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Anti-Markovnikov addition to alkenes with a neighbouring thioacetal function☆

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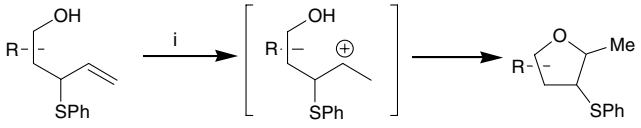
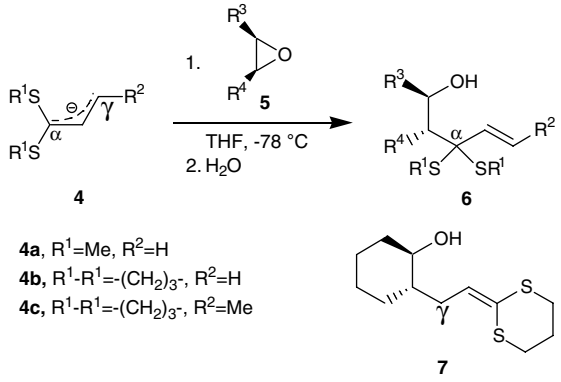
Abstract—The acid-induced cyclisation of unsaturated thioacetals **6** gives anti-Markovnikov products **9**, apparently involving sulfur elimination and readdition.

The cyclisation of 4-alken-1-ols ('bishomoallyl alcohols') mediated by electrophiles allows convenient access to tetrahydrofurans.[1–4] This is in accord with the 5-exo-trigonal mode of ring closure being an obviously particularly favoured process.[5] Formation of tetrahydrofurans **3** is also observed in the proton induced cyclisation of alkenols **1** with an allylic sulfide unit, as shown in Scheme 1.[6] However, here the proton transfer to the CC double bond may well be the rate-limiting step eliminating the need for a specific trajectory, but requiring adequate stabilisation of the charge in the intermediate carbocation **2**.[7] This is obviously achieved by obeying the Markovnikov rule, but additional stabilisation by the neighbouring sulfur in a thiiranium structure may be considered. The same cyclisation behaviour is a priori expected for alkenols **6** with a thioacetal unit,



1 2 3

Scheme 1. Reagents: (i) *p*-TsOH·H_2O benzene, 80 °C.



Scheme 2.

that is, just having one more sulfur than starting material **1**.

Precursors **1** are readily accessible from oxiranes and lithiated allyl sulfides.[8] Alkenols **6** with a thioacetal function can be synthesised analogously to **1** via ring-opening of epoxides **5** by the anions of acrolein or crotonaldehyde dithioacetals **4** (Scheme 2).

The attack of **5** occurs regioselectively at the position adjacent to the sulfur atoms; only in the ring-opening of cyclohexene oxide as oxirane component with **4b**, a small amount of the γ-product **7** along with **6e** was isolated (Table 1).

Treatment of alkenols **6** with *p*-toluenesulfonic acid analogous to the reaction **1** → **3** gives tetrahydropyrans **9** unexpectedly, and not the Markovnikov products **8**

Keywords: Cyclisation; Markovnikov rule; Regioselectivity; Tetrahydrofurans; Pyrans.

☆ Partly presented at the 19th International Symposium on the Organic Chemistry of Sulfur, Florence (July 1998); cf.: Schaumann, E.; Dreeßen, S., Schabbert, S., Tiedemann, R., *Phosphorus, Sulfur and Silicon* **1999**, *153/154*, 339–340.

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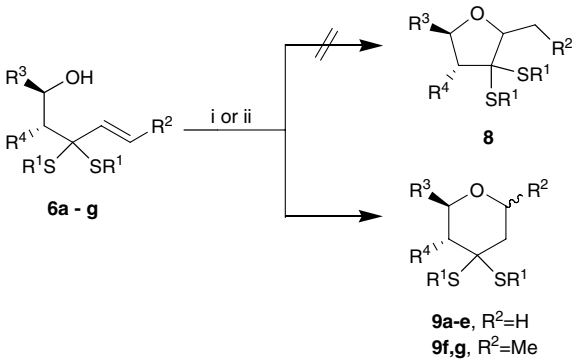
Table 1. Alcohols **6** from oxiranes **5** and carbanions **4**

