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# Reactions of Oxathio-Substituted Crotyllithium with Alkyl Halides and Carbonyl Compounds. An Example of an Ambident Nucleophile

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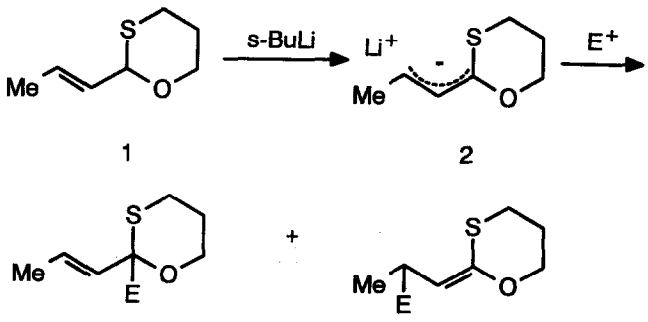
**Abstract:** The lithiated anion (**2**), obtained by treatment of 2-(1-propenyl)-1,3-oxathiane (**1**) with *sec*-BuLi, reacts with alkyl halides yielding substitution products predominantly at the α terminus; on the contrary, carbonyl compounds afford addition products at the γ terminus. The γ-adducts readily cyclize to spiro oxathianes.

The regioselectivity of unsymmetrically substituted allylic anions in reactions with electrophiles has been extensively studied.[2] Among the factors that control the regioselectivity may be included the nature of the attacking electrophile,[3] the nature[4] and the solvation[5] of the counterion, the effect of the substituents.[6] The reactions of allylic anions stabilized by halogen atoms with several organic substrates have been investigated by Seyferth, Mauzé and coworkers, and in our laboratory.[7] Carbanions stabilized by sulphur atoms have been well documented and, particularly, have been deeply investigated in umpolung[8] studies,[3,9] since Corey and Seebach first utilized 2-lithio-1,3-dithiane as an acyl anion equivalent.[10] On the contrary, the use of metallated 2-substituted 1,3-oxathiane is limited in synthetic organic chemistry, even if interesting differences in chemical




Scheme 1

behaviour between 1,3-dithiane and 1,3-oxathiane derivatives have been reported.[11] The purpose of the present paper is to describe the reactivity of lithiated 2-(1-propenyl)-1,3-oxathianyl anion towards different electrophiles, focusing the attention on the regioselectivity of the attack, that may occur at the α and/or γ terminus of the ambident anion (Scheme 1).

## RESULTS AND DISCUSSION

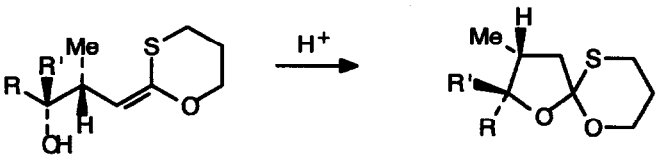
Treatment of crotonaldehyde with an equivalent amount of 3-mercaptopropanol in the presence of pyridinium *p*-toluensulfonate (PPTS) yielded 2-(1-propenyl)-1,3-oxathiane (**1**) in the *E* form. Oxathiane (**1**) resisted deprotonation by *n*-BuLi or LDA in tetrahydrofuran (THF) at -78 °C. Addition of *sec*-BuLi at that temperature gave rise to a weakly yellow solution that was quenched with $D_2O$. $^1H$ NMR and mass spectra of the deuteriated product showed almost 100% incorporation of deuterium at the heterosubstituted site of the propenylic system, indicating the formation of the anionic species lithium-2-(1-propenyl)-1,3-oxathiane (**2**). Oxathianyl anion (**2**) was allowed to react with different electrophiles, including carbonyl compounds and halkyl halides to yield addition and substitution derivatives, respectively. The results are reported in Table 1.

**Table 1.** Reactions of 2-(1-Propenyl)-1,3-Oxathianyl Anion (2) with Electrophiles

| entry | electrophile | α:γ,ratio[a] | yield,[b] % |
|---|---|---|---|
| 1 | $D_2O$ | 100:<1 | 83[c] |
| 2 | *n*-PrI | 100:<1 | 90[c] |
| 3 | *n*-BuI | 100:<1 | 94[c] |
| 4 | *n*-BuBr | 100:<1 | 92[c] |
| 5 | *n*-BuCl | 100:<1 | 65[c] |
| 6 | $Me_3SiCl$ | 100:<1 | 80[c] |
| 7 | PhCHO | <1:100 | 85[d] |
| 8 | PhCH=CHCHO | <1:100 | 78[d] |
| 9 | $PhCOCH_3$ | <1:100 | 71[d] |
| 10 | PhCOPh | <1:100 | 73[d] |

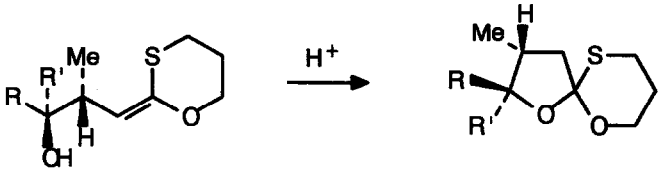
[a]By $^1H$ NMR (+/- 5%). [b]Isolated product. [c]Purified by Kugelrohr distillation. [d]Purified by column chromatography; total yield.

