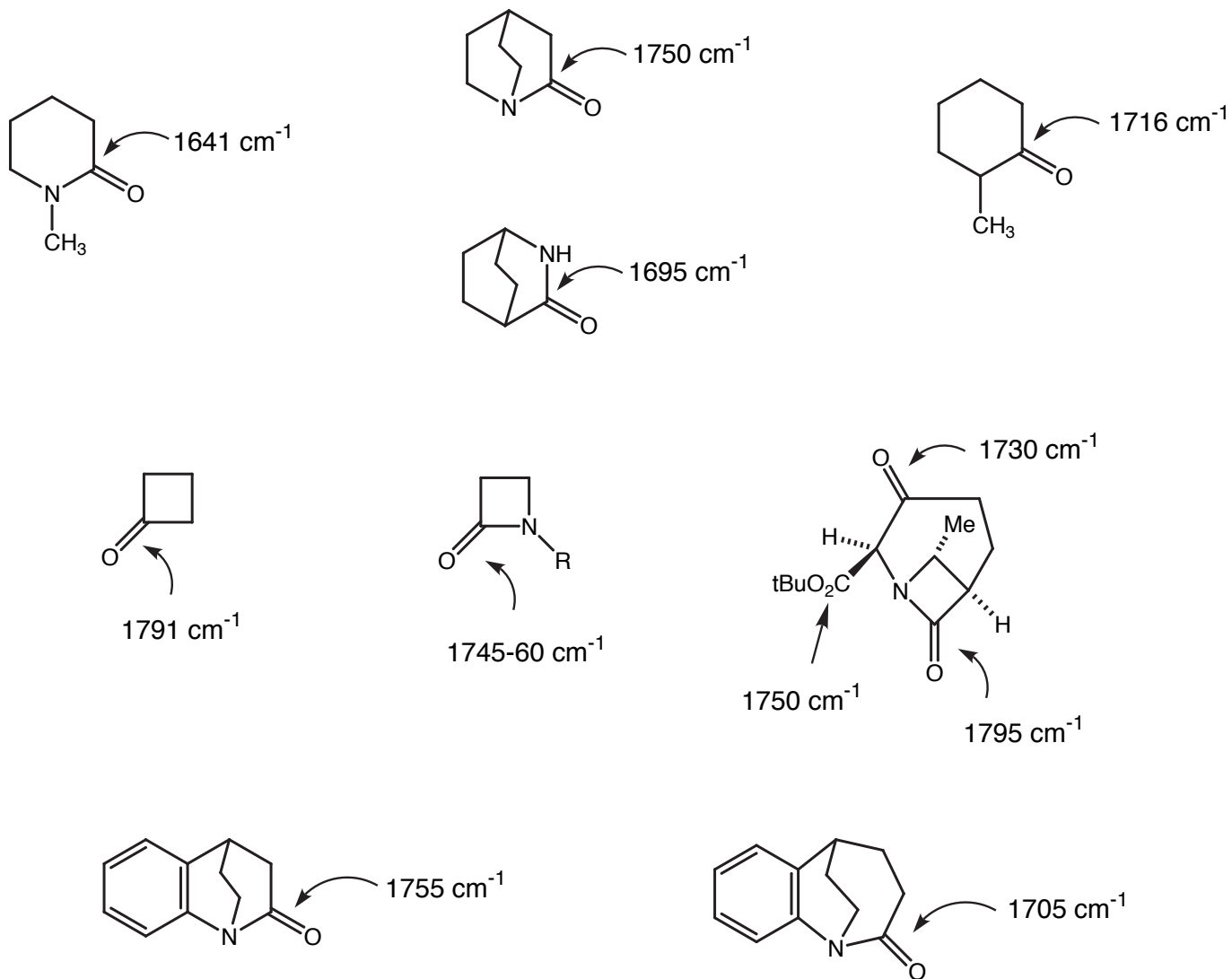
JACS 108, 6431 (1986) R.M. Williams, B.H. Lee

Synthesis- Spiro Pyrazolium Ylides



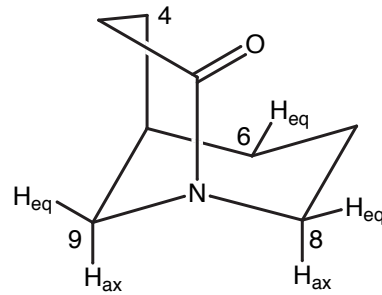
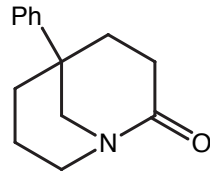
JOC 50, 909 (1985) J. Chucho et. al.

