

Synthesis of Hypervalent Iodonium Alkynyl Triflates for the Application of Generating Cyanocarbenes

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Abstract:

The procedures described in this article involve the synthesis and isolation of hypervalent iodonium alkynyl triflates (HIATs) and their subsequent reactions with azides to form cyanocarbene intermediates. The synthesis of hypervalent iodonium alkynyl triflates can be facile, but difficulties stem from their isolation and reactivity. In particular, the necessity to use filtration under inert atmosphere at -45 °C for some HIATs requires special care and equipment. Once isolated, the compounds can be stored and used in reactions with azides to form cyanocarbene intermediates.

The evidence for cyanocarbene generation is shown by visible extrusion of dinitrogen as well as the characterization of products that occur from O-H insertion, sulfoxide complexation, and cyclopropanation. A side reaction of the cyanocarbene formation is the generation of a vinylidene-carbene and the conditions to control this process are discussed. There is also potential to form a hypervalent iodonium alkenyl triflate and the means of isolation and control of its generation are provided. The O-H insertion reaction involves using a HIAT, sodium azide or tetrabutylammonium azide, and methanol as solvent/substrate. The sulfoxide complexation reaction uses a HIAT, sodium azide or tetrabutylammonium azide, and dimethyl sulfoxide as solvent. The cyclopropanations can be performed with or without the use of solvent. The azide source must be tetrabutylammonium azide and the substrate shown is styrene.

Keywords: Chemistry | Issue 79 | Iodine Compounds | Azides | Hydrocarbons | Cyclic | Nitriles | Onium Compounds | Explosive Agents | chemistry (general) | chemistry of compounds | chemistry of elements | Organic Chemicals | azides | carbenes | cyanides | hypervalent compounds | synthetic methods | organic

Article:

Introduction

The continued evolution of organic chemistry hinges on the design and development of new reactions. In particular, the discovery of new reactions that enable previously unimaginable synthetic routes bear ultimate significance. Towards this end, our group desired to convert two carbons of an alkyne and a nitrogen of an azide into a cyanocarbene.¹ This previously unknown transformation would allow for a significant increase in molecular complexity since the reactive cyanocarbene would rapidly react further. The initial effort was to use a nucleophilic alkyne and electrophilic azide, but triazoles were efficiently formed in this case as opposed to cyanocarbenes.² Using an umpolung approach, the second method uses an electrophilic alkyne and nucleophilic azide and products resulting from cyanocarbene reactions are fortunately formed in this case.³ There are many sources of nucleophilic azide, however, electrophilic alkynes are much less common. The group of Klaus Banert previously reported the proof-of-concept for this reaction using an alkynyl-chloride,⁴ but our group and the Banert group independently and contemporaneously determined that hypervalent iodonium alkynyl triflates (HIATs) are much better electrophiles for the reasons of stability and reactivity.^{3,6} We herein describe the synthesis, isolation, and reaction of these HIATs with azides to form and react in situ as cyanocarbenes.

Several safety precautions should be considered before proceeding with these experiments. Some hypervalent iodonium alkynyl triflates are unstable and will decompose, sometime violently, when exposed to air and light.⁷ To form the cyanocarbene intermediate, the procedure requires the use of azide sources. Azides are explosive and highly toxic.⁸ Proper personal protection equipment should be worn when handling these materials, especially organotin, and all manipulation of the reagents should take place in properly ventilated hoods. The cyanocarbene is a powerful and unstable reactive intermediate. Take care to perform experiments initially on small scales so that nitrogen gas evolution is controllable and never perform these reactions in closed systems. If scale-up of the reaction is desired, we strongly suggest the use of a safety shield.

