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Controlled One-Pot Sequence of Three Ad_E Reactions as a Novel Protocol for the Synthesis of Polyfunctional Compounds

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Abstract: Various silyl-capped nucleophiles have been shown to be reactive as the final components in ArS mediated coupling of two alkyl vinyl ether units and carbon nucleophile and thus a fairly general procedure for the assemblage of polyfunctinal compounds from simple precursors has been elaborated.

Earlier we have shown that episulfonium ions (ESIs) generated either *via* direct reaction of alkenes with cationoid sulfenium ion-like reagents or by the treatment of β-arylthioalkyl halides (adducts of Ad_E reaction of ArSCl with alkenes) with Lewis acids can be used as electrophiles for the alkylation of various carbon nucleophiles (Nu_C).[1] Interaction of ESIs with π-donors like aromatic compounds, allylsilanes, silyl vinyl ethers furnished the respective β-arylthioalkylated products as a result of addition of these electrophilic species at the double bond concomitant with the elimination of a proton (for aromatic π-donors) or trialkylsilyl cation (for silyl-capped nucleophiles). Of special interest was the observation that the ESI derived from alkyl vinyl ether (VE-I) reacted with the second alkyl vinyl ether (VE-II) utilized as Nu_C to give the next cationoid intermediate, presumably the five-membered thiophanium ion (TPI, see below). In this case the nature of the reaction product depended on the choice of the final nucleophile Nu used for the quenching of this intermediate and the overall result of the reaction corresponds to the sequential four component coupling in accordance with the following equation:

$$\mathbf{ArS^+ + VE\text{-}I + VE\text{-}II + Nu \rightarrow adduct}$$

If Grignard reagents were used as the final quenchers, this coupling resulted in creation of two novel C-C bonds.[2] Here we wish to report the results showing that the synthetic potential of the above-mentioned reaction sequence can be substantially broadened owing to the ability of employing a set of π-donors like allylsilanes or -stannanes, silyl vinyl ethers or silyl ketene acetals instead of Grignard reagents as Nu_C for the quenching of TPI intermediates.

Initial experiments were performed with methyl vinyl ether **1** used both as VE-I and as VE-II components (see Scheme), and TPI intermediate **2** was generated in CH_2Cl_2 in the presence of $TiCl_4$ at -78°C as described previously.[2,3] However no reaction between **2** and allyltrimethyl silane **3**, used as a final quencher Nu_C, occurred at this temperature even upon standing overnight and extensive decomposition of the reaction mixture was observed when the temperature was increased up to 20°C. Yet more careful tlc monitoring of the reaction at 0°C revealed that under these conditions intermediate **2** is sufficiently stable and reacts slowly with **3** to give the expected adduct **4** (about 5 hours were required for the complete conversion **2→4**, tlc data). The adduct **4** was formed as 1 : 1.2 mixture of diastereomers in 66% yield. Similar results were obtained with other Lewis acids like $SnCl_4$ or $ZnBr_2$ which were also employed previously for the generation of **2**.[2] The activity of $LiClO_4$ as a Lewis acid in a number of various reactions is well-documented in the literature.[4] We have found that the utilization of the system $LiClO_4$-$MeNO_2$ might be preferable for our reaction. Thus the TPI **2** formed with the help of this Lewis acid exhibited

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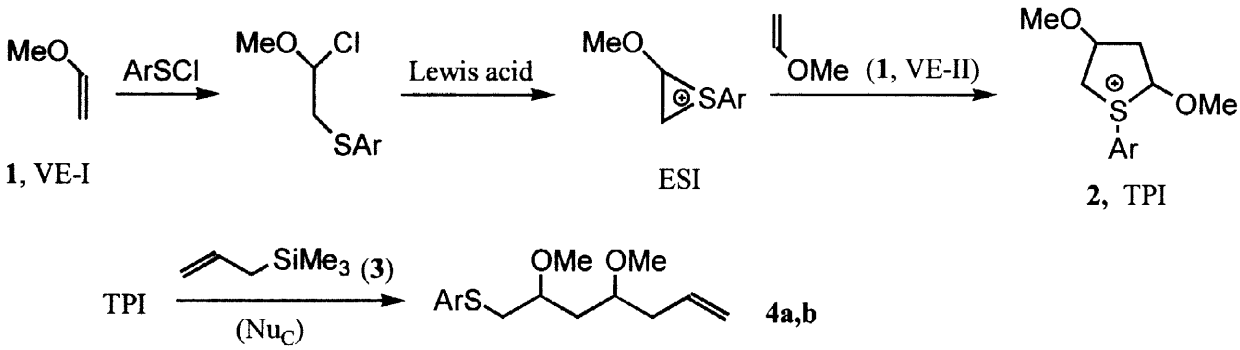
much higher stability (at least for 12 hours at 20°C) and upon treatment with **3** gave product **4** in 82% yield (see Table). This system turned out to be especially useful for the reactions involving participation of the acid sensitive Nu_C (see below). As expected[5] allyltributyl stannane **5** revealed a higher reactivity as a nucleophile in the reaction with electrophile **2** (generated in the presence of $TiCl_4$) and in this case the formation of adduct **4** occurred easily even at -40°C.

