Pergamon

Tetrahedron Letters 39 (1998) 5097–5100

TETRAHEDRON LETTERS

Bicyclo[3.3.0]octanone Formation by Fe(III) Mediated Ring Expansion-Transannular Cyclisation Reactions of Cyclopropyl Ethers

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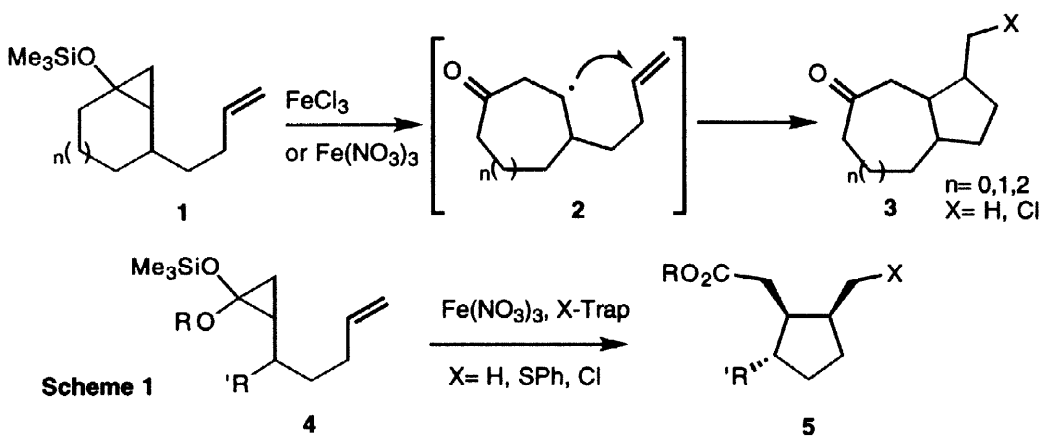
Received 30 March 1998; accepted 5 May 1998

Abstract: *Substituted bicyclo[5.1.0]octene derivatives undergo facile Fe(III) mediated radical ring expansion-transannular cyclisation reactions to give the corresponding bicyclo[3.3.0]octanones.* © 1998 Elsevier Science Ltd. All rights reserved.

In 1992 we reported[1] that cyclopropyl silyl ethers on treatment with Fe(III) underwent a tandem free radical ring expansion-cyclisation sequence to yield bicyclo[5.3.0] ring systems. This reaction has since proved to be general[2,3] for the synthesis of a variety of [n.3.0] ring systems from readily available starting materials (*e.g.* **1**→**3**, Scheme 1). The mechanism probably involves oxidative ring expansion to the carbocyclic radical **2** followed by 5-*exo* cyclisation to the bicyclic product **3**. We have recently extended this methodology to include the formation of cyclopentane esters[4,5] *via* the oxidative cyclisation of cyclopropanone acetals (*e.g.* **4**→**5**, Scheme 1). Overall this methodology allows the synthetic benefits of carbon centred radical chemistry to be utilised without recourse to the use of toxic trialkyltin hydride reagents. Furthermore, as the radicals generated in this way appear to have a longer lifetime (compared to trialkyltin methods) a number of external radical traps (*e.g.* PhSSPh) can be added to intercept the cyclised radicals thus adding further functionality to the products.[4]

