Reverse Polyvinylpyrrolidones (PVP)

By: Robert B Login

Years ago, Dr. Dandreau and I received several patents for reverse PVP whose structures are as shown in the following patents (POLYMERIZABLE PYRROLIDONYL OXAZOLINE MONOMERS, HOMOPOLYMERS AND COPOLYMERS; USP 4,933,463, Jun. 12, 1990.) (POLYMERIZABLE DERIVATIVES OF S-OXO-PYRROLIDINECARBOXYLIC ACID; USP 4,946,967 Aug. 7, 1990 also USP4,985,521 and USP 4,987,210 Jan. 22, 1991). In each case the monomers were derived starting from itaconic acid, a readily available natural product. The idea was that reversing the lactam away from the polymer backbone would result in a polymer more closely related to NMP (N-methyl pyrrolidone) than to PVP. NMP is an extremely valuable "super solvent" because of its solvency for organic compounds and its solubility both in water and many organic solvents. Obviously the business end of NMP is the lactam group which can be both nonionic, polar and ionic depending on its environment.

The advantage of reverse PVP would be greater solubility in solvents in which PVP is poorly soluble or insoluble. Furthermore PVP is not compatible nor does it complex with every pharmaceutical active and reverse PVP might fill in such gaps. Since NMP has a very good toxicity profile, would it be even better for reverse PVP? In fact low MW oligomers could be the ultimate in applications in which NMP is too volatile, such as paint removal at higher temperatures.

PVP may not be the best at complexation as the lactam is hindered, tucked away close to the polymer backbone. Although the complexes of PVP are stable, the intensity of

attractive forces between the PVP polymer and other molecules, such as iodine and phenolics, depends to a large extent on the steric properties surrounding the sites where such forces exist. Steric crowding, between the pyrrolidone lactam ring and the hydrocarbon back bone alter the intensity of attractive forces, and lower the stability of the complex. An examination of the structure of polyvinylpyrrolidone shows that steric crowding exists between the amide functional group of the lactam and the hydrocarbon backbone. This is due to the fact that the polymer is derived from vinylpyrrolidone monomer and the hydrocarbon backbone is bonded directly to the nitrogen atom of the lactam ring. Because of this crowding effect, certain molecules having a bulky nature fail to complex, or exhibit limited complexing, along the PVP chain.

The polymers claimed in the above said patents showed some of this improved reverse activity; however, in my opinion the reason why this concept didn't take off was that the monomers did not form high enough MW polymers (?), a problem that acrylamide monomers would overcome.

In previous reports on my web page (rloginconsulting.com), I have shown several potential reverse PVP ideas. But I will now concentrated my focus on amine containing candidates as shown in chart 1 (note; the acrylamide moiety is not shown for all and methacrylamide is assumed). (Meth)acrylamide is defined as both methacrylamide and or acrylamide. Chart 1 is not to be considered to be complete or exhaustive.

In addition said amines can be reacted with alkylating agents such as the allyl halides to generate diallyl tertiary amines or quaternary versions that can be readily polymerized to high MW polymers as indicated in previous reports availible on my web page.

