Selectivity of the Lewis acid-induced transformations of polyfunctional compounds containing a 4,6-dialkoxy-7-(arylthio)heptene moiety

Dmitrii S. Chekmarev,[a] Andrei V. Maskaev,[a] Georgy V. Zatonsky,[b] Margarita I. Lazareva,[b,c] Ron Caple[c] and William A. Smit*[b]

[a] *Higher Chemical College, Russian Academy of Sciences, 125047 Moscow, Russian Federation. Fax: +7 095 200 4204*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation.*
Fax: +7 095 135 5328
[c] *Department of Chemistry, University of Minnesota-Duluth, Duluth, Minnesota 55812, USA*

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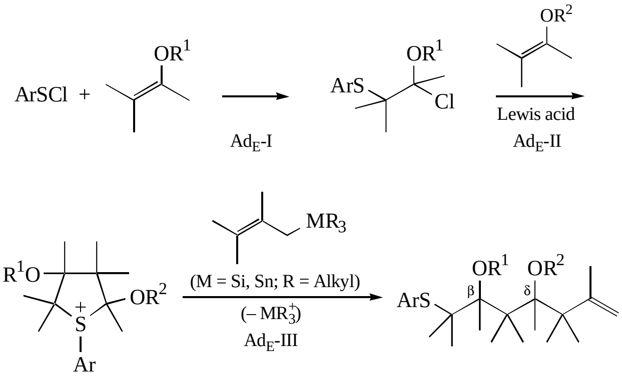
The interaction of the title adducts with Lewis acids may proceed as an attack at either β-alkoxy or δ-alkoxy group to the arylthio substituent leading to the formation of substituted cyclohexane or 1,3-diene derivatives, respectively.

As was reported earlier, a set of structurally diverse adducts containing a 7-arylthio-4,6-dialkoxyheptene moiety can be readily assembled from four simple precursors with the help of the one-pot protocol that involves three consecutive intermolecular Ad_E reactions (Scheme 1).[1(a)–(d)]



Scheme 1

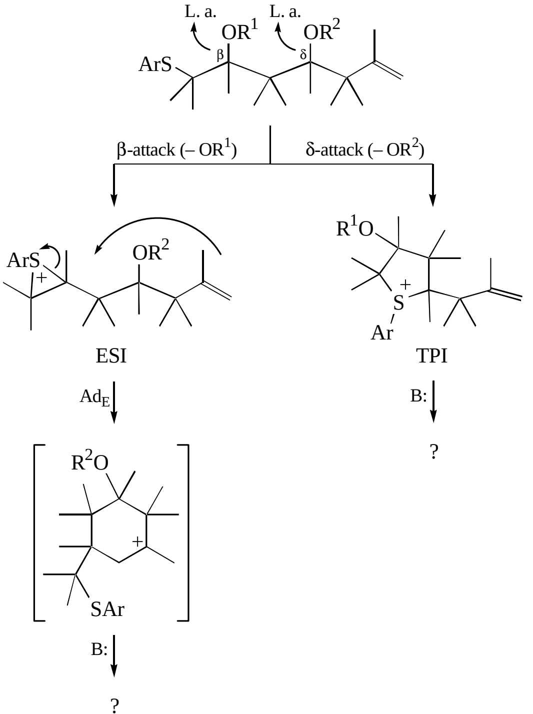
These compounds can be used as substrates for further reactions. We report here the Lewis acid-induced reactions of the title adducts.

It seems reasonable to assume that an initial attack of a Lewis acid could be directed at either β- or δ-alkoxy group of the adducts (Scheme 2). In both cases, the subsequent elimination of an alkoxy group should be facilitated by the nucleophilic assistance of the properly positioned arylthio substituent. Hence, the formation of either the episulfonium ion (ESI) or the thiophanium ion (TPI) as an intermediate is to be expected as an immediate result of the β- or δ-attack, respectively.

As found earlier,[2(a)–(e)] the ESI salts, once formed as transient intermediates, exhibit a rather high reactivity as electrophiles. In structurally related systems, they react readily with a nucleophilic double bond present in the substrate to give cyclic products. Hence, the β-attack should lead to the formation of cyclohexane derivatives as shown in Scheme 2.

At the same time, according to published data,[3] the TPI salts are stable and unreactive species; therefore, the final outcome of the δ-attack cannot be predicted certainly.