Alcohol	R^1	R^1	R^2	R^3	R^4	Yield (%)
6a	Me	Me	H	$BnOCH_2$	H	50
6b	$-(CH_2)_3-$		H	Me	H	82
6c	$-(CH_2)_3-$		H	Et	H	97
6d	$-(CH_2)_3-$		H	$BnOCH_2$	H	70
6e	$-(CH_2)_3-$		H	$-(CH_2)_4-$		65[a]
6f	$-(CH_2)_3-$		Me	Me	H	93
6g	$-(CH_2)_3-$		Me	Et	H	90

[a] Mp 45 °C. Additional 7% of the γ-adduct **7** were isolated.

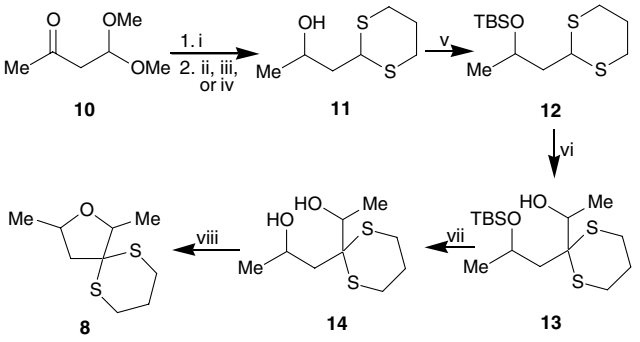


Scheme 3. Reagents: (i) 0.2 equiv *p*-TsOH·H_2O, toluene, 90 °C; (ii) 1 equiv *p*-TsOH·H_2O, CH_2Cl_2, rt.

(Scheme 3). The structure assignment of **9** is based on ^1H and ^{13}C NMR data; the characteristic feature is the presence of an OCH_2 (**9a**–**e**) or an OCHMe fragment (**9f**,**g**).

The yields of **9** are moderate to good. Remarkable is the very low yield in the formation of the methylthio derivative **9a**; attempts to cyclise alcohols **6** bearing phenylthio substituents (R^1 = Ph) under these conditions results in complete decomposition (Table 2).

The formation of **9** from alcohols **6** under ionic conditions is an apparent violation of the Markovnikov rule. To exclude thermodynamic control, that is, primary formation of tetrahydrofuran **8** and subsequent isomerisation to **9**,[9] we independently synthesised Markovnikov



Scheme 4. Reagents: (i) 1 equiv 1,3-propanedithiol, 0.2 equiv *p*-TsOH, benzene, 75%; (ii) baker's yeast, H_2O, $Na_4P_2O_7$, D-saccharose, 81%; (iii) 2 equiv L-Selectride, THF, 97%; (iv) 1.1 equiv $NaBH_4$, THF/EtOH-mixture, 97%; (v) 1.25 equiv TBSCl, 1.25 equiv imidazole, CH_2Cl_2, 97%; (vi) 1.1 equiv *n*-BuLi, 1.1 equiv acetaldehyde, THF, 88% two diastereomers; (vii) 1 equiv TBAF, THF, 92%, two diastereomers; (viii) 5 equiv *p*-TsCl, py, 79%, two diastereomers.

product **8** (Scheme 4). However, the obtained tetrahydrofuran **8** was absolutely stable under the reaction conditions of the cyclisation **6** → **9**. Consequently, it can be concluded that the formation of **9** from **6** occurs under kinetic control.

Further information on the mechanism of the cyclisation can be obtained from the use of uncommon, soft electrophiles like phenylselenyl halides or dimethyl(methylthio)sulfonium tetrafluoroborate.[10] Here, starting from **6e**,**g**, unstable dihydropyrans **16** are obtained, in which the dithiane ring has been opened by the sulfur or selenium electrophile (Scheme 5).

Obviously, the sulfur or selenium electrophiles attack primarily a sulfur atom of the dithiane ring, followed by the opening of the dithiane ring and formation of a sulfur-stabilised allyl cation **15**. Finally, nucleophilic attack of the alcohol function on the terminus of the allyl unit leads to the six-membered ring **16**.

