DOI: 10.1002/anie.201203062

Reactions of Hypervalent Iodonium Alkynyl Triflates with Azides: Generation of Cyanocarbenes**

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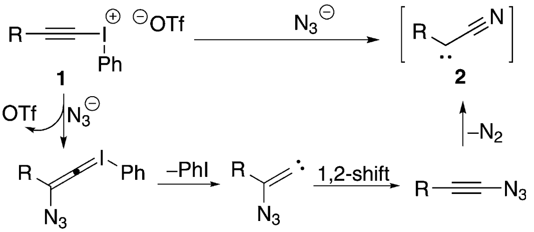
The creation of a fundamentally novel process can facilitate the development of shorter, and often more green, syntheses.[1] Additionally, those novel processes which have the potential to reveal otherwise unimagined pathways to valuable reactive intermediates from simple, readily available substances warrant closer investigation. Towards these goals, we report herein a new method to generate cyanocarbene intermediates (**2**) from hypervalent iodonium alkynyl triflates (HIATs; **1**) and azides, a reaction that converts an azide and two carbon atoms of an alkyne into dinitrogen and a cyanocarbene (Scheme 1). The value of this reactive intermediate, formed from readily available starting materials, is illustrated by three different carbene reactions including O−H insertion, sulfoxide coordination, and cyclopropanation.



Scheme 1. Formation of cyanocarbenes from HIATs.

Cyanocarbenes[2] and alkynyl azides[3] have both been studied from theoretical and experimental aspects for many years. In 2007, Prochnow et al. published a report that described the computationally calculated electronic structures and theoretical reactions of alkynyl azides, and concluded that they would rapidly decompose to form dinitrogen and cyanocarbenes rather than form alkynyl nitrenes.[3b] After this theoretical work, Banert et al. reported the reactions of chloroalkynes with sodium azide in dimethyl sulfoxide (DMSO) which resulted in the trapping of cyanocarbene products.[4a] The yields reported for products resulting from cyanocarbenes were in the range of 1–25% with an average yield of 11%. This proof-of-concept work is very significant, but the yields and reaction conditions, which required several days, are undesirable in terms of practicality. In the report by the Banert group, they showed that the more reactive bromo- and iodoalkynes did not yield products resulting from alkynyl azides **5** or cyanocarbenes **2**.[4b]

Our current research goal is to obtain cyanocarbene intermediates and have them react with a variety of substrates to form complex products in high yields. To accomplish these goals, HIATs (**1**, Scheme 1) have been employed as they are more electrophilic than the previously studied haloalkynes and also have manageable stabilities. Our proposed mechanism of substitution involves the addition of an azide source to the β-carbon atom of the alkyne, thereby forming iodoylide **3** which decomposes into iodobenzene and vinylidene **4**.[5] Vinylidene **4** can then undergo a 1,2-rearrangement by migration of either the azide or the R group to afford alkynyl azide **5**. This alkynyl azide has been shown to extrude dinitrogen to form cyanocarbene **2** which can react with a substrate.[3b,4] The synthesis and reactivity of HIATs (**1**) has been explored by Stang et al.[6] and variations of them have recently been synthesized by Waser et al.[7] and others.[8] Other umpolung alkyne variations[9] were investigated for the reactions reported herein[10] but the HIATs were chosen for their ease in synthesis and isolation. Briefly, the HIATs were formed by first converting terminal alkynes into the trimethylsilyl or tributylstannyl internal alkynes.[6a,11] The internal alkynes were then treated with Zefirov's reagent,[12] the product of the reaction of triflic anhydride and iodosobenzene, to form the alkynyl(phenyl)phenyliodonium triflate (**1**; R = Ph) or the alkynyl(*n*-pentyl)phenyliodonium triflate (**1**; R = *n*-pentyl).

Based on the hypothesis that HIATs are reactive in the presence of azides, and by the prior theoretical[2d,13] and experimental[3d,14] work showing that the resultant cyanocarbenes would be extremely reactive, the decision was made to study the reactions using the solvent alone to react with the cyanocarbenes (Table 1). The first reactions were run in the presence of water (with dichloromethane as a cosolvent), methanol, acetone, and DMSO, all of which facilitated the dissolution of sodium azide.

The product from the reaction of Ph-HIAT (**6**) with water (Table 1, entry 1) validated that the initial step of the mechanism involved the addition of azide to the electrophilic β-carbon atom. In this case, iodoylide **3** was protonated by

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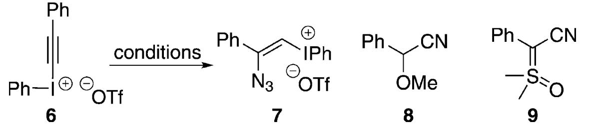
[**] Funding for this project from The University of North Carolina at Greensboro is gratefully acknowledged. The authors thank Dr. Franklin J. Moy (UNCG), Dr. Brandie Ehrmann (UNCG), and T. N. Graf and the Oberlies group (UNCG) for assisting with analysis of NMR spectra, mass spectrometry data, and HPLC usage, respectively. The authors also thank the Joint School of Nanoscience and Nanoengineering for the use of their NMR facilities to characterize some compounds.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201203062.

