LACTAM ACETALS IN ORGANICS SYNTHESIS

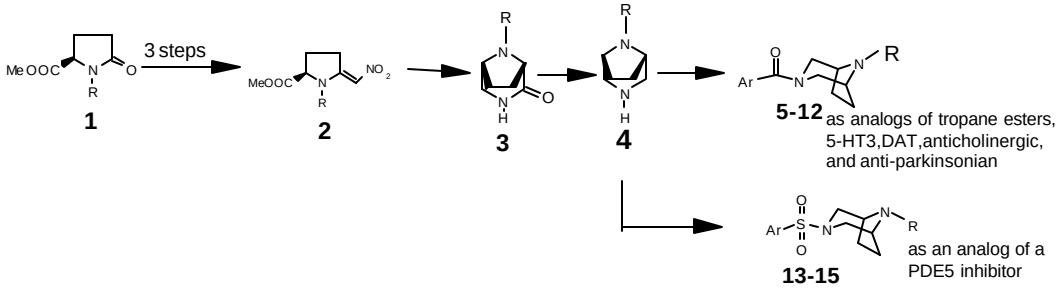
Author: Rakesh Kumar Singh, Dept. of Chemistry

The work carried out involves the exploration of some newer dimensions of activated lactam chemistry as substituted lactams or amides upon activation (such as by forming corresponding acetal) offer great potential for short path synthetic creativity and diversity generation, which is central to novel drug discovery research. However the work is hitherto unpublished for certain intellectual property reasons.The work can be divided into two parts and each part is summarized in following text.

(A): <u>Synthesis of various diazabicyclo[3.2.1]octane ring systems</u>:

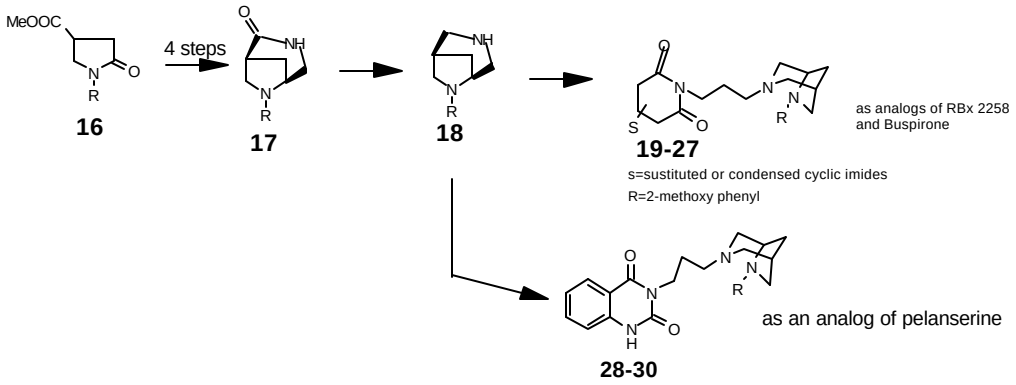
Diazabicyclo[3.2.1]octanes (**4,18**) are interesting from the point of view of the remarkable chemistry that go into their synthesis and their significant importance in medicinal chemistry as constrained analogs of piperazine or other cyclic diamine ring systems required for SAR development. Synthesis of these ring systems is very tedious and involves long drawn synthetic routes, therefore a general and easy, chirally pure and high yield access to them has long been desired. Lactams have comprehensive synthetic utility as reviewed by Nitya Anand et al in 1988. From there, it appeared possible, to construct such a ring system in a very short path, general and chirally pure way with high yields.

Lactam (**1**) was activated as thiolactam, sulfur extrusion of which afforded crucial nitroenamines (**2**) in 50-56 % yield, which were subsequently cyclized-reductively under catalytic transfer hydrogenation conditions to afford the diazabicyclo[3.2.1]octane-2-one ring (**3**) systems in 80-85 % yield. This reaction was accomplished under a novel protocol established by us using ammonium formate and Pd-C as catalyst. The new protocol is superior to classical hydrogenations in terms of higher yields, low cost ,easy monitoring of reaction progress, very short reaction time and reproducibility. Subsequent reduction of (**3**) afforded the targeted ring systems (**4**) in 70-72 % yields. All the intermediates and corresponding derivatives described below have been characterized by FT-IR, ^{1}HNMR, ^{13}CNMR, LC-MS, and elemental analysis (**scheme:1**). In the first place a number of aza-analogs (**5-12**)of various tropane class of drugs , and bicyclic analogs (**13-15**) of drugs containing piperazine have been prepared, have been evaluated in a HTS screening program to afford a useful lead in muscarinic activity .



