Tetrahedron Letters 53 (2012) 5663–5666

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Intramolecular cyclization and subsequent rearrangements of alkyne-tethered N-heterocyclic carbenes ☆

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ARTICLE INFO

*Article history:*
Received 17 July 2012
Revised 8 August 2012
Accepted 9 August 2012
Available online 17 August 2012

*Keywords:*
N-heterocyclic carbenes
Intramolecular cyclization
Diels–Alder cycloaddition

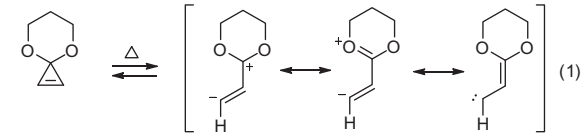
ABSTRACT

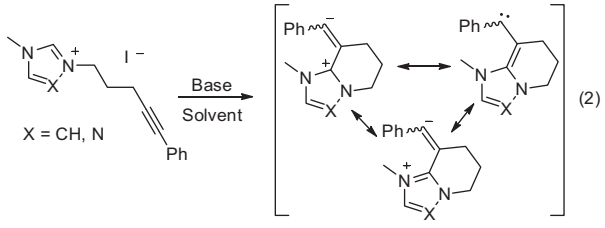
Alkyne-tethered imidazole and 1,2,4-triazole-based N-heterocyclic carbene precursors have been prepared and studies of the intramolecular reactions of carbenes are performed. Products consistent with intramolecular cyclizations and subsequent rearrangements were observed. Mechanistic studies using crossover experiments showed that the products did arise from intramolecular carbene additions. The reactions are proposed to go through vinylogous diaminocarbene intermediates similar to vinylogous dialkoxycarbenes formed during Boger cycloaddition reactions. Imidazole substituted dienes were observed to be the major products of tandem cyclization and elimination reactions that were observed for imidazole-based N-heterocyclic carbenes.



The unique characteristics of N-heterocyclic carbenes (NHCs) have been exploited in many synthetic applications ranging from ligands in transition metal catalyzed reactions to organocatalysis.[1–4] In organocatalysis, NHCs have most commonly been used to perform aldehyde umpolung reactions.[5] Generally imidazolium, thiazolium, and triazolium based-salts have been successfully employed. NHC catalyzed benzoin condensations between aldehydes have been utilized in numerous syntheses, employing the concept of reverse polarity to generate α-keto alcohols, either intermolecularly[6–11] or intramolecularly.[12–14] In the aza-benzoin variant, the coupling of aldehydes with acyl imines has been used to prepare α-amino and α-amido ketones.[15–18] An extension of the Benzoin reaction to α,β-unsaturated carbonyl compounds, namely the Stetter reaction, has been used extensively to generate 1,4-dicarbonyl compounds,[19] and has also been used with other Michael acceptors such as α,β-unsaturated nitriles and sulfones.[20] These reactions have been performed in both organic and aqueous media.[21,22] The reactivity largely mimics the types of transformations prevalent in biological systems performed by the co-factor thiamine, which can be considered a naturally occurring NHC.[6]

The applications of NHCs in organic synthesis have not been limited to catalysis, since NHCs are also nucleophilic carbenes and they can act as reactive partners with different substrates including maleimides,[23] alkenes,[24] isocyanates,[25] and alkynes such as dimethyl acetylenedicarboxylate (DMAD).[26,27] The products of these reactions resemble those obtained from other diheteroatom-substituted nucleophilic carbenes such as, for example, those generated from thermal elimination of carbene intermediates from norbornenone ketals,[28,29] from oxadiazolines using the method of Warkentin et al.,[30–33] or vinylogous dioxycarbenes generated from cyclopropenone ketals by the Boger reaction.[34,35] As shown in Eq. 1, the thermally promoted formation of the three carbon 1,3-dipole or π-delocalized vinyl carbene from cyclopropenone ketal starting material, followed the initial studies of the physical and chemical properties of these strained molecules by Baucom and Butler.[36] Herein, we have generated and studied analogous intermediates that constitute vinylogous NHCs through intramolecular addition reactions of NHCs onto intramolecular alkyne traps, as shown in Eq. 2.




