Pergamon

Tetrahedron Letters 39 (1998) 8787–8790

TETRAHEDRON
LETTERS

Structure and Reactivity of Thiophanium Salts, the Elusive Intermediates in ArS$^+$-Mediated One-pot Sequence of Three Ad$_E$ Reactions

Margarita I. Lazareva*[a,b], Yury K. Kryschenko[a,c], Ron Caple*[a], Darren Wakefield[a], Anthony Hayford[a],
William A. Smit*[b], Alexander S. Shashkov[b]

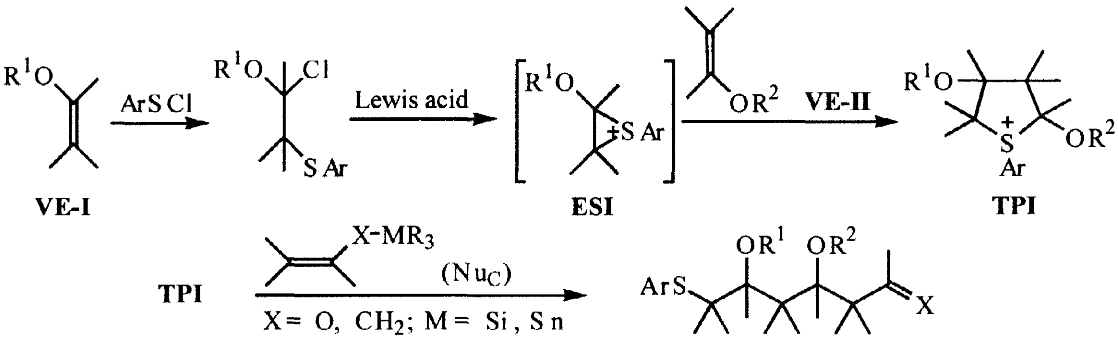
[a]Chemistry Department, University of Minnesota-Duluth, 10 University dr., Duluth, MN 55812, USA
[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr., 47, 117913 Moscow, Russia
[c]Higher College of Chemistry, Russian Academy of Sciences, 125819 Moscow, Russia

Received 6 July 1998; accepted 15 September 1998

Abstract: The structure of the previously postulated cationoid intermediate, presumably formed in ArS$^+$-mediated coupling of two vinyl ether units, was firmly established as (1*R**,2*R**,4*S**)-2,4-dimethoxy-3,3-dimethyl-1-*p*-tolylthiophanium salt and its reactivity was elucidated. © 1998 Elsevier Science Ltd. All rights reserved.

Recently we described a novel and versatile protocol for the one-pot multicomponent coupling leading to the assemblage of polyfunctional molecules from four precursors, namely, ArSCl, two vinyl ether units (VE-I and VE-II) and a silyl- or tin-capped π-donor in accordance with the reaction sequence shown in Scheme 1.[1a,b]

Scheme 1



This sequence starts with the well-known Ad$_E$ reaction of vinyl ethers (VE-I) with ArSCl resulting in the formation of the corresponding β-arylthio-α-chloroethers.[2] As was amply demonstrated in the previous studies, these adducts are capable of reacting with π-donors such as silyl enol ethers or ketene acetals in the presence of Lewis acids to give the corresponding β-arylthioalkylated adducts.[3a] The data on the course of these reactions inferred the intermediacy of episulfonium ions (ESI) generated *in situ*.[3b] In the reaction shown in Scheme 1 a second vinyl ether moiety (VE-II) is employed as a π-donor in the C-C bond forming reaction with ESI-like species, an interaction that leads to the formation of the next generation of a stabilized cationoid intermediate.[4] The latter turned out to be a sufficiently active electrophile to react with a set of various carbon nucleophiles (Nu$_C$), which included Grignard reagents[4] or π-donors.[1a,b] To account for these observations we advanced a suggestion that the ArS$^+$-mediated sequential coupling of VE-I and VE-II units results in the formation of a thiophanium ion (TPI) as the key intermediate in the tandem sequence given in Scheme 1.[1a,b,4]

