Iron(III)-mediated oxidative cyclisations of cyclopropanone acetals

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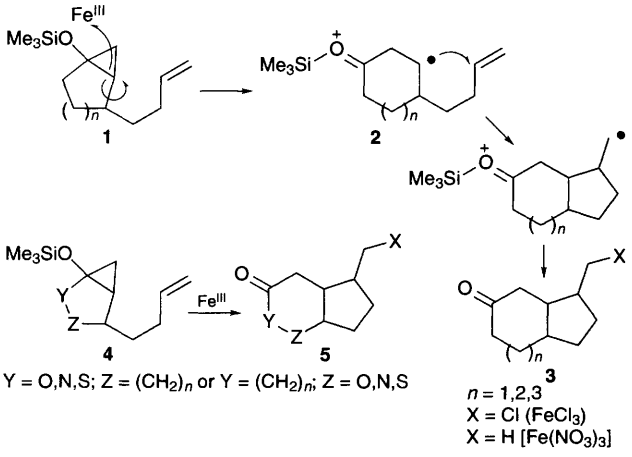
Treatment of the cyclopropanone acetals 7 or 11 with three different Fe^{III} species gives the lactone 9 and the ester 13 respectively *via* an oxidative cyclopropane cleavage followed by a 5-*exo* radical cyclisation–abstraction sequence.

In 1992 we described[1] a novel method for the synthesis of [*n*.3.0] bicyclic ketones **3** based on the ferric chloride induced ring expansion of cyclopropyltrimethylsilyl ethers **1**. We currently believe[2] that the reaction proceeds *via* SET oxidation [$Fe^{III} \rightarrow Fe^{II}$] of the cyclopropane ring, followed by 5-*exo* cyclisation of the resulting ring expanded β-keto radical **2** onto the butenyl side chain. Abstraction of either chlorine (from $FeCl_3$) or hydrogen [from solvent[3] with $Fe(NO_3)_3$] yields the final product (Scheme 1). It was our aim to extend this reaction to a variety of substrates containing heteroatoms within the carbocyclic ring, thus giving rise to functionalised heterobicyclic products (*i.e.* **4** → **5**).

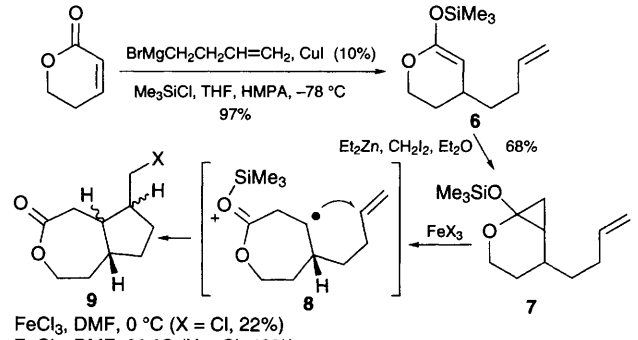
We now report the results of our preliminary studies on the Fe^{III} oxidative cyclisation reactions of cyclopropanone acetals, and the novel use of other iron complexes and final radical trapping species. Our initial system of study was the cyclopropanone acetal **7** which was easily assembled by using our now standard[2] conjugate addition/cyclopropanation sequence. We found that addition of butenylmagnesium bromide to 5,6-dihydro-2*H*-pyran-2-one in the presence of Me_3SiCl gave the silylketene acetal **6** in almost quantitative yield after distillation. This proved to be very labile and was immediately subjected to the Et_2Zn–CH_2I_2 cyclopropanation procedure to give the key cyclopropanone acetal **7** in 68% yield. Treatment of **7** with anhydrous ferric chloride in DMF under our standard conditions[2] gave the ring expansion/cyclisation product **9** (X=Cl) as anticipated, but in poor yield (22%) and as an inseparable mixture of diastereoisomers. Suspecting that the poor yield was due to slow reaction of the cyclopropane with $FeCl_3$ at 0 °C, this was repeated at 60 °C and a higher yield of 40% was obtained. Treatment of **7** with ferric nitrate in DMF[3] gave a better yield (66%) of the product **9** (X=H) resulting from hydrogen abstraction (Scheme 2). Again an inseparable mixture of diastereoisomers was formed with two major isomers predominating (1 : 1). Unfortunately it was not possible to assign the relative stereochemistry of these diastereoisomers by NMR spectroscopy.

