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# Domino Aza-Michael-*ih*-Diels–Alder Reaction to Various 3-Vinyl-1,2,4-triazines: Access to Polysubstituted Tetrahydro-1,6-naphthyridines

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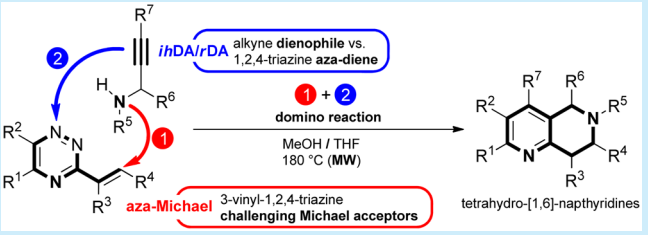
Supporting Information

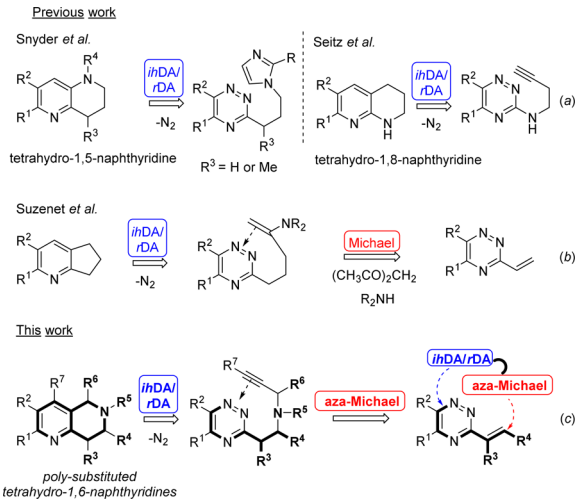
**ABSTRACT:** A straightforward domino aza-Michael-inverse-electron-demand-hetero-Diels–Alder/retro-Diels–Alder reaction between primary and secondary propargylamine derivatives and 3-vinyl-1,2,4-triazines is developed highlighting not only the uniqueness of this dual-heterocyclic platform but also a novel and unprecedented path to polysubstituted tetrahydro-1,6-naphthyridine scaffolds.




Increasing molecular complexity to extend the exploration of chemical space is a major goal for pharmaceutical industries. After a recognized decline of success in the clinic over the last two decades, recent studies have underlined the importance of architectures possessing saturated bonds.[1] The combination of heteroaromatic and saturated *N*-heterocycles aims to address this current issue,[2] leading to significant novelty in drug discovery programs.[3a] In that context, pyridine scaffolds associated with saturated cycles have displayed promising biological activities.[3] However, while several paths to polyfunctionalized tetrahydroquinolines and tetrahydroisoquinolines have been developed,[4] the formation of the valuable tetrahydronaphthyridines in various regioisomeric forms is still tedious and remains a prevalent synthetic challenge.[5] The fascinating and original reactivity of 1,2,4-triazines, which belong to a versatile group of azines, partially addressed this limitation.[6] They can indeed act as electron-deficient 4$\pi$-components able to undergo an inverse-electron-demand hetero-Diels–Alder (*ih*DA)/retro-Diels–Alder (*r*DA) sequence.[7] This powerful strategy enabled a straightforward access to diversely substituted pyridines,[8] among which some tetrahydro-1,5- and 1,8-naphthyridines bearing only limited substitution patterns were elaborated via an intramolecular *ih*DA/*r*DA sequence (Scheme 1, a).[9] These previous studies rely on either the well-established $S_NAr$ reactivity of the 1,2,4-triazine ring to introduce the dienophile part or a late construction of the aza-arene moiety.

However, the 1,6-isomers remain inaccessible through this useful approach mainly due to the lack of synthetic approaches to construct the required precursors. Recently, 3-vinyl-1,2,4-triazines aroused our interest since this original heterocyclic platform is prompted to behave as a Michael acceptor prior to the *ih*DA/*r*DA sequence.[10] This dual reactivity remains nevertheless underexploited and limited to the sole use of acetylacetone as nucleophile on unsubstituted vinyltriazine as Michael acceptors (Scheme 1, b).[10b] We are pleased to describe herein some breakthroughs toward unprecedented aza-Michael reaction on substituted vinyltriazines. Accordingly, propargylamine derivatives were found

**Scheme 1. Previous Results and Project Plan**

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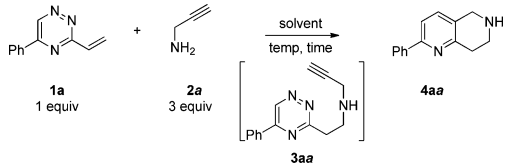
to be well suited to carry out a domino heteroconjugated addition-*ih*DA/*r*DA reaction on various 3-vinyl-1,2,4-triazines allowing the straightforward and original formation of variously functionalized tetrahydro-1,6-naphthyridines (Scheme 1, c).

