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Formation of cycloheptatrienes by alkyllithium induced cyclisation of polyunsaturated enol ethers

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Abstract—Two polyunsaturated enol ethers have been shown to react with *t*-butyllithium in THF with formation of cycloheptatriene derivatives as the major volatile products. This novel reaction is explained as a 7-*endo*-trig cyclisation of the allylic lithium derivative formed by deprotonation at C-5.

In connection with our work aimed at the synthesis of the naturally occurring (all-*Z*)-pentadeca-3,6,9,12-tetraen-1-yne (**1**, laurencenyne),[1] we tried to convert the enol phosphate derivative **2** into an ethynyl group; the transformation was particularly tempting since aldehyde **3a**, the precursor of the enol phosphate, was readily available to us.[2] There are examples of this type of transformation in the literature;[3] however, treatment of enol phosphate **2** with different bases gave no detectable amount of acetylene **1** in the product mixtures (Fig. 1). We then considered transforming an enol ether functionality into an ethynyl group. It is well documented that organolithiums normally metallate vinyl ethers at the α-position,[4] and acetylenes have been reported as products from such reactions.[5] Hence, we set out to test this possibility with aldehydes **3** as starting materials.

Aldehyde **3a** was converted to the dimethyl acetal **4a**,[6] which was further transformed with TMS triflate and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2[7] to enol ether **5a** in 81% yield, as a 1:5 mixture of 1*Z*- and 1*E*-isomers.[8] Reaction of **5a** with *t*-BuLi at −78 °C in the presence of DIPEA gave a mixture of products.[9] A volatile compound was obtained in 51% yield after separation from the high-boiling products by chromatography on alumina, and HRMS proved it to be a $C_{15}H_{20}$ hydrocarbon, but not desired acetylene **1**. The hydrocarbon exhibited UV absorption maxima (cyclohexane) at 211 nm (ε 15,700) and 243 nm (ε 4300), characteristic of 7-alkylcycloheptatrienes,[10] and further spectral data established the structure as (all-*Z*)-7-(2,5-octadienyl)-1,3,5-cycloheptatriene (**6a**).[11] As expected the signals in the ^{13}C NMR spectrum due to the olefinic carbons of the cycloheptatriene moiety appear at frequencies almost identical to those reported for 7-ethylcycloheptatriene.[12] When vinyl ether **5b**, prepared from acetal **4b**,[6] was treated with *t*-BuLi in the same way as described[9] for **5a**, cycloheptatriene derivative **6b**[11] was formed, albeit in only 25% yield. In both cases, cyclisation took place in the absence of DIPEA, but in lower yields. These results were indeed unexpected, but formation of cycloheptatrienes **6** can be rationalised as outlined in Scheme 1.

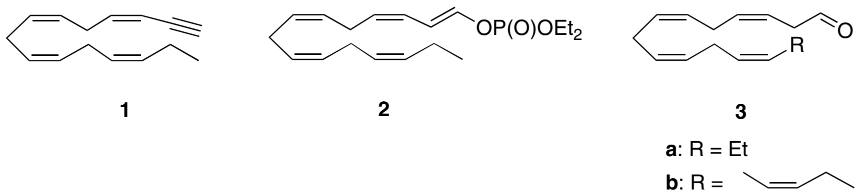

Figure 1.

Keywords: Cycloheptatrienes; Organolithium; Cyclisation.

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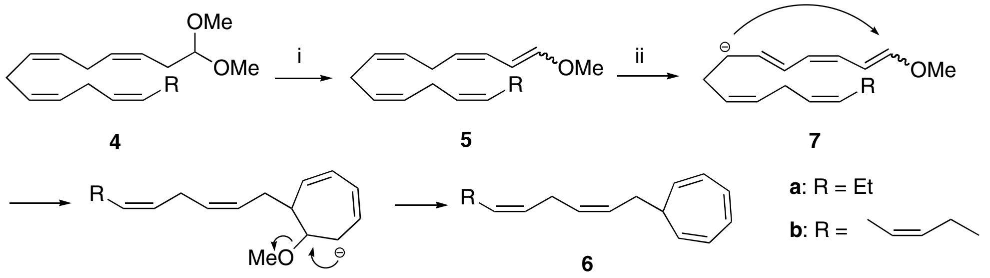

Scheme 1. Reagents and conditions: (i) TMS triflate, DIPEA, CH_2Cl_2, −20 to 0 °C; (ii) *t*-BuLi, DIPEA, THF, −78 to −10 °C, 3 h.

