Review Article

Recent Development in Alkynol Chemistry: Electrophilic Iodonium-Induced Rearrangements

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Received June 8, 2007; Accepted November 7, 2007

Abstract

Recent development in iodonium-induced reactions of alkynols is discussed and analysed herein. Classical Meyer-Schuster and Rupe rearrangements are described as a background to the main body of iodonium-induced reactions. α-Iodoenones derived from rearrangement of alkynols, known herein as the Iodo Meyer-Schuster reaction, links the classical Meyer-Schuster reaction to the novel reaction of iodonium-induced rearrangement of alkynols. The rearrangements leading to the formations of β-haloenones and β,β-dihaloenones and enals are discussed with mechanistic considerations, which include stereospecificity of the migrating group and the migratory aptitude differences between the phenyl and the alkyl groups. The role of solvents – namely the water content in organic solvent – is presented with mechanistic consideration of the role of the allenol, the halonium bridge cation intermediates and water in dictating each different reaction pathways. The application of the rearrangement reaction to biological interesting molecules such as glucofuranose and xylofuranose is discussed. Haloetherification reaction, the third type of halonium-induced alkynol reaction, was found to be the exclusive reaction in the halogenation of alkynol derivative of hexofuranoses.

***Key Words*:** Electrophilic halogenations; Alkynols; Iodonium ions; Meyer-Schuster and Rupe Rearrangements; β-Haloenones; β,β-Dihaloenones and enals; Ring expansion of alkynols

Introduction

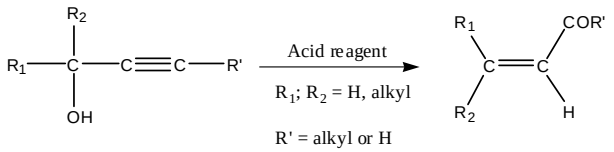
The Meyer-Schuster and the Rupe rearrangements are traditionally the best known reactions of alkynols. Both reactions afford α,β-unsaturated ketones or aldehydes from the starting alkynols. Since 1991, reactions involving alkynol functionality (sometime know as α-acetylenic alcohol) have been studied in order to enhance the understanding of this bifunctional reaction site, and also to develop useful synthetic synthons for synthesis that could be effected via organometallic exchange reactions, such as the Stille reaction. The aim of this article is to highlight and discuss, both in terms of the reactions and their mechanisms, the recent development of alkynol rearrangements induced by electrophilic halogenations. The products of such rearrangements are α-haloenones, β-haloenones or β,β-bromoiodoenones.

Meyer-Schuster and the Rupe rearrangement

Prior to 1991, alkynol chemistry involved acid or base catalysis, which afforded α,β-unsaturated enones. These reactions were known as either the Meyer-Schuster rearrangement or Rupe rearrangement. The

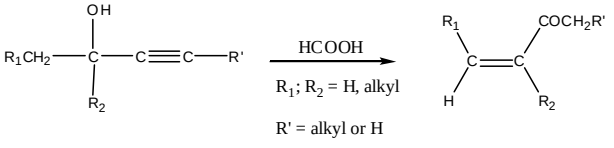
mechanisms of both rearrangements are related but differ in the types of intermediate formed during the course of the reactions (Swaminathan and Narayanan, 1971, Chabardes, 1988). The Meyer-Schuster rearrangement mechanism, which involved acid-catalysed rearrangement of both secondary and tertiary alkynols – affording α,β-unsaturated enones as the products, appears to involve an 1,3-hydroxyl shift (Scheme 1). In this reaction, the type of product, whether it is an enal or enone, depends on the type of group at the terminal end of the acetylene group. In the case of terminal acetylenic hydrogen, the reaction gives an α,β-unsaturated aldehyde (an enal) as the end product (see Scheme 1, when R' = H). When R' is an alkyl group, the end product of the Meyer-Schuster rearrangement is an α,β-unsaturated ketone (an enone).

Scheme 1



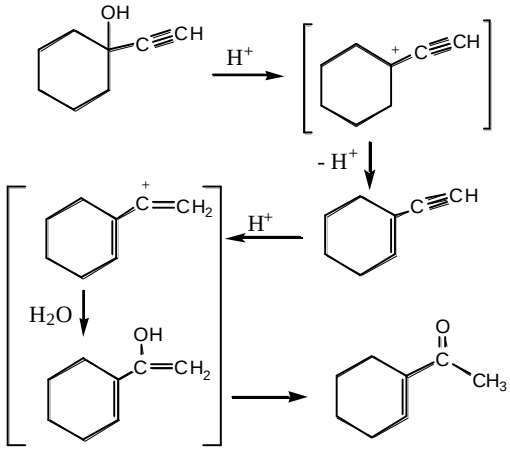
In the Rupe rearrangement, alkynols, upon acid-catalysis, are converted to only α,β-unsaturated ketones. Even if the terminal acetylenic group is a hydrogen, the reaction does not yield an aldehyde but proceeds to rearrange the alkynol to α,β-unsaturated ketone (see Scheme 2, when R' = H).

Scheme 2



The mechanisms for the two rearrangements are related but differ somewhat in some steps and in key intermediates. In the Rupe rearrangement, protonation occurs in the first step at the hydroxyl end of the alkynol (Scheme 3). In a probable slow and rate-determining step, the protonated hydroxy group is lost as water and the dehydrated alkynol forms an α-acetylenic carbocation, which then proceeds to lose a β-hydrogen to form a double bond, and thereby resulting in the formation of enyne intermediate (see Scheme 3).

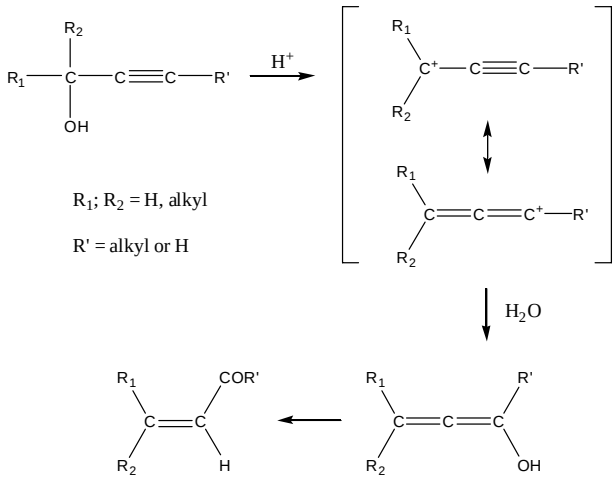
Scheme 3



Protonation of the terminal carbon of the acetylenic group results in the formation of a vinyl cation. Subsequent hydration at the vinyl cation and tautomerisation affords a keto group and the formation of α,β-unsaturated ketone as the end-product (Swaminathan and Narayanan, 1971 and Edens et al., 1977).

The mechanism for the Meyer-Schuster reaction, though related to the Rupe's, deviates from the latter in that an allene or an allenol is thought to be the key intermediate and not the enyne as described for the Rupe rearrangement. Like the proposed Rupe mechanism, the initial step of the Meyer-Schuster reaction involved the protonation of the hydroxyl group of the alkynol, which according to the kinetic study of Edens (Edens et al., 1977), could not determine whether this step was a specific or general acid catalysis (Scheme 4).