Scheme



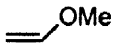
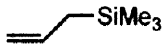
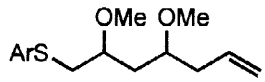
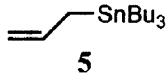
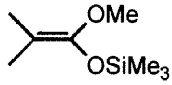
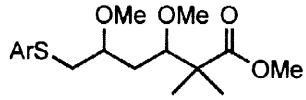
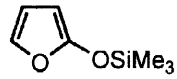
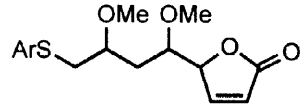
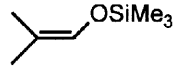
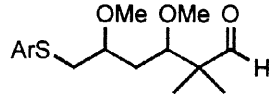
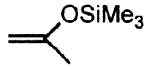
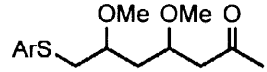
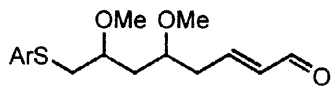
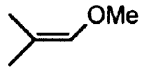
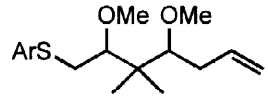
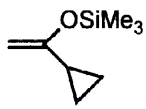
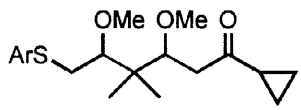
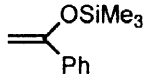
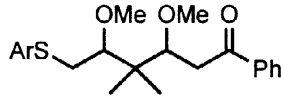
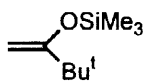
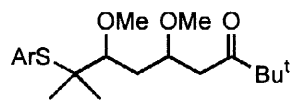
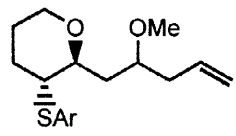
TPI **2** formed with $TiCl_4$ as a Lewis acid also reacted with silyl ketene acetals **6** and **7** and silyl vinyl ether **8** to give the respective adducts **9-11** (Table). However all attempts to use silyl vinyl ethers **12** and **13** as Nu_C under these conditions failed due to the extensive decomposition while the utilization of $LiClO_4$ as a Lewis acid secured the formation of the adduct **14** and **15** in satisfactory yields.

The reaction worked equally well for different combinations of vinyl ethers as for example: **1** (VE-I) + 1-methoxy-2-methylpropene **16** (VE-II) (entries 8-10), **16** (VE-I) + **1** (VE-II) (entry 11) or dihydropyran **17** (VE-I) + **1** (VE-II) (entry 12). Summary of the results presented in the Table also attests to the versatility of the coupling as regards to the variations in the structure of the final silyl-capped nucleophile.[6]

In the described coupling two novel C-C bonds are created and as a result, polyfunctional compounds with a fairly different pattern of functionality can be assembled in one stroke from simple building blocks with an independent variation in the nature of all components. It is also noteworthy that the overall conversion exemplified in the above Scheme actually represents an unprecedented example of a controlled one-pot sequence of three consecutive Ad_E reactions which proceed *via* the formation of two stabilized cationoid intermediates, identified as three- and five-membered S-arylsulfonium salts. This coupling belongs to the rare type of synthetic methods which are based on a tandem sequence of electrophile addition/nucleophile quenching steps (cf. data in ref.1). The demonstrated versatility and generality of this approach attest to its promise as an alternative and complementary protocol to the set of the well-developed methods which utilize the reversed polarity sequence of nucleophilic addition/electrophile quenching steps for the assemblage of various polyfunctional compounds widely employed as synthetic intermediates.[7] In this respect it is also relevant to add that current studies have shown the possibility of utilizing vinyl ethers bearing easily removable O-alkyl substituents (e.g. t-Bu or Bn) as VE-I and/or VE-II components.

