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Functionally Substituted Vinyl Carbanions, 29[1]

# Reaction of a β-Lithiated Acrylate with Oxetanes as Electrophiles

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**Funktionell substituierte Vinylcarbanionen, 29[1]**

**Reaktion einer β-lithiierten Acrylsäure mit Oxetanen als Electrophil**

β-Lithiiertes β-(Ethylthio)acrylat **1A** reagiert mit den Oxetanen **2** bzw. (±)-**5** in Anwesenheit von Bortrifluorid-Ether zu den entsprechenden γ-hydroxypropyl-substituierten Derivaten **3** bzw. **6**. Von den 2-Alkyl/phenyl-3-ethoxy-oxetanen (±)-**5** reagieren die *erythro*-Derivate deutlich rascher als die *threo*-Derivate.

β-Lithiated functionally substituted acrylates react with carbonyl compounds as electrophilic-nucleophilic species to give butenolides, tetronates, γ-lactones, and corresponding natural products[2,3]. With epoxides as electrophilic-nucleophilic species reaction was only observed when boron trifluoride-ether was added as a catalyst[4]. The α,β-unsaturated δ-lactones thus obtained provide a convenient entry into a variety of δ-lactone-type compounds. Enantiomerically pure epoxides were used for natural product syntheses[4,5]. Here we report on analogous reactions of oxetanes as electrophilic species.

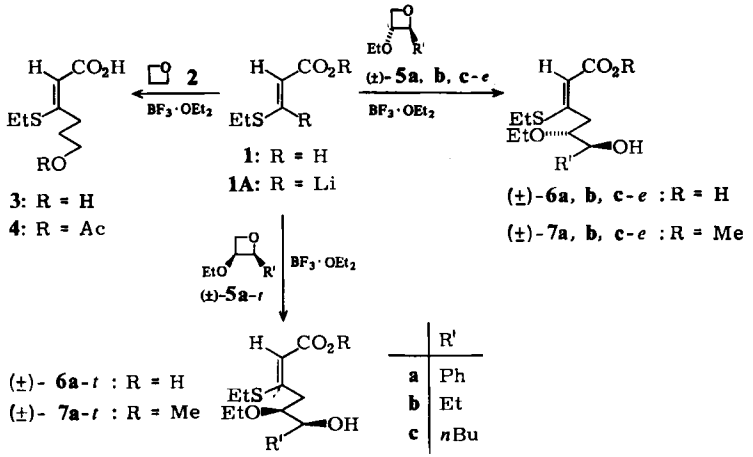



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Table 1. Analytical and physical data of compounds **4**, **7a–c–e**, and **7a–t**