Table 1: Reaction conditions to form and react cyanocarbenes.[a]



Entry	Solvent	T [°C]	Azide	Product	Yield [%][c]
1	CH_2Cl_2/H_2O[b]	25	NaN_3	**7**	39
2	MeOH	0	NaN_3	**7** + **8**	7 + 30
3	MeOH	25	NaN_3	**8**	75
4	MeOH	−40	NBu_4N_3	**7** + **8**	49 + 7
5	MeOH	0	NBu_4N_3	**7** + **8**	24 + 11
6	MeOH	25	NBu_4N_3	**8**	60
7	CH_2Cl_2/H_2O[b]	25	NBu_4N_3	**7**	22
8	Acetone	−40	NBu_4N_3	**7**	42
9	Acetone	25	NBu_4N_3	**7**	trace
10	DMSO	25	NaN_3	**9**	20
11	DMSO	25	NBu_4N_3	**9**	27

[a] Conditions: Ph-HIAT (**6**; 1 equiv) was dissolved in the indicated solvent, cooled to the indicated temperature, and the azide added (1 equiv). [b] 1:1 ratio. [c] Yield of isolated products.

water to yield iodonium alkene **7**. Though the yield of **7** is low, it was the only observable product of the reaction after workup to remove the by-products. The low yield is hypothesized to be due to volatile carbene products[15] and isolation difficulties such as lack of stability on silica gel and moderate sensitivity of **7** to light.[16] Iodonium alkene **7** was formed as a single diastereomer, as confirmed by nOe experiments, and is likely due to a thermodynamic effect (see below).

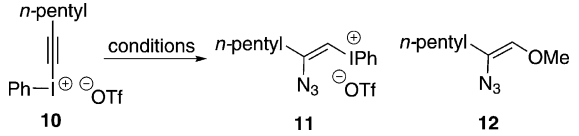
When HIAT **6** was reacted with sodium azide in methanol (Table 1, entry 2), two products were formed, iodonium alkene **7** and cyano ether **8**, which results from a formal O−H insertion. The formation of **8** is assumed to proceed through nucleophilic addition of the oxygen atom of methanol to electrophilic cyanocarbene **2** with a subsequent proton-transfer mechanism instead of a concerted O−H insertion reaction. This process is speculated based on the large bond dissociation energy for a typical O−H bond. By altering the temperature, the selectivity of the reaction could be altered (entries 3 and 4) and, gratifyingly, a 75% yield of cyano ether **8**, resulting from a cyanocarbene, could be isolated. This represents a 15-fold improvement in yield for the only other O−H insertion reaction of a cyanocarbene formed from an alkyne and an azide.[4a] It is hypothesized that protonation of iodoylide **3** happens more readily at lower temperature because there is not sufficient energy to rapidly cleave iodobenzene and form vinylidene **4**.

To further investigate the temperature dependence, and to make the reaction conditions more amenable to nonpolar substrates, tetrabutylammonium azide was used in place of sodium azide. The hygroscopic nature of tetrabutylammonium azide, and the fact that water protonates the iodoylide (Table 1, entry 1), mandated that all manipulations of this reagent be performed in a glovebox. The product selectivity with temperature variance using tetrabutylammonium azide in MeOH followed the same trend as when using sodium azide (compare entries 2 and 3 versus entries 4–6). Similar to the results with sodium azide, reactions run at ambient temperature yielded higher amounts of **8**, the product resulting from cyanocarbene formation.

When the reaction using tetrabutylammonium azide was run in the presence of water, the identical product was formed as with sodium azide (compare entries 1 and 7 in Table 1). Ph-HIAT (**6**) was also treated with acetone in an effort to afford a cyano epoxide (entries 8 and 9), however, the acidity of the α-hydrogen atom led to protonation of iodoylide **3**.[17] Increasing the temperature formed only trace amounts of **7** and a complex mixture of unknown products. For the reaction performed with DMSO as the solvent, a known product (**9**) which results from the cyanocarbene complexing with DMSO was observed (entries 10 and 11).[4a] The yield of the isolated product is low, however, these yields are twice as efficient as the previously reported formation of sulfoxide adduct **9**. The low yield can be partially attributed to the aqueous extraction workup and the lack of stability of the compound on silica gel. Both azide sources reacted similarly and provided approximately the same yield of product **9**.