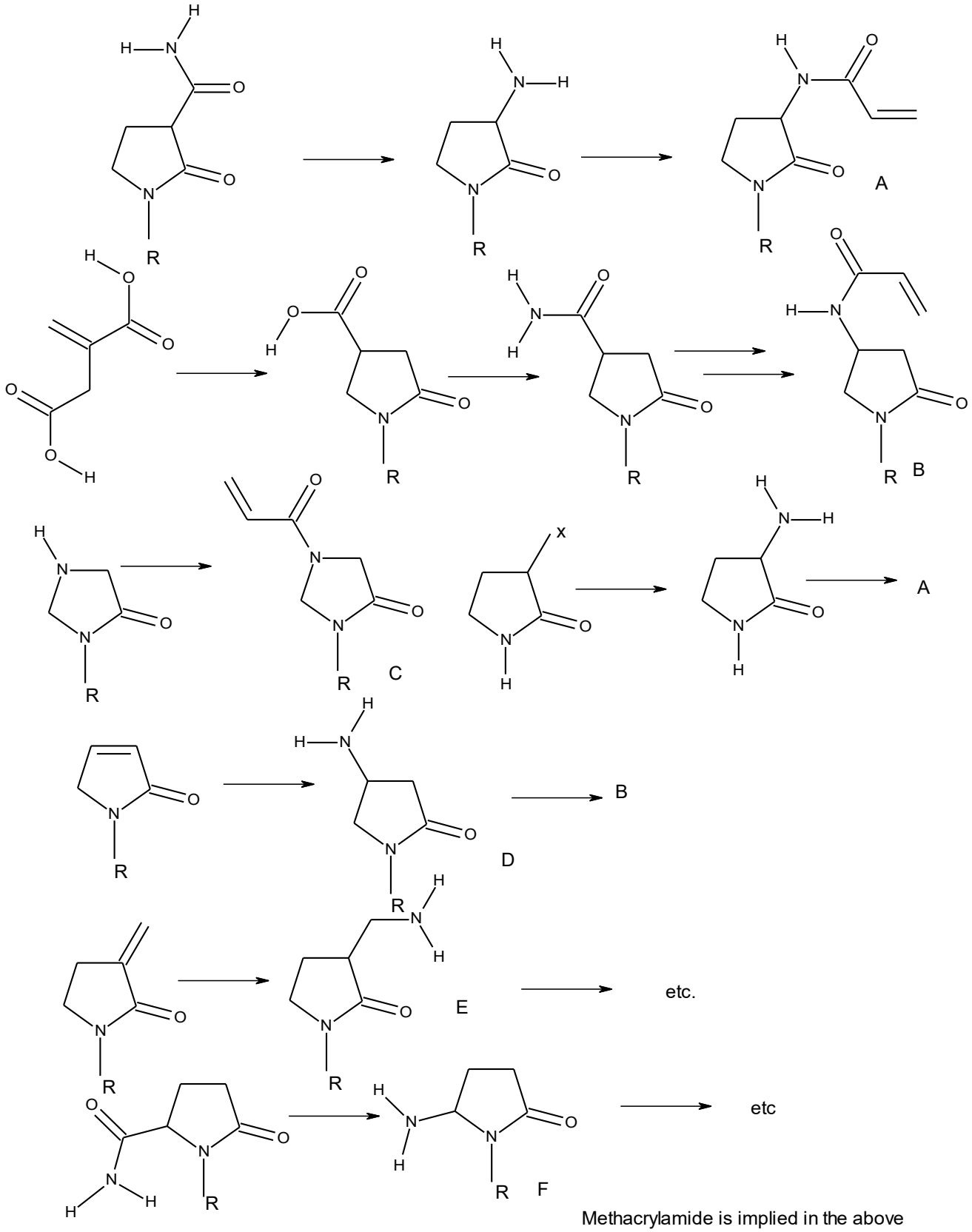


Chart 1

Amino pyrrolidones have a literature examples of which are as follows:

1. USP 2014/0187542 A1
2. Heterocycles vol. 64, p121, 2004
3. JOC 2003, vol 68,5618-5626
4. JOC 1999, vol. 64, 9668-9672
5. JOC 2009, vol. 74, 4177-4187
6. USP 5,705,456

Of the above, F in chart 1 the 5-amine of pyroglutamic acid is problimatic as its acetal like and is probably hydrolytically unstable ? However, I have found one example (Sisto et al. 4,728,725 Mar. 1, 1988) that indicates they are stable compounds and can be prepared from readily available pyroglutamate.

