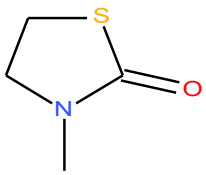
# Sulfur, Phosphorus or Silicone Containing Lactams

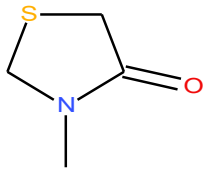
By: Robert B. Login, (web page rloginconsulting.com)

Pyrrolidone continues to interest me because it is so common in pharmaceuticals, biocides, excipients and in a variety of polymers. There are literally tens of thousands of references to it. So, I wandered if anybody had looked at analogs where one of the ring carbons was replaced with a third row atom?

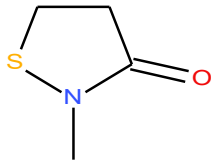
## Thiazolidinones:




3-methylthiazolidin-2-one




3-methylthiazolidin-4-one



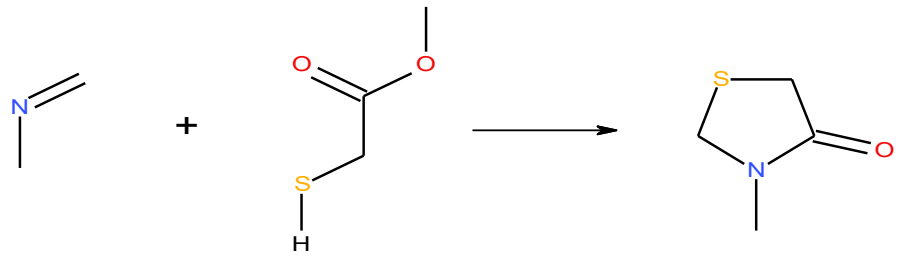

2-methylisothiazolidin-3-one

Of the three possible carbonyl positions on the ring, the 4-one position is in my opinion the most interesting. This is because it would exhibit sulfide chemistry not effected by interaction with neighboring moieties. Sulfides are very strong nucleophiles, hence they may have the ability to improve solvency as compared to NMP, this would be interesting; for example, in paint removers. R groups can be attached to nitrogen, especially those associated with the racetams affording inportant biological activity. With this in mind, I ran a search on Sci-finder, and received thousands of hits for all the related thiazolidin-4-one derivatives! The reason is because the thiazolidin-4-one has remarkable biological properties(1).

“biological activities, such as anti-inflammatory, anti-proliferative, antiviral, anticonvulsant, anti-diabetic, anti-hyperlipidemic, cardiovascular, anti-tubercular, antifungal, and antibacterial. Compounds such as; ralitoline (anti-convulsant), etozoline (antihypertensive),

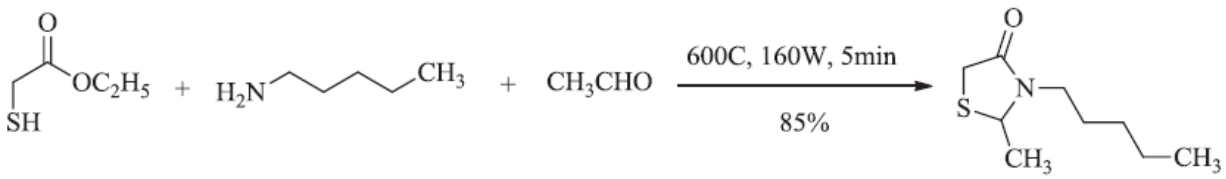
pioglitazone (hypoglycemic) and thiazolidomycin
(activity against streptomyces species), based on this pharmacophore
are already in the market. In recent years, 4-thiazolidinone
derivatives with anti-tumor activity on leukemia, melanoma, lung,
colon, CNS, ovarian, renal, prostate and breast cancers cell lines
have become a promising area of research."(1)

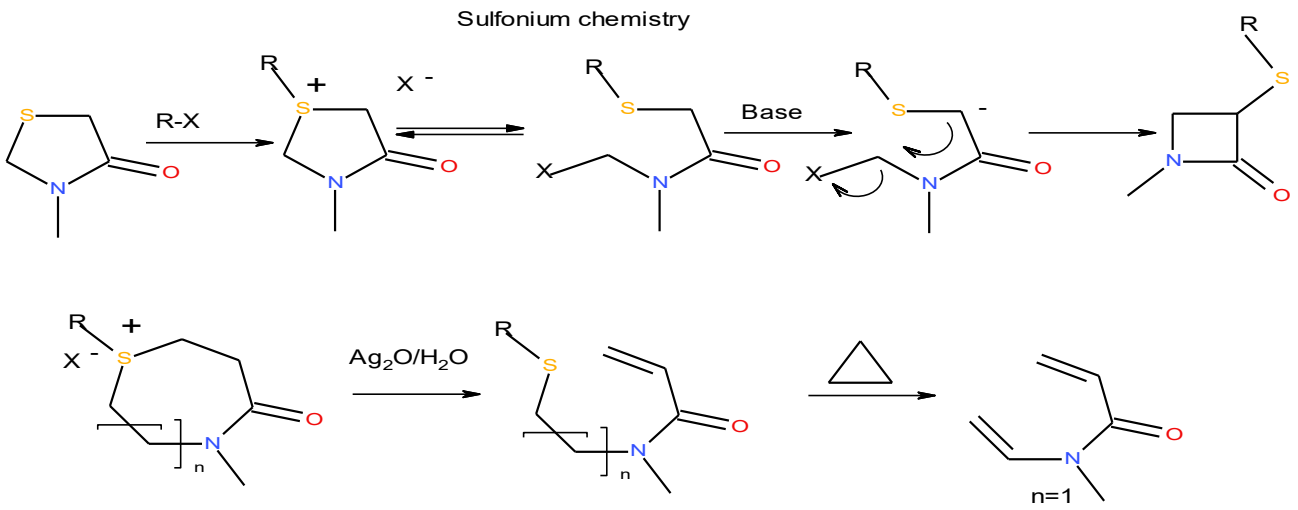
Synthesis of the N-methyl derivative is remarkably easy:




A preformed imine is shown but ammonium salts and paraformaldehyde can be employed to form the unsubstituted thiolactam. The reaction is usually run neat or in a solvent that will azeotrope the water formed when a carboxylic acid is used. The reaction works with a wide variety of carbonyls and amines, and can be viewed as a one pot three component reaction. If the N-vinyl imine is used (N-Methylenevinylamine CAS 38239-27-9 ), then the N-Vinyl Thiazolidin-4-one could be simply and economically synthesized!

A possible argument against thiazolidinones is foul odors. This is untrue as the following jasmone perfume analog does not smell of sulfide (microwave reaction conditions).(2)






The above scheme shows possible sulfonium reactions. Sulfides are nucleophiles but once a sulfonium forms, it can undergo 3 reverse reactions; reforming the starting RX, X- attacking ring position 5 or position 2. Position 5 is unlikely as it is an acidic proton site; therefor, 2 is the most likely because it is next to positive nitrogen reducing electron density on the 2 methylene making it electrophilic. If this occurs, then in the presence of base, a four membered lactam might result.

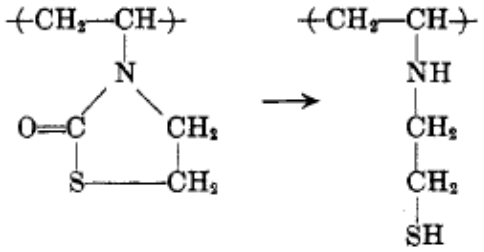
How much these sulfoniums can participate in the various ylid reactions would depend on the appropriate derivatives (not covered in this proposal).

The reaction with Ag2O, proceeds as shown because removal of the proton alpha to the carbonyl can form a stabilized acrylate. Treatment at high temperatures should also result in extrusion of sulfur(cheletropic reaction). This suggests using the Michael reaction of thiols with acrylates as a way of protecting the acrylate so that it can be converted to the amide without involving the competing amine Michael reaction. A thermal removal of sulfur, if it would occur at a acceptable temperature or with hv, would regenerate the acrylate.

