Pyrrolidone Dimers and Pendant Pyrromethane Polymers with MIP potential

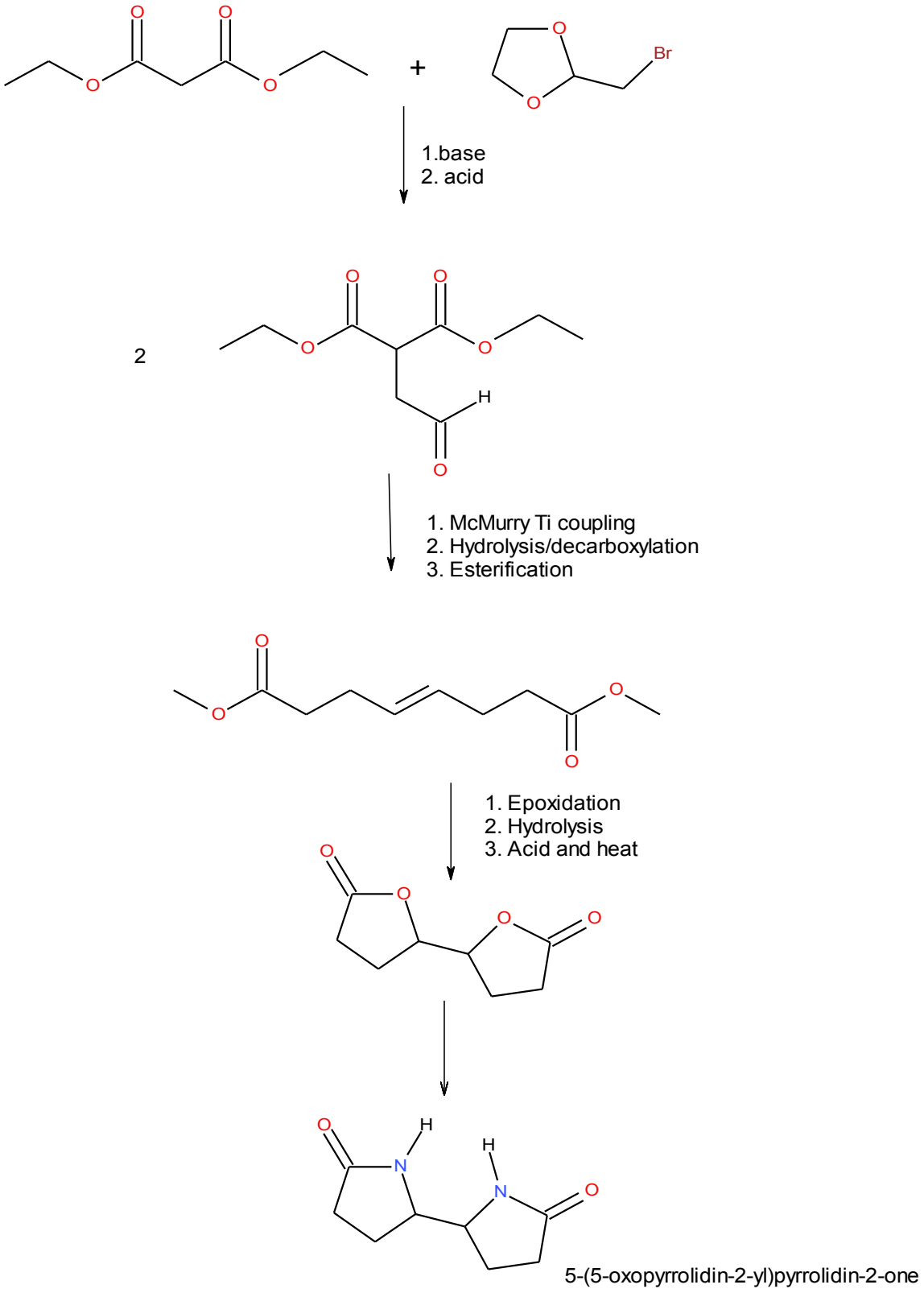
Proposed methods to synthesize Pyrrolidone Dimers of various structures.

By Robert B. Login

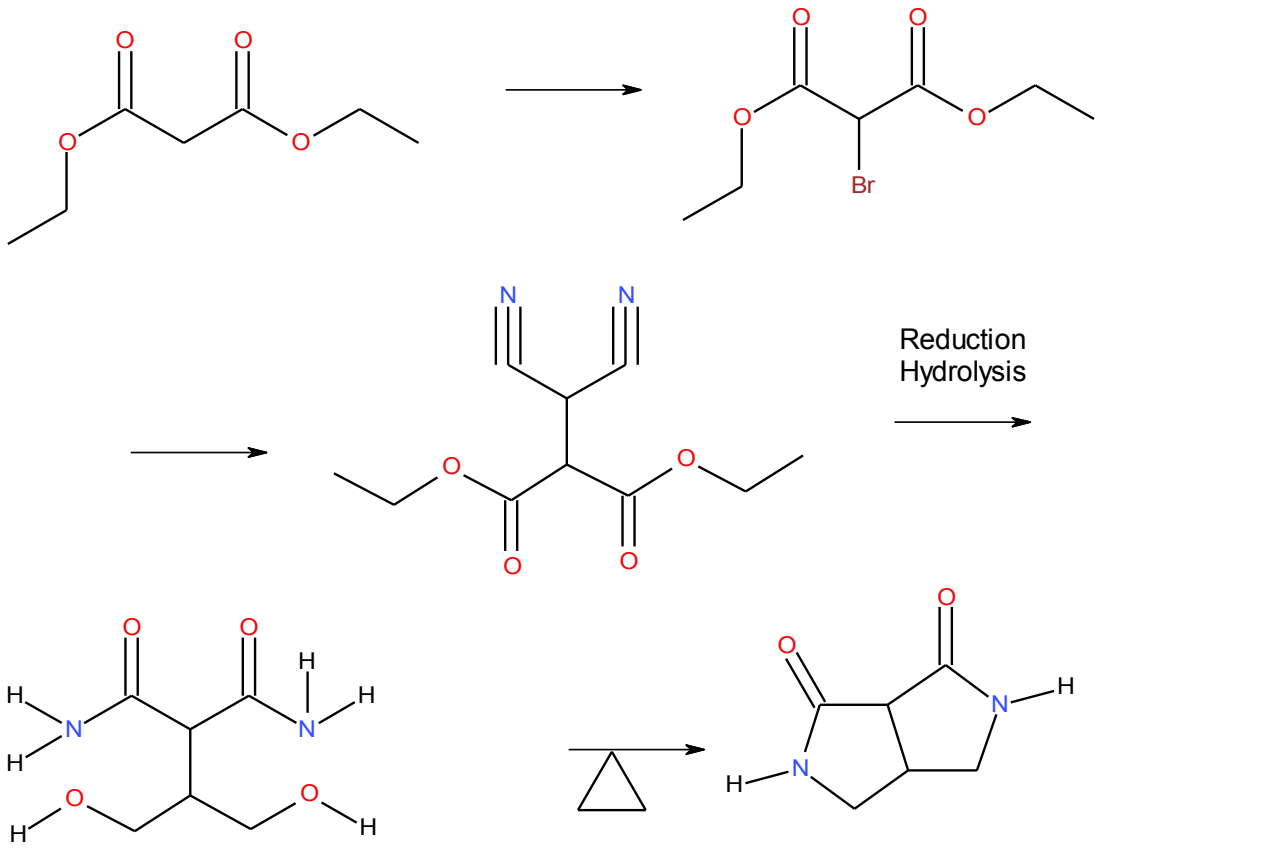
I have been interested in the pyrrolidone ring for many years and my interest has not abated. Commercial products such as the many Vinyl Pyrrolidone based polymers, the super solvent NMP and Surfadone Octyl and Dodecylpyrrolidone surfactants bear witness to the remarkable utility of the Pyrrolidone functionality. The reason is charge, it can be drawn in two resonance forms, one neutral and the other with positive charge on nitrogen and a negative charge on oxygen. Such charge separation confers water solubility. Obviously Pyrrolidone has some intermediate charge between these two extremes, but interestingly it can attract protons when in the presence of large anions. The complexation of phenolics, hydrogen peroxide and iodine with PVP are examples of this. However, I believe that new Pyrrolidone containing molecules could have significant value. I would be delighted to discuss my ideas for such compounds with anyone interested.

