Formation and in situ Reactions of Hypervalent Iodonium Alkynyl Triflates to Form Cyanocarbenes

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Formation and *in situ* Reactions of Hypervalent Iodonium Alkynyl Triflates to Form Cyanocarbenes

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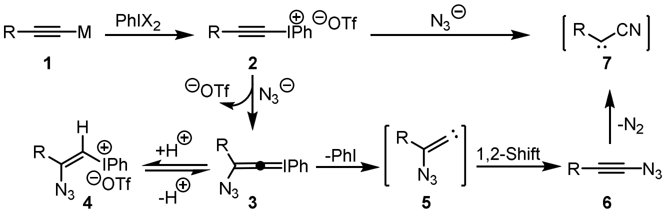
The conversion of readily available silylalkynes, iodobenzene diacetate, and azide anions was utilized to form and react cyanocarbenes. A copper(II)-catalyzed reaction was found to react in a different manner. Both of these methods benefit from the formation and *in situ* reaction of hypervalent iodonium alkynyl triflates in O-H insertion reactions.

A major goal of organic synthesis is the formation of a target molecule as efficiently as possible, which often involves the shortest sequence of steps.[1] To assist in this effort, the design and development of new reactions that convert simple, readily available starting materials into products with increased molecular complexity is of special priority. Furthermore, new reactions that are fundamentally novel are valuable since they enable different, potentially more efficient retrosynthetic disconnections. Towards this goal, our group has been interested in the reactions of alkynes and azides to transiently form alkynyl-azides (**6**) that would extrude dinitrogen to form cyanocarbenes (**7**, Scheme 1).[2] Although the reaction of nucleophilic alkynes and electrophilic azides were found to create triazoles,[3] it was determined that cyanocarbenes could be formed by using hypervalent iodine[4] to generate electrophilic alkynes and react them with nucleophilic azides.[2, 5] Reactions of the cyanocarbene explored include cyclopropanation, O-H bond insertion (via a stepwise process, not a concerted bond insertion), sulfoxide complexation, and more recently C-Cl insertion.[6]

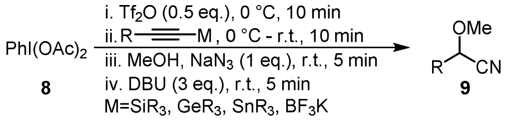


Scheme 1: Previous method for the formation of cyanocarbenes from HIATs.

Although this reaction was highly novel, it required the synthesis of a hypervalent iodonium-alkynyl triflates (**2**, HIATs) to be used as the source of electrophilic alkynes. The HIATs are specifically electrophilic at the β-carbon, at which point the azide source adds (Scheme 1). After a series of intermediates, including an iodoylide (**3**), vinylidene carbene (**5**), and alkynyl azide (**6**), the cyanocarbene (**7**) is generated. Although this method produced the first high yielding cyanocarbene reaction,[5a, b] it had two major drawbacks. First of all, this method required the formation and isolation of the HIATs which tend to have limited stability, and are even explosive in some instances. Secondly, all of the reactive intermediates that are required for generation of the cyanocarbene allow for a variety of side reactions to compete. The paper herein describes two processes for the *in situ* formation and reaction of HIATs that obviates the isolation of the HIAT. The first method uses either commercially available alkynes or readily available metallated alkynes, iodobenzene diacetate, and sodium azide to generate cyanocarbenes. The second method described utilizes a copper(II) catalyst to theoretically enable the direct addition of azide anion to the α-carbon, a process that bypasses most of the previously formed reactive intermediates that cause side reactions.

Reports on the theoretical and/or experimental evidence of cyanocarbenes[7] and alkynyl azides[6, 8] laid the ground-work for the establishment of methods to form these molecules. The utility of the reaction of HIATs and azides, however, is hampered by the accessibility of HIATs. Common methods to synthesize HIATs can be efficient, however, the isolation of the HIATs can be problematic and often require cold, anaerobic conditions.[9] Therefore, it was decided to create a method whereby the HIATs are formed and reacted *in situ* so that the process would be more approachable for the organic chemist community.

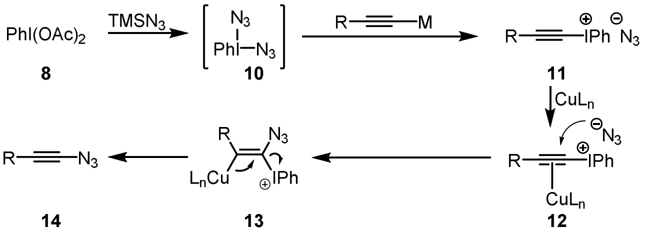
Investigation into new methods to generate cyanocarbenes started by naturally expanding our previous methods to an *in situ* reaction (Scheme 2) by the use of Kitamura's previously published reagent.[10] Since it was determined that the rearrangement of vinylidene carbene **5** to alkynyl azide **6** proceeds much more efficiently with aryl HIATs compared to an alkyl HIAT,[5a] only aryl groups were investigated in the presented work.