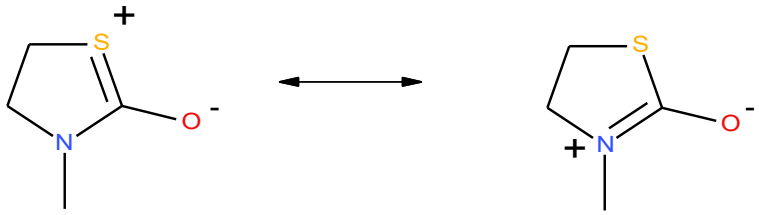
**N-Vinyl Thiazolidinones:**

After an extensive search for vinyl derivatives, I found only one reference to a polymerizable monomer;(3)

JOC Vol 30, 1965, p230.



Their goal was to hydrolyze the polymer to the amino thiol which they believed would confer protection from radiation; however, whatever reagent they tried failed to hydrolyze the polymer. Apparently this polymer is only soluble in DMF and conc. Sulfuric acid which I find hard to explain! Resonance association of the carbonyl with sulfur might confer resistance to hydrolysis?



Sulfur is a large atom that exhibits longer bonds and less overlap of 3p-2p double bonds to carbon, hence the proposed tautomer form on the left may not play much of a roll, but the lactam resonance would still produce a very polar molecule but this doesn't explain why the polymer is hydrolysis resistant. Also I don't think the sulfur is hydrophobic enough to account for the polymers unexpected solubility? One thought comes to mind that the polymer is very ionic and this causes ionic cross-links that require sulfuric acid to break? This explanation suggests that thiazolidin-2-one would make a very good surfactant head group.

I have not found any other N-Vinyl derivatives of thiozolidin-4-one or any other thiazolidinone except the above.

Thiazolidin-4-ones can be readily oxidized to the sulfoxide derivative. This is why its an excellent antioxidant and why the above vinyl monomer can only be polymerized by azo-bis type initiators.

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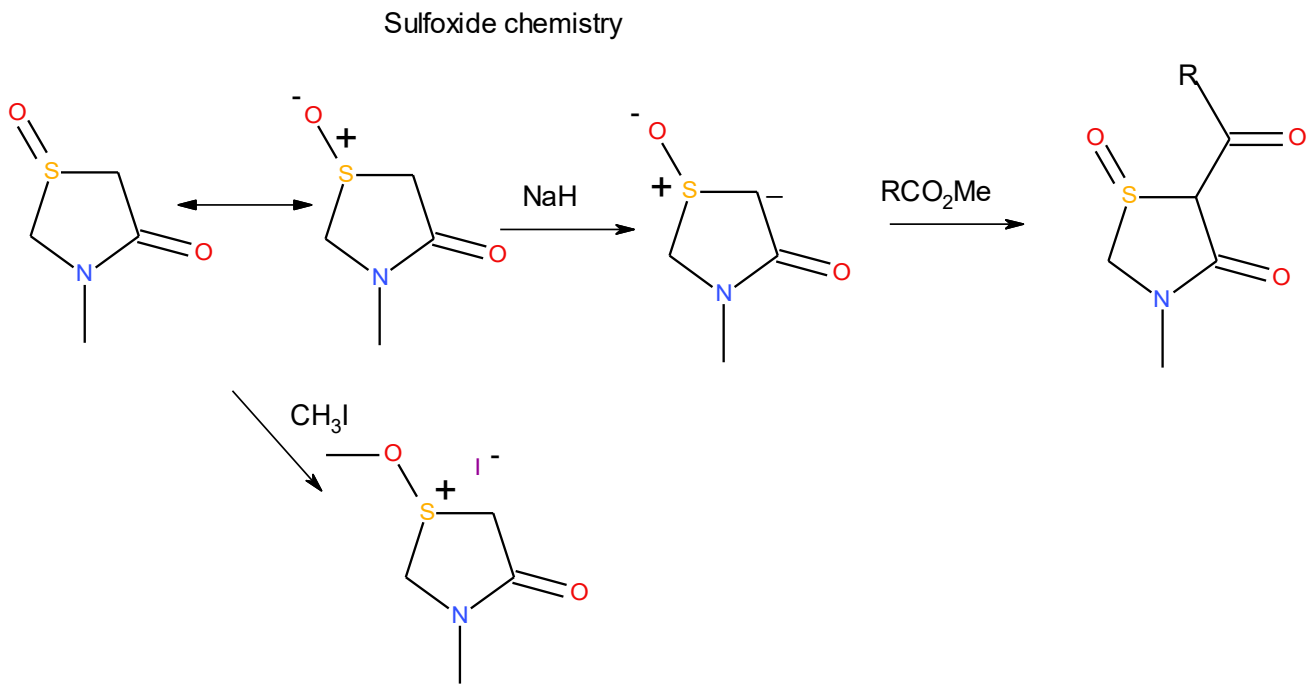
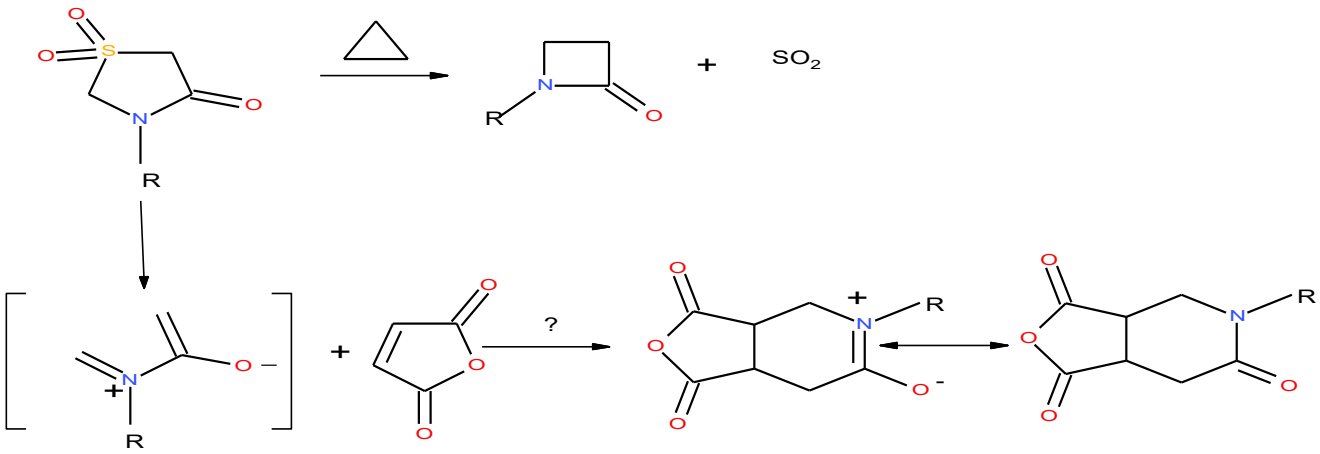
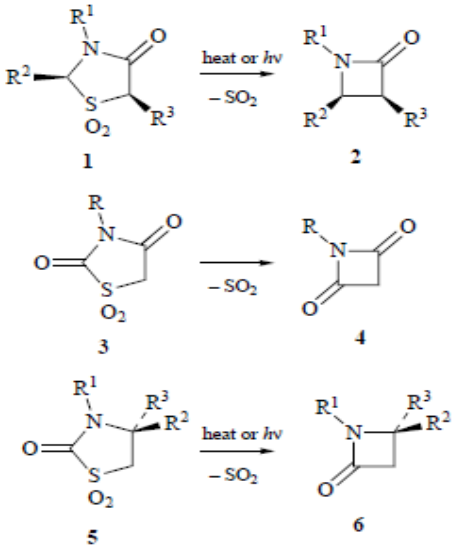



Some of its chemistry is shown in the above chart. Even with a positive charge on sulfur, its still nucleophilic and has a free pair of electrons. The 5 ring position is acidic and nucleophilic enough to be alkylated with various esters and carbonyls. The following ref. Illustrates many other interesting reactions:(4)

Sulfoxides can be further oxidized to sulfones:(5)



Other thiazolidinones can also extrude sulfur dioxide:(6)

