Pergamon

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β-Lactams by a Nickel Powder / Acetic Acid Mediated Radical Cyclisation.

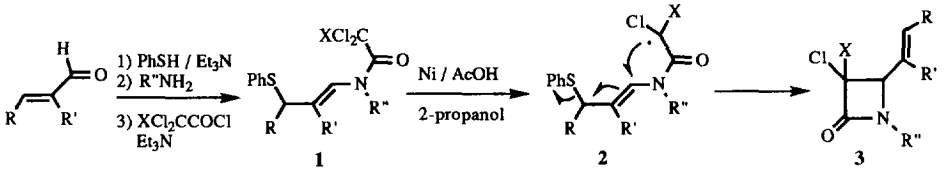
Béatrice Quiclet-Sire[a], Jean-Baptiste Saunier[a], and Samir Z. Zard[a,b]*

a) Institut de Chimie des Substances Naturelles, C. N. R. S.,
91198 Gif-Sur-Yvette, France

b) Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique, 91128 Palaiseau, France

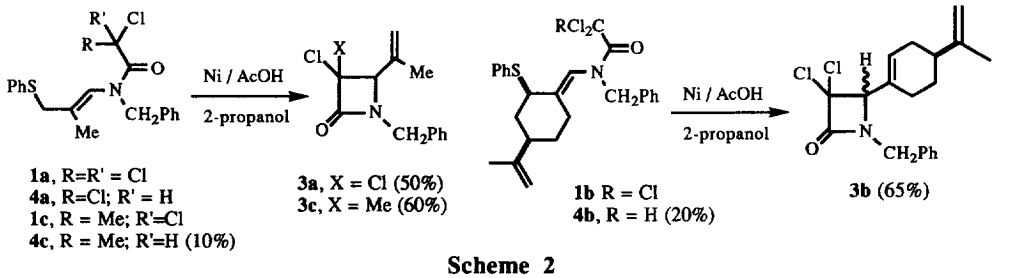
Abstract : N-Ethenyl trichloroacetamides undergo a radical cyclisation to give β-lactams and in some cases γ-lactams when exposed to nickel powder and acetic acid in refluxing 2-propanol.

A vast amount of work has been devoted over almost half a century to the partial and total synthesis of innumerable members and analogues of β-lactam antibiotics.[1] So far, the construction of the central β-lactam unit has relied on ionic chemistry in the broadest sense. Radical reactions have only recently been found to allow, under certain circumstances, the formation of such a strained ring.[2] With the exception of studies from the group of Pattenden[2a] who has used organocobalt derivatives, all the published work[2d-h] has involved tin hydride mediated radical cyclisations, with all the limitations imposed by such a system, in particular, the need in this case to work under high dilution (i.e. slow addition of stannane) and to stabilise with phenyl groups or sulfur substituents the radical from the (relatively slow) cyclisation step, in addition to the perennial problems associated with the removal of tin residues from the product. As part of our work on the use of nickel powder / acetic acid as a mild method for generating radicals[3] with sufficient life time to undergo difficult cyclisations, we wish to report our preliminary but quite promising results on the utility of this new process for the synthesis of β-lactams.