Spectroscopy-IR



Spectroscopy- NMR

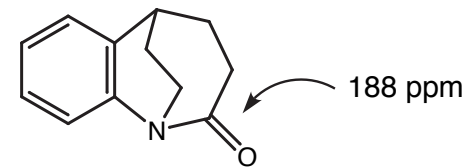
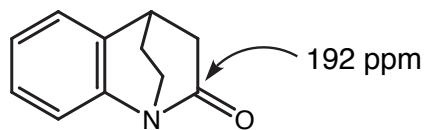
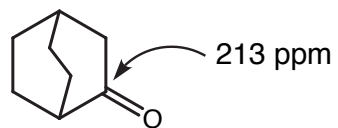
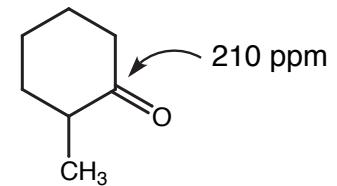
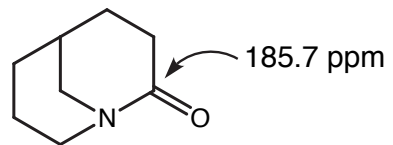
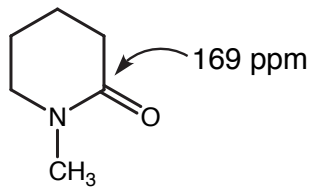
^1H