The synthetic value of this protocol as a preparative method will ultimately depend on the possibility of exerting rigorous control over its stereochemical outcome. It is known that diastereoselectivity of various Lewis acid catalyzed reactions can be controlled by the variation of reaction parameters.[8] Data obtained for the coupling leading to the formation of adduct **4** revealed that the ratio **4a** : **4b** varied only slightly (from 1 : 1.1 to 1 : 1.7) with changes in the Lewis acid ($ZnBr_2$, $SnCl_4$, $TiCl_4$, $LiClO_4$), ArS residue (ArS = 4-MeC_6H_4, 4-ClC_6H_4, or 2,4,6-$Me_3C_6H_2$), solvent (CH_2Cl_2, $MeNO_2$) or temperature (-40 - 20°C). Of greater importance is the steric bulkiness of silyl nucleophile as is evidenced by the predominant formation of one diastereomer when **6** or **8** was employed as a final quencher (entries 3 and 5). Preliminary data obtained in our group suggested that the utilization of alkoxycycloalkenes as VE-I secured a nearly complete diastereoselectivity of the coupling (manuscript in preparation). A consistent explanation for all these observations is hardly possible without a knowledge of the structure of the stabilized intermediate tentatively identified as TPI (e.g. **2**). Our current efforts are focused at the structural identification of these intermediates and at the evaluation of the relative importance of factor(s) controlling the stereochemical

Table. Coupling of Two Alkyl Vinyl Ether Units with the Silyl-Capped Carbon Nucleophiles.

Entry	VE-I	VE-II	Nu_C	Product	Yield, ratio of isomers (conditions)[9]
1	 **1**	**1**	 **3**	 **4a,b**	66%, 1:1.2 (A) 82%, 1:1.4 (B)
2	**1**	**1**	 **5**	**4a,b**	66%, 1:1 (A)
3	**1**	**1**	 **6**	 **9a,b**	77%, 1:9 (A)
4	**1**	**1**	 **7**	 **10a-d**	73%, 1:1:1:1 (A)
5	**1**	**1**	 **8**	 **11a,b**	61%, 1:9 (A)
6	**1**	**1**	 **12**	 **14a,b**	77%, 1:2 (B)
7	**1**	**1**	 **(E)-13**	 **(E)-15a,b**	40%, 1:1 (B)
8	**1**	 **16**	**3**		94%, 1:1.5 (B)
9	**1**	**16**			93%, 1:1 (B)
10	**1**	**16**			60%, 1:1 (B)
11	**16**	**1**			68%, 1:1.3 (B)
12	 **17**	**1**	**3**		82%, 1:1.5 (A)

outcome of their interaction with the final nucleophiles.

