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Exploring the Anionic Reactivity of Ynimines, Useful Precursors of Metalated Ketenimines

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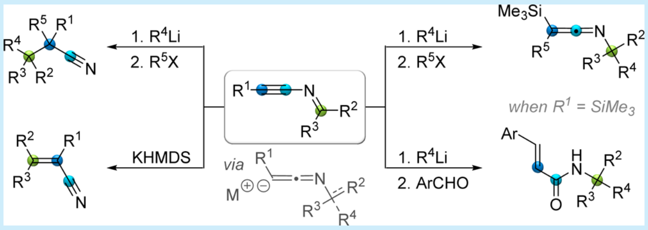
Supporting Information

ABSTRACT: Insights into the reactivity of ynimines under anionic conditions are reported. They were shown to be excellent precursors of metalated ketenimines, which can be generated in situ by the reaction of ynimines with organolithium reagents or strong bases. The metalated ketenimines can then be trapped with various electrophiles and, depending on their substitution pattern, afford original and divergent entries to various building blocks.



Due to the development of efficient methods for their synthesis,[1] ynamides **2**, stable surrogates of the more labile ynamines **1**, have recently emerged as remarkably useful and versatile building blocks in organic synthesis (Figure 1).[2]

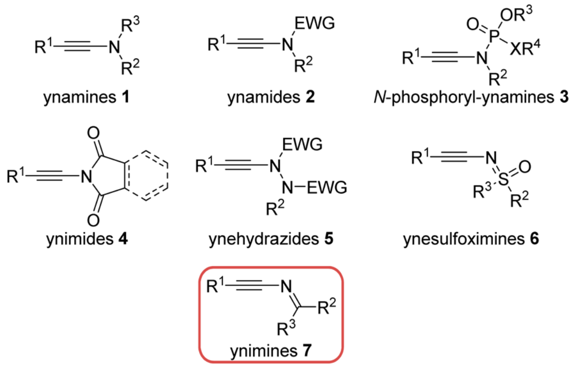


Figure 1. Ynamines, ynamides, ynimines, and other stabilized ynamines.

Their availability combined with their stability and unique reactivity has attracted the interest of an ever-increasing number of research groups. These building blocks have indeed been used for the design and development of an impressive number of original and efficient transformations including, among others, cycloadditions, cycloisomerizations, metal-catalyzed cyclizations, reductive couplings, radical transformations, ring-closing metathesis, and sigmatropic rearrangements.[2] They have also been shown to be excellent substrates in natural product synthesis,[3] a field in which the use of ynamides enabled the emergence of original bond disconnections[4] and heterocyclic chemistry.[5] In addition, the combination of the polarization of the triple bond due to the presence of the nitrogen atom and the possibility to use the electron-withdrawing group as a directing group makes them ideal substrates in anionic chemistry. In this context, the inter-/intramolecular carbocupration, carbolithiation, and carbozincation of ynamides were recently shown to proceed with high levels of selectivity and to provide useful entries to quaternary centers containing aldol products,[6] polysubstituted enamides,[7] 1,4-dihydropyridines,[8] pyridines,[8] and indoles,[9] while an Ireland–Claisen rearrangement from ynamides provided an efficient access to highly functionalized allenamides[10] and aminodienes.[11]

Besides these developments, new classes of ynamides have also emerged such as *N*-phosphoryl-ynamines **3**,[12] ynimides **4**,[13] ynehydrazides **5**,[14] ynesulfoximines **6**,[15] and ynimines **7**[16] (Figure 1). The development of these new ynamine surrogates clearly offers new perspectives in the chemistry of ynamides. For this reason, we recently became interested in the reactivity of ynimines **7**, compounds which have been only scarcely studied and whose use in organic synthesis is still rather limited,[16a,17] most certainly due to the lack of general methods for their preparation. These building blocks, which can now be readily prepared either by a copper-catalyzed alkynylation of imines with terminal alkynes[16a] or by their oxidative cross-coupling with copper acetylides,[16b] possess a remarkable

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sequence of six consecutive reactive sites including nucleophilic/basic, electrophilic, and acidic positions (Figure 2).

