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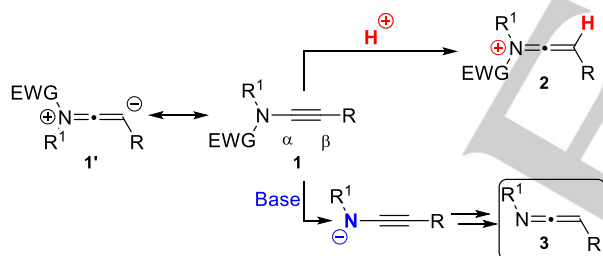
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Base-Mediated Generation of Ketenimines from Ynamides: Direct Access to Azetidinemines by an Imino Staudinger Synthesis

Eugénie Romero, Corinne Minard, Mohamed Benchekroun,[†] Sandrine Ventre,[†] Pascal Retailleau, Robert H. Dodd,* Kevin Cariou*

Abstract: Ynamides were used as precursors for the *in situ* generation of highly reactive ketenimines which could be trapped with imines in a [2+2] cycloaddition. This imino Staudinger synthesis led to a variety of imino-analogs « β -lactams, namely azetidinemines (20 examples), that could be further functionalized through a broad range of transformations.

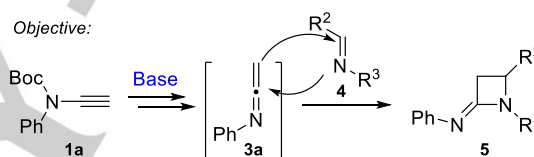
Ynamides (**1**) are versatile nitrogen-containing building blocks composed of an acetylene moiety directly attached to a nitrogen atom that generally bears at least one electron-withdrawing group that stabilizes the molecules.¹ The strong inherent polarization of the triple bond, that can be visualized by drawing the main mesomeric form **1'** generally drives their reactivity towards nucleophilic addition on the β position and reactions with electrophiles at the α position.¹ This trend can be further enhanced by acid activation, since protonation of the substrate yields keteniminium **2** (Scheme 1).²



Scheme 1. Ynamides: Inherent Polarization vs Acid and Base Activations

For our part, we have shown that using strongly basic conditions³ an unprecedented nucleophilic addition of various heteroarenes at the β position could take place.⁴ Moreover, depending on the substitution pattern of the nitrogen atom, the same basic conditions could lead to the loss of the electron-withdrawing group (EWG). In this latter case, base activation would trigger the cleavage of the EWG, leading to an amide that will eventually evolve towards ketenimine **3**.^{4,5}

In order to further expand the potential of this highly reactive intermediate (**3**), we sought to trap it in a [2+2] cycloaddition.⁶ By analogy with the well-established Staudinger synthesis of β -lactams,⁷ and based on the pioneering studies by Ghosez⁸ and Regitz,⁹ we envisioned that the *N*-phenylethenimine **3a** generated *in situ* from ynamide **1a** would be sufficiently electrophilic to react with imine **4** to ultimately give azetidimine **5** (Scheme 2).¹⁰ From our previous experience, an unsubstituted *N,N*-Boc-aryl-ynamide would be the best precursor for the generation of the ketenimine and we assumed an electron-rich nitrogen atom in the imine would favor the desired cycloaddition.



Scheme 2. *In situ* Generation of an Ethenimine and Trapping with an Imine

However, direct application of our previously disclosed reaction conditions⁴, i.e., 1.0 equiv. of ynamide, 1.0 equiv. of *t*-BuONa as base, DMF as solvent, with molecular sieves at room temperature proved totally ineffective, even after prolonged reaction time (Table 1, entry 1). We reasoned that the cycloaddition process required thermal activation and thus, while traditional heating (entry 2) was unsuccessful, switching to microwave conditions¹¹ allowed the reaction to take place (entry 3). By replacing the sodium salt by potassium (entry 4) or lithium (entry 5) *t*-butanolate the desired azetidimine **5aa** could be isolated with 46% and 47% yield, respectively. Doubling the amount of both the ynamide and the base ($X = 2$) had little effect (entry 6) unless the temperature was raised to 100 °C (entry 7) which allowed **5aa** to be isolated in 50% yield. This 50% threshold could be overcome by using silica gel as the additive instead of molecular sieves (entry 8, 54%). These optimized conditions were then applied to *p*-chlorobenzaldehyde-derived imine **4b** which led to the isolation of 64% of azetidimine **5ab** (entry 9). Improved formation of the latter was attempted by using a catalytic amount of a Lewis acid as the additive (entry 10, 50%) or as a co-additive (entry 11, 52%) but to no avail.

Having determined the optimal reaction conditions, we then explored the scope of this cycloaddition (Table 2). First, the influence of the substituents on the imine partners was assayed. Unsubstituted diphenyl aldimine **4c** allowed formation of the corresponding azetidimine **5ac** in only 22% yield (entry 3).

