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Organocatalyzed Thia-Michael Addition and Sequential Inverse Electron Demanding Diels−Alder Reaction to 3-Vinyl-1,2,4-triazine Platforms

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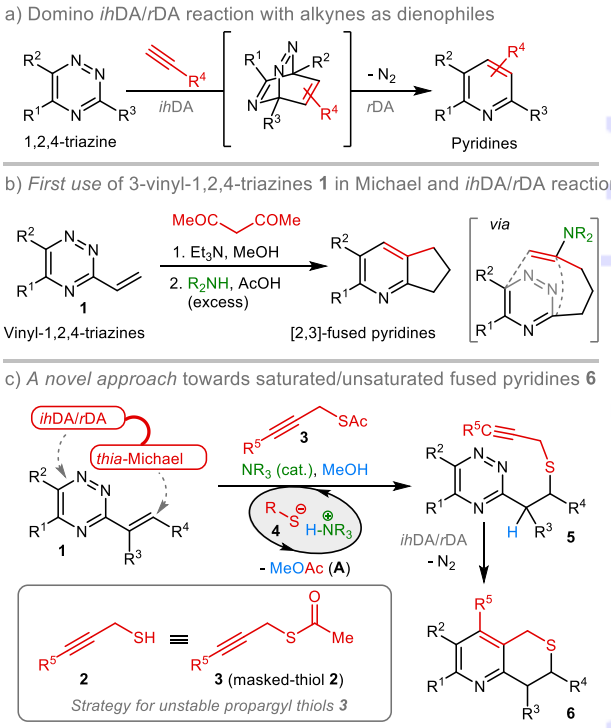
Abstract. This work highlights the use of 3-vinyl-1,2,4-triazines as original thia-Michael acceptors and inverse electron demanding Diels-Alder platforms en route to new 7,8-dihydro-5*H*-thiopyrano[4,3-*b*]pyridines. The required but rather unstable propargylthiol nucleophiles were successfully generated *in-situ* upon an innovative DBU-catalyzed methanolysis event of the corresponding propargyl thioacetate derivatives.

Keywords: triazine; organic catalysis; conjugate addition; propargylthiol; Diels-Alder reaction

Pyridines are privileged scaffolds in medicinal chemistry ubiquitously represented in pharmaceutical ingredients.[1] Among the myriad synthetic approaches towards this valuable heterocycle,[2] the domino *inverse-electron-demand-hetero*-Diels–Alder (*ih*DA)/*retro*-Diels–Alder (*r*DA) reaction between 1,2,4-triazine platforms and 2C-dienophiles such as alkynes has furnished synthetically useful pathways to pyridines displaying various substitution patterns (Scheme 1a).[3] The intramolecular strategies have also flourished and overcome the lack of reactivity of alkyne partners meanwhile addressing the regioselectivity issues towards the construction of fused non-aromatic/heteroaromatic fused bicycles.[3],[4] However, these cyclization approaches necessitate the pre-installation of a tether flanked by the dienophile. On the other hand, vinyl *N*-heterocycles, whose alkene-substituted pyridines are the most representative platforms, emerged as original and useful Michael-acceptors allowing an alternative way to provide substituted azaarenes.[5] Their unique reactivity markedly depends on the capability of the electron-poor azaarene moiety to stabilize the developing anionic charge subsequent to the 1,4-addition reaction.[5] Nonetheless, in this field of research, organocatalytic processes only appeared to be surfacing in recent years.[6]



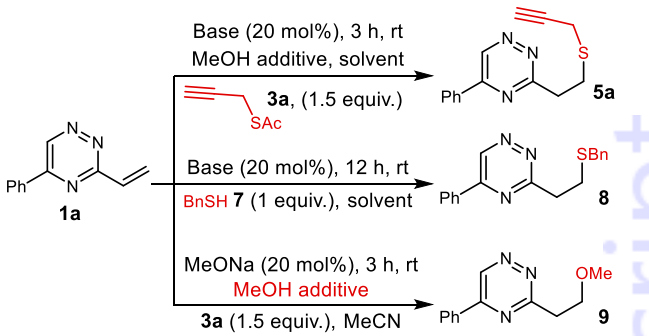
Scheme 1. Context of the methodology.