☆ This Letter is dedicated to Professsor John Warkentin (McMaster) on the occasion of his 80th birthday.

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http://dx.doi.org/10.1016/j.tetlet.2012.08.038

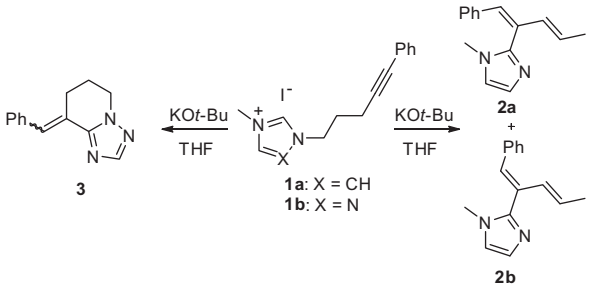
Vinylogous diheteroatom substituted carbenes show interesting reactivity that is consistent with both carbene and ylide resonance structures. For example, the cyclopropenone ketal used by Boger and co-workers can be thermally (70–80 °C) reacted with electron deficient olefins to yield the corresponding functionalized cyclopentene rings via formal [3+2] cycloaddition.[34,37] Reactions with less electron deficient olefins bearing a single electron withdrawing substituent provide the corresponding cyclopropanes as the products of [1+2] carbene cycloaddition arising from reaction of the singlet carbene.[38] The application of cyclopropenone ketal has been further extended to the reactions with aldehydes and ketones to give butenolide *ortho* esters via [3+2] cycloaddition.[39–42] Additionally, the thermal [3+4] cycloadditions of cyclopropenone ketal with α-pyrone afford annulated cycloadducts.[34] Recent studies have demonstrated that this type of reactivity can be attained in an intramolecular fashion as well.[37,43] While the reactivity at different temperatures and with different substrates from the intramolecular variant led to the formation of unexpected tricyclic or tetracyclic products, both arise from the common carbene intermediate. Furthermore, the intramolecular reaction shows tolerance to varying tether lengths and substitution patterns.[37,43]

Dipoles with vinylogous di-heteroatom-substituted carbene character have also been generated by intramolecular nucleophilic additions of diheteroatom-substituted carbenes onto alkyne groups giving rise to a number of interesting, if not unexpected products.[31,44] Given the unique chemical reactivity and diversity of reactions that dipoles with vinylogous diheteroatom substituted carbene character display, we sought to develop other dipoles using intramolecular nucleophilic additions of NHCs onto tethered alkynes, as shown in Eqn 2. These may in turn be utilized in pericyclic reactions giving rise to privileged scaffolds for molecules with unique medicinal properties. Herein we show that indeed such dipoles are accessible via the base-promoted intramolecular cyclization of alkyne-tethered azolium salts via an N-heterocyclic carbene intermediate. Interestingly, we find that these intermediates undergo further intramolecular rearrangement giving rise to novel heterocycle-substituted dienes.

Imidazolium (**1a,1c,** and **1d**) and triazolium (**1b**) salts comprising carbon tethers to alkyne moieties attached to a nitrogen were synthesized from 4-pentyn-1-ol and either imidazole or triazole starting materials according to the procedures described in the Supplementary data (Scheme S1). Briefly, 4-pentyn-1-ol was first alkylated at the terminal alkyne by Sonogashira coupling with an aryliodide.[45] Following mesylation of the corresponding alcohol and substitution with imidazole or 1,2,4-triazole,[46] the alkyne-tethered azoles were methylated providing the azolium iodide salts **1a–d**.