So far, the most interesting patent I have looked at is US 7,557,137 B2 which reveals several schemes to amino pyrrolidones. There are other related patents to the same assignee, the Bristol-Myers Squibb Company concerning this chemistry and the detail in them suggests a real interest. Unlike many other pharma patents, the examples are written in the past tense which indicates that the reactions were actually performed. Additional but less obvious methods to synthesize amino pyrrolidones or analogs are shown in chart 2:

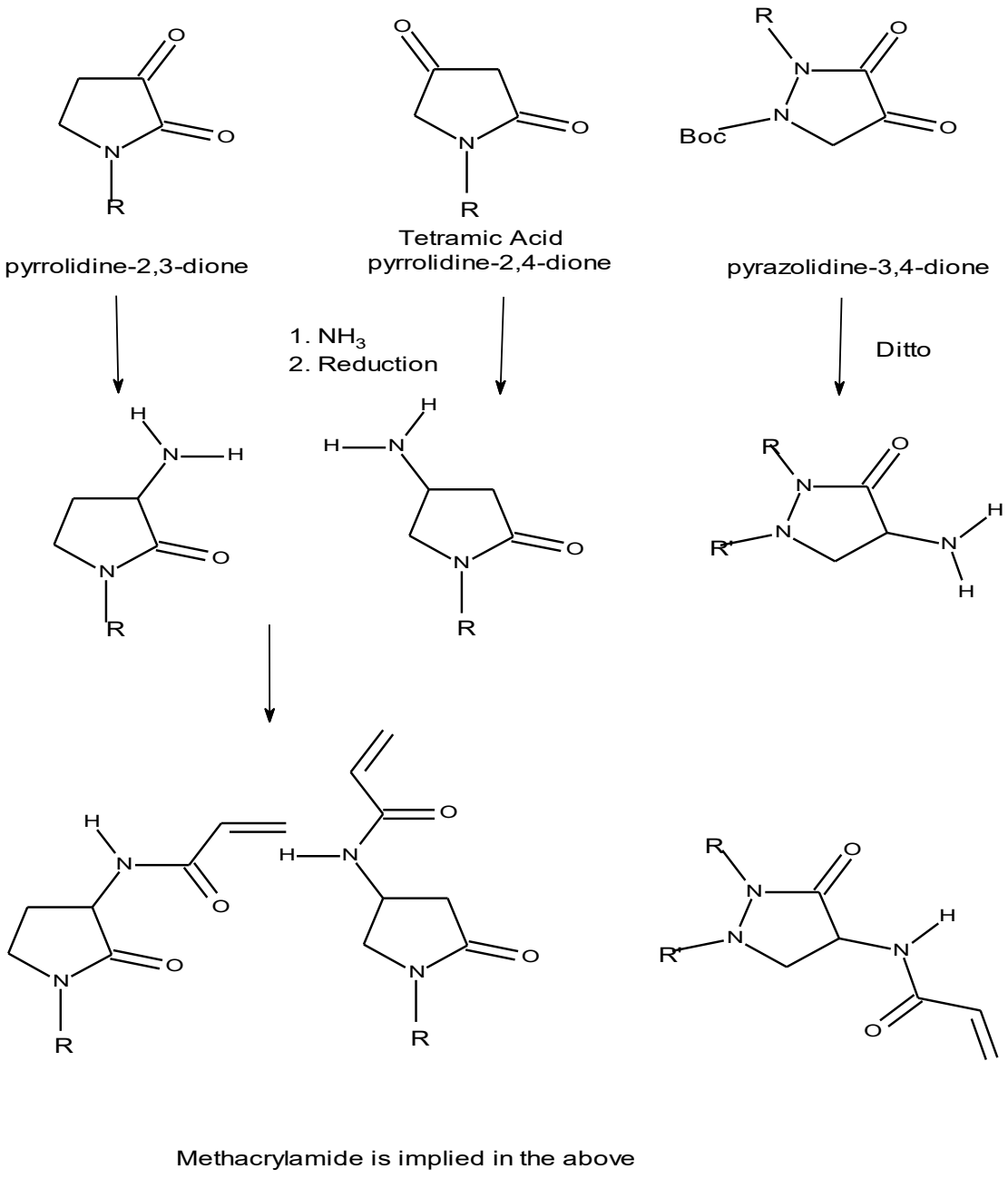


Chart 2

Now the chemistry I'm suggesting in charts 1 & 2 above is straight forward employing well known reactions. Going from amides to amines can be accomplished by several well known rearrangements such as the Hofmann, Curtius, Lossen,or Schmidt reactions.