Scheme 2: Method 1. Generation of cyanocarbenes and deprotonation of the alkenyl iodonium species (**4**).

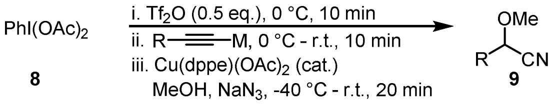
The decision to use Kitamura's reagent instead of other typical reagents such as Zefirov's reagent,[11] cyanophenyliodonium triflate,[12] Koser's reagent,[13] or other reagents[14] was based on solubility, the versatility of metals on the alkyne (M = Si, Ge, Sn, or B), chemoselectivity, and yield. Since the HIAT does not need to be isolated in this methodology, unstable HIATs can be generated and used immediately. Method 1 (Scheme 2) caused the alkenyl iodonium product (**4**) to re-enter the cycle by the addition of DBU, however, vinylidene carbene O-H insertion products still formed. The fundamental problem with Method 1 is that β-attack on the alkyne occurs and the rate of 1,2-shift to form the alkynyl azide competes with alternative vinylidene carbene reactivity. Thus, an alternative method was developed where α-attack might be possible.

A publication by Stang *et al.* showed that copper (I) would transform a hypervalent iodonium alkynyl tosylate to an alkynyl tosylate.[13b] It was theorized that the same process could apply to our system if the anion of the HIAT went through ligand exchange to an azide (Scheme 3). It was found that copper (I) catalysts led to Glaser coupling products but copper (II) catalysts formed the cyanocarbene products. The method shown in Scheme 3 was successful in the production of cyanocarbenes but had problems such as formation of $Cu(N_3)_2$, which is highly explosive, the use of tin-alkynes, and the insolubility of $PhI(N_3)_2$ at cold temperatures. Due to these problems, the method was not explored further but it did give some evidence that α-attack was occurring since no alkenyl iodonium or vinylidene carbene products were produced.



Scheme 3: Initial result which lead to the development of Method 2.

Building on the method shown in Scheme 3, a new method was developed. In Method 2 (Scheme 4), an *in situ* HIAT is formed from Kitamura's reagent and is then reacted with a methanol solution containing sodium azide and catalytic amounts of Cu(dppe)$(OAc)_2$. The dppe ligand is important because the Cu(dppe)$(N_3)_2$ formed in the reaction is soluble and thus lowers the safety hazards. Although ligand screening is ongoing, initial results suggest that other bidentate ligands (TMEDA) work successfully but tridentate ligands slow down catalyst activity. As mentioned in Scheme 3, the copper (II) catalyst facilitates an α-attack on the HIAT which then forms alkynyl azide directly without the need of a 1,2-shift. The alkynyl azide is then allowed to decompose to the cyanocarbene which is trapped by methanol. To confirm that the copper is not modifying the azido alkenyl iodonium intermediates, 25 mol% Cu(dppe)$(OAc)_2$ and alkenyl iodonium (**4**, R = Ph) were placed in MeOH but no reaction occurred even after 24 hours at room temperature. When DBU was added to a solution of iodonium **4** in the presence of Cu(dppe)$(OAc)_2$ in MeOH, products resulting from both cyanocarbene **7** and vinylidene carbene **5** were observed.[5a] This further validated that the reactions utilizing Method 2 (Scheme 4) are having azide delivered to the α-carbon instead of the β-carbon.



Scheme 4: Method 2 for the generation of cyanocarbenes by α-attack on the HIAT.

Before comparing the two methods, it was decided to first explore the optimal catalyst loading for the copper (II) catalyst using the Ph-HIAT (**2**, R = Ph; Table 1). It was determined that low copper catalyst loading (<25%) permitted the formation of products resulting from vinylidene carbene **5**. These by-products presumably formed via the uncatalyzed background pathway. Therefore, 25 mol % was used in subsequent reactions.

Table 1: Optimization of copper catalyst

Entry	Cu(dppe)$(OAc)_2$ (mol %)	Yield^{b}
1	100	37%
2	50	51%
3	25	45%
4	10	22%
5	5	25%
6	1	19%

^{a} Reaction conditions: Ph-HIAT (**2**, R = Ph, 0.10 g, 0.22 mmol) was dissolved in 1 mL of DCM and cooled to -40 °C. A separate solution of sodium azide (0.014 g, 0.22 mmol) and Cu(dppe)$(OAc)_2$ (mol % indicated in Table) in 5 mL methanol was prepared and transferred to the cold solution of Ph-HIAT (**2**). The solution was allowed to warm to r.t., concentrated, and purified by silica gel flash chromatography. ^{b} Isolated yields of **9a** (R = Ph).

The comparison between Method 1 and 2 was performed in which the metal on the alkyne was altered (Table 2). Although the yields are not drastically different between the different metals used, the reactions times were longer for silicon and germanium than they were for trifluoroborates and tin, as determined by monitoring the reactions by TLC.