The following proposals are shown without details on exactly how one would run the reactions but each step is based on well known chemistry. There is no guarantee that the reactions go as shown but I would not reveal them if I thought that. Such an approach is common in the patent literature where such proposals are considered paper reductions to practice.

If you see better ways to synthesize these compounds, or I spark interest in new pyrrolidone derivatives, then I would be delighted. But please let me know what you think because it is very satisfying to have feedback either positive or negative.

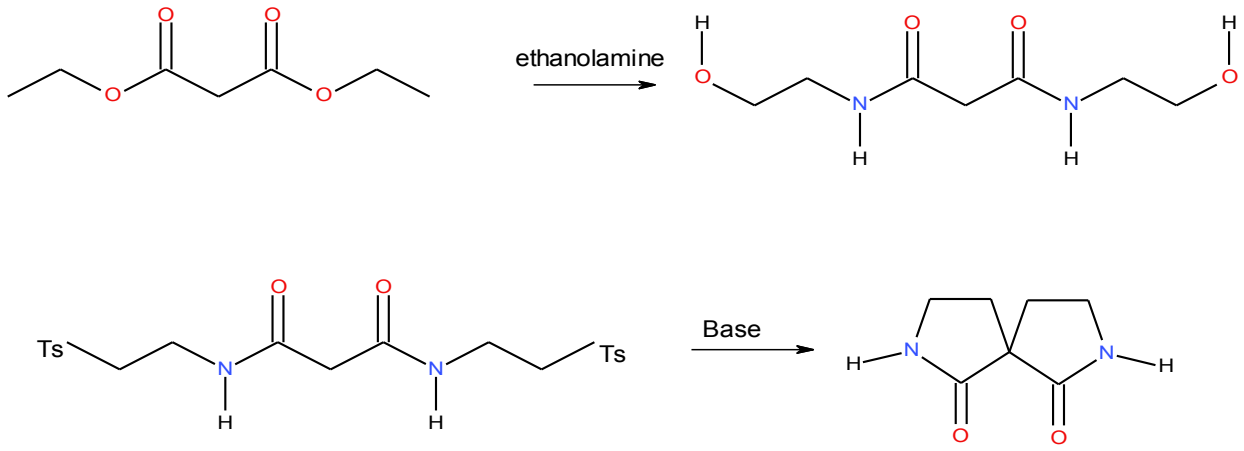

Br
1.base
2. acid
2
H
1. McMurry Ti coupling
2. Hydrolysis/decarboxylation
3. Esterification
1. Epoxidation
2. Hydrolysis
3. Acid and heat
5-(5-oxopyrrolidin-2-yl)pyrrolidin-2-one

Scheme 1



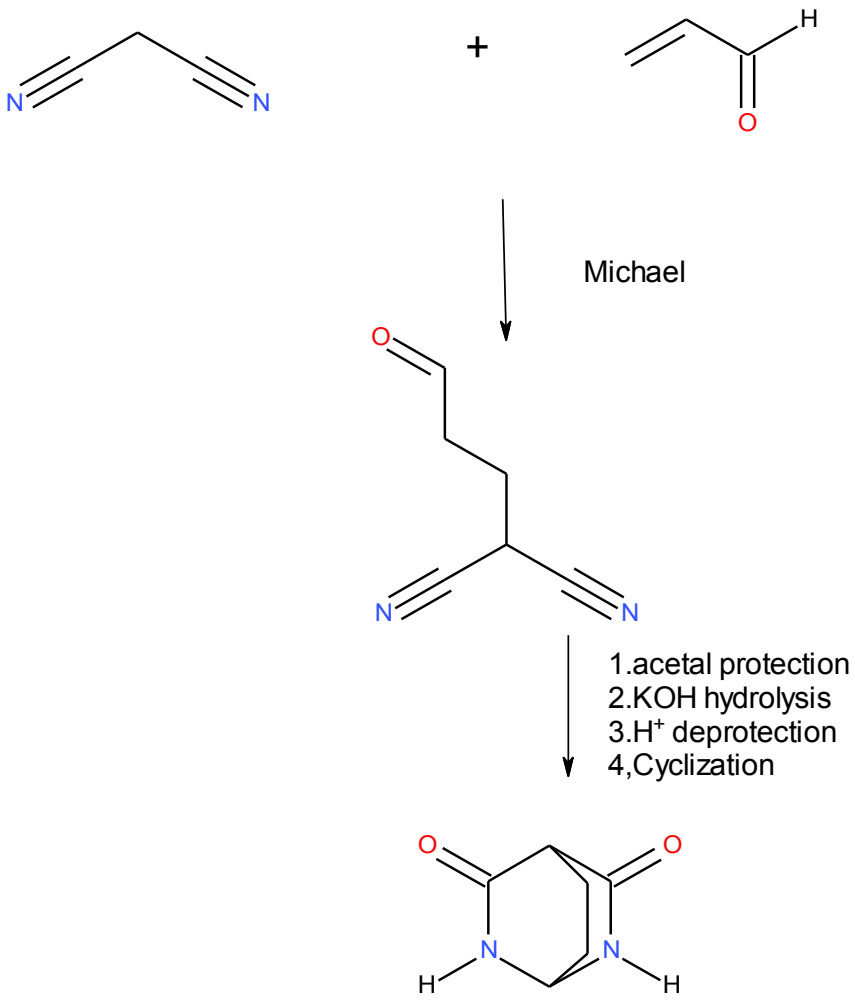
1,2,3a,5,6,6a-hexahydropyrrolo[3,4-c]pyrrole-3,4-dione

