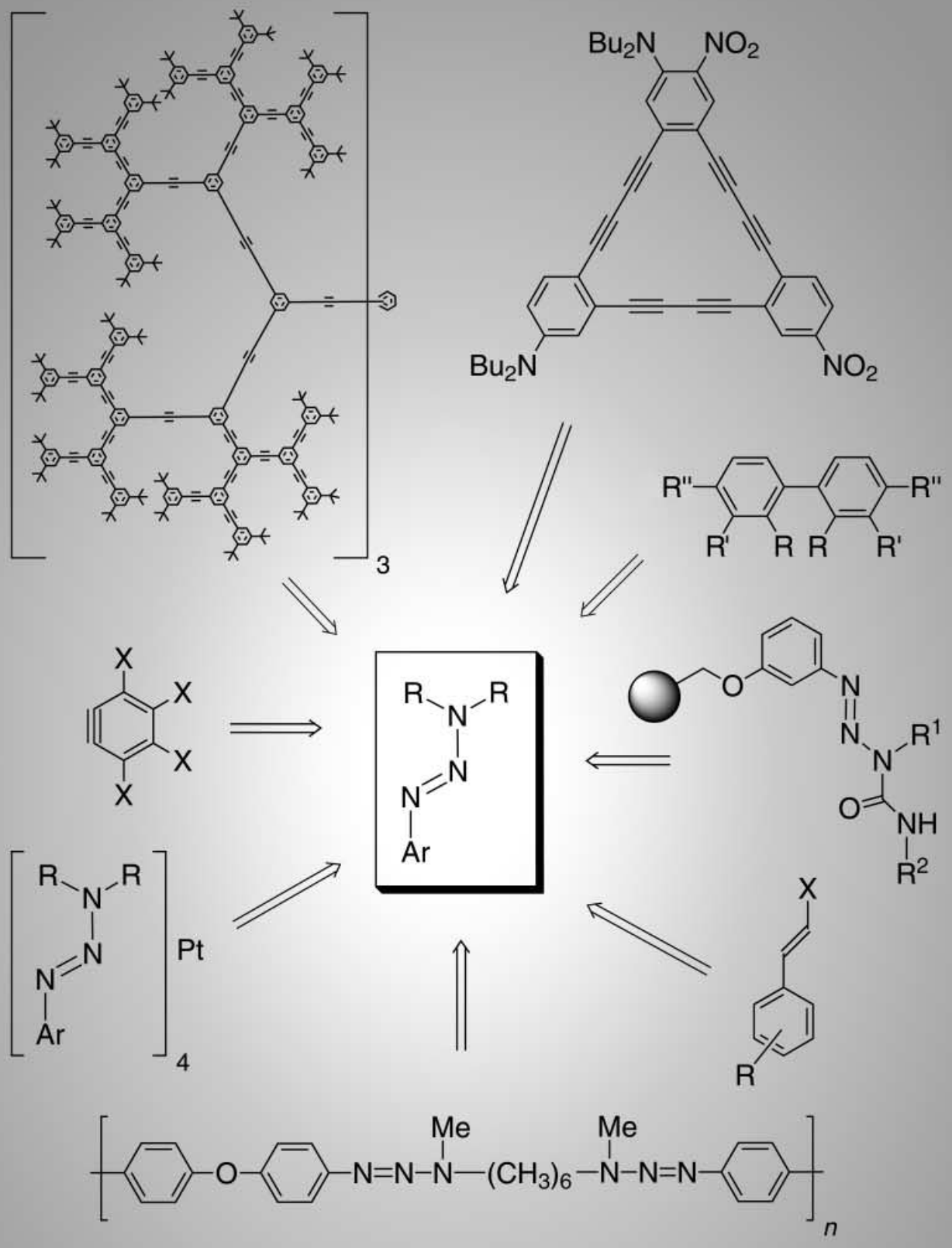
Triazenes: A Versatile Tool in Organic Synthesis



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Triazenes: A Versatile Tool in Organic Synthesis

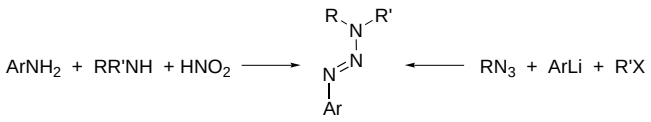
David B. Kimball and Michael M. Haley*

Triazenes (RN=N–NR′R″) are a class of compounds that hold much promise in preparative chemistry as they are reactive groups which are both stable and adaptable to numerous synthetic transformations. Useful to scientists in pharmacology, total synthesis, polymer technology, and the construction of novel ring systems, to name a few areas, triazenes also have a tendency to surprise chemists with new reactions and increasing applicability. This review highlights some of the recent advances and diversity possible with these types of systems.

1. Introduction

Triazenes are a very useful and diverse class of compounds. They have been studied for their anticancer potential,[1, 2] used as protecting groups in natural product synthesis[3] and combinatorial chemistry,[4] incorporated into polymer[5] and oligomer[6] synthesis, and used to form novel heterocycles.[7] Their biological activity derives from their ability to form diazonium salts that can alkylate DNA.[1, 2] Triazenes can also be transformed into several different reactive groups after treatment with the appropriate reagents. In the case of aryl triazenes, iodomethane-induced decomposition yields an iodoarene, which can react with acetylenes or alkenes under mild conditions to give cross-coupled products. If acid is used, both a diazonium and an ammonium species are generated and each can be utilized depending on the desired application.[8] Disubstituted triazenes can also form anions that are useful as ligands in organometallic chemistry.[9]

Triazenes are easily synthesized from readily available anilines or alkyl azides (Scheme 1). Anilines are typically treated with nitrite ion under acidic conditions to form a diazonium salt, which is quenched with a primary or secondary amine to provide the desired triazene in high yield. Dialkyl triazenes can be obtained from the reaction of an alkyl azide with the appropriate Grignard or alkyl lithium reagent. It is interesting to note that most triazene syntheses were optimized prior to the 1930s[10] and that some of the most useful preparative routes have changed little in the 100 years since their initial discovery.



Scheme 1. General synthetic routes to triazenes.

Although triazenes were extensively studied prior to 1950,[10] their versatility in organic synthesis has been greatly expanded during the past 30 years. The ease with which triazenes can be formed and selectively decomposed to give arenes or anilines with a proton in place of the triazene group has made them useful as linkers to solid supports. In the field of poly(phenylacetylene) synthesis, triazenes are indispensable for efficient convergent and iterative methodologies. Advances in triazene synthesis and the increasing ability to study modes of activity in the body has created renewed interest in their anticancer potential.

In this review, the synthetic utility of triazenes will be detailed, with an emphasis on recent developments. The triazenes discussed are straight-chain molecules that contain three contiguous nitrogen atoms, in which N1 is double-bonded to N2, which is linked by a single bond to N3 (e.g. RN=N–NR′R″). Both formation and usage will be discussed with respect to specific applications. Exhaustive treatment of the synthesis and properties of triazenes can be found in several reviews[8, 10–12] and is beyond the scope of this text. Instances in which triazenes are only transient intermediates, or the preparation is not practical on a preparative scale, will not be addressed.

2. Medical Applications of Triazenes

One of the most prevalent uses of triazenes is in the development of anticancer molecules. The therapeutic poten-

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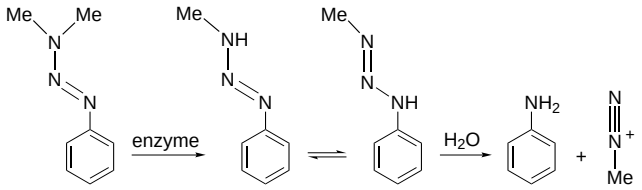
tial of a variety of triazenes has been extensively explored as well as their specific metabolic action.[1, 2, 13] For aryl and alkyl triazenes, proteolytic decomposition occurs under physiological conditions to give reactive alkyl diazonium compounds capable of alkylating DNA;[14, 15] consequently, these compounds are carcinogenic and/or mutagenic.[12] Several triazenes, however, show low animal toxicity while retaining their potency against specific tumor cell lines.[16, 17]

2.1. 1-Aryl-3,3-dialkyltriazenes

The most well-known triazene in anticancer study is 1-phenyl-3,3-dimethyltriazene (**1**).[2, 12–15] Several groups have provided strong evidence for enzyme-catalyzed demethylation as the initial step of metabolism, followed by rearrangement of the resulting disubstituted triazene and proteolytic loss of an aniline to generate a methyldiazonium ion (Scheme 2).[2, 13, 18–20] This species can then methylate DNA with the loss of dinitrogen.[14, 15, 20]