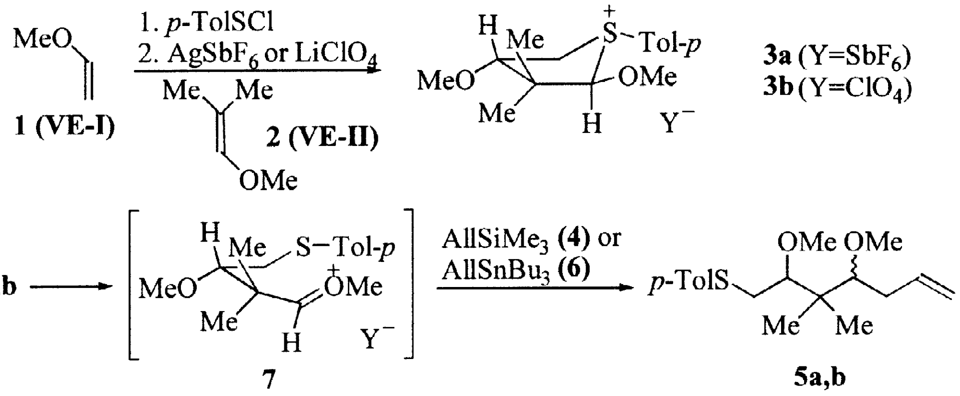
However, the validity of this suggestion remained questionable, especially in view of the previously published and somewhat contradictory evidence on the reactivity pattern of the five-membered cyclic sulfonium salts. In fact, as was shown for a number of the isolated S-alkyl and S-aryl thiophanium salts with a diverse pattern of substitution, these salts exhibit a well-pronounced tendency to react *via* a formation of σ-sulfurane or ylide intermediates and behave as rather poor electrophiles in the ring opening reactions with nucleophilic reagents.[5a,b] At the same time in several other cases such as aldol-like reactions[6a] or intramolecular

0040-4039/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01973-X

cyclizations,[6b] carried out with the substrates bearing an ArS-substituent at the γ–carbon atom to the incipient carbocationic center, the presumed thiophanium intermediates were thought to react as highly electrophilic species. Hence, literature data alone did not allow us to suggest a consistent explanation for the experimental observations on the course and reactivity of the coupling represented in Scheme 1[1a,b,4] and the elucidation of the structure and reactivity pattern of the intermediate tentatively identified as TPI became a matter of primary importance. Below are presented the results of the studies aimed at this goal.

Previous data demonstrated that a number of representative acyclic or cyclic vinyl ethers could be used as either VE-I or VE-II components in the coupling shown in Scheme 1.[1a,b,4] While various Lewis acids were found to be efficient, most often reactions were carried out with $TiCl_4$, $SnCl_4$ or with $LiClO_4$. Qualitative comparisons of the reaction course for various combinations of vinyl ether components clearly indicated that an enhanced stability should be expected for the cationoid intermediate produced in the coupling: *p*-TolSCl + methoxyethene **1** (VE-I) + 1-methoxy-2-methylpropene **2** (VE-II).[1b] Therefore our efforts were primarily focused at the study of this intermediate. Initial attempts to isolate the TPI generated from these components in the presence of $TiCl_4$ or $SnCl_4$ failed. On the contrary, the utilization of $AgSbF_6$ turned out to be quite efficient. The typical experimental procedure is as follows: interaction of **1** (1 eq.) with *p*-TolSCl (1 eq.) in CH_2Cl_2 at -70 °C followed by the addition of **2** (1.2 eq.) and $AgSbF_6$ (1 eq.) in CH_2Cl_2 solution resulted in the formation of the cationoid intermediate (Scheme 2) as was ascertained by tlc monitoring data (appearance of a single spot of the corresponding aldehyde or dimethyl acetal upon the quenching of an aliquot with water or methanol respectively, cf. data in reference 1b). The reaction mixture was filtered under Ar through a glass filter into a pre-cooled (-20 °C) ether-hexane mixture (1 : 1, abs.) and left in a cooler overnight. The resulting precipitate was decanted, washed with ether and recrystallized from CH_2Cl_2-ether mixture to give pure **3a**, as colorless hygroscopic crystals, yield 66% , m.p. 88-90 °C (dec.).

