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Nickel Powder Promoted *5-endo* Radical Cyclisations. A Concise Approach to *Erythrina* Alkaloids

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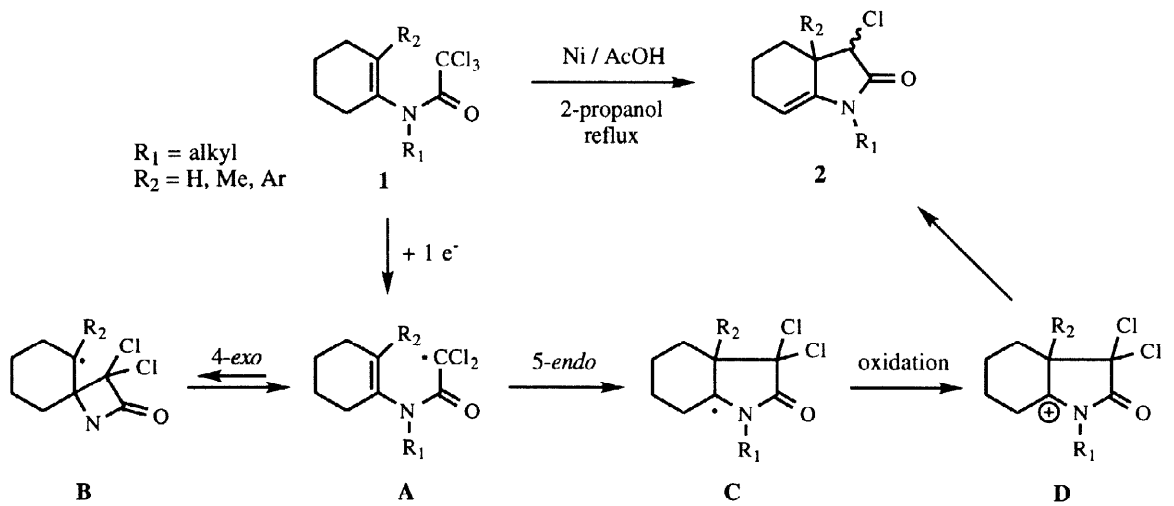
Abstract: N-Alkenyl trichloroacetamides **3** undergo, upon refluxing with nickel powder and acetic acid in 2-propanol, exclusive *5-endo-trig* cyclisation to afford functionalised lactams **4**; these are attractive precursors of erythrina alkaloids, as demonstrated by the expedient synthesis of 3-demethoxyerythratidinone **5**.

Recently, we reported a new method for the synthesis of β- and γ-lactams using nickel powder mediated radical cyclisations.[1] We described how the nickel powder / acetic acid[2] combination allows the generation of radicals from N-alkenyl-trichloroacetamides which undergo 4-*exo-trig* or 5-*endo-trig* cyclisations depending on the substrate. Particulary relevant was the case of trichloroacetamides **1** (Scheme 1) : subjected to nickel and acetic acid in refluxing 2-propanol, these derivatives are reduced to radicals **A** which give exclusively 5-*endo* adducts, even when the 4-*exo* cyclisation would have lead to a resonance stabilized, albeit more strained, radical **B** (R_2 = Ar). If the unusual behaviour of such radicals **A** has already been observed by ourselves[2d] and by others,[3] the oxidation step that follows the cyclisation is peculiar to our method and leads to a cation equivalent **D** which then undergoes elimination to give lactam **2** after further reduction. The oxidation process in what otherwise is a mild reducing medium is noteworthy, and presumably involves electron transfer from radicals **C** to the starting trichloroacetamides **1**.



Scheme 1

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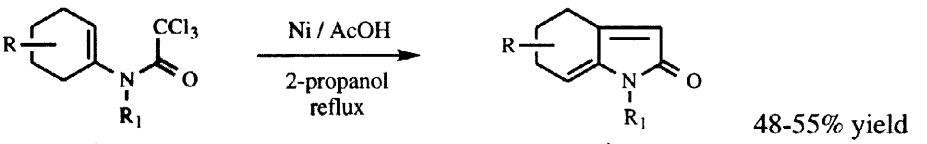
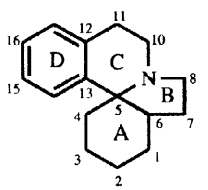
Thus, beginning with readily available trichloroacetamides, the *5-endo* cyclisation-oxidation sequence results in the creation of a new carbon-carbon bond and the introduction of a valuable double bond in the molecule. This convenient and mild procedure provides highly functionnalised γ-lactams, in contrast to classical reductive radical methods involving stannanes.[3a] For example, when R_2=H (**3**, Scheme 2), unsaturated lactams **4** are obtained. These have a considerable synthetic potential which we have not exploited yet. Since our first observations were recorded,[1] the obtention of related unsaturated compounds of type **4**, also by *5-endo* radical cyclisations have been reported, using either tributyltin hydride mediated,[4] or manganese(III)-promoted oxidative cyclisations[5]. This prompts us to disclose our results concerning the application the Ni / AcOH methodology to the synthesis of 3-demethoxyerythratidinone **5**, an erythrina alkaloid.



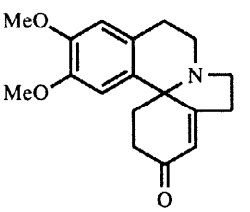
3 **4**

Scheme 2

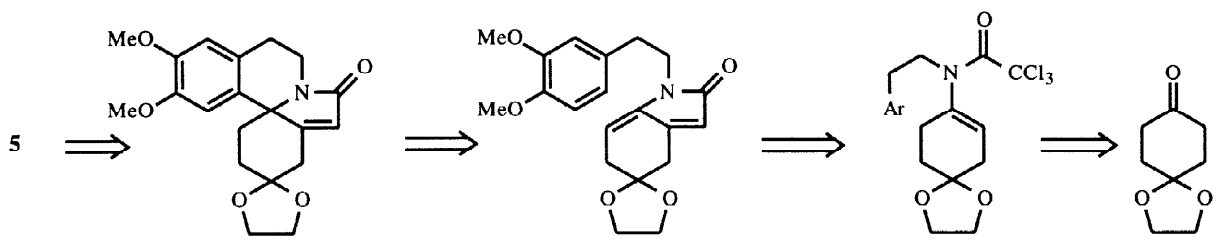
Erythrina alkaloids are a large class of natural products found in *Erythrina* plants (Leguminosae), which are attractive targets because of their curare-like activity.[6] 3-Demethoxyerythratidinone **5** was first isolated in 1973 by Barton and his collaborators from *Erythrina lithosperma*.[7] Even though several syntheses have been reported,[8] we felt that this compound could serve to illustrate our methodology and provide a basis for a general radical approach to *Erythrina* alkaloids. The strategy, outlined in Scheme 3, relies on the crucial Ni-induced radical cyclisation of **8** with concomitant formation of two double bonds to give **7**. Under acidic conditions, this unsaturated lactam should cyclise into **6** which can then be converted into 3-demethoxyerythratidinone **5** according to the literature procedure.[8a]



Erythrinan skeleton



3-Demethoxyerythratidinone **5**

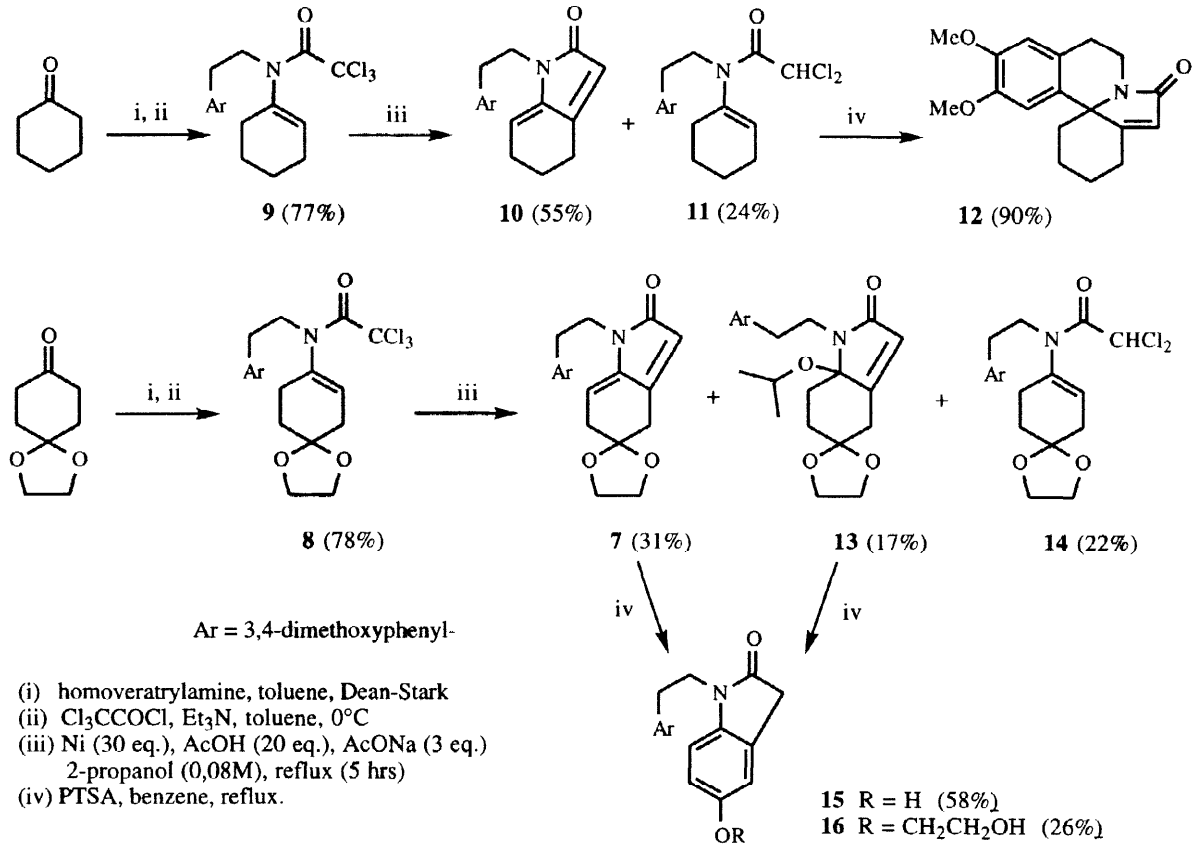


6 **7** **8**

Scheme 3

We first examined the viability of our strategy by starting with trichloroacetamide **9**, obtained from cyclohexanone by condensation with homoveratrylamine followed by acylation with trichloroacetyl chloride (Scheme 4). Upon treatment with nickel powder and acetic acid in refluxing 2-propanol in the presence of sodium acetate,[9] unsaturated lactam **10** was produced in 55% yield, along with reduced material **11** (24% yield). As expected from literature precedent,[8] exposure to toluenesulfonic acid in refluxing benzene indeed gave the tetracyclic erythrina skeleton **12** in high yield (90%). However, when trichloroacetamide **8** was subjected to the radical cyclisation, two different bicyclic products were obtained: the desired lactam **7** (31% yield) and its

isopropoxy derivative **13** (17% yield), in addition to the simple reduced open chain derivative **14** (22%). The mildness of the nickel powder reduction is clearly demonstrated by its tolerance of the acid-sensitive ketal group, but the reason for the formation of side-product **13** in this case is not clear at the moment. Nevertheless, both compounds **7** and **13** could in principle act as precursors for the cationic cyclisation leading to **6**.



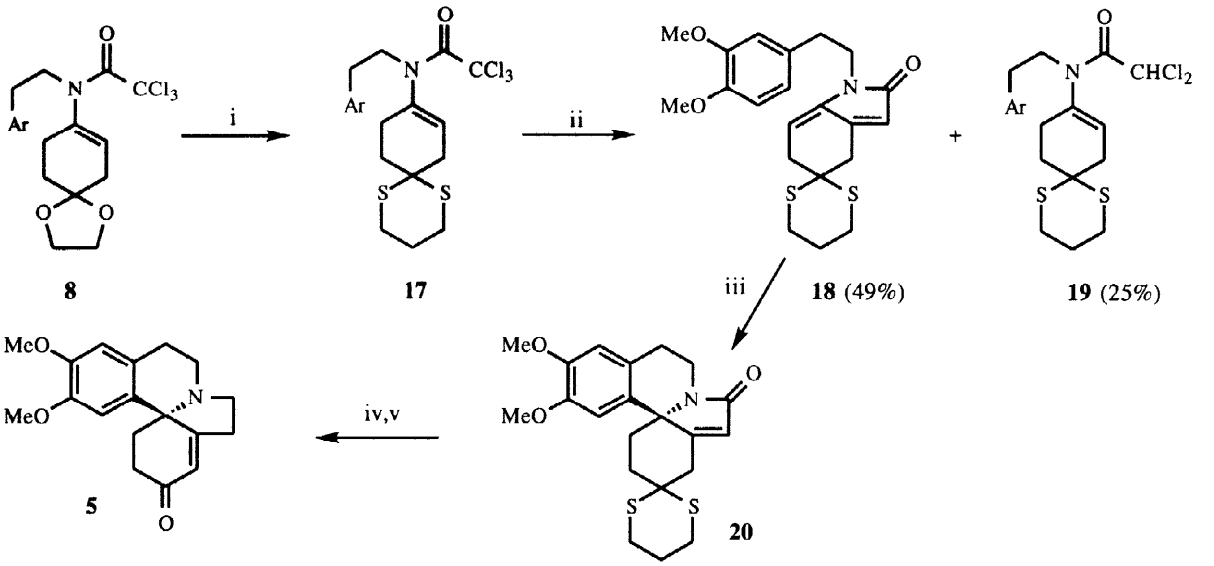
Scheme 4

Unfortunately, when **7** (or **13**) was submitted to the action of p-toluenesulfonic acid in refluxing benzene, a rapid reaction occurred to give two oxindole derivatives **15** and **16** in a 2:1 ratio and in 84% combined yield (Scheme 4). Similar aromatisations have already been observed during synthetic studies towards erythrina alkaloids[10] and are perhaps not surprising in the case of conjugated and acid-sensitive lactams like **7** or **13**. In the light of this disappointing observation, we decided to modify the protection of the C-2 ketone to avoid the untoward aromatisation.

The same sequence was then repeated starting with the more robust dithioketal derivative **17**, obtained from **8** in nearly quantitative yield by reaction with 1,3-propanedithiol in the presence of $BF_3.OEt_2$ (Scheme 5). This compound was subjected to standard radical conditions[9] to afford the unsaturated lactam **18** in 49% yield along with reduced material **19** (25%). Interestingly, the reaction time in this case was significantly shorter in comparison with that for **8** (2 hrs *vs* 5 hrs) and no isopropxy derivative was observed. Exposure of **18** to p-toluenesulfonic acid in refluxing benzene accomplished the desired cyclisation to furnish compound **20** in 84% yield. Finally, 3-demethoxyerythratidinone was obtained in two steps: reduction of the amide moiety with a combination of $LiAlH_4$ / $AlCl_3$ in cold ether (86%) and deprotection of the ketone (N-chlorosuccinimide / $AgNO_3$; 40%) with concomitant migration of the double bond to give 3-demethoxyerythratidinone **5** which was spectroscopically identical to the natural product.

The desired synthesis has been accomplished in 7 steps starting from cyclohexadione monoethyleneketal. None of the yields has been optimised and room for improvement certainly exists. But the purpose of this work

was chiefly to illustrate the utility of this novel Ni / AcOH mediated cyclisation which allows the introduction, in one operation and under quite mild conditions, of a new carbon-carbon bond and two double bonds.



(i) $HS(CH_2)_3SH$, $BF_3.OEt_2$, CH_2Cl_2, 25°C (95%); (ii) Ni / AcOH, 2-propanol, reflux (2 hrs); (iii) PTSA, benzene, reflux (84%); (iv) $LiAlH_4$, $AlCl_3$, THF, ether, 0°C (86%); (v) NCS, $AgNO_3$, CH_3CN / H_2O (40%).

Scheme 5

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References and notes

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9 The same result was obtained without sodium acetate (see ref. 1) but addition of this buffer during the reaction of **8** and **9** avoids the formation of 3-chlorinated byproducts. In contrast, cyclisation of **17** proceeded more cleanly and in better yield without sodium acetate in the reaction medium.

10 See ref. 8a and : Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, H. J.; Vilhuber, H. G.; Boettcher, K. *Chem. Ber.* **1970**, *103*, 615-638.