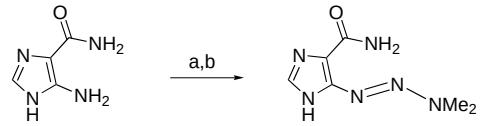
Dialkylphenyl triazenes of this sort are typically synthesized from anilines and secondary amines. A typical example is the synthesis of **1** from aniline and dimethylamine.[21] The



1

Scheme 2. Formation of the methyldiazonium ion from **1** under physiological conditions.

reaction conditions are surprisingly tolerant of a wide range of functional groups, including ester, halogen, and nitrile functionalities.[22, 23] Aryl systems other than those derived from aniline have been used to make dimethylaryl triazenes for antitumor study, the most active and well-studied of which is 5-(3,3-dimethyltriazeno)imidazole-4-carboxamide (**2**, Scheme 3),[24] also known as dacarbazine. Triazene **2** has been in clinical use for the treatment of malignant melanoma, soft-tissue sarcoma, and Hodgkin's disease since the late 1970s.[24] Dacarbazine is synthesized from 5-aminoimidazole-4-carboxamide (**3**) using acid and nitrite, then quenching with a solution of dimethylamine in methanol. The use and study of dacarbazine is now so ubiquitous that it is commercially available.



3 **2**

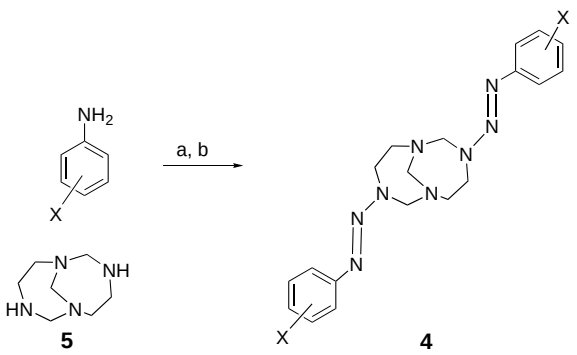
Scheme 3. a) HCl, $NaNO_2$, 75%; b) Me_2NH, MeOH, 48%.

Aryl triazenes connected by an alkane linker, which could potentially form lethal DNA cross-links, have been reported. Peori, Vaughan, and Hooper synthesized many "bistriazenes" for this purpose (Scheme 4).[25, 26] Aryl amines were converted into the diazonium species, then compounds of type **4** were formed from the reaction of this diazonium species with 1,3,6,8-tetraazabicyclo[4.4.1.1]undecane (**5**). Simpler alkyl linkers can also be used and are easily formed in good yield by coupling two equivalents of a diazonium salt with *N*,*N*′-dialkyl-1,2-ethylenediamine derivatives.[27]

M. M. Haley D. B. Kimball

Michael M. Haley was born in 1965 in Lake Charles, LA. After growing up in Tulsa, Oklahoma, he studied cyclopropene and cyclopropparene chemistry with Prof. W. E. Billups at Rice University (B.S. 1987, Ph.D. 1991). In 1991 he received a National Science Foundation Postdoctoral Fellowship to work with Prof. K. P. C. Vollhardt on [n]*phenylene chemistry at the University of California, Berkeley. In 1993 he joined the faculty at the University of Oregon where he is currently an Associate Professor of Chemistry and member of the Materials Science Institute. Among his awards are a National Science Foundation CAREER Award (1995), a Camille Dreyfus Teacher–Scholar Award (1998), and an Alexander von Humboldt Research Fellowship (2000). His current research focuses on the chemistry of dehydro- and dehydrobenzoannulenes, metallabenzenes, and other novel aromatic systems.*

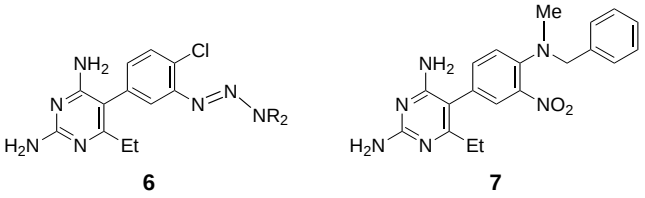
David B. Kimball was born in Salt Lake City, Utah, in 1973. He received his B.S. in chemistry from the University of Houston in 1995, where he studied heteroaromatic ligand synthesis for use in copper and ruthenium complexes under Professor R. P. Thummel. He obtained his M.A. in chemistry from the University of Oregon, where he worked with Professor Haley, studying aromaticity in phenylacetylene-based annulenes. He completed his Ph.D. studies in June 2002, in Professor Haley's group, investigating novel triazene cyclizations to form heterocycles, and is now a postdoctoral associate at Los Alamos National Laboratory.



X = *p*-NO_2, *p*-CN, *p*-COMe, *p*-CO_2Me, *p*-CO_2Et, *p*-Br, *o*-NO_2, *o*-CN

Scheme 4. a) HCl, $NaNO_2$; b) **5**, CH_2O.

More complex aryl systems have been used in conjunction with triazene chemistry for biological methylating purposes. Stevens et al. designed several dialkyl biaryl triazenes (**6**) based on the methylbenzoprim skeleton (**7**) for use as



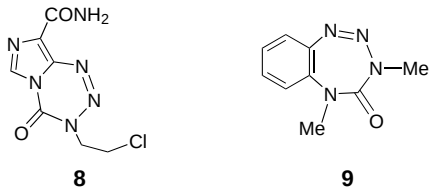
inhibitors of *Pneumocyctis carnii*.[28] Triazenes of type **6** combine antitumor potential with inhibitory action against a microorganism-specific dihydrofolate reductase enzyme,[28] which is chiefly responsible for pneumonia-related deaths in AIDS sufferers. Triazenes were prepared from the corresponding amines in the usual manner.

2.2. Acyl-Substituted Triazenes

Another class of triazenes which show potent antitumor activity are those bearing acyl substitution.[29] Although many were initially designed to be more stable versions of trialkyl triazenes,[30] the physiological fate of these compounds is now thought to be considerably more complex, possibly involving enzymatic deacylation.[1, 31] Some acyl-substituted derivatives show structural similarity to (2-chloroethyl)nitrosourea derivatives,[32] which are known to form lethal cross links in DNA.[33]

The simplest examples of acyltriazenes are those that contain a 1,3-dialkyl-3-acyl structure. Compounds of this type are obtained from the reaction of an acid chloride with a triazene anion. The disubstituted anions in turn are obtained by treating an alkyl azide with the appropriate alkyl lithium or Grignard reagent. A typical preparation is that reported for 3-carbethoxy-1,3-dimethyltriazene,[30] in which 1,3-dimethyltriazene is treated with potassium hydride, and subsequently with ethyl chloroformate, to give the desired product in 77% yield. Michejda and co-workers showed that dialkyl acyltriazenes undergo hydrolytic decomposition at physiological pH levels, and most have mutagenic activity towards strains of *Salmonella tyhimurium*.[30, 34] Another acyltriazene, 1-(chloroethyl)-3-methyl-3-methylcarbamoyl)triazene, showed enhanced cytotoxicity against strains of leukemia and melanoma.[1, 29] The synthesis of this compound also involved acylating a disubstituted triazine.

Studies with acyl-substituted triazenes have been motivated by the antineoplastic activity against malignant melanoma of the imidazo-1,2,3,5-tetrazin-4-one **8**,[35] which can be used as a



triazene precursor. This compound can be hydrolyzed to the open-chain triazene and thus form a possible alkylating agent. Jean-Claude and Just have prepared several tetrazepinones **9** based on this cyclic N-acyl motif.[16, 36, 37] The key feature of the synthesis involves ring formation by trapping an aryl diazonium species with an *ortho* amide. Systems such as these are among the most promising agents for clinical use.[16, 38, 39]

2.3. Hydroxymethyl Triazenes

Derivatives of hydroxymethyltriazenes have been prepared as a result of research indicating hydroxymethyltriazenes as the immediate oxidation products of dimethyltriazenes of the type **1**.[2, 17, 19] After reaction with cytochrome enzymes in the cell, loss of formaldehyde to generate highly reactive monomethyl triazenes is rapid in aqueous media. Rearrangement to the 1-methyl-3-aryltriazene then allows proteolytic decomposition to an aniline and a methyldiazonium ion.

The groups of Vaughan[40, 41] and Rosa[42, 43] have synthesized hydroxymethyl derivatives of triazenes for studies relating to the development of prodrugs. Rosa and co-workers have developed a general synthetic method for these systems, which involves loss of water in acidic solution followed by nucleophilic attack of the iminium ion by an alcohol.[44] Use of DMF as the solvent increases yields and allows less stable alcohols to be used.[43] In most cases, the synthesis is straightforward and high-yielding. Use of such triazine derivatives as prodrugs, however, is hampered by slow hydrolysis at pH levels near physiological conditions.[43]

2.4. Trialkyl and Dialkyl Triazenes

Trialkyl triazenes have received moderate attention in the literature as possible antitumor agents.[45] Although trialkyl triazenes were prepared by Dimroth[46] almost a century ago, a general synthesis of these compounds was only accomplished

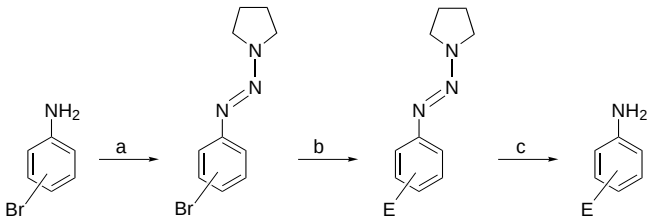
within the last 30 years.[47] Proteolytic decomposition to the alkyl diazonium species has been demonstrated using pH-buffered solutions, however, their practical effectiveness is hampered by instability.

One exception to the instability of exclusively alkane-substituted triazenes is a series of bis(methyltriazeno)alkanes or "bistriazenes" prepared by Blumenstein and Michejda.[48] Similar to the corresponding work of Vaughan and co-workers,[25, 26] these systems were designed to alkylate DNA at both ends of an alkyl linker, thereby linking the strands. The compounds prepared were formally disubstituted triazenes, which possess significant antitumor activity.[2] Unlike their dialkyl triazene analogues, however, these compounds formed stable solids, which could potentially increase their lifetimes under physiological conditions and allow them to be more effective in clinical use.

3. Triazenes Used to Protect/Generate an Amine

One of the simplest uses of triazenes is to protect or generate an amine. Although the formation of anilines from the acid-induced decomposition of aryl triazenes has been known for some time,[10] this particular use is rare as many other protecting groups are available.[49] Several authors, however, have shown that triazenes are indeed useful for this purpose. Triazenes, once generated, are stable to a variety of conditions[50] and their facile and efficient conversion into the corresponding amines has been demonstrated.[4, 51]

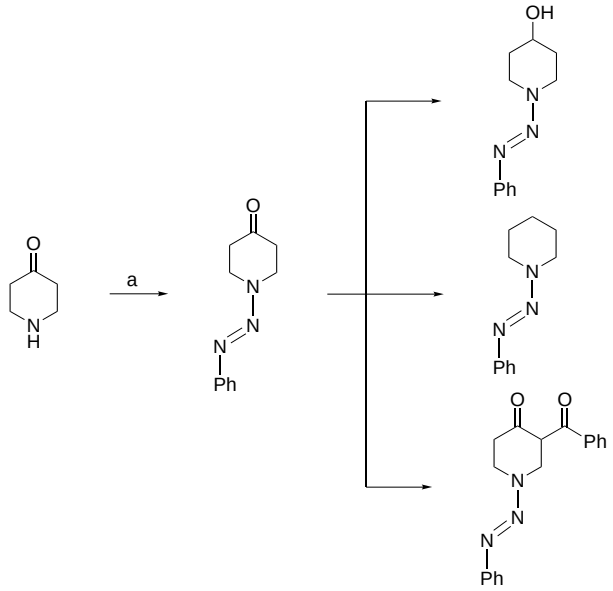
Triazenes are particularly useful aniline protecting groups when performing halogen-metal exchanges. Gross, Blank, and Welch used a series of triazene-protected bromoanilines for bromine–lithium exchange and subsequent reaction with electrophiles (Scheme 5).[52] The triazene protecting group



Scheme 5. a) 1. HCl, $NaNO_2$; 2. KOH, pyrrolidine; b) 1. *s*BuLi or *t*BuLi; 2. electrophile (E); c) Ni/Al, KOH, MeOH.

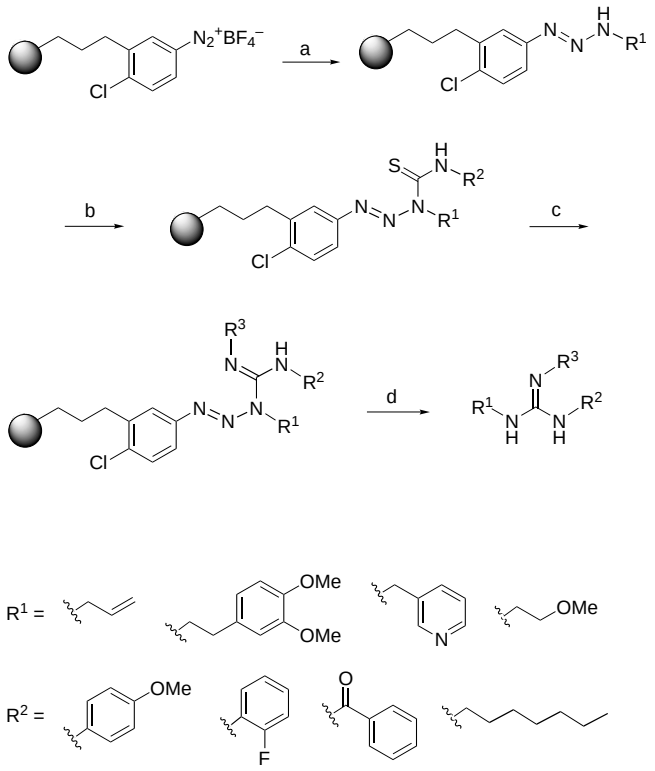
was used because of both its stability to electrophilic reagents and its compatibility with *meta*- and *para*-carbanion formation. The readily available bromoanilines were converted into the triazenes and metalated with *sec*- or *tert*-butyllithium to provide aryl carbanions that reacted smoothly with carbon, sulfur, and silicon electrophiles, or with deuterium oxide. The corresponding anilines were regenerated using nickel–aluminum alloy in methanolic hydroxide solution. These fairly mild conditions provide anilines from triazenes quantitatively in almost all cases.[51] A more recent example uses this same chemistry to generate a 17α-(4-aminophenyl)estradiol.[53] The key step in this synthesis was the addition of a lithiated phenyltriazene to estrone. The amine was subsequently obtained after hydrogenation in the presence of palladium.

Non-aromatic amines can also be protected efficiently as triazenes. Lazny et al. used the triazene group to protect 4-piperidone from later reactions involving hydride reduction and alcohol oxidation.[54] After 4-piperidone reacted with phenyldiazonium salt, the resulting triazene was stable to $LiAlH_4$, chromium-based oxidants, $NaBH_4$, and other reagents to give several useful products (Scheme 6). The amines were regenerated in good yield using 50% trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature. Other secondary amines that have been protected as triazenes for analogous purposes include piperazine derivatives,[55] proline derivatives,[55] 3-alkoxy-4-aryl piperidines,[56] and nortropanes.[55]



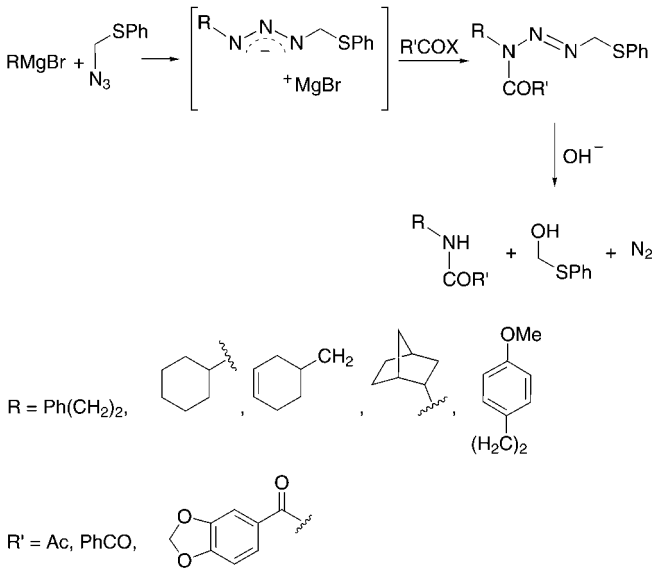
Scheme 6. a) PhN_2BF_4, Et_3N.

Bräse and co-workers have adapted triazenes to protect amines[57, 58] and amides[4, 59] for solid-phase organic synthesis. Using the triazene as a linker to a solid support, Bräse's group has prepared amide libraries from the reaction of polymer-bound aryl diazonium species with primary amines. The 1,3-disubstituted triazenes produced could be further alkylated or acylated in excellent yield using acid chlorides, isocyanates, or isothiocyanates (Scheme 7).[58] Synthesis of the solid-phase triazenes began with establishing a diazonium species on a solid support, which could be accomplished by treating polymer-bound anilines with a strong Lewis acid ($F_3B \cdot OEt_2$) and *t*BuONO in THF. These diazonium salt resins were remarkably stable to both isolation and thermal decomposition. Combining the diazonium species with primary or secondary amines produced triazenes that were suitable for further elaboration. Cleavage from the resins could be effected using TFA in CH_2Cl_2.



Scheme 7. a) R^1NH_2, THF, 12 h, $-10\,^\circ C \rightarrow$RT; b) NaH, DMF, R^2NCS, 2 h, RT; c) $AgNO_3$ or HgO, R^3NH, MeCN, 12 h, 45 °C; d) TFA, CH_2Cl_2, 5 min, RT.

Triazenes can also be used as intermediates for the generation of useful amines. Unlike typical syntheses, however, the amine is not used to form the triazene. Instead, an alkyl or aryl anion reacts with an azide. Trost and Pearson showed that this method works well for converting alkyl or aryl bromides into amines.[60, 61] The bromide compounds were first converted into the Grignard reagents and then treated with azidomethylphenyl sulfide (Scheme 8). The triazene



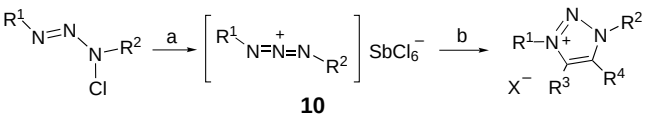
Scheme 8. Amide synthesis via acylated triazenes.

anion formed could be quenched either with a proton or an acyl source, depending on the substitution desired on the final amine. It is important to note that the less thermodynamically stable triazene is generated. The methylphenyl sulfide substituent on the azide dictates this configuration and promotes initial triazene formation. The sulfur atom also promotes decomposition to the desired amines by various nucleophiles. The authors found that aqueous formic acid would also release the amine or amide from the triazene.

4. Triazenes Used in Heterocycle Synthesis

Heterocycle synthesis is an important and complex area of organic chemistry. Interestingly, this field has been advanced as much by chance discoveries as by design. Triazene chemistry reflects this by showing a remarkable and sometimes unexpected tendency to form new heterocycles under various conditions. Although at times they are only fleeting intermediates, triazenes are often rational starting materials for heterocycles that are unattainable by other routes.

N-Chloro-substituted triazenes can react with dipolarophiles to give heterocyclic products. Jochims and co-workers have observed [3+2] cycloadditions between 1,3-diaza-2-azoniaallene ions (**10**, Scheme 9) and dipolarophiles such as



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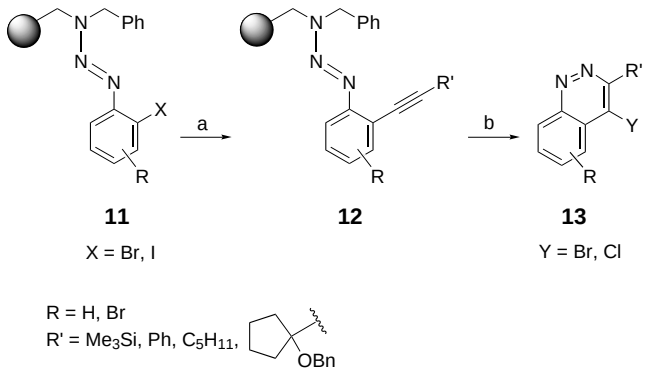
R^1, R^2 = 2,4,6-$Cl_3C_6H_5$
R^3 = H, Bu, *t*Bu, CH_2OH, Et, CH_2Cl, Me, Ph, CO_2Me
R^4 = H, Et, CH_2Cl, Ph, CO_2Me

Scheme 9. a) $SbCl_5$, CH_2Cl_2, $-60\,^\circ C$; b) $R^3C{\equiv}CR^4$, CH_2Cl_2, $-60 \rightarrow 23\,^\circ C$.

alkenes,[62] 1,3-butadienes,[63] alkynes, carbodiimides, and cyanamides.[64] The dipolar ions were prepared from the reaction of *N*-chlorotriazenes with Lewis acids, typically $SbCl_5$. Cycloadditions were performed at low temperatures, as a consequence of the instability of the chlorotriazenes and corresponding dipolar ions, to furnish 1,2,3-triazolium and tetrazolium salts. The triazenes themselves were synthesized from chlorine-rich anilinederivatives in the usual fashion by chlorination using *tert*-butylhypochlorite.

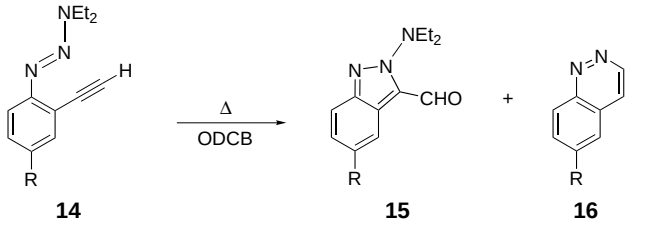
The Richter cyclization of an aromatic diazonium ion *ortho* to an acetylene functionality to give a cinnoline has been utilized extensively since its discovery in 1883.[65] The cinnolines produced are substituted at the 4-position as a result of nucleophilic attack on the acetylene to drive the cyclization. Bräse and et al. have modified this method to include triazenes as protected diazonium species (Scheme 10).[66] This modification also allows the triazenes to be attached to a solid support, benzylaminomethyl polystyrene, which greatly simplifies the purification of starting materials. Using anilines substituted at the *ortho* and *para* positions, formation of the diazonium ion followed by quenching with the solid-supported amine provides the aryl triazenes **11**. Iodo or bromo



Scheme 10. Synthesis of cinnolines. a) HC≡CR′, $Pd(OAc)_2$, NEt_3, DMF, 80 °C, 12 h; b) HY, acetone/H_2O, 47–95 %.

substitution *ortho* to the triazene allows Sonogashira coupling[67, 68] to give the required *ortho*-alkyne precursors (**12**). Cleavage from the resin under acidic conditions first provides the diazonium species which cyclizes to the cinnolines **13** in moderate to good yield. A significant limitation to the Richter cyclization, however, is that only 4-substituted cinnolines are produced. For cinnolines that are unsubstituted on the pyridazine ring, difficult procedures are necessary to remove these functional groups.

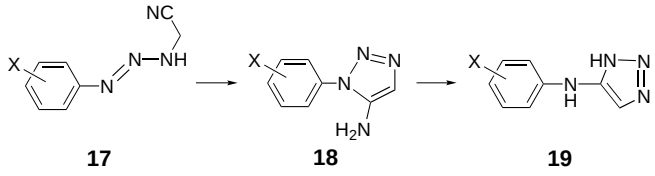
A new method for the generation of cinnolines as well as isoindazoles from aryl triazene moieties *ortho* to alkyne functionalities was recently developed by Haley and co-workers.[22] Heating the 1-(2-ethynylphenyl)-3,3-diethyltriazenes **14** (Scheme 11) to 170–180 °C in 1,2-dichlorobenzene



Scheme 11. Synthesis of isoindazoles and cinnolines. ODCB = 1,2-dichlorobenzene.

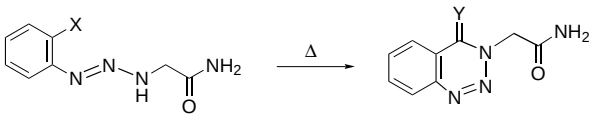
gave a mixture of isoindazole **15** and cinnoline **16** products. Neutral conditions were used which allow a greater range of functional groups to be attached to the resulting cinnoline or isoindazole. High yields (>90 %) of **16** were obtained by heating the starting triazenes to 190–200 °C. Comparable yields and exclusive formation of **15** could be accomplished at much lower temperatures (≈50 °C) when the cyclizations were performed in the presence of CuCl.[69]

Vaughan, Hooper, and co-workers have shown that other aryl triazenes functionalized with alkyl nitriles[70] or amides[71] can cyclize spontaneously or at elevated temperatures to give triazoles and benzotriazoles. Triazene derivatives which contained cyanomethyl substituents (**17**, Scheme 12) were prepared by reacting an aryl diazonium species with α-amino-acetonitrile under acidic conditions.[70] Cyclization to 5-amino-1-aryl-1,2,3-triazoles **18** and 5-(arylamino)-1,2,3-triazoles **19** could be achieved by heating the triazenes in refluxing ethanol. Some control could be exerted over which isomer prevailed, either by heating or by treating the triazenes with alumina; however, cyclizations were limited to *para*- and a few *ortho*-substituted arenes.



Scheme 12. Synthesis of 1,2,3-triazoles.

Amide analogues of these triazenes with activated *ortho* substituents on the arene (**20**, Scheme 13) cyclized with slight heat or spontaneously during purification to give 1,2,3-benzotriazine derivatives **21**.[71] Triazenes such as **20** were prepared similarly to their cyanomethyl analogues, using glycinamide hydrochloride in place of aminoacetonitrile. The success of the reaction, however, necessitated electron-withdrawing substituents on the aryldiazonium species. Both *ortho* methoxy- and ethoxycarbonyl as well as cyano-substituted aryl triazenes cyclized to **21**.



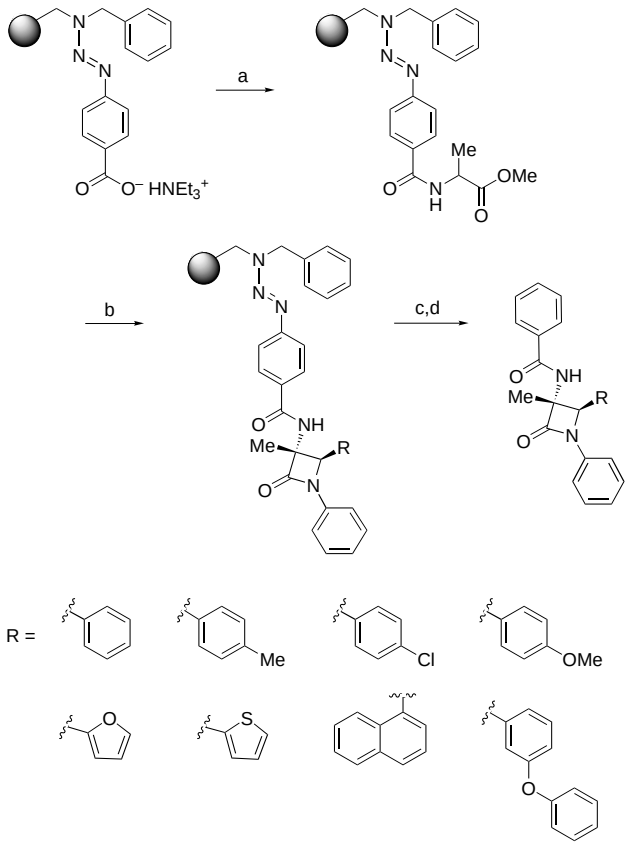
Scheme 13. Synthesis of 1,2,3-benzotriazin-4(3*H*)-ones and 1,2,3-benzotriazin-4(3*H*)-imines

5. Triazenes Used to Generate Other Functional Groups

Triazenes have been used to generate many different types of functional groups other than amines and heterocycles. The most prevalent of these is in the synthesis of reactive halides. Triazenes can be decomposed to give fluoride[72] and iodide[73] compounds useful for radiolabelling, and, in the case of iodoarenes, for the synthesis of phenylacetylene-based systems.[5, 6] The latter will be detailed in the following section. Other functional groups that can be produced from triazenes include phenols,[10] alkenes,[74] biaryls,[75, 76] and products resulting from aryne intermediates.[77]

Of course, the simplest functional group that can result from the decomposition of a triazene is a hydrogen atom. Although seemingly extraneous, this reaction is useful in solid-phase synthesis when a traceless linker is needed. Bräse and co-workers have used this method to produce a variety of substituted benzenes linked to a solid support through a triazene.[78–80] The products are cleaved from the resin under mild conditions to give the desired products in which a proton has replaced the triazene group in a traceless manner. Triazenes were synthesized by quenching a diazotized aniline

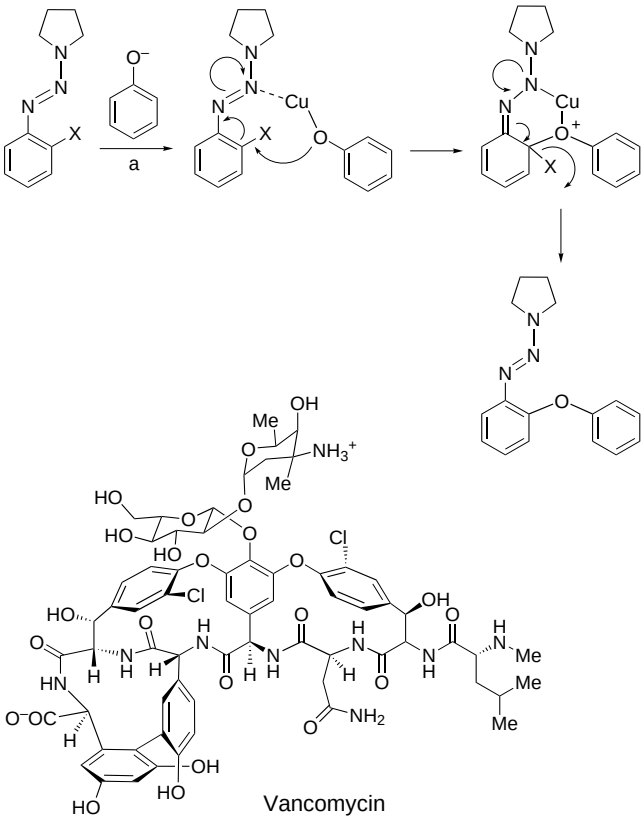
with benzylaminomethyl polystyrene resin. After appropriate reactions (Heck coupling, acylation), the triazenes were decomposed in the presence of trichlorosilane to yield the protonated arenes in good to excellent yield after simple filtration from the resin. Enders and co-workers have used this same methodology to synthesize β-lactams on a T1-triazene linker to a solid support (Scheme 14).[81] The diazonium salt of 4-aminobenzoic acid was linked to benzylamine resin, after which amidation provided the lactam precursors. Once the β-lactam was generated, cleavage from the resin gave the desired products in moderate yield, with excellent purity.



Scheme 14. a) Alanine methyl ester, 2-chloro-1-methylpyridinium iodide, NEt_3, CH_2Cl_2, RT, 12 h; b) 1. LiHMDS, THF, $-78\,^{\circ}C$; 2. RCH = NPh, $-78\,^{\circ}C \rightarrow RT$, 23 h; 3. H_2O; c) TFA/CH_2Cl_2; d) THF/DMF, $60\,^{\circ}C$, 15 min. LiHDMS = lithium bis(trimethylsilyl)amide.

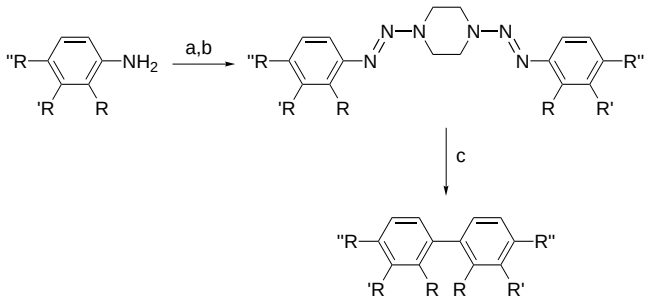
An interesting use of an aryl triazene was reported by Nicolaou in the total synthesis of vancomycin.[82–85] The triazene functionality served a dual purpose: to protect a reactive site for later conversion into a phenol and to aid in the construction of *ortho* biaryl ether functionalities (Scheme 15). The (*ortho*-haloaryl)triazenes were treated with phenolic counterparts in the presence of base and CuBr to afford the desired ethers. Sequential reaction of the 2,6-dihalogenated aryl triazene backbone with side chains terminated in phenols installed the necessary regiochemistry for each macrocyclic ring system.

