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ARYLSULFENYL CHLORIDE MEDIATED COUPLING OF THREE NUCLEOPHILIC FRAGMENTS WITH THE FORMATION OF TWO C-C BONDS

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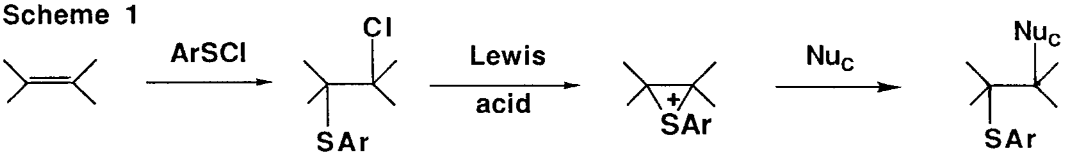
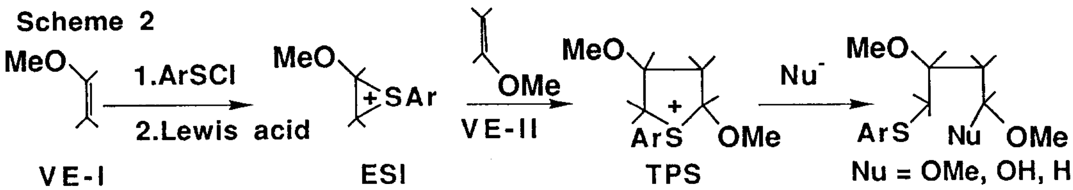
Abstract. The sequence of reactions ArSCl + vinyl ether-I + vinyl ether-II + organomagnesium reagents has been developed as a convergent protocol for assembling polyfunctional compounds from simple precursors.

β-Chloroalkyl aryl sulfides [1], represent a novel class of electrophiles capable of alkylating various π-donors, (Nu_C, e.g., aromatic compounds [2a], trimethylsilyl(TMS) enol ethers [2b], TMS ketene acetals [2c] or allylsilanes [2d]) leading to the formaion of the respective γ-arylthioalkylated products in good yields. Data on the regio- and stereochemistry of this reaction [3] provide convincing evidence for the intermediate formation of episulfonium ion (ESI) as the electrophilic species (Scheme 1).



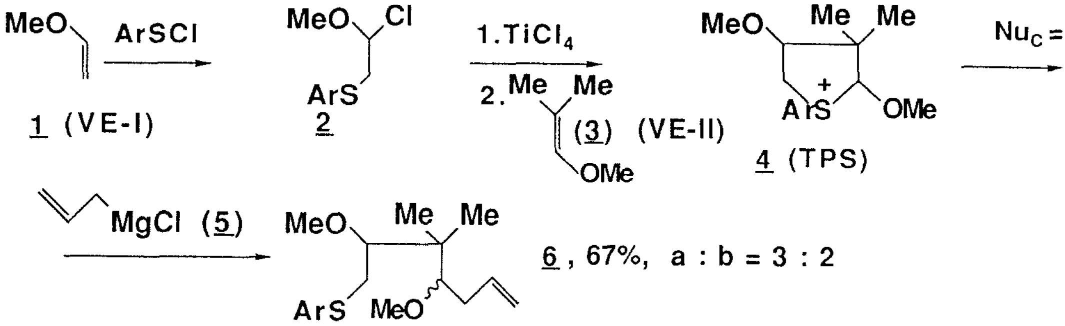
Recent studies revealed an interesting ramification of this process when vinyl ethers (VE's) were used both as precursors to form electrophiles (VE-I) and as π-donors at the alkylation step (VE-II)([4a], see Scheme 2). Since the nature of VE-I and VE-II can be varied independently [4a-4e] this sequence provides an interesting alternative to the crossed aldol condensation. In addition there are some peculiarities in this coupling which should be noted: (i) alkylation of VE-II with ESI gives cleanly a 1:1 adduct while the formation of oligomers is an almost inevitable complication in Ad_E reactions of VE's; (ii) the net result of the coupling depends on the choice of the nucleophile (Nu) used for quenching the reaction mixture. Thus substituted carbonyl compounds or their acetals are formed if Nu=OH or OR. Quenching with hydride donors resulted in the formation of the respective reduced derivatives [4a]. To account for these observations we assumed that the alkylation of VE-II proceeds *via* formation of the stable cationic intermediate tentatively ascribed to the structure of the thiophanium salt (TPS) [5].