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Table 1. Optimization of the [2+2] Cycloaddition between Ynamide **1a** and Imines **4a,b**.^a

1a, X equiv. + **4a**, Ar = Ph / **4b**, Ar = *p*-ClC₆H₄ → **5aa**, Ar = Ph / **5ab**, Ar = *p*-ClC₆H₄ (PMP = *p*-methoxyphenyl)

Entry	X	4	Base	Additive	Time	Heating	Yield, 5
1	1	4a	<i>t</i> -BuONa	M. S.	24 h	RT	0%
2	1	4a	<i>t</i> -BuONa	M. S.	24 h	60 °C	Traces
3	1	4a	<i>t</i> -BuONa	M. S.	1 h	80 °C μW	20% conv.
4	1	4a	<i>t</i> -BuOK	M. S.	1 h	80 °C μW	46%, 5aa
5	1	4a	<i>t</i> -BuOLi	M. S.	1 h	80 °C μW	47%, 5aa
6	2	4a	<i>t</i> -BuOK	M. S.	1 h	80 °C μW	45%, 5aa
7	2	4a	<i>t</i> -BuOLi	M. S.	1 h	100 °C μW	50%, 5aa
8	2	4a	<i>t</i> -BuOLi	SiO ₂ (1 equiv.)	1 h	100 °C μW	54%, 5aa
9	2	4b	<i>t</i> -BuOLi	SiO ₂ (1 equiv.)	1 h	100 °C μW	64%, 5ab
10	2	4b	<i>t</i> -BuOLi ^[b]	ZnOTf (10 mol%)	1 h	100 °C μW	50%, 5ab
11	2	4b	<i>t</i> -BuOLi ^[b]	SiO ₂ (1 equiv.) + ZnOTf (10 mol%)	1 h	100 °C μW	52%, 5ab

[a] Isolated yields. [b] A 2.2 M solution of *t*-BuOLi in THF was used.

This result appears consistent with the positive effect of having an electron-donating group on the nitrogen (entries 1,2) and an electron-poor aryl group on the carbon of the imine partner (entry 2). Imines derived from *meta*- (**4d**) and *ortho*-anisidine (**4e**)

were then reacted with ynamide **1a**, providing cycloadducts **5ad** and **5ae** in 26% and 37% yields, respectively (entries 4,5). These yield variations can be accounted for by standard electronic (*meta* vs. *para/ortho*) and steric (*ortho* vs. *para*) effects.

Table 2. Scope and limitations of the [2+2] Cycloaddition with Ynamides **1** and Imines **4**.^[a]

a. Scope :

1, 2.0 equiv. + **4** → **5**

b. Unreactive Ynamides :

PG = Ts, Ms, Ns R = Bn, allyl R' = Ph, *n*-Bu, TIPS

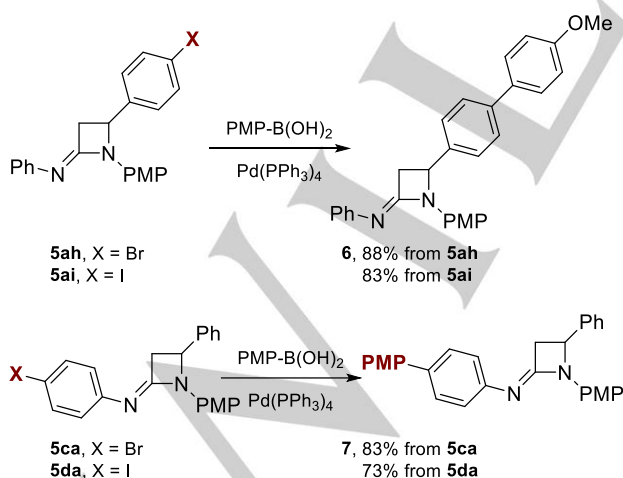
Entry	Ar, 1	Ar ² , Ar ³ , 4	Yield, 5 ^a
1	Ph, 1a	Ph, 4-MeO-C ₆ H ₄ , 4a	54%, 5aa ^{[b][c]}
2	Ph, 1a	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	64%, 5ab ^[b]
3	Ph, 1a	Ph, Ph, 4c	22%, 5ac ^[d]
4	Ph, 1a	4-Cl-C ₆ H ₄ , 3-MeO-C ₆ H ₄ , 4d	26%, 5ad ^[d]
5	Ph, 1a	4-Cl-C ₆ H ₄ , 2-MeO-C ₆ H ₄ , 4e	37%, 5ae ^[d]
6	Ph, 1a	Ph, 3,4,5-triMeO-C ₆ H ₄ , 4f	54%, 5af ^[b]
7	Ph, 1a	4-MeO-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4g	40%, 5ag ^[b]
8	Ph, 1a	4-Br-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4h	63%, 5ah
9	Ph, 1a	4-I-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4i	61%, 5ai ^[c]
10	Ph, 1a	4-MeO ₂ C-C ₆ H ₄ , Ph, 4j	4%, 5aj + 26%, 5aj ^[d]
11	4-Cl-C ₆ H ₄ , 1b	Ph, 4-MeO-C ₆ H ₄ , 4a	10%, 5ba ^[c]
12	4-Cl-C ₆ H ₄ , 1b	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	29%, 5bb
13	4-Br-C ₆ H ₄ , 1c	Ph, 4-MeO-C ₆ H ₄ , 4a	11%, 5ca
14	4-Br-C ₆ H ₄ , 1c	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	40%, 5cb
15	4-I-C ₆ H ₄ , 1d	Ph, 4-MeO-C ₆ H ₄ , 4a	10%, 5da
16	4-I-C ₆ H ₄ , 1d	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	29%, 5db
17	4-CF ₃ -C ₆ H ₄ , 1e	Ph, 4-MeO-C ₆ H ₄ , 4a	36%, 5ea
18	4-CF ₃ -C ₆ H ₄ , 1e	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	36%, 5eb
19	4-MeO-C ₆ H ₄ , 1f	Ph, 4-MeO-C ₆ H ₄ , 4a	22%, 5fa ^[c]
20	4-MeO-C ₆ H ₄ , 1f	4-Cl-C ₆ H ₄ , 4-MeO-C ₆ H ₄ , 4b	35%, 5fb

