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Base-Mediated Generation of Ketenimines from Ynamides: Addition of Hydrazones to Give Acetimidohydrazides**

Capucine Mahe,^[a, b] Agathe C. A. D'Hollander,^[b] and Kevin Cariou^{*[a]}

Under basic conditions, *N*-arylketenimines were generated *in situ* from *N*-Boc ynamides and reacted with various hydrazones. Under heating, an addition of the deprotonated

hydrazone onto the central carbon of the ketenimines takes place giving rise to various acetimidohydrazides.

Introduction

Ketenimines are the imino analogues of ketenes and, similarly, are highly reactive substrates, which often require the need to be formed *in situ* before reacting.^[1–3] One of the most widely used approach to generate ketenimines involves the combination of a sulfonylazide (such as tosylazide) and an alkyne, under copper catalysis,^[4,5] akin to azide-alkyne cycloaddition conditions (Scheme 1a).^[6] For our part, we have recently explored the conversion of an ynamide^[7–14] into a ketenimine^[15] (including unsubstituted ones) and showed that they could be trapped by heterocyclic nucleophiles^[16] or undergo cycloaddition reactions with imines^[17] (Scheme 1b) and azallylanions (Scheme 1c).^[18] In this latter example, the basic reaction conditions served to generate both the ketenimine **2** and the aza-allyl anion **4** from the ynamide **1** and the imine **3**, respectively. Under microwave heating, the cycloaddition took place, giving rise to a series of 5-membered heterocycles. These results prompted us to explore the implementation of this strategy to trigger reactions with heterodipoles such as nitrones or hydrazones. Only few examples of [3+2] cycloadditions between *N*-sulfonylketenimines (generated using copper catalysis) with heterodipoles such as, hydrazones^[19] or nitrones^[20] have been reported.

Results and Discussion

We thus undertook the exploration of the reactivity of *N*-Boc ynamides **1** as ketenimines precursor in the presence of various heterodipoles (Scheme 1d). We started our study with ynamide **1a** (Ar=Ph and R=H) but, whatever the conditions employed

(see SI for details), no identifiable adduct could be observed when the reaction was attempted with either nitron **5** or *N*-Ts- and *N*-Ac-hydrazones **6a** and **6b**, respectively (Scheme 2). The heterodipole generally did not react or decomposed if the conditions were too harsh (100 °C, long reaction times), while the ketenimines seemed to be generated, as evidenced by the characterization of its adduct with dimethylamine coming from DMF.^[18]

These disappointing results led us to reconsider our design. While we had chosen an electron poor (4-Cl-C₆H₄) aryl on the electrophilic moiety of the heterodipole, we had not fully considered the relative lack of nucleophilicity of the other moiety. We thus turned our attention to *N*-aryl rather than *N*-tosyl or *N*-acyl-hydrazones. Reacting equimolar amounts of hydrazone **6c** and ynamide **1a** at room temperature in DMF with 3 equivalents of *t*-BuOLi for 18 h allowed the formation of acetimidohydrazide **7ac** in 30% yield (Table 1, entry 1). The formation of this type of addition products had previously been reported using the copper-catalyzed generation of *N*-sulfonylketenimines.^[21–23] Further cyclization to a five-membered heteroaromatic derivative was only possible in a latter step using a Zn(II) catalyst and a stoichiometric amount of oxidant.^[21] As only the addition took place, a substoichiometric amount of Lewis acid (ZnOAc₂) was added, hoping it would improve the yield of the reaction^[17] and/or trigger the cyclization^[21] of **7ac**, but no improvement were observed. On the contrary, after prolonged reaction time, decomposition of the reagents occurred (Entry 2). Raising the temperature to 100 °C using a microwave heating for 1 h did increase the yield to 55%, despite an incomplete conversion of the ynamide (Entry 3). Quite logically, increasing the amount of ynamide **1a** (Entries 4 and 5) did not have a positive effect on the outcome. However, increasing the amount of hydrazone **6c** (and base) led to the formation of **7ac** in 68% yield (Entry 6). This was further improved by running the reaction at 80 °C, and 86% of **7ac** were isolated (Entry 7). Changing the ratio of reagents (Entry 8, 10), adding 10 mol% of ZnOAc₂ (Entry 9) or diminishing the amount of base (Entry 11) only had a detrimental effect on the reaction, which still proceed to give 63–76% yield of **7ac**.