The synthesis of many HIATs have been previously published including the use of Zefirov's reagent^{9,10}, and Koser's reagent,^{9,11} however, this video will be using the cyanophenyliodonium triflate reagent^{9,12} (Figure 1). Cyanophenyliodonium triflate was synthesized based on a previously reported literature preparation displayed.¹³ The reagent reacts with trialkyl-tin modified alkynes¹⁴ to form the desired product. After the HIAT is synthesized and isolated it can be reacted with azide to form a reactive cyanocarbene intermediate (Figure 2). There are several other methods that can be used to synthesize the iodonium alkynes such as using alkynyl silanes¹⁵ and alkynyl boronic esters¹⁶ but the method in the video was chosen because, in our experience, it had better efficiency and yield.

Our proposed mechanism^{3,5} (Figure 3) for this reaction involves the addition of an azide source to the β -carbon of the alkyne, thereby forming an iodo-ylide which decomposes to iodobenzene and a vinylidene-carbene. The vinylidene-carbene can then undergo a 1,2-rearrangement via migration of either the R-group or azide to afford an alkynyl-azide. The alkynyl-azide then extrudes dinitrogen to form a cyanocarbene which can react with a substrate. It should be noted that there can be formation of a hypervalent iodonium alkenyl triflate species, depending on conditions. The by-product is favored at lower temperatures in protic solvents where the protonation of the iodo-ylide is faster than the rearrangement to the alkynyl azide. Another

possible product that occurs during O-H insertion reactions is a vinyl ether where the vinylidene-carbene is trapped before the rearrangement to the alkynyl-azide can occur. The propensity to form this vinyl ether is determined by the R group.

One of the main advantages of this reaction is that after the carbene reacts, the resultant nitrile group is a convenient handle for further functionalization. Many synthons can be envisioned with this method and different products can be formed with the same substrates. Controlling the product mixture with temperature, concentration, and the R group of the alkyne is necessary.³ With proper insight upon how cyanocarbenes behave, the method shows a viable means to quickly adding chemical complexity to form a targeted molecule. Examples of how the cyanocarbene reacts include O-H insertion where the nucleophilic oxygen atom of the alcohol attacks the carbene and then proton transfer occurs, dimethyl sulfoxide complexation, where the carbene combines with the sulfur atom, and cyclopropanation where the carbene reacts with an alkene.

Protocol

1. Synthesis of Phenyl HIAT

1. Equip a dry 100 ml round-bottom flask with a magnetic stirrer and have the flask under an argon atmosphere. Clamp the flask to a stand and place it into a cryogen bath of acetonitrile and solid carbon dioxide pellets. Note: The cryogen should be approximately -45 °C.
2. Add 10 ml of dry dichloromethane to the cold flask and allow the solvent to equilibrate to the temperature of the cryogen. Note: The excess headspace in the flask is important for adding diethyl ether later to force precipitation.
3. Weigh 0.35 g (1 equiv.) of cyanophenylidonium triflate and quickly transfer it to the cold flask. Note: The solids should be fairly insoluble at this temperature.
4. Tare the mass of an empty syringe and then use it weigh 0.37 g (1 equiv.) of phenylethynyltributyltin.
5. Inject the phenylethynyltributyltin into the cold solution. Note: The dissolution of solids is an indication that the HIAT has been formed. The approximate time for dissolution is 30 min.
6. Add diethyl ether and hexane to force precipitation of the product. Note: If a precipitate does not form, evaporate the solvent under reduced pressure and add a mixture of diethyl ether and hexane to force precipitation of the HIAT.
7. Equip a vacuum flask with a Büchner funnel and pour the solution onto the funnel for filtration.
8. Collect the solids and store cold in an opaque container.

2. Synthesis of n-Pentyl HIAT

1. Equip a dry 250 ml three-necked round-bottom flask with a magnetic stirrer and have the flask under an argon atmosphere. Clamp the flask to a stand and place it into a cryogen bath of acetonitrile and solid carbon dioxide pellets. Note: The cryogen should be approximately -45 °C.

