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Polyfunctional adducts assembled with the help of a one-pot sequence of three Ad_E reactions as synthetically useful intermediates. The course of the Lewis acid induced transformations of the 4,6-dialkoxy-7-arylthioheptene moiety

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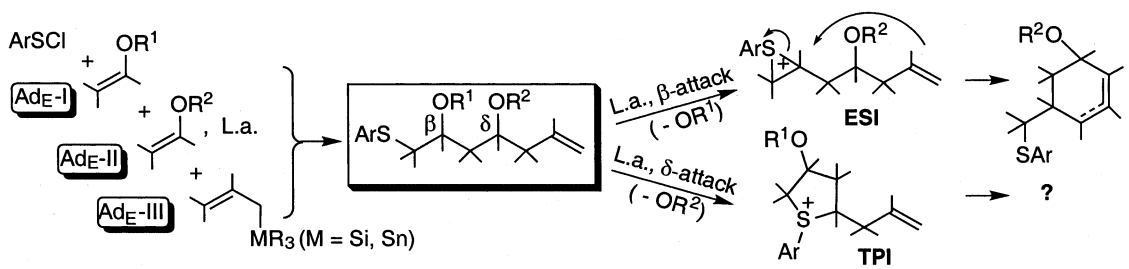
Abstract—Data on the selectivity of the Lewis acid induced transformations of the title adducts are presented and the routes leading to formation of products containing either cyclohexane or 1,3-dienes units are described.

As was shown earlier a wide set of adducts bearing the 4,6-dialkoxy-7-arylthioheptene fragment as a common moiety can be readily assembled from three alkene precursors via the arylthiomediated one-pot sequence of three Ad_E reactions (Scheme 1).[1a–c] Obviously, the synthetic usefulness of the elaborated protocol depends largely on the opportunity to exert an efficient control over the selectivity of further transformations involving the created polyfunctional moiety.

The presence of alkoxy substituents at both β- and δ-positions to the arylthio unit of the title adducts suggested two most plausible routes for an initial attack of Lewis acid (L.a.) (Scheme 1).

The episulfonium ion (**ESI**) intermediates once formed should readily undergo intramolecular cyclization[2a–d] and thus the formation of cyclohexane derivatives is to be expected as the most probable outcome of the β-attack. At the same time, the thiophanium ion (**TPI**) intermediates are known to be rather unreactive species[3] and hence the nature of the final products of the δ-attack could not have been predicted with any certainty.

Here we wish to report that the title adducts can undergo selectively either type of these transformations, their course being dependent on the substrate structure and reaction conditions.



Scheme 1.