Scheme 2



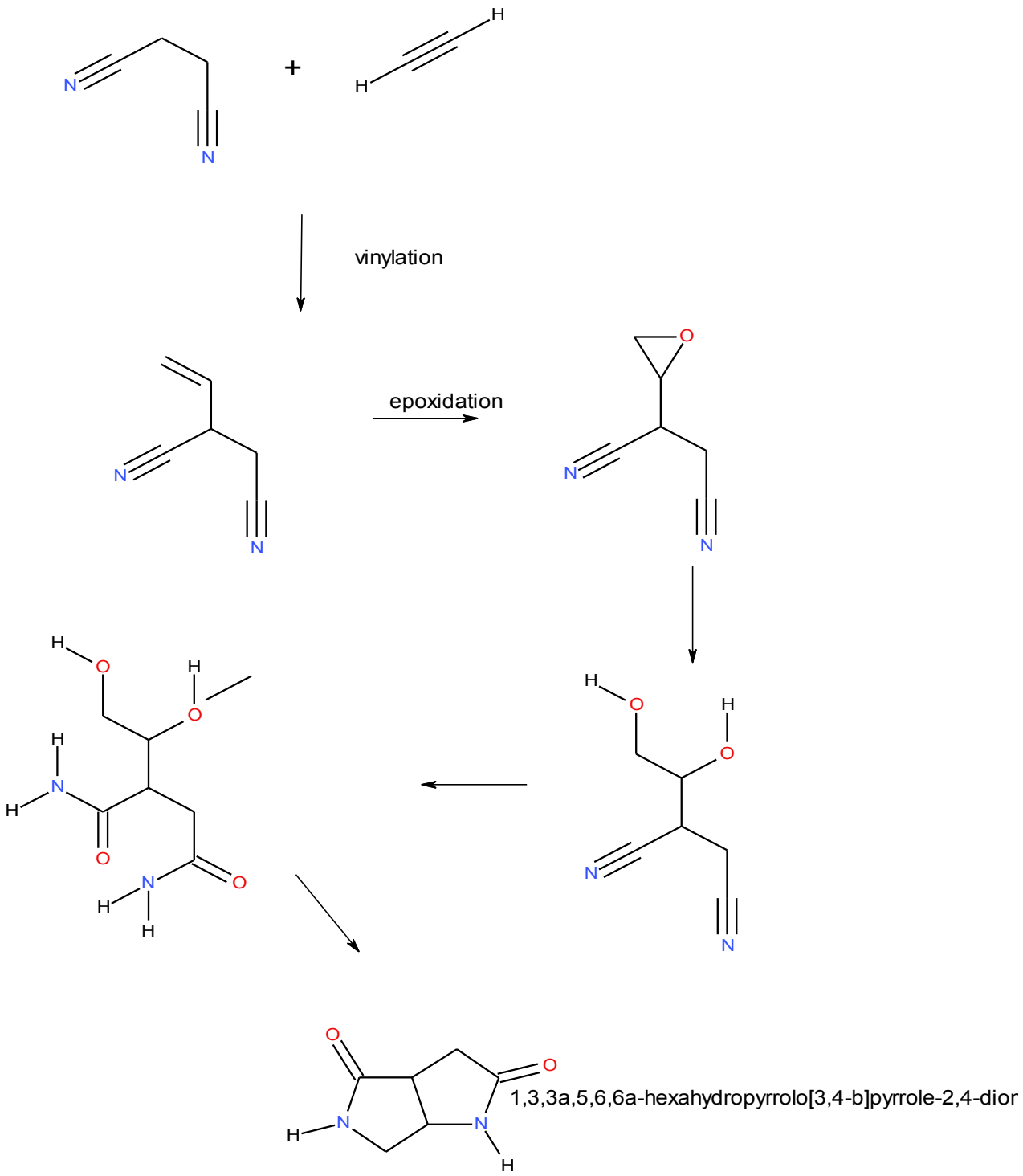
2,7-diazaspiro[4.4]nonane-1,6-dione

Scheme 3

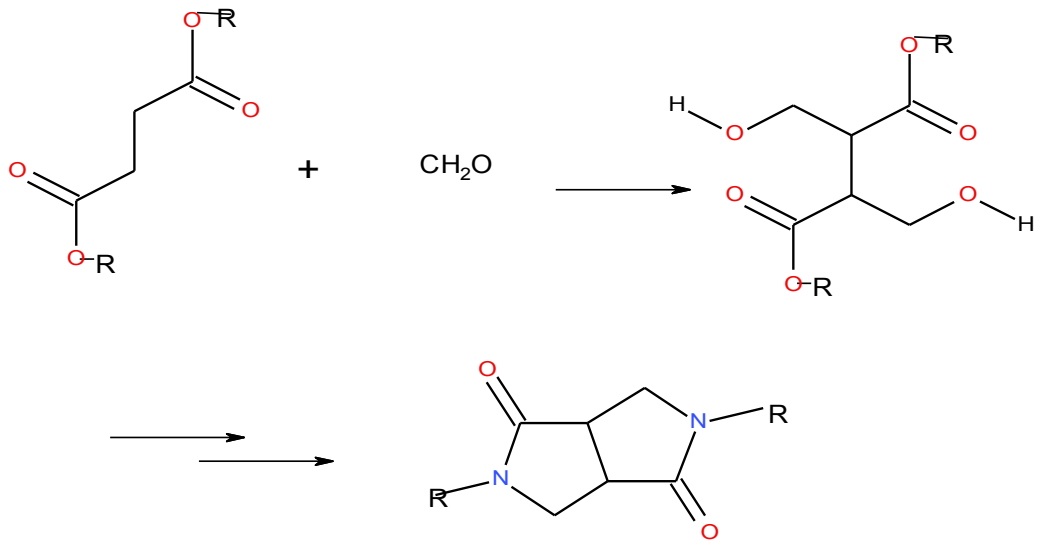


3,5-diazabicyclo[2.2.2]octane-2,6-dione

Scheme 4

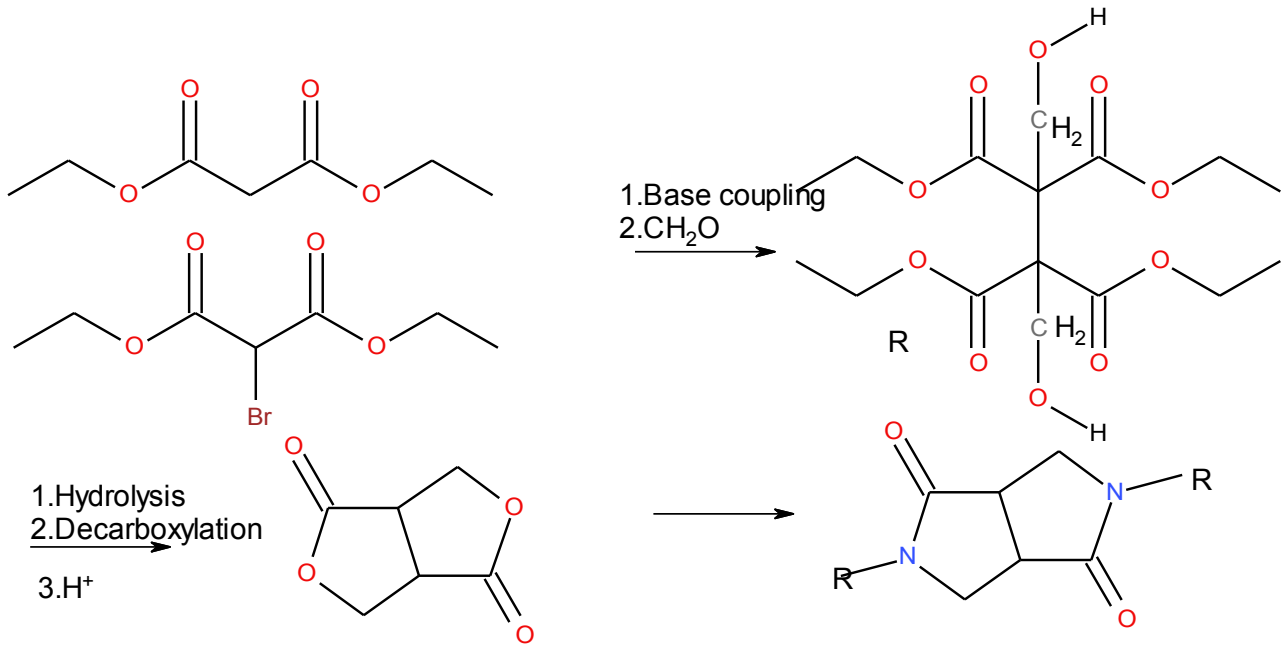

vinylation
epoxidation
1,3,3a,5,6,6a-hexahydropyrrolo[3,4-b]pyrrole-2,4-dior

Scheme 5

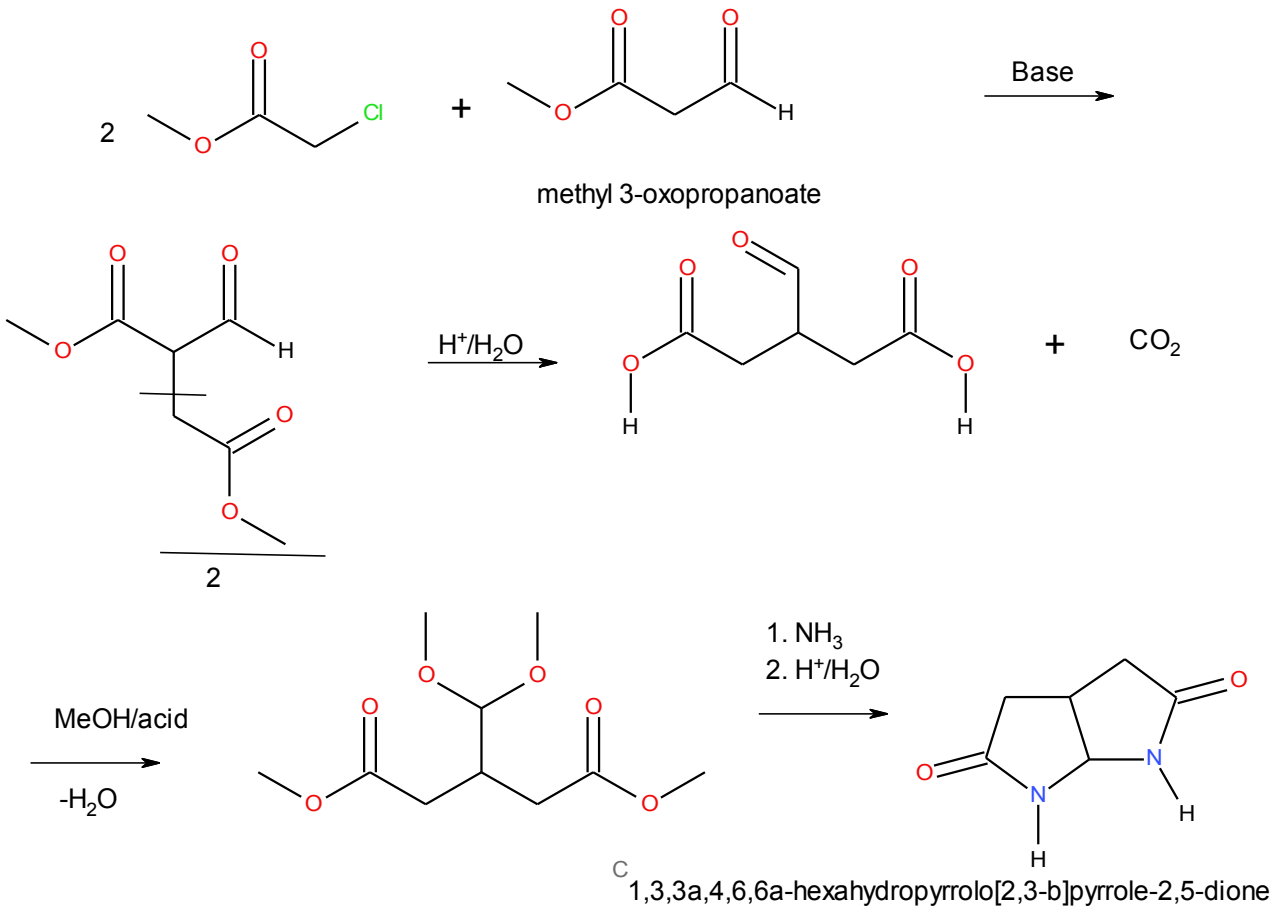


2,5-alkyl-1,3a,4,6a-tetrahydropyrrolo[3,4-c]pyrrole-3,6-dione

Scheme 6



Scheme 7



Scheme 8

Comments:
Scheme 1:

All of the RM's are commercially available. Esters do not interfere with the McMurry coupling and conversion of unhindered olefins to diols can be accomplished by several routes. The bis-BLO can also be condensed with various alkyl amines or diamines resulting in various derivatives with many useful properties. Long chain alkyl amines would result in gemini surfactants.

Scheme 2:
Diethyl 2-bromomaleate is commercially available as is malononitrile. I believe that esters are easier to reduce with hydrides than nitriles or (if hydrolyzed to amide) amides.

Scheme 3:

Condensation of ethanolamine with DEM should be facile. Conversion of the alcohols to tosylates or another good leaving group should be straightforward. Cyclization with base should proceed readily.

Scheme 4:
The Michael reaction of malononitrile with acrolien I would think is known? Careful hydrolysis should be easily accomplished. The aldehyde can be protected as an acetal if that should be necessary.

Scheme 5:
Succinonitrile is commercially available and should be vinylated when activated with a suitable base and acetylene. Conversion of the vinyl group to a diol can be accomplished by several means. The intermediate blo-dimer as in scheme 1 could be condensed with various amines.

Schemes 6 & 7:
Both depend on the ability to condense formaldehyde with activated esters. This might be difficult; however, the literature shows that malonates readily add formaldehyde.