[a] Isolated yields, using a 2.2 M solution of *t*-BuOLi in THF. [b] Solid *t*-BuOLi was used. [c] An X-ray structure was obtained, see Supporting Information for details.¹² [d] 10 mol% of ZnOTf₂ was used as the additive instead of silica gel.

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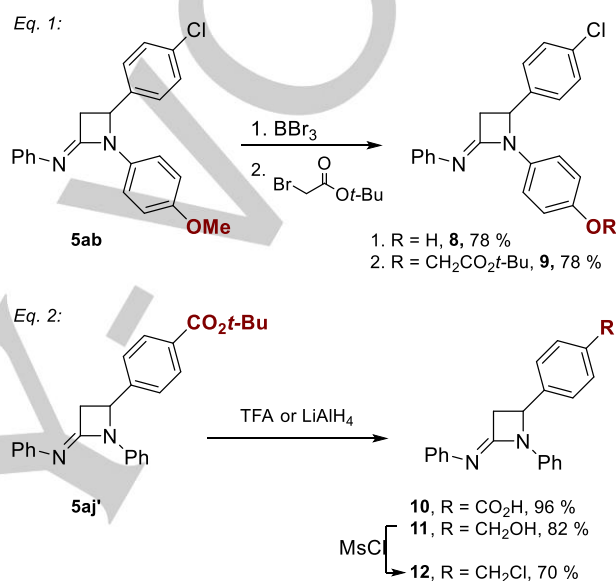
Strongly electron-enriched 3,4,5-trimethoxylated imine **4f** reacted smoothly with **1a** to give **5af** in 54% yield (entry 6) while dianisyl imine **4g** led to **5ag** in 40% yield (entry 7). In order to allow further functionalization, *p*-bromo- and *p*-iodobenzaldehyde-derived imines (**4h** and **4i**) were subjected to the reaction conditions and the desired adducts were obtained in 63% and 61% yields, respectively (entries 8,9). Imine **4j** bearing a methoxycarboxylate was then used, leading to an overall 30% yield of cycloaddition adduct **5a**, most of which had been transesterified to the corresponding *t*-butoxycarboxylate (**5aj**) during the course of the reaction (entry 10). While various substitution patterns on the imine partner were well tolerated, this was not the case for the ketenimine precursor. Indeed, a series of ynamides was evaluated for which no cycloaddition took place (Table 2, top-right *b*). These include: sulfonamides (GP = tosyl, mesyl and *p*-nosyl) and *N*-alkyl (R = benzyl or allyl) as well as *C*-aryl (R = phenyl, *n*-butyl and triisopropylsilyl) derivatives. The reaction did take place, however, when functionalized aryl groups such as *para* halo- (Cl, Br and I), trifluoromethyl- and methoxy-phenyl were incorporated on the ynamide partner (**1b-f**). All of these reacted with both imines **4a** and **4b** (entries 11-20) providing yields of cycloadducts ranging from 10-36% with imine **4a** (entries 11, 13, 15, 17 and 19) to 29-40% with imine **4b** (entries 12, 14, 16, 18 and 20). Compared with ynamide **1a**, yields were systematically lower and this can be attributed to a variety of factors difficult to unambiguously pinpoint since the substitution of this aryl presumably has an influence on both the generation of the active ketenimine and its subsequent stability and reactivity.

