RADICAL CYCLIZATION OF ALLYLIC HALOACETAMIDES A ROUTE TO CIS -FUSED 2-PYRROLIDONES AND PIPERIDONES*

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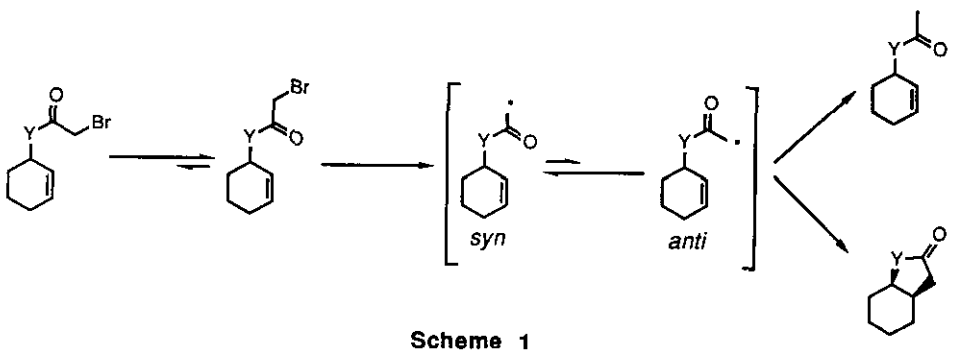
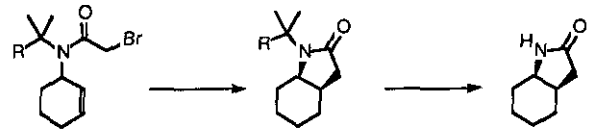
Abstract *A variety of N-protected haloacetamides undergo efficient radical cyclization to produce N-protected lactams. The protecting groups can be removed under a range of different conditions.*

Recently, we reported[1] the syntheses of various lactones using a free radical cyclization of bromoacetals and subsequent Jones oxidation. In an attempt to develop a more direct route, radical reactions of allylic bromoacetates (Y = O) (Scheme 1) were investigated. However, treatment with the usual stoichiometric tin hydride conditions (1.1 eq. Bu_3SnH, 0.1 eq. AIBN, PhH, 0.02M, 80°C) afforded only the products of simple reduction.[2,3] The ineffectiveness of the cyclization was ascribed to a preference of the initially generated radical to exist largely in the *syn* conformation,[4] making reduction the favored pathway. In support of this hypothesis we have found that the corresponding bromoacetamides[5] (Y = NR) can give good yields of addition products provided that a sufficiently large group (R) is employed. Presumably the *syn/anti* equilibrium (and therefore the cyclization/reduction ratio) is influenced by the steric nature of the group attached to nitrogen. An efficient radical cyclization route to cis-fused pyrrolidone and piperidones is interesting because of the widespread occurrence of related systems in natural products.[6]



Scheme 1

Treatment of bromoacetamide[7] **1** (Scheme 2) with stoichiometric tin hydride gave protected lactam **3** (77%) along with a trace of reduction product (2%). Similarly, bromoacetamide **2**, on reaction with tin hydride,[8] produced lactam **4** (73%) with no sign of any reduction. Next, in order to generate the more synthetically useful lactam **5**, the *tert-butyl group* was removed by subjecting **3** to the conditions reported by Rosenberg and Rapoport[9] (H_2SO_4, 50°C→R.T.) to give **5** (85%). The dimethylbenzyl group could also be efficiently removed. Thus, treatment of **4** with sodium in liquid ammonia as described by Guthikonda[10] produced the same lactam **5** (88%).



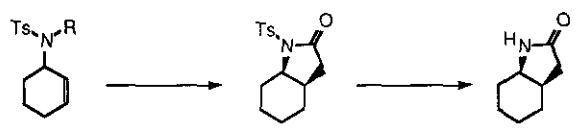
1 R = Me
2 R = Ph

3 R = Me
4 R = Ph

5

Scheme 2

Although the two preceding blocking groups were effective in promoting the cyclization reaction, it was felt that they would be unsuitable for a general methodology because of potential problems associated with their introduction and removal. What was required was a group that could be both easily introduced and easily removed, preferably starting from an unsubstituted allylic amine. In this context, bromoacetamide **7** (Scheme 3) was prepared from tosylamide **6** (5.4 eq. NaH, 2 eq. $BrCH_2COBr$, PhH, 80°C, 72%) and allowed to react with tin hydride to give the N-tosyl lactam **8** in excellent yield (75-85%). Following the procedure of Closson *et al.*,[11] the tosyl group was removed on treatment with sodium naphthalenide to give **5** (79%).