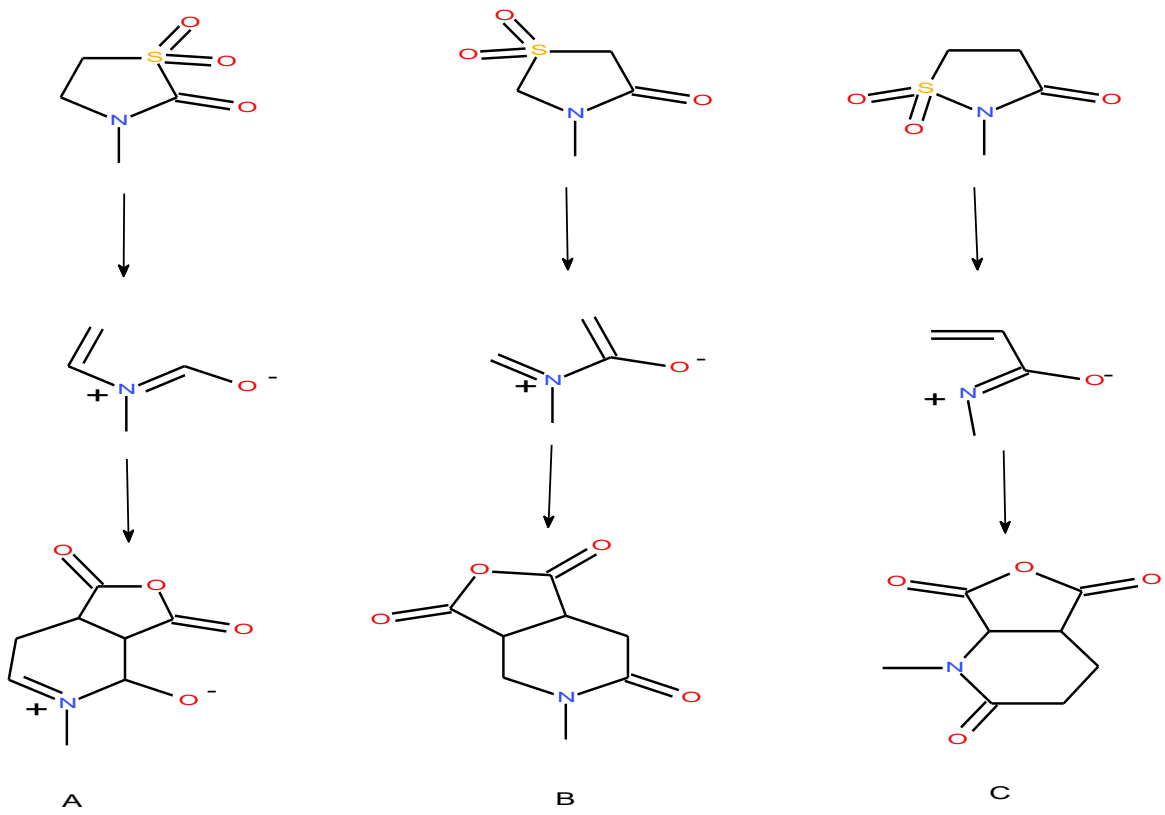



1 2 3 4 5 6

**Scheme 1**

I propose that this thermal SO2 extrusion(cheletropic reaction) can be employed in the Diels-Alder reaction because it is well known that butadiene can be conviently generated by this extrusion and will react insitu in the presence of dieneophiles. The mechanism of SO2 extrusion is believed to involve formation of a diradical, in the presence of maleic anhydride or other dieneophiles, the diradicals can, in my opinion, rearrange into the indicated diene. This reference even shows my proposed diene as a possibility. (7,8)

The following chart illustrates the Diels-Alder possibilities.




Compound A seems somewhat unlikely because the lactam resonance is lost.

SO2 gas is toxic but has many uses:

1) In the manufacturing of sulphuric acid, sulphites, and hydrogen sulphite.
2) In the sugar industry for refining and decolorizing sugar.
3) For refining kerosene, and other petroleum products.
4) As a disinfectant.
5) As a fumigant.
6) For bleaching delicate articles.
7) As antichlor, to remove the excess chlorine from substances that have been bleached by chlorine.
8) As a solvent for glue.
9) As a refrigerant in household refrigerators.
10) As a preservative for wines, meat, dry fruits etc.

The uses of sulphur dioxide are summarized in the figure 7.8.

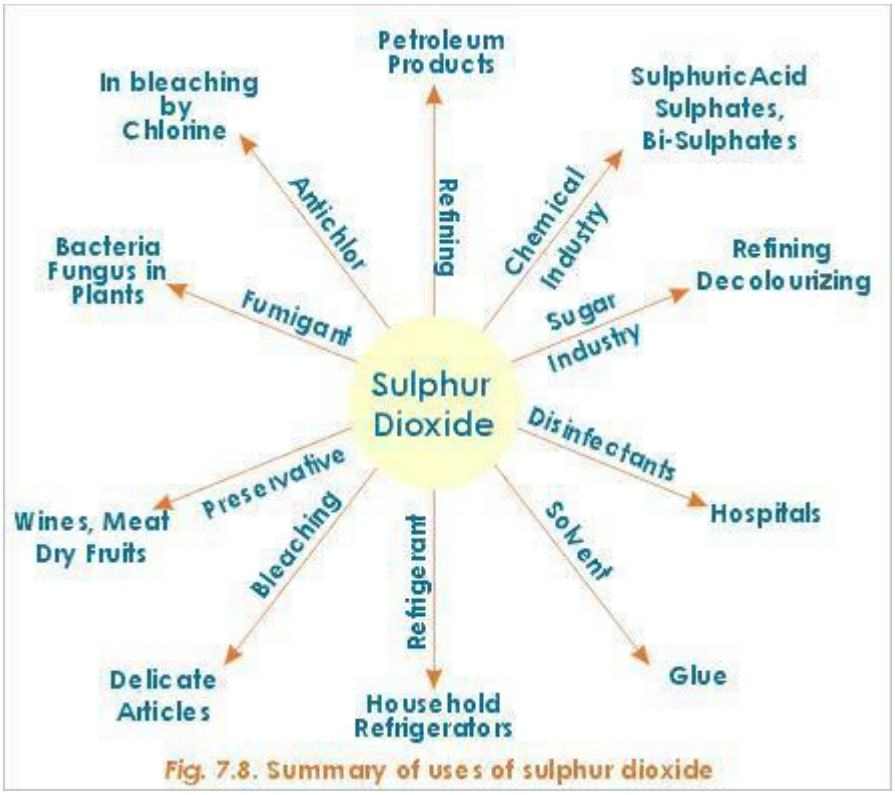
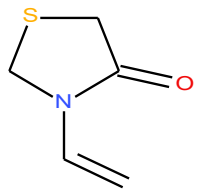


Fig. 7.8. Summary of uses of sulphur dioxide

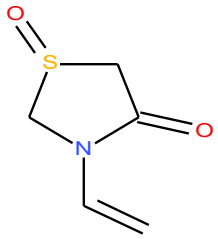
http://chem-guide.blogspot.com/2010/04/properties-and-uses-of-sulphurdioxide.html

Extrusion of SO2 would generate safe small amounts that might be easily handled and very useful in some of these applications. Especially polymeric 1,1-dioxo-3-vinyl-1,3-thiazolidin-4-one might be a valuable source of SO2. For example it could be coated on potentially compromised medical devices and could disinfect or fumigate them. Release of SO2 could be by heat and/or hv. Sensitive surfaces on medical plastics could be sterilized with UV for example avoiding damaging heat. A polymeric film that would release SO2 at body temperature would have the potential to sterilize inplants because release would attack bio-films which can force removal of the inplant.

