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Electrospray ionization mass spectrometric characterization of key Te(IV) cationic intermediates for the addition of $TeCl_4$ to alkynes

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Tellurium tetrachloride adds to alkynes via two pathways: a concerted *syn*-addition that yields *Z*-tri- and -tetrasubstituted alkenes or an *anti*-addition that yields *E*-alkenes. The mechanistic aspects of these divergent pathways for $TeCl_4$ addition to alkynes have been investigated by on-line electrospray ionization (tandem) mass spectrometry (ESI-MS(/MS)). Via ESI-MS(/MS), we have been able to intercept and characterize the active electrophile $TeCl_3^+$ in tetrahydrofuran (THF) solutions of $TeCl_4$, as well as its THF complex and several $TeCl_x(OH)_y^+$ derivatives. For the first time, also, key Te(IV) cationic intermediates of the electrophilic addition of $TeCl_4$ to alkynes were captured for gas-phase MS investigation. The detailed structural data of cyclic tellurane intermediates intercepted herein seems to provide insights into the coordinative behavior of the Te(IV) atom and its mode of action towards biological targets. Copyright © 2007 John Wiley & Sons, Ltd.

The synthesis of stereospecifically substituted alkenes is one of the major challenges in organic synthesis. We have found that organotellurium trihalides, specially trichlorides, which are the most intensely studied class of organotellurium(IV) compounds,[1] react with aryl alkynes to yield *Z*-vinylic tellurides.[2] Furthermore, whereas aryltellurium trichlorides react with aromatic alkynes in a *syn*-fashion to give *Z*-vinylic tellurides,[3] their reactions with 3-hydroxyalkynes **1** are unique since they give, via *anti*-addition and depending on the nature of the 3-substituents, either of the cyclic telluranes **4** or **5** (Scheme 1). These cyclic telluranes are probably formed through ring opening of a tellurenium intermediate **2** promoted by Cl^-, in stepwise mechanisms (Scheme 1, **a** and **b**) closely related to that of electrophilic addition of bromine to alkynes.[4,5]

Uemura and co-workers,[6] based on the transformation of the originally formed vinylic tellurium trihalides into *Z*-1,2-dihaloalkenes, concluded that $TeCl_4$ addition both to arylalkynes and to 3-hydroxy-1-propyne proceeds via a *syn*-process. As depicted in Scheme 1, however, we found distinct pathways when performing such reactions. The interesting biological activity displayed by organotelluriu-m(IV) compounds encouraged us to consolidate their structural data that are essential for further studies on the mode of action of such compounds towards thiol-dependent enzymes by docking methodologies.[7]

Since **4** and **5** have been demonstrated to efficiently inhibit human cathepsin B,[8] this new synthetic route to cyclic telluranes has gained importance. We proposed a chelated cationic intermediate to rationalize *anti*-addition of $TeCl_4$ to 3-hydroxyalkynes (Scheme 1) and, based on the rich chemistry of $ArTeCl_3$, we expected the same reactivity for $TeCl_4$.[9] $TeCl_4$ has usually been found to react similarly to $ArTeCl_3$, both acting as electrophiles in additions to aryl, alkenyl and alkynyl groups.[10,11] It is therefore important to investigate the addition of $TeCl_4$ to alkynes to establish the factors leading to formation of unexpected products in such reactions. To date, despite their chemical and biological interest, only a few tellurium compounds have been investigated by mass spectrometry (MS).[12–16] Electrospray ionization (ESI)-MS(/MS) is, however, rapidly becoming the technique of choice for mechanistic studies in chemistry and biochemistry[17–22] mainly owing to its unparalleled ability to 'fish', with high sensitivity and gentleness, ionic intermediates directly from reaction solutions into the gas phase, closely reproducing in the gas phase the ionic composition of the solution.[23–26] We have therefore performed ESI-MS and ESI-MS/MS experiments to investigate the proposed mechanisms involving Te(IV) cationic intermediates for $TeCl_4$ addition to alkynes.

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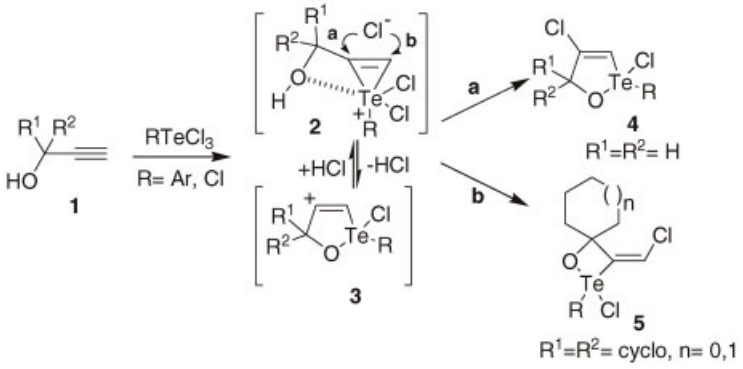

Scheme 1.

EXPERIMENTAL

All the experiments were performed in a high-resolution hybrid double quadrupole (Qq) and orthogonal time-of-flight (TOF) mass spectrometer (QTof, Micromass, Manchester, UK). The temperature of the nebulizer was 100°C. The ESI source and the mass spectrometer were operated in positive ion mode. The cone and extractor potential were set to 40 and 10 V, respectively. The scan range was *m/z* 50–1000. Tandem mass spectrometric (MS/MS) experiments were performed using Q1 mass selection of the desired precursor ion, q2 collision-induced dissociation (CID) with argon, and orthogonal TOF mass analysis of the CID product ions. The collision energy ranged from 5 to 25 eV, depending on the dissociation lability of the precursor ion. $TeCl_4$ (0.54 g, 2.00 mmol) and dry THF (15 mL) were added to a one-necked round-bottomed flask equipped with a $CaCl_2$ guard tube. The desired alkyne (2.20 mmol) was then added and the mixture was monitored on-line, at room temperature, for 1 h by ESI-MS at a flow rate of 0.01 mL min^{-1} using a microsyringe.

RESULTS AND DISCUSSION

$TeCl_4$ behavior of THF solutions

First, we investigated the positive ion ESI-MS behavior of $TeCl_4$ in tetrahydrofuran (THF), a common reaction solvent in which $TeCl_4$ is highly soluble. As Figure 1(a) shows, the ESI mass spectrum of $TeCl_4$ in THF at 25°C reveals several singly charged tellurium cations with characteristic $TeCl_n$ isotopic distributions. Firm structural assignments based on exact mass measurements (<10 ppm) and characteristic isotopic patterns for the many isotopologues of tellurium could therefore be obtained. The species $TeCl_3^+$ of *m/z* 235 (for simplicity, the *m/z* value is mentioned only for the most abundant isotopologue ion) and its THF complex $[TeCl_3{\cdot}THF]^+$ of *m/z* 307, as well as cationic species in which chlorides in $TeCl_3^+$ have been sequentially replaced by hydroxy anions, that is: $TeCl_2OH^+$ of *m/z* 217, $TeCl(OH)_2^+$ of *m/z* 199, and $Te(OH)_3^+$ of *m/z* 181, were observed. Note that these Cl^- by OH^- replacements must have occurred in the THF solution due to the presence of residual water. These Te(IV) cations were then mass-selected for structural investigation via CID in ESI-MS/MS experiments. For instance, the ions of *m/z* 235 (Fig. 1(b)), which are composed of a mixture of isotopologues, mainly: $[^{124}Te^{37}Cl_3]^+$, $[^{126}Te^{35}Cl^{37}Cl_2]^+$, $[^{128}Te^{35}Cl_2^{37}Cl]^+$, and $[^{130}Te^{35}Cl_3]^+$, dissociate by sequential loss of either a ^{35}Cl or ^{37}Cl radical to form pairs of isotopologue $[TeCl_2]^{+\cdot}$ and $[TeCl]^+$ product ions of *m/z* 200/198 and 165/163, respectively.

Therefore, the detection of $TeCl_3^+$ as well as its THF adduct $[TeCl_3{\cdots}THF]^+$ and the hydroxy replacement derivatives $[TeCl_n(OH)_m]^+$ indicates dissociation in solution of loosely bonded $[TeCl_3]^+Cl^-$ species. This ESI-MS finding is in accordance with previous studies that have suggested an

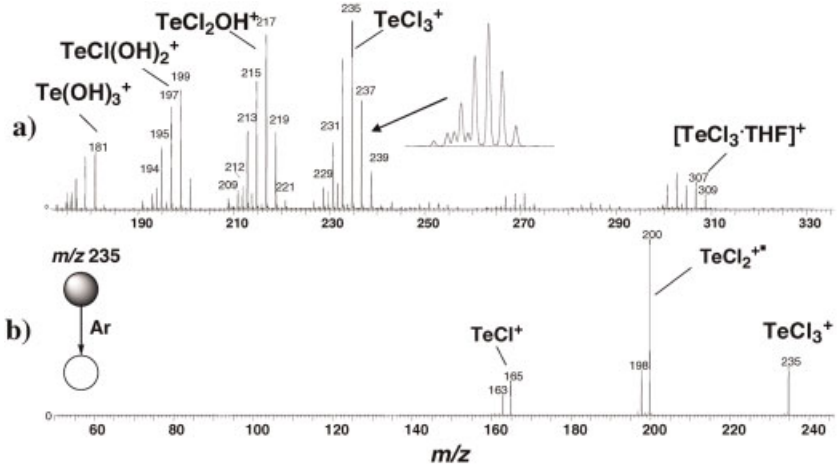

Figure 1. (a) ESI(+) mass spectrum of $TeCl_4$ solution in THF and (b) CID product ion spectrum of the species $TeCl_3^+$ of *m/z* 235. The insert in (a) corresponds to theoretical isotope patterns for the ion $TeCl_3^+$.

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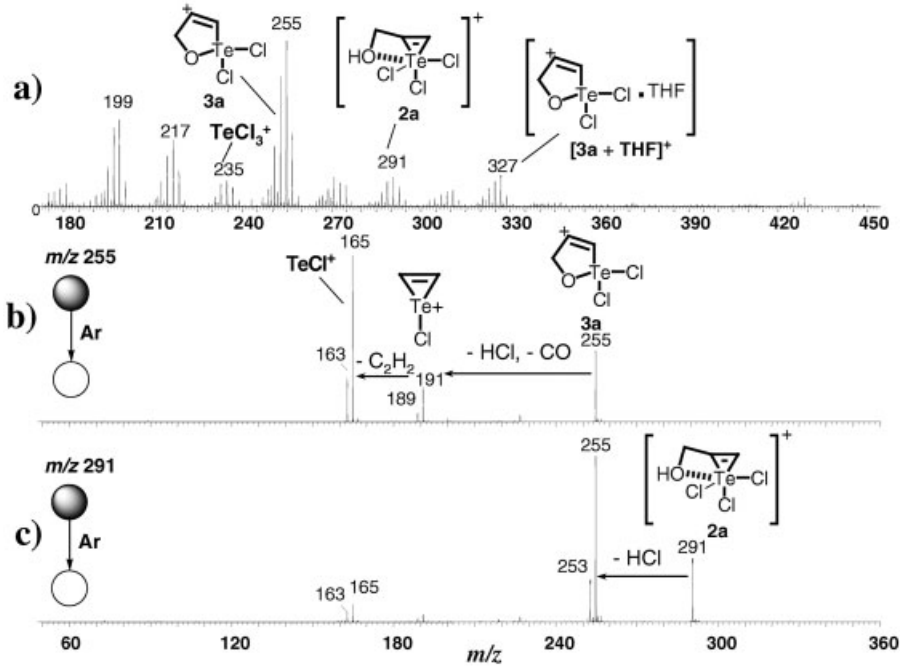
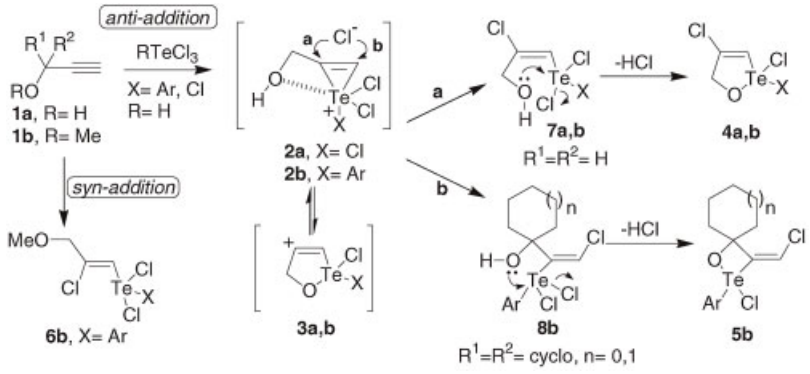


Figure 2. (a) ESI(+) mass spectrum for on-line screening of a solution of **1a**/$TeCl_4$ (1.0:0.9 equiv) in THF. CID product ion mass spectra of the intermediate species (b) **3a** of *m/z* 255 and (c) **2a** of *m/z* 291 intercepted from the reaction solution.

ionic character for $TeCl_4$ in solutions of polar coordinating solvents such as THF.[27] A similar ionic character in solution has recently been detected by ESI-MS for halogen dimers and pincer-type palladacycles.[28] $TeCl_4$ and also other Se, Te and Po tetrahalides span the 'covalent-ionic' border as they assume dual characteristics of molecular and ionic compounds. For $TeCl_4$, its dipole moment in benzene solution,[29,30] its solubility in nonpolar solvents, its nuclear quadrupole resonance spectrum,[31] and its Raman and infrared spectra[32,33] have all been presented as evidence for its molecular nature. However, molten $TeCl_4$ conducts electricity,[34] whereas the Raman and far-infrared spectra on molten, solid, and dissolved $TeCl_4$ have been most often interpreted as being consistent with the ionic formulation $[TeCl_3]^+Cl^-$. $[TeCl_3]^+$ has been isolated in the form of a complex with halide acceptors, such as $[TeCl_3]^+[AlCl_4]^-$.[35,36] The present ESI-MS detection of $[TeCl_3]^+$ species and its derivatives adds therefore to the evidence for the substantial ionic nature of $TeCl_4$.

ESI(+)-MS screening of $TeCl_4$ addition to 3-hydroxyalkynes

Figure 2(a) shows the ESI mass spectrum acquired after 10 min of reaction of $TeCl_4$ with 3-hydroxy-2-propyne (**1a**) in THF at 25°C (Scheme 1).[37] For this reaction the use of a faster microreactor[38] was unnecessary, actually inconvenient, since $TeCl_4$ addition to alkynes required several minutes to proceed. Owing to additions involving $[TeCl_3]^+$ and its derivatives (Fig. 2(a)), two key reaction intermediates **2a** and **3a** (Scheme 2) are detected for which the most intense isotopologues are those of *m/z* 291 and 255, respectively, as well as the species [**3a**+THF]$^+$ of *m/z* 327. Note the very characteristic *m/z* ratios and isotopic patterns for such species. **3a** of *m/z* 255 corresponds to the cationic, 'de-chlorinated' form of **4a**. In the gas phase, the isolated and long-lived vinylic cation **3a** may rearrange to a more stable form, such as via a 1,2-hydride rearrangement that would form a cyclic C-allylic oxonium ion. One isotopologue of each of the putative **2a** and **3a** is then selected and



Scheme 2.

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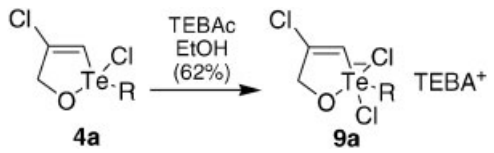

Scheme 3.

characterized via CID with nitrogen. Ion **3a** of *m/z* 255, a mixture of ^{35}Cl and ^{37}Cl isotopologues, dissociates mainly by the loss of both CO and HCl ($H^{37}Cl$ or $H^{35}Cl$) giving the pair of product ions of *m/z* 191 and 189 (Fig. 2(b)). Subsequent loss of acetylene then gives the pair of isotopologue $TeCl^+$ ions of *m/z* 165 and 163. Ion **2a** of *m/z* 291 (Fig. 2(c)) dissociates mainly by the loss of HCl giving the product ion of *m/z* 255, which dissociates in turn, probably by the same routes observed for the same ion sampled in the ESI-MS/MS experiment of Fig. 2(b). Such dissociation routes are therefore compatible with the putative structures of the unprecedented Te(IV) cationic intermediates **2a** and **3a**.

The major constituent of the mixture on the bench (ca. 58% by ^1H NMR) is **3a**, which was isolated as its colorless tellurate **9a**[39] (Scheme 3) by dissolving the crude oil in absolute ethanol followed by addition of triethylbenzylammonium chloride (TEBAc). X-ray analysis of the colorless crystals confirmed that indeed **9a** is the main product,[40] pointing to *anti*-addition of $TeCl_4$ to **1a** (Schemes 1 and 2). Formation of **4a** contrasts therefore with the results of Uemura and co-workers for the same reaction, in which a Z-stereochemistry for the product resulting from *syn*-addition was reported.[6] However, our result is consistent with the complete *anti*-stereospecificity of the addition of 2-naphthyltellurium trichloride to olefins through a cyclic telluronium ion intermediate **2** in this reaction.

The presence of a hydroxyl substituent in the terminal alkyne might be expected to have pronounced effects on the regioselectivity of addition, especially if the alkyne chain length and the hydroxyl group favor formation of a cyclic intermediate by heteroatom-tellurium chelation. Thus, propargylic alcohols can afford chelation control in $TeCl_4$ addition and the regioselectivity may be interpreted in terms of a five-membered chelation ring that could be responsible for the *anti*-addition of chloride, whereas in other alkynes the normal *syn*-addition is obtained by formation of a non-chelated intermediate.

We also monitored by ESI-MS the reactions of $TeCl_4$ with 1-ethynylcyclopentanol (**10a**) and 1-ethynylcyclohexanol (**10b**). The reaction between $TeCl_4$ and 1-ethynyl-1-cyclohexanol (**10b**) afforded a complex mixture of products. Unprecedented, key Te(IV) cationic intermediates of such reactions analogous to those observed in reactions of $TeCl_4$ with 1-ethynylcyclopentanol were also detected, with characteristic *m/z* ratios and isotopic patterns, as the ESI mass spectra shown in Fig. 3 (and Fig. 4 for 1-ethynylcyclohexanol) indicate. These gaseous ions were also subjected to CID and their product ion spectra showed similar dissociation behaviors to those of **3a** and **2a**. Their dissociation behavior is compatible with the proposed structures, as exemplified by the assignments of dissociation routes and the structures of the product ions displayed in Figs. 3(b) and 3(c).

In reactions of $TeCl_4$ with 1-ethynyl-1-cyclohexanol (**10b**), a single and rather unexpected product **11b** was also isolated in low yield (Scheme 4), as confirmed by conventional spectroscopic methods and X-ray analysis.[41] Scheme 5 delineates a multi-step mechanism by which we rationalize the unexpected formation of **11b** via the key intermediate **13**, the product of an *anti*-addition of $TeCl_4$ to the triple bond of **10**.

According to the proposed reaction mechanism outlined in Scheme 5, the chloride anion preferentially attacks the non-substituted carbon of the tellurenium(IV) intermediate **15**. These findings suggest that $TeCl_4$ indeed reacts with

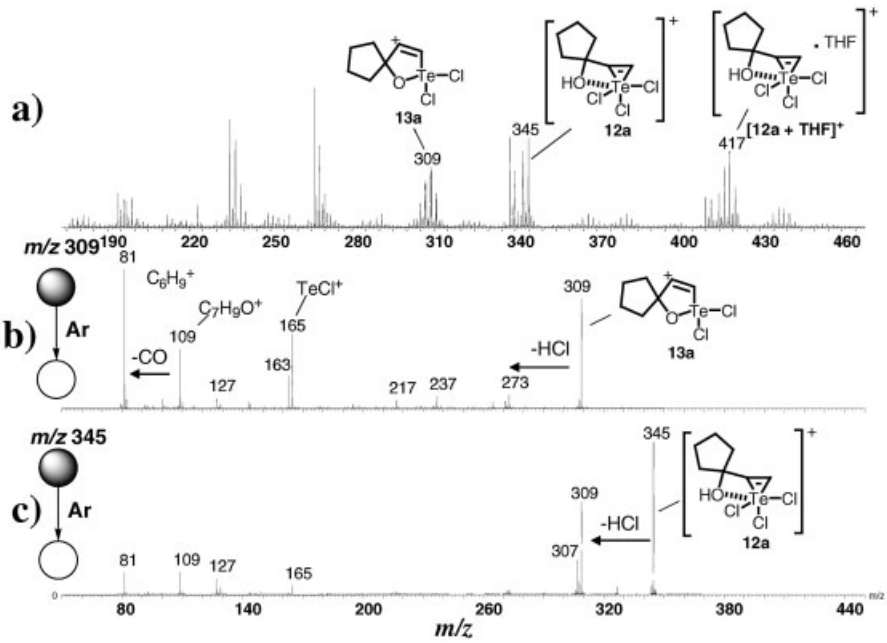

Figure 3. (a) ESI(+) mass spectrum of on-line screening of a solution of **10a**/$TeCl_4$ (1.0:0.9 equiv) in THF. Product ion spectra of the intermediate species found and intercepted from solution, that is (b) **13a** of *m/z* 309, and (c) **12a** of *m/z* 345.

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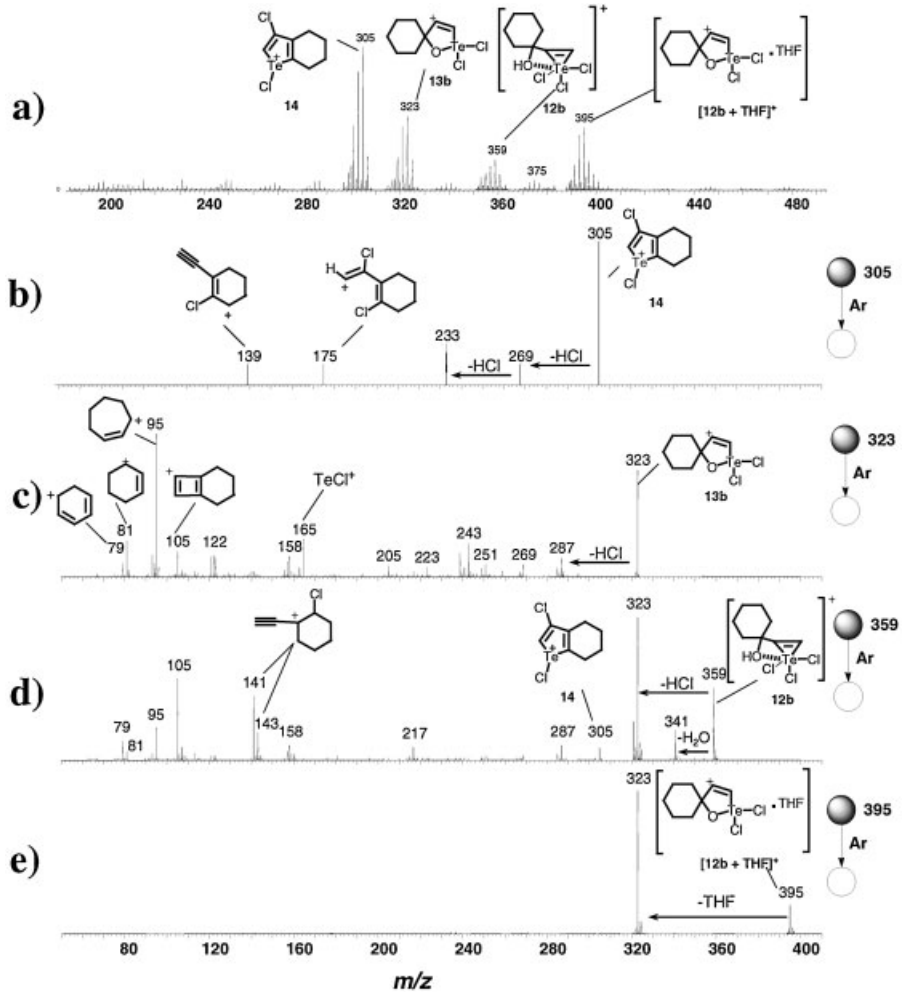
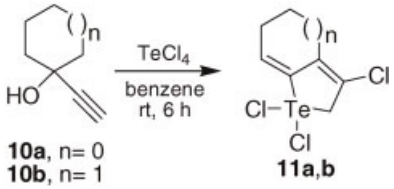
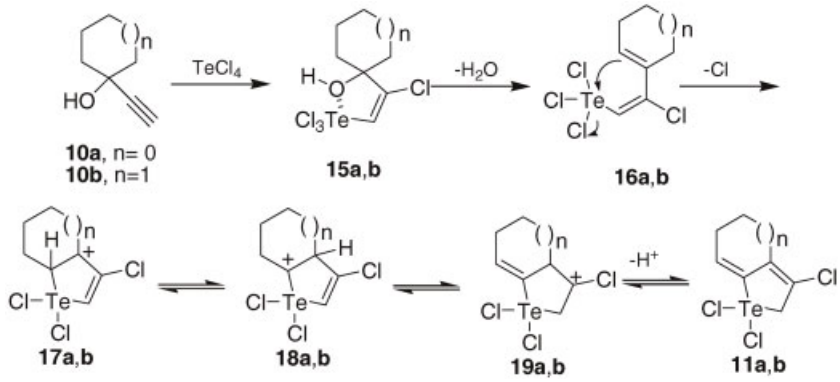


Figure 4. (a) ESI(+) mass spectrum for on-line screening of a solution of **10b**/$TeCl_4$ (1.0:0.9 equiv) in THF. Product ion spectra of the intermediate species found and intercepted from solution, that is, (b) **14** of *m/z* 305, (c) **13b** of *m/z* 323, (d) **12b** of *m/z* 359, and (e) [**12a**+THF]$^+$ of *m/z* 395.



Scheme 4.

alkynes similarly to *p*-methoxyphenyltellurium trichloride. Evidence for this similarity is provided by the observation that they both react with arylalkynes to form *Z*-vinylic tellurides, whereas reactions with 3-hydroxyalkynes give *E*-vinylic tellurides with structures reflecting the steric demand at the vicinal carbon of the tellurenium ring towards attack of the chloride ion on reaction intermediates (**3** in Scheme 1 and **15** in Scheme 5). In their reactions with



Scheme 5.

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structurally simple 3-hydroxyalkynes, such as **10a**, acceptable yields of the addition products were obtained, whereas reactions with alkynes prone to carbocation formation and rearrangement gave either poor yields of the addition product (1-ethynyl-1-cyclohexanol (**10b**)) or a complex mixture of products (1-ethynyl-1-cyclopentanol).

Although ESI-MS/MS experiments cannot tell a priori whether cyclic or acyclic cationic intermediates have been captured from solution, the *E*-stereoselectivity of the reaction points to either the cyclic tellurenium ions such as **2** or non-symmetric bridged carbocations such as **3**.

CONCLUSIONS

The addition of $TeCl_4$ to alkynes has been re-investigated. $TeCl_4$ is found to display reactivity towards alkynes similar to that of *p*-methoxyphenyltellurium trichloride whereas it reacts with aromatic and 3-hydroxyalkynes by different mechanisms as shown by the characteristic stereochemistries of the products. The complete *anti*-stereospecificity of the additions of $TeCl_4$ to all propargyl alcohols studied is consistent with a cyclic chelated telluronium ion intermediate (**3**) in this reaction. Using ESI-MS and ESI-MS/MS, we have been able to intercept and characterize the active electrophile $TeCl_3^+$ in THF solution of $TeCl_4$, as well as its THF complex and several $TeCl_x(OH)_y^+$ derivatives. Also, for the first time, on-line ESI-MS(/MS) monitoring permitted key Te(IV) cationic intermediates of the electrophilic addition of $TeCl_4$ to alkynes (**2a**, **3a**, **12a,b** and **13a,b**) to be captured from the solution and to be gently and directly transferred to the gas phase for mass measurement, determination of isotopic patterns, and structural investigation via collision-induced dissociation. Two of the reaction products reported herein (the cyclic telluranes **11a,b**) have been recently found to act as cysteine protease inhibitors,[8] hence the mechanistic aspects of such reactions revealed in this study may assist the design of new members of this class of potential anti-metastatic agents. The detailed structural data of **11** also provide insights into the coordinative behavior of the Te(IV) atom and its mode of action towards biological targets.[7,8]

Acknowledgements

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