Initial experiments were carried out with 2-methyl-4,6-dimethoxy-7-(*p*-methylphenylthio)hept-1-ene **1** prepared *via* the coupling *p*-TolSCl + methyl vinyl ether + methyl vinyl ether + trimethylmethallylsilane following the general protocol outlined in Scheme 1.[†] The interaction of this model compound with a Lewis acid may occur *via* either δ- or β-attack depending on the nature of the employed reagent. Thus, the treatment of individual diastereomers (**1a** or **1b**) or their mixture (**1a**,**b**) with 2 equiv. of trimethylsilyl triflate (TMSOTf) in CH_2Cl_2 at ambient temperature followed by the quenching of the reaction mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the formation of a mixture of conjugated dienes (*E*)-2-methyl-6-methoxy-7-(*p*-tolylthio)hepta-2,4-diene **2a** and (*E*)-2-methyl-6-methoxy-7-(*p*-tolylthio)hepta-1,3-diene **2b** in 50% total yield[‡] (**2a**:**2b** = 7:1, ^{1}H NMR data). The TLC monitoring of this reaction revealed an almost instantaneous conversion of **1a**,**b** (R_f = = 0.5, hexane–ethyl acetate, 5:1) into a highly polar intermediate ($R_f < 0.05$, hexane–ethyl acetate, 5:1), which was converted into final product **2a**,**b** (R_f = 0.6, hexane–ethyl acetate, 5:1) upon the treatment with DBU. These data suggested that, under the chosen conditions, the reaction of **1a**,**b** occured as an initial attack of TMSOTf at the δ-methoxy group to give an intermediate which was presumably identified as TPI salt **3**.[§] The latter underwent further ring opening and proton elimination upon the treatment with a base (Scheme 3). We assume that the predominant formation of **2a** is due to the isomerization of initially formed isomer **2b**, which is thermodinamically less stable.