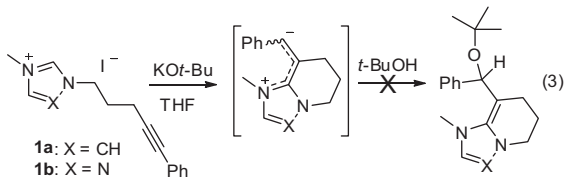
The reaction of imidazolium salt, **1a** with KO*t*-Bu (2 equiv) gave rise to the unusual rearrangement products **2a** and **2b** in 63% yield overall (Scheme 1). These products likely occurred via the addition of the in situ generated NHC onto the alkyne group either intramolecularly or by an intermolecular cascade of reactions. Interestingly, when **1b** was reacted under the same set of reaction conditions, the cyclized product **3** was obtained in 32% yield, suggesting that the vinylogous diaminocarbene and/or dipole from Eq. 2 may have been formed during the reaction. Reducing the number of equivalents of base to 1.0 and 0.5 only reduced the respective yields of the reaction products but no new products were isolable under these conditions.

Attempts to trap the carbene intermediate formed during reactions of **1a** and **1b** with *t*-BuOH were unsuccessful (Eq. 3). It is expected that carbene O–H insertion would follow a mechanism involving first proton transfer followed by nucleophilic attachment of the alkoxide anion.[47,48] The lack of trapped products can be accounted for if carbene was diverted through other intermolecular reactions too quickly, or if the O–H insertion products were not



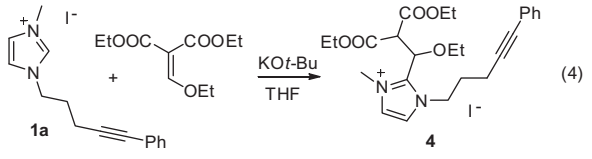

**Scheme 1.** Base-catalyzed rearrangement of azolium salts in THF.

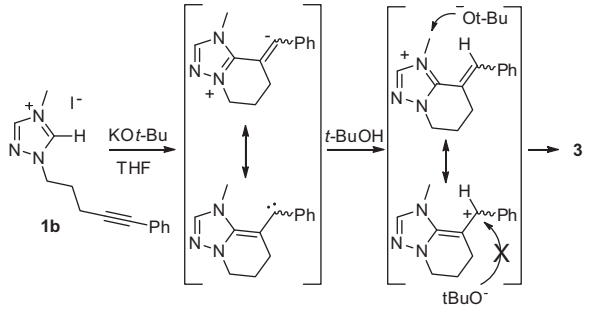
stable, or because *t*-BuOH acts as a catalyst toward the formation of products **2a–b** and **3** rather than undergoing O–H insertion reactions.




Boger and co-workers observed that methanol trapping of an analogous carbene led to protonation at the carbene center but addition of methoxide at a different carbon atom.[37] In the reaction involving triazolium salt **1b** with *t*-BuOH quenching, *t*-BuO⁻ may have alternatively reacted at the methyl carbon bound at *N*-4 of triazolium salt, leading to the formation of **3** (Scheme 2).

Further attempts to trap carbene intermediates from **1a** used diethyl(ethoxymethylene)malonate, a dienophile that has in the past been utilized in [3+2] cycloadditions with the Boger intermediate derived from cyclopropenone ketal. In our case this resulted in the formation of compound **4** (Eq. 4). It was also apparent that introducing heat was not favoring desired reactivity, rather promoted decomposition pathways and the formation of additional undesired products. Thus, it was believed that while deprotonation might be kinetically favored, the cyclization was not occurring in a timely fashion compared with intermolecular trapping. Further attempts to generate the vinylogous diaminocarbene and/or dipole intermediate prior to reaction with the dienophile trap did not yield any cyclized products, only **4**. This suggests that cyclization may be reversible.