It is clear from the above study that, compared[2] to the analogous cyclopropyltrimethylsilyl ethers (*e.g.* **1**, *n* = 2), the inclusion of a heteroatom dramatically alters the stereochemical outcome of these reactions. This is probably due to conformational differences between the ring expanded lactone radical **8** and the analogous carbocyclic radical (**2**, *n* = 2). This would be likely to have a profound effect on the stereochemical outcome of the 5-*exo*-radical cyclisation. We therefore decided to investigate the Fe^{III} oxidations of the simple cyclopropanone acetal **11** with a view to obtaining cyclic products which would be easier to analyse by spectroscopic techniques. To this end the silylketene acetal **10** was prepared in excellent yield by conjugate addition of butenylmagnesium bromide to ethyl acrylate. It is interesting to note that in this case DMPU could be substituted for HMPA with only a slight decrease in yield, which was contrary to our previous experience with related additions. Cyclopropanation of freshly prepared **10** gave access to the cyclopropanone acetal **11**, which proved stable enough to be stored for prolonged periods (Scheme 3).

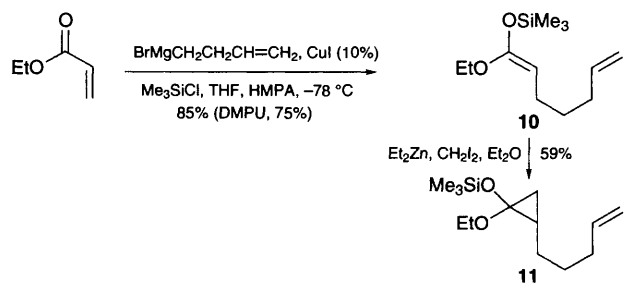
With multigram quantities of **11** in hand we carried out a detailed study of its oxidative cyclisation (Scheme 4) using a