Although its multistep, I would point out that pyrrolidone can be built one on top of another. For example:

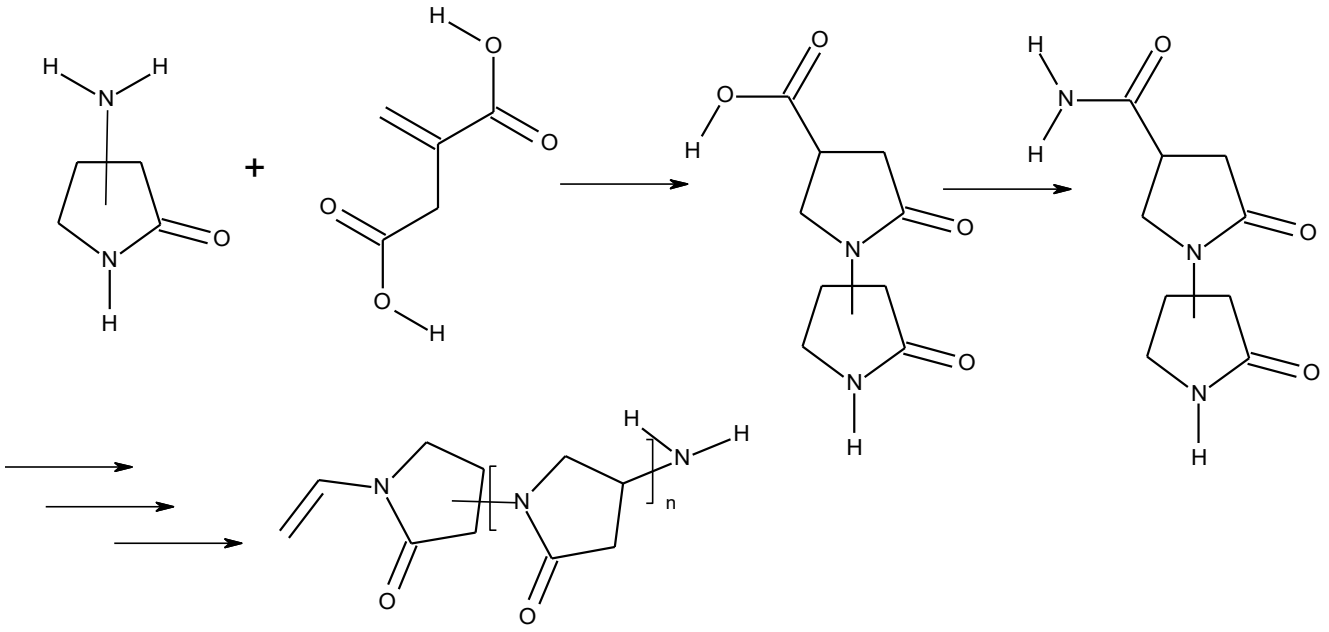


Chart 3

Any of said amino pyrrolidones can be condensed with BLO to produce bis NVP.