6 R = H
7 R = $BrCH_2CO$

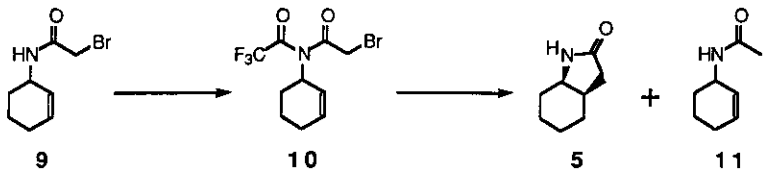
8

5

Scheme 3

The trifluoroacetyl group (Scheme 4) was found to be an especially efficient protecting group. Upon stirring a carbon tetrachloride solution of bromoacetamide **9** with trifluoroacetic anhydride[12] (3 eq.) in the presence of a 1.1 eq. of poly (4-vinylpyridine)[13], nearly pure bromoimide **10** (95%) was obtained after filtration through Celite® and evaporation of the solvent. Crude **10** could be treated with tin

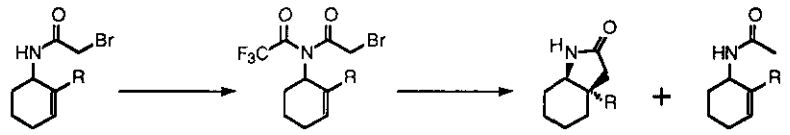
hydride (0.01M) and worked up with saturated aqueous potassium fluoride[14] to give deprotected lactam **5** (80-90% from **9**) directly, together with a small amount of reduction product, acetamide **11** (0-8% from **9**), also deprotected. Apparently, in addition to facilitating workup by precipitation of tin residues, the potassium fluoride solution was basic enough (pH 8) to effect hydrolysis of the initially formed imides.



9 **10** **5** **11**

Scheme 4

The effectiveness of the trifluoroacetylimide radical cyclization route to lactams led us to examine the scope of the reaction. We were especially interested to find how effectively quaternary centers could be produced, using the trifluoroacetyl blocking group. The substituted allylic amines required for this study were prepared using a combination of the methods of Laurent *et al.*[15] and Hassner *et al.*[16] Thus, bromoacetamide **12** (Scheme 5) was subjected to the trifluoroacetylation-cyclization-deprotection sequence as described above to give lactam **14** (65-75%) and acetamide **16** (9-22%). More efficiently, use of stoichiometric germanium hydride, a less reactive hydrogen atom donor,[17] (1.3-1.5 eq. Ph_3GeH, 0.3 eq. AIBN, PhH, 0.02M, 80°C) resulted in a larger amount of **14** (82%) together with some uncyclized **16** (6%). In a similar manner, with either tin or germanium hydride, lactam **15** (50-69%) and acetamide **17** (14-27%) were produced from bromoacetamide **13**.



12 R = Me
13 R = Ph

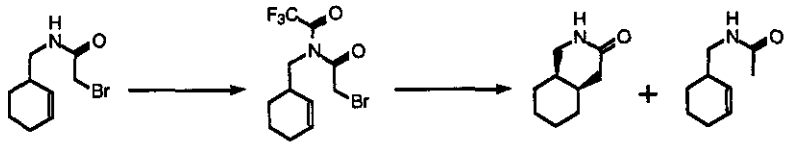
14 R = Me
15 R = Ph

16 R = Me
17 R = Ph

Scheme 5

As a further example of the generality of the method, we show that it is also useful for the construction of six-membered lactams: homoallylic bromoacetamide **18**[18] (Scheme 6) was subjected to the same three-step sequence, to give (tin hydride) lactam **19** (65%) and acetamide **20** (24%). In this case, use of germanium hydride resulted in an increased amount of cyclization and only **19** could be found (85%). Of note is the

apparent absence of any product arising from 1,5-hydrogen atom transfer. This can be contrasted with the results previously obtained with the homoallylic bromoacetal system.[1] It is likely that the two additional sp^2 centers in the connecting chain make the required essentially collinear arrangement[19] of attacking radical and transferable hydrogen harder to achieve, with a sufficient rate reduction so that hydrogen transfer no longer effectively competes with the cyclization or simple reduction pathways.



18 19 20

Scheme 6

ACKNOWLEDGMENT

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REFERENCES AND NOTES

* This paper is contributed in honor of Professor D.H.R. Barton whose energetic enthusiasm for chemistry contributes so much to our enjoyment of the field.

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