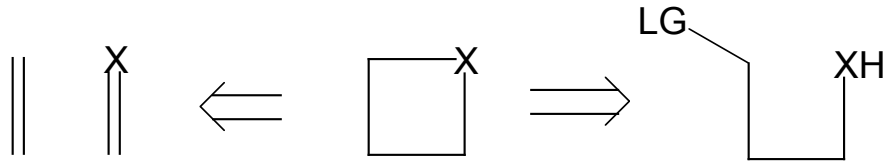
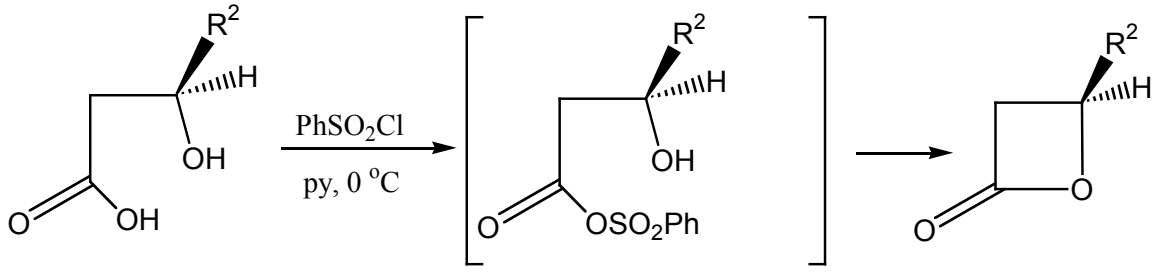
Alicyclic and Heterocyclic Chemistry. Lecture 8

Synthesis of four-membered rings (irreversible reactions only)

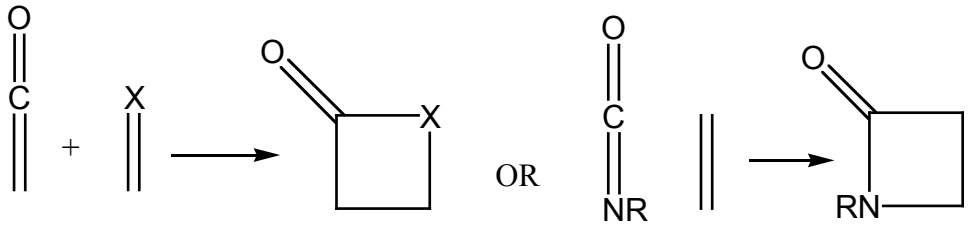
Because of the strain in the rings, the syntheses of this size of ring must be irreversible just as in the three-membered ring syntheses.
Although some four-membered rings may be made by S_N2 displacements as seen in the synthesis of three-membered rings (e.g. the Perkin synthesis), the most widely used methods for the larger rings are variations on formal [2 + 2] cycloadditions.



Intramolecular S_N2 Displacement
Cyclisation to give Oxetan-2-ones (β-Lactones): A very general and reliable method involves the reaction of the β-hydroxy acid with benzenesulphonyl chloride and two equivalents of pyridine at 0 ^oC and proceeds through the intermediate mixed benzenesulphonic anhydride since the stereochemistry at the carbon bearing the hydroxyl group is retained:



Formal [2 + 2] Cycloadditions
Thermal Cycloadditions of Cumulenes: Two general reactions are:



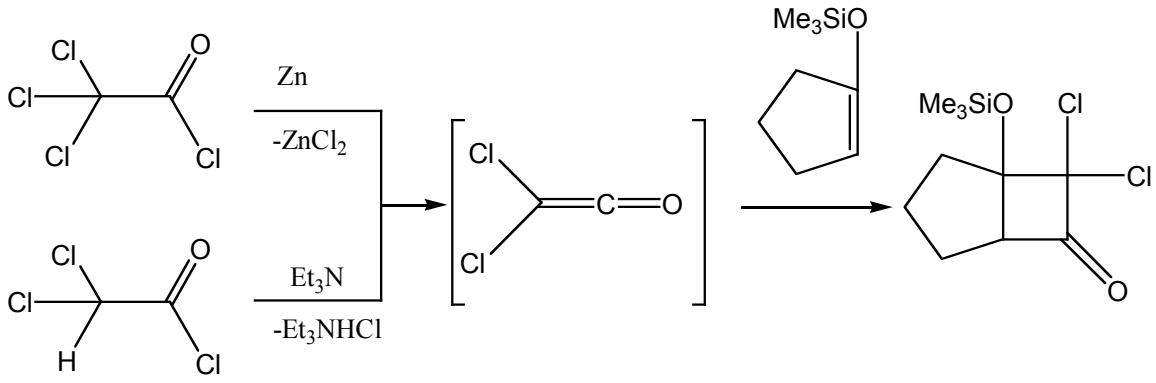
X = CR_2 , NAr

Cyclobutanones from Ketenes and Alkenes (X = CR_2) :

Most ketenes (except silylated ones) will do this but the more stable ones tend to react sluggishly. The order of reactivity of the ketenes is:

$Me_3SiCH{=}C{=}O << Ar_2C{=}C{=}O < ArCH{=}C{=}O \sim R_2C{=}C{=}O < RCH{=}C{=}O << Cl_2C{=}C{=}O$

Trimethylsilylketene is indefinitely stable at room temperature and does not react with alkenes whereas dichloroketene is so reactive that it must be generated in the presence of the alkene. The two most common routes to ketenes are the dehydrohalogenation of acyl halides or the dehalogenation of α-haloacyl halides:

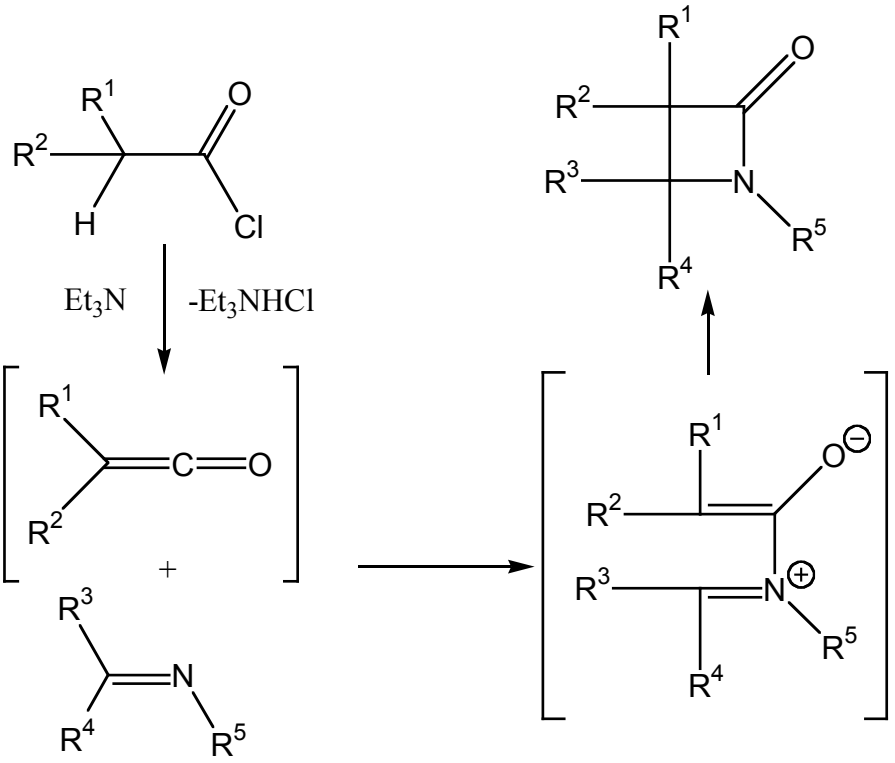


The reaction is generally regioselective in that the most nucleophilic carbon of the alkene becomes attached to the carbonyl group of the ketene, as above.

β-Lactams from Ketenes and Imines (the Staudinger Reaction) :

If we replace the alkene in the above reaction by an imine we should be able to make an 2-azetidinone. Just such a reaction was used by Staudinger in 1907 to make the first 2-azetidinone.