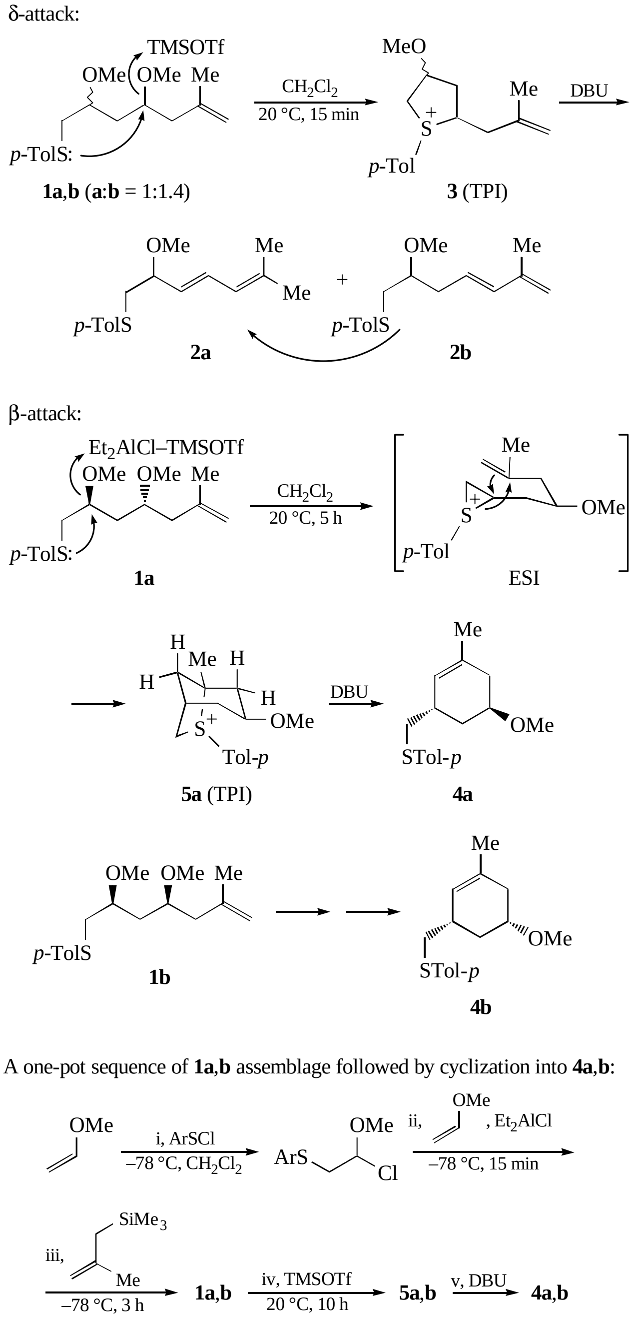


Scheme 2

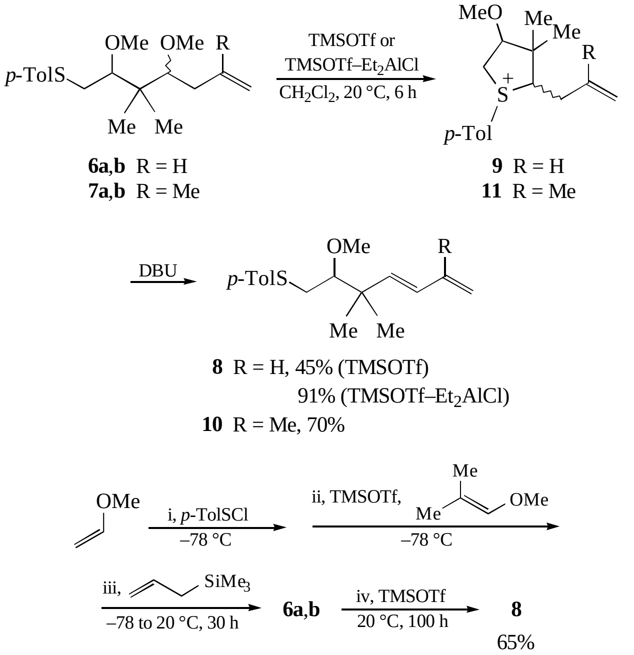
[†] General procedure for the preparation of the starting adducts was described earlier.[1(a),(b)]. Below are specified the reaction conditions (Lewis acid, solvent, temperature, time, yields and diastereomer ratio). **1a**,**b**: $LiClO_4$, $MeNO_2$, –25 °C, 3 h, 82%, 1:1.4. **6a**,**b**: $LiClO_4$, $MeNO_2$, –25 °C, 20 °C, 10 h, 94%, 1:1.1. **7a**,**b**: $LiClO_4$, $MeNO_2$, –25 °C to 20 °C, 20 h, 93%, 1:1.1. **12**: $TiCl_4$, CH_2Cl_2, –70 °C to 20 °C, 24 h, 65%, single diastereomer.

[‡] Yields refer to the isolated compounds purufied by flash chromatography on SiO_2. The identity of all compounds was established by ^{1}H and ^{13}C NMR data and elemental microanalyses.

On the other hand, the treatment of **1a** with a TMSOTf–Et$_2$AlCl mixture (1:1, 2 equiv.) followed by quenching with DBU afforded 1-methyl-3-(*p*-tolylthiomethyl)-5-methoxycyclohex-1-ene **4a** in 65% yield.[‡] The TLC monitoring of the reaction revealed the initial formation of a highly polar material ($R_\mathrm{f} < < 0.05$, hexane–ethyl acetate, 5:1). To isolate the latter, the reaction mixture formed upon the complete conversion of **1a** was poured into absolute CCl$_4$ at –20 °C. An oily precipitate was separated from the supernatant liquid; it was carefully washed with CCl$_4$ and dissolved in CD$_2$Cl$_2$. The presence of impurities did not allow us to carry out the complete analysis of ^{1}H NMR spectra of this sample. However, these NMR data are consistent with the structure of bicyclic TPI salt **5a**, as presented in Scheme 3.[¶] This compound is a true intermediate in the above transformation of **1a** since the treatment of isolated salt **5a** with DBU furnished the same product **4a**.



Scheme 3



Scheme 4

These data suggest that cyclohexane derivative **4a** was formed as a result of a multistep sequence starting with an initial attack of a Lewis acid (TMSOTf–Et$_2$AlCl) at the β-methoxy group followed by a nearly concerted intramolecular cyclization of the transient ESI-like intermediate to give stabilised bicyclic TPI salt **5a** [*cf.* refs. 2(*a*),(*d*),(*e*)], which can be further converted into the final adduct *via* sulfonium ring opening and proton elimination.