The acidity of 1,4-pentadiene is known,[13] but we have not found comparable data for vinyl ethers. On the other hand, both 1,4-pentadiene[14] and methyl vinyl ether[15] have been shown to undergo metallation with *t*-butyllithium under conditions similar to ours. Hence, it is reasonable to assume that deprotonation takes place at C-5 forming a doubly allylic lithium derivative. Subsequent cyclisation of this intermediate **7** followed by methoxide elimination leads to the observed cycloheptatrienes. This is formally a 7-*endo*-trig cyclisation that is favoured according to Baldwin's rules, while the alternative cyclisation path, 5-*endo*-trig, leading to a cyclopentadiene is disfavoured. We believe the effect of DIPEA is that of complexing the allylic lithium intermediate, but surprisingly the presence of TMEDA did not improve the yields.

Intramolecular addition of organolithiums to double bonds is a well documented reaction; cyclisations to five-membered carbocyclic and heterocyclic rings have been particularly well studied and the reaction is useful synthetically.[16] However, there seems to be no precedence in the literature for organolithium cyclisations leading to seven-membered rings, and neither have we found examples of organolithium additions to enol ethers. In conclusion, it appears that formation of cycloheptatrienes is to be expected from reactions of this class of enol ethers with organolithiums, and further studies are in progress aiming at the scope of this novel reaction.

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8. *Selected spectral properties.*
   Compound **5a**, *Z*-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.5$ Hz, 3H), 2.06 (m, 2H), 2.7–3.0 (m, 6H), 3.63 (s, 3H), 5.1–5.5 (m, 8H), 5.93 (br d, $J = 6.4$ Hz, 1H), 6.32 (br t, $J = 11.1$ Hz, 1H). *E*-isomer: δ 0.96 (t, $J = 7.5$ Hz, 3H), 2.06 (m, 2H), 2.7–3.0 (m, 6H), 3.58 (s, 3H), 5.2–5.5 (m, 7H), 5.72 (br d, $J = 6.4$ Hz, 1H), 5.8–5.9 (m, 1H), 6.58 (d, $J = 12.2$ Hz, 1H).
   Compound **5b**, *Z*-isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.5$ Hz, 3H), 2.06 (m, 2H), 2.7–3.0 (m, 8H), 3.64 (s, 3H), 5.2–5.5 (m, 10H), 5.93 (br d, $J = 6.1$ Hz, 1H), 6.32 (br t, $J = 11.2$ Hz, 1H). *E*-isomer: δ 0.96 (t, $J = 7.5$ Hz, 3H), 2.06 (m, 2H), 2.7–3.0 (m, 8H), 3.59 (s, 3H), 5.2–5.5 (m, 9H), 5.7–5.9 (m, 2H), 6.58 (d, $J = 11.9$ Hz, 1H).
9. *General procedure for reactions of the enol ethers* **5** *with t-butyllithium.* To a solution of enol ether **5** (0.86 mmol) in THF (5 ml), kept at −78 °C, *N*,*N*-diisopropylethylamine (0.95 mmol) and *t*-butyllithium (1.1 M in pentane, 0.95 mmol) were added. The mixture was stirred for 2 h while the temperature was allowed to rise to −20 °C. After an additional hour at this temperature the reaction was quenched with satd aq NH_4Cl solution, and extracted with ether. Evaporation of solvents under reduced pressure and chromatography of the residue on basic alumina gave hydrocarbon **6**.
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11. *Selected spectral properties.*
    Compound **6a**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.5$ Hz, 3H), 1.7–1.8 (m, 1H), 2.07 (m, 2H), 2.48 (m, 2H), 2.83 (m, 2H), 5.18 (dd, $J = 9.1$ and 5.4 Hz, 2H), 5.3–5.5 (m, 4H), 6.1–6.2 (m, 2H), 6.63 (br t, $J = 3$ Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 20.6, 25.8, 30.6 ($3 \times CH_2$), 38.9 (CH), 124.9, 126.3, 130.9 (cycloheptatrienyl CH=), 127.0, 127.3, 130.0, 132.0 ($4 \times CH{=}$).
    Compound **6b**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.7–1.8 (m, 1H), 2.08 (m, 2H), 2.5–2.6 (m, 2H), 2.7–3.0 (m, 4H), 5.19 (dd, $J = 9.1$ and 5.4 Hz, 2H), 5.3–5.5 (m, 6H), 6.1–6.2 (m, 2H), 6.64 (br t, $J = 3$ Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 20.5, 25.5, 25.8, 30.6 ($4 \times CH_2$), 38.9 (CH), 124.9, 126.2, 130.9 (cycloheptatrienyl CH=), 127.0, 127.5, 127.8, 128.5, 129.6, 132.0 ($6 \times CH{=}$).
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