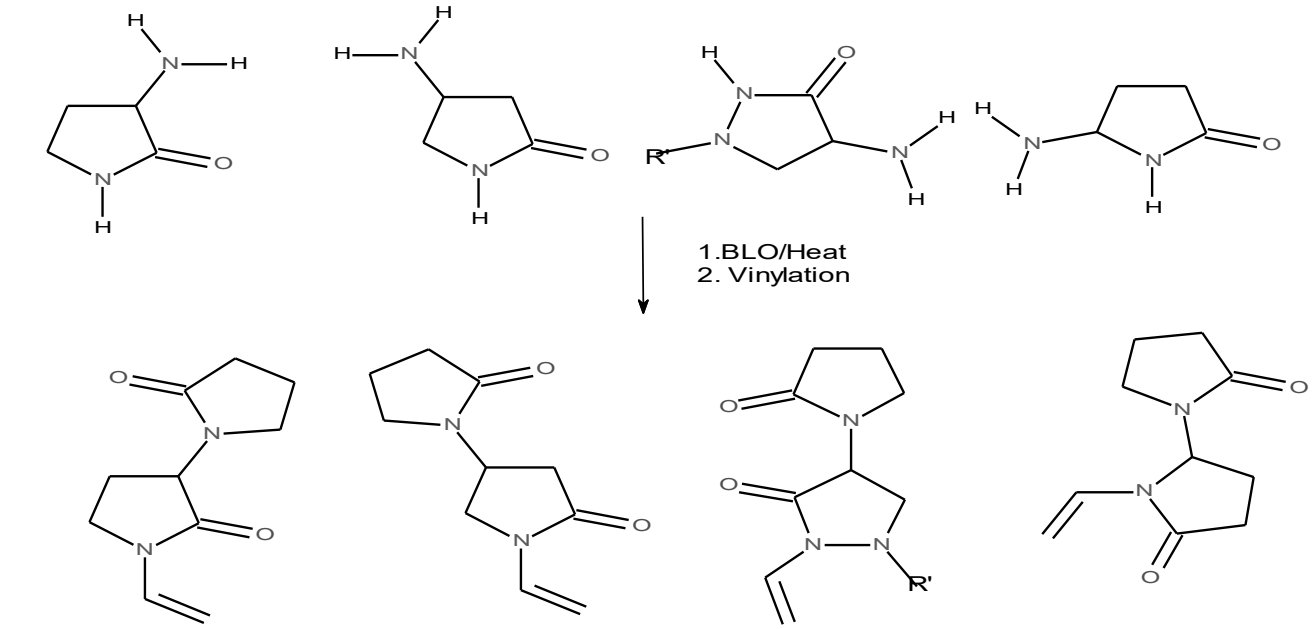


Chart 4

The subsequent polymers and copolymers would be prepared by free radical or controlled living polymerization. The reason for the bis- pyrrolidones is that the pyrrolidone further from the polymer backbone would be more available for

complexation. This is not the same as the idea for reverse pyrrolidone as previous stated but another way of improving upon PVP.