Biaryl synthesis can be accomplished through a variety of procedures. The most high yielding and selective of these use



Scheme 15. a) $CuBr \cdot Me_2S$, K_2CO_3, pyridine, MeCN, $75\,^{\circ}C$, 3 h.

transition-metal catalysis, as is the case with Suzuki couplings.[86] Triazenes, however, provide an alternative route to biaryls that is mild and avoids expensive catalysts. Patrick, Willaredt, and DeGonia have shown that TFA-promoted decomposition of aryl triazenes in benzene solution results in good yields of heterocoupled biaryl species.[76] Aryl triazenes used included nitro, halo, alkyl, and alkoxy substitution. Yildirir and co-workers synthesized a similar series of homocoupled biaryl compounds starting from bistriazenes that were prepared by quenching aryl diazonium compounds with piperazine (Scheme 16).[75] Decomposition of the triazenes and biaryl coupling occurred in the presence of acetic acid at $90\,^{\circ}C$. Biaryl yields, however, were poor, ranging from trace amounts to 31 %.

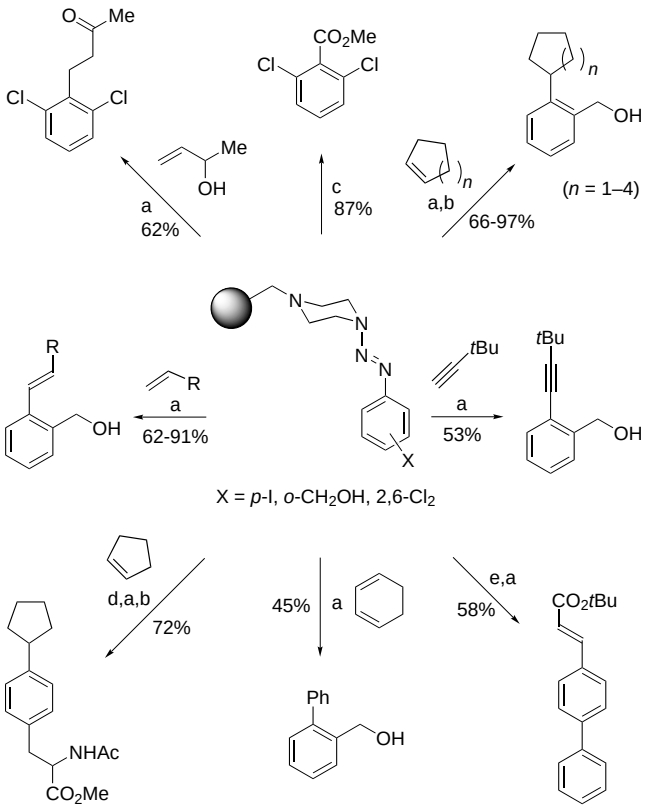


R = H, F, Cl, Br, I, NO_2, Me, COOH
R' = H, NO_2
R'' = H, F, Cl, Br, I, NO_2, Me

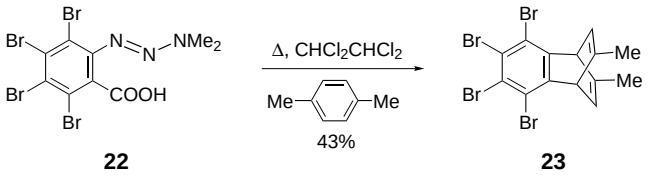
Scheme 16. a) $NaNO_2$, HCl; b) piperazine; c) AcOH, 85 – $90\,^{\circ}C$.

The production of phenols from aryl triazenes has been known, at least as a side reaction, almost as long as triazene synthesis itself.[10] This use of triazenes, however, has been limited until fairly recently. Typically, the conversion of anilines into phenols is done by generating the diazonium species and quenching with hydroxide ion.[87] The harsh conditions employed in this reaction often limit the substrates that can be employed. In the case of aryl triazenes, milder conditions can be used to generate the same phenols. Satyamurthy et al. used a sulfonic acid resin in water to decompose several triazenes to the corresponding phenols.[88] Yields were generally high except for nitroaryl triazenes. Similar to other solid-based reactions, column chromatography or other purification methods were unnecessary. This method was easily adapted to give oxygen isotope-enriched phenols by replacing the solvent with $H_2{}^{18}O$. Others have used similar means to generate phenols from triazenes in the arena of natural product synthesis.[3] Mild conditions and high yields make this route particularly suitable for sensitive and/or large molecules.

Heck coupling of an alkene to a suitably functionalized arene in the presence of a palladium catalyst is a very useful tool in organic synthesis.[89] Although haloarenes and aryl triflates are normally used for coupling to an alkene, diazonium species masked as triazenes can also be used. Sengupta and co-workers reported that aryl triazenes react with alkenes when treated with TFA or 42% HBF_4 and catalytic $Pd(OAc)_2$ in refluxing methanol.[74] The reaction time was short (45 minutes) and yields were good, with the exception of nitroarenes. Similar work has been done by de Meijere et al.[90] Heck reactions were performed on triazenes bound to a solid support and analogous methods were used to release the reactants from the resin as diazonium salts. Coupling of arene diazonium salts after release from solid supports has been extended to include Sonogashira coupling, Suzuki coupling, and other biaryl syntheses (Scheme 17).[91] This allows triazene-linked arenes to be used in combinatorial chemistry, as the synthesis can be automated.



Scheme 17. a) Alkene, alkyne, or diene, $Pd(OAc)_2$ or Pd/C, TFA, MeOH, 2 h, 40 °C; b) H_2 (1 bar), 2 h, 25 °C; c) (X = 2,6-Cl_2) CO (1 bar), $Pd(OAc)_2$, TFA, MeOH, 2 h, 40 °C; (X = *p*-I) CH_2=C(NHAc)CO_2Me, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C; e) (X = *p*-I), PhI, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C; R = Ph, CO_2tBu, 2-pyridyl, butyl, hexyl.



Scheme 18. Use of aryl triazenes for the formation of arynes.

Products resulting from an aryne intermediate can be obtained from heating aryl triazenes *ortho* to carboxylate in electron-poor systems. Buxton and Heaney synthesized four tetrahalo-substituted aryltriazene-2-carboxylate systems (e.g. **22**, Scheme 18) which formed cycloadducts (e.g. **23**) when heated in the presence of arenes.[77] Presumably the *ortho* acid first protonates the dimethylamino portion of the triazene, after which the diazonium ion is generated. Fragmentation and liberation of CO_2 and N_2 then give an aryne which can react with an arene in a [4+2] cycloaddition. In contrast to their diazonium salts, the starting triazenes are stable compounds that can be handled without special precautions and can be stored more easily.

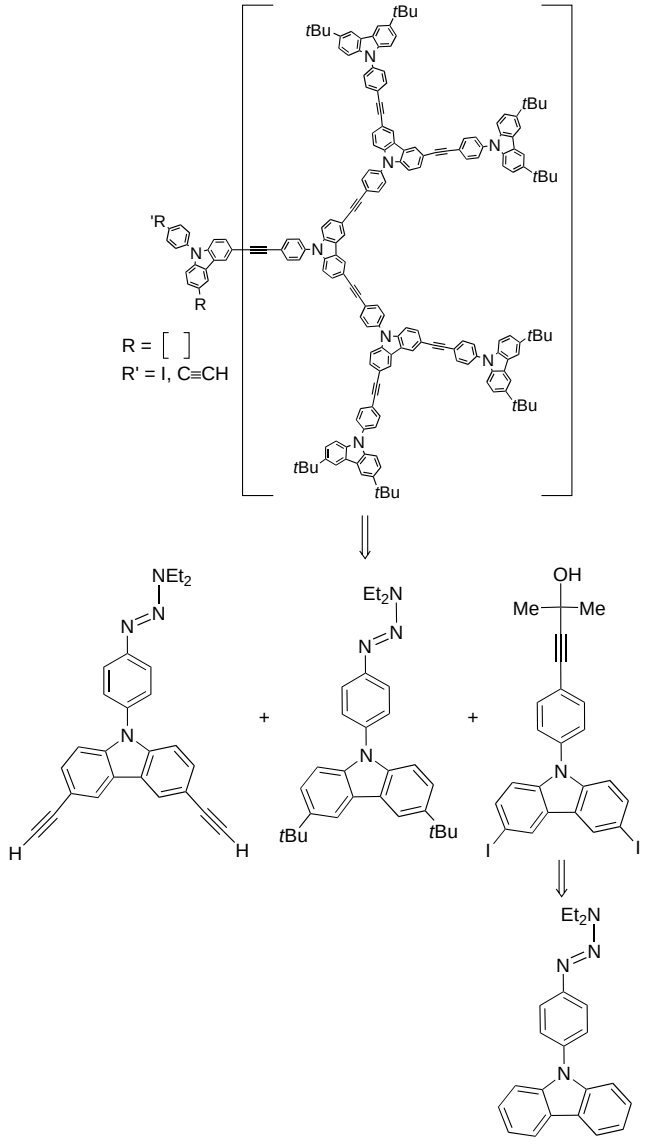
6. Triazenes Used in Phenylacetylene-Based Systems

Phenylacetylene molecules have been synthesized for applications ranging from nonlinear optics to liquid-crystal technology, from chemical sensors to light-harvesting materials, and from conducting polymers to shape-persistent molecules.[92] Phenylacetylenes are rigid, geometrically well-defined, conjugated building blocks that can be combined to give a multitude of architectures. Combined with modern cross-coupling techniques, these systems have become as widely applicable as they are readily available.