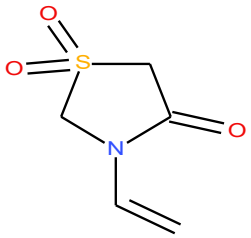
N-Vinyl Thiazolidin-4-ones



3-vinylthiazolidin-4-one



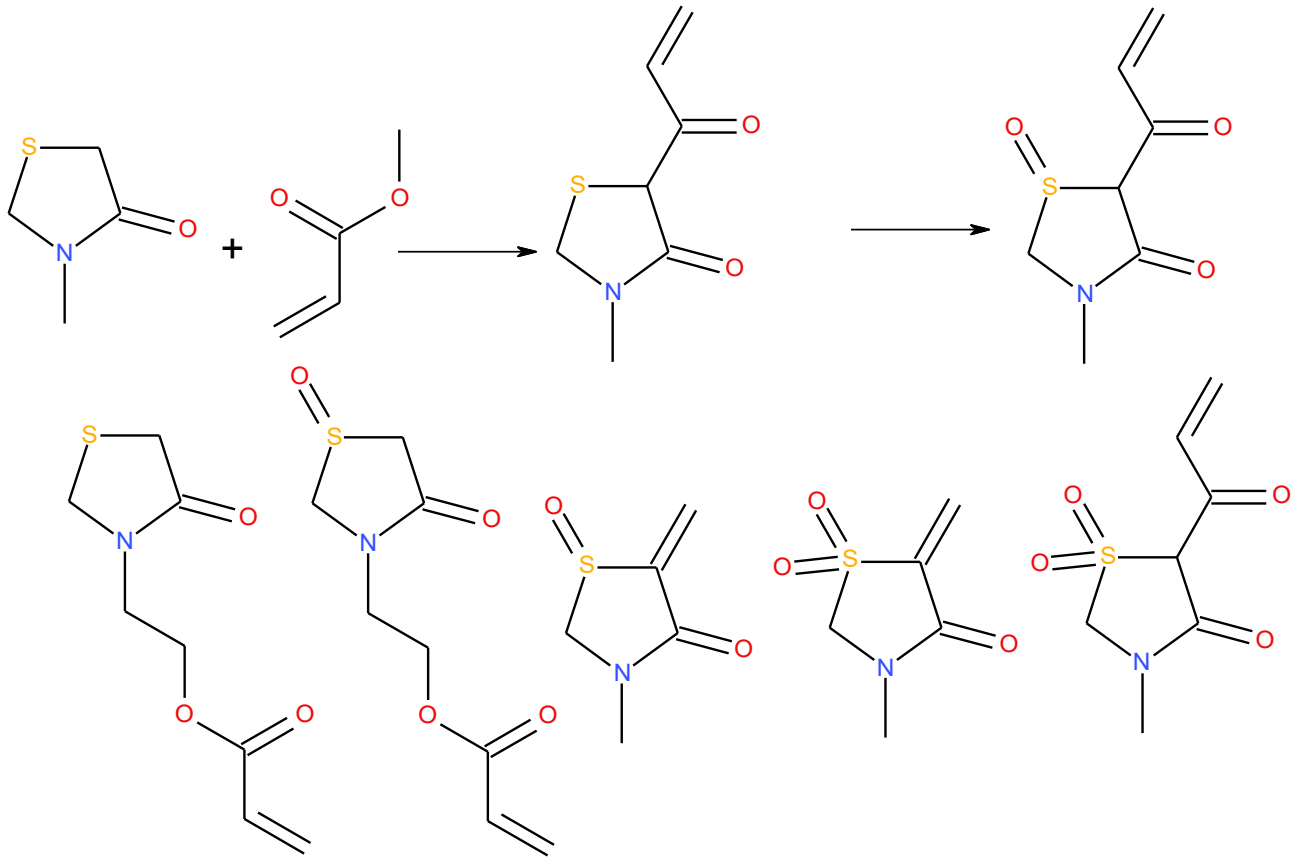
1-oxo-3-vinyl-1,3-thiazolidin-4-one



1,1-dioxo-3-vinyl-1,3-thiazolidin-4-one

The above possibilities would be interesting monomers. One reason is that the sulfur would be a site for further reactions such as oxidation and extrusion. Polymers and

copolymers of these monomers would be film formers that could be designed especially for SO2 extrusion, for the suggested medical applications. Would polymeric beta-lactams exhibit antibiotic activity?



Although not every possibility is illustrated in the above chart, I'm sure many others can be conceived of. The above charts also suggest possibilities for all the thiazolidinones. Extrusion of SO2 from polymers prepared from the sulfone of those monomers shown above or from other 2- or 3-ones thiazolidins  with the same idea would also be valuable monomers.

In conclusion, can the various forms of sulfur in cyclic thiazolidinone heterocyclic containing polymers exhibit useful properties? Can extrusion of  SO2 from polymeric examples to form beta-lactams confer antibiotic activity in monomeric and/or polymeric

motifs? Will sulfur and its derivatives confer unique surfactant and solvency when employed in these N-alkyl compounds? Etc. I believe many valuable applications will emerge from this chemistry.

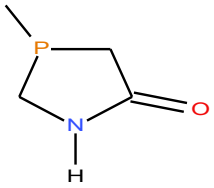
Thank you for reading this proposal!
Please contact me at rloginconsulting.com with questions or feed-back.

General References(10, 11, 12)

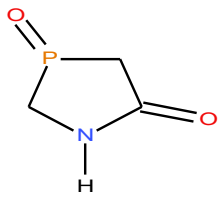
## Phosphorus Containing Lactam Derivatives

With the huge interest in thiazolidinones, I thought that the same might be the case with phosphorus? I discovered very interesting chemistry but not many references to pyrrolidone analogs.

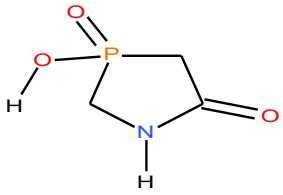
I propose that azaphospholidin-5-one heterocyclic (or larger rings) have the potential for significant utility.




3-methyl-1,3-azaphospholidin-5-one

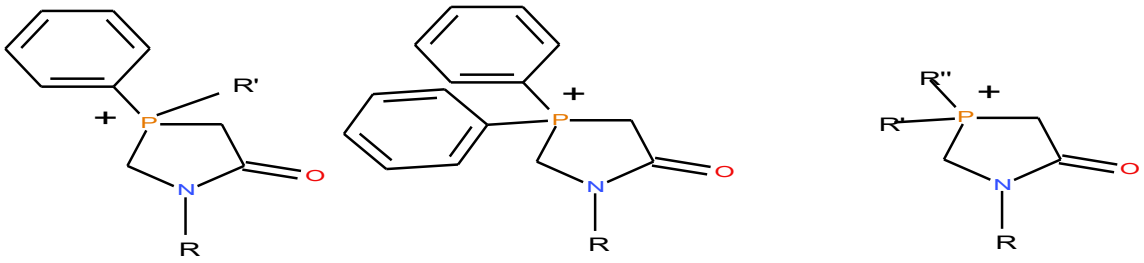



3-oxo-1,3-azaphospholidin-5-one




3-hydroxy-3-oxo-1,3-azaphospholidin-5-one

All of the above would afford unique chemistry that could be of real value. The phosphine for example has very interesting chemistry. Alkylation affords the phosphonium salt that has a literature indicating the potential for biological and anti-microbicidal activity. I would be interested in polymeric motifs as the literaure suggests they are more active as biocides because they adhere to bacteria cell walls more intensely than monomeric cationics.(13)



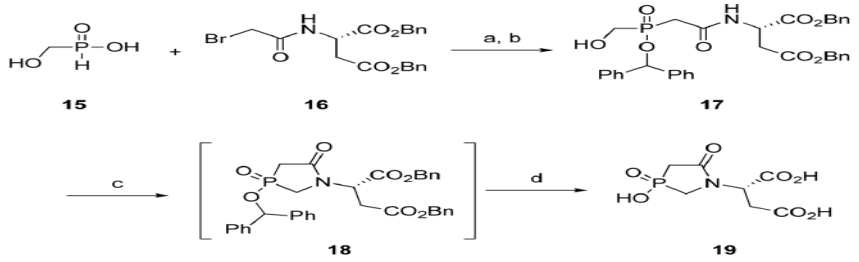
A small sampling of possible phosphonium compounds.

Intense interest in phosphinate analogs of amino acids is a current hot topic. Such amino acid analogs are tetrahedral like amino acid enzyme tetrahedral hydrolysis transition states; however, the phosphinates and phosphonates are hydrolysis resistant, and disrupt enzymes associated with disease because the target enzyme is deactivated by complexation of its metal ion. With the same peptide amino acid sequences involved in the disease but with the P-amino acid replacement in the peptide, the offending enzyme is trapped as a phosphinate or phosphate metal complex.