The interaction of the diastereomer **1b** with Et$_2$AlCl–TMSOTf followed the pattern established for **1a** (TLC monitoring) except that bicyclic intermediate **5b** is less stable and more reactive than **5a**. The conversion of this intermediate into final product **4b** (yield 59%) did not require the presence of DBU and proceeded easily upon the treatment of the reaction mixture with aqueous NaHCO$_3$. Adduct **4b**[‡] differs from product **4a** only in the configuration of the methoxy substituent. Hence, it follows that the conversions **1a** → **4a** and **1b** → **4b** proceed as highly diastereoselective reactions.

Finally, we also found that both the preparation of adducts **1a**,**b** (*via* four-component coupling, *cf.* Scheme 1) and the cyclizaton to give product **4a**,**b** (82%, **a**:**b** = 1:1.4) can be carried out as a one-pot sequence of three intermolecular and one intramolecular Ad$_\mathrm{E}$ reactions as represented in Scheme 3.[††] This unprecedented sequence[‡‡] resulted in the assemblage of a cyclohexane ring from simple precursors with the formation of three new C–C bonds.

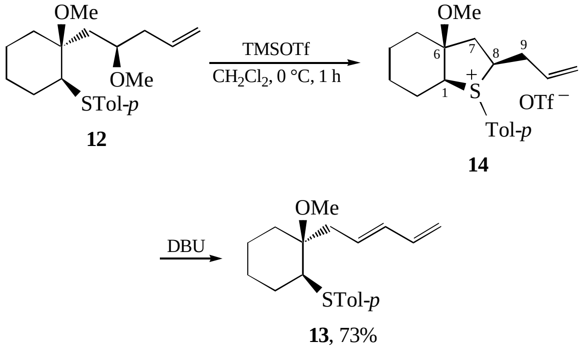
[§] The intermediacy of **3** was substantiated by the ^{1}H NMR monitoring of the reaction of **1a** with TMSOTf (CD$_2$Cl$_2$, 20 °C). After 2 h, the ^{1}H NMR spectrum indicated a nearly complete formation of a new compound, which was tentatively identified as thiophanium salt **3** by the appearance of downfield-shifted signals of the protons of the MeC$_6$H$_4$ fragment (0.3–0.5 ppm as compared to the respective signals in **1a**,**b** or **2a**,**b**) (*vide infra*).

[¶] Analysis of ^{1}H NMR spectra of crude salt **5a** revealed the presence of only one MeO singlet, the absence of olefinic proton signals, and a downfield shift of signals of the protons of the MeAr fragment typically observed in related sulfonium salts [*cf.* data in ref. 1(*c*),(*d*)].[§§]

[††] *Procedure of the one-pot preparation of* **4a**,**b**: To a stirred solution of *p*-TolSCl (0.159 mg, 1 mmol) in CH$_2$Cl$_2$ (20 ml) at –78 °C a solution of methylvinyl ether (0.174 mg, 3 mmol) in CH$_2$Cl$_2$ (2 ml) was added followed by the addition of Et$_2$AlCl (0.363 g, 3 mmol) in toluene (1.08 ml). The mixture was kept at the same temperature for 15 min and then methallylsilane (0.257 g, 2 mmol) was introduced. TLC monitoring revealed that after two more hours at –78 °C the formation of the adduct **1a**,**b** came to the completion. After that the temperature was raised up to 20 °C, TMSOTf (0.066 g, 3 mmol) was added and the reaction mixture was kept at ambient temperature for 5 h. Thereafter, TLC data indicated the complete disappearance of a spot corresponding to adducts **1a**,**b** (R_f = 0.50, hexane–ethyl acetate, 5:1) substituted by a spot of a highly polar compound (R_f < 0.05). Treatment of the reaction mixture with DBU at 20 °C followed by the usual workup furnished cyclic products **4a**,**b** (yield 82%, **a**:**b** = 1:1.4).[‡]

