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On The Ritter Reaction of Cyclic Hydroxyamines: Synthesis of Conformationally-Restricted Reduced Amide Dipeptide Isosteres

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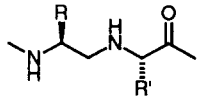
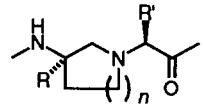
Abstract: The Ritter reactions of 3-alkyl-3-hydroxyazetidine or -piperidine derivatives give low yields of the desired products, whereas the 3-alkyl-3-hydroxy-pyrrolidine and 4-alkyl-4-hydroxy-piperidine derivatives react smoothly to give the corresponding acetamides. An alternative route to 3-acylamino-3-alkylpiperidines, which were designed as conformationally-restricted reduced amide dipeptide isosteres, was devised from nipecotic acid via a Hofmann rearrangement.

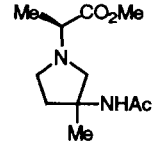
The reduced amide dipeptide isostere (**1**) has found widespread use as a transition state analogue in inhibitors of aspartic proteinases, and is probably most well-known as a scissile bond replacement in renin inhibitors.[1] More recently, its application to serine proteinase inhibitors has been demonstrated in the inhibition of isoprenylated protein endoproteinase,[2] and as a weak inhibitor of human cytomegalovirus proteinase.[3] As part of our efforts to design novel enzyme inhibitors, we were interested in synthesising conformationally-restricted reduced amide dipeptide isosteres (**2**) in which the dihedral angle (ω) is reduced from 180° in an attempt to mimic the amide bond "twisting" associated with the putative transition states of many proteolytic enzymes.[4]



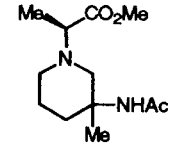
(**1**)



(**2**)



(**3**)



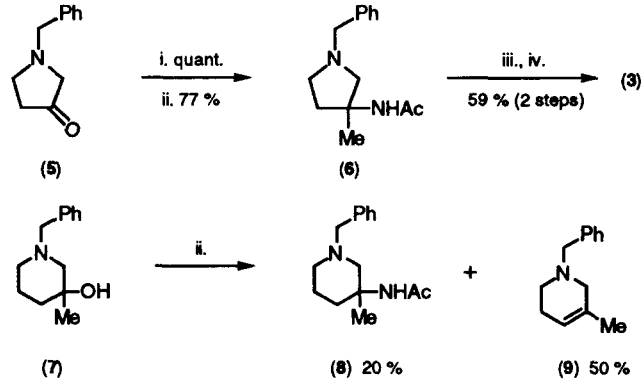
(**4**)

In particular, we were interested in preparing the five- (**3**) and six-membered (**4**) ring analogues corresponding to the dipeptide isostere Alaψ(CH_2NH)Ala in which molecular modelling predicts dihedral angles of 152° and 169° respectively.[5] Moreover, we wanted the option of extending each compound at either the *C* or *N* terminus and thus orthogonal protection was essential to allow their incorporation into longer peptide sequences.

Synthesis of compounds (**3**) and (**4**) was achieved following a literature precedent[6] for the preparation of (**6**) as shown in **Figure 1**. Thus, *N*-benzyl-3-pyrrolidinone (**5**) was treated with methyl magnesium bromide in THF-Et_2O at 0°C to give the tertiary alcohol in quantitative yield which was converted into the corresponding acetamide under the conditions of the Ritter reaction[7] in 77 % yield. Finally, removal of the benzyl protecting group by

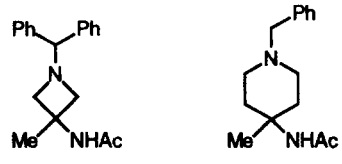
catalytic hydrogenolysis and alkylation of the secondary amine with methyl (*R*)-*O*-trifluoromethylsulphonyl lactate[8] furnished the target molecule (3) as a 1:1 mixture of diastereoisomers.

Figure 1



Reagents and Conditions: i. MeMgBr, THF-Et_2O, 0°C; ii. c.H_2SO_4, MeCN, 0-5°C; iii. H_2 Pd-C, EtOH, R.T.; iv. Methyl (*R*)-*O*-trifluoromethylsulphonyl lactate, $^iPr_2NEt$, CH_2Cl_2, R.T.

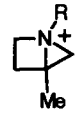
In the piperidine series, however, the Ritter reaction gave an unexpectedly low yield of the acetamide (8, 20 %) and a substantial amount of the alkene (9, 50 %). Intrigued by the very different reactivities of the five- *vs.* six-membered ring systems, we prepared *N*-diphenylmethyl-3-azetidinone[9] and subjected it to the same conditions. Interestingly, this, too, gave a low yield of desired product (10, 17 %). Moreover, when *N*-benzyl-4-piperidinone was subjected to the same two-step procedure, the acetamide (11) was obtained in an excellent 84 % overall yield.



