

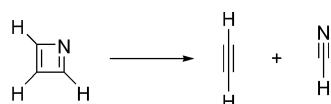
Synthetic Methods

Base-Induced Condensation of α -Chloro Oxime Derivatives Furnishes Alkynes**

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The carbon–carbon triple bond is a fundamental structural unit in natural and unnatural organic molecules. Alkynes also serve as important synthetic intermediates in a number of organic transformations, and their chemistry has recently received particular attention with respect to new materials. The alkynyl linkage is often a key building block in highly conjugated molecules used in light-emitting devices and molecular wires.^[1]

Azacyclobutadiene (azete) is a highly reactive and unstable molecule, the physical properties of which have been investigated experimentally and theoretically.^[2] Although the reaction of an isolable azacyclobutadiene kinetically stabilized by bulky substituents has been reported,^[2d–f] the utility of such compounds in organic synthesis has remained largely unexplored. In particular, azacyclobutadiene is known to undergo [2+2] cycloreversion to provide acetylene and hydrogen cyanide (Scheme 1).^[2b,h] However, no

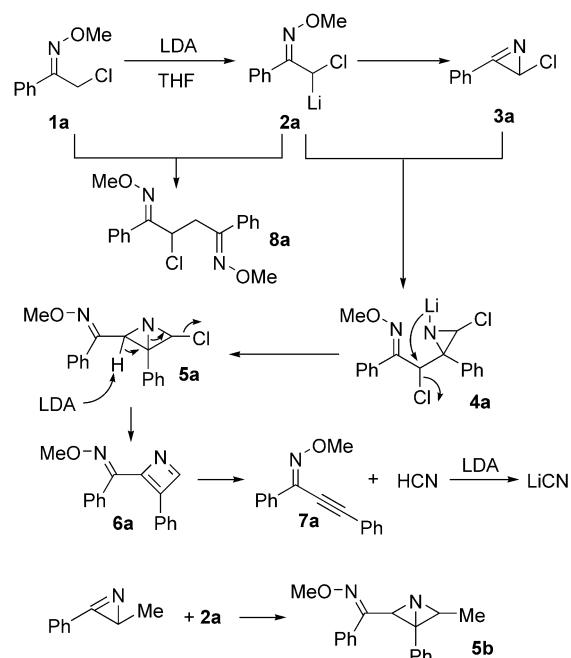


Scheme 1. Fragmentation of azacyclobutadiene.

applications of azacyclobutadienes for the preparation of alkynes have been reported. Here we wish to describe a base-induced novel condensation reaction of α -chloro oxime derivatives to furnish alkynyl oximes via an azacyclobutadiene intermediate.

The reaction of α -chloroacetophenone *O*-methyloxime (**1a**) with 1.1 equiv of lithium diisopropylamide (LDA) afforded 1,3-diphenylpropyn-1-one *O*-methyloxime (**7a**) and 2-chloro-1,4-diphenyl-1,4-butanedione bis(*O*-methyloxime) (**8a**) in yields of 7% and 38%, respectively.^[3] The forma-

tion of **7a** is rationalized by assuming the fragmentation of an intermediate 1-aza-2-chlorobicyclo[1.1.0]butane **5a** (Scheme 2).^[4] Deprotonation of **1a** affords the lithio oxime ether **2a**, which then undergoes Neber-type cyclization to



Scheme 2. Plausible reaction pathway.

provide the highly reactive azirine **3a**.^[5,6] The reaction of **3a** with **2a** affords **4a**, which yields 1-aza-2-chlorobicyclo[1.1.0]butane **5a**. The formation of **5a** is likely because **5b** was isolated in the case of the reaction of **2a** with 2-methyl-3-phenyl-2*H*-azirine. Removal of an α -proton of **5a** with LDA leads to the highly unstable azacyclobutadiene **6a** by ring expansion and elimination of chloride ion. The [2+2] cycloreversion of **6a** yields the alkynyl oxime ether **7a** accompanied by HCN, which is then deprotonated by lithium amide. Consequently, 2.0 equiv of lithium amide are necessary for the reaction. With this in mind, we treated **1a** with 2.2 equiv of lithium diisopropylamide at -78°C and allowed the reaction mixture to warm to room temperature. We obtained **7a** in 76% yield without the formation of **8a** (entry 1 in Table 1).^[7]

We examined the conversion of various α -chloro oxime ethers into alkynyl oxime ethers under the same conditions (Table 1). Oxime ether **1b** provided the corresponding alkynyl oxime ether **7b** in 81% yield, whereas **1c** furnished **7c** in poor yield along with other unidentified products. The low yield was ascribed to the lower stability of the corresponding lithio oxime ether **2**. However, the addition of 0.5 equiv of magnesium bromide increased the yield of **7c** up to 70% yield. A noteworthy observation is the fact that the reaction in the presence of MgBr_2 proceeded even at -78°C , suggesting that magnesium bromide acts as a Lewis acid and accelerates the conversion of **2** into **3**.

In order to verify the reaction mechanism, an additional experiment was performed. When the reaction mixture

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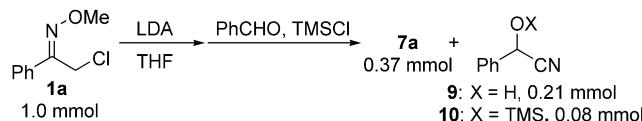
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Table 1: Self-condensation of α -chloro oxime ethers.

