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Radical-chain cyclisation of unsaturated acetals and thioacetals in the presence of thiols as polarity-reversal catalysts

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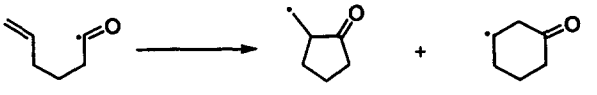
Abstract

Polarity-reversal catalysis by thiols has been applied to promote the radical-chain cyclisation of 2-(pent-4-enyl)-substituted 1,3-dioxolanes, 1,3-dithianes and 1,3-dithiolanes to give spirocyclic products.

Keywords: cyclisation; radicals; radical reactions; catalysis; thiols.

Cyclisation of unsaturated acyl radicals has been applied widely for the formation of cyclopentanone and cyclohexanone derivatives.[1] Although the prototype hex-5-enoyl radical **1** undergoes 5-*exo* cyclisation more rapidly than 6-*endo* ring closure, the product radical **2** can subsequently rearrange intramolecularly under relatively mild conditions to give the thermodynamically more stable radical **3**.[2] Loss of carbon monoxide from the acyl radicals, resulting in low yields of cycloalkanone products, can also become a major problem if substituents are present at C-2. These complications can be avoided if the acetal group is employed as a masked carbonyl function (e.g. Eq. 2), because rearrangement of the kinetically-favoured 5-*exo* cyclisation product **5** to the more stable radical **6** does not take place at moderate temperatures and α,α-dialkoxyalkyl radicals of the type **4** are much more resistant to unimolecular bond cleavage (β-scission in this instance) than are acyl radicals. Cyclisation of substituted derivatives of the prototype radical **4** has been exploited by a number of groups as a key elementary step in C–C bond-forming reactions of relevance to organic synthesis.[3–7]



1 **2** **3** (1)

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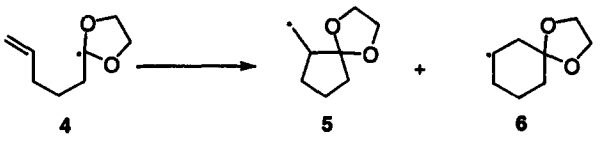
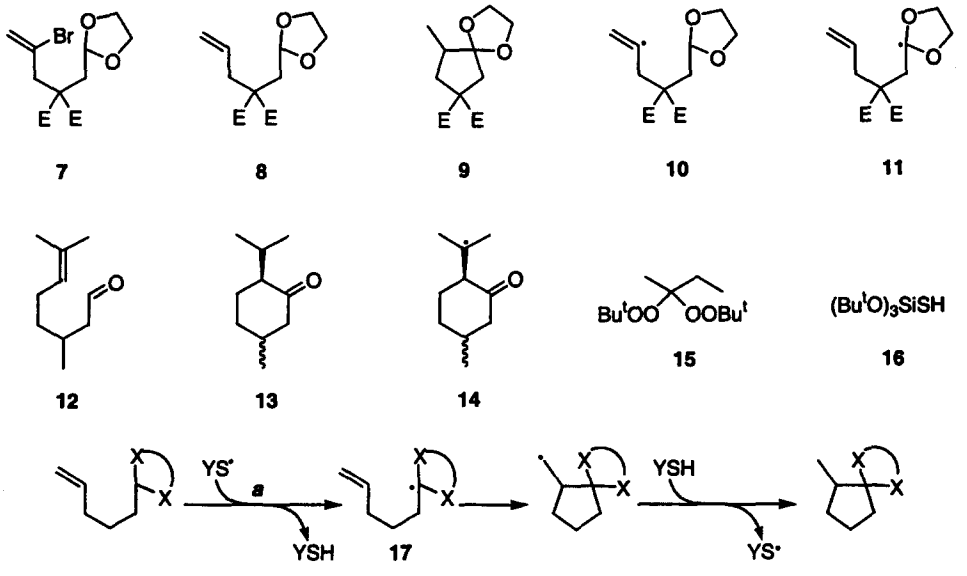


4 5 6 (2)

