During 1972 and 74, H. Rapoport et.al. explained in detail the amazing synthesis of this type of compound and its rearrangement to 3M2P.


Scheme 1: Rapoport et. al. synthesis and rearrangement mechanism(1974). Although discovered earlier by others, Prof. Rapoport explained the mechanism of this rearrangement accurately, in great detail and should have his name associated with this rearrangement!

My proposal is based on the scheme 1 yield of 3-methylene-2- pyrrolidone(3M2P) being...
95% in the final step (12a to 3M2P with acetic anhydride) which suggests that a cost-effective synthesis of 3-carboxy-1-methylpyrrolidine (PCA) would be very valuable. If cost-effective, it might make 3M2P a commercial success.

In my previous proposal I reviewed many references dealing with the preparation of 3M2P.

With Rapoport's procedure, it looks like the itaconic route seems very reasonable. In addition, itaconic acid is prepared from bio-mass and would be a renewable green starting compound.


It seems to me that the itaconic route is the most convenient and possibly the most cost effective.


This paper shows an alternative to Ac2O.
The above is a review of the pyrrolidone route which is a three step synthesis as is the itaconic route. So this comes down to overall cost. The itaconic route also has the advantage of being green.

**Review of additional 1-Substituted 3-Pyrroolidinylcarboxylic acids;**
What follows are some of the literature dealing with PCA.


Same workers but now on a patent:
This patent describes several approaches to 3-carboxy derivatives:

Branched alkyl pyrrolidines of formula (I) are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and neuropathological disorders. Processes for the preparation and intermediates useful in the preparation are also disclosed.
The problem here is the price of the above ylid.

Also:


A possible inexpensive ylid!

Scheme 2: The obvious reactions to form 3M2P

\[
\begin{align*}
\text{CH}_3\text{NHCH}_2\text{CO}_2\text{H} + (\text{CH}_2\text{O})_n & \rightarrow \begin{array}{c} \text{CH}_3 \\ \text{N} \\ \end{array} \\
\text{CO}_2\text{Me} & \rightarrow \begin{array}{c} \text{R}_2 \\ \text{R}_1 \\ \text{R}_3 \\ \end{array} \\
\text{ylid} & \rightarrow \begin{array}{c} \text{CO}_2\text{Me} \\ \text{ylid} \\ \text{Ac}_2\text{O} \\ \text{heat} \\
\end{array} \\
\end{align*}
\]


Note: I'm assuming that 4b can be reduced to a potential Rapoport rearrangement compound.


Here again reduction of the pyrrolidone should be possible.

5. Transformations of 2 to pyrrolidine-3-carboxylic acid and $\beta^2$-amino acid derivatives

Synthesis of $(3S,5R)$-5-methylpyrrolidine-3-carboxylic acid (3) via 2g (Scheme 3)


Here again reduction of the pyrrolidone should be possible.

5. Transformations of 2 to pyrrolidine-3-carboxylic acid and $\beta^2$-amino acid derivatives

Synthesis of $(3S,5R)$-5-methylpyrrolidine-3-carboxylic acid (3) via 2g (Scheme 3)

The esters of formula III are prepared by simple condensation of an amino ester of formula IV

\[
\begin{align*}
\text{IV} & \quad \text{wherein } R \text{ and } R_3 \text{ are as defined above with a ketoester of formula V}
\end{align*}
\]


Schnettler et al.

PYRROLE-3-CARBOXYLATE CARDIOTONIC AGENTS

Primary Examiner—Douglas W. Robinson
Attorney, Agent, or Firm—Stephen L. Nesbitt

In some of the following schemes the free carboxylic acid and pyrrolidine are shown but in reality they should be shown as the corresponding salts.

Scheme 3: Some ideas that if workable should be cost-effective. A-D employ inexpensive RM's. E-G might not work because the base can attack the bromine first but still worth a try? H-J here again the bromine might be a problem; however, if larger rings are desired this could be a possibility?
Scheme 4: Another suggested synthesis. Not sure if the Br would survive the reduction? See:


I would think there are simpler ways to synthesize the 3 Br derivative? However once in hand, the rest seems straightforward.

Scheme 5: Tetramic acids are readily prepared and should be an inexpensive route to PCA's.

Scheme 6: I think if the above works, it would be a low cost route. The R groups can be selected from more active leaving groups should that be necessary. Conversion to PCA can be accomplished by the
least expensive previously illustrated reductions.

Scheme 7: Tetramic acid can be treated with a Wittig etc to form the methylene. Reduction forms the pyrrolidine which can be oxidized to the starting compound or the product.

Scheme 8: Here I present the possibility of trapping the intermediate B as a free radical polymerizable monomer. Can C be the only product or is a mixture with D also produced? Can E also undergo this rearrangement? Compounds G-J are other rearrangement possibilities? I'm suggesting that B type intermediates have a life-time long enough for the above polymer possibilities.

Scheme 9: Can itaconic acid react with ethanol amine resulting in C for example? It is known that B can be dehydrated to C. I think that G would not undergo the rearrangement? Can the N-vinyl
derivative survive the other reactions? “I” would afford an interesting crosslinker. Also the polyester E would be interesting as a biodegradable possibility?

Scheme 10: Can the pyrrolidine nitrogen be sterically blocked too favor another attached amine? Can this be applied to other diamines? Can the application of the Rapoport's rearrangement be expanded?
The potential flaw here is that the free amine can be attacked by acetic anhydride but it would inactuality be protected by neutralization with acetic acid; however, the idea seems worth a try?

Scheme 11: Pyrrolizines, indolizine and related bicyclic ideas.

Thank you for reading these proposals!

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