Deuteriated water reacts exclusively at the α (**3**) carbon of crotyllithium, evidencing that this is the hard nucleophilic centre. According to the hard and soft acids and bases (HSAB)[12] theory, the heterosubstituted terminus should preferentially react with hard electrophiles. Hard electrophiles should be considered $ClSi(CH_3)_3$ and carbonyl compounds;[13] consistently, $ClSi(CH_3)_3$ reacts at the α site of crotyllithium; on the contrary, the tested aldehydes and ketones react at the γ site (**4**). The structure of the γ-adduct was inferred in the $^1H$ NMR spectrum, by the appearance of a up-field doublet at *ca.* δ 1.0 attributable to the resonance of the γ-$CH_3$ group. The γ-addition was not diastereoselective (*syn/anti ca.* 1/1, by $^1H$ NMR analysis). The $^1H$ NMR and mass spectra of the γ-addition products (**4**) were carried out on the crude reaction products since, while undergoing the chromatographic purification, they spontaneously cyclize to spiro oxathiane (**5** - **6**; Scheme 2); in particular in the case of cinnamaldehyde the spiro oxathiane was the only isolated compound, also before the chromatographic purification.[14] Alkyl halides, that should be expected softer electrophiles,[15] give mainly the product corresponding to the attack at the α site. The same regiochemical outcome has been previously reported for ketene thioacetalides.[3,9(a),16] The α alkylation product invariably has a *trans*-configuration: the structure was characterized by the presence of a large coupling constant ($J$ = 16 Hz) in the resonance of β and γ vinyl protons in the $^1H$ NMR spectrum.



4a-anti, R = Ph; R' = H
4b-anti, R = CH=CH=Ph; R' = H
4c-anti, R = Ph; R' = Me
4d, R = R' = Ph

5a, R = Ph; R' = H
5b, R = CH=CHPh; R' = H
5c, R = Ph; R' = Me
5d, R = R' = Ph

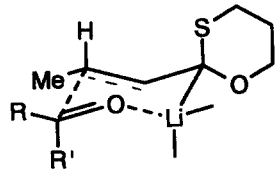


4a-syn, R = Ph; R' = H
4b-syn, R = CH=CHPh, R' = H
4c-syn, R = Ph; R' = Me
4d, R = R' = Ph

6a, R = Ph; R' = H
6b, R = CH=CHPh; R' = H
6c, R = Ph; R' = Me
5d, R = R' = Ph

Scheme 2

To account for the regioselectivity in the reaction of crotyllithium with aldehydes and ketones, a six-centre transition state (**7**) can be considered, where lithium at the α site co-ordinates the carbonyl oxygen, and leads to the γ addition product.[17] A second alternative would consider that the γ regioisomer is formed by a two-step electron-transfer process. A mechanistic pathway of this type has been demonstrated for reactions of Grignard reagents with ketones,[18] and has been previously considered.[3] However, there are factors which speak against an electron transfer mechanism: the absence of pinacol-type products,[7(a)] and of the α-γ dimer of the anion.[3] Further investigation will be required to establish the validity of this hypothesis.



## EXPERIMENTAL SECTION

All the reactions involving organolithium reagents were carried out under argon atmosphere in flame dried glassware. THF was dried by distillation from benzophenone ketyl. *sec*-BuLi (1.4 M solution in cyclohexane) was purchased from Aldrich. All chemicals commercially available were reagent grade and were used without further purification. $^1$H NMR spectra were recorded on a Hitachi Perkin Helmer R-24B 60 MHz high resolution spectrometer in $CDCl_3$, using TMS as internal standard. Mass spectra were recorded at 70 eV with a HP 5970 B mass selective detector connected to a HP 5890 GC, cross-linked methyl silicone capillary column. Preparative column chromatography was carried out on silica gel Merck Kieselgel 60 with diethyl ether-petroleum ether (40-70) as an eluant (5:95). 3-Mercaptopropanol was synthesized according to the literature.[19]

