Vinylcyclopropylacyl Radicals. Intramolecular Ketene Additions leading to Concise Syntheses of Cyclohexenones

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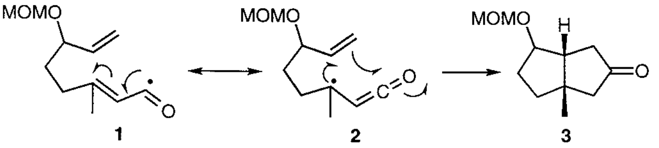
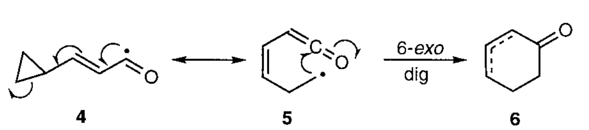
Abstract: Treatment of a range of vinylcyclopropyl selenyl esters with Bu$_3$SnH-AIBN produces cyclohexenone products (50-60%) *via* 6-*exo*-dig radical cyclisations involving ketene intermediates.

Acyl radicals derived from saturated carboxylic acid derivatives are valuable intermediates in synthesis, particularly when they are applied in polycycle constructions using cascade reactions involving consecutive additions to alkene electrophores.[1] In recent studies we have described some preliminary investigations of the scope for *unsaturated* acyl radicals in synthesis.[2] Thus, we were able to show that these intermediates could react *via* their α-ketene alkyl radical equivalents,[3] by addition to a proximate alkene bond followed by tandem cyclisation onto the ketene electrophore, resulting in a neat one-pot synthesis of diquinanes *e.g.* **1** → **2** → **3** (76%). In order to extend the scope of unsaturated acyl radicals in synthesis, we have now evaluated the chemistry of vinylcyclopropylacyl radicals. In this *Letter* we show how these intermediates undergo facile rearrangement and 6-*exo*-dig radical cyclisation involving ketene carbonyl electrophores leading to concise syntheses of cyclohexenones, *viz* **4** → **5** → **6**.

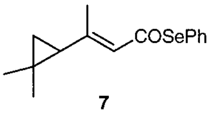
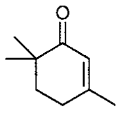
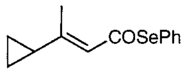
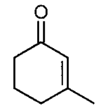
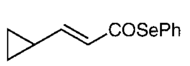
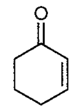
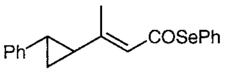
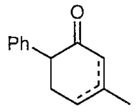
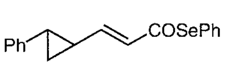
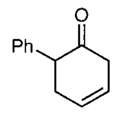




Although a range of methods are now available for the synthesis of acyl radical intermediates we have found that treatment of phenylselenyl esters (derived from carboxylic acids) with Bu$_3$SnH-AIBN (benzene, reflux) remains one of the most reliable and practical procedures.[4] Thus, a variety of conjugated vinylcyclopropane carboxylic acids corresponding to constitution **4** were first prepared,[5] and then converted into their corresponding phenylselenyl esters by treatment with *N*-phenylselenophthalimide and Bu$_3$P. When a solution of the trimethyl substituted vinylcyclopropane selenyl ester **7** in dry benzene at reflux was treated with Bu$_3$SnH (2 equivalents added dropwise over 2h) in the presence of AIBN (1 equivalent), work-up and chromatography led to the cyclohex-2-enone **8** in 60% yield.[6] In a similar manner the vinylcyclopropyl ester **9** produced the cyclohexenone **10** (48%), but the analogue **11** devoid of β-methyl group substitution on the alkene bond, failed to give cyclohex-2-enone **12** itself on treatment with Bu$_3$SnH-AIBN under a range of reaction conditions. The phenyl substituted vinylcyclopropyl selenyl esters **13** and **15** likewise both led to 6-phenyl substituted cyclohexenone products on treatment with Bu$_3$SnH (addition over 5h) - AIBN (10mol%). In the case of **15** only the Δ^3-isomer **16** was isolated, whereas both the Δ^2- and the Δ^3-isomers of **14** were produced from **13** (Table 1).

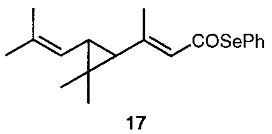
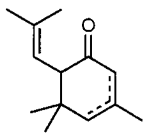
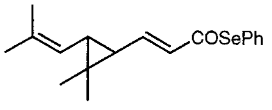
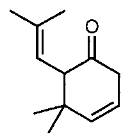
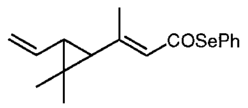
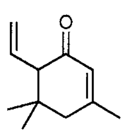
In each of the aforementioned vinylcyclopropylacyl radical-cyclohexenone ring conversions we believe that they result from intramolecular 6-*exo* dig cyclisations of alkyl radicals onto ketene carbonyl electrophores produced from delocalisation of the acyl radical precursors through their conjugated vinylcyclopropane systems, *cf* **4** → **5** → **6**.

Table 1

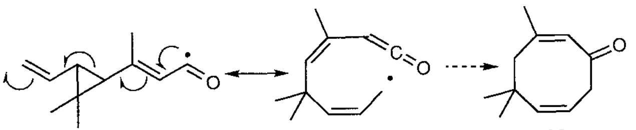
Selenyl Ester	*Cyclohexenone*	*Yield*
 **7**	 **8**	60%
 **9**	 **10**	48%
 **11**	 **12**	0%
 **13**	 **14**	Δ^2 - 51% Δ^3 - 15%
 **15**	 **16**	40%

In an examination of the scope for cyclopropyl conjugated selenyl esters in the elaboration of cyclooctenones, using the principles established above with six-ring synthesis, we also synthesised the additionally conjugated vinylcyclopropyl selenyl esters **17**, **18** and **19**. To our disappointment however neither of these esters produced corresponding cyclooctenone products, *e.g.* **20**, on treatment with Bu$_3$SnH-AIBN. Instead they each gave rise to the same familiar (2-vinyl substituted) cyclohexenone products (Table 2) in modest yields.