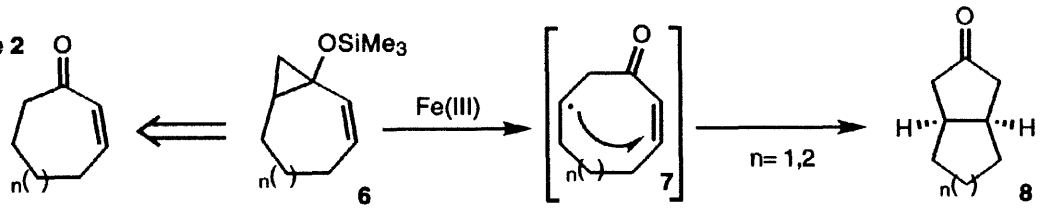


Scheme 1

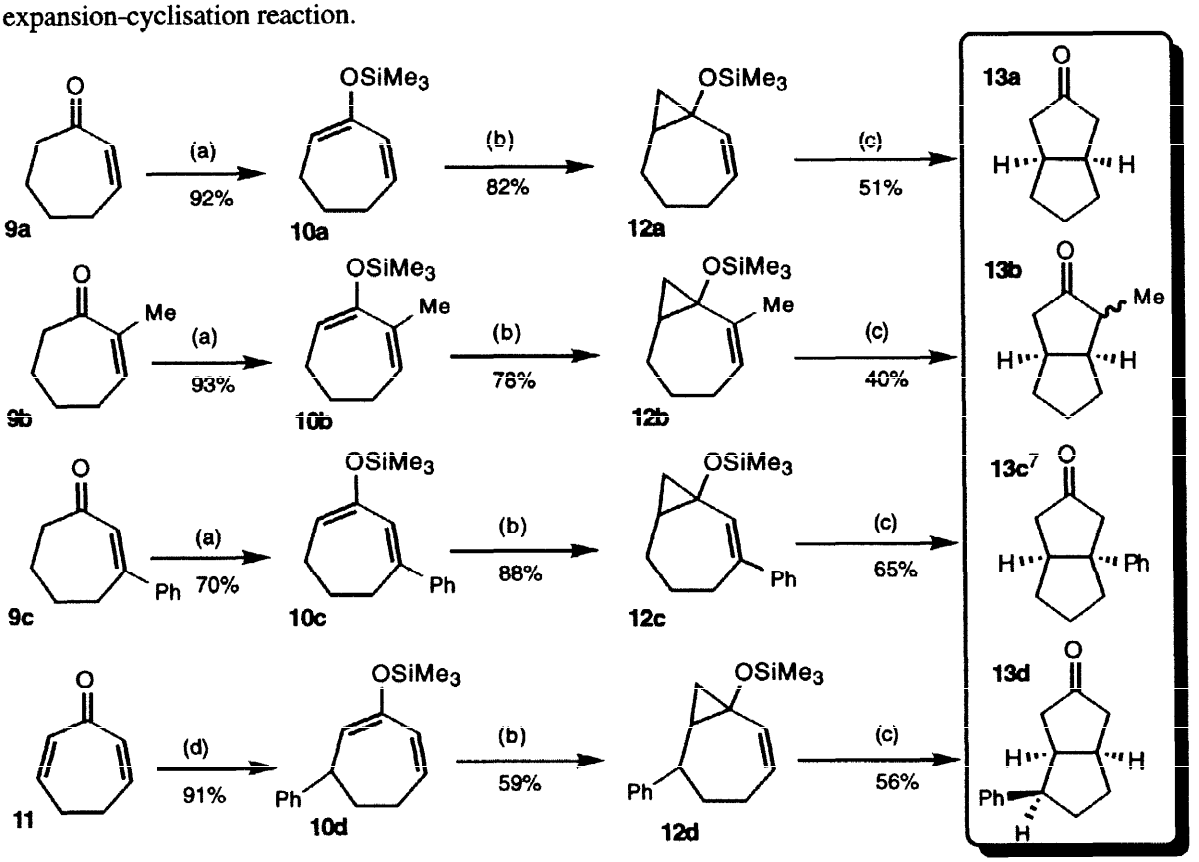
In the present work we elected to study the possibility of broadening the scope of this reaction with a view to trapping the intermediate carbocyclic radical (*i.e.* **7**) by transannular cyclisation onto a suitably positioned double bond. This would allow the synthesis of bicyclic ketones such as **8** from cyclopropyl ethers such as **6** derived from readily available medium-ring enones (Scheme 2). Although conversion of **7** to **8** involves essentially a 5-*endo* cyclisation, there is literature precedent for this mode of transannular radical cyclisation.[6]