Figure 2. Schematic overview of the reactivity of ynimines.

Provided that the reactivity of ynimines can be finely controlled, they should therefore behave as remarkably useful and versatile building blocks, especially in anionic chemistry. We indeed report in this manuscript that, upon reaction with organolithium reagents or strong bases, ynimines are readily transformed into a wide array of products including alkanenitriles, alkenenitriles, ketenimines, and *α*,*β*-unsaturated amides.

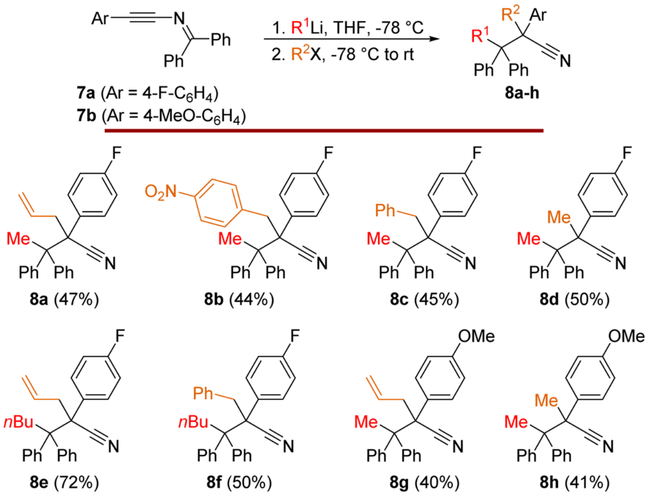
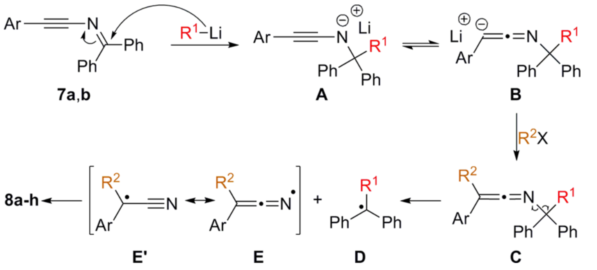


Figure 3. Reaction with alkyllithiums: from ynimines to alkanenitriles via ketenimines.

We started our investigations on the reactivity of ynimines under anionic conditions by examining the outcome of the reaction between non-enolizable benzophenone-derived ynimines **7a**,**b** and organolithium reagents (Figure 3). These reagents could potentially either perform a carbolithiation of the triple bond[18] or add to the imine moiety to generate lithiated enamines or ynamines, respectively, the latter being potentially in equilibrium with the corresponding lithiated ketenimine, compounds that could all be trapped by an appropriate electrophile. Ynimine **7a** was therefore reacted with 1 equiv of methyllithium in THF at −78 °C followed by the addition of allyl bromide and furnished, to our surprise, the corresponding alkanenitrile **8a** which could be isolated in 47% yield. The nature of this unexpected rearranged product could be confirmed by replacing allyl bromide with *p*-nitrobenzyl bromide, which gave the corresponding adduct **8b** whose structure could be elucidated by X-ray diffraction analysis. Benzyl bromide and iodomethane were found to be equally efficient terminal electrophiles and gave the corresponding nitriles **8c** and **8d** in fair yields. Methyllithium could in addition be replaced by *n*-butyllithium with similar efficiency (**8e**,**f**), and electron-rich ynimine **7b** was also found to be a suitable substrate. In all cases, the one-pot sequence gave the corresponding nitriles possessing two consecutive quaternary carbon atoms from readily available ynimines with reasonable efficiency. Interestingly, no other products resulting from competitive dimerization of the starting ynimines[16a,19] or carbolithiation were observed.