Table 2

Selenyl Ester	*Cyclohexenone*	*Yield*
 **17**		Δ^2 - 50% Δ^3 - 12%
 **18**		20%
 **19**		55%

To complement the investigations highlighted above, we also studied the reactivity of the acyl radical produced from the cyclopropane carboxylic acid ester **22a**.[7] Hitherto we had shown that the analogous ester **22b**, having geminal-dimethyl substitution on the alkene bond, underwent dimerisation to **21** on treatment with Bu_3SnH-AIBN.[2] Much to our satisfaction however reaction between a hot benzene solution of **22a** and Bu_3SnH (added over 5h) - AIBN (10mol%) led to the corresponding cyclohex-3-enone **23** in 52% yield.



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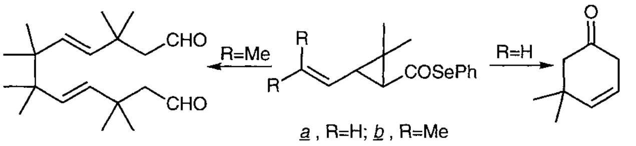


21 **22** **23**

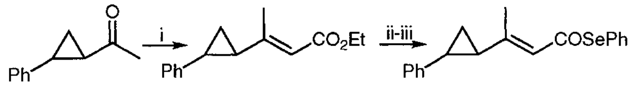
The present studies have uncovered some interesting and new chemistry associated with vinylcyclopropylacyl radicals leading to concise syntheses of cyclohexenones. Clearly there are subtleties associated with this chemistry, not least the importance of alkene and cyclopropane ring substitution in determining the efficacies of cyclisation, and extensions to other ring syntheses could be anticipated. These and related studies are in progress.

Acknowledgements

We thank the EPSRC for a studentship (to NH) and Astra Charnwood for financial support.

References and Notes

1. See: Chen, L.; Gill, G.B.; Pattenden, G.; Simonian, H.; *J. Chem. Soc., Perkin Trans,* **1996**, *1*, 31, and extensive bibliography contained therein.
2. Hayes, C.J.; Pattenden, G.; *Tetrahedron Lett.*, **1996**, *37*, 271. See also Astley, M.P.; Pattenden, G.; *Synthesis*, **1992**, 101.
3. For references to α–ketene alkyl radicals see: Tidwell, T.T.; *Ketenes*, John Wiley, New York, **1995**. Davies, A.G.; Hawari, J.A.; Muggleton, B.; Tse, M.; *J. Chem. Soc., Perkin Trans. II*, **1981**, 1132. Davies, A. G.; Sutcliffe, R.; *J. Chem. Soc., Perkin Trans. II*, **1980**, 819. Salem, L.; *J. Am. Chem Soc.*, **1974**, *96*, 3486. Dauben, W.G.; Cogen, J.M.; Ganzer, G.A.; Behar, V.; *J. Am. Chem. Soc.*, **1991**, *113*, 5817. Wolff, S.; Agosta, W.C.; *J. Am. Chem. Soc.*, **1983**, *105*, 1292. Adam, W., Berkessel, A.; Peters, E.; Peters, K.; von Schnering, H.G.; *J. Org. Chem.*, **1985**, *50*, 2811. Matlin, A.R.; Wolff, S.; Agosta, W.C.; *Tetrahedron Lett.*, **1983**, *24*, 2961.
4. For bibliography see ref. 1. See also: Crich, D.; Yao, Q.; *J. Org. Chem.*, **1996**, *61*, 3566.
5. The α,β-unsaturated selenyl esters were prepared from the corresponding α,β-unsaturated carboxylic acids following treatment with *N*-phenylselenophthalimide and Bu_3P. The α,β-unsaturated carboxylic acids were in turn obtained from the alkyl esters produced by conventional Wadsworth-Emmons reactions involving the lower homologous carbonyl compounds.



Reagents: i, NaH, $PO(OEt)_2CH_2CO_2Et$, THF,Δ ; ii, NaOH, EtOH, H_2O, Δ; iii, *N*-PSP, Bu_3P, CH_2Cl_2, -30°C, 72%.

6. All new compounds showed satisfactory spectroscopic data together with microanalytical and/or mass spectrometry data. Typical procedure for conversion of the vinyl cyclopropane **7** into the cyclohexenone **8**: A solution of the selenyl ester (50mg, 0.17mmol) in dry degassed benzene (54ml) containing AIBN (28mg, 0.17mmol) was stirred and heated to reflux. A solution of *n*-Bu_3SnH (99mg, 92μl, 0.34mmol) in dry degassed benzene (2ml) was added dropwise (*via* a syringe pump) over 2hrs to the heated mixture which was then stirred and heated under reflux for a further 2hrs. After cooling to room temperature the solvent was removed *in vacuo* and the residue was then purified by chromatography on silica gel eluting with petrol/diethyl ether (5:1) to afford the cyclohexenone **8** (14mg, 0.1mmol, 60%).
7. For structural studies with cyclopropylacyl radicals see: Davies, A.G., Sutcliffe, R., *J. Chem. Soc. Perkin Trans. II*, **1982**, 1483. See also: Zelechonok, Y; Silverman, R.B.; *J. Org. Chem.*, **1992**, *57*, 5785.