The mechanism outlined in Scheme 2 suggested interesting synthetic opportunities with carbon nucleophiles (Nu_C) and here we present some results attesting to the promise of this approach. Initially, standard π-donors, like TMS enol ethers or trimethylallyl silanes were tried as quenchers of TPS [cf. 2b,c]. To our dismay these nucleophiles proved to be rather unreactive and at best only trace amounts of the desired products could be detected (PMR,MS) in the reaction mixtures [6].

However, if stronger nucleophilic reagents, such as organomagnesium compounds, were used as the Nu_C, the results were very rewarding. Thus, when methyl vinyl ether (1)(VE-I) was sequentially treated in CH_2Cl_2 at -70°C with p-TolSCl [7], $TiCl_4$ and methyl 2-methyl-propen-1-yl ether (3)(VE-II), a reaction complex, (presumably, TPC 4) was formed. The quenching of this complex with an ethereal solution of allyl magnesium chloride (5) (ratio: ArSCl:1:3:5 = 1:1:1:2) at -70°C, followed by treatment with $NaHCO_3$-ether led to the formation of 5,5-dimethyl-4,6-dimethoxy-7-p-tolylthiohept-1-ene (6) (Scheme 3), isolated as a colorless oil in 67% yield (stereoisomers 6a:6b = 3:2) [8]. Thus, the polyfunctional compound 6 was assembled from simple precursors *via* a one pot sequence of three reactions leading to the formation of two C-C bonds.

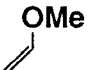
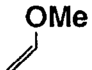
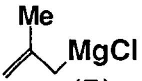
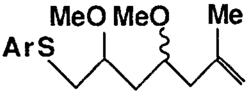
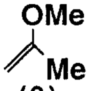
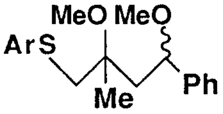
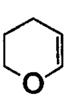
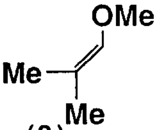
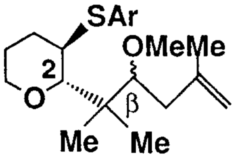
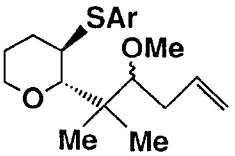
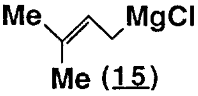
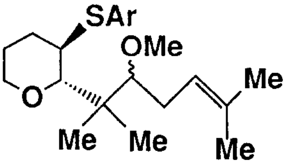
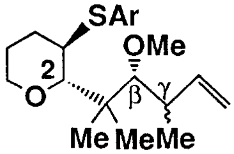
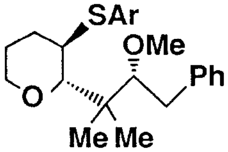
Scheme 3



A number of variations in the nature of all the reactants involved was checked. The data summarized in Table clearly indicate that a variety of vinyl ethers can be used at the steps leading to the formation of TPS (cf. the data in ref [4]). Besides 5 and other allylic derivatives like 7, 15, and 17, benzyl (20) and phenyl (10) magnesium halides are sufficiently active to be used as Nu_C. Attempts to use methyl or vinyl magnesium halides were not successful.