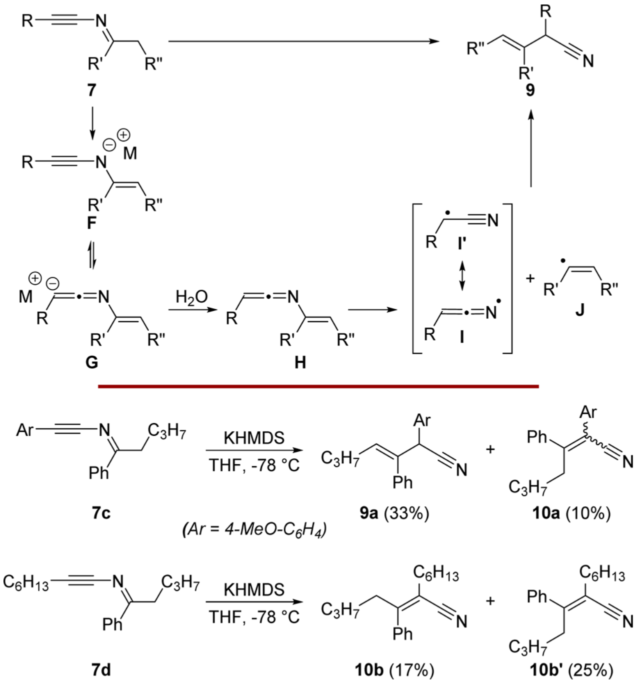
Scheme 1. Possible Mechanism for the Transformation of Ynimines to Alkanenitriles



A possible mechanism that accounts for this transformation is shown in Scheme 1. Addition of the organolithium reagent to the starting ynimine **7** would provide a lithiated ynamine **A**, which would be in equilibrium with the lithiated ketenimine form **B**. Trapping this intermediate with the electrophile would afford a transient unstable ketenimine **C** which would then rearrange, as previously documented from related ketenimines,[20] via a radical pathway involving radical intermediates **D** and **E**/**E′**,[21] to the corresponding nitrile **8**.[22,23] In this case, the generation of a stabilized benzhydryl radical **D** would account for the rapid rearrangement of **C** to **8**.

Based on these results, we envisioned that *N*-vinyl-metalated ketenimines **G** (Scheme 2) analogous to **B** might be obtained by deprotonation starting from enolizable ynimines **7** instead of addition of an organolithium reagent to the imine moiety. Upon protonation, a transient *N*-vinyl-ketenimine **H** would be

Scheme 2. Generation of Metalated *N*-Vinyl-Ketenimines by Deprotonation of Ynimines and Their in Situ Transformation to Allylic/Vinylic Nitriles



formed that should then rearrange to allylic nitriles **9**. To test this hypothesis, ynimine **7c** was treated with KHMDS, which was found to be more efficient than LiHMDS, in THF at −78 °C followed by hydrolysis. To our delight, the expected allylic nitrile **9a**[24] could be isolated, although with a modest yield (33%), from the reaction mixture along with conjugated nitrile **10a** resulting from the isomerization of **9a**. This isomerization was found to be complete starting from ynimine **7d** which gave a mixture of diasteroisomeric conjugated nitriles **10b**[24] and **10b′**[24] resulting from a deprotonation/isomerization/hydrolysis/rearrangement/isomerization sequence.

In order to block the radical rearrangement of the intermediate ketenimines, we next envisioned stabilizing both these ketenimines and their metalated form by incorporating a silicon substituent at the terminal carbon atom. Silylated ynimine **7e** was therefore successively reacted with various alkyllithium reagents and electrophiles under the standard reaction conditions used for the formation of alkanenitriles (Scheme 1). The presence of the silyl substituent indeed strongly modified the reactivity since stable ketenimines **11a–f**[25,26] could now be isolated in good to excellent yields without the need for any purification (Figure 4).[27] Methyllithium and *n*-butyllithium gave similar results for these reactions, and the intermediate lithiated ketenimines could be conveniently trapped with a variety of electrophiles including allyl, benzyl, *p*-nitrobenzyl bromides and methyl iodide. Compared to other methods for the synthesis of ketenimines, which typically involve an elimination from imidoyl halides, a Staudinger aza-Wittig reaction, or an isonitrile-based process,[28] our sequence, which is however limited to the preparation of silylated ketenimines, provides a useful entry to these building blocks.