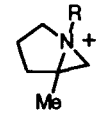
(10) (11)

The differences in yields may be attributed to the relative reactivities of the incipient carbocations and their ability to form the bicyclic ammonium ions (12) to (15); once such intermediates have been formed, other competing reaction pathways exist and models suggest that steric congestion hinders their reaction with acetonitrile to give the desired product. Formation of (12) is favoured by both the relief of ring strain in rehybridisation of C(3) from sp^2 to sp^3, and the formation of a relatively stable intermediate,[10] whilst in (14), the nitrogen atom can similarly stabilise the carbocation by the formation of a relatively stable fused aziridinium ion.[11] Thus, in both these cases, the formation of ammonium salts can facilitate other reaction pathways and hence lead to lower yields of desired products. However, intermediates (13) and (15) are two very highly strained azetidines[12] and their formation is therefore precluded energetically, leaving the carbocations free to react with the nitrile in the expected manner.

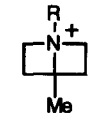
(12)



(13)

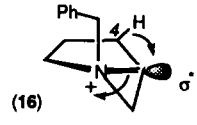


(14)

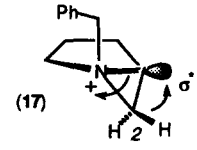


(15)

Support for the involvement of fused aziridinium ions as intermediates has recently been provided by Back's group in their work on contractions of the A-ring in azasteroids,[13] and by Harding[14] and Cossy[15] in their studies into the interconversion of the pyrrolidine and piperidine ring systems. Moreover, the regioselective formation[16] of alkene (9) further points to the intermediacy of the ammonium ion (14), since elimination of a proton from the *carbocation* would be expected to lead to a mixture of 2,3- and 3,4-alkenes. As shown below, Hofmann elimination[17] with loss of a proton from C(4) (piperidine numbering) is an *anti*-periplanar process and is only possible in (16); loss of the C(2) proton (17) is disfavoured as the orbitals which are required to overlap lie orthogonally to each other.



(16)

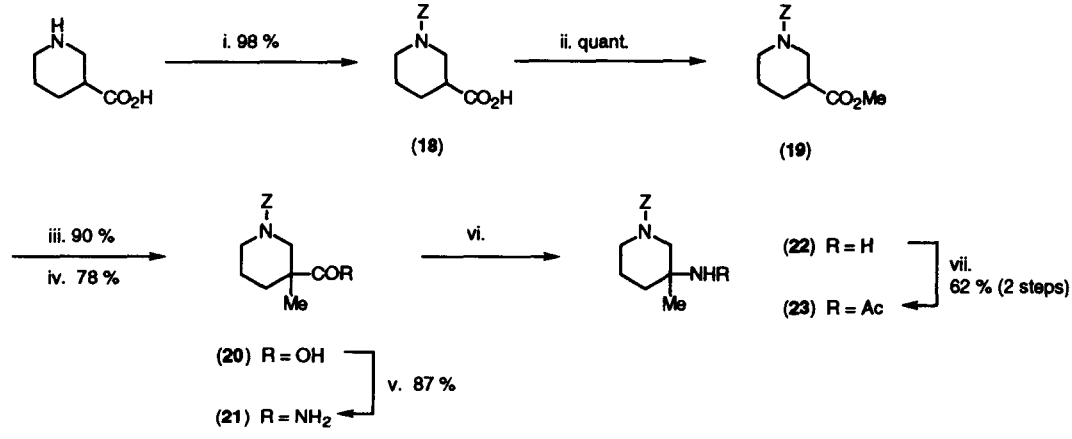


(17)

Favoured Disfavoured

Still requiring a reliable route to an orthogonally-protected piperidine, we examined a number of alternative strategies and devised a successful route from nipecotic acid which is shown in **Scheme 1**.

Scheme 1



Reagents and Conditions:
i. Cbz-Cl, $NaHCO_3$, dioxan; ii. HCl-MeOH; iii. $LiN(TMS)_2$, THF, -60°C, then MeI, DMPU, to R.T.; iv. NaOH, THF-H_2O; v. *iso*-butylchloroformate, Et_3N, THF, 0°C, then NH_3(aq); vi. $PhI(OCOCF_3)_2$, pyridine, MeCN; vii. Ac_2O, DMAP, pyridine.

Nipecotic acid was protected under standard conditions to give the *N*-benzyloxycarbonyl methyl ester (**19**) in excellent yield. Introduction of the methyl group to form the quaternary centre was achieved *via* alkylation of the lithium enolate with methyl iodide in DMPU.[18] Saponification of the ester and conversion to the amide (**21**) proceeded smoothly, and Hofmann rearrangement of the amide in the presence of bis-(trifluoroacetoxy)iodobenzene[19] gave the primary amine (**22**)[20] which was directly acetylated to give the orthogonally-protected piperidine (**23**). Compound (**23**) was then converted to the desired isostere (**4**) by hydrogenolysis of the *Z* group and alkylation with methyl (*R*)-*O*-trifluoromethylsulphonyl lactate.

In conclusion, we have seen that the outcome of the Ritter reactions of cyclic hydroxyamines is highly dependent on the relative ease of neighbouring group participation by the ring nitrogen in stabilising the incipient carbocation; this is in agreement with related work by other groups.[13-15] The orthogonally-protected reduced amide dipeptide isostere (**23**) has been synthesised in seven high-yielding steps[21] by an alternative route which should allow the preparation of derivatives having various ring sizes and, indeed, the preparation of homochiral material. The results of our studies into the use of these reduced amide replacements in enzyme inhibitors will be reported in due course.

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21. All compounds gave satisfactory analytical data and the sequence shown in **Scheme 1** could be performed on a multi-gramme scale.

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