For more detail see:(14)

The azaphospholidin-5-one heterocyclic motif has not been evaluated to any extent as far as I know. This is based on the phosphonium, aminophosphinate and phosphonate (massive) literature (that I was able to access) and a SciFinder structure search. The following article is the only example of the five-membered version that I have found. References to the six-membered version should be more numerous because the majority of aminophosphinate compounds are set-up for six-membered ring closure.(15)

2-(3-Hydroxy-3,5-dioxo-3l5-[1,3]azaphospholidin-1-yl)-succinic acid (19)—
"The more elaborate "cyclo-PALA" heterocycle **19** was synthesized according to Scheme 4.The known hydroxymethyl-*H*-phosphinic acid **15** undergoes a sila-Arbuzov reaction with bromide **16**, and the crude mixture is esterified with diphenyldiazomethane to afford **17** (hydrogenolysis of **17** gives hydroxymethyl inhibitor **3** in quantitative



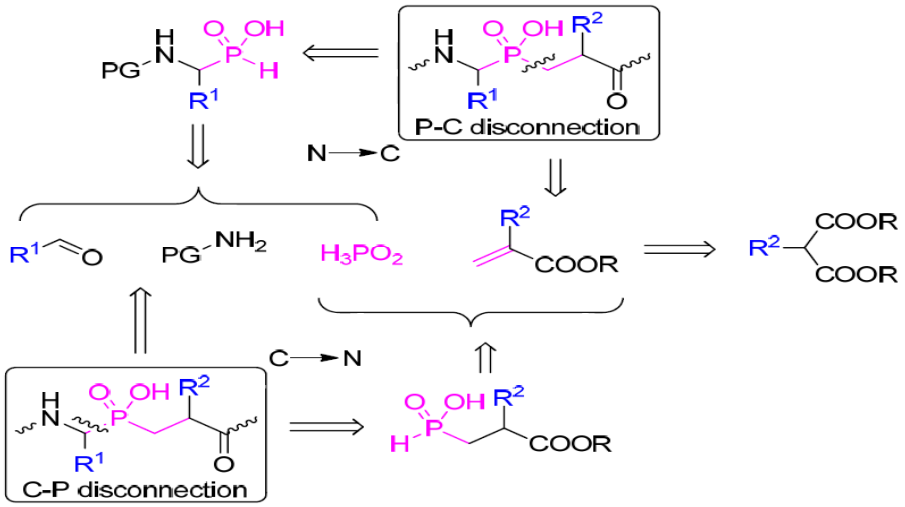
**Scheme 4.**
Reagents and conditions: (a) N-(bromoacetyl)-L-aspartic acid dibenzyl ester **16** (1.0 equiv.), HMDS (2.5 equiv.), TMSCl (2.5 equiv.), toluene, reflux, 14 h; (b) $Ph_2CN_2$, toluene, 50 % from **15**; (c) DIAD (1.0 equiv.), $Ph_3P$ (1.0 equiv.), THF, 30 min, r.t.; (d) $H_2$, Pd/C, THF/$H_2O$, 24 h, 44 % from **17**.

yield). Intermediate **17** was cyclized using Mitsunobu conditions to produce crude **18**, which was hydrogenolyzed directly to the 5-membered amide **19.”**

Why so few references to five-membered phosphinate lactams, when the sulfur analog, thiazolidin-5-one has thousands?

Mucha's review(16) affords a detailed account of the various methods of preparing aminophosphinate compounds.

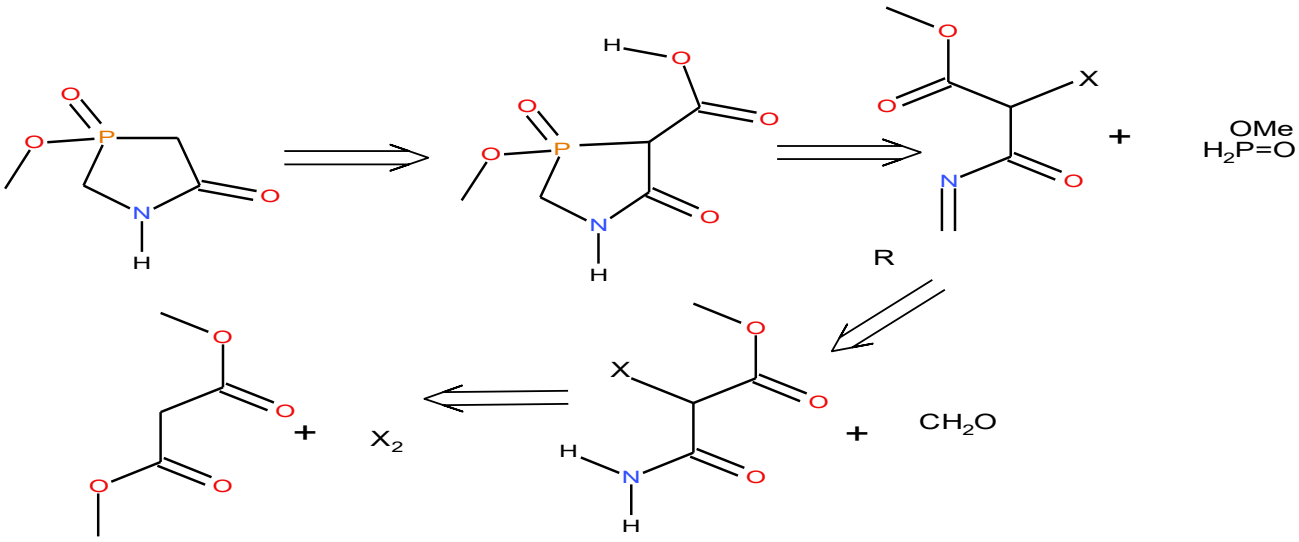
**Scheme 1.** Retrosynthetic analysis of the phosphinic dipeptide scaffold.