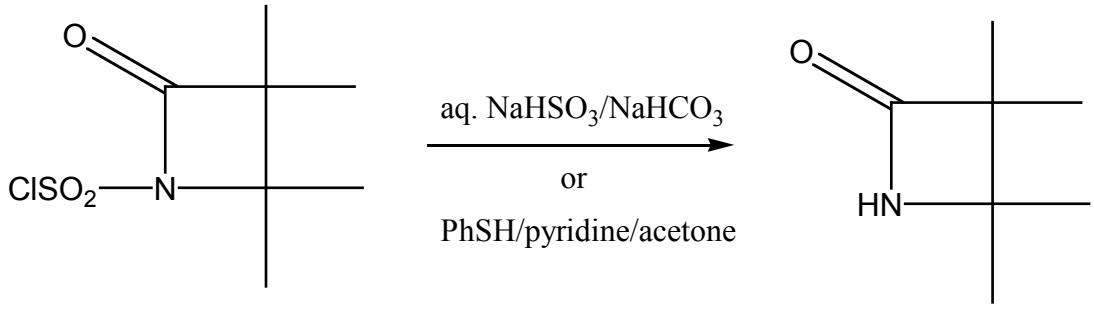
The reaction appears to go through polar intermediates rather than by a pericyclic process since it speeds up in polar solvents and, in some cases, such intermediates have been detected:



Note that R^5 cannot be H since the imine would be unstable and R^5 is usually Ar.

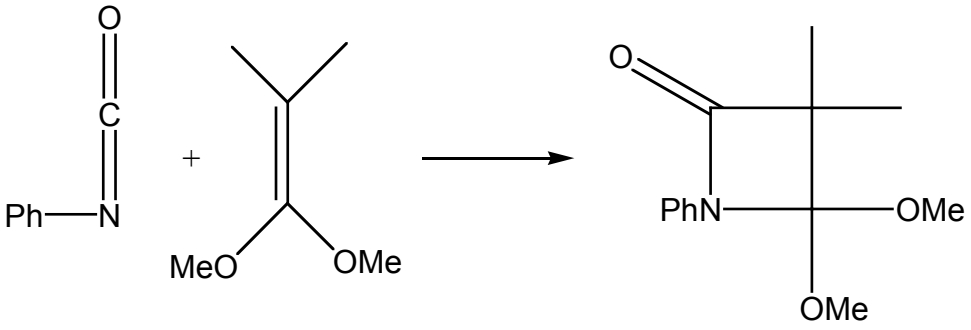
β-Lactams from Isocyanates and Alkenes :

The cycloaddition of isocyanates and alkenes provides one of the best routes to β-lactams. By far the most important isocyanate is chlorosulphonyl isocyanate, $ClSO_2NCO$, which because of its high reactivity will react with a wide range of alkenes. Also the resultant β-lactam can be readily converted into the N-unsubstituted derivative by gentle hydrolysis or gentle nucleophilic attack:



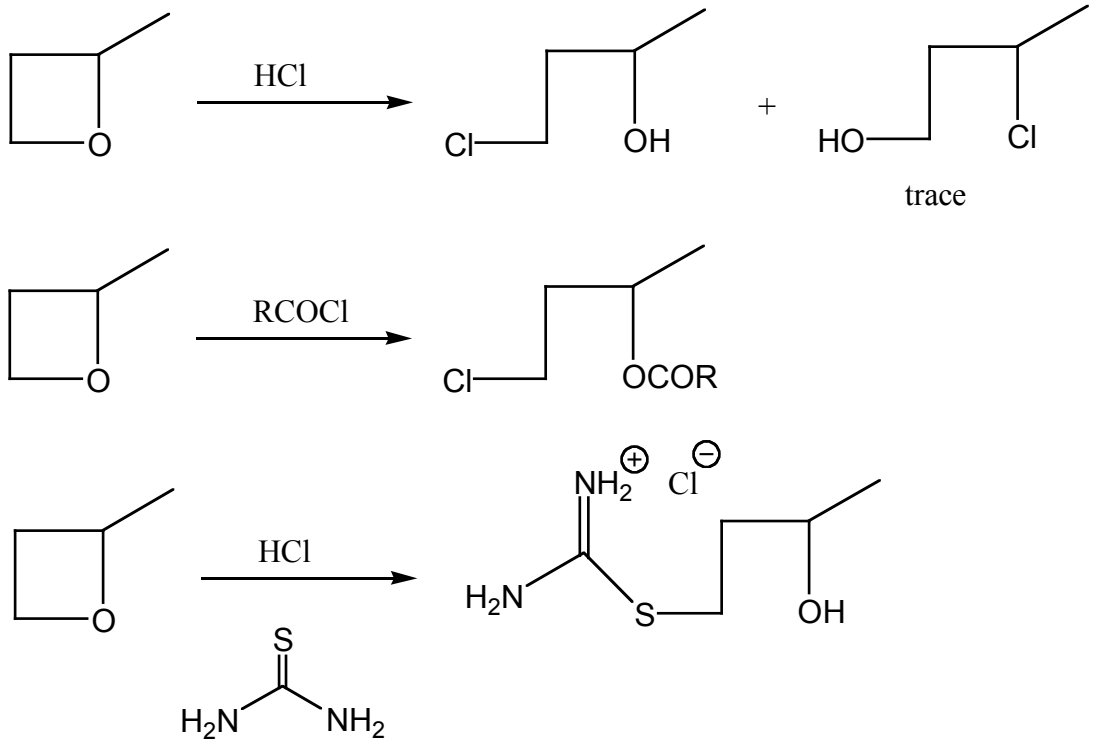
As in the addition of ketenes to imines, it is believed that a dipolar mechanism may hold for these cycloadditions too.