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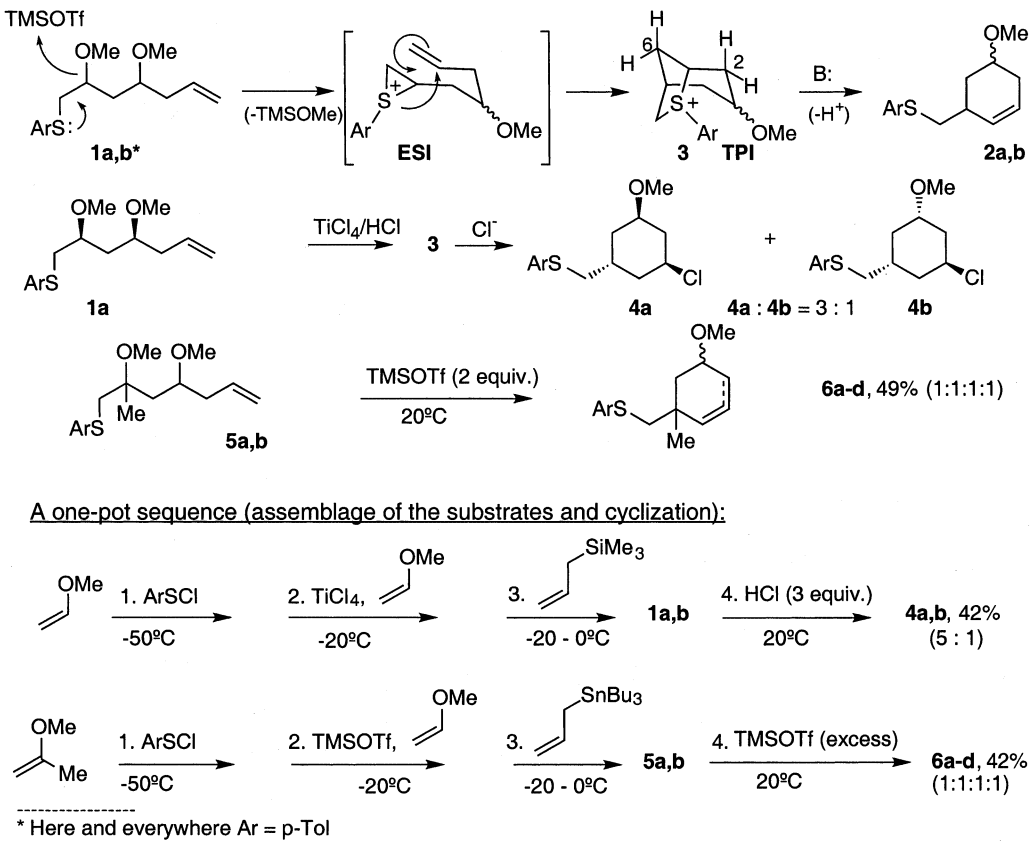
The β-attack route was shown to be a highly preferred pathway for the transformation of the adduct **1** (prepared by the coupling: *p*-TolSCl+methyl vinyl ether+methyl vinyl ether+allyltrimethyl silane[1a]). Thus, the treatment of **1a**,**b** (mixture of diastereomers[4]) in CH_2Cl_2 with 2–3 equiv. of trimethylsilyl triflate (TMSOTf) at ambient temperature for 4 h resulted in a complete conversion of **1a**,**b** (R_f=0.5, hexane–ether 10:1) into a highly polar compound (R_f <0.1). Quenching of the reaction mixture by DBU (20°C, 2 h) followed by the usual work-up furnished the product **2a**,**b** in 65% yield as an unseparable mixture of two diastereomers in a ratio 1.8:1.[5] These observations suggested that the transformation of **1a**,**b** into the product **2a**,**b** (Scheme 2) proceeded via an intermediate formation of the bicyclic cationic intemediate, the stabilized thiophanium ion **3** (Scheme 2), which underwent the base-induced proton elimination from the C-6 center and sulfonium ring opening (cf. with the data in Ref. 2a). Attempts to isolate salt **3** in a free state failed but its intermediacy was ascertained by the data on the ^{1}H NMR monitored reaction of the individual diastereomer **1a** with TMSOTf (CD_2Cl_2, 20°C).[6]

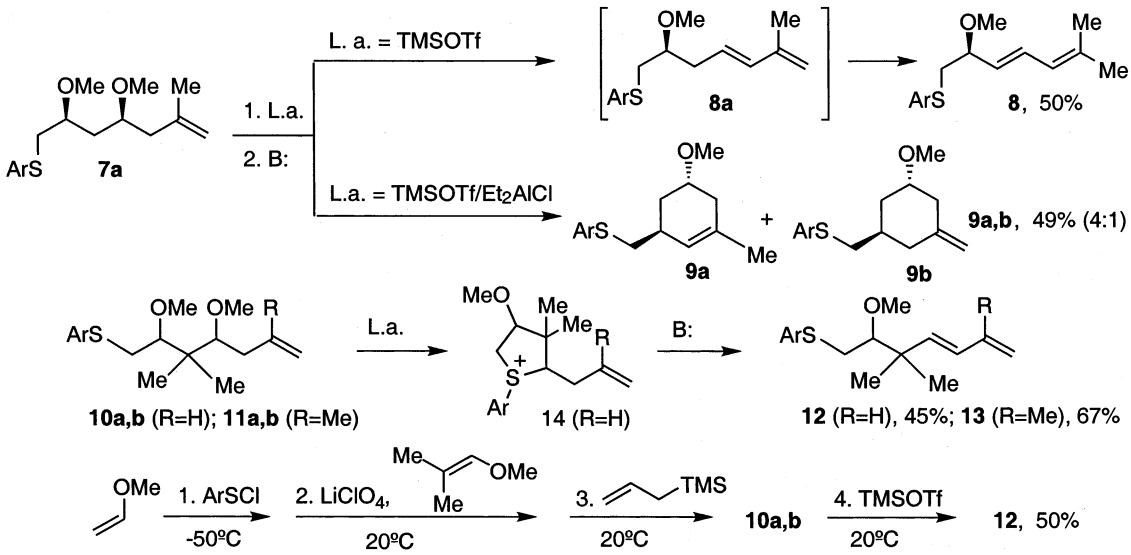
Cyclization of diastereomer **1a** triggered by the $TiCl_4$–HCl system gave the chloroadduct **4a**,**b** in 45–50% yield,[5,7] obviously due to the reaction of the intermediate **3** with Cl^- present in the reaction medium. We have also found that preparation of the substrate **1a**,**b** and its cyclization to give **4a**,**b** can be carried out as a *tandem sequence of three intermolecular and one intramolecular Ad_E reactions* as is shown in Scheme 2. As a result *the one-pot assemblage of the cyclohexane framework from three alkene precursors with a formation of three novel C–C bonds* was achieved!