W coupling $\text{H}_{\text{eq}}-\text{H}_{\text{eq}}$ C^{s} 6,8,9
none to C-4

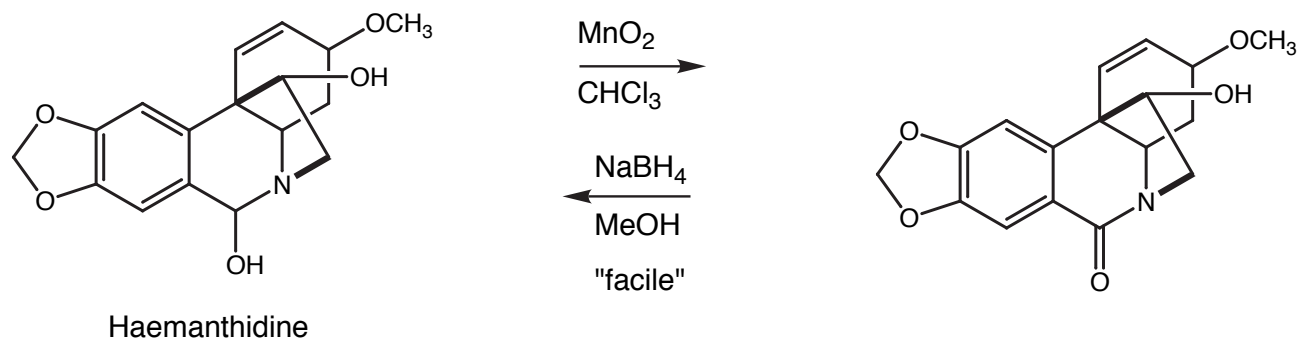
JCS Chem Comm 814 (1981) G.L. Buchanon

^{13}C

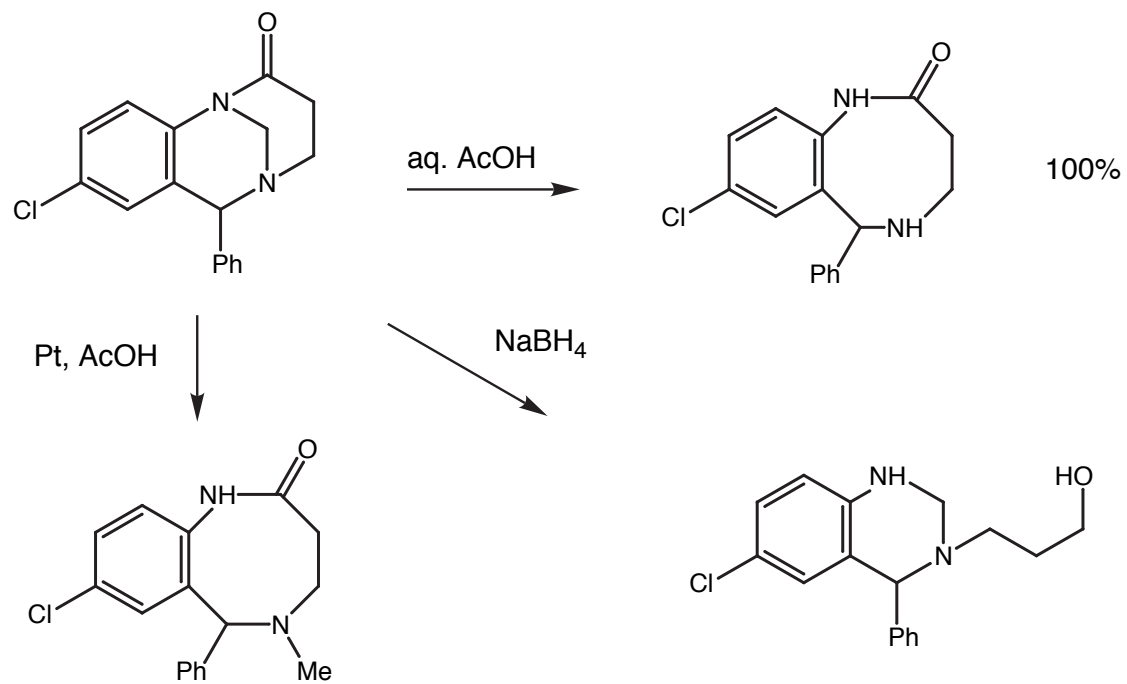


Reactivity-Reduction

JACS 80, 2590 (1958) S.Uyeo, H.M. Fales, R.J. Highet, W.C. Wildman

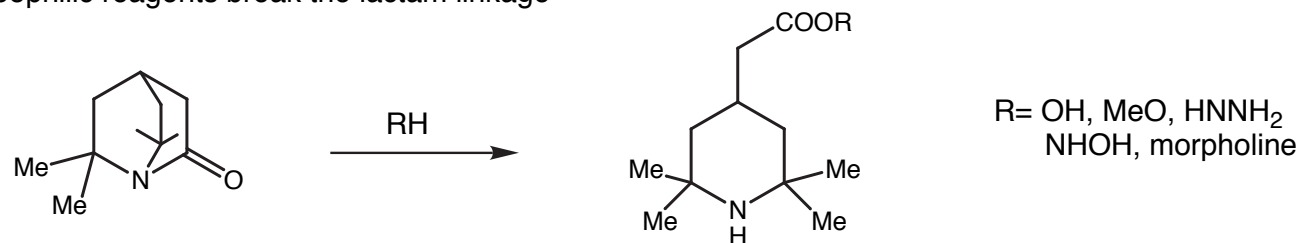


JOC 34, 183 (1969) M. Denzer, H. Ott

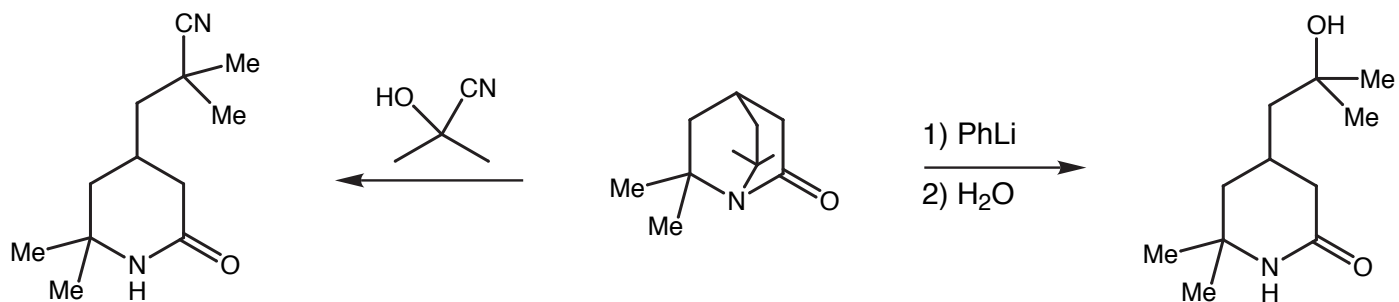


Reactivity-General

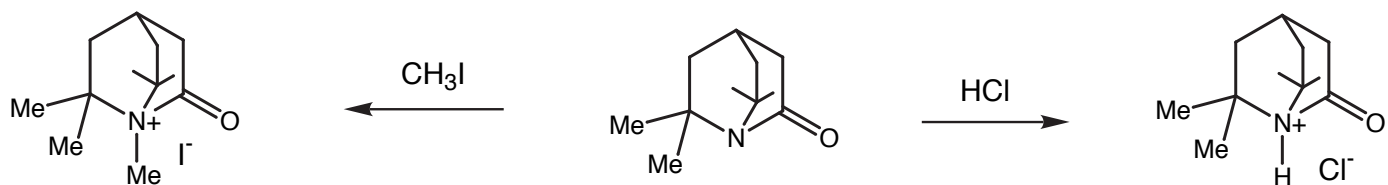
1) Protic nucleophilic reagents break the lactam linkage



2) Nucleophilic reagents, aprotic media break the N-C(CH₃)₂ bond

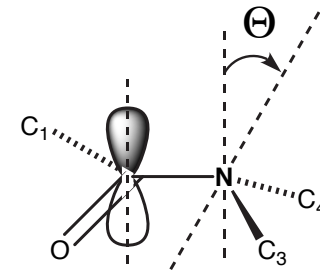
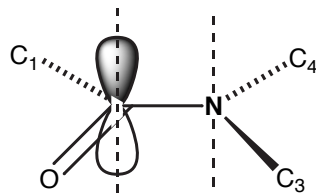
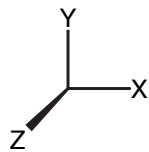