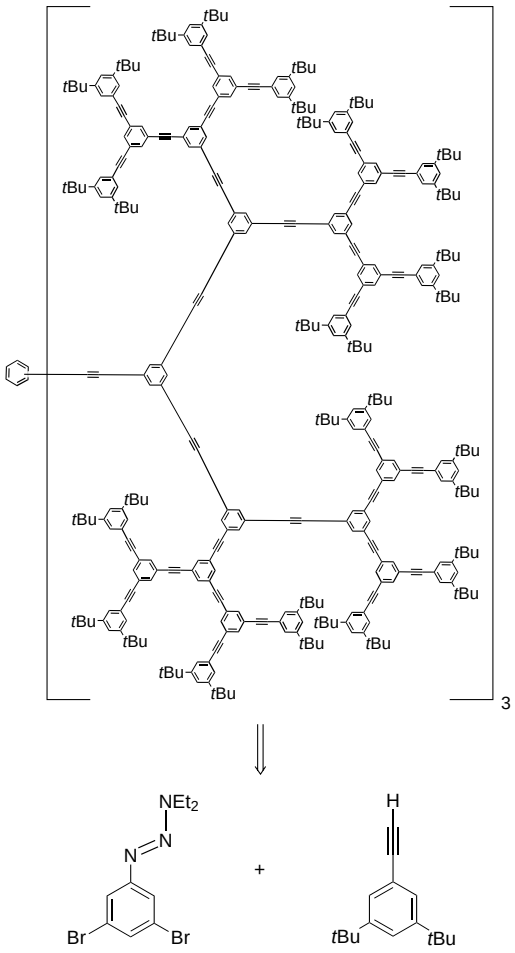
The chemistry of extended phenylacetylene-based systems relies heavily on the availability of iodoarenes. Most acetylene coupling strategies in the past two decades have been dominated by Pd-mediated reactions,[67, 68] which link an acetylene to an iodoarene. Although other haloarenes can be used, none are more efficient or as effective as iodoarenes. Any method, therefore, which generates site-specific iodoarenes easily and in high yield would be invaluable for preparing large, shape-specific phenylacetylene systems. Such a method was found by Moore et al. when they treated aryl triazenes with iodomethane at a high temperature.[23] The reaction conditions cause decomposition of the triazene to a diazo-

nium species and the dinitrogen component is effectively replaced with iodine. This process is site-specific and nearly quantitative for a variety of arenes. The same effect can be accomplished using trimethylsilyl halides at lower temperatures[93] or under microwave irradiation,[73] by treating triazenes with I_2 in 1,2-dichloroethane,[94] or by using NaI and a cation-exchange resin.[95] As will be seen shortly, however, iodomethane is the preferred reagent.

The Moore group has assembled a wide array of phenylacetylene macrocycles and dendrimers. The general synthetic route is based on a highly efficient strategy of triazene formation, acetylene coupling/deprotection, triazene decomposition, and further coupling. These steps can give a wide range of large, shape-specific phenylacetylene architectures rapidly and in good yield. The power of this relatively simple process is reflected both by its widespread use as well as by the large variety of possible products. Some examples from Moore and co-workers include phenylcarbazole dendrimers (Scheme 19),[96] phenylacetylene dendrimers (Scheme 20),[6] and phenylacetylene macromolecules



Scheme 19. Synthesis of phenylcarbazole dendrimers.

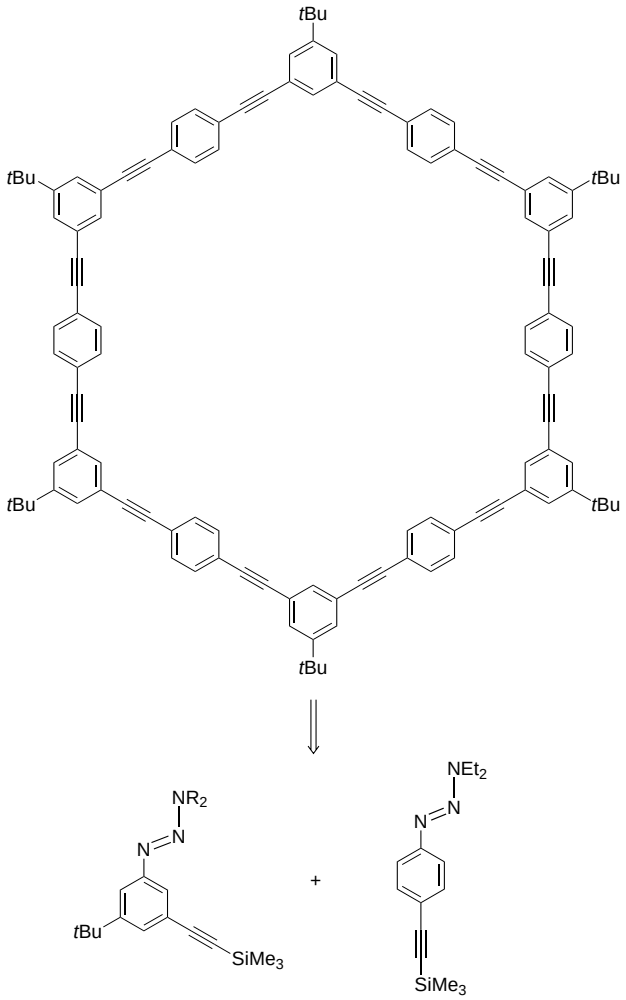


Scheme 20. Synthesis of phenylacetylene dendrimers.

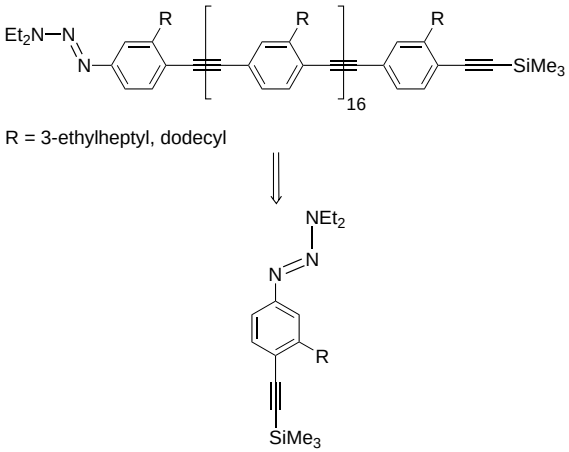
(Scheme 21).[6] Each of these systems share a common theme; they all contain key triazene intermediates in their iterative syntheses.

Tour and co-workers have also synthesized phenylacetylene systems based on an analogous strategy.[5, 97] Using iterative couplings and deprotections, Tour and co-workers produced long phenylacetylene rods for application as molecular wires.[5, 97] Again, their systems usually contain key triazene intermediates which are essential for rapid and efficient synthesis of linear phenylacetylene polymers (Scheme 22). For solubility as well as simplification of purification, these systems are often linked to solid supports, which can be easily accomplished through a triazene linker.[5, 97] This linker and other triazene intermediates decomposed on exposure to iodomethane, to generate the iodoarenes. Other groups have used this same approach to synthesize similar phenylacetylene rods for nonlinear-optical[98] applications and liquid-crystalline[99] applications based on the functionality of the side chain.