Other isocyanates react only with electron-rich alkenes when the most nucleophilic carbon of the alkene becomes attached to the carbonyl of the isocyanate (see the addition of ketenes to alkenes above):

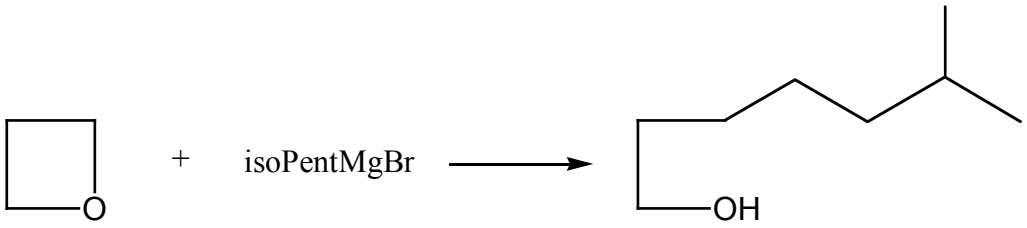


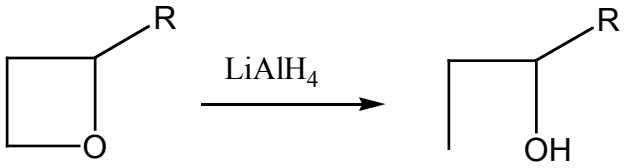
Reactivity of Four-membered Rings

Electrophilic/Nucleophilic Attack on Oxetanes and Azetidin-2-ones :
Oxetanes may be cleaved in an S_N2 manner under acidic/Lewis acidic conditions, the nucleophilic part of the acid attacking the less substituted carbon atom in substituted oxetanes:

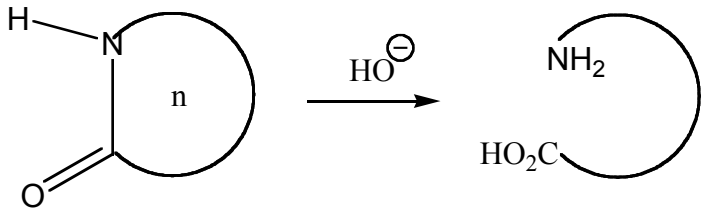


Oxetanes are much less susceptible to cleavage by nucleophiles in the absence of acid than are oxiranes. However, Grignards, cuprates and lithium aluminium hydride will react, probably because the metal can act as a Lewis acid e.g.:



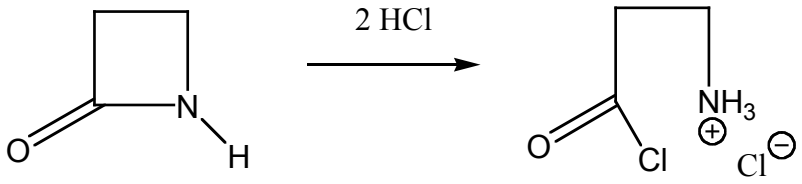


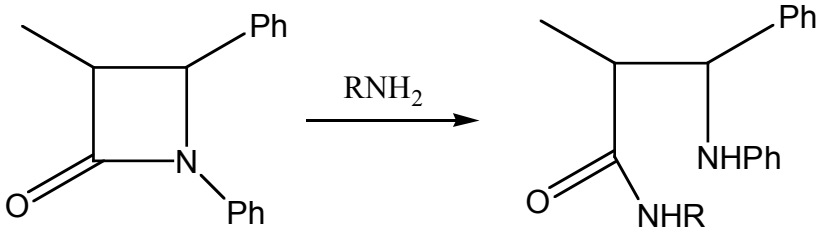
The angle strain in azetidin-2-ones (β-lactams) makes them more susceptible towards hydrolysis than their five-membered (γ-lactams) and six-membered (δ-lactams) counterparts:



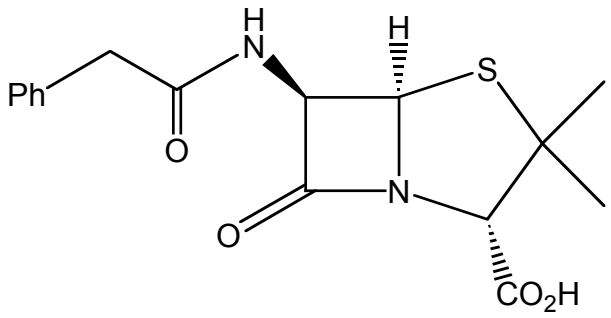
n =	6	5	4
Relative Rate =	1	9	73

They are also opened under acidic and neutral conditions quite readily:

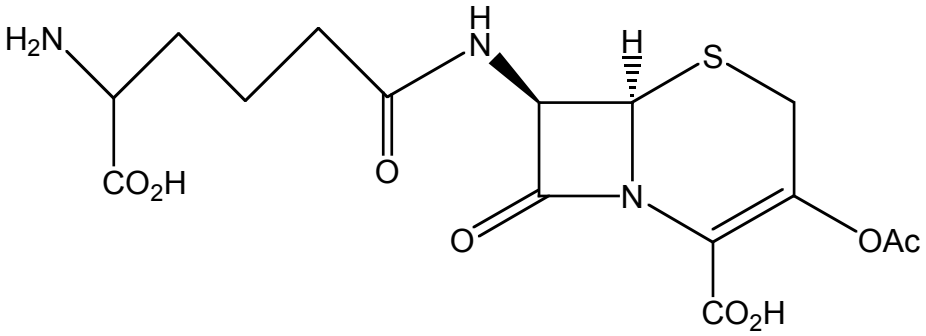




Indeed, the ready reaction at the carbonyl group may be the basis for the anti-bacterial action of the penicillins and cephalosporins.

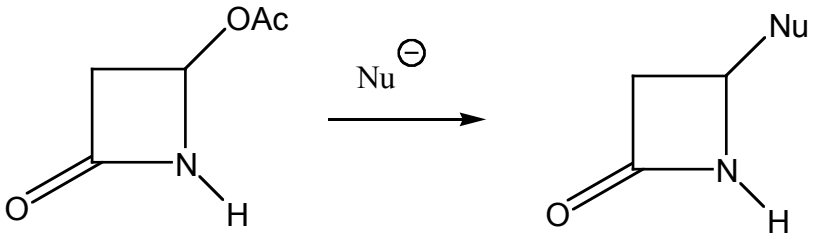


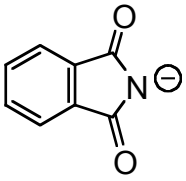
Penicillin G



Cephalosporin C

Azetidin-2-ones bearing a potential leaving group in position 4 may also suffer nucleophilic attack at that carbon without ring opening. The most commonly used derivative for this purpose is the 4-acetate which may be easily made from chlorosulphonyl isocyanate (CSI) and vinyl acetate. The acetate is then removed by a wide range of sulphur, oxygen and nitrogen nucleophiles which provides a large number of azetidin-2-ones which may not be so readily made by the cycloaddition route from CSI:



$Nu^- = ArS^-, ArO^-, RO^-, N_3^-, ArSO_2^-,$ 

The reactions are believed to proceed through the intermediate azetinone: