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Spirolactams by a Novel *ipso*-Radical Cyclisation and Loss of Aromaticity

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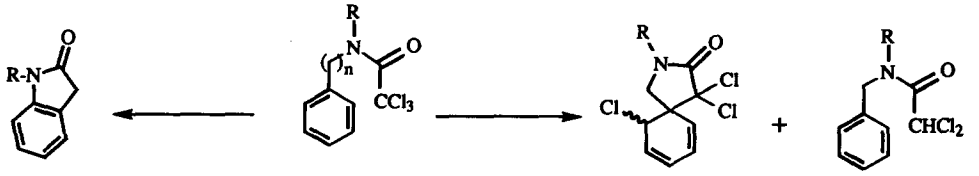
Abstract : Spirolactams are obtained by *ipso* radical cyclisation when various substituted N-benzyl trichloroacetamides are subjected to the nickel powder / acetic acid reducing system.

The synthesis of cyclohexane derivatives starting from aromatic compounds is a common and powerful strategy which relies however on a limited number of reactions. Catalytic hydrogenation normally leads to complete reduction of the aromatic ring,[1] in contrast to the Birch and related reductions[2] which are by far the most general and useful processes. Phenols can be oxidized to quinone derivatives[3] or alkylated[4] and further modified to give eventually non aromatic substances. Microbial dihydroxylation[5] is also emerging as a versatile tool for breaking the aromatic system, leading at the same time to chiral starting materials. Carbene additions[6] and some organometallic reactions[7] can sometimes lead to non-aromatic derivatives but so far these approaches have had a rather limited impact on synthesis. Radical additions to an aromatic nucleus, apart from being often too slow when compared with the other options open to the radical species, are usually followed by rearomatization.[8] We now report a novel and unexpected radical cyclisation onto an aromatic ring where aromaticity is not restored and which leads to a variety of highly substituted spirolactams.



1, R = $PhCH_2$-
4, R = i-Pr-
6, R = t-Bu-

2, R = $PhCH_2$- (30%)
5, R = i-Pr- (41%)
7, R = t-Bu- (65%)

3, R = $PhCH_2$-

Scheme 1

We recently found that a combination of nickel powder and acetic acid was capable of reducing oxime esters[9a] and α-haloamides[9b] in such a way that the intermediate radical species (iminyl radicals in the former instance) can be captured before further reduction to the anion level takes place. With α-haloanilides (e.g. **1**, n=0),[9c] the initial α-carbonyl radicals undergo cyclisation to the aromatic ring to give an oxindole in synthetically useful yields.

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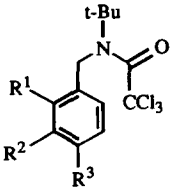
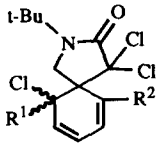
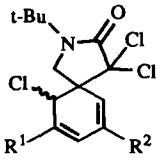
However, when we attempted to extend the process to the synthesis of quinolones by reducing N,N-dibenzyltrichloroacetamide **1** under our usual conditions, we were surprised to isolate a significant amount (30%, ca 1:1 mixture of epimers) of spiro compound **2** in addition to dichloroacetamide **3**, which arises through simple dechlorination of the starting material without cyclisation. The yield of spiro derivative could be improved by replacing the benzyl by an isopropyl group (**4** ---> **5**; 41%) or even better by the bulkier t-butyl group[10] (**6** ---> **7**; 65%). Such radical cyclisations to give spiro structures are normally followed by fragmentation or rearrangement,[11a] but an important exception was recently reported by Citterio and his colleagues.[11b] They found that Mn(III) oxidation of a benzyl malonate in the presence of an alkyne produced a vinylic radical intermediate which in some cases underwent *ipso* cyclisation to give finally a spiro cyclohexadienone derivative.



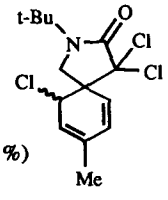
8, R^1 = Me; R^2= R^3 = H
9, R^2 = Me; R^1= R^3 = H
14, R^1= R^2 = H; R^3 = Me
17, R^1= R^2 = H; R^3 = OMe
19, R^1= R^2 = H; R^3 = F
20, R^1= R^3 = H; R^2 = $OCH_2CH{=}CH_2$



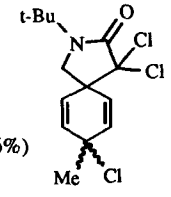
10, R^1= Me; R^2 = H
11, R^1= H; R^2 = Me
(**10** + **11**: 69%)



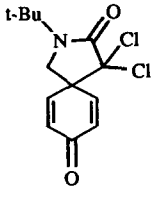
12, R^1= Me; R^2 = H
13, R^1= H; R^2 = Me
(**12** + **13**: 74%)



15 (21%)



16 (46%)

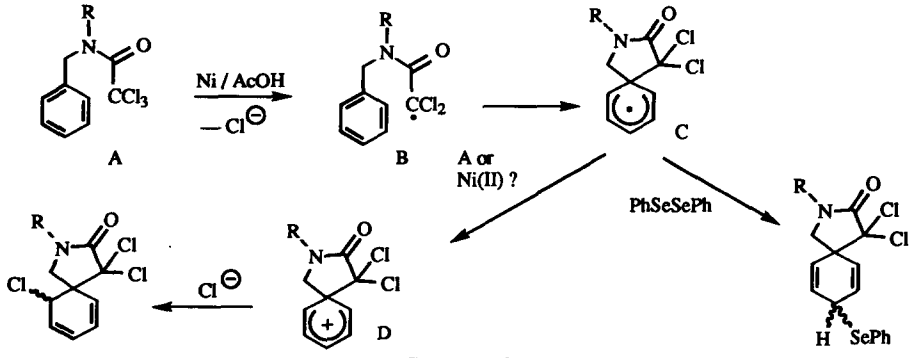


18
(15% from **17**;
25% from **19**)

The nickel / acetic acid mediated cyclisation reaction was extended to other N-benzyl trichloroacetamides with various substituents on the aromatic ring. Thus, as would be expected, ortho- and meta-methylbenzylamides **8** and **9** afforded the respective isomeric pairs of spirolactams **10**, **11** and **12**, **13** in 69% and 74% combined yield. In contrast, the para isomer **14** led to two types of spirolactams, **15** (21%) and **16** (46%), again each as a *ca* 1:1 mixture of epimers. In the case of p-methoxybenzylamide **17**, spirodienone **18** was formed in low yield (15%). Surprisingly, the same dienone was obtained from the p-fluoro analogue **19** in a slightly better yield (25%).

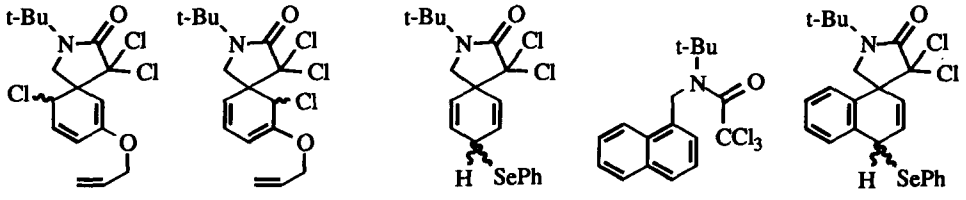
The formation of these spirolactams presumably involves the intermediacy of a cyclohexadienyl radical **C** which is oxidized into **D** by electron transfer to the starting trichloroacetamide **A** as outlined in scheme 1. Cyclohexadienyl radicals are known to be easily oxidized,[12] and some precedent for the

oxidation of radicals by electron transfer to halides exists.[13] Although this means that the process could be catalytic in nickel, the reaction becomes too slow when only small amounts of nickel powder are used. The alternative possibility of the intermediate cyclohexadienyl radical being oxidized by a Ni(II) salt cannot yet be ruled out but seems *a priori* less likely. Whatever the exact mechanism in operation, it is really surprising that no rearomatization takes place under the mildly acidic reaction conditions, neither at the radical nor at the cationic stage.



Scheme 2

In an unsuccessful attempt to capture the intermediate cyclohexadienyl radical with an internal olefin, we performed the reaction using N-t-butyl-N-3-(2-propenyloxy)benzyl trichloroacetamide **20** but could only isolate the "normal", rather fragile product, as a mixture of two pairs (1:1.5) of diastereomers **21a** and **21b** in 25% yield. Like benzyl and allyl radicals in general, cyclohexadienyl radicals are probably relatively unreactive towards an unactivated olefin.[14] Neither was TEMPO effective in trapping the intermediate spiro radical but this could be due to the reversibility of the radical combination,[15] reflecting once more the stabilised nature of the cyclohexadienyl radical. We had better luck using diphenyl diselenide as a trap. Thus, starting from trichloroacetamide **6**, selenide **22** was produced in 56% yield as a 1:6 mixture of epimers. A similar transformation took place with N-naphthylmethyl trichloroacetamide **23** to give selenide **24** in 62%yield. Interestingly, in this case, the reaction was not clean in the absence of diphenyl diselenide.



21a **21b** **22 (56%)** **23** **24(62%)**

The mildness and selectivity of *plain* nickel powder as a reducing agent may be judged by its ability to distinguish between the starting trichloroacetamide and the product which itself is a

dichloro-spirolactam and hence potentially reducible by the metal / acetic acid combination.[16] It is worth pointing out that the use of zinc / acetic acid or tributylstannane as reducing agents only led to dechlorination of the starting trichloroacetamide without cyclisation.

In summary, we have uncovered a rare example of a radical addition to an aromatic nucleus without the aromaticity being ultimately restored in the final product. This novel process allows the construction in one step of highly functionalized, complex spirolactams from almost trivial starting materials. None of the yields reported have been optimized, and further improvements and variations can be envisaged.

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16. Typical experimental procedure: To a solution of the N-benzyl trichloroacetamide (1 mmol) in 2-propanol (6 ml) is added acetic acid (20 mmol) then nickel powder (1.77g; used as received from Acros, formerly Janssen, but material from other sources seem to work equally well). The resulting mixture is heated to reflux for a few hours under an inert atmosphere until consumption of the starting material, then cooled and filtered through a pad of celite. The filtrate is diluted with ether and washed first with water then with dilute sodium bicarbonate and finally dried over sodium sulfate and concentrated under reduced pressure. The residue is purified by flash chromatography on silica in the usual manner. In order to obtain the phenylselenide adducts 22 and 24, diphenyl diselenide (3 mmol) is dissolved in the medium before addition of the acetic acid and the nickel powder. The high field shift of the nmr signals of the aromatic protons to the olefinic region is diagnostic. The spectral characteristics of compounds **15** and **16** are given as an example: **15** (1:1 mixture of two epimers): white crystals; mp 93-95°C (ether-pentane); IR (film) 1717 cm^{-1}; δ_H (200MHz) 5.8-6.0 (1H, m); 5.6-5.8 (2H, broad); 4.1 (1H, m); 3.2 (2H, m); 1.40 and 1.41 (9H, two singlets for the t-Bu- group); 1.13 and 1.06 (3H, two singlets for the methyl group). Found (%): C, 51.91; H, 5.63; N, 4.32; Calc. for $C_{14}H_{18}Cl_3NO$: C, 52.11; H, 5.62; N, 4.34. **16** (1:1 mixture of two epimers): white crystals; mp 162-165°C (ether-pentane); IR (film) 1719 cm^{-1}; δ_H (200MHz) 6.02 (2H, dd, J_1 = 4Hz; J_2 = 10Hz); 5.80 (2H, dd, J_1 = 4Hz; J_2 = 6Hz); 3.26 and 3.28 (2H, two s); 1.42 and 1.41 (9H, two singlets for the t-Bu- group); 1.11 and 1.08 (3H, two singlets for the methyl group). Found (%): C, 52.58; H, 5.64; N, 4.11; Calc. for $C_{14}H_{18}Cl_3NO$: C, 52.11; H, 5.62; N, 4.34.

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