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A Versatile Radical Based Synthesis of γ–Lactams Using Nickel Powder /Acetic Acid.

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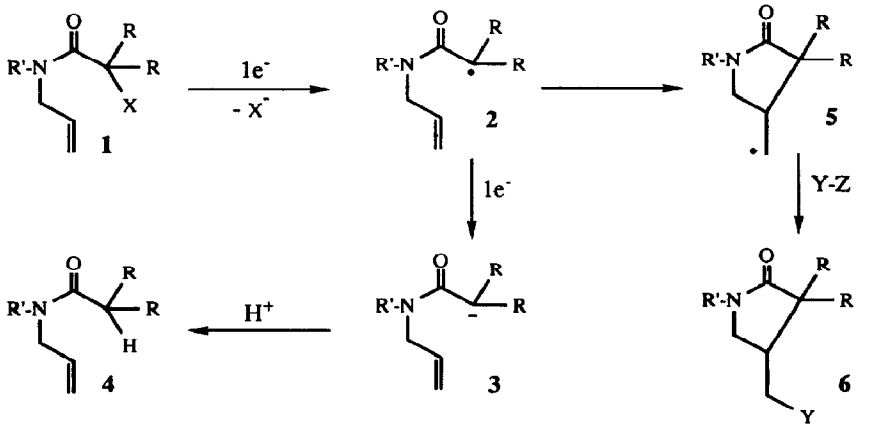
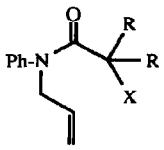
Abstract: A variety of γ–lactams are obtained from suitable of α-haloamides by a radical cyclisation mediated by a combination of nickel powder and acetic acid.

We have recently reported that nickel powder, in combination with an organic acid such as acetic acid, constituted a very mild reducing agent capable of cleaving an oxime ester into a carboxylate ion and an iminyl radical. The key feature of this system is that the iminyl radicals thus produced is sufficiently long-lived to undergo useful radical reactions, and this property was applied in a practical procedure for inverting the 13-methyl group in 17-ketosteroids.[1] We have now found that this combination is capable of reducing certain halogenated derivatives to give carbon centered radicals which can also be captured in a variety of ways. In this Letter, we wish to describe an efficient, versatile, and yet practical synthesis of γ-lactams from suitable haloamides, which is different from our earlier approach based on a novel radical chemistry of xanthates.[2] The synthesis of lactams using radical reactions is becoming increasingly popular,[3] but it is the very recent appearance of a paper on the electrochemical reduction of haloamides in the presence of nickel complexes[4] that prompts us to disclose our preliminary findings in this area.

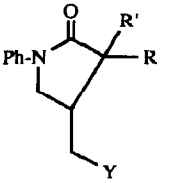


Scheme 1

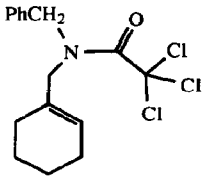
Our present approach hinges upon the mechanistic reasoning outlined in scheme 1. Thus, reduction of the haloamide **1** gives the corresponding radical 2 which, with most reducing agents, is converted into the equivalent of anion **3** (and hence to amide **4** upon protonation) too rapidly to be of any use in a radical based synthetic process. We have found that with nickel powder / acetic acid under appropriate conditions, the second electron transfer step is sufficiently slow so that the intermediate radical can cyclise into lactam **5**. The sequence may then be terminated in a number of ways, allowing in this manner the introduction of a variety of functional groups in the last step.