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References and Notes

1. For the pertinent data see a review, Smit, W. A.; Caple, R.; Smoliakova, I. P. *Chem. Rev.*, **1994**, 94, 2359-2382.
2. Smoliakova, I. P.; Caple, R.; Magnuson, V. R.; Polyakov, V. R.; Smit, W. A.; Shashkov, A. S.; Ohinov, B. D. *J. Chem. Soc. Perkin Trans. 1*, **1995**, 1065-1069; see also references cited therein.
3. Intermediate **2** was formed nearly quantitatively as estimated by 92% isolated yield of 3-methoxy-4-*p*-tolylthiobutanal upon the quenching of the reaction mixture with water.
4. For the utilization of $LiClO_4$ as a catalyst in the reactions involving intermediacy of carbocationic species, see for example: Mukaiyama aldol addition, Reetz, M. T.; Raguse, B.; Marth, C. F.; Hugel, H. M.; Bach, T.; Fox D. N. A. *Tetrahedron*, **1992**, 48, 5731-5742; Reetz, M. T.; Fox D. N. A. *Tetrahedron Lett.*, **1993**, 34, 1119-1122; addition of allylstannanes to aldehydes, Henry, K. J., Jr.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.*, **1992**, 33, 1617-1620; 1,2-methyl shifts in ESI-like intermediates, Borisov, A. B.; Bodrikov, I. V.; Borisova, G. N.; Bel'sky, V. K.; Smit, W. A.; Lutsenko, A. I. *J. Chem. Soc. Mendeleev Commun.*, **1996**, 52-53.
5. Yamamoto, Y.; Asao, N. *Chem. Rev.*, **1993**, 2207-2293.
6. Typical experimental procedure runs as follows: *Method A:* To a solution of *p*-TolSCl (0.159 g, 1 mmol) in CH_2Cl_2 (20 ml) at -78°C were added sequentially a solution of vinyl ether **1** (0.058 g, 1 mmol) in CH_2Cl_2 (1 ml), a solution of $TiCl_4$ (0.190 g, 1 mmol) in CH_2Cl_2 (1 ml) and once more a solution of **1** (0.058 g, 1 mmol) in CH_2Cl_2 (1 ml). After 30 min $Me_3SiCH_2CH{=}CH_2$ **3** (0.229 g, 2 mmol) was added, and the temperature was allowed to raise up to 0°C. The reaction mixture was stirred 5 h at this temperature, quenched with aq. $NaHCO_3$ (20 ml), and extracted with diethyl ether (2x20 ml). Column chromatography of the organic residue on SiO_2 (hexane:ethyl acetate = 5:1) gave 4,6-dimethoxy-7-*p*-tolylthiohept-1-enes **4a** (0.084 g, yield 30%) and **4b** (0.101 g, yield 36%).
Method B: To a solution of *p*-TolSCl (0.159 g, 1 mmol) in $MeNO_2$ (20 ml) at -20°C were added sequentially a solution of vinyl ether **1** (0.116 g, 2 mmol) in $MeNO_2$ (2 ml) and anhydrous $LiClO_4$ (0.426 g, 4 mmol). After 15 min $Me_3SiCH_2CH{=}CH_2$ **3** (0.229 g, 2 mmol) was added, and the temperature was allowed to raise up to ambient. The reaction mixture was stirred overnight. Usual workup and column chromatography gave the mixture of **4a,b** in ratio 1:1.4, yield 82%. **4a**, R_f=0.4; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.66 (m, 2H, CHC*H*$_2$CH), 2.25 (m, 2H, C*H*$_2$CH=), 2.28 (s, 3H, *Me*Ph), 2.99 and 3.02 (2dd, 2H, CH_2S; J_1=7.5 Hz, J_2=8.6 Hz, J_3=13.2 Hz), 3.32 (s, 3H, MeO), 3.34 (s, 3H, MeO), 3.38 (m, 1H, C*H*OMe), 3.54 (m, 1H, C*H*OMe), 5.04 (m, 2H, CH_2=), 5.77 (m, 1H, CH=), 7.06 and 7.27 (2d, 4H-arom, *J*=8.0 Hz) ppm; **4b**, R_f=0.33; ^{1}H-NMR ($CDCl_3$, TMS) δ 1.80 (m, 2H, CHC*H*$_2$CH), 2.25 (m, 2H, C*H*$_2$CH=), 2.29 (s, 3H, *Me*Ph), 3.01 and 3.04 (2dd, 2H, CH_2S; J_1=3.6 Hz, J_2=4.1 Hz, J_3=13.4 Hz), 3.29 (s, 3H, MeO), 3.31 (s, 3H, MeO), 3.32 (m, 1H, C*H*OMe), 3.43 (m, 1H, C*H*OMe), 5.05 (m, 2H, CH_2=), 5.78 (m, 1H, CH=), 7.07 and 7.27 (2d, 4H-arom, *J*=8.0 Hz) ppm.
7. Perlmuter, P. *Conjugated Addition Reactions in Organic Synthesis, Tetrahedron Organic Series*; Pergamon: Oxford, 1992.
8. Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press, Inc: Boca Raton, 1996.
9. In all cases Ar = *p*-Tol. Yields are given for the isolated mixture of diastereoisomers. Consistent analytical and spectral data (^{1}H- and ^{13}C-NMR, HRMS) were obtained for all new products. Diastereomeric ratios were determined from ^{1}H-NMR data and confirmed by the isolation of individual isomers (flash chromatography on SiO_2).