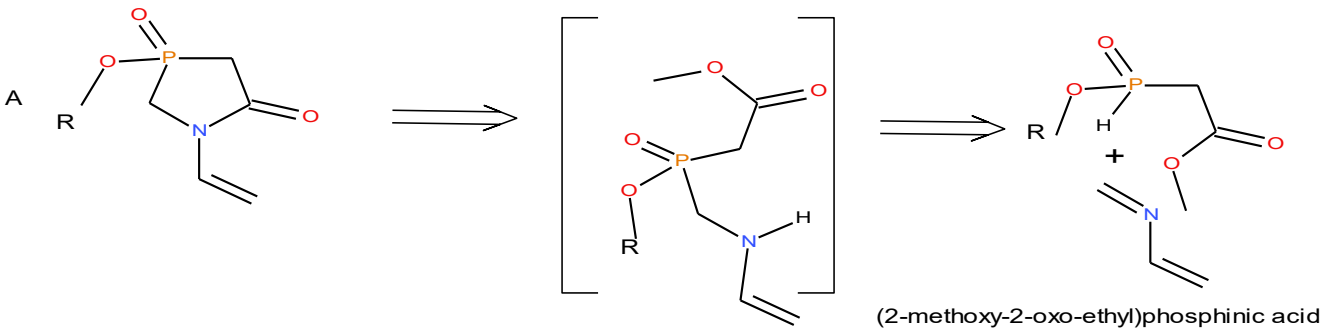


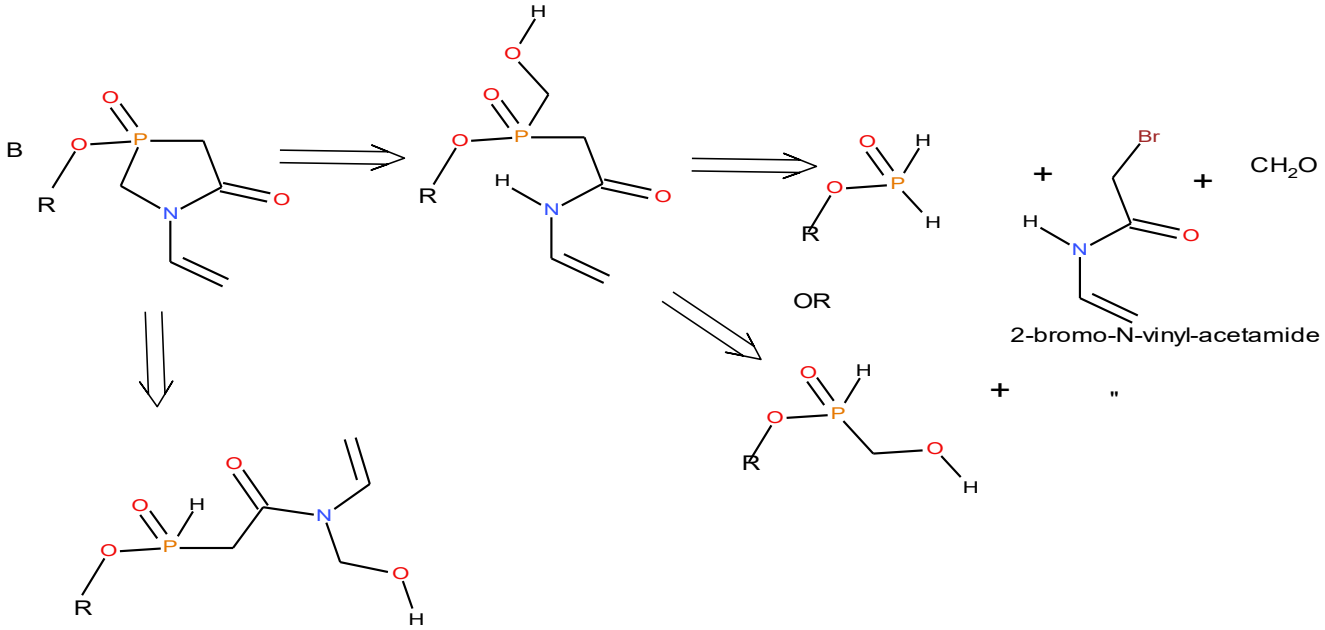

He illustrates the various ways to make these derivatives. Phosphinates are added to Michael acceptors or to chloroacetates, for example. If the amine and the carboxylate are then connected together, a five or six-membered lactam ring would result .

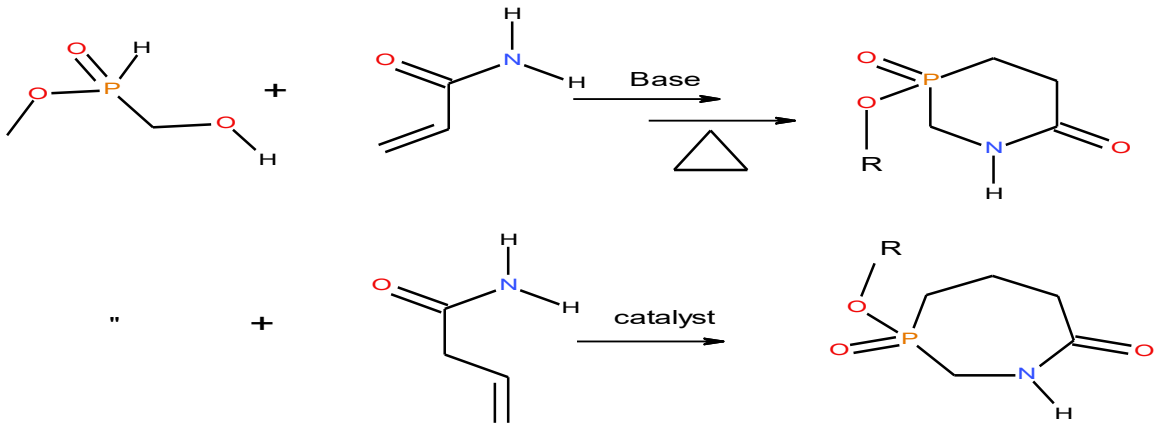
Other useful references:(17, 18, 19)

The following charts shows my ideas in outline form for preparing five-membered ring phosphinate lactams. My goal is to ultimately synthesize the N-Vinyl derivative.(20, 21)

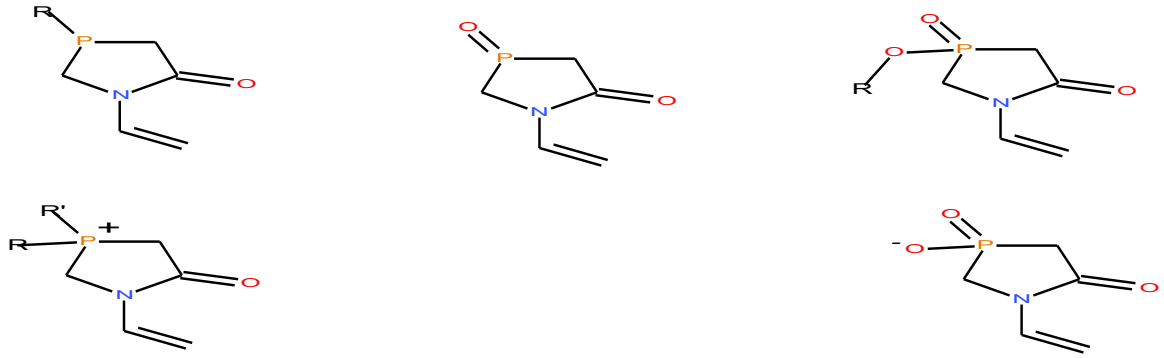

OMe
H2P=O
R
X2
CH2O


A
R
(2-methoxy-2-oxo-ethyl)phosphinic acid


B
R
OR
Br
CH2O
2-bromo-N-vinyl-acetamide
"



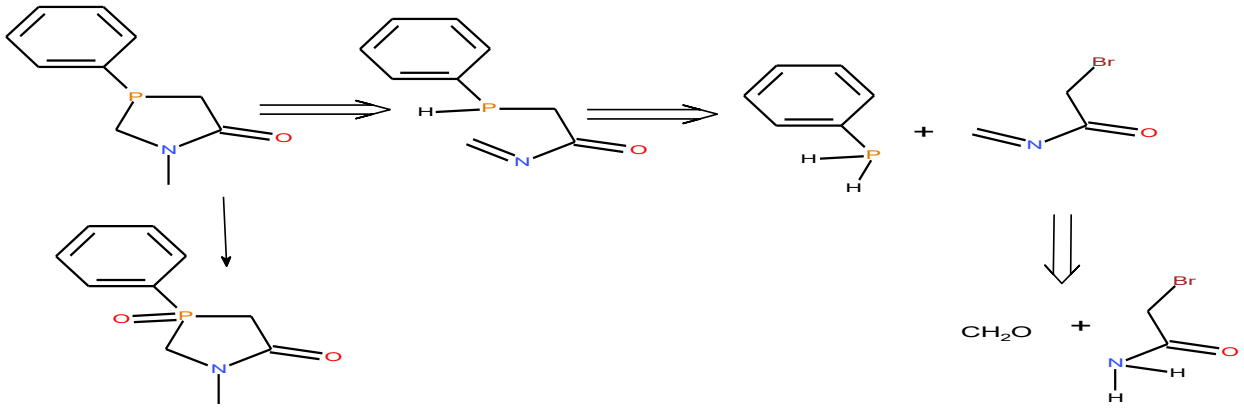

The above ideas employ a variant of the Kabachnik-Fields reaction. Ethenamine,N-methylene-(CAS 38239-27-9 ) actually is a known compound. The idea here is that ethenamine, N-methylene reacts with both the H-phosphinic acid and the alpha-bromocarboxylate ester in a one pot reaction. Scheme B is an alternate approach that involves intermediates that might be more readily available. Both A&B would be very cost effective ways of synthesizing this interesting vinyl monomer. It should be readily polymerized much like NVP; however, certain peroxy initiators could very well oxidize the phosphinic to phosphonate.



Phosphinics are hydrolytically stable compounds; therefore, polymers based on the above monomers sould be water soluble. Said polymers would contain significant amounts of phosphorus and could be flame-retardant. If the R group is H(phosphinate example) then it would be acidic and would inhanced the polymers ability to complex various heavy metals. With various R groups, the above monomer based (co)polymers could be tested as antibiotics and in other medical applications.

Another use would be as complex agents for metals useful for medical diagnosis.

Another idea employs primary phosphines such as phenylphosphine and others. These reactions are illustrated in the following scheme:

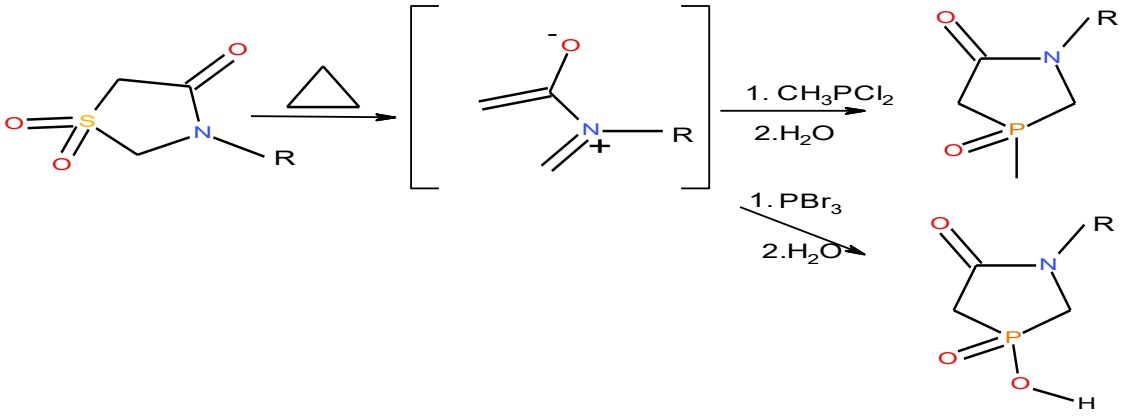


Phosphines can be readily oxidized to the oxide.

