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C−H Insertion by Alkylidene Carbenes To Form 1,2,3-Triazines and Anionic [3 + 2] Dipolar Cycloadditions To Form Tetrazoles: Crucial Roles of Stereoelectronic and Steric Effects

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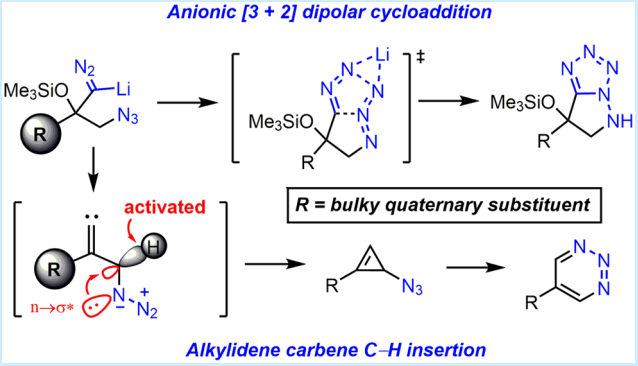
Supporting Information

ABSTRACT: The synthesis of 1,2,3-triazines and bicyclic tetrazoles from α-azido ketones is described. The common intermediate generated from lithiated trimethylsilyldiazomethane and α-azido ketones diverges depending on the steric bulk of the substituents. The formation of 1,2,3-triazines via a C−H insertion of alkylidene carbene to form 3-azidocyclopropene, followed by its rearrangement, is supported by density functional theory calculations. Tetrazole formation proceeds via a facile anionic [3 + 2] dipolar cycloaddition between a lithiated diazo moiety and an azido group facilitated by the chelation of a lithium ion.



The reactivity of alkylidene carbenes has been exploited in various synthetic transformations (Scheme 1).[1] Most prototypic transformations of alkylidene carbenes are insertion reactions into C−H, N−H, O−H, and O−Si bonds to form five-membered carbo- and heterocycles (eq 1).[2] Alkylidene carbenes also undergo a 1,2-shift of a hydride or a π-functional group (alkene, arene, alkyne) to generate alkynes[3] or participate in an addition reaction with alkenes to generate alkylidene cyclopropanes (eq 2).[4] Also, the site-selective insertion into a bridgehead C−H bond relying on the conformation-dependent electronic effect of oxygen was exploited for the synthesis of the platensimycin skeleton (eq 3).[2q] In the context of expanding the scope of alkylidene-carbene-mediated transformations,[5] we have demonstrated that acyclic and cyclic ketones containing a heteroatom functional group at the α-position react with lithiated trimethylsilyldiazomethane (LTMSD) to generate the corresponding alkylidene carbenes, which showed unusual reactivity profiles depending on the nature of the α-substituent (eq 4).[6]

In light of the crucial role of the α-substituent in steering the reactivity of the nearby alkylidene carbene moiety, we turned our attention to the alkylidene carbene containing an α-azido substituent. On the basis of the electron-donating nature of an azide functionality, the n → σ* (C−H) hyperconjugation would activate the corresponding C−H bond toward α-insertion by alkylidene carbene to generate cyclopropene **A**, which, because of its high ring strain, would spontaneously rearrange to form 1,2,3-triazine **B** (eq 5).[7] On the contrary, the polar azido group can directly interact with the empty p orbital of the alkylidene carbene to form a six-membered ring zwitterion **C**, which ultimately generates 1,2,3-triazine **B** via the formation of the intermediate **D** and its 1,3-H shift (eq 6). In addition, we surmised that the steric bulk of the R substituent would further gear the carbenic carbon closer to the C−H bond via the bond angle (∠) compression.[8] To test these hypotheses, we systematically investigated the reactions of α-azido ketones, and herein we describe the formation of novel bicyclic tetrazoles and α-insertion to form azido cyclopropenes that rearrange to generate 1,2,3-triazines.