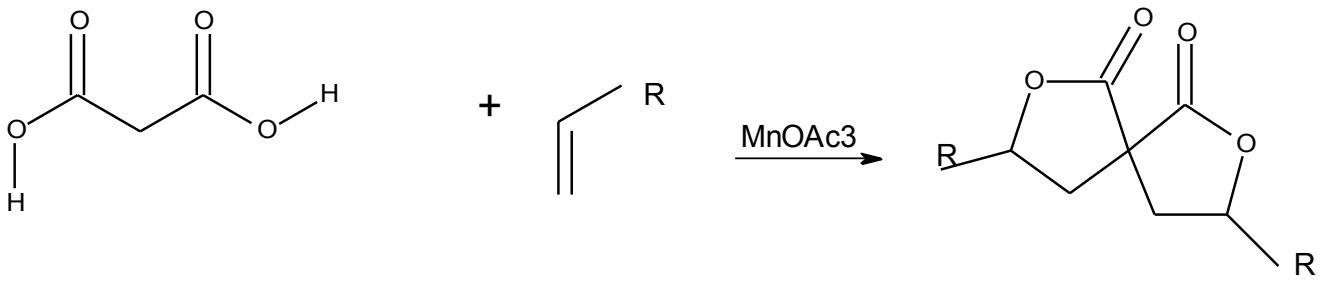
Scheme 8
Although somewhat complicated it does show one possible way to prepare the pyrrolidone dimer with the nitrogens next to each other. It depends on the availability of the 3-oxopropionate and the decarboxylation of the condensate and when the aldehyde needs to be protected?

All of the above can also be conceived of as N-Alkyl Pyrrolidone dimer derivatives. For example if the N-Methyl derivative is produced, it would be an interesting high bp solvent with very low vapor pressure, properties of value in hydraulic fluids with the added benefit of water solubility. Should the N-Alkyl group confer surface activity then this would be an approach to the Gemini surfactants which in many respects are superior to other types of surfactants. This would expand the Surfadone line of specialties.

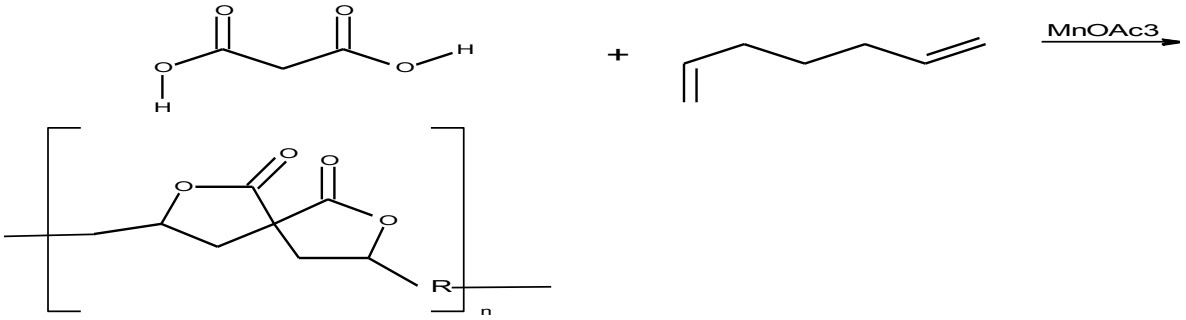
In some of the above, the reactions can be stopped at the lactone intermediate which can then be reacted with diamines to afford polyamides and under the right conditions polypyrrolidones that would compliment PVP chemistry. The lactone dimers can also react with alcohols such as diols to produce polyesters that should be more easily hydrolyzed after use, to innocuous byproducts, fitting the requirements of the growing field of polymers for drug delivery. The reaction of these pyrrolidone dimers with formaldehyde could lead to very unique porphyrins with a variety of applications.

In conclusion, dimer butyrolactones and pyrrolidones can have many applications. They can be prepared in several variations by straight forward chemistry. In fact, in a previous

report(Pyrrolidone Backbone Polymers, a pdf on my web page), I mentioned several other routes to these structures and recommend that the pdf be reviewed. For example:

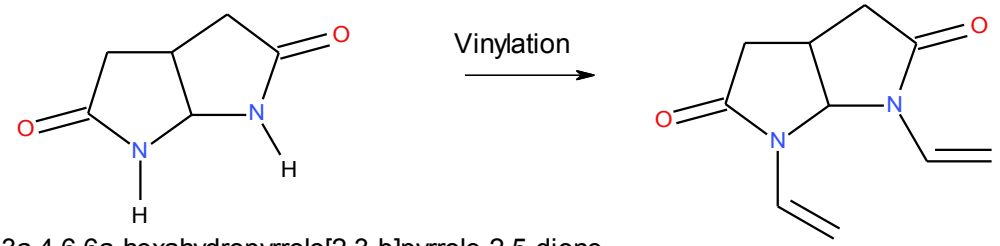


If the olefin is a diolefin then a polymer should be synthesized.

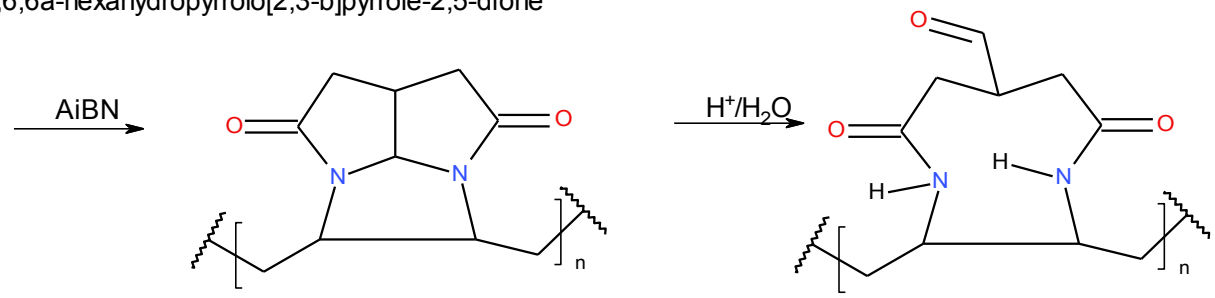


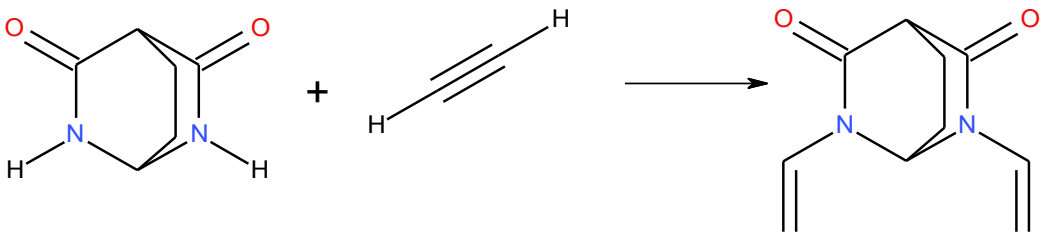
<u>Vinyl Derivatives and Cyclopolymerization</u>:

Several pyrrolidones can be vinylated. Molecular models indicate that the vinyl groups are close together. This would allow for cyclopolymerization.