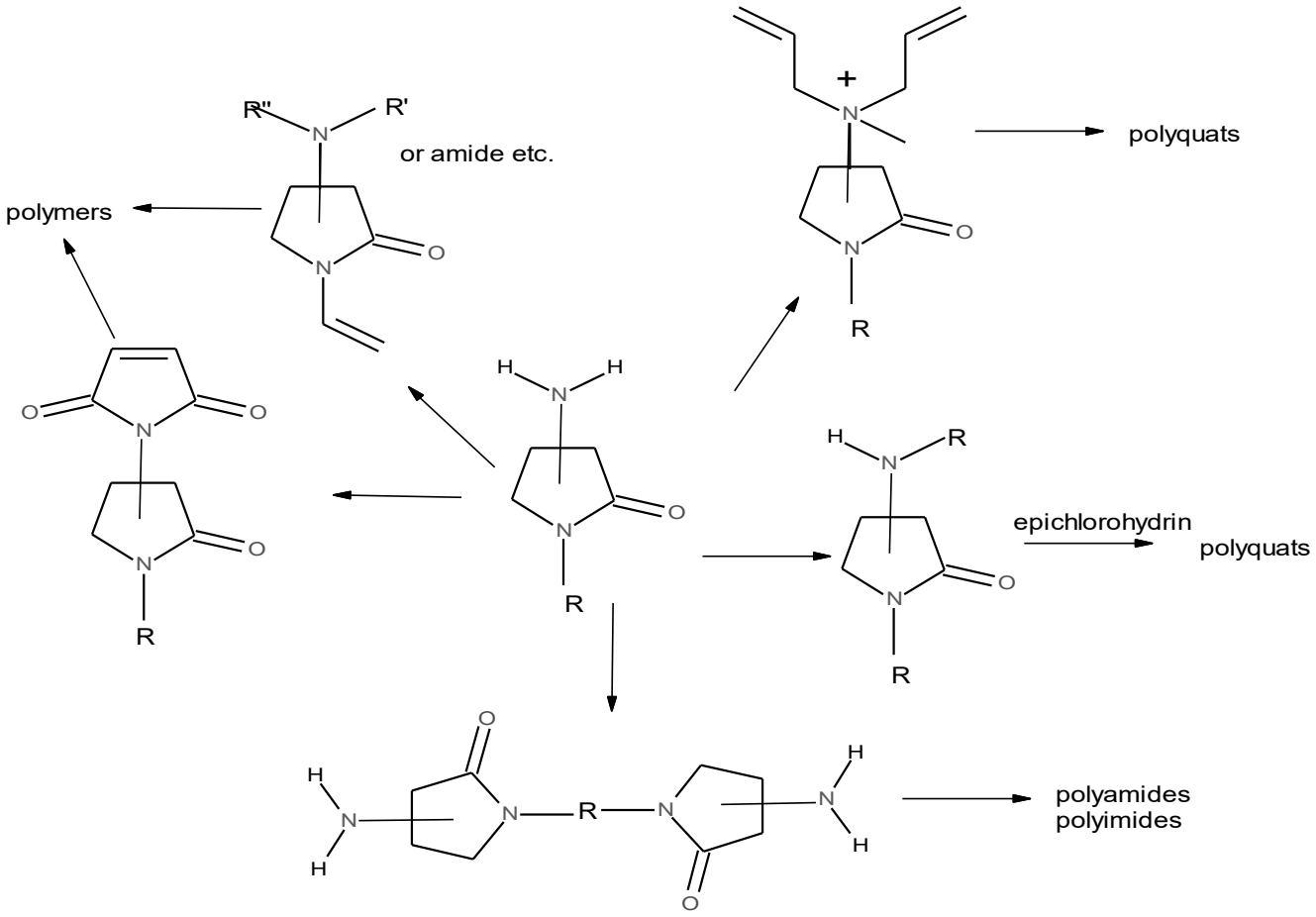
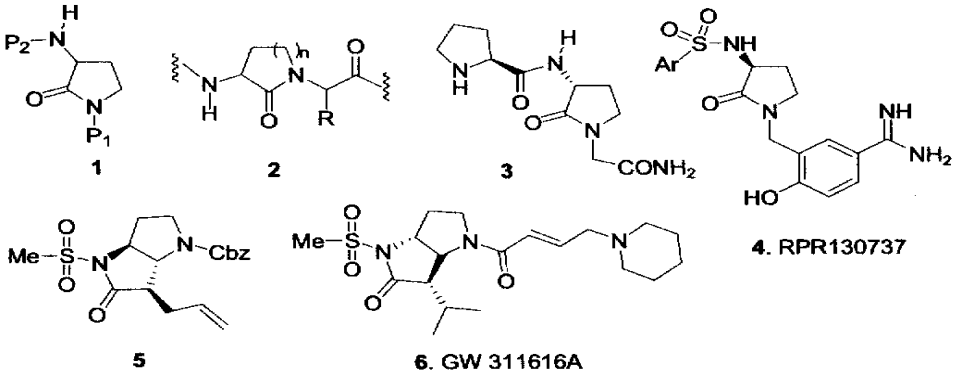
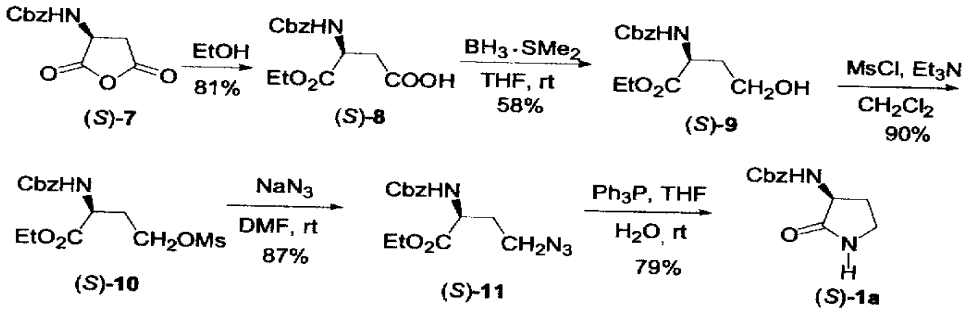