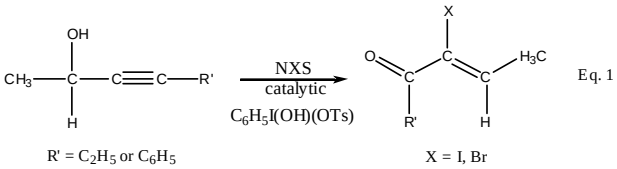
Scheme 4



Ab initio study of the mechanism of the Meyer-Schuster reaction by Andres et al. suggests that the acid catalysis is most likely to be specific rather than general, given the fact that the reaction is usually conducted in highly acidic media (Andres et al., 1988). Unlike the Rupe mechanism, the protonated OH group in the Meyer-Schuster mechanism does not undergo a dehydration step to form the enyne as proposed in the Rupe's mechanism (see Schemes 3 and 4). Instead an allene is formed, leaving the protonated OH group (water molecule) to be loosely attached to the carbon centre, in what can be described as perhaps an "ion-pair" relationship. Theoretical study by Andres et al. supports the aforementioned route, in which the water molecule partially leaves the carbon centre. The study further suggests, which was not so evident from the earlier kinetic study of Edens, that a new water molecule attacks the γ-allenic carbon (original carbon with the OH group is defined as "α"), resulting in the formation of the intermediate allenol. The earlier kinetic study, which could not differentiate different types of water molecule entering and leaving the allene, suggested that the protonated hydroxyl group migrates in a 1,3 manner across the allene. Recently, a new theoretical study of the Meyer-Schuster and the Rupe reactions by Yamabe et al. probed deeper into the exact roles of surrounding water molecules and hydronium ions in dictating the mechanisms of the two reactions, and especially into the formations of the enyne and the allenol intermediates in the Rupe and the Meyer-Schuster rearrangement, respectively (for further details see Yamabe et al., 2006).

Iodo Meyer-Schuster rearrangement

In 1991 Angara and Mc Nelis reported novel formations of α-iodoenones and α-bromoenones from a reaction involving secondary alkynols and halonium producing systems (Angara and Mc Nelis, 1991). Unlike previous reports of the Meyer-Schuster rearrangement, which involved strong acids catalysis or catalytic titanium-copper/silver (Chabardes, 1988), pyridinium hydrochloride as isomerisation catalyst of pyridine propargylic alcohols (Erenler and Biellmann, 2005) or gold-catalysed rearrangement of ethoxyalkynyl carbinols (Lopez et al., 2007), the finding of Angara and Mc Nelis marked for the first time the use of halonium ions in the rearrangement of alkynols to afford α-haloenones as the end-product (equation 1).

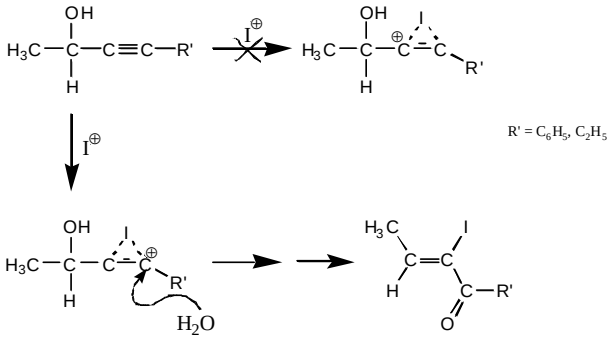


Eq. 1

The use of a hypervalent iodine compound as catalyst was novel, and in addition the employment of *N*-iodo or *N*-bromosuccinimide (combined with catalytic hypervalent iodine compound) as the mild source of electrophilic iodonium or bromonium ions was also novel. In a later work of Mc-Nelis involving electrophilic aromatic halogenations of polyalkylbenzene, the combination of *N*-iodo or *N*-bromosuccinimide with catalytic amounts of a hypervalent iodine compound, hydroxy(tosyloxy) iodobenzene, was demonstrated to produce electrophilic iodonium and bromonium species, by affecting ring halogenations of polyalkylbenzenes (Bovonsombat et al., 1992, Bovonsombat and Mc

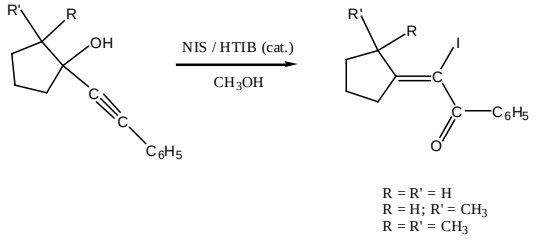
Nelis, 1993a). Hence, the attacking species in the isomerisation of secondary alkynol to α-iodo or α-bromoenones were electrophilic iodonium and bromonium ions in nature. Unlike the Meyer-Schuster reaction, the halonium preferred site of attack is thought to occur at the acetylenic group and not at the hydroxy group, to produce a vinyl cation *alpha* to the phenyl (equation 1, where R' = C_6H_5). In the case of hex-3-yn-2-ol, the preferred site of formation of the vinyl cation is also *alpha* to the ethyl group of the acetylenic unit (equation 1, where R' = C_2H_5), rather than *alpha* to the alcoholic carbon, which would encounter enhanced destabilisation due to the electronegativity of the oxygen of the hydroxy group. Hydration is thought to occur at the vinyl cation, with subsequent tautomerisation and the lost of the OH group leading to formation of α-haloenones as the end-product (see Scheme 5).

Scheme 5



The stereochemistry of the α-haloenone was assigned to be *Z*-geometry based on comparisons of the (*Z*)-chloro analogue of 2-iodo-1-phenyl-2-buten-1-one, (*Z*)-2-chloro-1-phenyl-2-buten-1-one. The ^{1}H-NMR absorption of the vinyl hydrogen of the (*Z*)-2-chloro-1-phenyl-2-buten-1-one was found to be 6.77 ppm, which would be consistent with the vinyl hydrogen being *cis* to the carbonyl of the benzoyl group (Angara and Mc Nelis, 1991). The vinyl hydrogen of 2-iodo-1-phenyl-2-buten-1-one, derived from iodination of 4-phenyl but-3-yn-2-ol (equation 1, R' = C_6H_5), was found to have an absorption at δ 6.75 (quartet, J = 6.5Hz, 1H), similar to the data found for (*Z*)-2-chloro-1-phenyl-2-buten-1-one. With this data, the *Z*-geometry was assigned to the product of iodo-induced isomerisation of the alkynol.

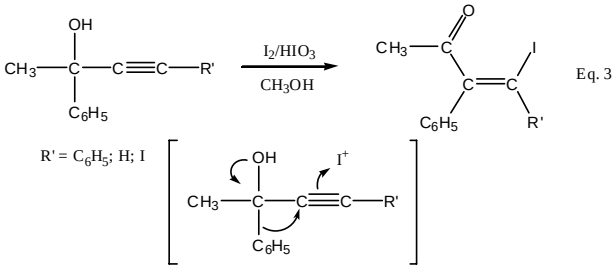
The principle of halonium-induced isomerisation of alkynols to α-haloenone was also applied to cyclic alkynols, as shown in equation 2. The investigation into what is now called the "Iodo Meyer-Schuster" rearrangement became more active with the development of novel and more powerful halonium producing systems. Two reports citing electrophilic halogenations of polyalkylbenzene using a combination of *N*-halosuccinimide and catalyst acids, and a novel combination of hydroxy (tosyloxy) iodobenzene (HTIB) and iodine or bromine (Bovonsombat et al., 1992; Bovonsombat and Mc Nelis, 1993a) were the foundation for the investigation of the behaviour of cyclic alkynols towards halonium ions. During the same time as these aromatic halogenations methods were reported, the behaviour of linear bromoalkynols and bromoethynylcyclopentanols towards halonium species were investigated. In these investigations halonium ions were employed at room temperature in polar aprotic solvent such as acetonitrile to affect ring expansion of cyclic alkynols and a phenyl shift in the linear bromoalkynol, which led to the formations of β-haloenones or β,β-dihaloenones as the end-products. By means of subtle structural and electronic changes at the alkyne end, as shown in equations 1 and 2, further insight could be gained into the reaction pathways of halonium-induced alkynol rearrangement.



With a phenyl group at the terminal end of the alkyne, electrophilic iodination of the cyclic alkynol did not afford a ring expansion product, but gave instead an Iodo Meyer-Schuster product, as shown in equation 2 (Bovonsombat and Mc Nelis, 1993d). A similar finding was also observed in the case of iodination and bromination of linear alkynols, as shown in equation 1 (Angara and Mc Nelis, 1991). Moreover, the starting alkynols, 1-phenylethynylcyclopentanol – as shown in equation 2, when R' = R = H - did not undergo a Rupe rearrangement. 1-Ethynylcylopentanol and its analogues could have taken the Rupe reaction path, since α,β-elimination of an equivalent H_2O molecule from the ring structure should be facile. This would have produced an enone with its alkene unit located in the ring instead of being *exo* to the ring as shown in equation 2. The absence of the Rupe rearrangement pathway of 1-ethynylcylopentanol and its analogues (including 1-phenylethynylcyclopentanol) could be attributed to the initial formation of the vinyl cation induced by iodination of the alkyne, instead of initiating the loss of the hydroxyl group in the first step. As with the above explanation for the conversion of linear alkynols to α-haloenones, it is highly probable that the electrophilic iodination occur at the alkyne resulting in formation of a benzylic vinyl cation (see scheme 5, where R' = C_6H_5). Subsequent hydration, tautomerisation and dehydration lead to a 2-(cyclopentylidene)-2-iodo-1-phenylethanone structure (Scheme 5 and equation 2). Absence of vinyl hydrogen signal further reinforces the absence of the Rupe reaction pathway. The relative position of the vinyl iodine was established by exchanging the iodine with a hydrogen using a palladium catalysed hydride exchange reaction and comparing this product with the product obtained directly from a Meyer-Schuster reaction which was conducted on the original starting alkynol using mercuric sulphate as the catalyst. The products of the Meyer-Schuster reaction and the iodide-hydride exchange were shown by spectroscopic means to be identical (Bovonsombat and Mc Nelis, 1993d).

β-Haloenones

In the Meyer-Schuster and the Iodo Meyer-Schuster reactions, alkynols are converted to enone and α-iodoenones, respectively. However, in a different development involving alkynol reactions, Janas et al. found that in the presence of iodine and several of its oxides, alkynols bearing a phenyl at the alcohol-bearing carbon readily underwent a phenyl shift to afford β-iodoenones instead of α-iodoenones, as shown in equation 3 (Janas et al., 1985). The phenyl shift from the tertiary hydroxy-bearing carbon was also observed despite a phenyl group present at the terminal alkyne, which based on previous discussion concerning the acetylenic unit bearing a terminal phenyl group should form a vinyl cation in the benzylic position relative to the terminal phenyl group and thereby dictating the site of the keto group and the final outcome towards the formation of a Meyer-Schuster product (equation 3). However, a Meyer-Schuster product was not observed. A β-iodoenone, resulting from the phenyl shift from the tertiary carbon, was observed instead with yields of 40 to 60%. The remaining product in the reaction was methyl ether adduct of the starting alkynol (Janas et al., 1985).

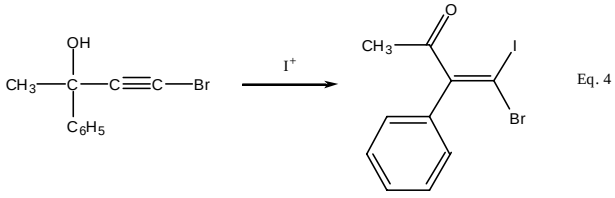


Eq. 3

β,β-Dihaloenones

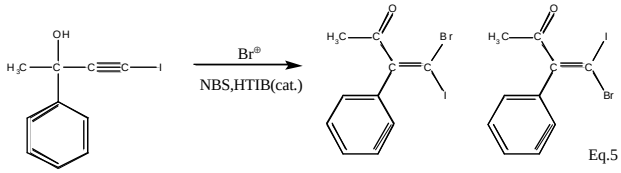
Central to the conversions of alkynols to α-haloenones, β-haloenones and β,β-dihaloenones (the subject of review in this section) are the methodologies to afford facile halonium species using *N*-halosuccinimides (Bovonsombat and Mc Nelis, 1993a) or from a novel combination of hydroxy(tosyloxy)iodobenzene (HITB) and molecular iodine or bromine with the latter

resulting in 2 reactive equivalents of halonium ions per molecular halogen (Bovonsombat et al., 1992). Without these mild halonium producing methodologies, which permit alkynols and aromatic halogenation to be reacted at room temperature, alkynol reactions could not be investigated easily due to the severity of the conditions used in other halonium producing systems. Suitable solvents for *N*-halosuccinimides and HITB-molecular iodine or bromine combination systems include methanol, chlorinated solvents, acetonitrile and acetone, all common organic laboratory solvents. Using these iodonium-producing or bromonium-producing agents, the reactions of haloalkynols afforded a variety of *β,β*-dihaloenone products (equations 4, 6 and 7). The role of hypervalent iodine compounds in the formation of *β,β*-dihaloenones, for both cyclic and acyclic alkynols, has been extensively reviewed by Koser and Varvoglis (Koser, 2001 and Varvoglis, 2001). The genesis of the *β,β*-dihaloenones products was the result of phenyl shift or ring expansion of the original alkynols (see equations 4, 6 and 7).



Eq. 4

The reaction of tertiary alkynols with iodonium-producing agents afforded *β,β*-dihaoenones, as shown in equation 4 (Angara et al., 1992). When such brominated tertiary alkynol, 4-bromo-2-phenyl-3-butyn-2-ol, is mixed with a combination of either HTIB-molecular iodine or *N*-iodosuccinimide and catalytic amounts of *p*-toluenesulphonic acid, (*Z*)-4-bromo-4-iodo-3-phenyl-3-buten-2-one was obtained with greater than 90% selectivity and over 90% conversion. The stereochemistry of (*Z*)-4-bromo-4-iodo-3-phenyl-3-buten-2-one was proved by converting the dihaloenone to a diphenyl adduct, whose geometry was shown by ^{1}H-NMR absorption to be opposite to the known *E*-isomer (Angara et al., 1992). In pursuit of further support for the *Z*-geometry, the vinyl iodine atom was replaced by means of palladium catalysed reaction with a hydrogen atom. Based on the vinyl hydrogen ^{1}H-NMR adsorption data, the replaced hydrogen - hence the original iodine atom - was found to be *syn* to the carbonyl, and therefore consistent with the *Z*-isomer assignment. Absent in the reaction product mixture (equation 4) was the *E*-isomer of 4-bromo-4-iodo-3-pheyl-3-buten-2-one.



Eq.5

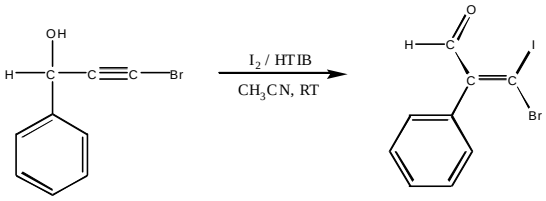
E-Isomer : Z -Isomer
2 : 1

The *E*-isomer, on the other hand, was found with a ratio of 2 to 1 to the *Z*-isomer, when the iodinated alkynol, 4-iodo-2-phenyl-3-butyn-2-ol, was treated with *N*-bromosuccinimide and catalytic amounts of hydroxy(tosyloxy)iodobenzene in methanol. The same combination of reagents and starting material failed to yield either the *Z* or the *E*-isomer of the mixed *β,β*-dihaloenone in refluxing acetonitrile. With bromine and stoichiometric HTIB in acetonitrile for eighteen hours at room temperature, the ratio of *Z* to *E*-isomers of the mixed *β,β*-dihaloenones were 6 to 1 with the conversion of 90%. The appearance of the *Z*-isomer in the bromination of the iodoalkynol starting material and the absence of the *E*-isomer in the iodination of the brominated alkynol suggest the stereospecificity of the iodonium attack on the alkyne and the lack of stereospecificity on the part of the bromonium attack on the alkyne. The bromonium ion attack on the alkyne part of the alkynol was postulated to give an open vinyl cation compared to a bridged iodonium ion across the alkyne. This leads to the possibility of isomerisation due to carbon-carbon bond rotation prior to the phenyl shift with a phenyl shift capable of occurring *anti* and as well as *syn* to the bromonium ion. On the other hand the

iodonium ion, due to its larger size, is more capable of forming a bridged halonium ion across the alkyne and thereby making a *syn* phenyl shift prohibitive and permitting only an *anti* shift to occur.

β,β-Dihaloenals

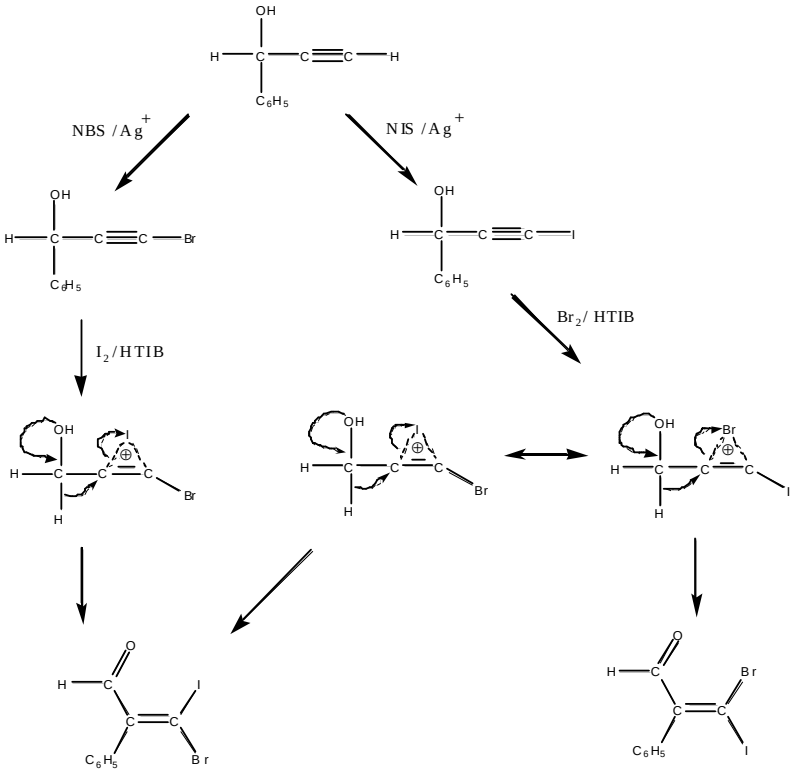
With combinations of HTIB and iodine or *N*-iodosuccinimide and catalytic amounts of *p*-toluenesulphonic acid, terminal brominated secondary alkynol was converted with high selectivity and conversion to (*Z*)-*β,β*-bromoiodoenals (Bovonsombat and Mc Nelis, 1992).



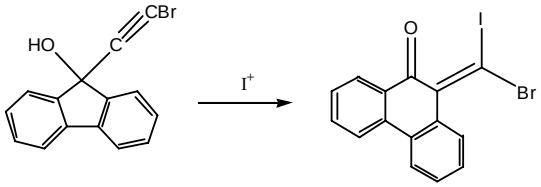
Eq. 6

In contrast to the previous example of a secondary alkynol reaction, which afforded α-iodoenones as the end-product (shown in equation 1), the reaction involving terminal brominated secondary alkynol gave exclusively a *β,β*-dihaloenal with the same combination of iodonium-producing system used in the former case. Like the previous example of *β,β*-dihaloenone, the iodonium attack on the alkyne, thereby resulting in the formation of a bridged iodonium, yielded only a partial vinyl cation on the internal side of the alkyne moiety, which is also one carbon removed from the terminal alkyne carbon carrying an electronegative bromine atom. Due to the fact that the phenyl shift occurred *anti* to the iodonium-bridge, only the *Z*-isomer was detected in the product. In consonant with the previous example of *β*, *β*-dihaloenone, the difference between the bromonium and the iodonium ions in controlling the stereospecificity reoccurs in the bromination of iodinated secondary alkynol, which gave none of the *E*-isomer of 3-bromo-3-iodo-2-phenylpropenal, the expected main product of the bromination of 3-iodo- 1-phenylprop-2-yn-1-ol. (*Z*)-3-bromo-3-iodo-2-phenylpropenal was obtained instead with 22% selectivity and along with 27% of 3,3-diiodo-2-phenylpropenal (Scheme 6).

Scheme 6



Given the above finding, it appears that the bromonium ion, due to its smaller size compare to the iodonium ion, has less ability to form a complete bridged ion. Equilibration occurs rapidly between the bromonium ion and the iodine atom. This equilibration has to occur faster than the phenyl shift since the product arising out of an iodonium-bridge is observed and while none is observed from a bromonium-bridge intermediate. Despite the lack of the *E*-isomer product formation with bromination of iodinated alkynol, the high selectivity and conversion to the *Z*-isomer still represent a useful path towards the formation of a useful and versatile synthetic template, capable of synthesis of complicated enones and enals.

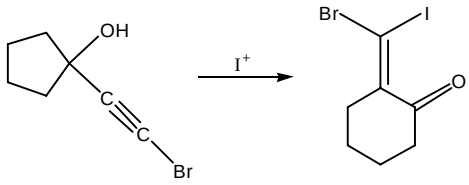


Eq. 7

Iodonium-induced phenyl shift reaction of alkynol has been extended to a phenanthrene system, as shown in equation 7 (Bovonsombat and Mc Nelis, 1994). The phenyl shift, which in fact involves the ring expansion of the five-membered ring, occurred readily with combinations of either HTIB/iodine or with *N*-iodosuccinimide and catalytic *p*-toluenesulphonic acid. The geometry of the dihaloenone product was *Z*-isomer, as exemplified by the mass spectrum cracking pattern of the product which showed remarkable similarity to the patterns of the previous *Z*-isomer products of the phenyl shifts of the secondary and tertiary alkynols, and while it stood in contrast to the cracking pattern observed for the *E*-isomer of the linear enones and enals (for further details on mass spectrum cracking pattern between *Z* and *E*-dihaloenones, see Bovonsombat and Mc Nelis, 1993b).

Ring expansion reactions

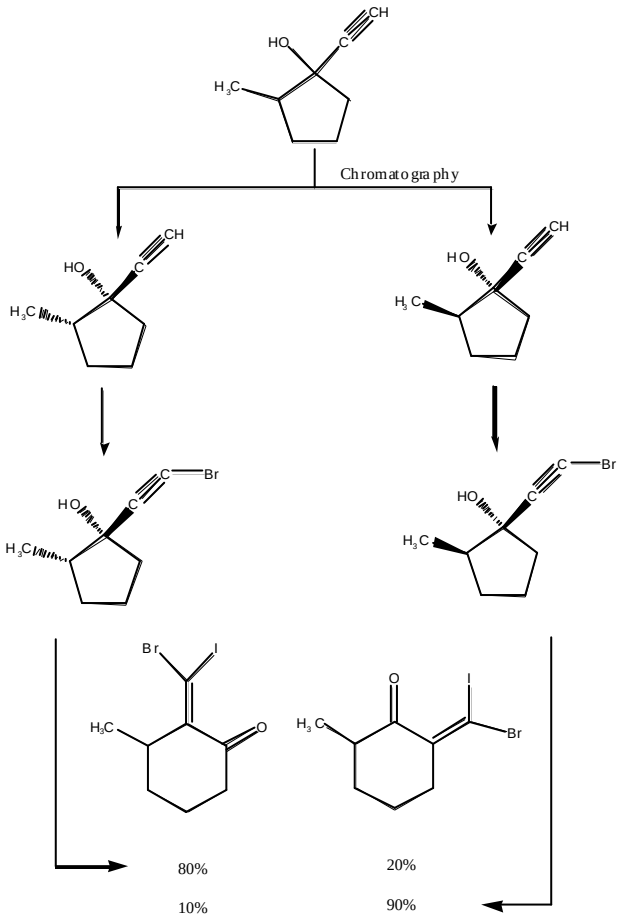
Electrophilic halogenation of ethynylcyclopentanol represents a challenge since the starting alkynol can readily undergo dehydration, which can result in the formation of enyne or the Meyer-Schuster product (equation 2). Application of the iodonium producing systems, specifically the combination of HTIB and iodine, to 1-bromoethynylcyclopentanol resulted in an alkyl shift that gave a cyclohexanone ring due to the ring expansion of the cyclopentanol ring, as shown in equation 8 (Bovonsombat and Mc Nelis, 1993b). As with the previous cases for the formations of β, β-bromoiodoenones and β,β-bromoiodoenal, the assignment of the *Z*-isomer was based on ^{1}H-NMR absorption of the hydrogen, exchanged at the iodine, and by other spectroscopic analysis such as mass spectrum cracking pattern comparisons between those of the *Z*-isomer and the *E*-isomer (Bovonsombat and Mc Nelis, 1993b).



Eq. 8

1-Bromoethynyl-2-methylcyclopentanol and 1-bromoethynyl-2,2-dimethylcyclopentanol were also subjected to the ring expansion reaction conditions (HTIB and stoichiometric iodine in acetonitrile at room temperature). The initial reported structures of the ring expansion reactions of both 1-bromoethynyl-2-methylcyclopentanol and 1-bromoethynyl-2,2-dimethylcyclopentanol were later found to be incorrect. Herault and Mc Nelis re-examined the end products of the ring expansion reaction of these two bromoalkynols and found that the shifts were not a straightforward shift of tertiary and quaternary carbons as expected for 1-bromoethynyl-2-methylcyclopentanol and 1-bromoethynyl-2, 2-dimethylcyclopentanol, respectively. In the case of the former the shift from the secondary carbon (C-5 of the cyclopentanol skeleton) is more preferred (see Scheme 7).

Scheme 7

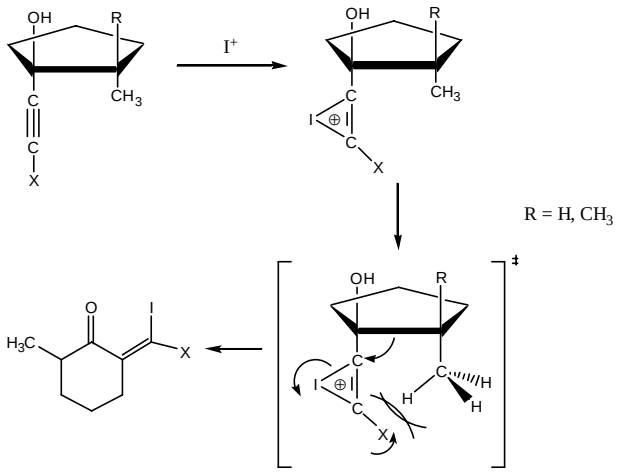


The discussion pertaining to the competition between secondary and tertiary carbon shifts, as observed in the ring expansion reactions of 1-ethynyl-2-methylcyclopentanol, is dealt with in the next section.

Secondary carbon versus tertiary carbon shift

In the study of Herault and Mc Nelis, the alkyl shift, and hence the end resulting ring expansion, was established by investigating the role of steric hindrances of the iodonium-bridge and the neighbouring alkyl groups at the adjacent C-2 position (Herault and Mc Nelis, 1996). In this study, Herault and Mc Nelis investigated the mechanism of the ring expansion of 2-substituted-1-haloethynylcyclopentanol (see Schemes 7 and 8). In their investigation, both isomers of 1-haloethynyl-2-methylcyclopentanols were treated with iodonium-producing agent, resulting in the ring expansion reaction which was found to have occurred stereoselectively. The stereoselectivity of the ring expansion depends on the relative positions of the methyl group on the 2nd carbon (at C-2 position) and the hydroxy group on the adjacent carbon (shown as *cis* to each other in Scheme 8).

Scheme 8

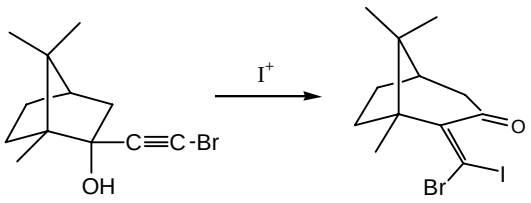


If the methyl group on C-2 were *cis* to the hydroxy group, the product formed is 2-(dihaloethylidene)-3-methylcyclohexanones which corresponds to the tertiary carbon (C-2) shift in the ring expansion (see Scheme 7). In this shift, the iodonium-bridge can freely adopt an antiperiplanar conformation to the shifting C-2 carbon without experiencing steric hindrance. As the iodine atom shifts towards the terminal end of the alkyne, the other halogen atom, originally part of the terminal alkyne, has to swing towards the shifting carbon centre. This movement of shifting halogens occurs without hinderance since the affected alkynyl group is *trans* to the methyl. On the other hand, if the methyl group were *cis* to the ethynyl unit, the shifting of the halogen (as shown in Scheme 8) would bring steric impedance onto the hydrogens of the methyl group. Hence, ring expansion corresponding to the secondary carbon shift (C-5) occurs instead to avoid the steric effect experienced in the case of the tertiary carbon (C-2)

shifting. This occurs when the 2-methyl is *trans* to the 1-hydroxy (or *cis* to the haloethynyl group), and therefore the resulting product is 2-(dihaloethylidene)-6-methylcyclohexanones (see Schemes 7 and 8).

Ring expansion of complex ring systems

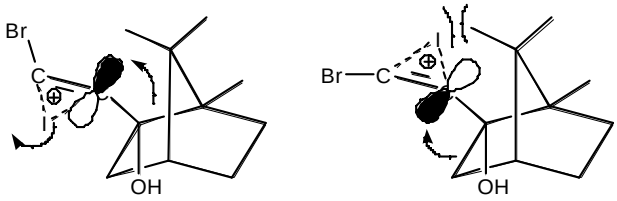
The ring expansion reactions of 1-ethynylcyclopentanol and its derivatives give insights into the mode of alkyl shift. Complex ring systems such as camphor, norcamphor and homoadamantanone represent another challenge to the ring expansion reaction. With such complex ring systems, there is a question of whether the skeletal structure of the bicyclic and tricyclic ring systems could be retained during the course of treating these rings with iodonium producing system. Thus, an haloethynyl camphor derivative, 2-*exo*-bromoethynyl-1,7,7-trimethylbicyclo [2.2.1]heptan-2-ol, was treated with HTIB and iodine in acetonitrile at room temperature, and gave 2-[(*Z*)-bromoiodomethylidene]-1,8,8-trimethylbicyclo [3.2.1]octan-3-one with 60% yield, as shown in equation 9 (Bovonsombat and Mc Nelis, 1993c).



Eq. 9

Spectral and analytical data were consistent with the structure assignment of 2-[(*Z*)-bromoiodomethylidene]-1,8,8-trimethylbicyclo [3.2.1]octan-3-one and the *Z*-configuration of the halogens. The shift of the quaternary carbon (C-1) is consistent with the finding of Herault and Mc Nelis, which in their study found that steric hindrance of the iodonium - due to the presence of neighbouring substituted carbon – can prevent the shift of the carbon centre with greater migratory aptitude and allowing the centre with the so-called "lesser" migratory aptitude to shift instead (Scheme 9).

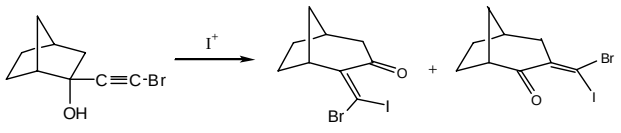
Scheme 9



C-1 Shift C-3 Shift

In this case as shown in scheme 9, the quaternary carbon is expected to have greater migratory aptitude than the secondary carbon (C-3). The shifting of the quaternary carbon, C-1 centre, would present the iodonium-bridge with none of the steric hindrance with the neighbouring C-3 centre and the methyls of the C-7 bridgehead. On the other hand the shift of the C-3 centre, the secondary carbon, would bring the iodonium bridge close to the methyl group at C-1 and most importantly, due to the antiperiplanar positioning of the iodonium bridge to the shifting C-3 centre, would place the iodonium in close proximity to the methyl of the bridge C-7, which would produce an enhanced steric effect (Scheme 9).

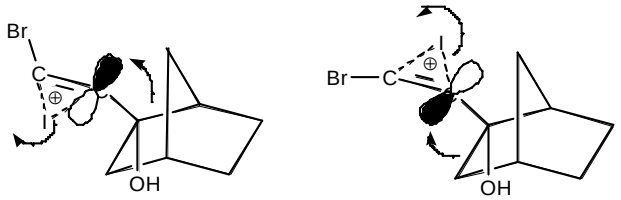
In contrast to the camphor system, which gave one product of one carbon type shift, the ring expansion reaction of norcamphor gave 2 products, each resulting from different carbon shifts, as shown in equation 10 (Djuardi et al., 1994). For the norcamphor system, methyl groups at bridgeheads of both C-1 and C-7 are absent. Therefore, the iodonium-bridge can be formed across the triple bond and capable of being antiperiplanar to both C-1 and C-3 centres without experiencing steric hindrance from the C-7 bridgeheads. Hence both C-1 and C-3 can shift – while the iodonium-bridge assumes an antiperiplanar conformation – with equal aptitude and therefore giving rise to the two types of products.



Eq.10

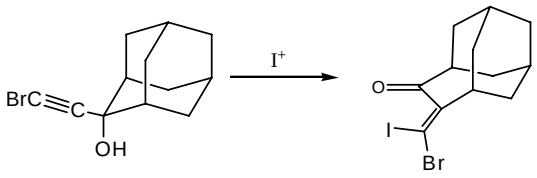
In order to eliminate the possibility that the two products could be of *Z* and *E*-isomer of an alkyl shift, the alkynol derivative of norcamphor was derivatised to its iodoalkynol adduct and treated to HTIB and iodine in acetonitrile at room temperature. Two products were again formed and thereby eliminating the possibility of *E* and *Z*-isomer, since the presence of the diiodo at the terminal alkene unit would not give geometric isomerism. The two products formed during iodination of the iodo alkynol adduct of norcamphor further supports the notion that both C-1 and C-3 centres shifted and also the role of the methyl at C-7 bridgehead in interfering with the formation of the iodonium-bridge antiperiplanar to the shifting group (Scheme 10).

Scheme 10



C-1 Shift C-3 Shift

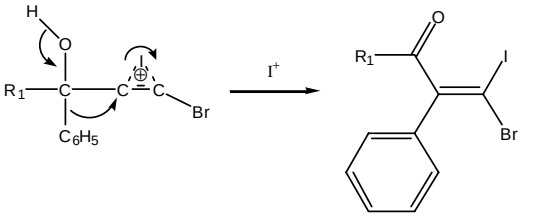
Both camphor and norcamphor rearrangements are examples of the ring expansion reaction of bicyclic ring systems. Both examples demonstrated total skeletal integrity retention during the course of the ring expansion reaction. With homoadamantanone, a tricyclic ring system, the ring expansion reaction was able to convert this tricyclic ring system to its (*Z*)-*β*, *β*-bromoiodoenone analogue with complete skeletal integrity retention, as shown in equation 11 (Bovonsombat and Mc Nelis, 1995). Using HTIB and iodine combination in acetonitrile at room temperature, 2-bromoethynyltricyclo[3.3.1.1^{3,7}]decan-2-ol was converted to 5-(*Z*)-bromoiodomethylidenetricyclo [4.3.1.1^{3,8}]undecan-4-one with 63% yield. Spectral analytical data of the product was consistent with the *Z*-isomer assignment and the incorporation of the carbonyl and the alkene units in the newly formed ring.



Eq. 11

***Z*-geometry versus *E*-isomer of the *β*,*β*-dihaloenones**

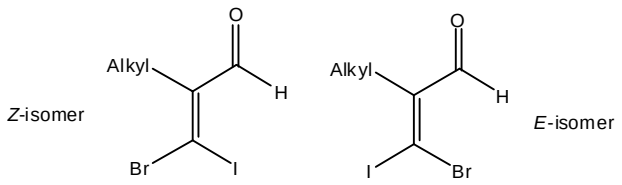
Despite a wealth of spectroscopic data (Angara et al., 1992, Bovonsombat and Mc Nelis, 1993b) and the ligand exchange experiments (Angara et al., 1992) supporting the *anti* shifts, the relative positions of both iodine and bromine to the carbonyl are still not absolutely conclusive.



Eq. 12

Ring expansion reaction involving *exo*-8-(bromoethynyl)-*endo*-8-hydroxypentacyclo [5.4.1.0^{2,6}.0^{3,10}.0^{5,9}]undecane, as reported by Marchand et al., casts further controversy to the exact location and geometry of the halogens to the carbonyl (Marchand et al., 1995). By means of X-ray structural analysis of the products, Marchand et al. established that their ring-expanded product was exclusively an *E*-isomer, that is the vinyl iodine – made from iodonium attack on the acetylenic functionality containing terminal bromine – is *anti* to the carbonyl and the acetylenic terminal bromine assumes the vinyl position *syn* to the carbonyl. This isomer is contrary to the *Z*-isomer reported earlier by Mc Nelis et al (Angara et al., 1992, Bovonsombat and Mc Nelis, 1993b). The ring expansion work of Marchand et al. could be a special case of the Mc Nelis rearrangement, which might involve fast equilibration between bromonium and iodonium ion bridges (Bovonsombat and Mc Nelis, 1993b). Indeed, further study is required in order to solve the mystery of the *E*-isomer versus the *Z*-isomer (Scheme 11).

Scheme 11



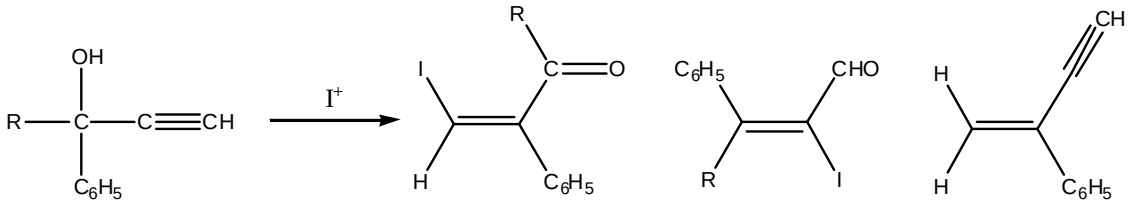
Nevertheless though, the work of Marchand et al. further emphasises the need to determine the absolute structures of the earlier products of (*Z*)-bromoiodoenones of camphor, adamantane and phenanthrene ring expansion analogues. Although the establishment of the *Z*-geometry of the *β,β*-dihaloenones has already been made by means of spectroscopic studies (Angara et al., 1992, Bovonsombat and Mc Nelis, 1993b) and ligand or hydrogen exchanges at the vinyl position (Angara et al., 1992, Bovonsombat and Mc Nelis, 1992, Bovonsombat and Mc Nelis, 1993b), X-ray structural analyses would be the next logical step to unequivocally determine the exact structures of the *β, β*-dihaloenone analogues of camphor, adamantane and others.

Solvent effect

The solvent study of Herault and Mc Nelis helped to clarify the competitive nature of the Iodo Meyer-Schuster (IMS) reaction, shift rearrangement and dehydration of alkynols, which for the dehydration reaction leads to an enyne, see equation 13 (Herault and Mc Nelis, 1997).

Based on previous reports concerning the conversions of alkynols to *β,β*-dihaloenones, the shift reaction appears to be favoured by the presence of terminal electronegative bromine atom, which upon iodonium attack on the alkyne moiety would favour the formation of internal vinyl cation – as opposed to the terminal and relatively less stable vinyl cation. With this particular vinyl cation set up, the shift rearrangement is therefore favoured. In the solvent study of Herault and Mc Nelis, however, the basic behaviour of alkynol (without terminal bromine, which would heavily favour only one type of vinyl cation) towards iodonium species is studied. Using combinations of *N*-iodosuccinimide(NIS) and *p*-toluenesulphonic acid (*p*-TsOH) as catalyst or HTIB with iodine combination, the competitive differences between the shift rearrangement, Iodo-Meyer Schuster reaction and the dehydration pathway were determined using 2-phenyl-2-butynol and 1,1-diphenylpropynol as model alkynols (R = C_6H_5 or CH_3 in equation 13).

As in the previous reports concerning the formations of *β,β*-dihaloenones, HTIB and iodine in dry acetonitrile condition favoured the shift migration that resulted in the formations of (*Z*)-4-iodo-3-phenyl-2-butenone and (*Z*)-3-iodo-1,2-diphenyl-2-propen-1-one with almost quantitative yields from the starting 2-phenyl-2-butynol and 1,1-diphenylpropynol, respectively. With combinations of NIS and varying amounts of *p*-TsOH, which unlike the HTIB and iodine combination produces no by-product iodobenzene upon work up, gave different results depending on whether acetonitrile was dry or not. These results give further insight into the competitive nature of the mechanisms between shift rearrangement, IMS



Eq. 13

Shift rearrangement Product

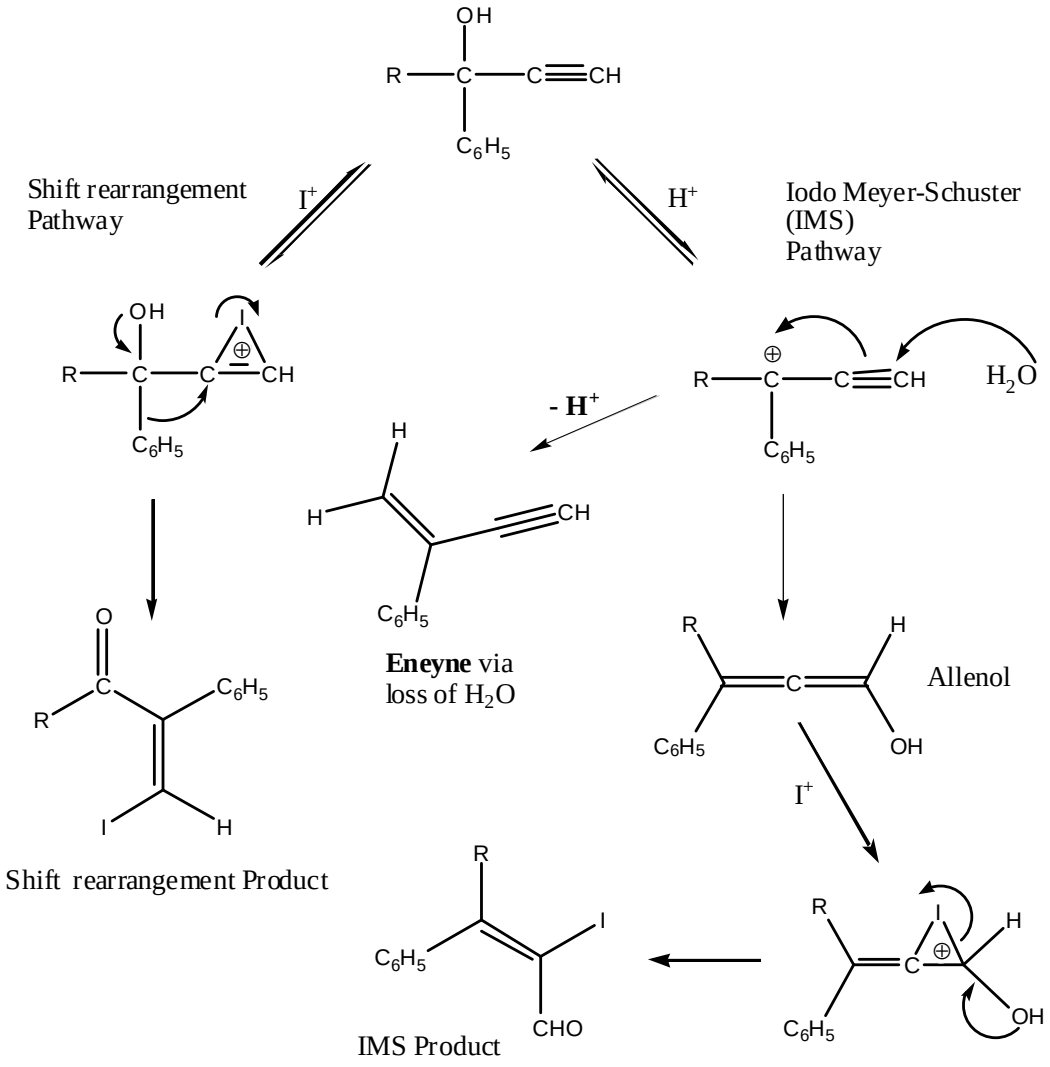
Iodo Meyer-Schuster (IMS) Pathway

Eneyne via loss of H_2O

and dehydration pathway. In dry acetonitrile, using the combination of NIS and *p*-TsOH, the shift reaction did not occur for both 2-phenyl-2-butynol and 1,1-diphenylpropynol. Instead products arising out of IMS and dehydration reactions dominate. The mechanistic explanation is due to the absence or presence of small amounts of water in acetonitrile, which permits the dehydration pathway – via an acetylenic cation – to dominate (Scheme 12). The cation formed can then rearranged to an allenol via the re-attacking of the water molecule at the cation centre. Iodonium attack on the allenol then leads to the formation of the IMS product.

Loss of proton from the acetylenic cation intermediate of 2-phenyl-2-butynol leads to the enyne product (see Scheme 12). Addition of water to acetonitrile – amounts varying from 1 to 10% by volume – pushed the reaction of alkynol with iodonium species towards the shift rearrangement instead of the IMS and/or dehydration paths. The addition of water which results in the shift reaction instead of the IMS pathway, is consistent with the picture of the lack of formation of the allenol, derived from the loss of a water molecule from the alkynol. The presence of plentiful water molecules in the reaction prevents the loss of a

Scheme 12



water molecule from the alkynol, by shifting the equilibrium towards the reactant side, the starting alkynol (Scheme 12).

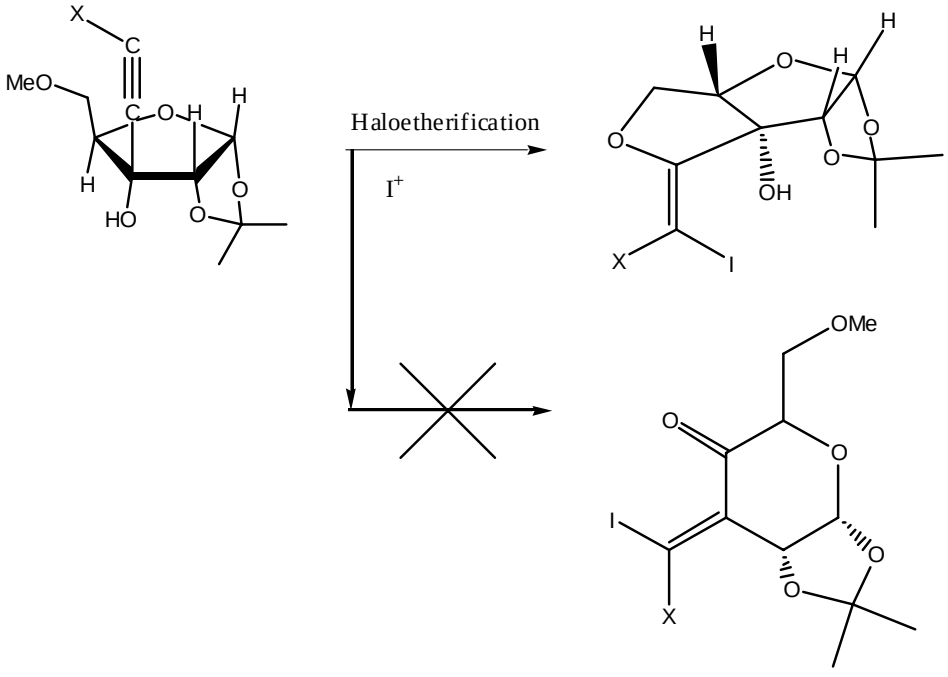
Iodonium ion induced rearrangements alkynols of hexofuranoses

Application of iodonium-induced alkynol rearrangement to sugars gave a new and third type of reaction. In the first study of the iodonium-induced rearrangement reaction, commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose was converted to its alkynol adduct, 3-ethynyl-1,2-*O*-isopropylidene-5-*O*-methyl-α -D-pentofuranose. Treatment of 3-haloethynyl-1,2-*O*-isopropylidene-5-*O*-methyl-α-D-pentofuranose with either combination of NIS and catalytic amounts of *p*-TsOH in 5% aqueous acetonitrile or combination of HTIB and iodine in dry acetonitrile did not give the ring-expanded product as expected (Scheme 13).

Instead, a product arising out of haloetherification was obtained in high yields. Due to the relative positions of the primary methyl ether and the ethynyl group, intramolecular cyclicsation - caused by the attack of the ether oxygen onto the iodonium-induced vinyl cation, was more facile that the C-4 shift, as shown in scheme 13 (Djuardi and Mc Nelis, 1999). Subsequently after intramolecular haloetherification, methyl group of the original ether is then lost to give the product shown in scheme 13.

In another example of iodonium-induced rearrangement of alkynol derivatives of sugars, haloalkynol derivative of 1,2,5,6-di-*O*-(1-methylethylidene)-α-D-glucofuranose was halogenated in dry acetonitrile. Unlike the above example, C-5 and C-6 positions of the glucofuranose were blocked by acetonide group, which would render its attack on the alkyne moiety more difficult or not possible due to steric hindrance. Upon halogenations of the bromo analogue of alkynol derivative of 1,2,5,6-di-*O*-(1-methylethylidene)-α-D-glucofuranose, the anticipated ring-expanded products were not obtained. The C-4 centre of the glucofuranose had not shifted to the vinyl cation. Instead of the ring expansion reaction and like the previous cited case, the glucofuranose underwent

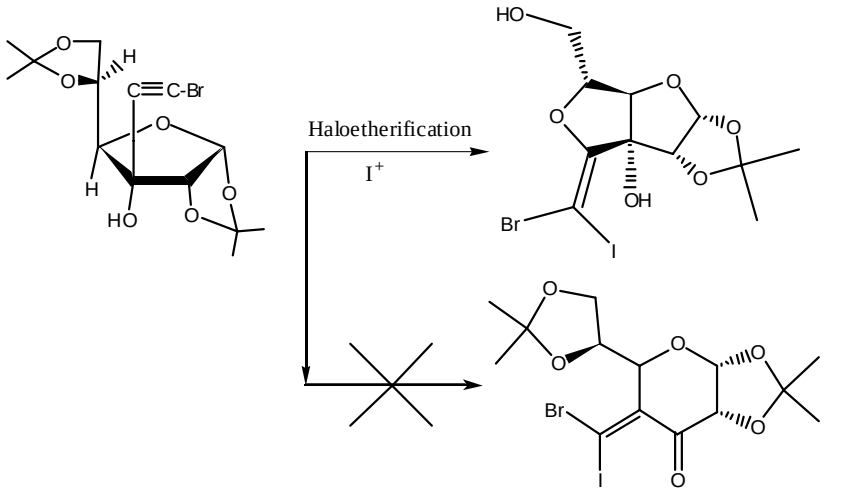
Scheme 13



intramolecular haloetherification (Blandino and Mc Nelis, 2002), despite the presence of sterically hindering acetonide group protecting the oxygens of C-5 and C-6 positions (Scheme 14). As with the above example, which occurred with the lost of the methyl group of the ether, haloetherification in this case also occurred with the loss of the acetone group.

alkynols towards electrophiles. Depending on the types of alkynols, halogenations of alkynols can lead to α-haloenones, β-haloenones, β,β-dihaloenones, β,β-dihaloenals and β,β-dihaloethers. In the case of certain secondary and tertiary alkynols containing terminal alkyl or aryl group at the end of ethynyl unit, halogenations of these alkynols lead to α-haloenones.

Scheme 14



Ring-expanded product

Conclusions

In the classical Meyer-Schuster and Rupe rearrangements, alkynols upon treatment with strong acids are converted to α,β-unsaturated enones or enals, depending on the alkyne structure of the starting alkynols. The Meyer-Schuster reaction, via an allenol, gives either an α,β-unsaturated enones, if the terminal group of the alkyne is an alkyl group, or an α,β-unsaturated enal if the alkyne portion of the alkynol is an acetylene. On the other hand the Rupe reaction, which gives α,β-unsaturated enones, is thought to occur via an enyne intermediate, caused by the loss of the hydroxy group and a β-hydrogen. Due to the enyne intermediate, the Rupe reaction usually gives α,β-unsaturated enone, even if the group at the end of the alkyne is a hydrogen.

Iodonium-induced reactions of alkynols represent an evolution of the understanding of the chemistry of alkynols towards electrophiles. Depending on the types of alkynols, halogenations of alkynols can lead to α-haloenones, β-haloenones, β,β-dihaloenones, β,β-dihaloenals and β,β-dihaloethers. In the case of certain secondary and tertiary alkynols containing terminal alkyl or aryl group at the end of ethynyl unit, halogenations of these alkynols lead to α-haloenones. With the phenyl group located at the hydroxy carbon and not at the terminal end of the alkyne, halogenation of this type of alkynols can lead to β-haloenones, which are the result of the phenyl shift. With alkynols containing terminal bromine or iodine atom, halogenations of these tertiary and secondary alkynols lead to the formations of β,β-dihaloenones or β,β–dihaloenals, respectively. The intermediate for the halogenation of these alkynols is thought to be a halonium bridge ion, with the bromonium bridge ion tending to be more open than the iodonium-bridge, which leads to reduced stereospecificity.

The role of water has been shown to be important in dictating the type of intermediate, the reaction path and the type of products that form upon halogenations of alkynols. These paths can lead to the formations of α-haloenones, β-haloenones or a mixture of both. The type of group at the terminal end of the acetylenic unit

of the alkynol has been found to dictate the location of the vinyl cation, which can be at one of the two carbons of the acetylenic unit, depending on their relative stability. The position of the vinyl cation ultimately leads to formations of α-haloenones, β-haloenones or β,β-dihaloenones/enals.

Finally, the products of the halogenations of alkynols such as α-haloenones, β-haloenones, β,β-dihaloenones, β,β-dihaloenals and β,β-dihaloethers are potential synthetic templates that could be used as synthons for palladium-catalysed ligand exchange reactions such as the Stille (Stille, 1985), the Suzuki (Suzuki, 1991) and the Sonogashira (Chinchilla and Najera, 2007) reactions. These palladium-mediated ligand exchange reactions offer the possibility of converting these haloenones or dihaloenones to molecules of greater complexity that could be used as a stepping stone for the synthesis of natural products or towards new structures that could have interesting biological activities.

Acknowledgements

We are grateful to the Director's Initiative Fund of Mahidol University International College for financial support of this project. We are indebted to Dr. Sirirat Choosakoonkriang of the Department of Chemistry of Silpakorn University for spectroscopic analyses and also to Miss Josie Vayro for assisting with the preparations of the dihaloenone compounds. Finally, this paper is dedicated to the late Professor Edward J. McNelis and Dr. Geetha J. Angara.

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