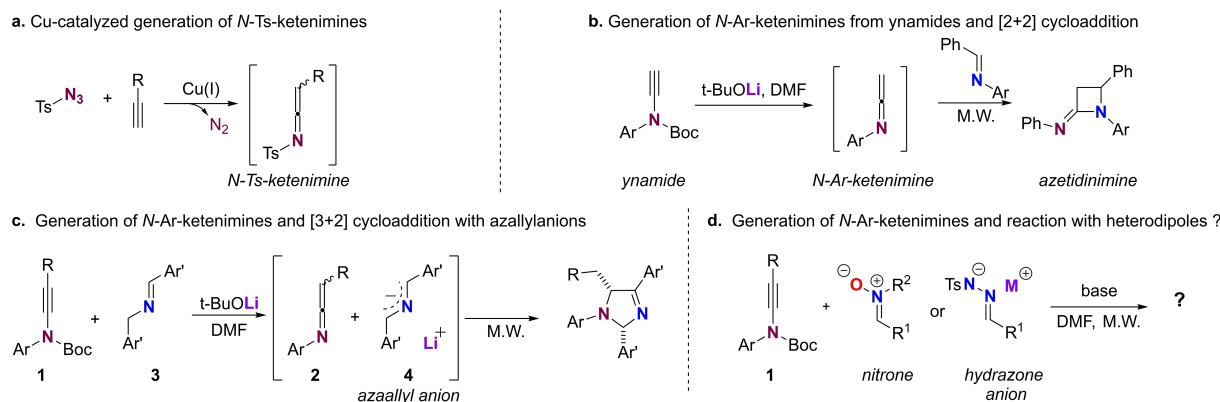
Having determined the optimal reaction conditions, the scope of this transformation was then explored (Scheme 3). The first variations were brought to the ynamide partner. A chloride, a methoxy group or an iodide at the *para* position of the aryl

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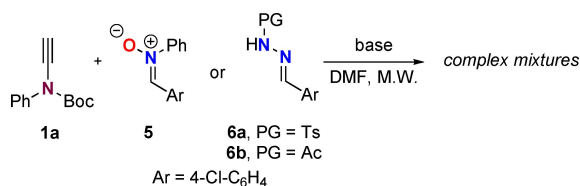
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Scheme 1. Copper(I)-catalyzed formation of ketenimines (a) vs. generation of *N*-Ar-ketenimines from ynamides (b); [3+2] cycloaddition with azallylanions (c) and objectives of the study (d).



Scheme 2. First attempts with nitrones and tosylhydrazones.

ring **Ar** were well tolerated and the addition products **7bc–7dc** were isolated in 94%, 76% and 54% yield, respectively. Electron-withdrawing groups (CF₃ and NO₂), however, only led to complex mixtures, presumably because of the destabilization of the ketenimine intermediate. Ynamides bearing a bulky group (TIPS) or an aromatic (Ph) on the triple bond did not react, but an alkyl chain was well tolerated and **7ec** (R = *n*-Bu) was obtained in 86% yield. Good yields were also obtained for a cyclopropyl-substituted ynamide (**7fc**, 58%). However, **7gc**, bearing a protected ethoxy moiety, could only be isolated in 11% yield, despite the use of a robust *tert*-butyldiphenylsilyl