To further explore these reactions, an aliphatic HIAT, *n*-pentyl-HIAT (**10**), was synthesized and used under similar reaction conditions (Table 2). Interestingly, **10** reacted differently with MeOH (entries 1–4). The major product is iodonium alkene **11** in all instances with some production of vinyl ether **12**, presumably from O−H insertion from the vinylidene. This O−H insertion is again assumed to occur through nucleophilic addition of methanol to the carbene. There were also trace amounts of what appears to be the O−H insertion product from the cyanocarbene (analogous to structure **8**). It should also be noted that only *Z*-vinyl ether **12** was formed under all reaction conditions, which was confirmed by nOe experiments. Similar to the reactions with **6**, the major product for the reactions of **10** in the presence of water was iodonium alkene **11**, and it reacted in a completely diastereoselective fashion (entries 5 and 6).

Table 2: Reactions of *n*-pentyl-HIAT (**10**).[a]

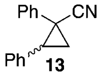
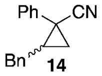
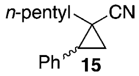


Entry	Solvent	T [°C]	Azide	Product	Yield [%][c]
1	MeOH	25	NaN_3	**11** + **12**	23 + 4
2	MeOH	0	NaN_3	**11** + **12**	18 + 4
3	MeOH	25	NBu_4N_3	**11** + **12**	28 + 14
4	MeOH	−40	NBu_4N_3	**11** + **12**	19 + 11
5	H_2O/CH_2Cl_2[b]	25	NaN_3	**11**	36
6	H_2O/CH_2Cl_2[b]	25	NBu_4N_3	**11**	30

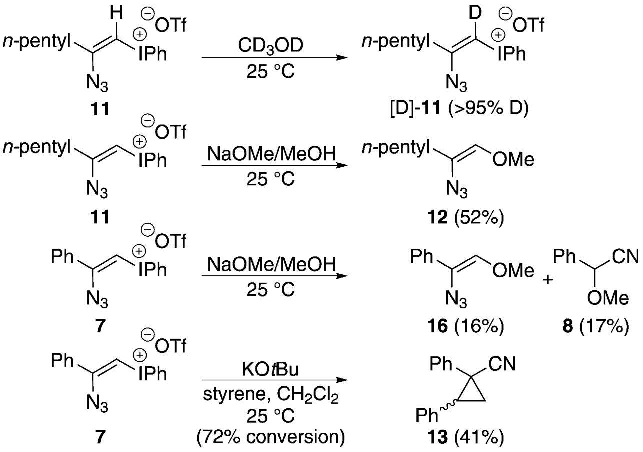
[a] Conditions: *n*-pentyl-HIAT (**10**; 1 equiv) was dissolved in the indicated solvent, cooled to the indicated temperature and the azide was added (1 equiv). [b] 1:1 ratio. [c] Yield of isolated products.

With reaction conditions for forming cyanocarbenes obtained, additional substrates and reaction types were examined (Table 3). The formation of cyanocarbenes was further validated by the reactions with styrene and allylbenzene when using **6** (entries 1–4), as cyclopropanation reac-

Table 3: Cyclopropanation reactions of cyanocarbenes.[a]

Entry	Solvent	Reagents	Product	Yield [%][b]
1	CH_2Cl_2	styrene, **6**	 **13**	40
2	–	styrene, **6**		61
3	CH_2Cl_2	allylbenzene, **6**	 **14**	18
4	–	allylbenzene, **6**		50
5	CH_2Cl_2	styrene, **10**	 **15**	25
6	–	styrene, **10**		42

[a] Conditions: Ph-HIAT (**6**) or *n*-pentyl-HIAT (**10**) was dissolved in a minimum amount CH_2Cl_2 and 1 equiv of substrate or 10 equiv of substrate (solventless reactions) followed by the addition of 1 equiv of NBu_4N_3. Reactions were performed at room temperature in the glove box. [b] Yield of isolated products.



Scheme 2. Mechanistically insightful use of iodonium alkenes.

tions occurred in moderate yields. This reactivity is unlike the results previously reported by Moriarty et al. where iodoylides of 1,3-carbonyl compounds require a metal catalyst to enable intermolecular cyclopropanations of styrene.[18] To expand the scope of this reaction, **10** was used in the reaction with styrene (entries 5 and 6). Importantly, in the absence of a good nucleophile, such as an alkoxide, or an acidic proton, the vinylidene rearranged with both HIATs and reacted as a cyanocarbene. The reactions produced both diastereomers with no stereoselectivity. The solventless reactions produced higher yields of cyanocyclopropanes than the reactions which dissolved the tetrabutylammonium azide and the HIAT in CH_2Cl_2 (entries 2, 4, and 6). The lower yield obtained when using CH_2Cl_2 can be attributed to an unknown, unstable CH_2Cl_2 reaction product which could not be isolated in a pure form. Attempts were made to isolate the product from the reaction of the **10** with allylbenzene, however, the presumed cyclopropanation product was not stable to various purification techniques.