0040-4039/98/$19.00
PII: S0040-4039(98)00935-6

Scheme 2

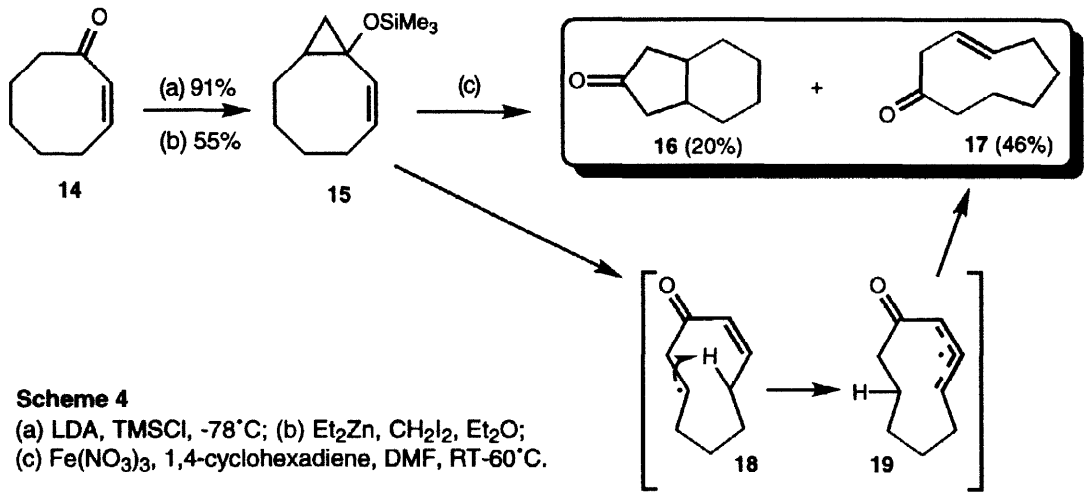


In the first instance we investigated the transannular cyclisation of cyclooctenone systems which would be formed by oxidative ring expansion of the corresponding cycloheptenes. Treatment of the 2-cycloheptenones **9a,b,c** with LDA followed by enolate trapping with TMSCl gave the trimethylsilyloxycycloheptadienes **10a,b,c** in good to excellent yields. The cycloheptadiene **10d** was formed in excellent yield from the cycloheptadienone **11** by copper catalysed conjugate addition[3] of phenylmagnesium bromide. These silyl enol ethers all underwent slow (24-48h) but selective cyclopropanation to give the corresponding bicyclo[5.1.0]octenes **12a-d** in moderate to excellent yields. Treatment of these with ferric nitrate in DMF gave moderately good yields of the anticipated bicyclic ketones **13a-d** arising from the proposed tandem oxidative ring expansion-cyclisation reaction.



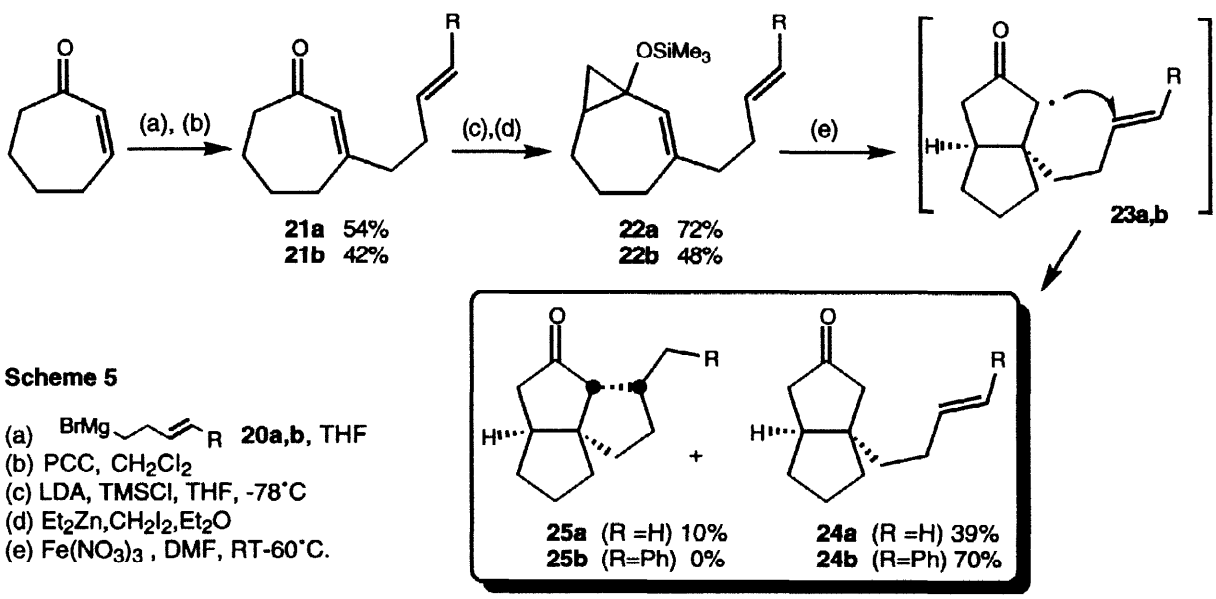
Scheme 3: (a) LDA, TMSCl, -78°C; (b) Et_2Zn, CH_2I_2, Et_2O; (c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, RT-60°C; (d) PhMgBr, CuI (10%), TMSCl, HMPA, THF, -78°C.