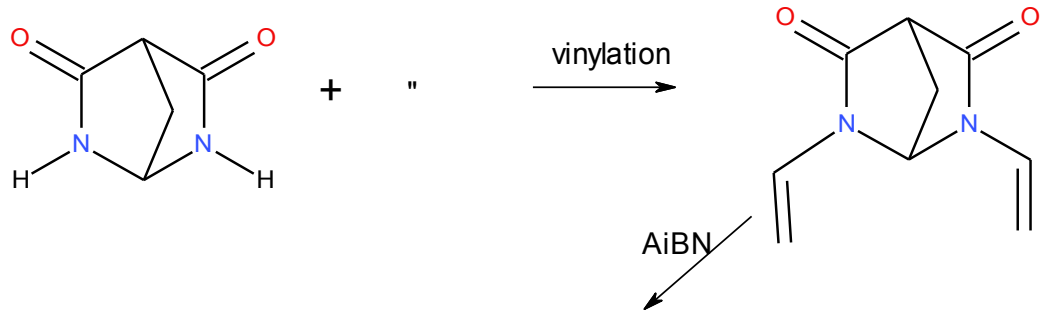


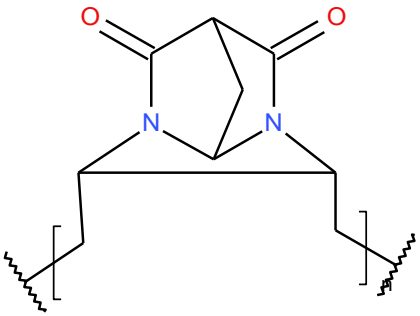
1,3,3a,4,6,6a-hexahydropyrrolo[2,3-b]pyrrole-2,5-dione



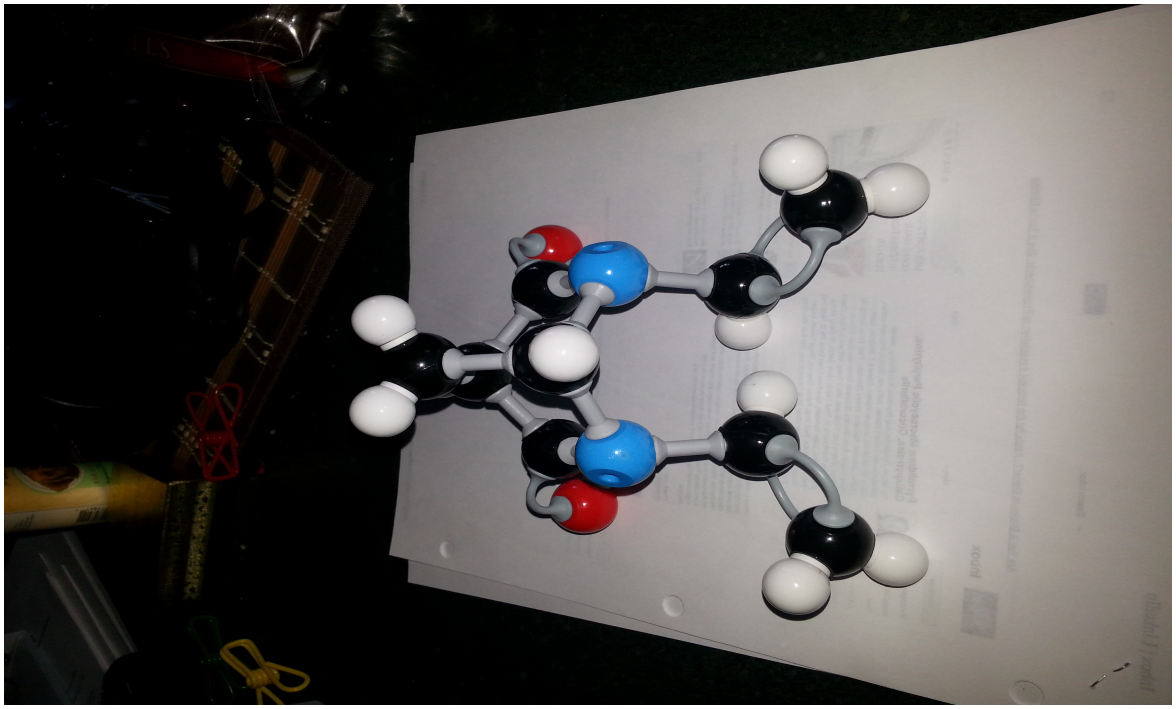


Molecular models show the vinyl groups in close proximetry





Molecular models show a less strained cyclopentane ring.



If vinyl If pyrrolidone did not exist, and someone proposed the multistep process required for its manufacture along with the process for its polymerization then I believe it would have never been scaled up as the current chemical specialty industry is very risk adverse. However, a small enterprise could succeed with new chemistry eventually selling their business for many times the investment. I would very much like to help someone bring forth new chemistry because I have enjoyed successfully doing this.

Claims:
The process to synthesize each example and it's structure as broadly as possible.
Vinylation and cyclopolymerization of bicyclic and related pyrrolidones.
Formation of Macrocyclic polymers by treatment of dimer pyrrolidones with aldehydes.
Synthesis and structures of Gemini dimer pyrrolidone surfactant derivatives.
Dimer lactones as components of polyamides or polyesters

Formation of Pyrromethane Pendant MIP's(Molecular Imprinted Polymers)

Dipyrromethanes can be synthesized from various aldehydes in the presence of excess pyrrole. Such dipyrromethanes can be converted in to porphyrins, in various ways, by further treatment with aldehydes, or pyrroles or pyrromethanes, and acids followed by oxidation. Polymerizable monomers containing aldehyde functionality can be employed to generate these dipyrrolemethanes and subsequently polymerized. Mixing these pendant dipyrromethane polymers with target molecule templates followed by for example formaldehyde cross-linking results in a cross-linked matrix from which the template molecule can be removed by suitable washing. The resulting matrix containing some porphyrogins can be treated with hydrogen peroxide to generate porphyrins and unsaturated pyrrolinone moieties.