We commenced our exploration by comparing the reactivity of a pair of ketones with significantly different steric factors at the α-carbon. The initial reaction was carried out with α-azido ketone **1a** (R = Ph)[9] and LTMSD (THF, −78 °C to rt), which afforded **3a** (22%) and **3a′** (32%), whereas under identical conditions, ketone **1b** (R = *t*-Bu) provided only bicyclic tetrazole **2b** in 71% yield (Scheme 2). These results indicate that depending on the steric bulk of the R substituent, **IN1** can directly cyclize to generate **2b**, it survives until the reaction is quenched by a proton to generate **3a**,[6] or it undergoes the elimination of $LiOSiMe_3$ to generate **IN2**, which then rearranges to propargyl azide **3a′**.[10]

At this juncture, we reasoned that the steric bulk of the R substituent might promote the formation of 1,2,3-triazine **4** from **IN2** by exerting the *exo*-Thorpe−Ingold effect.[11] Also, the increased steric bulk will facilitate the elimination of $LiOSiMe_3$ to generate alkylidene carbene **IN2** more efficiently over cyclization product **2**. With these hypotheses in mind, we

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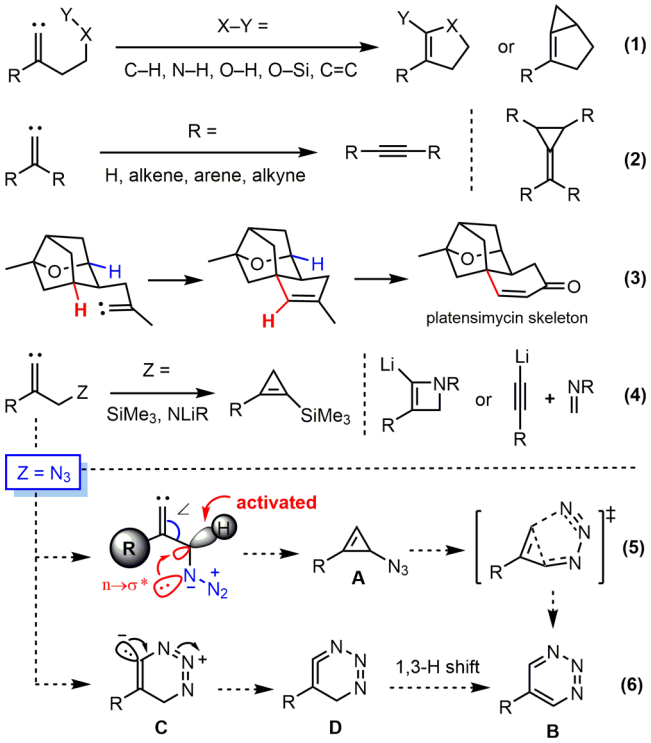
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Representative Transformations of Alkylidene Carbenes



Scheme 2. Reactivity Dependency on a Steric Factor

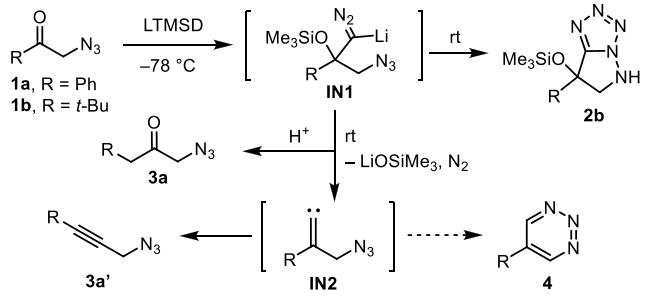
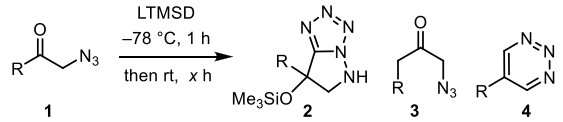


Table 1. Reactions of α-Azido Ketones Containing Noncyclic Alkyl Substituents[a,b]



Entry	Ketone	Time (x)	Tetrazole	Homologated	Triazine
1	**1b**, R = Me	1	**2b** (71%)		
2	**1c**, R = Ph	2	**2c** (88%)	X-ray structure of **2c**	
3	**1d**	0.5	**2d** (35%)	**3d** (13%)	
4	**1d**	3	**2d** (74%)		
5	**1e**	5	**2e** (75%)		
6	**1f**	1		**3f** (69%)	
7	**1g**, R^1 = Ph, R^2 = Me	1			**4g** (53%)
8	**1h**, R^1 = Ph, R^2 = Et	1			**4h** (53%)
9	**1i**, R^1 = ^{n}Pr, R^2 = Me	1			**4i** (41%)

[a]Reaction conditions: trimethylsilyldiazomethane (1.2 equiv), *n*-BuLi (1.3 equiv), azido ketone **1** (1.0 equiv) in THF, under N_2 at −78 °C for 1 h, then at rt for *x* h. [b]Isolated yield.

explored various ketones **1** containing a quaternary carbon at the α′-position of α-azido ketones. It was found that intermediate **IN1** could remain in the reaction mixture, even at room temperature, but in most cases, it can cyclize to tetrazole[12] compound **2**. With a narrow range of the structural space of the quaternary carbon-containing R substituent, eventually 1,2,3-triazine[13] **4** could be generated.