7, R= X= Cl
10, R= Me; X= Br



8, R= R'=Cl ; Y=H
9, R= Cl; R'=Y=H
11, R= R'=Me; Y=H
12, R= R'=Me; Y=Br
13, R= R'=Cl ; Y=SePh
14, R= R'=Me; Y=SePh
20, R= R'=Cl; Y=CN
21, R= R'=Y=Cl



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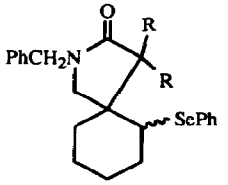
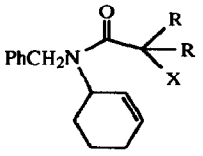
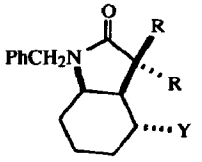


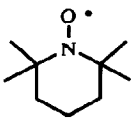
18, R= R'=Cl
19, R= Cl; R'=H





15, R= X= Cl
24, R= Me; X= Br
29, R= Cl; X= H

16, R= Cl ; Y= SePh
22, R= Cl; Y=H
23, R= Cl; Y=Br
25, R= Me; Y=Br
28, R= Cl; Y= OH (α+β)



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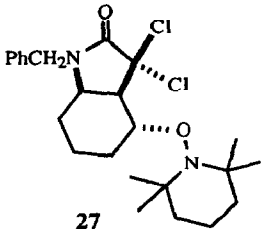

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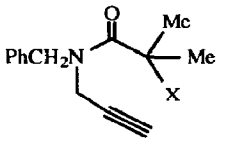
The following examples will illustrate some of the various possibilities. Thus, slow addition (over ca. 2 hours) of N-allyl trichloroacetanilide **7** to an excess of nickel powder in a refluxing mixture of acetic acid and 2-propanol and further heating for 3 hours gave lactams **8** and **9** in 20% and 29 % yield respectively. Over-reduction to monochlorolactam **9** could be largely suppressed by adding the starting trichloroacetamide all at once and by carefully monitoring the reaction. Under these conditions, the yield of **8** increased to 56%. 2-propanol acts not only as a solvent but also as a hydrogen atom donor, quenching thereby the carbon radical formed upon cyclisation (cf. **5** in scheme 1). The yield of **8** could be further improved by using a better hydrogen donor such as a thiol. Thus, in the presence of 3 equivalents of tert-dodecanethiol, the yield of **8** jumped to 76%. The fact that the starting trichloroacetamide is selectively reduced in the presence of the product, a dichlorolactam, illustrates the unique properties of our system.

Dimethylbromoacetanilide analogue **10** also reacted smoothly with nickel powder in acetic acid-2-propanol, but the major product turned out to be bromolactam **12**, isolated in 68% yield. The expected reduced product **11** was the minor component (23%) of the mixture. Compound **12** arises in all likelihood by a radical chain bromine atom transfer process (Kharasch type reaction[5]) where the nickel / acetic acid system is simply behaving as an efficient initiator. When 2-propanol was replaced by cyclohexane, a much

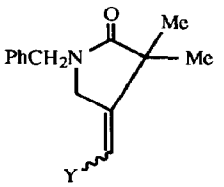
poorer hydrogen donor, none of the reduced lactam **11** was formed, and bromide **12** became the sole product (85%). In contrast, when the reaction was repeated in the presence of tert-dodecanethiol, it is the reduced lactam **11** that strongly predominated, and could be isolated in high yield (82%).

Hydrogen donation is not the only way to terminate the sequence. For example, transfer of a phenylseleno group can be accomplished simply by adding an excess (3 eq.) of diphenyl diselenide. In this way, selenides **13** and **14** were obtained from **7** and **10** in 55 and 73 % yield respectively. Bicyclic and spiro lactams could also be prepared under analogous conditions, as illustrated by the conversion of trichloroacetamide **15** into lactam **16** in 91% yield and trichloroamide **17** into a mixture of **18** (35%) and **19** (45%). For reasons which are not yet clear, partial over-reduction could not be avoided in the latter example. Nevertheless, it is noteworthy that under the reaction conditions diphenyl diselenide itself is apparently not reduced into phenylselenol.