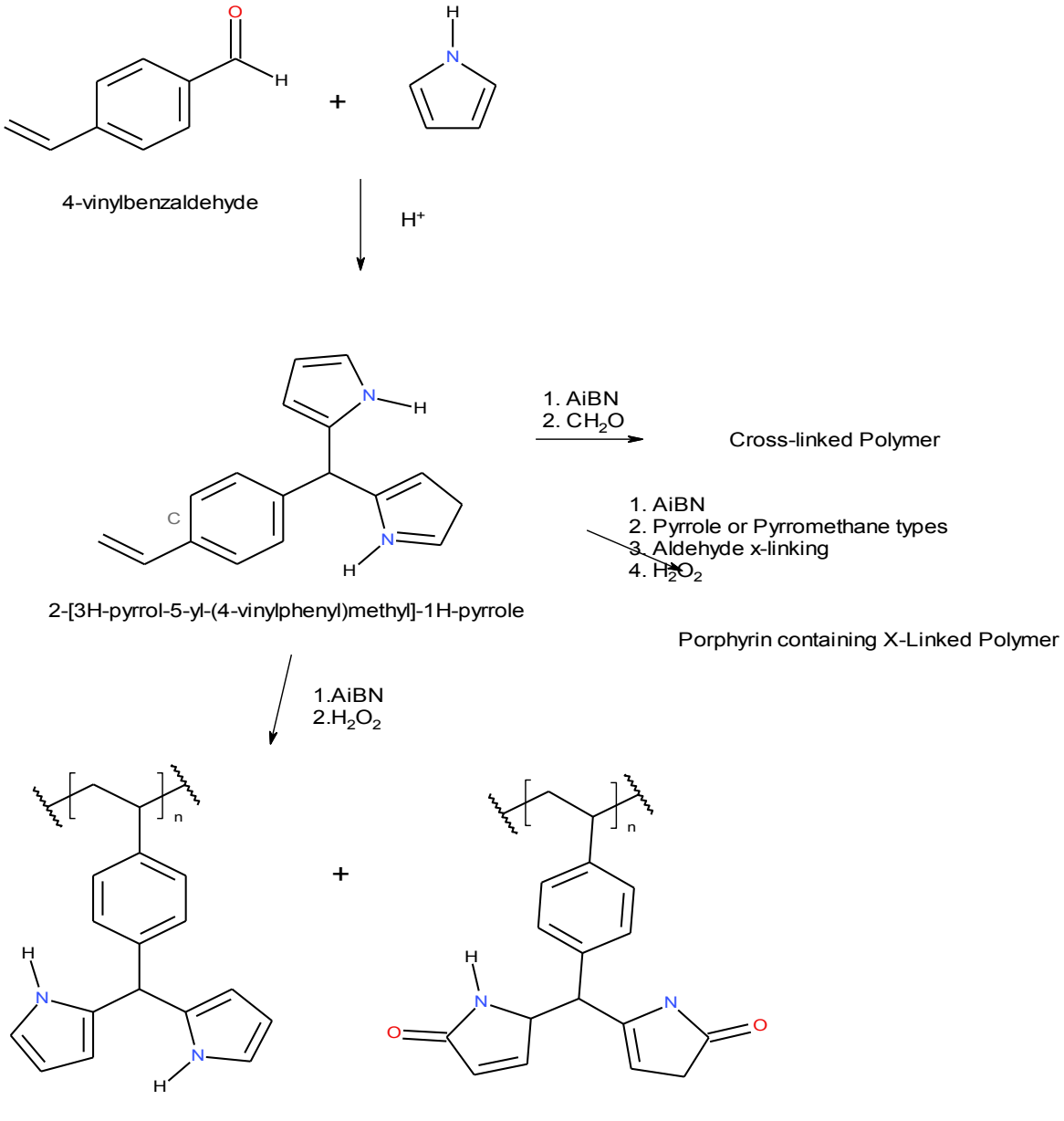
The literature concerning pyrrole derivatives converted to dipyrromethanes is extensive and such derivatives can be employed in a vinyl polymer context to more effectively accommodate template compounds. Vinyl benzaldehyde, an example of a polymerizable monomer, has been employed to prepare polymerizable porphyrins. In the present case, the dipyrrolemethane monomers, unlike the existing literature, are not converted to porphyrins and then polymerized, but polymerized first. If porphyrins are desired then they can be generated after polymerization in various ways.

Polymers containing pendant dipyrromethanes (or tri or tetrapyrromethanes) are potent moieties by themselves for template complexation without the requirement of also having porphyrins as part of the outcome of cross-linking. Therefore FR polymerization with well known vinyl or acrylic cross-linkers can result in unique MIPs even with or without subsequent treatment with additional aldehydes and acid and oxidation to form

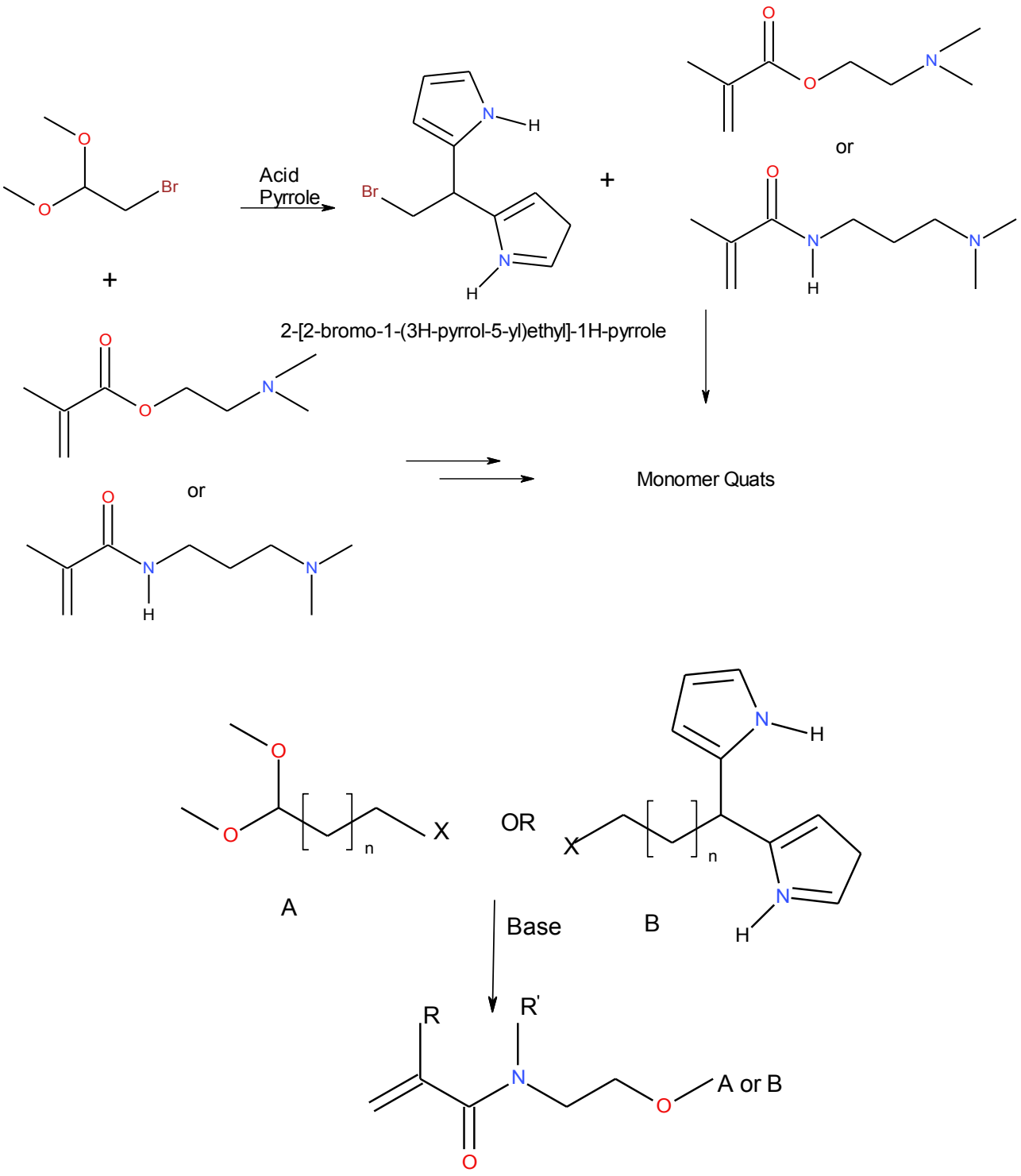
some porphyrins. Therefore, cross-linking can be accomplished in the typical way during polymerization or after polymerization or a combination of both.