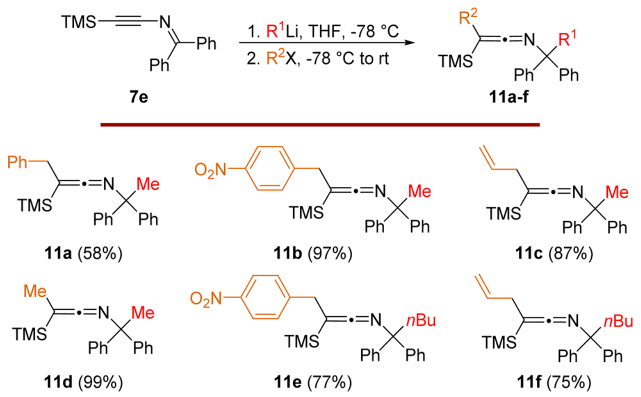


Figure 4. Synthesis of stable ketenimines from silylated ynimines.

To bring these studies one step further and in order to fully exploit the presence of the trimethylsilyl group, we finally evaluated the possibility of trapping the intermediate lithiated silylketenimines **K** (Figure 5) with aromatic aldehydes. The nucleophilic addition of **K** to these aldehydes should indeed allow for the formation of α-alkoxysilylketenimines **L**, which could potentially evolve through either a [1,3]-Brook rearrangement, a nucleophilic addition of the alkoxide to the central carbon atom of the ketenimine moiety, or a Peterson-type olefination. The latter, which was found to be operative in our case, would yield to [3]-azacumulene **M**[29] which, upon hydrolysis, would generate α,β-unsaturated amides **12**. As shown by results summarized in Figure 5, ynimine **7e** could indeed be transformed to conjugated amides **12a–d** upon reaction with 1 equiv of an organolithium reagent in THF at −78 °C followed by reaction with an aldehyde and warming the reaction mixture to room temperature. These results, which further demonstrate the synthetic utility of ynimines as precursors of metalated ketenimines—compounds which can hardly be generated using other methods—also represent the first examples of a Perterson olefination yielding to [3]-azacumulenes.

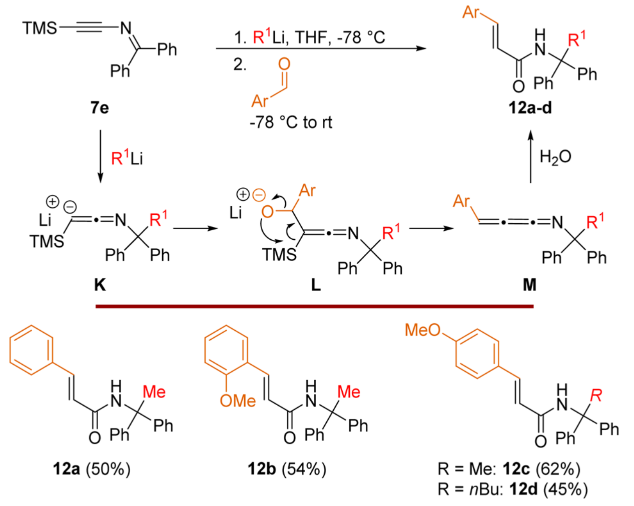


Figure 5. Synthesis of α,β-unsaturated amides from silylated ynimines.

In conclusion, we have shown that ynimines, compounds that are readily prepared by direct alkynylation of imines with terminal alkynes or copper acetylides, are excellent precursors of metalated ketenimines. They can be generated in situ by the reaction of ynimines with organolithium reagents or strong bases and trapped with various electrophiles including water, alkyl iodides, allyl/benzyl bromides, and aldehydes. Substitution of the triple bond in the starting ynimines by alkyl or aryl groups allow for the formation of unstable ketenimines which spontaneously rearrange to highly substituted saturated and unsaturated nitriles. In sharp contrast, a dramatic change in reactivity was observed starting from silyl-substituted ynimines which, upon transformation to the corresponding lithiated ketenimines, afford stable silylketenimines or conjugated amides upon reaction with alkyl halides and aldehydes, respectively.

Altogether, these results bring useful insights into the reactivity of ynimines under anionic conditions and further expand the synthetic utility of these underrated building blocks.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and cif files for compounds **8b** and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) The configuration of the alkenes in **9a**, **10b**,**b′** was demonstrated by NOESY experiments. See the Supporting Information for details.

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