Chart 5

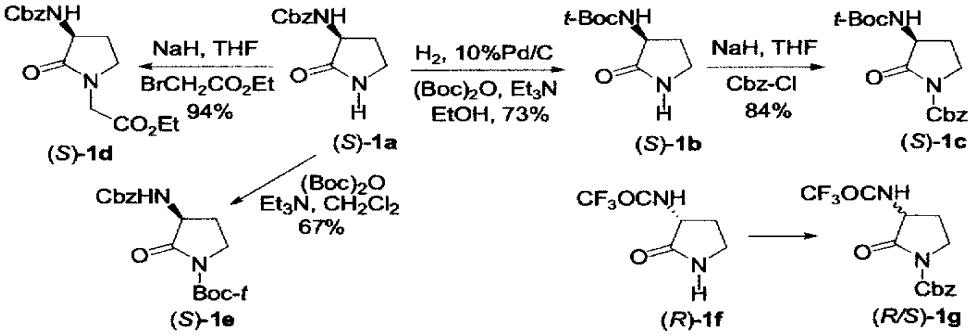
Chart 5 is designed to show the potential scope of some polymers that could be prepared from aminopyrrolidones.

Published applications for aminopyrrolidones revolve around biological activity but unlike the previously described derivatives, these are based on regioisomers with one enantiomer or the other. Structures such as the following illustrate this situation:





Scheme 1



Scheme 2

CONCLUSION

In summary, starting from (*S*)-aspartic acid, we have achieved the chemoselective syntheses of five (3*S*)-3-amino-2-pyrrolidinone derivatives (**1a** ~ **1e**) in high enantiomeric purity (as verified on **1c**). The (*S*)-3-amino-2-pyrrolidinone derivatives thus synthesized are useful building blocks for designing pharmaceutically interesting compounds.

See: Heterocycles Vol. 64, 2004, 121-128

Methods to prepare stereoisomers revolve in some cases around the Blaise reaction:

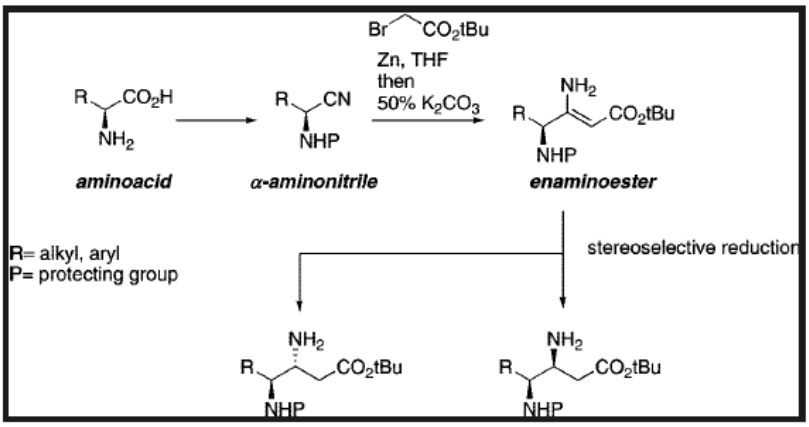
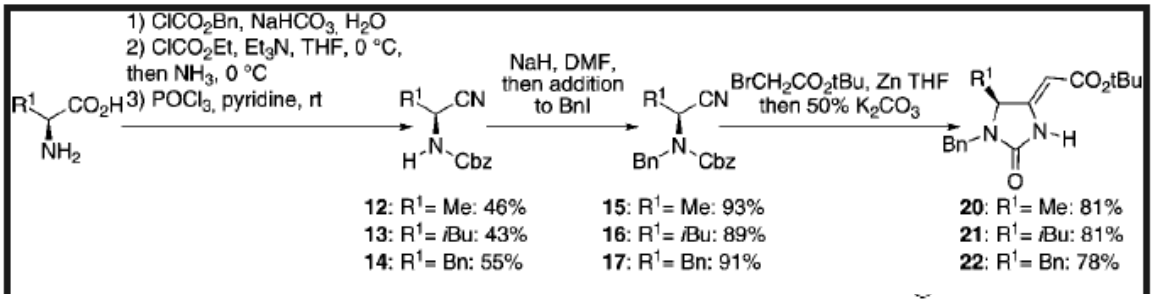
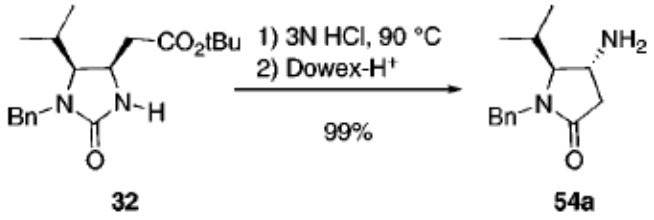


FIGURE 4. Strategy for the synthesis of β,γ-diamino acids from α-amino acids by the Blaise reaction.

Blaise Reaction with Amino Acid Derived Amino Nitriles



SCHEME 12. Hydrolysis of *cis*-Imidazolidinone 32



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Numerous patents are also concerned with the stereoisomers of these amines. For example: AMINO GROUP-CONTAINING PYRROLIDINONE DERIVATIVE US 2014/0187542 A1 and ANTI-INFLAMMATORY AGENTS US 2009/0203739 A1 and so on.

I claim:

1. Polymers and copolymers based on (meth)acrylamide substituted pyrrolidone monomers comprising wherein the (meth)acrylamide nitrogen amide is either attached to a pyrrolidone ring directly or through carbon chains or is actually part of the heterocyclic ring.
2. The polymers of claim 1 in which the said carbon chain is C1-C10 alkyl group.
3. The polymers of claim 1 in which said (meth)acrylamide nitrogen amide is attached at the 3, 4 or 5 position of the pyrrolidone moiety either directly or through said alkyl group.
4. The copolymers of claim 1 in which said comonomers are selected from acrylate, methacrylate or vinyl acetate or vinylpyrrolidone monomers in which at least 10% of said copolymers are said (meth)acrylamide pyrrolidone derivatives.
5. The polymers and copolymers of claim 1 in which said polymers are prepared by free radical polymerization generated by free radical initiators or controlled living polymerization techniques.
6. Vinylpyrrolidone monomers containing a second pyrrolidone attached to the vinylpyrrolidone through the second lactam nitrogen which is attached at the 3, 4 or 5 position on the vinylpyrrolidone ring.
7. The monomers of claim 6 polymerized with free radical initiators or controlled living polymerization.
8. The monomers of claim 6 polymerized with either vinyl pyrrolidone or vinyl esters or (meth)acrylamide, or (meth)acrylates wherein said bis-pyrrolidone monomers are at least 10% of said copolymers.