3) Quaternization reactions that leave the bicyclic ring intact occur with HCl and CH₃I

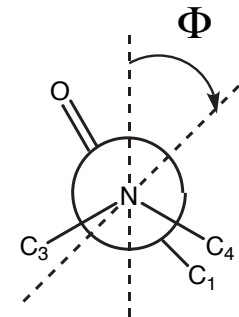
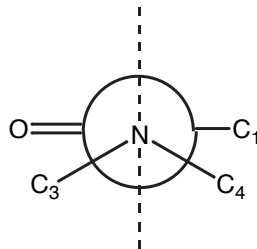


Twist and Tilt Deformations

Tilt Angle Θ

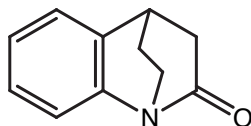


Twist Angle Φ



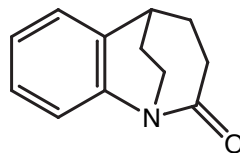
JOC 51, 2676 (1986) V. Somayaji, R.S. Brown

Reactivity-Twist vs Tilt



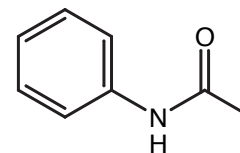
MMod
Twist Angle $\Phi \sim 90^\circ$
Tilt Angle $\Theta \sim 15-20^\circ$

$k_{OH} \text{ M}^{-1}\text{s}^{-1}$
 2.62×10^2



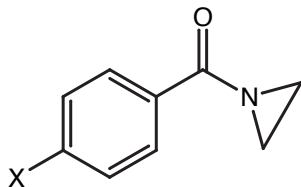
X-ray
Twist Angle $\Phi = 30-35^\circ$
Tilt Angle $\Theta = 15-20^\circ$

$k_{OH} \text{ M}^{-1}\text{s}^{-1}$
 6.0×10



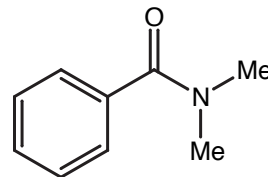
$k_{OH} \text{ M}^{-1}\text{s}^{-1}$
 7.55×10^{-6}