In quest to merge the best of these two worlds, we recently introduced 3-vinyl-1,2,4-triazine derivatives **1** as a versatile platform able to undergo both a 1,4-conjugated addition reaction and the subsequent intramolecular *ih*DA/*r*DA reaction (Scheme 1b).[7] This novel strategy was initially proven by a Michael reaction of acetylacetone (C-C bond formation) to 3-vinyl-1,2,4-triazines **1** having a unsubstituted vinyl

pendant. However, the conjugated addition process required a large amount of triethylamine as a base. Then, the acetyl motif allowed an enamine-based domino *ih*DA/*r*DA-elimination sequence to give [2,3]-fused pyridines.[3],[7],[8] On this background, we undertook to probe the reactivity profile of (1) more substituted vinyl-triazines **1** as (2) unprecedented *hetero*-Michael acceptors for C-S bond formation upon (3) organocatalytic conditions (Scheme 1c). Accordingly, we envisaged the use of propargylthiol derivatives **2** as a dual entities not only allowing a thia-Michael reaction to give product **5** but affording also the opportunity to lead to the subsequent intramolecular *ih*DA/*r*DA reaction (Scheme 1c).[9] Additionally, this sequence would provide a novel approach and versatile construction of 7,8-dihydro-5*H*-thiopyrano[4,3-*b*]pyridines **6**, whose very few general synthetic approaches are reported despite the biological relevance of this scaffold.[10] We are pleased to report herewith the first sequential domino thia-Michael-*ih*DA/*r*DA reaction to 3-vinyl-1,2,4-triazine derivatives **1**, meanwhile affording an organocatalytic strategy to manipulate unstable propargylthiol **2**.

Due to the known volatility and instability of the propargylthiol **2a** (R^5 = H, Scheme 1c), Moyano and Pericàs proposed the use of propargyl thioacetate derivative **3a** as stable masked-thiol which was liberated *in-situ* as lithium thiolate species upon treatment by $LiAlH_4$.[11],[12] We postulated that a tertiary-amine as a Brønsted base would promote the deacetylation reaction of **3a** along with the nucleophilic addition of methanol to provide a catalytic amount of the corresponding ammonium propargylthiolate **4** en route to the thia-Michael product **5** (Scheme 1c). At the onset of this hypothesis (Table 1), it was shown that no reaction took place between vinyl-triazine **1a** and acetyl derivative **3a** (1.5 equivalent) in the presence of methanol but without any base (entry 1). To our delight, a screening of organic bases in MeCN (entries 2-4, 20 mol%) revealed that strong guanidine amine bases furnished the expected thia-Michael product **5a** with promising 32-43% of conversion (entries 3-4). The amidine DBU turned to be the optimal organocatalyst giving rise to complete (> 99%) and clean transformation of vinyl-triazine **1a** into product **5a** in 3 hours as long as methanol additive is used (entries 5-6). A rapid survey of solvents (entries 7-9) revealed that methanol afforded a slightly faster process allowing a conversion of 99% in 1 hour whereas 70% was obtained in acetonitrile (entries 5 and 7). However, this outcome was also counterbalanced by the apparent decomposition (precipitation events) of the acetyl compound **3a** used in excess in methanol likely though the rapid concentration of the unstable propargylthiol **2a** and derivatives in the reaction medium. Then, we made use of the stable benzylthiol **7** as a model *S*-nucleophile to probe the thia-Michael reaction into the formation of **8** (Table 1, entries 10-14). It was demonstrated that a base is crucial for the success of the conjugated addition reaction and DBU is a superior organocatalyst than *i*Pr_2EtN in toluene (entries 10-12), although their efficiency was comparable in acetonitrile (entries 13-14). Eventually, the use of sodium methanolate as a base led only to the oxa-Michael product **9** highlighting the usefulness of the soft DBU/MeOH strategy (entry 15).

Table 1. Optimization of the thia-Michael reaction.[a]



Entry	Base	Solvent/ Additive	**3a** or **7**	Product (%)[b],[c]
1	-	MeCN/MeOH	**3a**	**5a**, 0
2	DABCO or DMAP or *i*Pr_2EtN	MeCN/MeOH	**3a**	**5a**, 0
3	MTBD	MeCN/MeOH	**3a**	**5a**, 43
4	TMG	MeCN/MeOH	**3a**	**5a**, 32
5	DBU	MeCN/MeOH	**3a**	**5a**, >99 (70)
6	DBU	MeCN/-	**3a**	**5a**, traces
7	DBU	MeOH/-	**3a**	**5a**, >99 (>99)
8	DBU	THF/MeOH	**3a**	**5a**, 35
9	DBU	PhCl/MeOH	**3a**	**5a**, 95
10	DBU	toluene/-	**7**	**8**, >99
11	*i*Pr_2EtN	toluene/-	**7**	**8**, 6
12	-	toluene/-	**7**	**8**, 0
13	DBU	MeCN/-	**7**	**8**, 93
14	*i*Pr_2EtN	MeCN/-	**7**	**8**, >99
15	MeONa	MeCN/MeOH	**3a**	**9**, 83