Table 2: Investigation of metal alkynes and method variance

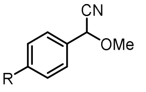
Entry	Metal	Method^{a}	Temperature^{b}	Time^{c}	Yield^{d}
1	BF_3K	1	-40 °C	< 1 min	31%
2	BF_3K	2	-40 °C	< 1 min	39% (16%)^{e}
3	TMS	1	r.t.	10 min	28%
4	TMS	2	r.t.	10 min	29%
5	$GeEt_3$	1	r.t.	10 min	48%
6	$GeEt_3$	2	r.t.	10 min	48% (16%)^{e}
7	$SnBu_3$	1	-40 °C	< 1 min	39%
8	$SnBu_3$	2	-40 °C	< 1 min	41%

^{a} Reaction conditions followed either Scheme 2 (Method 1) or Scheme 4 (Method 2) using HIAT **2** (R = Ph). See SI for specifics. ^{b} Temperature required for HIAT formation. ^{c} Time required for HIAT formation. ^{d} NMR yields of **9a** (R = Ph). ^{e} Yield in parenthesis is the vinylidene carbene O-H insertion product.[5a]

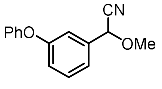
The next series of experiments were intended to monitor the scope of the reaction by using different *in situ* prepared HIATs and reacting them with MeOH (Table 3). Most of the HIATs in this study are relatively unstable and tend to decompose when isolation of the pure HIAT was attempted. The O-H insertion likely involves nucleophilic addition of the oxygen of methanol to the electrophilic carbene followed by proton transfer. It should be noted that the more electron-deficient alkynes required higher temperatures and longer times to form the HIATs and were also lower yielding to form the products (entries 1,2 versus entries 3,4) with no observable product with the nitro-group (entries 4-6).

Table 3: Substrate Scope

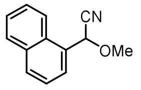
Entry	R	Method	Yield^b	Product
1	anisole	1	12%	**9b**
2	anisole	2	50%	**9b**
3	*p*-trifluomethyl-phenyl	1	4%	**9c**
4	*p*-trifluomethyl-phenyl	2	19%	**9c**
5	*p*-nitrophenyl	1	0%	**9d**
6	*p*-nitrophenyl	2	0%	**9d**
7	*m*-phenoxy-phenyl	1	24%	**9e**
8	*m*-phenoxy-phenyl	2	24%	**9e**
9	naphthyl	1	16%	**9f**
10	naphthyl	2	64%	**9f**



R = OMe **9b**
R = CF_3 **9c**
R = NO_2 **9d**



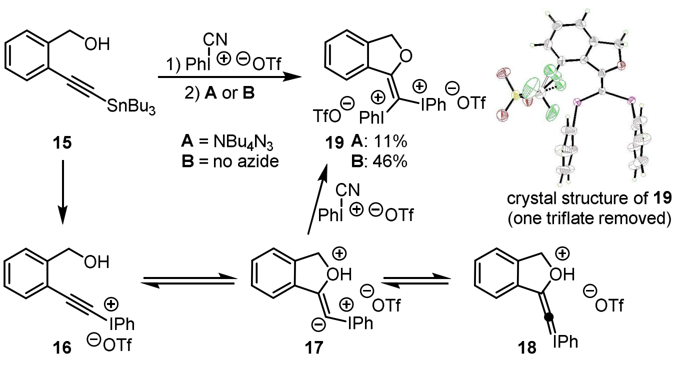
9e



9f

^{a} Reaction conditions followed either Scheme 2 (Method 1) or Scheme 4 (Method 2). See SI for specifics. ^{b} Isoloated yields.

To diversify this methodology, an intramolecular substrate was explored. An inherent difficulty with this approach is that any nearby nucleophile that can attack the electrophilic cyanocarbene can also add into the HIAT. An example of this occurrence is shown in Scheme 5 where the hydroxyl group attacks the β-carbon before the azide. Unfortunately, the conditions of Method 1 and 2 also led to no appreciable amount of the desired intramolecular cyanocarbene product, however, a white precipitate formed in all the reactions. Analysis by X-ray crystallography determined that a 1,1-diiodonium alkene (**17**) had formed. To validate the reaction and structure, azide was removed as a reagent and 1,1-diiodonium alkene **17** was again isolated. This compound is the first structure of this type and was unambiguously characterized using X-ray crystallography (see Supporting Information for X-ray data and more details).



Scheme 5: Novel method for the synthesis of 1,1 diiodonium alkenes

The described work shows the development of two methods for the generation of cyanocarbenes from alkynes and azides using commercially available hypervalent iodine sources. Both methods include an *in situ* generation of hypervalent iodonium alkynyl triflate but are mechanistically different in how the azide attacks the alkyne. Although the yields can be similar between methods, there is less side-product formation when using a copper catalyst (Method 2). Other reactions such as cyclopropanation and intramolecular reactions remain of current research interest in the group.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, graphical spectra, and crystallographic data for **19**. See DOI: 10.1039/c000000x/

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