JOC 15, 2676 (1986) V. Somayaji, R.S. Brown



Twist Angle $\Phi \text{ } 0 \pm 10^\circ$
Tilt Angle $\Theta \text{ } 34^\circ$

<u>X</u>	$k_{OH} \text{ M}^{-1}\text{s}^{-1}$
OCH ₃	0.27
H	1.1
Br	2.8
NO ₂	16.9



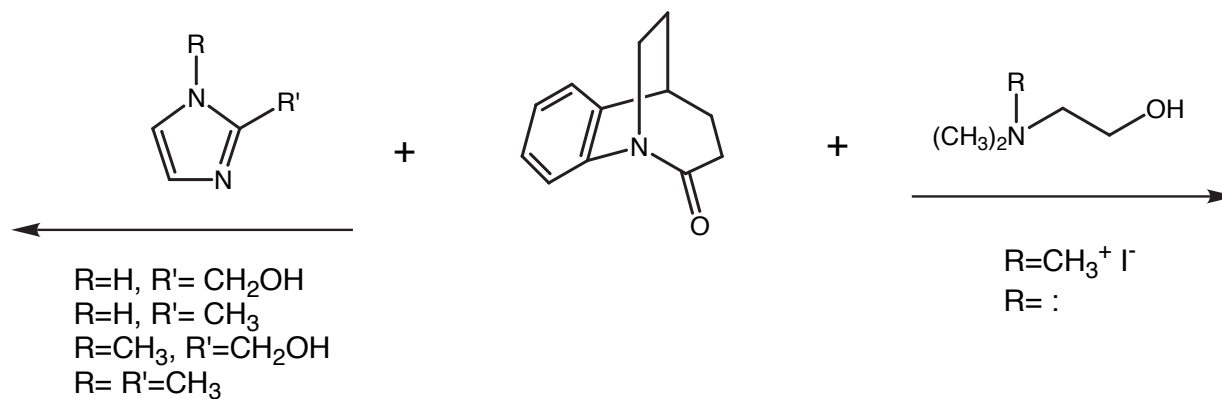
$k_{OH} \text{ M}^{-1}\text{s}^{-1}$ 6.0×10^{-6}

JOC 52, 805 (1987)
H.S. Tilk, R.S. Brown

JOC 51, 4866 (1986) V. Somayaji, K.I. Skorey, R.S. Brown, R.G. Ball

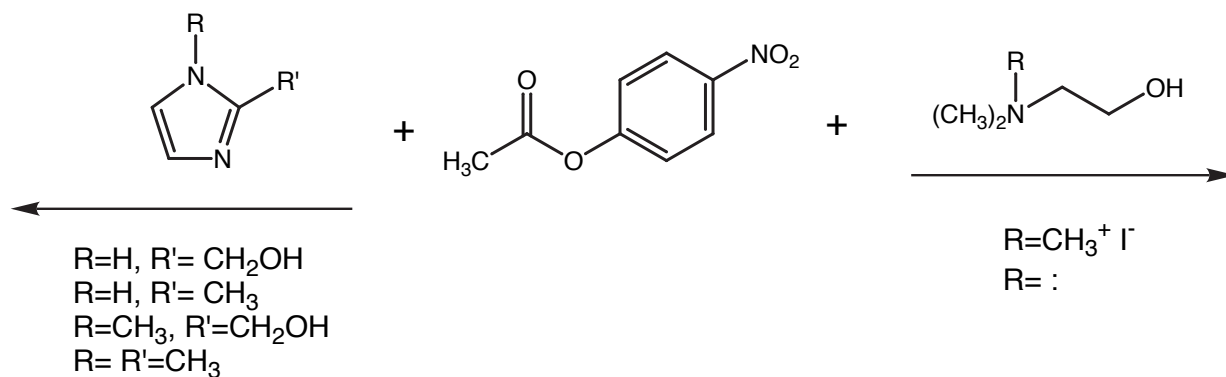
Acylation of β -Amino Alcohols

Model for Serine Protease



JOC 51, 4866 (1986) V. Somayaji
K.I. Skorey, R.S. Brown, R.G. Ball

Acylation of β -Amino Alcohols



JOC 51, 4866 (1986) V. Somayaji
K.I. Skorey, R.S. Brown, R.G. Ball

Mechanism of Rotomase Enzymes

Science 863 (1990) M.K. Rosen, R.F Standert, A. Galat, M. Nakatsuka, S.L. Schreiber