[a] *Reaction conditions*: **1a** (0.1 mmol), base (20 mol%), solvent (1 ml, 0.1M) at rt either in the presence of acetyl propargylthiol **3a** (1.5 equiv.) and MeOH (10 equiv.) for 3 h or BnSH **7** (1 equiv.) for 12 h. [b] Conversion with regard to **1a** determined by ^{1}H NMR of the crude product. [c] In bracket outcome after 1 hour. TMG: *N*,*N*,*N*',*N*'-tetramethylguanidine, MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene. DABCO: 1,4-diazabicyclo[2.2.2]octane. DMAP: 4-dimethylaminopyridine. DBU: diazabicyclo[5.4.0]undec-7-ene.

An NMR investigation revealed that Hünig base (*i*Pr_2EtN) was unable to achieve the deacetylation reaction of **3a** in the presence of methanol (see ESI). Contrariwise, 20 mol% of DBU allowed the rapid methanolysis reaction leading to the formation of 20% of methyl acetate **A** (^{1}H NMR ratio **3a**/**A** = 80/20) after one hour (Figure 1). Interestingly, the

disappearance of **3a** continued slowly afterwards. However, the obtained products, among which the expected thiolate **4**, were not identified by NMR likely due to instability issue.

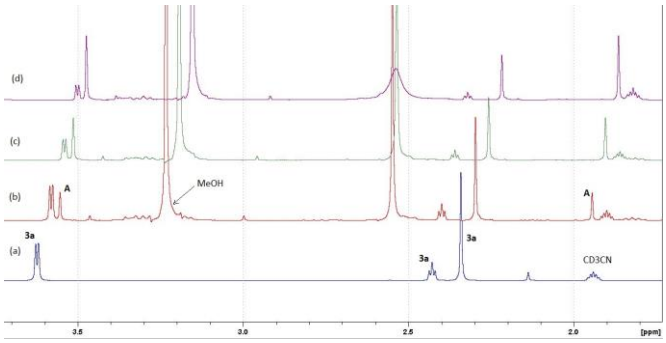
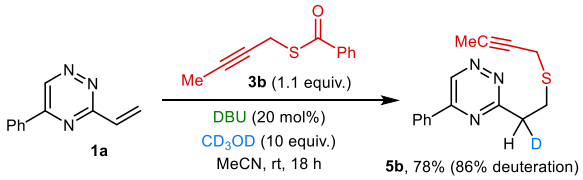


Figure 1. ^{1}H NMR (CD_3CN) monitoring of the deacetylation event of propargyl thioacetate **3a** furnishing methyl acetate **A**. (a) **3a** (0.15 mmol), in CD_3CN (1 mL), rt. (b) **3a** (0.15 mmol), DBU (0.02 mmol) and MeOH (1 mmol), rt, 1 h (**3a**/**A**: 80/20). (c) After 3 h (**3a**/**A**: 60/40). (d) After 14 h (**3a**/**A**: 42/58).

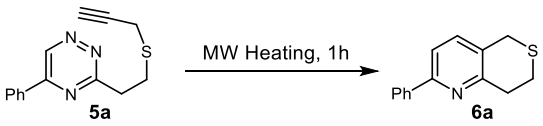
Most notably, by means of CD_3OD in the presence of propargyl thiobenzoate **3b**, preventing the parasitic hydrogen-deuterium exchanges with acidic protons of **3a** (see ESI), the corresponding deuterated-product **5b** was obtained with 78% yield and 86% D incorporation (Scheme 2). This testifies that: (1) the protonation event mainly takes place at the α-position of the triazine following a thia-Michael-protonation sequence and (2) MeO**H** is the proton source, likely *via* the formation of thiolate$^-$DBU**H**$^+$ ion-pair **4** by methanolysis (Scheme 1c). Accordingly, one can assume that the strong basicity of DBU is well-balanced to allow both the deacylation event of propargyl thioacetate derivatives **3** and the 1,4-nucleophilic addition reaction without retarding the subsequent protonation event; a prerequisite to regenerate the DBU organocatalyst.