***2-(1-Propenyl)-1,3-oxathiane***

To a solution of 3.2 g (35 mmol) of 3-mercaptopropanol and 2.4 g (35 mmol) of crotonaldehyde in 50 mL of anhydrous benzene was added PPTS 80 mg (0.3 mmol). The mixture was refluxed for 1 h in a Marcusson apparatus, then cooled at room temperature and washed successively with aqueous $NaHCO_3$ (5%), and water. The toluene solution was dried ($K_2CO_3$), filtered and concentrated under *vacuum* to yield a crude oil which was distilled to give 2.5 g (52%) of pure 2-(1-propenyl)-1,3-oxathiane (**1**): bp 85 °C (11 mmHg); MS, *m/z* (relative intensity) 144 (64, $M^+$), 129 (57), 74 (65), 41 (100); $^1$H NMR ($CDCl_3$) δ 1.75 (3 H, dd, $J$ = 6, 1 Hz), 1.80-4.25 (6 H, m), 5.15 (1 H, d, $J$ = 6 Hz), 5.25-6.15 (2 H, m). Anal. Calcd. for $C_7H_{12}OS$: C, 58.29; H, 8.39. Found: C, 58.12; H, 8.31.

***General Procedure for Reaction of Crotyllithium (2) with Electrophiles***

Under an atmosphere of argon 1.0 mL of *sec*-BuLi (1.4 mmol, 1.4 M in cyclohexane) was added dropwise with a syringe to a solution of 180 mg of (**1**) (1.25 mmol) in anhydrous THF (5 mL) at -78 °C. After stirring for 60 min, during which the temperature rises at *ca.* -60 °C, the resulting solution of crotyllithium (**2**) was cooled at -78 °C. A solution of desired electrophile (1.25 mmol) in THF (1.5 mL) was added dropwise. After being stirred for 2 h, the reaction was quenched by addition of water. The mixture was extracted with diethyl ether, the ethereal layer washed two time with brine, dried ($Na_2SO_4$) and, after filtration, concentrated under *vacuum*, to afford an oil that was analysed by TLC and $^1$H NMR before being purified by column chromatography or Kugelrohr distillation.

*Deuteriated Water: 3 a.* MS, *m/z* (relative intensity) 145 (88, $M^+$), 130 (75), 74 (98), 56 (78), 41 (100); $^1$H NMR ($CDCl_3$) δ 1.75 (3 H, dd, $J$ = 6, 1.2 Hz), 1.80-4.35 (6 H, m), 5.45 (1 H, d, $J$ = 16 Hz), 5.85 (1 H, dq, $J$ = 16, 6 Hz). Anal. Calcd. for $C_7H_{11}DOS$: C, 57.89; H, 7.64. Found: C, 57.93; H, 7.60.

*n-Propyl Iodide: 3 b.* MS, *m/z* (relative intensity) 186 (42, $M^+$), 143 (98), 113 (84), 69 (100), 41 (99); $^1$H NMR ($CDCl_3$) δ 0.95 (3 H, t, $J$ = 6 Hz), 1.80 (3 H, dd, $J$ = 6, 1.2 Hz), 1.10-4.35 (10 H, m), 5.30 (1 H, dq, $J$ = 16, 1.2 Hz), 5.95 (1 H, dq, $J$ = 16, 6 Hz). Anal. Calcd. for $C_{10}H_{18}OS$: C, 64.46; H, 9.74. Found: C, 64.80; H, 9.69.

*n-Butyl Iodide: 3 c.* MS, *m/z* (relative intensity) 200 (5, $M^+$), 143 (60), 69 (92), 41 (100); $^1$H NMR ($CDCl_3$) δ 0.95 (3 H, t, $J$ = 6 Hz), 1.75 (3 H, dd, $J$ = 6, 1.2 Hz), 1.05-4.15 (12 H, m), 5.25 (1 H, dq, $J$ = 16, 1.2 Hz), 5.95 (1 H, dq, $J$ = 16, 6 Hz). Anal. Calcd. for $C_{11}H_{20}OS$: C, 65.94; H, 10.06. Found: C, 65.65; H, 9.96.

*Chlorotrimethylsilane: 3 d.* MS, *m/z* (relative intensity) 216 (3, $M^+$), 201 (12), 143 (84), 73 (50), 69 (100), 41 (95); $^1$H NMR ($CDCl_3$) δ 0.10 (9 H, s), 1.80 (3 H, d, $J$ = 6 Hz), 1.60-4.05 (6 H, m), 5.40 (1 H, d, $J$ = 16 Hz), 5.85 (1 H, dq, $J$ = 16, 6 Hz). Anal. Calcd. for $C_{10}H_{20}OSSi$: C, 55.50; H, 9.32. Found: C, 55.45; H, 9.38.

*Benzaldehyde:* γ-*syn-4 a.* $^1$H NMR ($CDCl_3$) δ 0.95 (3 H, d, *J* = 6 Hz), 1.60-4.10 (7 H, m), 4.40 (1 H, d, *J* = 6 Hz), 5.75 (1 H, d, *J* = 8 Hz), 7.20 (5 H, s). γ-*anti-4 a.* $^1$H NMR ($CDCl_3$) δ 1.00 (3 H, d, *J* = 6 Hz), 1.60-4.10 (7 H, m), 4.60 (1 H, d, *J* = 6 Hz), 5.65 (1 H, d, *J* = 9 Hz), 7.20 (5 H, s); MS *m/z* (relative intensity) 250 (2, $M^+$), 143 (100), 105 (44), 77 (49), 69 (100), 41 (47).