| Compound | Yield[a] [%] | m.p. [°C] | Molecular Formula | Analysis Calcd. | Found | $^1$H-NMR (250 MHz, $CDCl_3$, TMS int.)[b] δ-values |
|---|---|---|---|---|---|---|
| (2E)-6-Acetoxy-3-(ethylthio)-2-hexenoic acid (**4**) | 51 | 70 | $C_{10}H_{16}O_4S$ (232.2) | C 51.70<br>H 6.94 | 51.91<br>7.16 | 11.2(br.s,1H,COOH), 5.42(s,1H,H-2), 4.20(t,2H,2H-6,J=6Hz), 2.9 (q,4H), 2H-4 and S-$CH_2$-$CH_3$, J=7Hz), 2.0 (s, 3H,$COCH_3$), 2.0-1.7 (m,2H,2H-5), 1.3 (t,3H,$CH_3$,J=7Hz). |
| Methyl (±)-erythro-(2E)-5-Ethoxy-3-(ethylthio)-6-hydroxy-6-phenyl-2-hexenoate (**7a-e**) | 55 | oil | $C_{17}H_{24}O_4S$ (324.4) | C 62.94<br>H 7.45 | 62.71<br>7.40 | 7.5-7.2(m,5H,$C_6H_5$), 5.51 (s,1H,H-2), 4.75(dd,1H,H-6,J=5.2 and 3.6Hz), 3.75 (m,1H,H-5),3.65(s,3H,OMe), 3.5-3.25 (m,4H,OH,H-4, and O-$CH_2$-$CH_3$), 2.8 (m, 3H,H-4' and -S-$CH_2$-$CH_3$), 1.3 (t,3H, S-$CH_2$-$CH_3$,J=7.3Hz), 1.0 (,3H,O-$CH_2$-$CH_3$,J=7Hz). |
| Methyl (±)-threo-(2E)-5-Ethoxy-3-(ethylthio)-6-hydroxy-6-phenyl-2-hexenoate (**7a-t**) | 31 | oil | $C_{17}H_{24}O_4S$ c) (324.4) | | | 7.5-7.2(m,5H,$C_6H_5$), 5.51 (s,1H,H-2), 4.75 (dd,1H,H-6,J=5.3 and 3.6 Hz), 3.75 (m,1H,H-5), 3.65(s,3H,OMe), 3.5-3.25 (m,3H,OH and O-$CH_2$-$CH_3$), 3.10 (dd,1H,H-4,J=14.1 and 3.5 Hz), 2.95 (dd,1H,H-4',J=14.1 and 8.5 Hz), 2.75 (q,2H,-S-$CH_2$-$CH_3$,J=7.3 Hz), 1.3 (t,3H, -S-$CH_2$-$CH_3$,J=7.3Hz), 1.05 (t,3H,O-$CH_2$-$CH_3$,J=7 Hz). |
| Methyl (±)-erythro-(2E)-5-Ethoxy-3-(ethylthio)-6-hydroxy-2-octenoate (**7b-e**) | 50 | oil | $C_{13}H_{24}O_4S$ (276.3) | C 56.50<br>H 8.74 | 56.52<br>8.70 | 5.55(s,1H,H-2), 3.70(s,3H,OMe),3.55 (m,4H,H-5,H-6, and O-$CH_2$-$CH_3$), 3.15 (dd,1H,H-4,J=14 and 3.7Hz), 2.95(dd, 1H,H-4',J=14 and 7.6Hz), 2.8(q,2H,S-$CH_2$-$CH_3$,J=7.6Hz), 2.65 (br.s,1H,OH), 1.7-1.5 (m,2H,2H-7), 1.35 (t,3H,S-$CH_2$-$CH_3$,J=7.6Hz), 1.15 (t,3H,O-$CH_2$-$CH_3$,J=7Hz), 1.0 (t,3H,3H-8,J=7Hz). |
| Methyl (±)-erythro-(2E)-5-Ethoxy-3-(ethylthio)-6-hydroxy-2-decenoate (**7e-e**) | 45 | oil | $C_{15}H_{28}O_4S$ (304.2) | C 59.18<br>H 9.27 | 59.01<br>9.13 | 5.54 (s,1H,H-2), 3.7 (m,4H,H-6 and OMe), 3.5 (m,3H,H-5 and O-$CH_2$-$CH_3$), 3.25 (dd,1H,H-4,J=13.3 and 6.3Hz), 2.88 (dd,1H,H-4',J=13.3 and 6.4Hz), 2.80 (q,2H,S-$CH_2$-$CH_3$,J=7.3Hz), 2.70 (d,1H,OH,J=6Hz), 1.6-1.25 (m,9H,2H-7, 2H-8,2H-9, and S-$CH_2$-$CH_3$), 1.2 (t,3H, O-$CH_2$-$CH_3$, J=7Hz), 0.9 (t,3H,3H-10, J=7Hz). |

[a] Yields refer to pure isolated products. – [b] Bruker WM 250 Cryospectrometer. – [c] Not analyzed.

β-(Ethylthio)acrylic acid (**1**) was converted with two equivalents of *tert*-butyllithium into the corresponding dilithiated species **1A**[4,6]. Addition of oxetane (**2**)[7] in the presence of boron trifluoride-ether as a catalyst afforded hydroxypropylation product **3**; ring closure to the corresponding ε-lactone was not observed. Reaction with acetic anhydride in pyridine furnished exclusively *O*-acetyl derivative **4**. Interesting stereoselectivities were observed with the *erythro*- and *threo*-oxetanes (±)-**5a,c–e** and (±)-**5a–c–t**, respectively, which were obtained via known [2 + 2]-photocycloaddition procedures[8]. Reaction of **1A** with (±)-**5a–e** gave via attack at the $CH_2$ group of (±)-**5a–e** the *erythro*-isomer (±)-**6a–e**, which was transferred with diazomethane into methyl ester (±)-**7a–e**. Similarly, from (±)-**5a–t**