Scheme 2. Deuteration experiment.

Thereafter, we undertook the investigation of the intramolecular *ih*DA/*r*DA reaction on the crude propargyl product **5a** (obtained after evaporation) due to the sensitivity of this compound to oxidation upon purification through column chromatography (Table 2).[13] However, after heating under microwave (MW) irradiation at 200 °C in chlorobenzene for 1 hour a low 27% NMR yield was measured (entry 1). It turned out that either the presence of DBU or the excess of propargyl thiol derivatives **2a**-**3a** elicited side reactions leading to complex mixtures beside the cycloaddition pathway. Pleasingly, by means of an acidic washing of the reaction mixture followed by a solvent exchange, the resulted crude product **5a** underwent a smooth cyclization process to yield the expected fused-pyridine **6a** in 78% yield (entry 2). These results (74-76%) were secured with similar yields on two mmol scale irrespective to the use of MW irradiation heating or conductively heating (entry 2). Importantly, these reaction conditions displayed less than 5% of the retro-thia-Michael product **1a**. It was found that neither lower temperature (175 °C, entry 3) nor other solvents (entries 4-7) surpassed the reaction in chlorobenzene at 200 °C for 1 hour.

Table 2. Optimization of the cycloaddition reaction.[a]



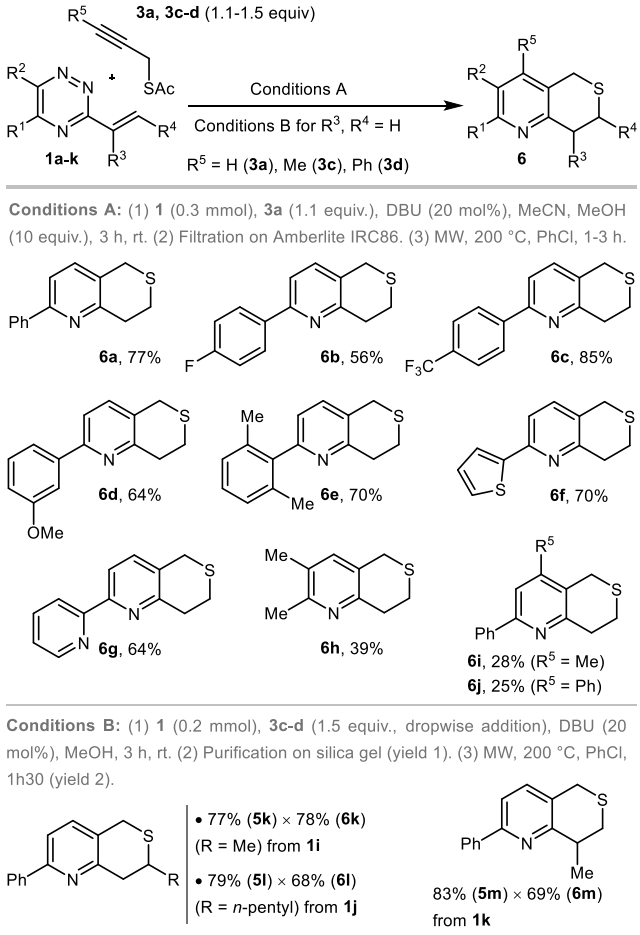
Entry	T (°C)	Solvent	Product **6a** (%)[b]
1	200	PhCl	27[c]
2	200	PhCl	78 (74)[d] (76)[e]
3	175	PhCl	56
4	200	$PhCF_3$	74
5	200	Ethylene glycol	42
6	200	NMP	45
7	200	$PhNO_2$	59

[a] *Reaction conditions*: carried out on the crude product **5a** (0.1 mmol) obtained after acidic-extraction and evaporation of the reaction media, diluted in 2 mL of solvent upon microwave irradiation. [b] NMR yield determined by an internal standard over two-steps. [c] On the crude product **5a** after evaporation but without work-up. [d] Reaction carried out in a conductively heated Monowave 50 reactor. [e] 76% of isolated yield when carried out on 2 mmol scale.