Upon recognition of the crucial role of the steric effect in controlling the reaction pathways we decided to examine the steric effect of the alkyl substituent with α-azido ketones, with a systematic variation of the steric factors (Table 1). *gem*-Dimethyl-containing α-azido ketones **1b** and **1c** reacted with LTMSD smoothly and afforded tetrazoles **2b** and **2c** in 71 and 88% yield, respectively (entries 1 and 2). The structure of tetrazole **2c** was confirmed by an X-ray crystallographic analysis. With **1d** as the substrate, tetrazole **2d** and homologated ketone **3d** were obtained in 35 and 13% yield (entry 3) by running the reaction for 0.5 h, but only tetrazole **2d** was obtained in 74% yield when the reaction was carried out for 3 h (entry 4). An alkyne at a remote position from the carbonyl group did not affect the formation of tetrazole, and thus **2e** was obtained in good yield (75%), although a relatively longer reaction time was required (entry 5). Surprisingly, substrate **1f** with an ester functionality at the α′-position provided product **3f** (69%), which is derived from the protonation of the diazo moiety, followed by the substitution of N_2^+ with water (entry 6). Interestingly, when the *gem*-dimethyl group in **1c** was replaced with a *gem*-diethyl (**1g**) and a *gem*-dipropyl group (**1h**), only triazines **4g** and **4h** were generated, both in 53% yield (entries 7 and 8). Similarly, diethylpropyl-containing substrate **1i** afforded triazine **4i** in slightly lower yield (41%) (entry 9). These outcomes suggest that the formation of tetrazole **2** and 1,2,3-triazine **4** highly depends on the steric effect of the substituent around the reaction center.

These results prompted us to further explore the reactivity and selectivity of other α-azido ketones containing cycloalkyl substituents (Table 2). A variety of α-azido ketones containing a cyclohexyl substituent provided tetrazoles in moderate to good yield. α-Azido ketones **1j** and **1k** containing an α-silyloxy group reacted with LTMSD to provide tetrazoles **2j** and **2k** in 80 and 94% yield, respectively (entries 1 and 2). Similarly,

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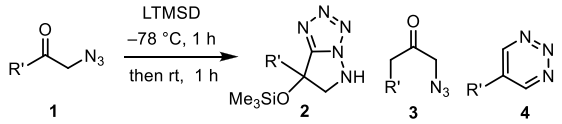
Table 2. Reactions of α-Azido Ketones Containing Cycloalkyl Substituents[a]



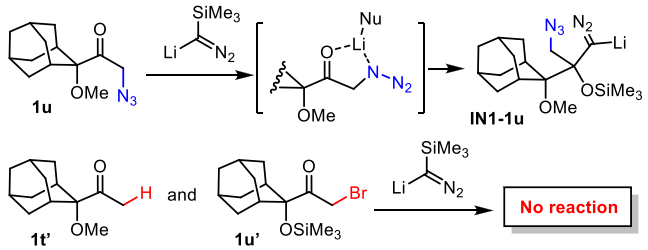
Entry	Ketone	Tetrazole	Homologated	Triazine
1	**1j**, R = $OSiMe_3$	**2j** (80%)		
2	**1k**, R = OTBS	**2k** (94%)		
3[c]	**1l**, R = Ph	**2l** (66%)		
4	**1m**, R = C(H)=C(H)Me	**2m** (62%)		
5	**1n**, R = $CH_2CH_2CH_3$	**2n** (33%)		**4n** (31%)
6[d]	**1o**	**2o** (86%)		
7[e]	**1p**		**3p** (78%)	**4p** (22%)
8	**1q**, R = C(H)=C(H)Me	**2q** (70%)		
9	**1r**, R = $CH_2CH_2CH_3$	**2r** (69%)		
10	**1s**	**2s** (58%)		X-ray structure of **4t**
11	**1t**, R = $OSiMe_3$			**4t** (42%)
12	**1u**, R = OMe			**4u** (44%)

[a]Reaction conditions: trimethylsilyldiazomethane (1.2 equiv), *n*-BuLi (1.3 equiv), azido ketone **1** (1.0 equiv) in THF, under N_2 at −78 °C for 1 h, then rt for 1 h. [b]Isolated yield. [c]2 h. [d]0.5 h. [e]60 °C, 16 h.