On this basis, a mechanism for the formal anti-Markovnikov cyclisation **6** → **9** can be given: initial protonation of a dithiane sulfur in **6** and dithiane ring-opening gives cation **15** (E = H), which does not

Table 2. Cyclisation to **9**

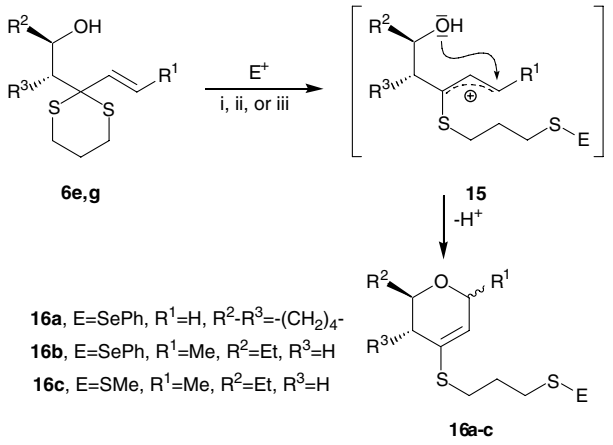
9	R^1	R^1	R^2	R^3	R^4	Method[a]	Yield (%)
9a	Me	Me	H	$BnOCH_2$	H	ii	13
9b	$-(CH_2)_3-$		H	Me	H	ii	31[b]
9c	$-(CH_2)_3-$		H	Et	H	i	42
9d	$-(CH_2)_3-$		H	$BnOCH_2$	H	i	18
9e	$-(CH_2)_3-$		H	$-(CH_2)_4-$		i	38[c]
9f	$-(CH_2)_3-$		Me	Me	H	i	44[d]
9g	$-(CH_2)_3-$		Me	Et	H	i	84[d]

[a] cf. Scheme 3.

[b] Typical analytical data for **9b**; mp 41 °C; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.0 Hz, 3H, CH_3), 1.63 (dd, ^2J = 14.0 Hz, ^3J = 11.2 Hz, 1H, MeCHCH_2), 1.86–2.10 (m, 3H, SCH_2CH_2, MeCHCH_2), 2.14–2.27 (m, 2H, OCH_2CH_2), 2.74–2.98 (m, 4H, SCH_2), 3.76–3.98 (m, 3H, MeCH, OCH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 68.6 (CH), 63.6 (CH_2), 47.8 (C), 45.1 (CH_2), 37.3 (CH_2), 25.84 (CH_2), 25.82 (CH_2), 25.7 (CH_2), 21.4 (CH_3). Anal. Calcd for $C_9H_{16}OS_2$: C 52.92, H 7.90, O 7.84, S 31.34. Found: C 53.05, H 7.89, O 7.99, S 31.24.

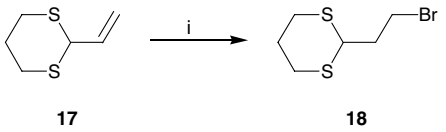
[c] Mp 71 °C.

[d] Mixture of two diastereomers.