Mindful of having a convenient protocol in hands, we carried out a filtration of the crude reaction mixture through a weak acid cation exchange resin (Amberlite IRC86) in order to remove the DBU base (Table 3, conditions A). Then, the intramolecular *ih*DA/*r*DA reaction was achieved upon MW irradiation after a solvent exchange. Accordingly, we were pleased to observe the formation of the fused-pyridine **6a** in 77% isolated yield over two-steps from the corresponding vinyl-triazine **1a**. This protocol was successfully applied to various 5-substituted vinyl-triazines to synthesize the corresponding pyridines having a *para*- (**6b**-56% and **6c**-85%), *meta*- (**6d**-64%) and even di*ortho*-substituted phenyl ring (**6e**-70%) with overall yields ranging from 56 to 70%. A heteroaryl connected to the triazine ring was also tolerated as demonstrated with the elaboration of thienyl **6f** (70%) and pyridine **6g** (64%) derivatives. Next, the formation of 2,3-dimethyl fused-pyridine **6h** was achieved with 39% isolated yield. Interestingly, it was demonstrated that this sequence

could be extended to substituted alkynes **3c-d** (R^5 = Me, Ph) which furnished the crude thia-Michael intermediates **5i-j** with more than 98% of conversion. However, the corresponding cyclized-products **6i-j** displaying substituents at the 2 and 4 positions were obtained with modest 23-28% yields. These last examples might result from the more challenging cycloaddition events due to steric hindrance issues.

Table 3. A thia-Michael-*ih*DA/*r*DA sequence.[a]



[a] Isolated yields after silica gel column chromatography.

We subsequently tackled the thia-Michael addition reaction to triazines **1** flanked by α- or β-functionalized alkene pendants (Table 3, conditions B). Unfortunately, only traces of the Michael product **5k** was observed by mixing the vinyl-triazine **1i** (R^4 = Me) and propargyl thioacetate **3a** in MeCN in the presence of methanol (conditions A). The 1,4-nucleophilic addition reaction appears to be highly sensitive to steric hindrance at the β-position of the vinyl-pendant of triazine **1**. To our delight, by adding dropwise the thioacetate partner **3a** in methanol, in order to prevent a rapid decomposition of the corresponding thiol intermediate **2a** in this solvent (vide supra), we succeeded in the formation of thia-Michael adduct **5k** with 77% isolated yield after a flash column chromatography purification (see SI for more details). Next, the intramolecular *ih*DA/*r*DA reaction into fused-pyridine **6k** was carried out in 78% yield. These conditions were also successfully achieved to yield β-pentyl **6l** (79×68% yields) and α-methyl **6m** (83×69% yields) pyridine derivatives. The fact that the thia-Michael reaction was never completed (86-95% of conversion into adduct **5k-m**) may be explained by an equilibrated process upon thermodynamic control. Indeed, the cycloaddition reaction into products **6k-m** also gave rise to the formation of 9-17% of vinyl-triazine **1i-k** upon MW irradiation.

In summary, we have demonstrated that 3-vinyl-1,2,4-triazines are useful platforms for the synthesis of 7,8-dihydro-5*H*-thiopyrano[4,3-*b*]pyridine derivatives *via* an original sequence based on a thia-Michael reaction and the subsequent *ih*DA/*r*DA-process. This successful outcome was based on the innovative use of propargyl thioacetates, as convenient sources of rather unstable propargylthiol nucleophiles thanks to the organocatalytic DBU-based methanolysis event; a process that might find further application in synthesis.

Experimental Section

General Procedure

To a solution of 3-vinyl-1,2,4-triazine **1a-h** (0.3 mmol, 1 equiv.), the appropriate thioacetate **3a, 3c or 3d** (0.33 mmol, 1.1 equiv.) and methanol (3.0 mmol, 10 equiv.) in acetonitrile (3 mL) was added DBU (9 µL, 0,06 mmol, 20 mol%). The resulting solution was stirred for 3 hours at room temperature and filtered through a AMBERLITE IRC86-H form column. Resin was rinced with methanol and the filtrate was evaporated under reduced pressure. Chlorobenzene (6 mL) was added and the resulting mixture was placed in a microwave vial (30 mL). The vial was sealed and the solution was heated at 200 °C for 1-3 hours under microwave irradiation. After cooling down to room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to yield the desired 7,8-dihydro-5*H*-thiopyranopyridine **6a-j**.

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[13] The crude propargyl product **5a** could be stored for weeks at -20 °C without decomposition, despite the sensitivity to oxidation of this intermediate during the column chromatography purification.

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