2. Assemble a Schlenk filtration apparatus on the flask so that the filtration can be performed quickly and at a cold temperature. Grease and clamp together each joint of the apparatus. Note: The filtration system can be constructed by several means but it is important that the system has the capability to push with inert gas and pull with a vacuum through a glass filter.
3. Add 10 ml of dry dichloromethane to the cold flask and allow the solvent to equilibrate to the temperature of the cryogen. Note: The excess headspace in the flask is important for adding hexane later to force precipitation.
4. Weigh 0.35 g (1 equiv.) of cyanophenylidonium triflate and quickly transfer it to the cold flask. Note: The solids should be fairly insoluble at this temperature.
5. Tare the mass of an empty syringe and then use it weigh 0.44 g (1 equiv.) of tributyltin heptyne.
6. Inject the tributyltin heptyne into the cold solution. Note: The dissolution of solids is an indication that the HIAT has been formed. The approximate time for dissolution is 30 min.
7. Inject 75 ml of hexane into the extra headspace of the flask to form a precipitate.
8. Place the collection flask under vacuum.
9. Unclamp the apparatus from the stand and carefully tilt it to pour the solution onto the glass filter. Open the collection flask vacuum to pull the liquid through. Note: Do not allow the vacuum to pull air into the vessel.
10. Dismantle the apparatus and scrape the solids off the filter once the filtration is complete. Once the solid is removed from the filtrate it is less air and temperature sensitive and can be handled open to air.
11. Collect the solids and store cold in an opaque container.

3. O-H Insertion of Cyanocarbenes Made from Phenyl HIAT

1. Equip a dry 50 ml round-bottom flask with a magnetic stirrer and have the flask under an argon atmosphere. Clamp the flask to a stir plate and inject 20 ml of dry methanol to the flask.
2. Weigh 0.300 g (1 equiv.) of the previously synthesized Phenyl HIAT and quickly add it to the flask.
3. Add 0.047 g (1 equiv.) of sodium azide to the flask. Note: The solution will darken over time and nitrogen gas is generated by cyanocarbene formation.
4. Let the reaction continue for as long as bubble formation occurs. The approximate time for completion is 20 min.
5. Expose the solution to air and evaporate the solvent using reduced pressure.
6. Add dichloromethane to the residual liquid and perform aqueous extraction to remove the sodium triflate. Collect the organic phases of dichloromethane and dry with anhydrous sodium sulfate.
7. Decant the solution and evaporate using reduced pressure.
8. Perform column chromatography to purify the cyanocarbene product.

4. Cyclopropanation Cyanocarbene Reaction Using Phenyl HIAT

1. Weigh 0.125 g (1 equiv.) of tetrabutylammonium azide in a glovebox and place it in a dry 10 ml round-bottom flask equipped with a magnetic stirrer.
2. Cap the 10 ml round-bottomed flask containing the tetrabutylammonium azide, remove it from the glovebox, and place it on a stir plate under argon gas using a Schlenk line.
3. Add 1.0 ml of styrene to the flask and allow the flask to stir. Note: The azide does not need to dissolve.
4. Quickly add 0.200 g (1 equiv.) of Phenyl HIAT to this slurry and place the septum back on the flask that is connected to a Schlenk line. Note: The solution should immediately darken and generate nitrogen gas by cyanocarbene formation.
5. Allow the reaction to continue for as long as bubble formation occurs. The approximate time for completion is one minute.
6. After the bubbles have stopped, expose the solution to air and perform column chromatography to purify the product.

Representative Results

Figure 1 illustrates the synthesis of a HIAT by using cyanophenylidonium alkynyl triflate. The HIAT can then be used to generate cyanocarbenes which will undergo O-H insertion of cyclopropanation. The O-H insertion reaction with Phenyl HIAT produces 2-methoxy-2-phenylacetonitrile in up to a 75% yield. The cyclopropanation reaction with Phenyl HIAT produces 1,2-diphenylcyclopropanecarbonitrile in up to a 61% yield. Although not demonstrated in the video, dimethyl sulfoxide complexation can occur with the cyanocarbene intermediate when reacting with dimethyl sulfoxide to produce the DMSO-adduct in 27% yield.