Scheme 1

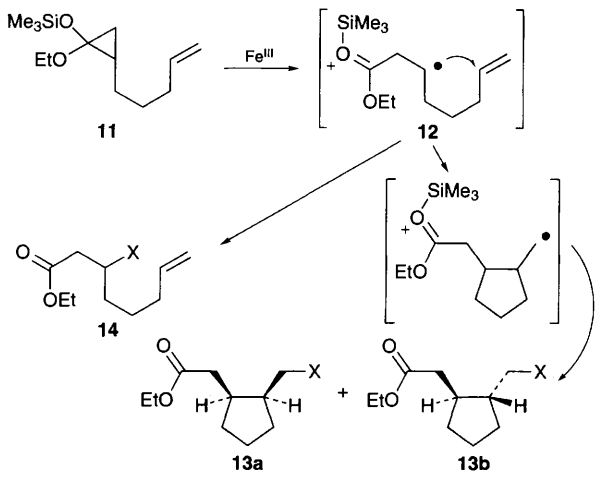


Scheme 2



Scheme 3

variety of Fe^{III} species and conditions, the results of which are detailed in Tables 1 and 2. The oxidation of **11** with ferric chloride (Table 1), as previously shown for **7**, was found to be temperature sensitive. For example in entry 1 a good yield of cyclopropane cleaved material was observed, but the major product was the uncyclised material **14** (X=Cl). This was attributed to the fact that the oxidative cleavage of the cyclopropane ring was slow at 0 °C and therefore the concentration of unreacted ferric chloride was able to build up in solution. When cleavage to the β-propionyl radical **12** takes place it is then quenched by chlorine abstraction from $FeCl_3$ at a rate faster than 5-*exo* radical cyclisation to the desired product. This was proved by repeating the addition of $FeCl_3$ at 60 °C (entry 2) which completely reversed the situation to give cyclised **13** (X=Cl) as the major product. Extending the addition times to 5 h at 60 °C allowed the almost exclusive formation of **13** (X=Cl), although at the expense of the overall yield (entry 3). We then turned our attention to the use of the previously reported[4] complex $[FeCl_2(DMF)_3][FeCl_4]$. This proved to be very similar in reactivity to ferric chloride itself and also gave the best ratios of **13**:**14** at elevated temperatures and longer addition times. In fact this complex is superior to ferric chloride in that there is less of a reduction in yield at elevated temperatures. Also, from a practical point of view, as this complex is air and moisture stable it is possible to manipulate it without the glove bag protocol required for anhydrous ferric chloride.[2] Table 2 details the reaction of **11** with anhydrous ferric nitrate in the presence of a number of radical traps. With ferric nitrate alone (entry 1) the cyclised ester **13** (X=H) was obtained as the sole product in 54% yield. As mentioned earlier we believe that this product arises *via* hydrogen atom abstraction from the solvent by the final cyclised radical. As there is no uncyclised material formed it is quite likely that this abstraction is a slow process relative to 5-*exo* cyclisation. We reasoned, therefore, that it should be possible to add external radical traps[5] and use this in some cases to incorporate further functionality (X) into the final products. Thus, using cyclohexa-1,4-diene as a hydrogen atom source[6] (entry 2) gave the cyclised ester **13** (X=H) as before but in a much higher yield of 78%. Use of diphenyldisulfide as a trap (entry 3) gave a good yield of the sulfide **13** (X=SPh) without any formation of the corresponding uncyclised sulfide **14** (X=SPh). The use of *N*-chlorosuccinimide (entry 4) gave a 9:1 mixture of **13**:**14** (X=Cl) respectively in good yield (76%). This was a very significant result as the ferric nitrate–NCS combination would appear to be superior, in terms of yield of cyclised product, to all of the results obtained in Table 1. A competition experiment between ferric chloride and diphenyldisulfide (entry 6) gave only products resulting from chlorine atom abstraction, thus demonstrating that the rate of chlorine atom abstraction from ferric chloride is rapid compared to the other atom donors used. In summary, this preliminary study demonstrates that cyclopropanone acetals readily undergo the Fe^{III} mediated radical oxidative cyclisation reactions which we have previously observed with cyclopropyl ethers. Furthermore, ferric nitrate, either on its own or in combination with radical traps, shows promise as a non-tin method for the generation and cyclisation of β-propionyl and related radicals.



Scheme 4

Table 1 Oxidative cyclisation of **11** with $FeCl_3$ and $[FeCl_2(DMF)_3][FeCl_4]$

Entry	Conditions (Addition time)[a]	Yield (%)	13[d]:14	X
1	$FeCl_3$,[b] DMF, 0 °C, (0.5 h)	79	1:2.5	Cl
2	$FeCl_3$,[b] DMF, 60 °C, (0.5 h)	66	3.6:1	Cl
3	$FeCl_3$,[b] DMF, 60 °C, (5 h)	47	19:1	Cl
4	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF, 0 °C, (0.5 h)	86	1:2.5	Cl
5	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF 0 °C, (5 h)	78	1:2.67	Cl
6	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF r.t., (5 h)	79	1:1	Cl
7	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF 40 °C, (5 h)	53	9.3:1	Cl
8	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF 60 °C, (0.5 h)	89	2:1	Cl
9	$[FeCl_2(DMF)_3][FeCl_4]$,[c] DMF 60 °C, (5 h)	69	5.4:1	Cl

[a] Times refer to the dropwise addition of Fe^{III} species in DMF to a solution of **11**. [b] 2.2 equiv. [c] 1.1 equiv. [d] In all cases *cis*-**13a** was the major isomer (80–90%). r.t. = room temperature.

Table 2 Oxidative cyclisation of **11** with $Fe(NO_3)_3$ and external radical traps

Entry	Conditions (Addition time)[a]	Yield (%)	13[b]:14	X
1	$Fe(NO_3)_3$,[c] DMF, 0 °C, (0.5 h)	54	1:0	H
2	$Fe(NO_3)_3$,[c] cyclohexa-1,4-diene, DMF, 0 °C, (0.5 h)	78	1:0	H
3	$Fe(NO_3)_3$,[c] $(PhS)_2$, DMF, 0 °C, (0.5 h)	66	1:0	PhS
4	$Fe(NO_3)_3$,[c] *N*-Cl-succinimide, DMF, 0 °C, (0.5 h)	76	9:1	Cl
5	$Fe(NO_3)_3$,[c] *N*-Br-succinimide, DMF, 0 °C, (0.5 h)	Complex mixt.	—	—
6	$FeCl_3$, $(PhS)_2$, DMF, 0 °C, (0.5 h)	67	1:1.67	Cl

[a] Times refer to the dropwise addition of $Fe(NO_3)_3$ in DMF to a solution of **11**. [b] In all cases *cis*-**13a** was the major isomer (80–90%). *cis*- and *trans*-isomers assigned by nOe experiments. [c] 2.2 equiv.

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