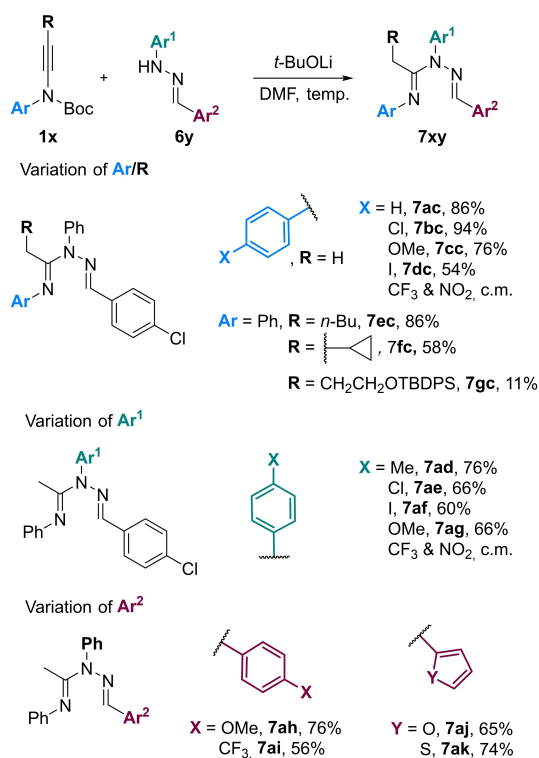
protecting group. Various 4-chloro-benzaldehyde-derived *N*-arylhydrazones were then reacted with ynamide **1a**. Again, strong electron-withdrawing groups (CF₃ and NO₂) were not compatible with the reaction conditions, but the adducts bearing an alkyl (**7ad**), a halogen (**7ae**, **7af**) or an alkoxy (**7ag**) *para* substituent on the *N*-phenyl ring **Ar**¹ were isolated in good yields (60–76%). Finally, several examples of aniline-derived hydrazones with diverse **Ar**² groups were reacted with **1a**. Phenyl, 4-anisyl (EDG), 4-trifluoromethanophenyl (EWG) as well as furanyl and thiophenyl rings (heteroaromatics) were found to be suitable for the reaction to proceed and yielded the corresponding acetimidohydrazides **7ah–7ak**.

Despite many trials, with various Lewis acids and in the presence or absence of oxidants,^[21] the cyclization of adducts **7** into the corresponding pyrazoles was never observed. Nevertheless, it was possible to further derivatize these acetimidohydrazide, for example through a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction, to obtain biaryl **8** in 78% yield (Scheme 4).

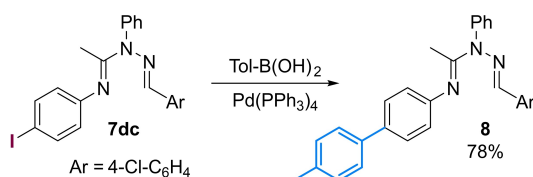
Table 1. Optimization of the reaction conditions.

Entry	equiv. 1a / equiv. 6c	t-BuOLi (equiv.)	Additive	Solvent (0.2 M)	Time	Temp.	Yield 7ac [%] ^[a]
1	1:1	3.0	none	DMF	18 h	R.T.	30 ^[b]
2	1:1	3.0	Zn(OAc) ₂ (10 mol %)	DMF	18 h	R.T.	c. m. ^[b]
3	1:1	3.0	none	DMF	1 h	100 °C	55 ^[b]
4	1.5:1	3.5	none	DMF	1 h	100 °C	49 ^[b]
5	1.5:1	4.0	none	DMF	1 h	100 °C	55 ^[b]
6	1:2	4.0	none	DMF	1 h	100 °C	68
7	1:2	4.0	none	DMF	1 h	80 °C	86
8	1:1	4.0	none	DMF	1 h	80 °C	65 ^[b]
9	1:1	4.0	Zn(OAc) ₂ (10 mol %)	DMF	1 h	80 °C	63 ^[b]
10	2:1	4.0	none	DMF	1 h	80 °C	65
11	1:1	3.5	none	DMF	1 h	80 °C	76

[a] Isolated yields. [b] The conversion of **1a** was incomplete; c.m. = complex mixture.



Scheme 3. Scope of the reaction.



Scheme 4. Suzuki-Miyaura cross-coupling.

Conclusion

Overall, we have been able to further explore the reactivity of ketenimines generated from ynamides, by reacting them with various heterodipoles. While nitrones and EWG-substituted hydrazones were found to be incompatible with the reaction conditions, *N*-arylhya-zones were suitable reacting partners. This led to the formation of diversely substituted acetimidohydrazides in good to excellent yields. We believe these nitrogen-rich building blocks could find applications in coordination chemistry or medicinal chemistry, considering the various uses of hydrazones in these fields.^[24,25]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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