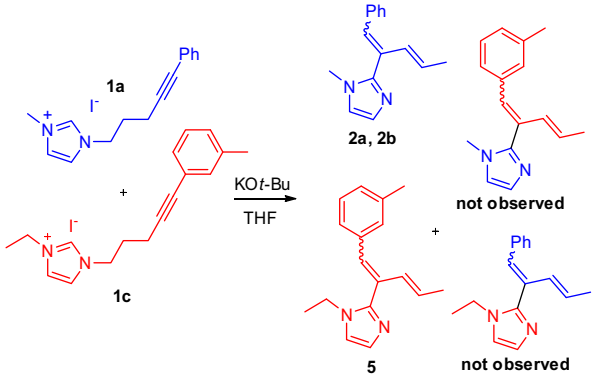

**Scheme 2.** Proposed mechanism for the formation of **3**.

The (*Z*,*E*) and (*E*,*E*) diastereomeric diene rearrangement products, **2a** and **2b**, were initially observed as the major products by treatment of **1a** with an excess of KO*t*-Bu (2–10 equiv). In order to confirm that these products were formed through intramolecular nucleophilic addition rather than intermolecular reactions, we synthesized the imidazolium salt **1c** and performed a cross-over experiment as shown in Scheme 3. The incorporation of an aryl group onto the alkyne with a methyl in the *meta* position allows for the tracking of these components during cross-over reactions containing equimolar concentrations of **1a** and **1c**. No cross-over products were observed, indicating that the products were forming exclusively through an intramolecular rearrangement.

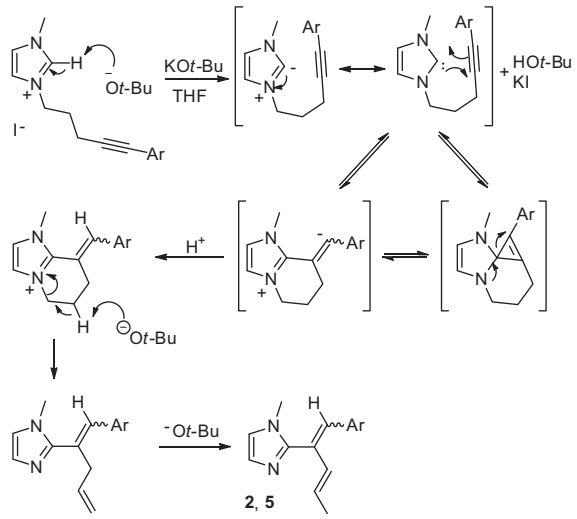
A better understanding of the elimination pathway was gained through crossover experiments, suggesting that a mechanism as shown in Scheme 4 was operative. The inability to trap the reactive intermediates prompted further investigation into the pathway. We decided to substitute the hydrogen atoms in alkyne tether that were proposed to be involved in the elimination step of the mechanism leading to the novel diene, with gem di-methyl groups, thus avoiding the elimination pathway.

The imidazolium salt **1d** containing a gem-dimethyl substituent as shown in Scheme 5 was synthesized through a short sequence described in the Supplementary data (Scheme S2) and was tested under our base-promoted cyclization conditions for the formation of diene products. According to the proposed mechanism, **1d** should essentially shut down the pathway leading to diene products. Treating the gem-dimethyl imidazolium salt **1d** with an excess of KO*t*-Bu in THF failed to yield any diene product, as expected. This further supports the proposed mechanism for diene formation as presented in Scheme 4. A significant amount of the urea byproduct **6** was isolated, suggesting that the reactive intermediate, without a reactive partner and inability to eliminate, favored formation of the oxidized product **6** (Scheme 5). It has been previously proposed that this kind of reactivity occurs from a Wanzlick intermediate in the case of bridged imidazolylidenes reacting with triplet oxygen.[49] However, formation of the vinylogous diaminocarbene and/or dipole intermediate may be reversible and that formation of **6** may have been facilitated by water. Nonetheless, the presence of the gem-dimethyl group prevented diene formation.