Porogens are solvent in which the polymerization takes place and is required because it generates the porous MIP particles when it is eventually removed. It can be found by experimentation.

At some point in this chain of events, hydrogen peroxide at some efficacious level can be added, then conversion of some of the pendant pyrroles are transformed into unsaturated pyrrolinones. This maybe unavoidable as some oxidation would be required to convert porphyrogins to porhyrins should that be required. It is well known that hydrogen peroxide reacts with pyrroles to form pyrrolinones but other oxidizing agents could be employed to synthesize porphyrins, possibly avoiding pyrrole oxidation to pyrrolinones.
Di and polypyrromethanes complexes with a wide variety of molecules and compounds especially those the are anionic. Many drugs have anionic functionality or are salts with anionic counter-ions. Copolymerization with water soluble monomers such as vinyl pyrrolidone or acrylic acid amongst others can results in water soluble or dispersable polymers that can complex with water soluble template drugs. If said drugs are solvent soluble other comonomer choices would apply. Obviously copolymers can be fine tuned to function with selected templates.



The above scheme leaves out the template and porogen which are understood to be used along with free radical cross-linkers as necessary to successfully prepare desired MIPs.



If A is employed, then the resulting aldehyde can be used to form pyrromethanes.

The general idea here is that the bromo-dipyrrolmethane derivative or the bromoacetaldehyde dimethyl acetal or similar acetals can be employed to synthesize a wide variety of derivatives that can have an aldehyde that will condense with pyrroles. The quat monomers shown above are interesting examples and many others can be

visualized.

If porphyrin compounds are desired then after polymerization of the dipyrrolemethane quat monomer for example, various pyrroles and or di- or polypyrrolemethanes can be added to the resulting polymer solution with aldehyde to condense, catalyzed by acid, with the pendant dipyrrolemethanes. This approach may also result in some cross-linking. Work-up would entail washing out the small molecules resulting in water swollen gels in the case of quat monomers.

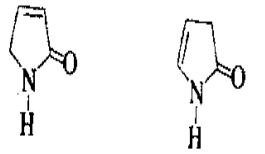
The value of these specialties is going to depend on the end uses. Since most drugs are delivered in sold tablet form, powdered MIP's excipients that template said actives to release them where desired, would be valuable. The monomers described here would be used along with comonomers, cross-linkers, porogens etc.. Water swollen gels would result when water sensitive monomers are used depending on the nature of the other monomers and cross-linkers. Non-cross-linked soluble polymers because of their positive charge would be of interest as personal care specialties and not MIPs..

References:
Rather than just issuing a list, what follows are excerpts from some relevant references. Except for the first, the rest of them can be accessed on the internet in their entirety.

3.5.3. Oxidation by Chemical Reagents

3.5.3.1. Hydrogen Peroxide, Peracids, and Other Peroxides

Angeli and Alessandri[47] reported in their early work that, in acetic acid, pyrrole polymerizes by the action of hydrogen peroxide to give ill-defined oxygenated material; so-called pyrrole black. Since this observation, the hydrogen peroxide oxidation of pyrroles attracted the attention of numerous research groups and has been subject of several reviews.[1–4] The study of the hydrogen peroxide oxidation of unsubstituted pyrrole in buffers at various pH values (1.1–9.0) has shown that pyrrole blacks are formed only in strongly acidic medium. In neutral media, 3-pyrrolin-2-one (**5.62**) is always formed, together with its isomer **5.63** in a ratio of about 9:1.[45–48] The pyrrolinones **5.62** and **5.63** are the probable precursors[49] for the dimeric,[52] trimeric,[53,54] and tetrameric[49] compounds **5.64**–**5.66**, which have been also isolated from the reaction mixtures. The mechanism of their formation is outlined in Scheme 5.7.[3] The best yields of



5.62 5.63

The above are excerpts from volume 1 pyrroles in the Heterocyclics series.

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Review

Molecularly Imprinted Polymers: Present and Future Prospective

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Abstract: Molecular Imprinting Technology (MIT) is a technique to design artificial receptors with a predetermined selectivity and specificity for a given analyte, which can be used as ideal materials in various application fields. Molecularly Imprinted Polymers (MIPs), the polymeric matrices obtained using the imprinting technology, are robust molecular recognition elements able to mimic natural recognition entities, such as antibodies and biological receptors, useful to separate and analyze complicated samples such as biological fluids and environmental samples. The scope of this review is to provide a general overview on MIPs field discussing first general aspects in MIP preparation and then dealing with various application aspects. This review aims to outline the molecularly imprinted process and present a summary of principal application fields of molecularly imprinted polymers, focusing on chemical sensing, separation science, drug delivery and catalysis. Some significant aspects about preparation and application of the molecular imprinting polymers with examples taken from the recent literature will be discussed. Theoretical and experimental parameters for MIPs design in terms of the interaction between template and polymer functionalities will be considered and synthesis methods for the improvement of MIP recognition properties will also be presented.

The following USP are also available on Google patent.

USP 5,360,880; Polymerizable Porphyrins

USP 6,872,786; Molecular Imprinted Polymeric Sensor....

USP 7,022,862; Scalable Synthesis Of Dipyrromethanes

USP 2012/0126214; ...Dipyrrin-Substituted Porphyrinic Macrocycles

USP 7,476,316; MIPs for selective removal of inorganic contaminants....

USP 7,901,948; Use Of Molecular Tweezers.....

There are many other references available but the above are typical examples.

Claims:

Free radical polymerizable Monomers are prepared from pyrroles and vinyl or acrylic substituted aldehydes catalyzed by acids, subsequently polymerized with or without vinyl or acrylic cross-linkers subsequently cross-linked with additional aldehydes or treated with additional dipyrromethanes forming porphyrinogens, which can be oxidized to porphyrins and pyrrolinones with hydrogen peroxide.

Dipyrromethanes comprising the reaction of halogen substituted acetals with pyrroles.

Acrylic tertiary amine compounds quaternized with said halogen substituted dipyrrolemethanes.

Reaction of said halogen substituted acetals with said acrylic tertiary amine compounds.

Reaction of acrylic hydroxyalkylamides with said various halogen compounds resulting in acrylic amidoalkyl dipyrromethanes.

Molecular Imprinted Polymers prepared as above except that a selected template compound is present in the porogen with or without free radical cross-linkers and potentially post polymerization cross-linked with aldehydes and acid catalysts.

Subsequent oxidation with hydrogen peroxide generates porphyrins and pyrrolinones.

I would be delighted to discuss any of these ideas with anyone interested. Please contact me at:

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Thank you