Scheme 2



The structure of **3a** as (1*R**,2*R**,4*S**)-2,4-dimethoxy-3,3-dimethyl-1-*p*-tolylthiophanium hexafluoroantimonate was unambigiously established by a single crystal X-ray analysis.[7] The detailed analysis of ^1H and ^{13}C NMR data demonstrated that the configuration of this compound remained undisturbed upon dissolving it in CD_2Cl_2 or CD_3NO_2 at +20 °C.[8] Utilization of $LiClO_4$ as a Lewis acid in a slightly modified procedure also enabled us to isolate the perchlorate **3b** as a viscous oil which revealed ^1H and ^{13}C NMR spectral patterns fully identical to that of **3a**.

Isolation of the TPI salts **3a,b** as stable compounds suggested a unique opportunity to study directly the reactions of these pre-made cationoid intermediates with Nu_C and thus to compare their reactivity pattern with that of the presumably similar intermediates generated from the same components *in situ*. As was shown earlier[1b] an interaction of the intermediate, identified as **3b** and generated *in situ* in the presence of a large excess of $LiClO_4$ in $MeNO_2$, with allylsilane **4** occured at 20 °C within 24 hours and furnished a 94% yield of the adduct **5a,b** as a 1 : 1.5 mixture of diastereomers. In the present study we have found that the reaction of the pre-made salt **3b** with **4** in $MeNO_2$ solution occurred under essentially the same conditions and gave a 65% yield of the same mixture of diastereomers **5a,b**.

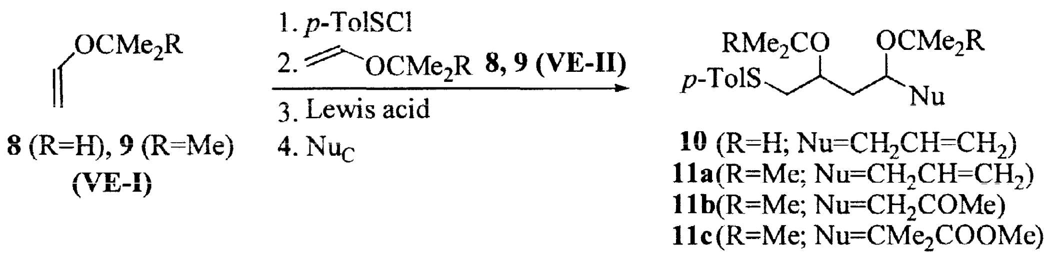
Rather unexpectedly the salt **3a** turned out to be almost unreactive toward **4** and only trace amounts of **5** were detected by tlc monitoring when the reaction mixture was kept 36 hours at ambient temperature. However when the same reaction was carried out in the presence of excess $LiClO_4$ (4 eq.), it gave the expected adducts **5a,b**, albeit in a rather low yield (20%, **a** : **b** = 1 : 1). If a more reactive carbon nucleophile, namely tri-*n*-butylstannane **6** was employed, the formation of **5a,b** proceeded readily even in the absence of $LiClO_4$ (yield 52%, **a** : **b** = 1 : 1). These results clearly demonstrated that the pre-made salts **3a,b** exhibit a reactivity pattern closely similar to that of the intermediates generated *in situ*.

The stereochemical outcome of the interaction of **3a,b** with **4** or **6** suggested the following mechanistic rationale for this reaction. *A priori* two limiting mechanisms could be considered for this process, namely a direct nucleophilic attack at C-2 center concomitant with the ring opening (S_N2 mechanism) or initial opening of the five-membered ring to give an open oxocarbenium ion **7** (Scheme 2) followed by the interaction of the latter with a nucleophile (S_N1 mechanism).[9] If the former mechanism were operative, the reaction of **3a,b** with **4** should have proceeded with an inversion of configuration at C-2 and resulted in a highly diastereoselective formation of the corresponding diastereomer of the adduct **5**. The observed low level of the diastereoselectivity suggests that in all likelyhood the reaction follows an S_N1 route *via* the formation of the transient carbenium ion-like intermediate **7**. Hence it is actually the latter species which plays the role of an active electrophile reacting with the Nu_C **4** or **6**. The above-mentioned effect of the $LiClO_4$ additives on the rate enhancement for **3a** + **4** reaction could be considered as an additional argument supporting this suggestion.[10]