To further substantiate the hypothesized mechanism in Scheme 1, the iodonium alkenyl triflates **7** and **11** were analyzed in subsequent reactions (Scheme 2). Evidence that the iodoylide **3** (Scheme 1) can undergo reversible protonation was shown by complete hydrogen–deuterium exchange when **11** was dissolved in CD_3OD and sat for 48 hours (see ^1H NMR spectra in the Supporting Information). Since the iodonium alkenes are likely in equilibrium with iodoylide **3**, the diastereoselective nature of forming **7** and **11** is likely due to thermodynamic control. Moreover, when **11** was treated with basic methanol, azide-substituted vinyl ether **12** was formed in 52% yield (Scheme 2). Presumably, the basic conditions generate the iodoylide **3** which reenters the carbene pathway described in Scheme 1.[19] Although formation of **12** could be explained by an addition/elimination mechanism, this does not account for the H/D exchange that was observed in deuterated methanol.

To test if the aromatic group facilitates the elimination of iodobenzene and subsequent rearrangement to the cyanocarbene, **7** was investigated. Unlike the analogous reaction of **11**, the cyano ether **8** was observed along with the previously reported vinyl ether **16**.[3g] Vinyl ether **16** is likely formed because of the presence of the more nucleophilic methoxide as compared to the previously neutral reaction conditions used for experiments in Table 1. Thus, it appears that the phenyl group assists in the formation of the alkynyl azide **5** from vinylidene **4**. This assistance could be due to either the phenyl group migrating more easily than the alkyl group (traversing a Meisenheimer complex) or the aryl group assisting in the migration of the azide group by stabilizing charges at the benzylic position. More information about this mechanism will be published in due time. Gratifyingly, when the alkenyl iodonium **7** was treated with potassium *tert*-butoxide in the presence of excess styrene, the cyclopropane **13** was isolated in 41% yield (Scheme 2). These results solidify the proposed hypothesis that deprotonation of the alkenyl iodonium compounds yield vinylidenes, and subsequently cyanocarbenes.

This report describes a method to obtain cyanocarbene reactive intermediates by reacting electrophilic iodonium alkynes with azides. The reactions presented herein are the highest yielding for formation of cyanocarbenes[20] from alkynes and azides and also cover a breadth of reactivity including O–H insertion, sulfoxide complexation, and cyclopropanation. Empirical data suggests the formation of the iodoylide **3** and the azide-substituted vinylidene **4** prior to formation of the cyanocarbene **2**. Further investigation into the reaction mechanism and potential practical uses of this reaction process are currently underway.

Received: April 20, 2012
Revised: May 14, 2012

Keywords: azides · carbenes · cyanides · hypervalent compounds · synthetic methods

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[15] Iodobenzene was removed under high vacuum and presumably other volatile by-products were removed since the mass recovery was always significantly less than 100% after subjecting the reaction mixture to the vacuum, even after acounting for the loss of iodobenzene and dinitrogen. Prior to subjection to high vacuum, an aldehydic peak was observed by ^{1}H NMR spectroscopy, thus implicating formation of benzaldehyde. However, this compound was too volatile to be separated from iodobenzene and definitively identified.

[16] If left for relatively short periods of time, alkene **7** turns black and forms iodobenzene along with a mixture of undetermined oligomeric products.

[17] The authors freshly distilled the acetone prior to the reaction, however, a small amount of exogenous water as the source for protons in this reaction cannot be excluded.

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Synthetic Methods

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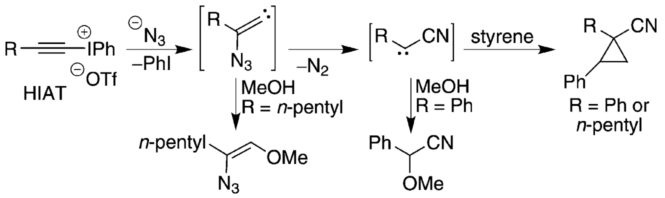
Reactions of Hypervalent Iodonium Alkynyl Triflates with Azides: Generation of Cyanocarbenes



HIAT me, baby, one more time: Cyanocarbenes have been formed by the reaction of azides with hypervalent iodonium alkynyl triflates (HIATs). Experimental evidence supports the potential intermediacy of an azide-substituted vinylidene or alkynyl azide, both of which could form a cyanocarbene. Trapping of the vinylidene and cyanocarbene includes O–H insertion, dimethyl sulfoxide coordination, and cyclopropanation reactions.