Having a wide panel of azetidinimines at our disposal we then turned our attention to their use for further functionalization. Satisfyingly, this unusual four-membered ring proved to be quite tolerant to a broad range of reaction conditions, obviating the necessity of extensive optimization. First, Suzuki coupling was used as a typical Pd-catalyzed cross-coupling reaction. Thus, an additional *p*-methoxyphenyl moiety could be added with excellent yields on both the *C*-aryl (**6**) or iminoaryl (**7**) part of the scaffold, using either bromo- (**5ah** & **5ca**) or iodo-azetidinimines (**5ai** & **5da**) (Scheme 3).



Scheme 3. Ynamides: Inherent Polarization vs Acid and Base Activations

A strong Lewis acid such as boron tribromide (Scheme 4, Eq. 1) could be employed, without any noticeable degradation of the amidine ring, to selectively cleave the methyl group of **5ab** to give phenolic azetidinimine **8**. The latter could in turn be alkylated with *t*-butyl bromoacetate to give **9** in 78% yield. Finally, treatment of carboxylate (**5aj**) with a strong acid such as trifluoroacetic acid or a strong reducing agent such as lithium aluminum hydride gave respectively carboxylic acid **10** (96%) and primary alcohol **11** (82%), leaving the four-member ring untouched. Benzyl alcohol **11** could furthermore be transformed into the corresponding chloride **12** in 70% yield, using methanesulfonyl chloride.



Scheme 4. Further Functionalization around the Azetidinimine Ring

In conclusion, we have taken advantage a specific mode of activation of ynamides under basic conditions to generate *N*-arylethenimines from Boc-aryl-ynamides and react them with imines in a [2+2] cycloaddition. This reaction further ascertains the intermediacy of the ketenimine intermediate and paves the way for other types of cycloadditions. Moreover, the azetidinimines resulting from this imino Staudinger synthesis can undergo a broad array of chemical transformations that leave the 4-membered amidine ring intact. This work should allow for further exploration around this particular heterocyclic scaffold which can be viewed as an imino-analog of monocyclic β -lactams.¹³ Studies in these directions are currently ongoing in our laboratory and will be reported in due course.

Experimental Section

Imine **4a** (63 mg, 0.3 mmol, 1.0 equiv.), ynamide **1a** (130 mg, 0.6 mmol, 2.0 equiv.) and SiO_2 (18 mg, 0.3 mmol, 1.0 equiv.) were successively added in a microwave sealable tube and placed under argon before the addition of *t*-BuOLi (48 mg, 0.6 mmol, 2.0 equiv.) followed by extra dry DMF (900 μL). The sealed tube was placed in a microwave apparatus for 1 h at 100 $^\circ\text{C}$. The crude material was purified by flash chromatography on silica gel (10% ethyl acetate in heptane as eluent) to provide azetidinimine **5aa** with 54 % yield (53 mg, yellow solid).

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Author Contributions

K. C. and R. H. D. designed and supervised the experiments and wrote the manuscript, C. M. and S. V. optimized the reaction conditions and initiated the scope study, E. R. and M. B. expanded the scope and performed the functionalization of the compounds. P. R. performed the X-ray crystallography. These authors contributed equally. The authors declare no competing financial interests.

Keywords: ynamides, ketenimines, [2+2] cycloaddition, azetidiniamines, Staudinger synthesis

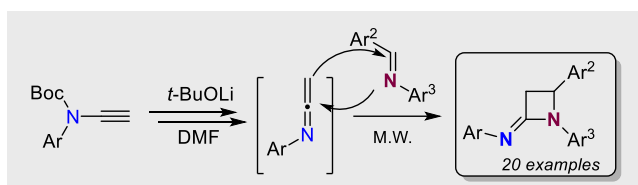
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- [11] See Supporting Information for details.
- [12] CCDC 1546588. 1546592 (**5aa**, **5ba**, **5ai**, **5fa**, **6** respectively) contain the crystallographic data for this paper.
- [13] In the context of antibiotic resistance, monocyclic β -lactam antibiotics (monobactams) such as aztreonam hold a special position due to their unique properties, see: C. Ramsey, A. P. MacGowan, *J. Antimicrob. Chemother.* **2016**, *76*, 2704 and references therein.

COMMUNICATION

Entry for the Table of Contents

Layout 2:

COMMUNICATION



Base Jump: Under strong basic conditions ynamides gave highly reactive ketenimines which could be trapped with imines in a [2+2] cycloaddition. This imino Staudinger synthesis led to a variety of imino-analogs of β -lactams, namely azetidinimines (20 examples), that could be further functionalized through a broad range of transformations.

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Base-Mediated Generation of Ketenimines from Ynamides: Direct Access to Azetidinimines by an Imino Staudinger Synthesis