tetrazoles **2l** and **2m** also were obtained in 66 and 62% yield, respectively (entries 3 and 4). Although seemingly not significantly different from the others in the series, only ketone **1n** containing a propyl group provided triazine **4n** in 31% yield along with tetrazole **2n** in 33% yield (entry 5). α-Azido ketone **1o** containing an adamantyl group afforded tetrazole **2o** in 86% yield (entry 6), whereas azido cyclopentyl-containing ketone **1p** mainly afforded **3p** (78%), a protonated product of the corresponding intermediate, along with triazine **4p** in 22% yield (entry 7). Also, structurally similar azido ketones **1q** and **1r** provided tetrazoles **2q** and **2r** in 70 and 69% yield (entries 8 and 9). A moderate yield of tetrazole **2s** was generated (58%) from cyclobutyl-containing substrate **1s** (entry 10). Adamantane-based α-silyloxy and α-alkoxy azido ketones **1t** and **1u** provided only triazines **4t** and **4u** in 42 and 44% yield, respectively, without forming the corresponding tetrazoles.

It was found that the α-azido group is crucial for the addition of LTMSD sterically hindered ketones (Scheme 3).

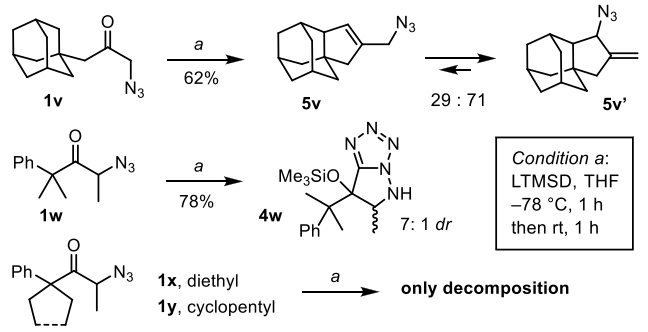
Scheme 3. Activating Role of α-Azido Group for the Carbonyl Addition of a Bulky Nucleophile



The corresponding ketones **1t′** and **1u′** are inert to LTMSD, and these ketones were recovered intact under identical conditions. For α-azido ketones, most likely the lithium-chelated ketone is more active toward the nucleophile, which can overcome the severe steric hindrance, whereas ketones **1t′** and **1u′** do not have this activating mechanism to compensate the steric hindrance.[14] Furthermore, the α-azido group stabilizes the intermediate **IN1** such that in most cases the elimination of $LiOSiMe_3$ from **IN1** is relatively slow compared with the corresponding adduct lacking the azido group.

The effect of structural change was further examined. For example, α-azido ketone **1v** containing a quaternary center at the β-position generated only C−H insertion product **5v**, which is in equilibrium with an allylic transposed azide (Scheme 4). The additional methyl group in **1w** at the carbon

Scheme 4. Effect of Different Substituent Patterns



bearing an azide did not change its reactivity compared with **1c**, providing tetrazole **4w** as a 7:1 mixture of diastereomers. On the contrary, structurally similar ketones **1x** and **1y** only lead to the decomposition of the starting material. These results clearly indicate the importance of the right position and balance of the steric factors on the α,α′-carbons of the ketone for the formation of tetrazoles.[15]

To gain insight into the mechanism for the formation of bicyclic tetrazoles **2** and 1,2,3-triazines **4**, density functional theory (DFT) calculations were carried out.[16] For tetrazole formation, the initial adduct **IN1** rearranges to **IN2**, which can undergo an anionic [3 + 2] dipolar cycloaddition[6c,17] with a relatively low activation barrier (9.4 kcal/mol) via a lithium-ion-chelated transition state **TS2** (Figure 1). The initial cycloadduct **IN3** then rearranges to a more stable aromatic form **IN4**, the protonation of which ultimately leads to