Curran and Shen[3] have applied the 1,5-hydrogen-atom transfer reactions of appropriate vinylic radicals to generate derivatives of **4** and related α,α-disubstituted hex-5-enyl radicals and the same approach was adopted by Crich, Bertrand and co-workers in their systematic studies of the diastereoselective cyclisation of analogous species containing chiral 1,3-dioxolan-2-yl and 1,3-dioxan-2-yl groups.[4,5] For example, radical-chain reaction of the vinylic bromide **7** with tributyltin hydride yields a mixture of the open-chain reduction product **8** and the spirocyclic product **9** (E=MeO_2C- throughout). The initially-formed vinyl radical **10** undergoes competitive trapping by the tin hydride and 1,5-H-atom transfer to give **11**, 5-*exo* cyclisation of which is followed by tin-hydride quenching to give **9**.[3]

We have reported previously[8] that the radical-chain cyclisation of citronellal **12** to give menthone (the *trans*-isomer) and isomenthone (the *cis*-isomer) **13** is promoted by thiols, which act as polarity-reversal catalysts[9] for the abstraction of hydrogen from the aldehyde by the cyclised radical **14**. Since α,α-dialkoxyalkyl radicals (like acyl radicals) are nucleophilic, it seemed reasonable that thiols might similarly catalyse the radical-chain cyclisation of unsaturated acetals of the type **8**, without the need to resort to 1,5-H-atom transfer and tin-hydride mediation as a means to generate the intermediate 1,3-dioxolan-2-yl radical **11**. The propagation steps of the envisaged chain mechanism are shown in Scheme 1 and we report here preliminary results that demonstrate the viability of the proposed catalytic process.



Scheme 1.

When the dioxolane **8**[10] (2.0 mmol) and the peroxyketal initiator **15**[11] (DTBPB, 5 mol%) were heated together in octane (2 cm^3) at 125°C for 2 h, polymeric material was formed and ca. 10% of the starting material remained (by ^1H NMR analysis); none of the spirocyclic product **9** was detectable. However, when this reaction was repeated in the presence of tri-*tert*-butoxysilanethiol[12] **16** (5 mol%), conversion to **9** was essentially quantitative and this compound was isolated in 92% yield; no product resulting from 6-*endo* cyclisation of **10** was detected. The thiol-catalysed cyclisation of **8** was also carried out at lower temperatures in the presence of dilauroyl peroxide (DLP) at 80°C or di-*tert*-butyl hyponitrite (TBHN) at

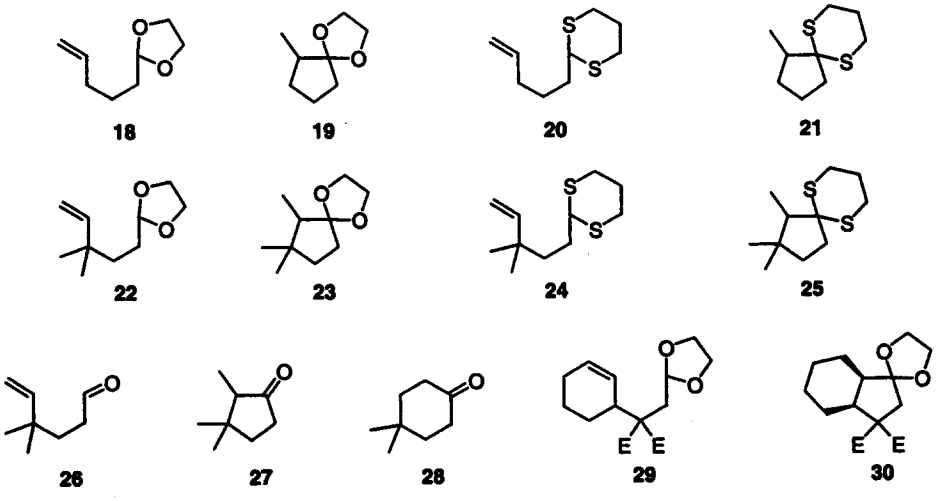
Table 1
Cyclisation of **8** catalysed by tri-*tert*-butoxysilanethiol **16** in octane solvent