Rotomase Inhibitors- Leucine Twisted Amide Mimics

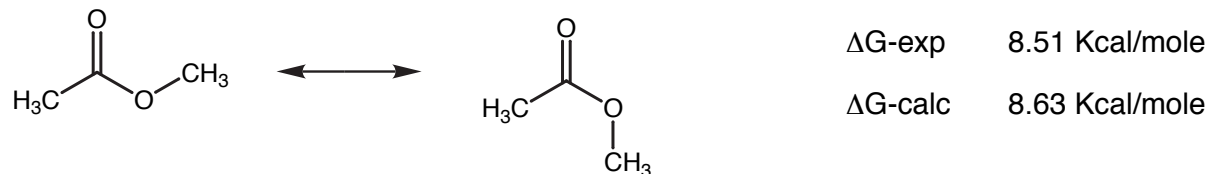
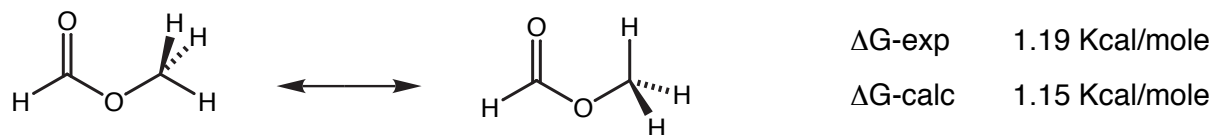
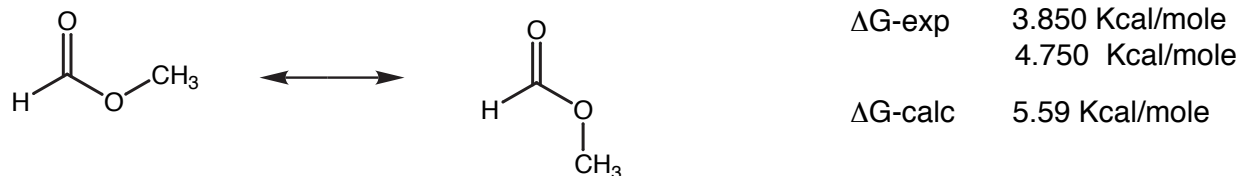
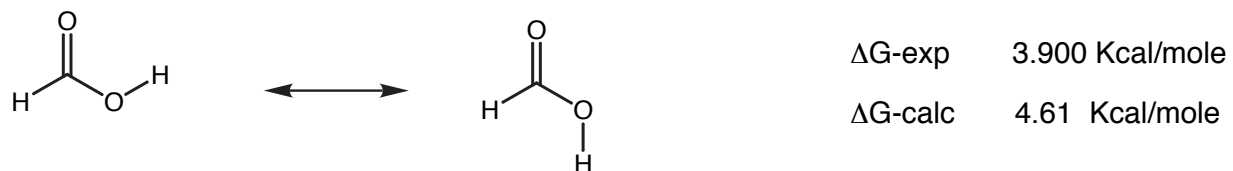
Biochemistry 3813 (1990) R.K. Harrison, R.L. Stein
JOC 4984 (1990) M.W. Albers, C.T. Walsh, S.L. Schreiber

Rotomase Inhibitors

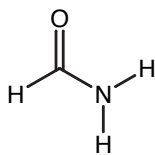
Science 251, 283 (1991) S. L. Schreiber

Rotational Barriers, Amide and Ester Resonance

K.B. Wiberg, K.E. Laidig JACS 109, 5935 (1987)



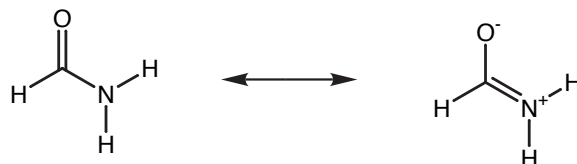
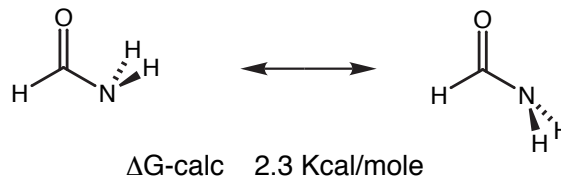
Amide Resonance?