We next examined the possibility of forming the 6,5-ring system *via* this strategy. Treatment of 2-cyclooctenone **14** with LDA/TMSCl followed by cyclopropanation gave the cyclopropylsilyl ether **15** in good yield. Oxidative ring expansion gave the desired 6,5-bicyclic ketone **16** along with a major product which was identified as the deconjugated cyclononenone **17**. The formation of **17** can be explained by assuming the intermediate ring expanded carbocyclic radical **18** undergoes 1,5-hydrogen atom abstraction to give the allylic radical **19** followed by termination.



Scheme 4
(a) LDA, TMSCl, -78°C; (b) Et_2Zn, CH_2I_2, Et_2O;
(c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, RT-60°C.

Finally, we examined the possibility of intercepting the transannularly cyclised radical *via* a further 5-*exo* cyclisation onto a suitably placed alkene. Treatment of 2-cycloheptenone with the butenyl Grignard reagents **20a,b** gave the corresponding alcohols which upon oxidation[8] with PCC gave the 3-substituted-2-cycloheptenones **21a,b** in moderate overall yield. Enol ether formation followed by selective Simmons-Smith cyclopropanation gave the cyclisation precursors **22a,b** in good yields. With **22a** (R =H) oxidative cyclisation gave predominately the mono-cyclisation product **24a** and only minor amounts of the triquinane **25a**[9] arising from cyclisation of the radical **23a** were detected. The poor yield of **25a** was initially rationalised by the fact that **23a** is an electrophilic radical and would therefore cyclise slowly onto non-electron rich double bonds. Furthermore, cyclisation of **23a** leads to a less stable primary radical and as a consequence this cyclisation may be reversible. It was therefore anticipated that the phenyl derivative **22b** (R=Ph) would undergo cyclisation more readily since a more stable radical would be formed. However, treatment of **22b** with ferric nitrate gave only the mono-cyclised product **24b** (R=Ph) in good yield. This reluctance to cyclise is difficult to rationalise considering that Curran's elegant synthesis[10] of silphiperfol-6-ene involved the successful cyclisation of α-keto radicals such as **23a,b**. It may be possible that in our case reduction of the α-keto radicals **23a,b** with the Fe(II) formed *in situ* leads to an enolate anion which would then be unable to undergo cyclisation.



Scheme 5

(a) BrMg⁄⁄R **20a,b**, THF
(b) PCC, CH_2Cl_2
(c) LDA, TMSCl, THF, -78°C
(d) Et_2Zn,CH_2I_2,Et_2O
(e) $Fe(NO_3)_3$, DMF, RT-60°C.

In summary, we have shown that the Fe(III) oxidative ring expansion-transannular cyclisation of cyclopropyl ethers is a useful method for the rapid formation of a number of substituted bicyclo[3.3.0]octanones from readily available starting materials. A cascade sequence involving oxidative ring expansion followed by tandem radical cyclisation as a potential method for the construction of triquinanes such as **25a,b** was less successful due to premature termination of the radical sequence prior to final cyclisation.

Acknowledgements: We would like to thank the Engineering and Physical Sciences Research Council (EPSRC) for the provision of a research grant (GR/L23765).

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