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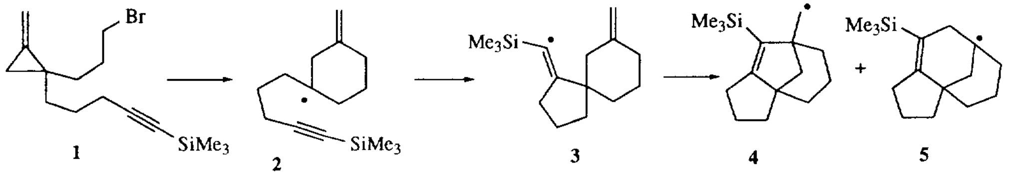
Synthesis of Spirocycles by Radical Cyclisations of Methylenecyclopropane Derivatives

Marco Santagostino and Jeremy D Kilburn*

University of Southampton, Department of Chemistry, Southampton SO17 1BJ

Abstract - The radical cyclisations of methylenecyclopropane derivatives **8**, **11**, **12**, **14** and **16** have been studied, and provide a route to spirocyclic systems.

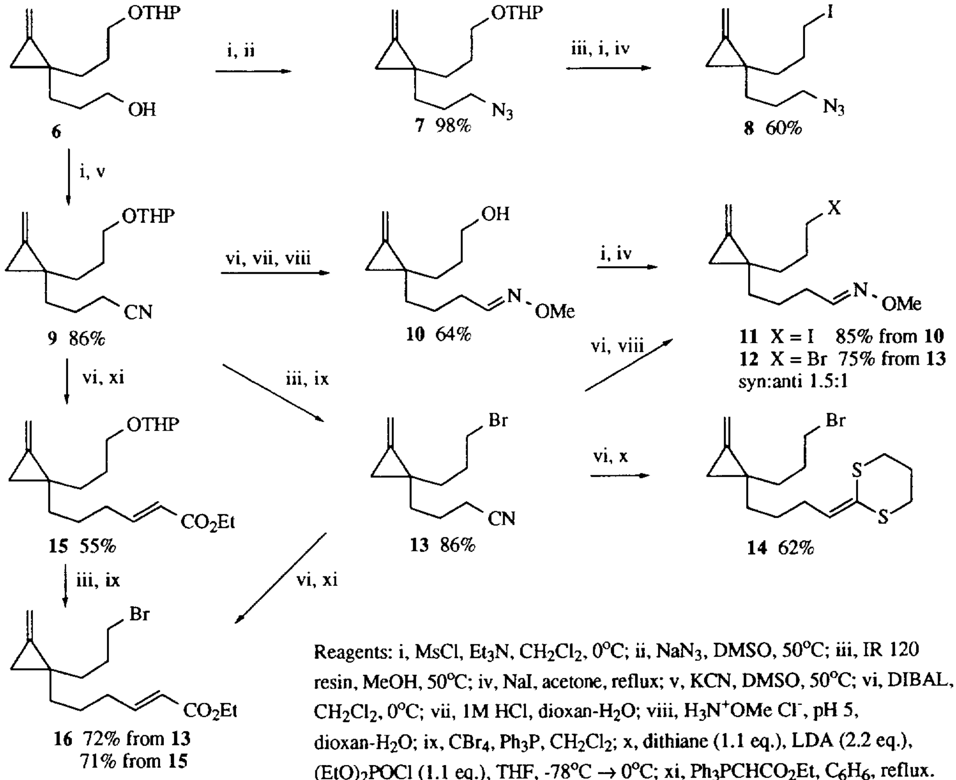
As part of our studies on radical cyclisations of methylenecyclopropane derivatives[1] we recently described[2] a reaction in which radical cyclisation of **1** ultimately led to the tricyclic radicals **4** and **5** *via* the spirocyclic vinyl radical **3** (Scheme 1).



SCHEME 1

When we first set out to investigate the radical cyclisations of 1,1 disubstituted methylenecyclopropane derivatives, such as **1**, we had anticipated that we would form spirocyclic products such as **3**, but further cyclisation to give **4** and **5** was unexpected. In order to probe the generality of the above sequence we have now prepared a series of related radical precursors in which we have changed the tethered alkyne functionality, used in **1**, to give an azide **8**,[3] oxime ethers **11** and **12**,[4] ketenedithioacetal **14**[5] and an α,β unsaturated ester **16**. We have studied the radical cyclisations of these compounds and wish to report the results of these studies in this paper.

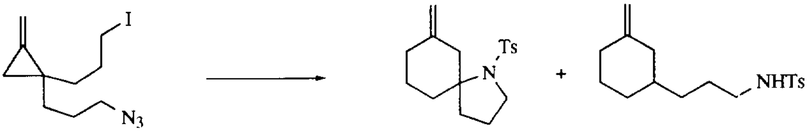
The radical precursors **8**, **11**, **12**, **14** and **16** were all prepared from alcohol **6**[2] using standard transformations as outlined in Scheme 2.[6]



SCHEME 2

Reagents: i, MsCl, Et_3N, CH_2Cl_2, 0°C; ii, NaN_3, DMSO, 50°C; iii, IR 120 resin, MeOH, 50°C; iv, NaI, acetone, reflux; v, KCN, DMSO, 50°C; vi, DIBAL, CH_2Cl_2, 0°C; vii, 1M HCl, dioxan-H_2O; viii, $H_3N^+OMe\ Cl^-$, pH 5, dioxan-H_2O; ix, CBr_4, Ph_3P, CH_2Cl_2; x, dithiane (1.1 eq.), LDA (2.2 eq.), $(EtO)_2POCl$ (1.1 eq.), THF, -78°C → 0°C; xi, Ph_3PCHCO_2Et, C_6H_6, reflux.