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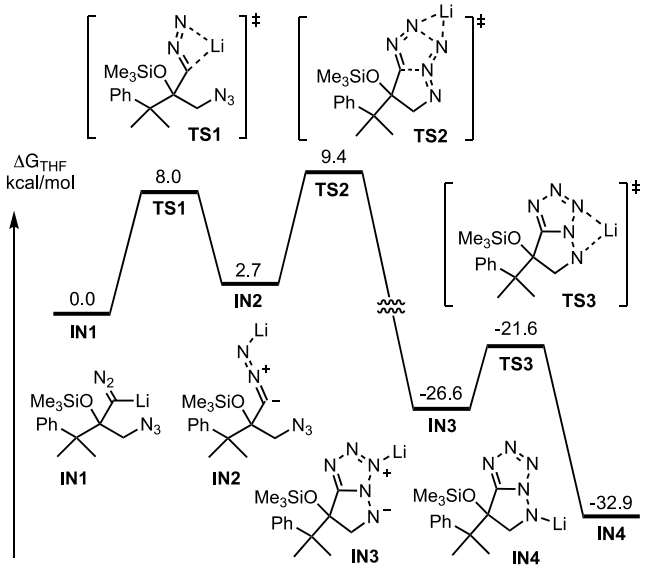

Figure 1. DFT-calculated reaction mechanism for the formation of tetrazole **2c**.

tetrazoles **2**. For the formation of 1,2,3-triazine **4**, it is expected that two different mechanistic pathways are plausible, as shown in Scheme 1.[18]

The calculations show that the C−H insertion pathway from alkylidene carbine **IN5** has a relatively low barrier via **TS4** (3.5 kcal/mol) to generate azido cyclopropene **IN6**, which rearranges to 1,2,3-triazine **4** via **TS5** (Figure 2). Although

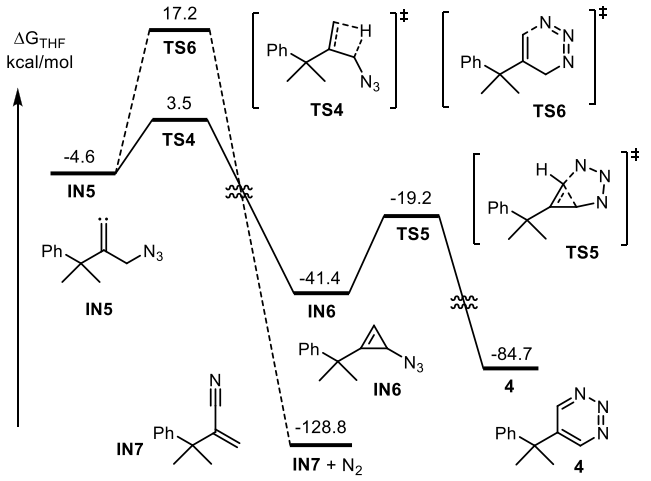

Figure 2. DFT-calculated reaction mechanism for 1,2,3-triazine formation via the C−H insertion pathway.

the activation barrier for this rearrangement is relatively high (22.2 kcal/mol), in most cases, the triazine products formed at room temperature. Unexpectedly, the mechanism involving the interaction between the carbenic carbon and the terminal nitrogen of the azide to form a six-membered ring transition state **TS6** (17.2 kcal/mol) has much higher barrier, which only leads to fragmentation to form product **IN7**.

In conclusion, we have discovered unprecedented reactions to form 1,2,3-triazines via an azido cyclopropene intermediate, followed by its rearrangement, and bicyclic tetrazoles via an anionic [3 + 2] dipolar cycloaddition from a common intermediate derived from lithiated trimethylsilyldiazomethane and α-azido ketones. The selectivity and efficiency for these reactions crucially depend on the hypersensitive steric effect of the substituents on α-azido ketones. DFT calculations show that the formation of tetrazole is the consequence of a facile anionic [3 + 2] dipolar cycloaddition between a lithiated diazo moiety and an azido group, which is due to the chelation of a lithium ion with the nitrogen-based dipole and dipolarophile. DFT calculations also bolster that the formation of 1,2,3-triazines involves an initial C−H bond insertion by the alkylidene carbene at the carbon bearing an azido group to form 3-azidocyclopropenes, which subsequently rearrange to more stable 1,2,3-triazines. The generality of the anionically activated [3 + 2] dipolar cycloaddition of diazo-compound-based dipoles will be further investigated in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04548.

Experimental procedures, characterization data, X-ray crystallographic data, and DFT calculations data (PDF)

Accession Codes

CCDC 1957606 and 1959780 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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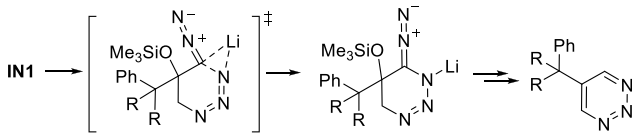

R = Me, 25.6 kcal/mol; R = Et, 27.6 kcal/mol

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