Aryl triazenes have been used extensively in the synthesis of dehydrobenzoannulenes. Haley and co-workers have produced annulenes with mono-,[100] di-,[101] and triacetylene[102] linkages (**24** – **26**, respectively) between benzene rings using different triazene precursors. For these macrocycles, judicious use of aryl triazene precursors governs the eventual

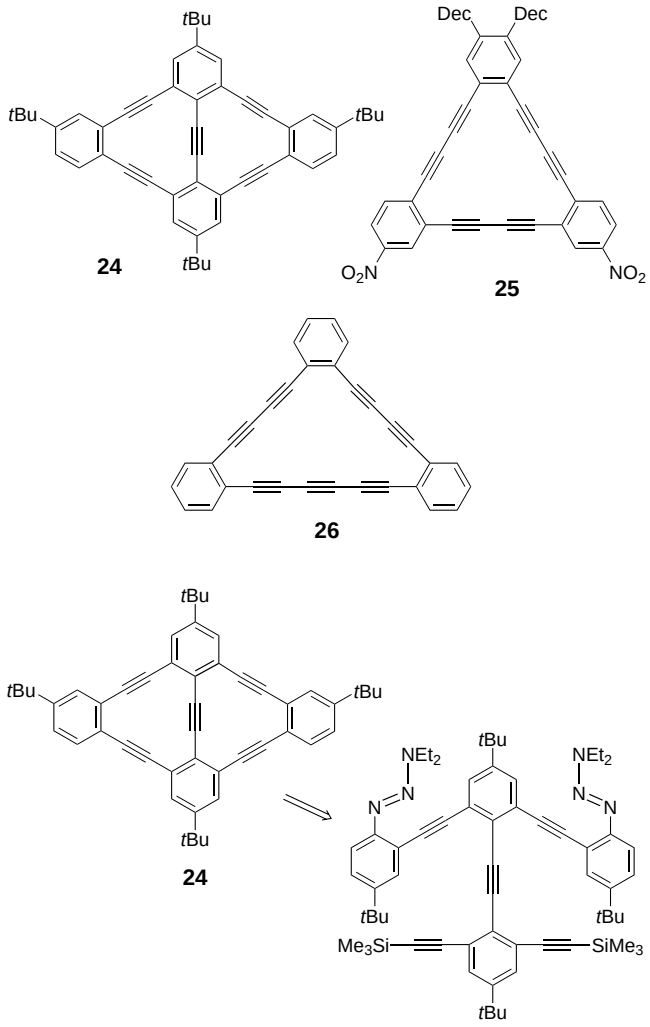


Scheme 21. Synthesis of phenylacetylene macrocycles.



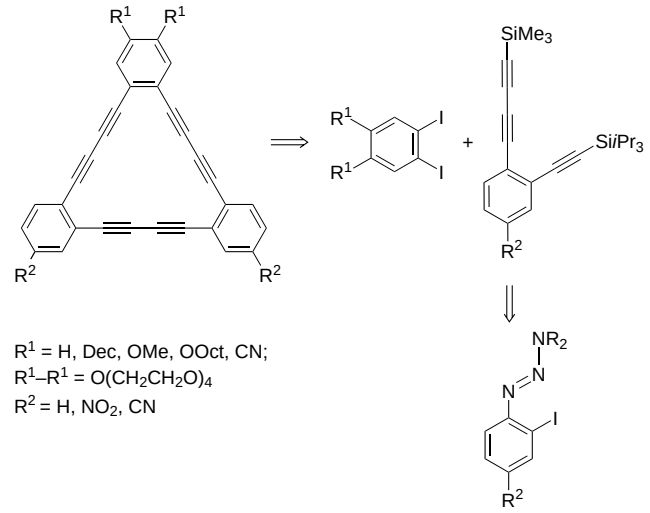
Scheme 22. Synthesis of molecular wires using triazenes.

annulene topology or substitution pattern. In monoacetylene systems, the triazene masks a reactive site that must be converted into an iodoarene and coupled intramolecularly with a nearby acetylene for cyclization to occur (Scheme 23). The ready availability of *para*-substituted aniline derivatives



Scheme 23. Triazenes in the synthesis of monoacetylene-bridged annulenes.

makes the generation of "push–pull" annulenes straightforward, as the triazene simplifies the formation of the necessary phenyltriyne building blocks (Scheme 24).[101]

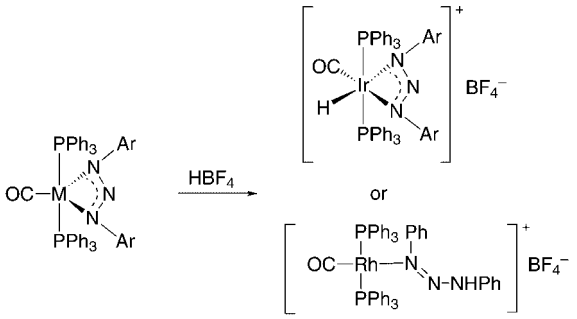


Scheme 24. Triazenes in the synthesis of diacetylene-bridged donor–acceptor annulenes.

Along these same lines, there are two recent reports of the use of aryl triazenes for later conversion into iodoarenes, both for their site-specificity and for synthetic ease. Dendritic porphyrins with phenylacetylene linkers were synthesized by Gossauer and co-workers.[103] The *para*-substituted phenylacetylene connecting rods were prepared through successive coupling, iodomethane-induced triazene decomposition, and further coupling. Icosahedral carboranes, $C_2B_{10}H_{12}$, can also be prepared through the use of triazene precursors.[104] These compounds result from the reaction of an acetylene with decaborane, $B_{10}H_{12}$, and are useful for a variety of high-temperature ceramic and polymer applications.[104] Vinas and co-workers prepared methyl 5-ethynyl-3-iodobenzoate and methyl 3,5-diethynylbenzoate from a triazene precursor and treated each with decaborane to produce mono- and bis(arylcarboranes).[104] The low yields obtained for cluster formation detract from their potential use in polymer applications.

7. Complexation Chemistry of Triazenes

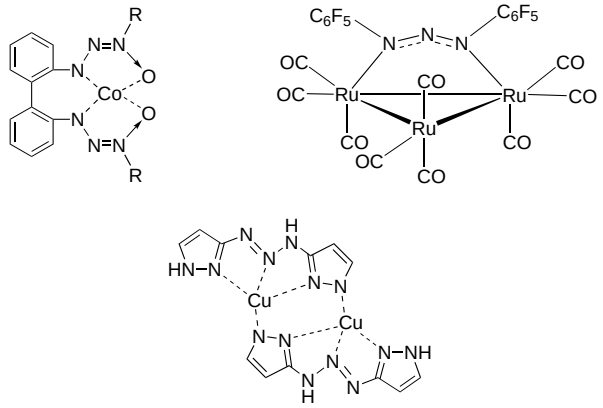
Although many triazene–metal complexes have been reported, their usefulness in organometallic synthesis has not been well explored. One notable account dealt with the interaction of disubstituted triazenes with metal perchlorates. Iley et al. observed decomposition products analogous to those from proton-catalyzed processes when alkyl aryl triazenes were treated with Fe^{2+}, Zn^{2+}, or Cu^{2+} sources.[105] Because many triazenes used for anticancer applications suffer from instability in vivo, these findings are significant considering that these ions are all abundant in the blood stream as well as throughout the body. Another report detailed the reaction of diaryl triazene complexes of rhodium and iridium with HBF_4 (Scheme 25).[106] It was hoped that



Scheme 25. Protonation of triazene–transition-metal complexes.

such a reaction would induce decomposition of the coordinated triazene to give an $[RN_2]^+$ ligand. This was not observed, however, and protonation of the triazene (M = Rh) or formation of a hydrido complex (M = Ir) resulted instead.

Interest in triazene–metal complexes mainly derives from their structural properties. Triazene ligands can vary in their electron-donor ability, as well as their potential to form bridging compounds or act as bidentate ligands (Scheme 26).[9, 107] A number of metals can be bound to



Scheme 26. Different coordination modes of triazene ligands in complexes.

triazenes, including nickel,[108] copper,[109] platinum,[110] cobalt,[111, 112] ruthenium,[9] and osmium.[9] In fact, hydroxytriazenes have been used extensively in the spectrometric determination of metals.[113] These triazenes can be used to detect minute amounts of metals such as nickel and cobalt even in the presence of other cations in solution.

8. Outlook

The future of triazenes in organic synthesis is very promising. New uses and reactions of triazenes are appearing in the literature more and more frequently. Of particular utility is the conversion of triazenes into iodoarenes and their use as linkers to solid supports. Indeed, instances in which extended phenylacetylene systems are synthesized without the use of triazene building blocks are rare. Their use as links to a solid support, either for traceless cleavage or as an amine/amide protecting group, is a very useful addition to combinatorial chemistry. It is very likely that triazenes will continue to expand the field of heterocycle synthesis as well.

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