Entry	Starting cmpd.	Ar	Cond. ^[a]	Prod.	Yield [%]	Sel. [Z/E]
1	1a	Ph	A	7a	76	>95/5
2	1b	4-MeO-C ₆ H ₄	A	7b	81	>95/5
3	1c	4-Cl-C ₆ H ₄	A	7c	19	>95/5
4	1c	4-Cl-C ₆ H ₄	B	7c	70	95/5
5	1d	4-Br-C ₆ H ₄	B	7d	65	94/6
6	1e	2-naphthyl	C	7e	67	>95/5

[a] Conditions: A: LDA (2.2 equiv), -78°C to room temperature; B: LDA (2.5 equiv), MgBr₂ (0.5 equiv), -78°C , 3 h; C: same conditions as B, but -78°C to room temperature.

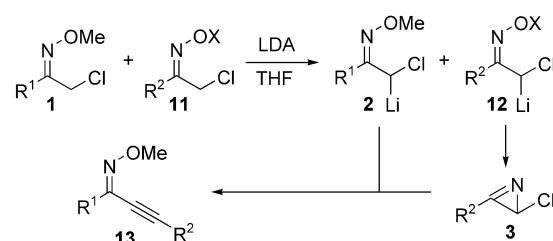
derived from **1a** in the absence of MgBr₂ was treated with benzaldehyde and TMSCl, mandelonitrile (**9**) and its silylated product **10** were obtained along with **7a** (Scheme 3). This supports the generation of HCN from the fragmentation of **6a**.



Scheme 3. Trapping of HCN with an aldehyde. TMS = trimethylsilyl.

Next, we attempted to perform a cross-condensation reaction. The reaction of **2** with 2-halo-2*H*-azirine **3** would furnish alkynyl oxime ethers. Although the synthesis of azirines has been extensively explored, there are very few reports on the synthesis of haloazirine **3**.^[8] The reaction of chlorine azide with chloroalkenes followed by elimination of hydrogen chlorides yields the corresponding chlorovinylazides, which can be converted into chloroazirines. However, not only is this complicated synthetic route inconvenient but also haloazirines are unstable (e.g., 2-chloro-3-ethyl-2-methyl-2*H*-azirine rearranges into 2-chloro-2-ethyl-3-methyl-2*H*-azirine).^[8c] We therefore turned our attention towards a preparation of haloazirines *in situ* (Scheme 4).

Deprotonation of **1** and **11**, which possesses a good leaving group on the nitrogen atom,



Scheme 4. Cross-condensation of oxime derivatives.

affords **2** and **12**, respectively. If the cyclization of **12** proceeds much faster than that of **2**, haloazirine **3** is selectively generated and then reacts with **2** to furnish alkynyl oxime ether **13**. With this working hypothesis, we examined the reaction of various imines derived from α -chloroacetophenone.

After screening a series of leaving groups, we found that oxime *p*-toluenesulfonate (X = Ts, **14**) and ethoxycarbonate (X = EtOCO, **15**) are both good partners with oxime methyl ether **1** in this cross-condensation.^[9] It is noteworthy that the cross-condensation reaction proceeded even at -78°C , whereas homocondensation did not occur without magnesium bromide at -78°C . Furthermore, no homocondensation product was obtained in any reaction.

With the cross-condensation protocol in hand, we synthesized a variety of alkynyl oxime ethers (Table 2). Several observations are worth noting: 1) Alkyl-substituted α -chloro oxime ethers **1h-j**, which have α -protons on both sides, afforded the corresponding products in moderate to good yields (entries 9–12). 2) The use of **14j** with R² = Me afforded none of the desired product. 3) The initial stereochemistry of

Table 2: Cross-condensation of α -chloro oxime derivatives.

Entry	1, R ¹	14 or 15, R ² ^[a]	Prod.	Yield [%]	Sel. [Z/E]
1	1a, Ph	14c, 4-Cl-C ₆ H ₄	13ac	73	94/6
2	1a, Ph	15l, iPr	13al	63	>95/5
3	1a, Ph	14j, Me (Z/E = 88/12)	–	–	–
4	1b, 4-MeO-C ₆ H ₄	14a, Ph	13ba	68	>95/5
5	1c, 4-Cl-C ₆ H ₄	14a, Ph	13ca	65	>95/5
6	1c, 4-Cl-C ₆ H ₄	15a, Ph	13ca	63	>95/5
7	1f, Ph- <i>CH</i> =	15a, Ph	13fa	54	84/16
8 ^[b]	1g, <i>t</i> Bu	14a, Ph	13ga	63	62/38
9	1h, <i>c</i> -C ₅ H ₉	14a, Ph	13ha	73	>95/5
10	1i, <i>n</i> -C ₈ H ₁₇	14a, Ph	13ia	69	>95/5
11	1i, <i>n</i> -C ₈ H ₁₇	15l, iPr (Z/E = 57/43)	13il	74	>95/5
12	1j, Me	14a, Ph	13ja	57	>95/5
13	1k,	15a, Ph	13ka	40	ca. 1/4

[a] Configuration of **14** and **15** is Z/E = >95/5 except for entries 3 and 11. [b] Reaction temperature -78°C to room temperature.

the oxime carbonates does not have a significant effect on the reaction (entries 2 and 11).^[10]

In conclusion, we have achieved a facile synthesis of alkynyl oxime ethers from α -chloro oxime derivatives with lithium diisopropylamide. This reaction probably involves azacyclobutadienes as a key intermediate. Further efforts to verify the reaction mechanism and develop applications of this highly reactive heterocycle are currently under way in our laboratory.

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Keywords: alkynes · nitrogen heterocycles · oximes · small ring systems

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- [9] The corresponding oxime methanesulfonate and benzoate provided **13ca** in yields of 38% and 51%, respectively.
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