(**Scheme:1)**

Similarly starting from lactam (**16**) following the sequence of reactions as described in (**scheme:1**) novel bicyclic amine (**18**) was prepared in 60-65 % yield. A number of bicyclic constrained analogs (**19-27**) of various drugs or leads containing aryl piperazines have been prepared and have been evaluated for adrenoceptor and anti-hypertensive activity(**28-30**) **(scheme: 2)**.They were all found inactive in screening.

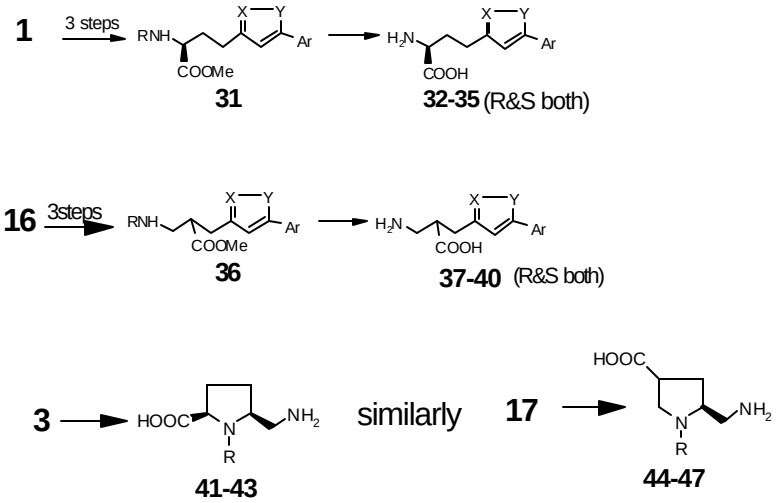


(Scheme:2)

(**B**): **A general synthesis of various classes of optically active unnatural amino acids:**

unnatural amino acids are of significant current importance for many reasons, the most important is site-specific in-vitro and in-vivo incorporation into proteins and living cells, which has been achieved by many groups, this is likely to eventually address various fundamental questions regarding folding, activity, and specificity of proteins and mechanism of life as manifested in cells. Another equally important application lies in conformational and topographical requirement studies of various bio-active peptides.

lactams (**1** and **16**) were activated as thiolactams which underwent facile sulfur extrusion reaction established by Eschenmosser et al to generate an array of various enaminones in 80% yields. These enaminones are good c-c-c electrophilic synthons which underwent regio-specific ring chain transformation reaction when submitted to bi-nucleophilic attack to afford protected optically active N^{ξ}-hetrocyclic amino acid (**31** and **36**)of a type that depends on ring size and position of substitution of lactam. These were next deprotected afford our targeted amino acid (**32-35** for α) and (**37-40** for β) in excellent yields in multi gram scale. These amino acids have been characterized fully by UV-Visible, FT-IR, ^{1}HNMR, ^{13}CNMR, LC-MS, chiral HPLC and elemental analysis. Further the hydrolysis of lactams **3** and **17** gave compounds **41-43** and **44-47** respectively(**scheme-3**)



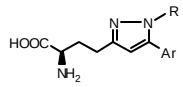
(Scheme:3)

(C) : <u>Incorporation of newly synthesized unnatural amino acids into bio-active peptides:</u>

A potent antibacterial hexapeptide (**48**) identified through combinatorial approach by Houghten R.A. et al. was chosen as model peptide. As this hexapeptide consisted of three arginine residue it was found of interest to evaluate these N-hetrocyclic amino acid towards any potential for mimicking arginine residue. Hence a library of 10 hexa-peptides has been generated through Solid Phase Organic Synthesis(SPOS) using Rink Amide as solid support, by carrying out replacement of each arginine with **32** and **33**.These peptides have been characterized by ESMS and purified by reverse phase HPLC and have been evaluated for antimicrobial activity, which however showed no activity in-vitro. Various physico-chemical studies on and around these hexapeptides are currently under progress.

Ac-R-R-W-W-R-F-NH_2 (**48**)
Ac-**X**-R-W-W-R-F-NH_2
Ac-R-**X**-W-W-R-F-NH_2
Ac-R-R-W-W-**X**-F-NH_2
Ac-**X**-**X**-W-W-R-F-NH_2
Ac-**X**-**X**-W-W-**X**-F-NH_2 (here **X**=**32**,**33**)

Where **32** and **33** stands for



32 R=H
33 R=Ph

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