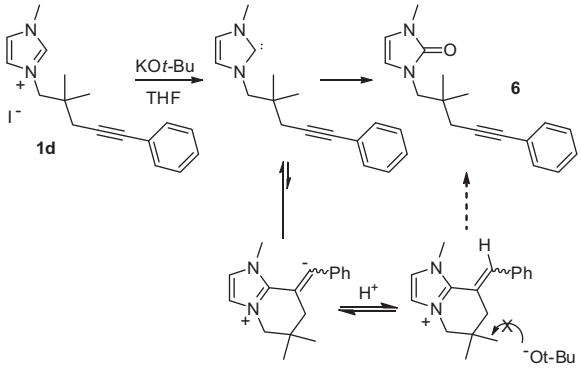
Dienes **2a,b**, **5**, and **7** have not been reported previously, and themselves are structurally interesting, particularly due to the imidazole moiety that has the potential to tune the reactivity of diene depending on its protonation/ligation state. To demonstrate the unique properties of the obtained dienes, [4+2] cycloadditions were conducted to determine if the reactivity could be tuned for Diels–Alder reactions. According to Scheme 6, *E*,*E* diene **7**, obtained




**Scheme 3.** Cross-over experiment to establish intramolecularity of rearrangements of imidazolium salts.



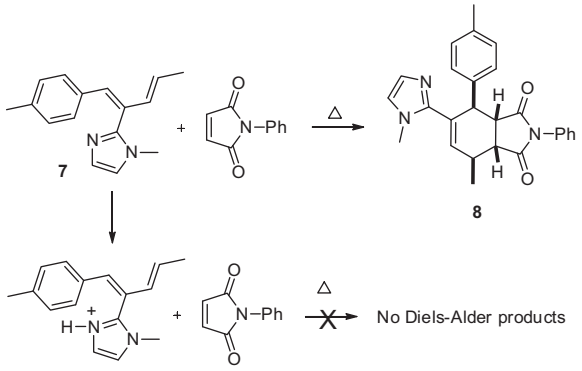

**Scheme 4.** Proposed mechanism for the formation of dienes **2a**,**b**, **5** and **7**.




**Scheme 5.** Attempted cyclization of gem-dimethyl alkyne tethered imidazolium salt **1d**.

from cyclization of imidazolium salt **1e**, was reacted with *N*-phenyl maleimide in toluene, heated to 80 °C for 24 h, and underwent [4+2] Diels–Alder reaction. The thermodynamically favored *exo* cycloadduct **8** was isolated in 76% yield. Interestingly, when the solution was acidified with dilute perchloric acid or *p*-toluenesulfonic acid, no Diels–Alder reaction products were obtained. This is consistent with a dramatic change in the electron demand of diene upon protonation. These data suggest that these dienes can be further modified and reacted with dienophiles to generate unique imidazole linked products and that these reactions are tunable through protonation or through metal coordination of the imidazole nitrogen atom.

In summary, we have synthesized and tested the reactivity of alkyne tethered NHC precursor azolium salts in base promoted intramolecular cyclizations. The triazolium salt **1b** led to the isolation of a de-methylated cyclic product **3**, whereas imidazolium salts **1a,1c** and **1e** led to unique diene products **2a,b**, **5,** and **7**, respectively. The possible mechanisms leading to these various products have been proposed and tested by various experiments including cross-over experiments and the blocking of an elimination pathway through site-specific introduction of methyl groups in place of acidic hydrogen atoms. The unique rearrangement products observed here both expand our understanding of the chemistry of NHCs and provide further opportunity for their use in synthesis since they represent an interesting class of heterocycle-substituted dienes. Applications of the imidazole-linked diene




**Scheme 6.** Diels–Alder reactions of diene **7** with *N*-phenyl maleimide.

products obtained from intramolecular cyclization of imidazolium salts in cycloaddition reactions are being pursued.

## Acknowledgments

This research was financially supported in part by the Natural Sciences and Engineering Council of Canada (NSERC). We thank Kenneth Chan for assistance with MALDI mass spectrometry.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.038.

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