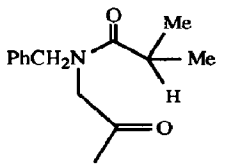
We have also succeeded in transfering a cyano group, albeit in only modest yield, by incorporating an excess (10eq.) of ethyl cyanoformate ($NCCO_2Et$) into the medium. When the reduction of **7** was carried out in 2-propanol as solvent, a mixture of nitrile **20** (30%) and the unsubstituted derivative **8** (35%) was obtained. Clearly in this case, the competition between transfer of the cyano group and hydrogen abstraction was slightly more in favour of the latter process. When cyclohexane was used as solvent, the yield of nitrile **20** decreased slightly (25%) and another side-product appeared. This turned out to be the trichlorolactam **21** (45%), again a product of halogen transfer. Transfer of a cyano group from methyl cyanoformate has been described in an earlier study by Tanner and Rahimi.[6]



30, X= Br
34, X= H



31, Y= H
32, Y= Br



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Most aliphatic or aromatic chlorides, bromides, and even iodides are not affected (or reduced very slowly) by the combination of nickel powder and acetic acid. Such mildness and selectivity can be used to perfom some interesting transformations. It is remarkable, for instance, that bromotrichloromethane (3eq.) can be included as a bromine transfer agent for the last step in the sequence starting from **15** which now leads to bromodichlorolactam **23** in 52% yield instead of the simply reduced product **22**. The obtention of such mixed halides as **23** by a Kharasch reaction would have required as starting material the corresponding bromodichloroacetamide (i.e. **15**, with X=Br and R=Cl), a rather inaccessible derivative. The possibility of adding bromotrichloromethane to the mixture can in fact be used to improve the yield of the Kharasch type bromine transfer reaction. Thus heating compound **24** alone in with nickel powder / acetic acid / 2-propanol gave bromide **25** in only 58% yield, whereas in the presence of 3 eq. of bromotrichloromethane the yield of **25** increased to 78%.

In yet another variant, the carbon radical from the cyclisation of **15** could be captured with 2,2,6,6-tetramethylpiperidinyloxy **26** (TEMPO), itself apparently not affected by the reducing system, to give hydroxylamine **27** as a single isomer in 60% yield. The hydroxylamine group is not reduced under the

reaction conditions but could in principle be cleaved to the corresponding alcohol **28** (α) by a stronger reducing agent. The desired alcohol may be directly produced by using molecular oxygen as a radical trap, subject to certain modifications in the experimental procedure. Thus stirring under air a mixture of **15** and nickel powder in neat acetic acid at room temperature for eight days afforded 25% of alcohol **28** (as a 5:1 mixture of the α and β isomers). Some reduced but uncyclised material (**29** ; 40%) was also isolated.

Whe have finally examined one case of cyclisation onto an acetylenic group, which proved to be moderately efficient. Under the usual conditions, bromoisobutyramide **30** produced the expected lactam **31** in 46% yield contaminated by vinylic bromide **32** (ratio of **31/32** : 4:1), arising from a bromine transfer reaction. Some starting material remained (17%), but the main side product turned out to be ketone **33**, isolated in 18 % yield. This ketone results from the formal hydration of the triple bond; curiously, however, exposure of isobutyramide **34** to similar reaction conditions did not produce any such ketone. Further work to clarify the underlying factors in this minor but unexpected transformation is in progress.

In summary, the approach to substituted lactams described in this preliminary report allies cheapness and simplicity in terms of reagents and experimental procedure.[7] None of the reported yields has been optimized, and only a small fraction of the possible variations has so far been explored. The nickel powder / acetic acid system appears to exhibit an interesting reactivity profile and a number of further extensions and modifications are currently being examined.

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7. Typical experimental procedure: A mixture of haloamide (1 mmole), acetic acid (20 eq.), appropriate external trap (thiol; diselenide etc..), and nickel powder (30eq.) in 2-propanol (6ml) was heated to reflux under an inert atmosphere until thin layer chromatograghic analysis indicated essentially complete reaction (usually several hours). The reaction mixture was then filtered through Celite, diluted with water (20ml), neutralised with sodium bicarbonate, and finally extraced with ether. The organic layer was dried, concentrated, and the residue purified by flash chromatography.

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