This reasoning could be also applied for the interpretation of both the previously published and recently accumulated data on the steric course of the coupling carried out with different sets of acyclic VE components (for a general equation, see Scheme 1). Thus a rather low diastereoselectivity reported earlier for a number of the Lewis acid mediated couplings *p*-TolSCl + **1** + **1** + Si/Sn-capped π-donors (typically ratios of the diastereomers varied within the limits of 1 : 1.1 - 1.5)[1a,b] can be easily accounted for in the terms of the above mechanism, which envisages the transformation of the TPI generated *in situ* into the open oxocarbenium ion species (cf. **3** → **7**, Scheme 2) at the product determining step. In line with this mechanism is also the observation that the use of *p*-ClC_6H_4SCl or 2,4,6-$Me_3C_6H_2SCl$ instead of *p*-TolSCl in these reactions did not alter significantly the stereochemistry of the coupling despite the variations in the bridging ability of the S-aryl group (at best the diastereomers ratio might be increased up to a value of 1 : 1.7).[1a,b]

In addition we have also checked the possibility of affecting the diastereoselectivity of the reaction by varying the bulkiness of O-alkyl substituents in the starting substrates. It was found that the utilization of *i*-propyl or *t*-butyl vinyl ethers **8** and **9** as VE-I and VE-II components did not lead to a substantial increase in the stereoselectivity (Scheme 3). In all cases studied the respective adducts **10** and **11a–c** were formed in good yields as mixtures of diastereomers with a ratio being never better than 1 : 2.2 regardless of the variations in the reaction parameters (Lewis acid: Et_2AlCl, $SnCl_4$, $(i\text{-}PrO)_2TiCl_2$; Nu_C: 2-siloxypropene, O-methyl O-trimethylsilyl dimethylketene acetal, stannane **6**).[11]

Scheme 3



8 (R=H), **9** (R=Me)
(VE-I)

10 (R=H; Nu=$CH_2CH=CH_2$)
11a(R=Me; Nu=$CH_2CH=CH_2$)
11b(R=Me; Nu=CH_2COMe)
11c(R=Me; Nu=CMe_2COOMe)

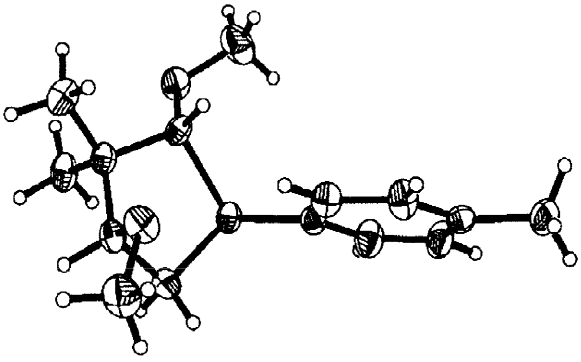
Hence one may conclude that the above variations in the size of O-alkyl group are not sufficient to affect substantially the conformational mobility of the presumably formed oxocarbenium ion intermediate **7** and this factor alone cannot be employed to exert any effective control over the steric outcome of the described coupling.

In conclusion, it is relevent to add that for a number of yet unreported cases we have been able to achieve a rather high diastereoselectivity of the described reaction sequence, especially if the cyclic vinyl ethers were employed as VE-I component. Identification of the factor(s) controlling the steric outcome of these reactions obviously necessitates the elucidation of the structural peculiarities of the intermediates formed in these reactions. This problem is now under intensive study in our group and the results will be published shortly.

Acknowledgments. This research was supported by the National Science Foundation (Grant No. 8921358), the Donors of the Petroleum Resarch Fund, administered by the American Chemical Society (Grant No. 27420-B1), the U.S. Civilian Research and Development Foundation (Award No. RC2-141) and the Russian Foundation for Basic Research (Grant No. 98-03-32970a). Special thanks are made to Dr. Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory of the University of Minnesota for X-ray structure analysis.

References and Notes

1. (a) Lazareva, M. I.; Kryschenko, Y. K.; Hayford, A.; Lovdahl, M.; Caple, R.; Smit, W. A. *Tetrahedron Lett.* **1998**, 39, 1083-1086; (b) Lazareva, M. I.; Kryschenko, Y. K.; Dilman, A. D.; Hayford, A.; Caple, R.; Smit, W. A. *Izv. Acad. Nauk, Ser. Khim.* **1998**, 924-932; *Russ. Chem. Bull.* **1998**, 47, 895-904.
2. Toyoshima, K.; Okuyama, T.; Fueno, T. *J. Org. Chem.* **1978**, 43, 2789-2792.
3. (a) See for example: Ibragimov, M. A.; Lazareva, M. I.; Smit, W. A. *Synthesis* **1985**, 880-884; (b) for a review, see: Smit, W. A.; Caple, R.; Smoliakova, I. P. *Chem. Rev.* **1994**, 94, 2359-2382.
4. 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; for the additional references, see ref. [3b].
5. (a) Pertinent literature data can be found in the review, Dittmer, D. C.; Patwardhan, B. H. Cyclic Sulfonium Salts. In *The Chemistry of the Sulfonium Group*; Stirling, C. J. M.; Patai, S. Eds.; John Wiley & Sons Ltd.: Chichester, 1981; Ch. 13, pp. 389-521; see also, in the same edition: Knipe, A. C. Reactivity of Sulfonium Salts, Ch. 12, pp. 313-355; (b) e.g., ring opening of 1,2,4-triphenylthiophanium perchlorate by the attack of AcO^--nucleophile was shown to require a prolonged boiling in AcONa/AcOH system; see: Bodrikov, I. V.; Chumakov L. V.; Pryadilova, A. N.; Nisnevich G. A.; Gatilov, Yu, V.; Bagryanskaya, I. Yu.; Mamatyuk, V. I.; Dolenko, G. N.; Barhash, V. A. *J. Org. Khim.* **1984**, 20, 2257-2267; *Chem. Abstr.* **1985**, 184934m.
6. (a) Hashimoto, Y.; Sato, Y.; Kudo, K.; Saigo, K. *Tetrahedron Lett.* **1993**, 34, 7623-7626; (b) Liu, C.; Kudo, K.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1996**, 61, 494-502.
7. The structure of **3a** (SbF_6^- not shown): Crystallographic data will be given in the full paper.



8. ^{1}H NMR (CD_2Cl_2, ppm) 1.18 s, 3H (Me), 1.32 s, 3H (Me), 2.45 s, 3H (*Me*Ph), 3.49 s, 3H (MeO), 3.57 s, 3H (MeO), 3.40, 3.98 and 4.30 all dd AMX system, 3H (CH_2CH), 5.86 s, 1H (CH), 7.50 and 7.80 AB, 4H (arom.). NOE observations fully corroborated the *anti* configuration of both MeO groups as well as MeO group at C-2 and S-aryl-substituent as is shown in the structure of **3a** (Scheme 2).
9. Both mechanisms were shown to be operative in nucleophilic displacement of sulfonium group for the acyclic compounds, but to the best of our knowledge very scarce data are available for the similar reactions of thiophanium salts (see ref. [5a]).
10. Accelerating effects of $LiClO_4$ additives on the rate of various carbocationic processes is a well documented albeit not fully understood phenomenon. See for example data in: Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, 34, 1119-1122; Henry, K. J., Jr.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, 33, 1617-1620.
11. Products **10-11a–c** were prepared in 56-75% yield using previously described general procedure.[1b] Consistent ^{1}H and ^{13}C NMR, HRMS and/or elemental analysis data were obtained for all products. Ratios of diastereomers were determined from ^{1}H NMR and GC-MS analysis data.