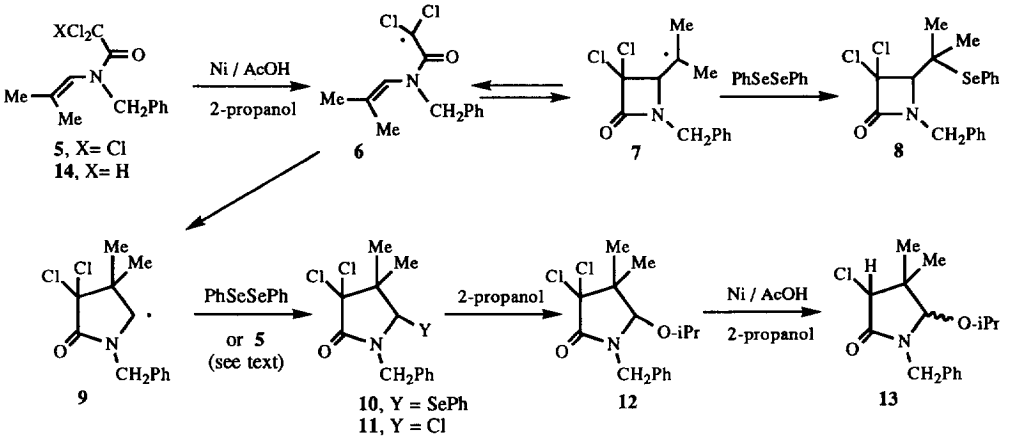
Scheme 1

The formation of a small ring by a radical process is generally a reversible process.[4] One way for driving the equilibrium in the desired direction, apart from the expedient of stabilising the cyclised radical which is limited in scope, consists in introducing a fast irreversible step, such as a fragmentation, following the cyclisation. With our nickel powder / acetic acid based method, which does not operate through a chain mechanism, this can be most easily done by planning the cyclisation on an allylic sulfide, as outlined in Scheme 1. A conceptually similar approach for the synthesis of cyclopropanes has been described earlier by Cekovic and Saicic[5] using the powerful Barton decarboxylation reaction.



Scheme 2

The required precursors are made from α,β-unsaturated aldehydes as shown in scheme 1. Thus compound **1a**, prepared from methacrolein, thiophenol and benzylamine, gave the expected β-lactam **3a** in an unoptimized yield of 50% upon exposure to nickel powder and acetic acid in refluxing 2-propanol. In a similar manner, enamide **1b** derived from perillaldehyde afforded β-lactam **3b** in 65% as a mixture of two diastereomers along with a smaller amount (20%) of the monoreduced enamide **4b**. One of the chlorines in the trichloroacetamide may be replaced by a substituent as in the dichloropropionamide **1c** which furnished β-lactam **3c** in 60% yield and 10% of uncyclised monochloroenamide **4c** after a rather slow reaction (36 hours instead of the few hours required for the previous examples). It seems therefore possible to construct β-lactams modified in the 3- and 4-positions, the presence of the chlorine atoms next to carbonyl group and the olefin in the side chain providing a handle for further transformations (e.g. ozonolysis; hydroboration etc.).



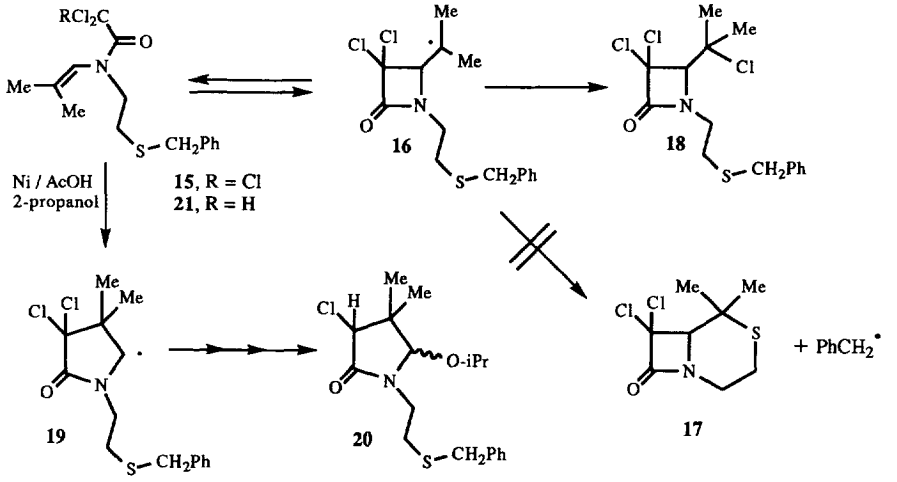
Scheme 3

In order to drive the process towards β-lactam formation, the fragmentation step may be replaced by a fast intermolecular capture of the cyclised radical with a highly radicophilic reagent such as diphenyl diselenide. This is illustrated by the conversion of enamide **5** into β-lactam **8** (40%) by treatment with nickel powder / acetic acid in the presence of 2 equivalents of diphenyl diselenide (Scheme 3). A small amount (15%) of selenide **10** was formed presumably by capture of radical **9**, itself the product of an unusual 5-endo-dig cyclisation of the initial radical **6**. Interestingly, when the diselenide trap was omitted, no β-lactam