Which of the various ideas would lead to a biologically active P-Lactam remains to be determined.(22)

All of the above suggested chemistry is based on well known phosphorus reactions(an excellent reference is “A Guide to Organophosphorus Chemistry” by L. D. Quin).

As a final idea I have taken a reaction of SO2 chemistry as described in my proposal “Sulfur Containing Lactams”(above). SO2 can be extruded from cyclopentene derivatives to result in a butadiene that will react with dieneophiles. This is a well known method of conveniently handling butadiene rather than butadiene itself(a gas). As reviewed in my proposal, the cheletropic reverseable addition or extrusion of SO2 from thiazolidinones should form a transient diene that could be trapped by dieneophiles. I propose that the McCormack reaction can be employed as follows:




I think this would be the simplest way to these analog pyrrolidones. Although from

1967, the following book has a detailed review of Cheletropic reactions of sulfur and phophorus and is a good place to start if you are interested;

**1,4-Cycloaddition Reaction: The Diels-Alder Reaction in Heterocyclic ...**

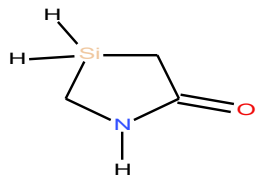
edited by Jan Hamer; Academic Press, 1967.

Thank you for reading! Please contact me at rloginconsulting.com with any comments or questions.

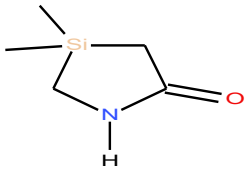
General References:(23, 24, 25)

**Silicone containing lactams:**

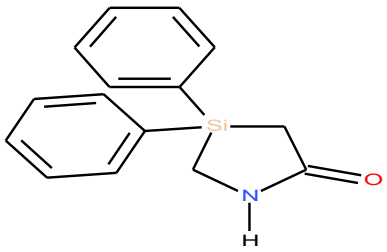
Having delved into sulfur and phosphorus substituted lactams, the last third row atom of interest is silicone. These third row atoms have several similar properties, they are less electronegative, larger, with longer bond lengths as compared to their second row cogeners. They use 3s, 3p and have 3d orbitals but currently the use of 3d orbitals, once used to explain 5 & 6 bonds with 3s3p3d hybridization is no longer the case; now 3p sigma star bonds are used to explain hypervalency. Usually silicone as with carbon uses sp3 bonds to 4 substituents in a tetrahedral arrangement.



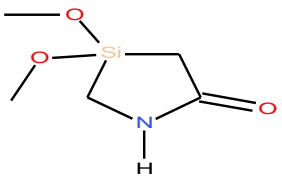
1,3-azasilolidin-5-one



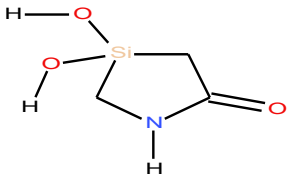
3,3-dimethyl-1,3-azasilolidin-5-one



3,3-diphenyl-1,3-azasilolidin-5-one



3,3-dimethoxy-1,3-azasilolidin-5-one



3,3-dihydroxy-1,3-azasilolidin-5-one

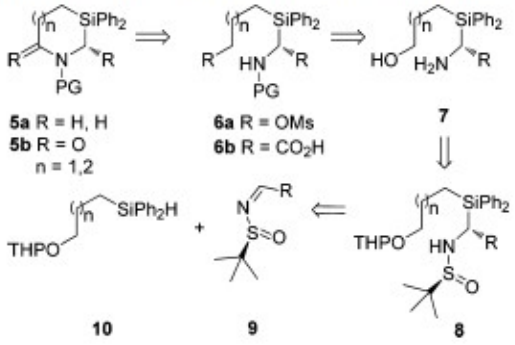
Chart 1

The above chart illustrates several 1,3-azasolidin-5-ones and as with sulfur and

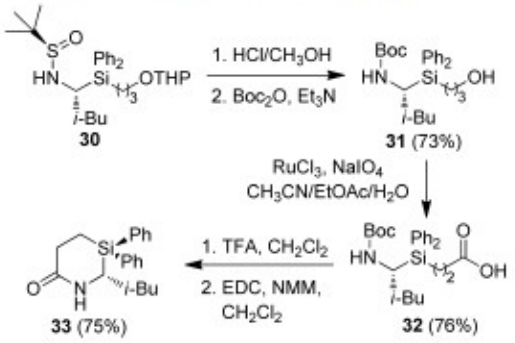
phosphorus, I believe the 5-one position is the most interesting because it is not next to the amide nitrogen or carbonyl. The 5-one position has derivatiseable methylenes next to silicone where further reactions can occur. Furthermore, silicone at this position can be tetrahedral acting as a isostere that cannot be attacked by enzymes in silanediol peptide mimics.

After studying organosilicone chemistry and searching the literature, I found one reference that shows the cyclohexane derivative. Their procedures are illustrated in the following schemes:(26,27)

**Scheme 1.** Retrosynthetic Analysis of the Silaheterocycles **5**

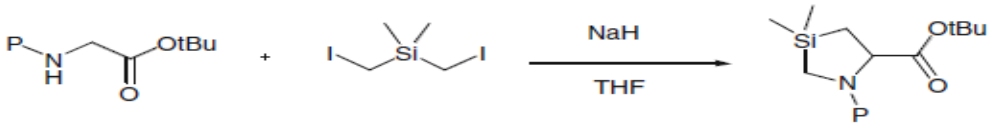



**Scheme 3.** Preparation of Piperidinone **33**




*Org. Lett.,* Vol. 12, No. 15, **2010**

The following procedure seems much simpler resulting in the ester at the 5 position. The problem now is to convert the ester to the 5 carbonyl.(28,29)




1: P=Boc

2: P=Z

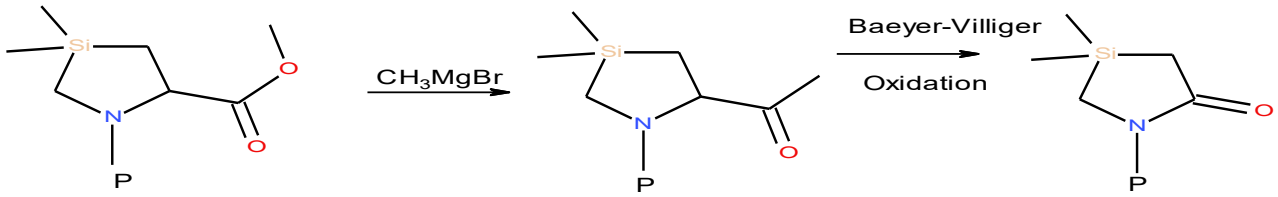
3

4: P=Boc

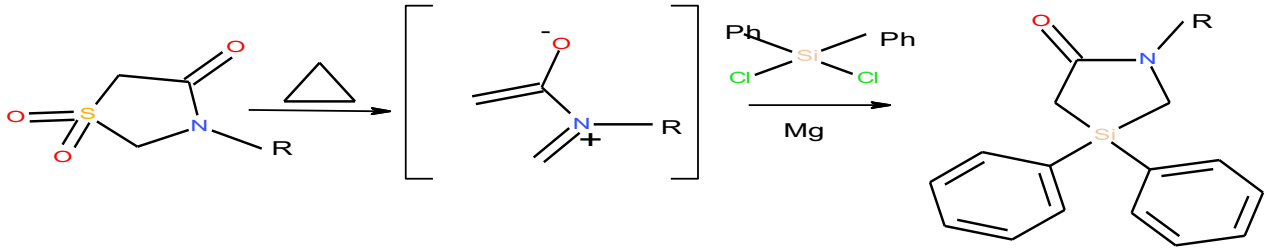
5: P=Z

**Baeyer-Villiger Oxidation:**

The following scheme 3 shows a possible method to prepare the lactam. I would replace the tBu ester then prepare the ketone and finally B-V oxidation.