*Benzaldehyde: cis-spiro-6 a.* $^1$H NMR ($CDCl_3$) δ 0.60 (3 H, d, *J* = 7 Hz), 1.60-2.80 (6 H, m), 3.10-4.70 (3 H, m), 5.15 (1 H, d, *J* = 7 Hz), 7.20 (5 H, s). *trans-spiro-5 a.* $^1$H NMR ($CDCl_3$) δ 0.65 (3 H, d, *J* = 6 Hz), 1.60-2.80 (6 H, m), 3.10-4.70 (3 H, m), 5.20 (1 H, d, *J* = 9 Hz), 7.20 (5 H, s); MS *m/z* (relative intensity) 250 (16, $M^+$), 176 (44), 158 (65), 129 (44), 105 (58), 74 (66), 41 (100). Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25. Found: C, 66.85; H, 7.29.

*Cinnamaldehyde: cis-spiro-6 b.* $^1$H NMR ($CDCl_3$) δ 0.95 (3 H, d, *J* = 6.5 Hz), 1.60-4.05 (9 H, m), 4.70 (1 H, dd, *J* = 8, 6.5 Hz), 6.05 (1 H, dd, *J* = 16, 6.5 Hz), 6.55 (1 H, d, *J* = 16 Hz), 7.15 (5 H, br s). *trans-spiro-5 b* $^1$H NMR ($CDCl_3$) δ 1.0 (3 H, d, *J* = 6 Hz), 1.60-4.05 (9 H, m), 4.60 (1 H, dd, *J* = 8, 6.5 Hz), 6.10 (1 H, dd, *J* = 16, 6.5 Hz), 6.60 (1 H, d, 16 Hz), 7.20 (5 H, br s); MS, *m/z* (relative intensity) 276 (86, $M^+$), 156 (53), 142 (100), 129 (65), 91 (32), 41 (26). Anal. Calcd. for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.30; H, 7.24.

*Acetophenone:* γ-*syn-4 c.* $^1$H NMR ($CDCl_3$) δ 0.90 (3 H, d, *J* = 7 Hz), 1.50 (3 H, s), 1.60-4.10 (7H, m), 4.75 (1 H, d, *J* = 9.5 Hz, 7.25 (5 H, br s).γ-*anti-4 c.* $^1$H NMR ($CDCl_3$) δ 0.85 (3 H, d, *J* = 7 Hz), 1.48 (3 H, s), 1.60-4.10 (7 H, m), 4.90 (1 H, d, *J* = 9.5 Hz), 7.25 (5 H, br s); MS, *m/z* (relative intensity) 264 (13, $M^+$), 191 (53), 145 (92), 131 (87), 129 (939, 105 (100), 91 (72), 77 (53), 41 (86).

*Acetophenone: cis-spiro-6 c.* $^1$H NMR ($CDCl_3$) δ 0.60 (3 H, d, *J* = 7 Hz), 1.70 (3 H, s), 1.10-4.60 (9 H, m), 7.25 (5 H, br s). *trans-spiro-5 c.* $^1$H NMR ($CDCl_3$) δ 0.55 (3 H, d, *J* = 7 Hz), 1.70 (3 H, s), 1.10-4.65 (9 H, m), 7.25 (5 H, br s); MS, *m/z* (relative intensity) 264 (11, $M^+$), 191 (53), 145 (100), 131 (86), 129 (939, 105 (87), 91 (57), 77 (57), 41 (88). Anal. Calcd. for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.62. Found: C, 68.10.; H, 7.68.

*Benzophenone:* γ *4 d.* $^1$H NMR ($CDCl_3$) δ 0.90 (3 H, d, *J* = 7 Hz), 1.60-4.10 (7 H, m), 4.90 (1 H, d, *J* = 9 Hz), 7.00-7.55 (10 H, br s). MS, *m/z* (relative intensity) 326 (8, $M^+$), 234 (53), 129 (100), 105 (19), 91 (98), 77 (22), 41 (43). *spiro 6 d.* $^1$H NMR ($CDCl_3$) δ 0.85 (3 H, d, *J* = 7 Hz), 1.60-4.10 (9 H, m), 7.00-7.55 (10 H, br s). MS, *m/z* (relative intensity) 326 (14, $M^+$), 234 (87), 129 (92), 105 (100), 93 (91), 77 (57), 41 (55). Anal. Calcd. for $C_{20}H_{22}O_2S$: C, 73.58; H, 6.79. Found: C, 73.40; H, 6.73.

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