In order to achieve the optimized conditions, the aza-Michael addition was first examined. 5-Phenyl-3-vinyl-1,2,4-triazine **1a** was selected as the model substrate, and the reaction was performed with propargylamine **2*a*** in various solvents (Table 1). First, methanol was used, and the need for

**Table 1. Optimization for the Aza-Michael Reaction and the One-Pot Procedure**




| entry | temp (°C) | time (h) | solvent | yield (%)[a] **1a**/**3a*a***/**4a*a*** |
|---|---|---|---|---|
| 1 | rt | 24 | MeOH | 0/81[b]/0 |
| 2 | rt | 24 | THF[c] | 100/0/0 |
| 3 | 180[f] | 3.5 | MeOH | 0/0/59 (53)[b] |
| 4 | 180[f] | 3.5 | THF | 12/0/18 |
| 5 | 180[f] | 3.5 | THF | -/0/52[d] |
| 6 | 180[f] | 3.5 | THF/MeOH[e] | 0/0/47, (45)[b] |

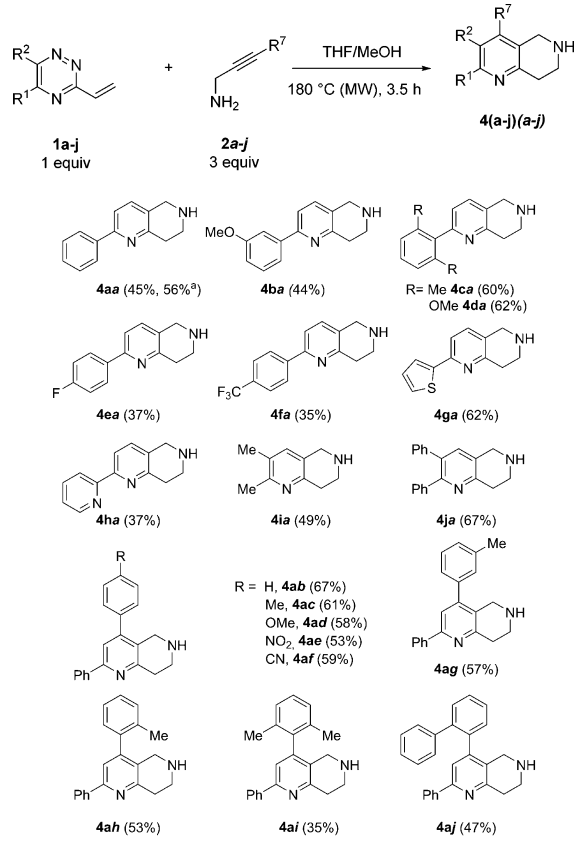
[a]NMR yield with $Bn_2O$ as internal standard. [b]Isolated yield. [c]Same issue for PhCl and toluene. [d]Result obtained starting from **3a*a***. [e]A mixture of THF/MeOH (1/1) was used. [f]Microwave irradiations were used.

an excess of amine was rapidly identified since the completion of the reaction was observed with only 3 equiv of propargylamine (entry 1, see the Supporting Information for details). We were pleased to isolate **3a*a*** in 81% yield, validating 3-vinyl-1,2,4-triazines as efficient Michael acceptors toward primary amines. Other polar and nonpolar aprotic solvents such as THF, toluene, or chlorobenzene, generally preferred for the anticipated *ih*DA/*r*DA sequence, were inappropriate and underlined the crucial need of the protic solvent for the success of the reaction (entry 2, see the SI).

To initiate an *ih*DA/*r*DA reaction with the best solvent in hand for the aza-Michael step, 5-phenyl-3-vinyl-1,2,4-triazine **1a** and propargylamine **2*a*** were heated under microwave (MW) irradiation in methanol. After 3.5 h at 180 °C, **4a*a*** was obtained in excellent overall 53% yield, highlighting 3-vinyl-1,2,4-triazine as a competent platform for the aza-Michael addition followed by the domino *ih*DA/*r*DA reaction (entry 3). Next, in order to attain the temperature required for the *ih*DA/*r*DA sequence without facing a critical pressure issue, a more appropriate solvent was used, such as THF (entry 4). However, even at high temperature, the aza-Michael addition remained delicate. This limitation in the absence of protic solvent was confirmed when the aza-Michael adduct **3a*a*** was directly used as the starting material in THF (entry 5). In this case, **4a*a*** was formed in 52% yield. Fortunately, an additional amount of methanol in THF enabled us to overcome this lack of reactivity, and the desired product was successfully isolated in 45% yield after column chromatography under reasonable pressure conditions (entry 6). Further attempts to diminish the reaction time or the temperature showed no improvement (see SI).