was produced; instead, we isolated pyrrolidinone **12**, again in moderate yield (55%; 5:1 mixture of diastereomers) along with some simply reduced material **14** (30%). Clearly, the 4-exo cyclisation is reversible under the reaction conditions and, in the absence of a trap, radical **6** is sufficiently long-lived to undergo an unusual but irreversible 5-endo-cyclisation leading to **9**. This is followed by a formal oxidation of the latter species, presumably into the labile trichlorinated intermediate **11**, which then reacts with isopropanol to give dichlorolactam **12**. Finally, this compound is further reduced by nickel powder / acetic acid into monochloro derivative **13**. The order of the last two steps can of course be reversed.

The causes behind the reductive removal of the chlorine atoms α to the carbonyl in the case of **12** are not clear at the moment. The reductive potential could be quite sensitive to the substituents on the nitrogen and perhaps also to steric factors (steric compression in this case may also play a role). As for the formation of intermediate **11**, it could occur either by a direct chlorine atom transfer from the starting trichloroacetamide **5** to radical **9**, or by electron transfer to give the equivalent of a cation (interestingly an oxidation step in a mild reducing medium) which is then quenched by a chloride anion (derived from fragmentation of the radical anion co-produced in the electron transfer process). Even though the end result is the same in both cases, we prefer the latter pathway since we observe such behaviour only with easily oxidised radicals[3b,c] (e. g. α to a heteroatom, allylic, or tertiary as in the example below).

The 5-endo-cyclisation process has previously been observed in the case of stannane mediated cyclisations, and has recently been exploited by Ikeda and co-workers[2h] in a short synthesis of cotinine. In our case, it is remarkable that the cyclisation occurs so readily despite the hindering presence of the geminal methyl groups on the terminus of the double bond. From a synthetic standpoint, the γ-lactams resulting from the present process are more heavily functionalised than those obtained by the stannane method, easier to purify and, because of the kinetics inherent to our reducing system, there is no special need for high dilution.



Scheme 4

We have also attempted to force the formation of the β-lactam ring by coupling the cyclisation with an irreversible homolytic substitution on a sulfide group, thus allowing the formation of two rings at the same time as shown in Scheme 4. However, exposure of **15** to the usual reaction conditions did not produce any

such derivative (e.g. **17**). A modest amount (24%) of β-lactam **18** was isolated, along with γ-lactam **20** (34%) and dichloroacetamide **21** (35%). Clearly, the substitution on sulfur is too sluggish to compete with the other reactions open to radical **16** (and to radical **19** which also did not undergo substitution on sulfur). Moreover, in contrast to its analog **7** and possibly because of slightly less steric compression, the ring opening of **16** is slow enough to allow its partial oxidation to eventually a tertiary chloride which can now be isolated.

In summary, we have demonstrated the applicability of our nickel powder / acetic acid reducing system to the production of substituted β-lactams. The exact course taken depends on the balance of many subtle factors. Further studies and extensions are currently under way.

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6. Typical experimental procedure: A solution of N-alkenyl trichloroacetamide (1mmol) and acetic acid (20 mmol, 1.14 ml) in dry 2-propanol (12 ml) containing excess nickel powder (30 mmol, 1.76g) was stirred under reflux in an inert atmosphere. The reaction, monitored by T.L.C., needed 0.5 to 36 hours to go to completion depending on the substrate. The mixture was then cooled to room temperature, filtred over celite and, after rinsing the celite with ether, water (20 ml) was added to the filtrate which was then neutralised with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water, brine, then dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (heptane- ethyl acetate) to give the observed products in the yields stated.

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