The protocol outlined in Scheme 1 was also employed for the preparation of adducts **6a**,**b** and **7a**,**b**.[†] Treatment of **6a**,**b** with TMSOTf (CH_2Cl_2, 20 °C) resulted in a fast disappearance of the starting material and appearance of a highly polar compound (TLC monitoring data, *cf.* data for the similar reaction of **1a**,**b**). The subsequent treatment of the reaction mixture with DBU furnished conjugated diene **8** in 45% isolated yield[‡] (Scheme 4). This transformation also proceeds *via* the intermediate formation of thiophanium salt **9**. Much to our surprise, the reaction of **6a**,**b** with TMSOTf–Et_2AlCl followed the same δ-attack route to give the same diene **8** (91% yield). The presence of an additional methyl susbstituent at the double bond of adduct **7a**,**b** did not affect the reaction course, and diene **10** was formed as the only isolable product regardless of the nature of the Lewis acid used. Dienes **8** can also be obtained in 65% yield using a one-pot procedure, which involves the *in situ* assemblage of starting adducts **6a**,**b** from the respective precursors followed by treatment of these adducts with an additional amount of the same Lewis acid (TMSOTf) under a slightly more severe conditions (Scheme 4).

As was shown earlier, the sequence outlined in Scheme 1 can also be used for the coupling of cyclic vinyl ethers as the alkene components, which resulted in the highly diastereoselective formation of cyclic adducts.[2(*d*)] These adducts react with Lewis acids *via* a δ-attack. Thus, the reaction of adduct **12**[†] with either TMSOTf or TMSOTf–Et_2AlCl with the subsequent treatment of the resulting complex with a base gave diene **13** in 70–80% yield (Scheme 5).[‡] The intermediacy of TPI salt **14** in this conversion was established by the results of NMR monitored experiment which indicated an almost instantaneous formation of this intermediate as the only observable product upon the treatment of **12** with TMSOTf.[§§] The structure of **14** was unambiguously proved by ^1H and ^{13}C NMR spectroscopy with the use of 2D protocols (homo- and heteronuclear correlations, NOESY and ROESY).



Scheme 5

At present it is hardly possible to advance a fully consistent explanation of the observed sensitivity of the reaction outcome to the nature of the substrates and/or reagents. However, above results clearly demonstrate a possibility to control the selectivity of the Lewis acid-induced transformation of the title multifunctional adducts and thus attest to the promise of further studies in this field.

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[‡‡] It is noteworthy that among more than dozens of various reaction types employed in the one-pot multistep sequences cationic reactions are most typically represented by the intramolecular electrophilic cyclizations.[4]

[§§] *Preparation and NMR data of salt* **14**: To the stirred solution of **12** (0.033 g, 0.3 mmol) in CD_2Cl_2 (5 ml) at 0 °C TMSOTf (0.041 g, 0.2 mmol) was added. After 30 min, TLC data indicated the complete conversion of **12** into a highly polar compound. The solution was transferred into an NMR tube, and the ^1H and ^{13}C NMR spectra were immediately recorded at 20 °C. ^1H NMR (500 MHz, CD_2Cl_2) δ: 1.41 (m, H_a at C-3), 1.51 (m, H_a at C-4), 1.63 (m, H_a at C-5), 1.69 (m, H_e at C-4), 1.91 (m, H_e at C-2), 1.98 (m, H_e at C-3), 2.11 (dd, H_A at C-7, J_1 12.3 Hz, J_2 14.0 Hz), 2.19 (m, H_a at C-2), 2.25 and 2.43 (m, 2H at C-9), 2.40 (m, H_e at C-5), 2.51 (s, 3H, Me_{Ar}), 2.92 (dd, H_B at C-7, J_1 6.0 Hz, J_2 14.0 Hz), 3.29 (s, 3H, MeO), 4.06 (dd, H_a at C-1, J_1 4.2 Hz, J_2 12.5 Hz), 4.23 (m, H at C-8), 4.82 and 5.24 (dd, 2H at C-11, J 10.3 and 17.2 Hz), 5.52 (m, H at C-10), 7.75 and 7.71 (dd, $4H_{Ar}$). ^{13}C NMR, δ: 19.0 (C-4), 21.3 (Me_{Ar}), 23.0 (C-2), 24.8 (C-3), 28.3 (C-5), 33.5 (C-9), 40.5 (C-7), 49.0 (MeO), 58.0 (C-8), 70.9 (C-1), 82.0 (C-6), 119.2 (C-11), 131.5 (C-10), 131.8, 133.0, 132.2 and 147.4 (Ar).