Scheme 3 (P protecting group)




Scheme 4

Scheme 4 illustrates my idea, a version of the McCormack reaction that takes advantage of the cheletropic extrusion of sulfur dioxide to produce an in-situ dieneophile. (30-32)

Monomers:

The chart 2 illustrates potential vinyl monomers.

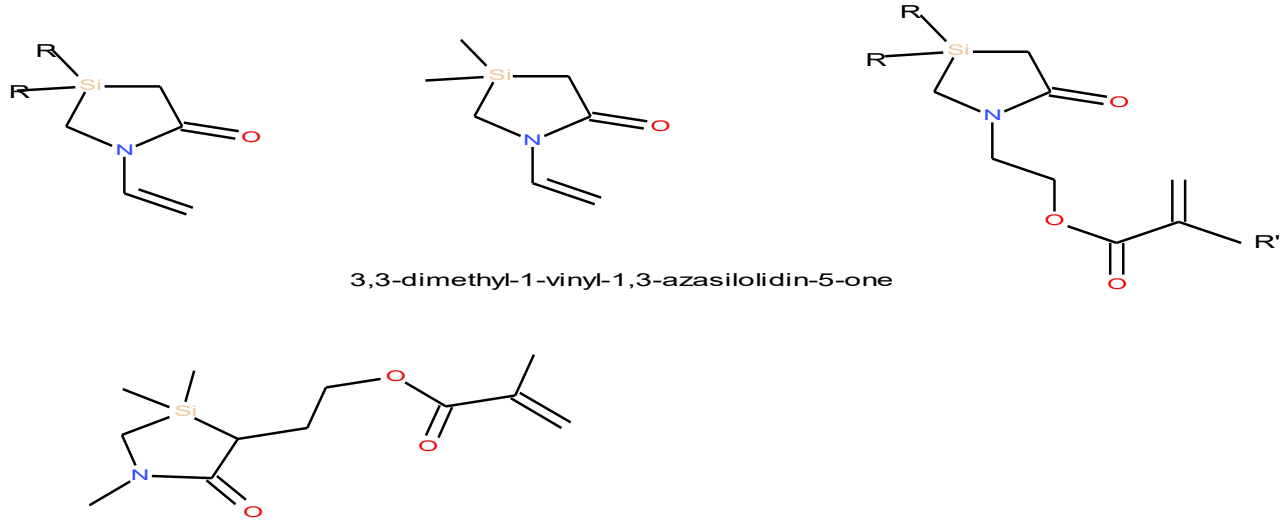
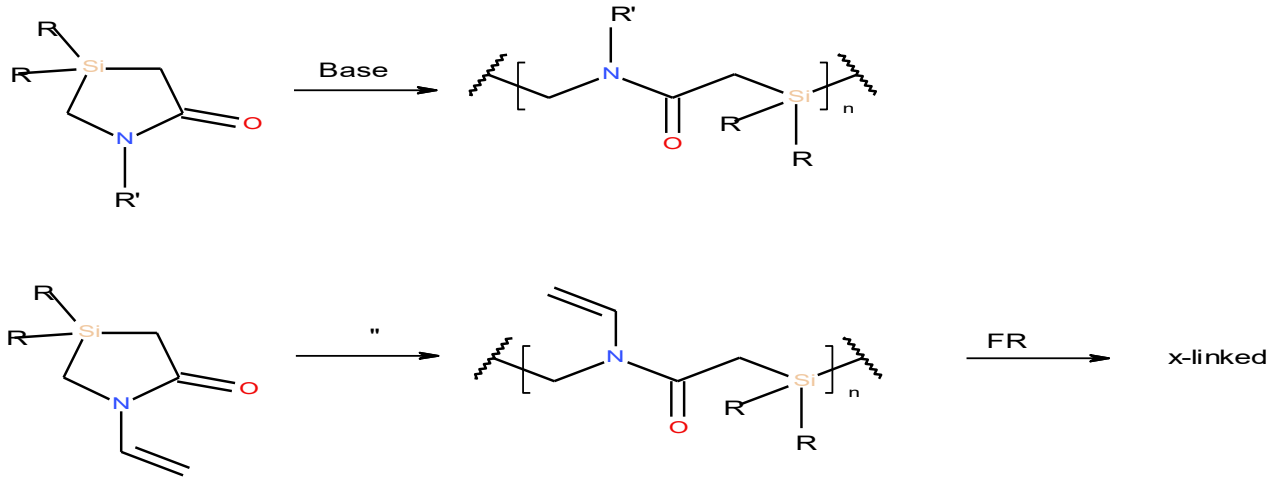


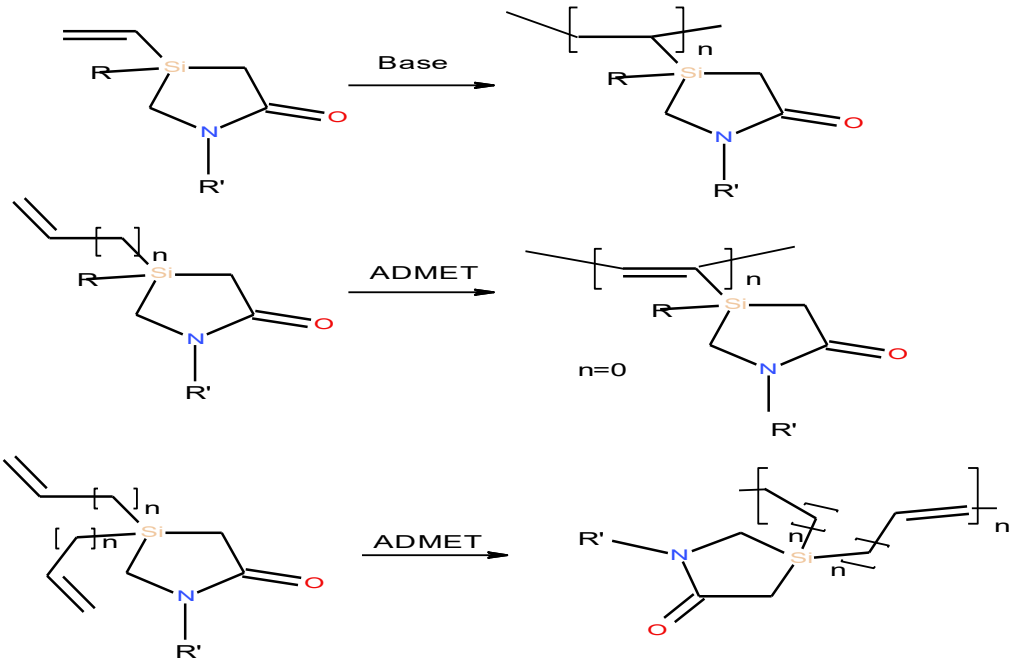

Chart 2

Sp3 bonds to silicone are much longer than those to carbon; therefore, the 1,3-azasilolidin-5-one five membered heterocycle must be very strained because of the long silicon bonds. This suggests that polymerization to a linear structure would relieve this strain and it would be a base catalyzed polymerization. A nylon 4 silicon might be possible whereas polymerization of pyrrolidone itself is not facile. Chart 2, monomers would afford vinyl or acrylic polymers that would cross-link readily with a catalytic base.




The previously described sulfur and phosphorus lactams, if the idea of long bonds causing ring strain in five membered lactams results in a propensity for ring opening polymerization, would also apply to these atoms. Which of these heterolactams would polymerize versus some other reaction is the question? The value of answering this question is the potential application of these nylon derivatives? Both sulfur and phosphorus can form sulfonium or phosphonium cationic polymers with a variety of applications. Phosphorus can also contribute flame retardency to nylon. Silicone might

be a site for eventual degradation of nylon when disposed of in the environment.




Reference 33

Thank you for reading these proposals. Please contact me at rloginconsulting.com with any questions or comments. My web site contains safe down loadable pdfs with a variety of ideas that I hope you will find interesting!
Dr. Robert B. Login

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