The stereochemistry of the coupling is also interesting. If both VE-I and VE-II were acyclic the final products 6, 8, or 11 are formed with moderate stereoselectivity. When dihydropyran 12 is used as VE-I, the addition across the cyclic double bond occurs with complete anti stereospecificity [3,4]). At the same time the stereochemistry of the formation of the stereogenic centers at the side chain revealed a pronounced sensitivity to the reaction conditions. It was rewarding to find out that nearly complete stereospecificity could be achieved with $TiCl_4$ as a Lewis acid. In fact, only a single diastereoisomer (from a possible four) with anti-configuration of the substituents at C_β and C-2 was detected upon NMR analysis of the products 13,14,16 and 20 [9]. The use of other Lewis acids leads to a fairly different stereoselectivity pattern. Thus adduct 13, formed with $SnCl_4$, consists of nearly a 1:1 mixture of diastereomers. A similar reaction with $AgBF_4$ yields preferentially syn adduct 13b with the a:b ratio being dependent on the nature of the initial electrophile (a:b = 1:3 or 2:3 for Ar=p-MeC_6H_4

Table

Entry	VE-I	VE-II	Nu_C	Product*	Yield [8], ratio of isomers**
1.	 (1)	 (1)	 (7)		8a,b 69%, 5 : 2
2.	 (9)	1	PhMgBr (10)		11a,b 60%, 5 : 2
3.	 (12)	 (3)	7		13a,b 62%, >19 : 1
4.	12	3	 (5)		14a,b 70%, >19 : 1
5.	12	3	 (15)		16a,b 20%, >19 : 1
6.	12	3	 (17)		18a,b 71%, 4 : 1
7.	12	3	$PhCH_2MgBr$ (20)		20 78% m.p.110ºC

* In all cases $TiCl_4$ was used as a Lewis acid and $p\text{-}MeC_6H_4SCl$ as an initial electrophile.

** a : b refers to anti : syn diastereomers respectively [9].

or $p\text{-}ClC_6H_4$ respectively). Entry 6 represents the case of a coupling which is stereospecific as regards the ring carbons and C_β and, stereoselective at the $C\gamma$ center. While no satisfactory explanations can be advanced at the present to account for the observed dependence, these results indicate the possibility of elaborating conditions for controlling the stereochemistry of the overall process [10].

In summary, we suggest a convergent protocol for the synthesis of polyfunctional compounds which involves a one pot coupling of four components. This protocol is based on the ability of the ArS group to stabilize a positive charge both at β- and δ-carbon atoms of carbocationic intermediates [11]. In this way, the initial electrophile ArS^+ is employed as a sewing tool for the consecutive stitching of three nucleophilic fragments in accordance with the general equation: $\underline{\mathbf{ArS^+}} + \underline{\mathbf{VE\text{-}I}} + \underline{\mathbf{VE\text{-}II}} + \underline{\mathbf{R}}^{-}$. The present results provide an additional example of the synthetic potential of the previously outlined methodology of the stepwise Ad_E reactions [12].

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5. Closely related 2,4-diaryl-S-aryl thiophanium salts have been prepared and their structure determined; see Barhash, V.A., et al. *Zhournal Org. Khim.*, **1984**, *20*, (8), 2257.

6. The low reactivity of the 5-membered cyclic sulphonium salts toward nucleophilic attack is well documented; see for the references, Dittmer, D.C., Patwardhan, B.H., "Cyclic sulphonium salts" in the monograph "The Chemistry of Sulphonium Group," Stirling, C.J.M., Patai, S., Wiley, New York, 1981, chapter 13.

7. Formation of adduct $\underline{\mathbf{2}}$ proceeds almost instantly in a quantitative yield; cf. data in Toyoshima, K., Okuyama, T., Fueno, T.Y., *J. Org. Chem.*, **1978**, *43*, (14), 2789.

8. Yields are given for purified compounds. Their identity was established by microanalysis and spectral (PMR, CMR, MS) data. Isomeric ratios were determined from PMR.

9. Stereochemistry of the adducts was deduced from a comparison of NOE pattern in PMR spectra of individual diastereosiomers; the details will be published in the full paper.

10. The sensitivity of the steric course of crossed aldol-like reactions to variations in the reaction conditions is a well documented phenomenon. See for example, Evans, D.A., Nelson, J.V., Taber, T.R., "Topics in Stereochemistry," 1982, v. 13, p. 1 and ref.[3b].

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