Reaction of the adduct **5a**,**b**[4] with TMSOTf also followed the β-attack route and produced the unseparable 1:1:1:1 mixture of the isomers **6a**–**d**.[5,8] The same mixture of the products was also prepared with the help of the 'non-stop' protocol which involved a one-pot assemblage of **5a**,**b** from the starting alkene components followed by its cyclization upon treatment with an additional amount of the Lewis acid (Scheme 2).

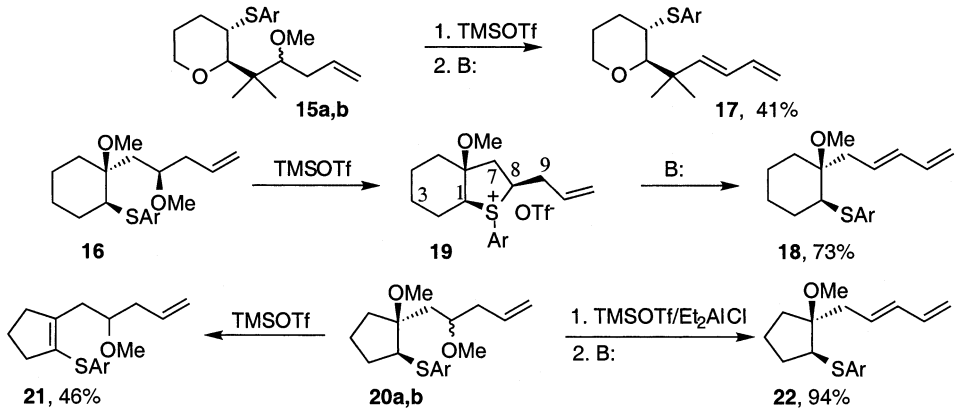
Variations in the nature of the Lewis acid may serve as a switch to channel the reaction along either δ- or β-attack routes. Thus, the interaction of the adduct **7a**[4] with TMSOTf proceeded, rather unexpectedly, as the δ-attack and produced the 1,3-diene **8**[5] (Scheme 3) presumably via an initial formation of the less stable diene **8a**. However, the utilization of Et_2AlCl–TMSOTf as a stronger Lewis acid gave the cyclized adducts **9a**,**b**.[5,9] At the same time δ-attack turned out to be a major pathway for the substrates **10a**,**b**[4] or **11a**,**b**[4], which yielded 1,3-dienes **12**[5] or **13**[5] as the sole products regardless of the conditions used (TMSOTf for **10a**,**b**; Et_2AlCl–TMSOTf for **11a**,**b**). Data of the ^{1}H NMR monitored experiment revealed a nearly instantaneous formation of the TPI **14** (cf. data in Refs. [6,10]) upon the treatment of **10a**,**b** with TMSOTf. Product **12** was also assembled from three alkene precursors via a one-pot sequence as is shown in Scheme 3.



Scheme 2.



Scheme 3.



Scheme 4.

Interaction of the adducts **15a**,**b**[4] or **16**[4] with TMSOTf gave the corresponding 1,3-dienes **17**[5] or **18**[5] (Scheme 4). The intermediate **19** formed in the latter reaction was isolated (as an oil) and its structure was firmly established by NMR spectra studies.[10] Surprisingly, the reaction of **20a**,**b**[4] with TMSOTf proceeded with elimination of β-methoxygroup to give the diene **21a**,**b**.[5] Formation of the conjugated diene **22**[5] from **20a**,**b** occurred under the action of Et_2AlCl–TMSOTf.