There are two azide sources used to react with HIATs in this method. When polar conditions are available the use of sodium azide is advised because it is easier to handle open to air. When the reaction conditions are non-polar, or sodium azide is not soluble enough, tetrabutylammonium azide can be used. Tetrabutylammonium azide is hygroscopic and handling of the reagent is best performed in a glovebox. As the video demonstrates, tetrabutylammonium azide does not need to be completely soluble in the reaction conditions and thus allows for a solventless reaction to be possible. When performing the Phenyl HIAT/styrene cyclopropanation reaction in minimal amounts of dichloromethane the reaction yield decreases by approximately 20%.³

Synthesis of Hypervalent Iodonium Alkynyl Triflate (HIAT)

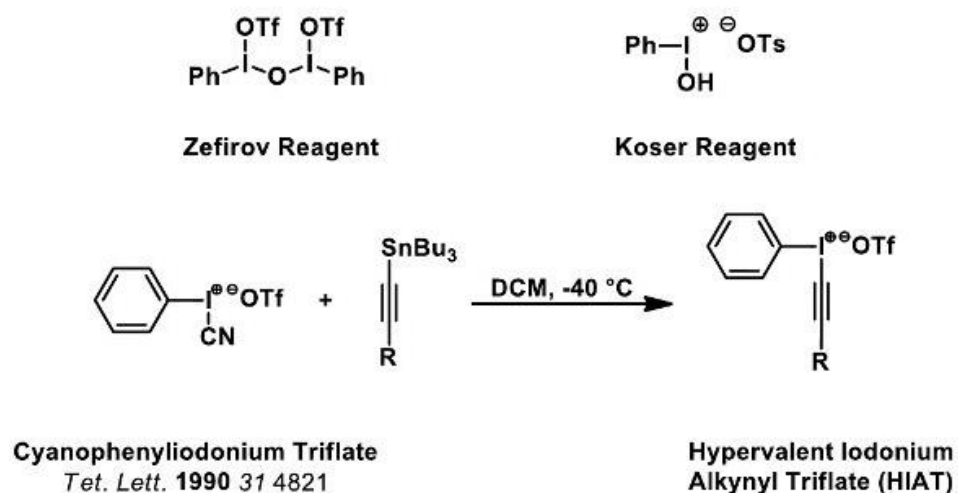


Figure 1. Synthesis of Hypervalent Iodonium Alkynyl Triflate (HIAT).

Reactions using HIATs to form Cyanocarbenes

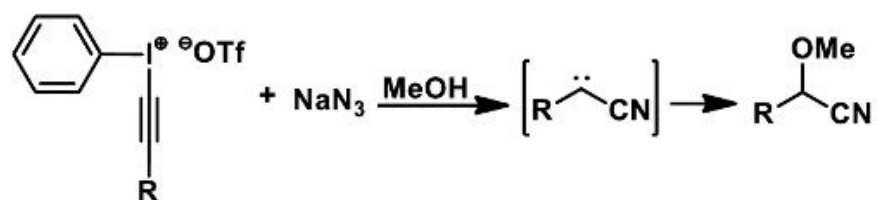


Figure 2. O-H Insertion Reaction Demonstrating the Cyanocarbene Intermediate.