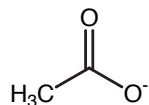
Rotational Barrier

Exp 18-19 Kcal/mole
Calc 15.3 Kcal/mole

"calculated satisfactorily"

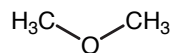


Calc. R_{C-O} Å



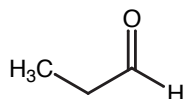
1.233

model for 50%
charge transfer



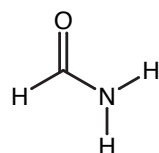
1.400

C-O single bond



1.188

no resonance

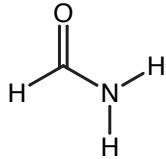
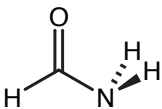
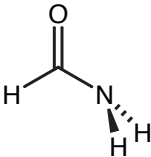


1.193

indicative of a normal C=O
double bond, little evidence
of loss of double bond character

K.B. Wiberg, K.E. Laidig
JACS 109, 5935 (1987)

Amide Resonance?

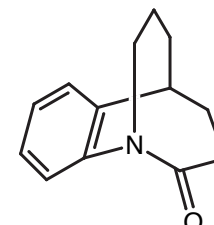
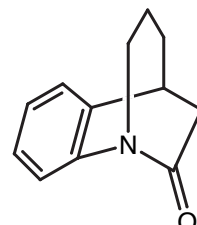
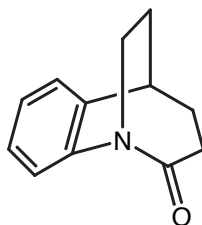
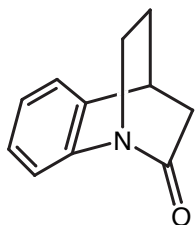
Calculated energies, dipole moment and bond lengths			
	planar	A	B
DE Kcal/mole (calc)	0.0	15.34	17.60
μ (D)	4.095(3.85exp)	1.573	4.080
$r_{C=O}$	1.1927	1.1832	1.1789
r_{C-N}	1.3489	1.4273	1.4230
r_{C-H}	1.0910	1.0876	1.0943
r_{N-H}	0.9957	1.0055	1.0046
	0.9923		

C-N bond length decreases 0.08Å suggests some double bond character
 But, C-O bond length increases by only 0.01Å suggesting C=O relatively unaffected by rotation

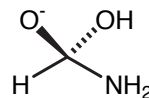
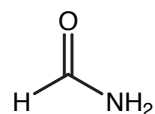
Calculated Electron Populations (units-electrons)

planar	N 8.476	C 4.020	O 9.392
A	N 8.222	C 4.242	O 9.343
	Δ -0.254	Δ +0.222	Δ -0.049
B	N 8.209	C 4.226	O 9.318
	Δ -0.267	Δ +0.206	Δ -0.074

Twisted Amides- Support for No Amide Resonance



Twist	90	31	36	16
Tilt	15-20	25	16.4	10
k_{OH} $M^{-1}s^{-1}$	260	60	17	5.52×10^{-4}



gas phase
"barrierless"
by calculation

solution high energy barrier to formation

- solvent interactions on TS and products
- must be due to structural changes for rehybridization at N. Twist amides don't have to rehybridize and therefore have a faster rate of hydrolysis (destabilized GS).

JACS 112, 6383 (1990) R.S. Brown et.al.

Atomic Size Dependence of Bader Electron Populations: Significance for Questions of Resonance Stabilization

JACS 113, 2865 (1991) Charles L. Perrin

Bader electron populations (used by Wiberg) exaggerate electron density at electronegative atoms. The resulting atomic charges are judged to be unreliable, especially as evidence against resonance in carboxylate anions and related species.

" At this time we decline to judge whether resonance is important for carboxylates and related species. Our results do not justify any conclusions except the one that some previous objections to resonance are unfounded."