Having established the reaction conditions, a wide range of 3-vinyl-1,2,4-triazines and propargylamines were examined as displayed in Schemes 2 and 3. The scope is a salient aspect of

**Scheme 2. Modification of the Pyridine Part**

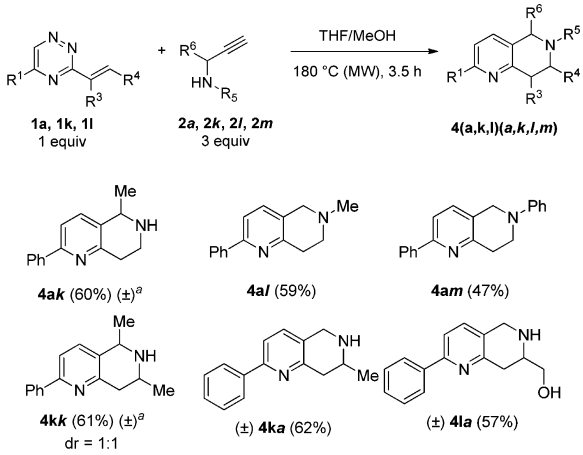



[a]Reaction performed on a 2 mmol scale.

this methodology since various original polyfunctionalized tetrahydro-1,6-naphthyridines were obtained in good yields over this three-step cascade reaction.

First, 5-aryl-3-vinyltriazines were successfully used, giving access to the corresponding 2-aryl-tetrahydro-1,6-naphthyr-

**Scheme 3. Modification on the Piperidine Part**




[a]The propargylamine **2*k*** was used as the HCl salt, and $K_2CO_3$ (3 equiv) was added to the solution for the one-pot procedure.



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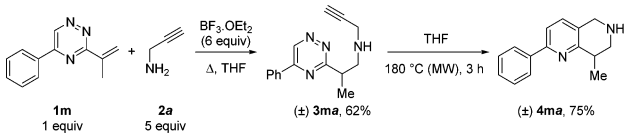
idines bearing substituents in the *meta*- (**4ba**, 44%), di-*ortho*- (**4ca** and **4da**, 60% and 62%, respectively), and *para*- (**4ea** and **4fa**, 37% and 35% respectively) positions of the phenyl ring (Scheme 2). Our method can also be extended to heteroaryl substituents since 2-pyridyl and 2-thienyl were well tolerated (**4ga** and **4ha**). In this series, 3-vinyl-1,2,4-triazine ($R^1$ = H, $R^2$ = H) and 5-methyl-3-vinyl-1,2,4-triazine ($R^1$ = Me, $R^2$ = H) were not evaluated due to their challenging synthesis. Next, the 2,3-dimethyl and 2,3-diphenyl derivatives **4ia** and **4ja** were obtained in 49% and 67% isolated yield, respectively. Then the modification of the propargylamine part was examined. Various 3-arylpropargylamines were submitted to our experimental conditions, and the desired 4-aryl-tetrahydro-1,6-naphthyridines were isolated with overall yields ranging from 35 to 67% (**4ab**-**aj**). Overall, the reaction tolerates different electron-donating (Me, OMe) and electron-withdrawing groups ($NO_2$, CN) in the *ortho*, di-*ortho*, *meta*, and *para* positions of the phenyl ring. On the C4 position, our cascade reaction exhibits very little steric effect (**4ah**–**aj**).

Recently, it has been reported that increasing the number of $sp^3$-hybridized carbons as well as stereogenic carbon contribute to decrease the toxicity.[1c] Therefore, we turned our attention on introducing substituents on the piperidine part of the tetrahydro-1,6-naphthyridines (Scheme 3). First, $C_{sp3}$- and *N*-substituted propargylamines were successfully used as **4ak**–**am** and **4kk** were efficiently synthesized allowing access to C5- and *N*-functionalized tetrahydro-1,6-naphthyridines.

Next, the more challenging 3-vinyl-1,2,4-triazines **1k**–**m** substituted in the $\alpha$ or $\beta$ positions of the alkenyl moiety were examined. Interestingly, reaction with a methyl or a hydroxymethyl group in the $\beta$-position gave the expected products **4ka** and **4la** in 62% and 57% yield, respectively, regardless of steric hindrance.

Nonetheless, with 5-phenyl-3-(prop-1-en-2-yl)-1,2,4-triazine **1m**, the desired bicyclic product **4ma** was not isolated under our original experimental conditions. A slight loss of planarity (and conjugation) between the alkenyl and the triazine parts for steric reasons could explain this lack of reactivity. Therefore, an optimization was carried out on this substrate (see the Supporting Information for details). To overcome this limitation, the reaction was performed in the presence of $BF_3{\cdot}Et_2O$ (6 equiv) in refluxing THF with a larger excess of **2a** (5 equiv). Under these conditions, **3ma** was isolated in 62% yield and directly engaged in the *ih*DA/*r*DA sequence (Scheme 4).

**Scheme 4. Synthesis of 4ma**




After irradiation, **4ma** was successfully obtained in 75% yield, allowing the efficient introduction of a wide range of functional groups in each position of the tetrahydro-1,6-naphthyridine ring.

In summary, we report herein a novel three-step domino transformation exploiting the versatile reactivity of 3-vinyl-1,2,4-triazines. This $\alpha,\beta$-unsaturated $4\pi$ deficient scaffold demonstrated a high synthetic usefulness being at first an efficient aza-Michael acceptor toward primary and secondary propargylamines allowing afterward a straightforward and unique access to diversely substituted tetrahydro-1,6-naphthyridines thanks to a subsequent *ih*DA/*r*DA process.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02132.

Experimental details and characterization data for all new compounds, table of optimization for the synthesis of **3ma**, and a complete list of compounds synthesized (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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