Mechanistic Details for Cyanocarbene Reaction

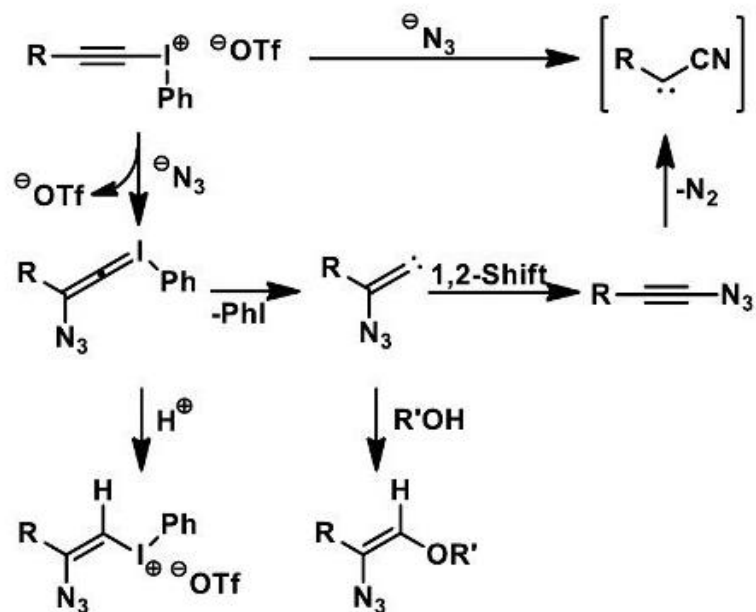


Figure 3. Proposed Mechanism for Cyanocarbene Formation.

Cyanocarbene Reactions

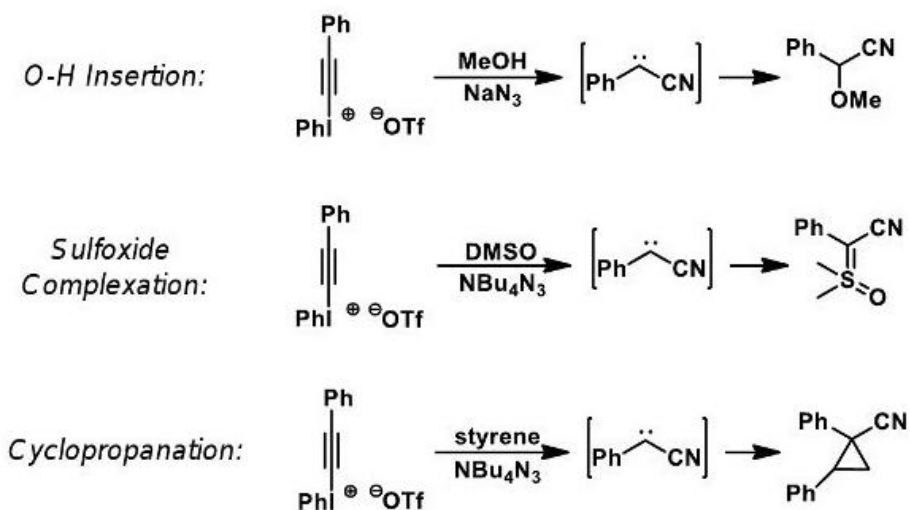


Figure 4. Reactions of Cyanocarbenes.

Discussion

Hypervalent iodonium alkynyl triflates, or HIATs, are formed and can be reacted with azide sources to form cyanocarbenes. It is very important that all necessary precautions are taken since many of the reagents and intermediates shown in this video are potentially explosive and highly

toxic. Although the high level of reactivity can be dangerous if ill-prepared, it is shown in this video that the inherent reactivity of the compounds can be harnessed by capturing the cyanocarbenes in various reactions such as O-H insertion and cyclopropanation.

The synthesis of other HIATs has been attempted with varying success. The difficulty often comes in the isolation of the solid from the byproducts or that the HIAT degrades rapidly and cannot be used in subsequent reactions. Crystallization of the HIAT can be performed in solvents such as diethyl ether, hexane, chloroform and acetonitrile to obtain analytically pure materials.¹⁷

Future applications of this method can be extended to other novel cyclopropanations, C-H insertions and, in unique instances, intramolecular reactions. The cyanocarbene acts more electrophilically than typical carbenes but for most purposes the reactivity with normal carbenes should be congruent.

One of the most important aspects of this reaction is that it converts a relatively inert alkyne to a more reactive HIAT and then to an extremely unstable cyanocarbene. It is also worth noting that over the course of the reaction the alkyne and azide are transformed into a cyanocarbene and nitrogen gas. This new reaction thus enables previously unimagined synthetic pathways to construct molecules of significance.

Disclosures

The authors declare that they have no competing financial interests.