Scheme 5. Reagents: (i) **6e**, 1.5 equiv PhSeCl, THF, −78 °C, 25% **16a**; (ii) **6f**, 1.1 equiv PhSeBr, 1.5 equiv NEt_3, THF, −78 °C, 57% **16b**, two diastereomers; (iii) **6f**, 1 equiv $Me_2S(SMe)BF_4$, THF, −60 °C, 75% **16c**, two diastereomers. Typical analytical data: major diastereomer (yield 41%); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 5.40$ (ddd, 1H, $J = 2.3$, 1.4, 0.9 Hz, 3-*H*), 4.14 (dddq, 1H, $J = 6.6$, 3.9, 3.1, 1.4 Hz, 2-H), 3.30 (dddd, 1H, $J = 10.4$, 7.2, 5.2, 3.2 Hz, 6-H), 2.54 (t, 1H, $J = 7.0$ Hz, SCH_2CH_2), 2.53 (t, 1H, $J = 7.0$ Hz, SCH_2CH_2), 2.49 (t, 2H, $J = 7.0$ Hz, SCH_2CH_2), 2.10 (dddd, 1H, $J = 16.4$, 10.4, 3.5, 2.3 Hz, 5-*H*), 1.99 (s, 3H, SCH_3), 1.89 (dddd, 1H, $J = 16.4$, 3.2, 2.6, 0.9 Hz, 5-H), 1.86 (m, 2H, $J = 7.0$ Hz, SCH_2CH_2), 1.56 (ddd, 1H, $J = 13.5$, 7.4, 7.2 Hz, CH_2CH_3), 1.36 (ddd, 1H, $J = 13.5$, 7.6, 5.2 Hz, CH_2CH_3), 1.20 (d, 3H, $J = 6.6$ Hz, CH_3), 0.90 (dd, 3H, $J = 7.6$, 7.4 Hz, CH_3CH_2). ^{13}C NMR (100 MHz, C_6D_6): $\delta = 130.8$ (*o*, C-4). 125.7 (+, C-3), 75.6 (+, C-6), 72.1 (+, C-2), 36.6, 28.7 (+, SCH_2CH_2), 35.5 (−, C-5), 29.1 (−, CH_3CH_2), 28.3 (−, SCH_2CH_2), 22.8 (+, SCH_3), 21.9 (+, CH_3), 10.0 (+, CH_3CH_2). Minor diastereomer (yield 34%); ^{1}H NMR (200 MHz, C_6D_6): $\delta = 5.39$ (ddd, 1H, $J = 2.8$, 2.0, 0.8 Hz, 3-H), 4.35 (dddq, 1H, $J = 9.6$, 6.5, 5.0, 2.0 Hz, 2-*H*), 3.50 (dddd, 1 H, $J = 7.7$, 7.4, 5.0, 4.2 Hz, 6-H), 2.51 (t, 2H, $J = 7.0$ Hz, SCH_2CH_2), 2.48 (t, 2H, CH_2CH_2), 2.00 (ddd, 1H, $J = 9.4$, 4.2, 0.8 Hz, 5-H), 2.00 (s, 3H, SCH_3), 1.84 (m, 2H, SCH_2CH_2), 1.63–1.23 (m, 1H, 5-H), 1.55 (ddd, 1 H, $J = 13.6$, 7.5, 7.4 Hz, CH_2CH_3), 1.33 (ddd, 1H, $J = 13.6$, 7.3, 5.0 Hz, CH_2CH_3), 1.12 (d, 3H, $J = 6.5$ Hz, CH_3), 0.90 (dd, 3H, $J = 7.5$, 7.3 Hz, CH_3CH_2). ^{13}C NMR (50 MHz, C_6D_6): $\delta = 130.0$ (*o*, C-4), 125.3 (+, C-3), 69.5 (+, C-6), 69.3 (+, C-2), 36.6, 28.8 (−, SCH_2CH_2), 35.2 (−, C-5), 28.3 (−, CH_3CH_2), 28.2 (−, SCH_2CH_2), 22.8 (+, SCH_3), 20.2 (+, CH_3), 10.1 (+, CH_3CH_2).

cyclise to a strained oxetane but to a dihydropyran **16** (E = H). Under the acidic reaction conditions, finally recyclisation to **9** occurs. Considering the temporary elimination of sulfur, it is no surprise that for a methylthio substitution this return of sulfur proceeds only to a limited extend (**9a**). Moreover, other reaction pathways can be envisaged for intermediates **15** (E = H) or **16** (E = H) and this may well explain the moderate yields of **9b–g**. In any case, primary attack of the electrophile on sulfur makes the formation of Markovnikov product **8** impossible (Scheme 6).



Scheme 6. Reagents: (i) 4 equiv HBr in HOAc, 5 °C, darkness, 76%.

Finally, we checked whether the influence of a thioacetal unit on the regiochemistry of electrophilic addition is limited to intramolecular reactions. Interestingly, the addition of hydrobromic acid to 2-vinyl-1,3-dithiane (**17**) under ionic conditions gives anti-Markovnikov product **18** in good yield.

Thus, the reversal of regiochemistry in electrophilic attacks on unsaturated thioacetals appears to be a general phenomenon.

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