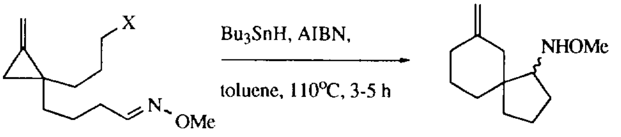
Cyclisation of iodide **8** (Scheme 3) followed by *in situ* trapping of the resulting amine products with *p*-toluenesulphonyl chloride, gave the azaspirocycle **17**, *via* the anticipated radical cascade sequence, along with the monocyclic amine **18**, formed as a consequence of the reduction of the azide prior to initiation of the cascade. In common with Kim *et al*,[3] we found that reduction of the azide could be suppressed using tris(trimethylsilyl)silane[7] in place of tributyltinhydride, giving a reasonable yield of the azaspirocycle **17**.



8	**17**	**18**
Bu_3SnH, AIBN, toluene, 110°C, then TsCl, DMAP	8%	34%
$(Me_3Si)_3SiH$, AIBN, toluene, 110°C, then TsCl, DMAP	53%	4%

SCHEME 3

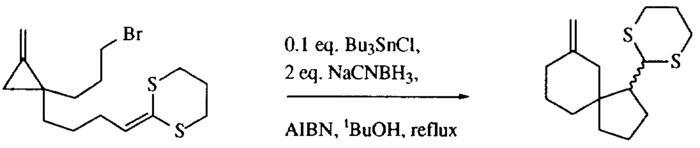
Cyclisation of the oxime ethers **11** and **12** (Scheme 4) gave the methoxyamine substituted spiroundecane as an inseparable 1:1 mixture of diastereoisomers in reasonable yield, with starting material also recovered. Yields and stereoselectivity were unaffected by the oxime geometry.



19 (1:1 mixture of diastereoisomers)

SCHEME 4	**11** X = I	syn	→	47% + 12% starting material
	11 X = I	anti	→	52% + 12% starting material
	12 X = Br	syn/anti	→	46% + 30% starting material

Similarly, cyclisation of bromodithiane **14** (Scheme 5) gave the substituted spiroundecane **20** again as an inseparable 1:1 mixture of diastereoisomers, along with small amounts of reduced starting material. The cyclisation could be effected using standard tinhydride conditions, or using the Stork method,[8] and in each case ^1H NMR of the crude reaction mixture indicated yields > 80%, although isolated yields were considerably lower.



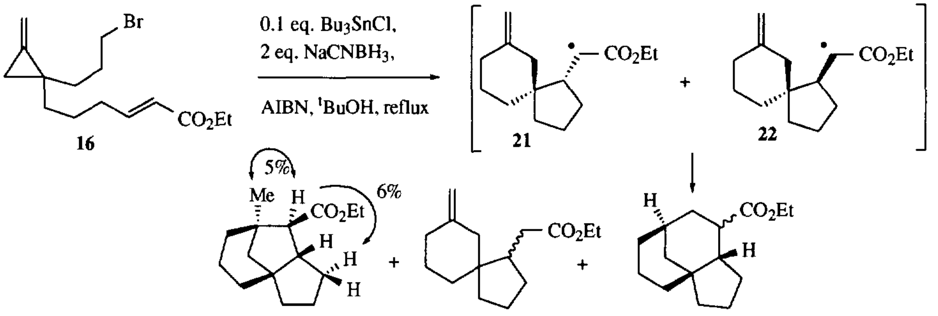
14

20 49%
(1:1 mixture of diastereoisomers)

SCHEME 5

In none of the above cyclisations were any tricyclic products, analogous to **4** and **5** (Scheme 1) detected in the reaction mixtures.

Cyclisation of bromoester **16**, however, gave a mixture of products (Scheme 6). The tricyclic ester **23**, was isolated in 31% yield as a single diastereoisomer, and presumably results from a 5-*exo* cyclisation of radical **22** onto the cyclohexylmethylene (cf. formation of **4**, Scheme 1). The relative configuration of the ester bearing carbon was determined by nOe measurements (as shown).[9] The spirocyclic esters **24** were isolated as an inseparable 3:1 mixture of diastereoisomers in 61% yield, but contaminated with a further product, tentatively assigned as tricyclic ester **25**,[10] and presumably formed by 6-*endo* cyclisation of intermediate radical **22** (cf. formation of **5**, Scheme 1).



SCHEME 6

23 31% **24** 61% (>80% pure) **25**
(3:1 mixture of diastereoisomers)

Ozonolysis of **24** cleanly gave the corresponding ketoesters, again as a 3:1 mixture of diastereoisomers, which were separable by column chromatography, thus allowing characterisation.[6]

In conclusion we have found that radical cyclisations of suitably substituted methylenecyclopropane derivatives provides a novel route to spirocyclic compounds, although further cyclisation to give tricyclic products can occur in certain circumstances.

Acknowledgements.

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5. For radical cyclisations onto ketenedithioacetals see Harrowven, D. C., Browne, R. *Tetrahedron Lett.*, **1994**, *35*, 5301.
6. All new compounds were characterised by IR, MS, ^{1}H and ^{13}C NMR, with ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectra, where necessary, to aid the assignments. Full details will be reported in due course.
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9. The stereochemistry of the ring junctions is assumed based on steric and ring-strain considerations. Thus it is improbable that radical **21** would undergo further cyclisation to give a highly strained tricyclic system.
10. The structure of **25** is based on an otherwise unassigned peak in the ^{1}H NMR (δ_H 2.82 (1H, dt, J 6, 12 Hz, CHCO$_2$Et)) and otherwise unassigned peaks in the ^{13}C NMR of the isolated mixture of **24** and **25**.

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