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References

- Hyatt IFD, Meza-Aviña ME, Croatt MP. Alkynes & Azides: Not Just for Click Reactions. *Synlett*. 2012;23(20):2869–2874.
- Meza-Aviña ME, Patel MK, Lee CB, Dietz TJ, Croatt MP. Selective Formation of 1,5-Substituted Sulfonyl Triazoles Using Acetylides and Sulfonyl Azides. *Organic Letters*. 2011;13(12):2984–2987.
- Hyatt IFD, Croatt MP. Reactions of Hypervalent Iodonium Alkynyl Triflates with Azides: Generation of Cyanocarbenes. *Angewandte Chemie International Edition*. 2012;51(30):7511–7514.
- Banert K, Hagedorn M, Wutke J, Ecorchard P, Schaarschmidt D, Lang H. Elusive ethynyl azides: trapping by 1,3-dipolar cycloaddition and decomposition to cyanocarbenes. *Chemical Communications*. 2010;46(23):4058–4060.

- Koumbis A, Kyzas C, Savva A, Varvolis A. Formation of New Alkynyl(phenyl)iodonium Salts and Their Use in the Synthesis of Phenylsulfonyl Indenes and Acetylenes. *Molecules*. 2005;10(10):1340–1350.
- Banert K, Arnold R, Hagedorn M, Thoss P, Auer AA. 1-Azido-1-Alkynes: Synthesis and Spectroscopic Characterization of Azidoacetylene. *Angewandte Chemie International Edition*. 2012;51(30):7515–7518.
- Zhdankin VV, Stang PJ. Chemistry of Polyvalent Iodine. *Chemical Reviews*. 2008;108(12):5299–5358.
- Bräse S, Banert K. *Organic Azides - Syntheses and Applications*. West Sussex: John Wiley & Sons Ltd; 1002.
- Stang PJ. Alkynyl- and Alkenyl(phenyl)iodonium Compounds. *Angewandte Chemie International Edition*. 2003;31(3):274–285.
- Hembre RT, Scott CP, Norton JR. Conversion of olefins to ditriflates by μ -oxobis[(trifluoromethanesulfonato)(phenyl)iodine]. *Journal of Organic Chemistry*. 1987;52(16):3650–3654.
- Stang PJ, Surber BW, Chen Z, Roberts KA, Anderson AG. Acetylenic Esters. Preparation and Mechanism of Formation of Alkynyl Tosylates and Mesylates via Tricoordinate Iodonium Species. *Journal of the American Chemical Society*. 1987;109(1):228–235.
- Zhdankin VV, Crittall CM, Stang PJ, Zefirov NS. A general approach to unsymmetrical tricoordinate iodinanones: Single step preparation of mixed iodosobenzene sulfonates PhI(X)OSO₂R, via reaction of iodosobenzene with Me₃SiX. *Tetrahedron Letters*. 1990;31(34):4821–4824.
- Lee H, Jung Y, Yoon Y, Kim BG, Kim Y. Angularly Fused Triquinanes from Linear Substrates through Trimethylenemethane Diyl [2 + 3] Cycloaddition Reaction. *Organic Letters*. 2010;12(11):2672–2674.
- Beauchard A, Phillips VA, Lloyd MD, Threadgill MD. Synthesis of 2-(4-carboxybutenyl)- and 2-(4-carboxybutynyl)-cyclopentene-1-carboxamides. *Tetrahedron*. 2009;65(39):8176–8184.
- Kitamura T. An Alternative Synthesis of Alkynyl(phenyl)iodonium Triflates Using (Diacetoxyiodo)benzene and Alkynylsilanes. *Synthesis*. 1998;10:1416.
- Bouma MJ, Olofsson B. General One-Pot Synthesis of Alkynyliodonium Salts and Alkynyl Benziodoxolones from Aryl Iodides. *Chemistry A European Journal*. 2012;18:14242.
- Williamson BL, Stang PJ, Preparation Arif AM. Molecular Structure, and Diels-Alder Cycloaddition Chemistry of β -Functionalized Alkynyl(phenyl)iodonium Salts. *Journal of the American Chemical Society*. 1993;115(7):2590–2597.