Results presented in this paper clearly demonstrate the possibility to control the selectivity of the Lewis acid induced transformations of the multifunctional adducts which could be easily prepared with the help of consecutive intermolecular Ad_E reactions.[1a–d] Even more important is the finding that both the preparation of the adducts and their subsequent conversion into cyclohexane derivatives or products bearing 1,3-diene moiety can be achieved as a result of a one-pot sequence of four cationic reactions (three intermolecular plus one intramolecular). In this respect it is noteworthy that among the plethora of diversified reactions employed in the tandem or consecutive transformations very few belong to the category of cationic transformations.[11]

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4. For preparation of the adducts, see Refs. 1b,d. Yields and diastereomer ratios: **1a**,**b**, 66%, 1:1.2; **5a**,**b**, 98%, 1:1.5; **7a**,**b**, 99%, 1:1.5; **10a**,**b**, 46%, 1:1.2; **11a**,**b**, 93%, 1:1.1; **15a**,**b**, 94%, 4:1; **16**, 65%; **20a**,**b**, 61%, 1:3.
5. Yields (non-optimized) refer to the isolated products. Flash chromatography (SiO_2, eluent: hexane–ethylacetate, 20:1) was used for separation of the isomers or purification of the mixtures thereof. Structure of the products was established by the microanalysis data and ^1H (500 MHz) and ^{13}C NMR spectra (125 MHz). Composition of the unseparable mixtures of isomers and the identities of the components were determined by GC–MS and NMR data. According to the NMR data the crude product mixtures contained the isolated compound(s) as the major component(s) contaminated with 2–3 minor impurities (total content of the latter never exceeds 10–15%).
6. After several hours vinyl proton signals of **1a**,**b** disappeared and the pattern of the newly emerged signals corresponded to that expected for the salt **3**. The observed downfield shifts of ^1H signals of MeC_6H_4 fragment (ca. 0.5 ppm, as compared to these of **1a**,**b**) is typical for the arylsulfonium salt (e.g. data in Ref. 1c,d, see also Ref. 10).
7. Diastereoisomers **4a** and **4b** were isolated as individual products[5] and were shown to differ only by the configuration at C-3 center. It is unclear whether the isomerization at this center occurred at the cyclization step or as a result of product equilibration.
8. The formation of positional isomers in the mixture **6a–d** could be ascribed to a substantial steric hindrance for the approach of base to the C-6 center owing to the presence of Me-group at the bridgehead poition of the corresponding cationoid intermediate, an analog of **3**.
9. The presence of up to 20% of *exo*-methylene isomer **9b** was ascertained by ^1H NMR data.
10. NMR parameters for **19**: ^1H NMR (500 MHz, $CDCl_3$, δ): 1.41 (m, 1H, H_a at C-3), 1.51 (m, 1H, H_a at C-4), 1.63 (m, 1H, H_a at C-5), 1.69 (m, 1H, H_e at C-4), 1.91 (m, 1H, H_e at C-2), 1.98 (m, 1H, H_e at C-3), 2.11 (dd, $1H_A$ at C-7, $J_1=12.3$, $J_2=14.0$), 2.19 (m, 1H, H_a at C-2), 2.25 and 2.43 (2 m, 2H at C-9), 2.40 (m, 1H, H_e at C-5), 2.51 (s, 3H, MeAr), 2.92 (dd, $1H_B$ at C-7, $J_1=6.0$, $J_2=14.0$), 3.29 (3H, s, MeO), 4.06 (dd, 1H at C-1, $J_1=4.2$, $J_2=12.3$), 4.23 (m, 1H at C-8), 4.82 (d, 1H at -C-11, $J=17.2$), 5.24 (d, 1H at C-11, $J=10.3$), 5.52 (m, 1H at C-10), 7.55 and 7.71 (2d, 4H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 19.0 (C-4), 21.3 (MeAr), 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 (C-Ar). Signal assignments were made with the help of 2D protocols ($\{^1H–^1H\}$, $\{^1H–^{13}C\}$ and NOESY).
11. Reviews: Tietze L. F. S. *Chem. Rev*. **1996**, *96*, 115; Hudlicky T. *Chem. Rev*., **1996**, *96*, 3. In fact intramolecular electrophilic cyclizations represent the only type of sequential cationic transformation referred to in these reviews.