Entry	Initiator (mol%)	Mol% thiol	Bath temp. (°C)	Yield **9**[a] (%)	Unreacted **8**[a] (%)
1	DTBPB (5)	None	125	0[b]	10
2	DTBPB (5)	5	125	>98[c]	0
3	DLP (5)	None	80	0[b]	30
4	DLP (5)	5	80	86	14
5	DLP (2 x 5)	2 x 5	80	97	3
6	TBHN (5)	None	60	0[b]	92
7	TBHN (5)	5	60	55	45
8	TBHN (2 x 5)	2 x 5	60	97	3

a Approximate values estimated by ^{1}H NMR spectroscopy. *b* Polymeric material was formed. *c* Isolated yield 92%.

60°C as initiators and the results are presented in Table 1; all reactions were very clean and essentially only **8** and **9** were detected by ^{1}H NMR spectroscopy at all stages.

The electron-withdrawing ester groups in **8** evidently facilitate the thiol-catalysed cyclisation reaction, probably by making the double bond mildly electron deficient and by reducing the ease of hydrogen-atom abstraction from the allylic CH groups. Thus, when the compound **18** was heated in octane in the presence of the thiol **16** (2×5 mol%) and DTBPB (2×5 mol%),[13] the 5-*exo* cyclisation product **19** was produced in only 10% yield and most of the starting material remained. Divalent sulfur is more effective than oxygen at increasing the rate of hydrogen-atom abstraction from an attached CH group by electrophilic radicals[3,7,14] and thiyl radicals fall into this category; hence step *a* of Scheme 1 should be facilitated when X=S compared with X=O. Hex-5-enyl radicals of the type **17** (X=S) are known to undergo efficient 5-*exo* cyclisation[3,7] and so we turned our attention to dithioacetals as substrates. Treatment of the 1,3-dithiane **20** with DTBPB (2×5 mol%) and the silanethiol **16** (2×5 mol%) under the standard conditions[13] gave the compound **21** in 55% yield and the corresponding 1,3-dithiolane behaved similarly; in the absence of thiol no spirocyclic product was obtained from **20**.



The 1,3-dioxolane **22**, which lacks the allylic CH groups present in **18**, gave **23** in 68% yield at 125°C under the standard conditions and again there was no cyclisation in the absence of thiol. Moving to the 1,3-dithiane **24** afforded **25** in 87% yield.

On the negative side, however, it appears that an inhibitor is formed in some systems and this can cause

the cyclisation reaction to stop prematurely. For example, the yield of **23** was not raised from ca. 68% by addition of more thiol and initiator, followed by further heating, while if the mixture of **23** and unreacted **22** was first isolated and *subsequently* treated with thiol and initiator at 125°C the cyclisation proceeded to completion.

For comparison, thiol-catalysed cyclisation[8] of the aldehyde **26** was examined under the standard conditions at 125°C and at 80°C using DLP as initiator (2×5 mol%). In both cases cyclisation was quantitative, but at 125°C the ratio of 2,3,3-trimethylcyclopentanone **27** to 4,4-dimethylcyclohexanone **28** was 5:95 (by GLC), while at 80°C it was 15:85, indicating the involvement of the ring-expanding 1,2-rearrangement process[2] referred to earlier.

Thiol-catalysed cyclisation of the cyclohexenylmalonate **29**, which involves intramolecular radical addition to an internal double bond, proved somewhat problematic. Under the standard conditions[13] the yield of **30** was negligible and most of the starting material was recovered unchanged. We have found previously that triphenylsilanethiol can be a particularly efficient polarity-reversal catalyst in situations where competing abstraction from allylic CH groups causes difficulties[15] and we note that **29** differs from **8** in having a tertiary allylic CH group and two secondary allylic CH groups that are not deactivated by near-by ester substituents. In support of allylic hydrogen abstraction as a likely culprit, when triphenylsilanethiol (50 mol%) was used as catalyst in place of **16** and four portions of **15** (4×10 mol%) were added as initiator over 4 h at 125°C using octane solvent, the compound **30** was isolated in 60% yield.[16]

Further work is in progress to establish the scope of thiol-catalysed radical-chain cyclisation of unsaturated acetals and thioacetals and to optimise the conditions in order to improve yields and extend the generality of the reaction.