compounds (±)-**6a**–*t* and (±)-**7a**–*t*, respectively, were obtained. However, a 1:1 mixture of excess (±)-**5a**–*e,t* yielded compounds (±)-**6a**–*e* and (±)-**6a**–*t* in a >15:1 ratio, thus demonstrating the much higher reactivity of the *erythro*-oxetane **5a**–*e*. The same result was observed with 1:1 mixtures of compounds (±)-**5b**–*e,t* and (±)-**5c**–*e,t*. Compounds (±)-**5b** afforded the diastereoisomers (±)-**6b**–*e* and (±)-**6b**–*t* in a >10:1 ratio; from this mixture only the *erythro*-methyl ester **7b**–*e* was isolated and identified. From compounds (±)-**5c** only the *erythro*-isomer (±)-**7c**–*e* could be isolated after diazomethane treatment of the crude reaction product of (±)-**6c**.

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## Experimental Part

*General Procedure for the Synthesis of Compounds* **4**, (±)-**7a**–**c**–*e, and* (±)-**7a**–*t*: To a solution of 5.0 mmol of **1** in 30 ml of dry tetrahydrofuran at −80°C is added dropwise under nitrogen 8.4 ml of a 1.3 M solution of *tert*-butyllithium in *n*-hexane. The mixture is stirred at the same temp. for another 2 h and then 5.0 mmol of $BF_3 \cdot OEt_2$ (distilled over $CaH_2$) is introduced dropwise into the flask with a syringe against a flow of nitrogen. Immediately after $BF_3 \cdot OEt_2$ addition 5.5 mmol of oxetane **2** or (±)-**5a**–**c** is introduced and the reaction temp. is allowed to reach 0°C over 1 h. A saturated solution of 15 ml of sodium hydrogen carbonate is then added and the temp. allowed to reach 20°C. The reaction mixture is poured into water, acidified with HCl to pH 1, and extracted with dichloromethane (4 × 100 ml). The organic phase is washed with 100 ml of water, dried over sodium sulfate and evaporated. The obtained compounds **3** and **6a**–**c** were transferred into *O*-acetyl derivative **4** by treatment with excess acetic anhydride/pyridine and into methyl esters (±)-**7a**–**c** by treatment with excess diazomethane in ether. The products were purified by flash chromatography on silica gel (Merck, 230–400 mesh ASTM) with petroleum ether (b.p. 35–80°C)/ethyl acetate (4:1) as solvent system. For yields, elemental analyses, and $^1H$ NMR data see Table 1.

CAS Registry Numbers

**1**: 101541-97-3 / **1a**: 101519-17-9 / **2**: 503-30-0 / **3**: 101541-98-4 / **4**: 101541-99-5 / (±)-**5a**-*e*: 101542-00-1 / (±)-**5a**-*t*: 101542-01-2 / (±)-**5b**-*e*: 101542-04-5 / (±)-**5b**-*t*: 101542-05-6 / (±)-**5c**-*e*: 101542-09-0 / (±)-**5c**-*t*: 101542-10-3 / (±)-**6a**-*e*: 101565-08-6 / (±)-**6a**-*t*: 101542-02-3 / (±)-**6b**-*e*: 101542-06-7 / (±)-**6b**-*t*: 101542-07-8 / **6c**: 101542-12-5 / (±)-**7a**-*e*: 101565-12-2 / (±)-**7a**-*t*: 101542-03-4 / (±)-**7b**-*e*: 101542-08-9 / (±)-**7c**-*e*: 101542-11-4

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[1] Part 28.: *N. C. Barua* and *R. R. Schmidt*, Tetrahedron, accepted for publication.
[2] *R. R. Schmidt*, Bull. Soc. Chim. Belg. **92**, 825 (1983); *R. R. Schmidt* in Organic Synthesis an Interdisciplinary Challenge, V th IUPAC Symposium, *J. Streith, H. Prinzbach, G. Schill* editors, p. 281, Backwell Scientific Publications, Oxford 1985.
[3] *N. C. Barua* and *R. R. Schmidt*, Synthesis, accepted for publication.
[4] *N. C. Barua* and *R. R. Schmidt*, Synthesis, accepted for publication.
[5] *N. C. Barua* and *R. R. Schmidt*, Tetrahedron, accepted for publication.
[6] *R. Betz*, Thesis, Universität Konstanz 1984.
[7] Compound **2** is commercially available from Aldrich Company.
[8] [8a] *G. Jones II*, Org. Photochem. **5**, 1 (1981). – [8b] *S. H. Schroeter* and *C. M. Orlando jr.*, J. Org. Chem. **34**, 1181 (1969).

[10/86]