Acknowledgements

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10. This compound[3] (b.p. 98–100°C at 0.04 mmHg) was prepared by treatment of the sodium salt of dimethyl malonate with 2-bromomethyl-1,3-dioxolane in DMF–benzene at 80°C for 16 h, followed by alkylation of the sodium salt of the malonate product with allyl bromide.
11. Obtained from Peroxid-Chemie and handled as a 50% w/w solution in involatile aliphatic hydrocarbons. The half-life of this peroxide is ca. 1 h at 125°C.
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13. Representative procedure: A solution in dry octane (2.0 cm^3) containing the malonate **8** (0.52 g, 2.0 mmol), tri-*tert*-butoxysilanethiol (14 μl, 5 mol%) and DTBPB (23 μl of 50% solution, 5 mol%) was placed in a pre-heated oil bath at 125°C and stirred under argon for 2 h. The solvent was removed by evaporation under reduced pressure and the residue

was subjected to flash chromatography on silica gel (hexane:diethyl ether, 5:1 v/v as eluent) to give dimethyl 9-methyl-1,4-dioxaspiro[4.4]nonane-7,7-dicarboxylate **9**[3] as a clear oil (0.48 g, 92%). δ_H (500 MHz, $CDCl_3$ solvent, *J*=in hertz) 0.94 (3H, d, *J*=6.8, 9-Me), 1.95 (1H, dd, *J*=13.3 and 11.5, 8-H^A), 2.21 (1H, m, 9-H), 2.39 (1H, d, *J*=14.3, 6-H^A), 2.50 (1H, dd, *J*=13.3 and 7.6, 8-H^B), 2.57 (1H, d, *J*=14.3, 6-H^B), 3.72 (6H, s, 2 OMe), 3.92 (4H, m, 2 OCH_2); δ_C (125.8 MHz) 12.1, 38.8, 40.2, 42.8, 52.8, 52.9, 55.6, 64.8, 65.2, 116.1, 172.1, 172.6. (Incomplete NMR data for this compound were given in Ref. 3). In reactions where the thiol and initiator were added twice, 5 mol% of each was present initially and the second 5 mol% portion of each was added after 40 min; the total reaction time was extended to 2.5 h.

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16. Compound **29** (m.p. 65–66°C) was prepared in a similar way to **8**:[10] δ_H ($CDCl_3$) 1.28 (1H, m), 1.54 (1H, m), 1.77 (2H, m), 1.93 (2H, m), 2.28 (2H, dd, *J*=11.8 and 4.9), 2.94 (1H, m), 3.70 (3H, s, OMe), 3.72 (3H, s, OMe), 3.80 (2H, m), 3.90 (2H, m), 5.08 (1H, t, *J*=4.9), 5.72 (2H, br s, vinylic H); δ_C 22.3, 24.5, 24.9, 37.1, 40.4, 52.0, 52.3, 58.8, 64.6(9), 64.7(3), 102.0, 127.7, 128.8, 170.8, 171.1. Compound **30**: δ_H ($CDCl_3$) 1.15–1.70 (8H, m), 2.31 (1H, d, *J*=15.2), 2.37 (1H, m), 2.78 (1H, ddd, *J*=9.5, 7.1 and 6.5), 2.89 (1H, d, *J*=15.2), 3.70 (3H, s, OMe), 3.71 (3H, s, OMe), 3.77 (1H, m), 3.89 (2H, m), 3.94 (1H, m); δ_C 22.2, 22.6, 24.0, 24.2, 43.1, 43.5, 44.2, 52.4, 52.7, 60.9, 63.9, 65.0, 117.0, 170.4, 172.2. Satisfactory spectroscopic data and elemental analyses were obtained for all new compounds reported herein.