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Sequential Michael Addition and Enamine-Promoted Inverse Electron Demanding Diels–Alder Reaction upon 3-Vinyl-1,2,4-triazine Platforms

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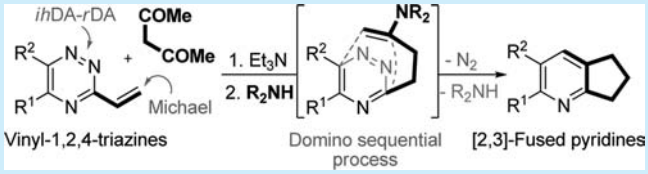
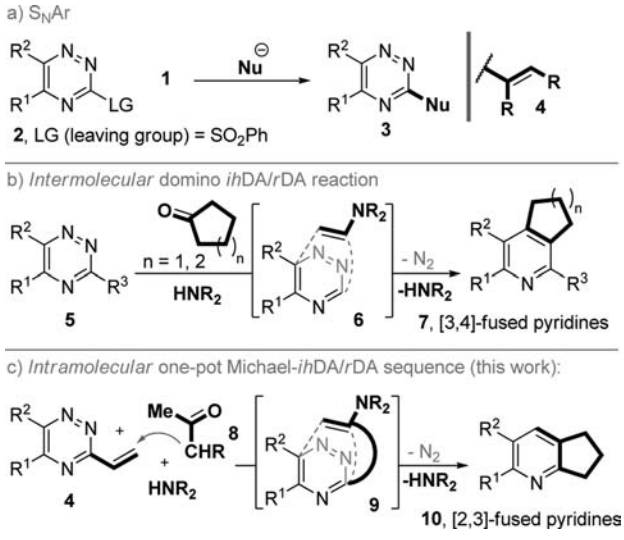
Supporting Information

ABSTRACT: An original one-pot Michael addition-*ih*DA/*r*DA sequence was achieved from 3-vinyl-1,2,4-triazine platforms used as unprecedented Michael acceptors. This sequence provides a novel access to functionalized [2,3]-fused pyridine derivatives via a unique enamine promoted intramolecular *ih*DA reaction of 1,2,4-triazine intermediates.



1,2,4-Triazine derivatives **1** belong to an important class of heterocycles encompassing applications in medicine and agrochemistry, but there are also useful building blocks in organic synthesis (Scheme 1).[1] As depicted in Scheme 1a, these

Scheme 1. Chemistry of 1,2,4-Triazines and Project Plans



π-electron-deficient triazines **1**, flanked by a suitable leaving group, undergo aromatic nucleophilic substitution (S_NAr) reactions to give functionalized products **3** (Scheme 1a). Furthermore, these heterocyclic platforms **5** are capable of undergoing domino inverse-electron-demand hetero-Diels–Alder (*ih*DA)/retro-Diels–Alder (*r*DA) reactions with various 2C dienophiles that allow for a straightforward access to substituted pyridine derivatives **7** (Scheme 1b), which are ubiquitous derivatives in pharmaceutical ingredients.[2] In this context, Boger and colleagues developed a robust strategy using enamine reactants as electron-rich dienophiles[2,3] involved in the domino *ih*DA/*r*DA reactions as depicted in Scheme 1b (transient intermediate **6**).[4,5] This approach both fulfills the stereoelectronic requirement of the *ih*DA reaction of **6** and secures the final rearomatization event while eliminating the secondary amine group. For instance, [3,4]-fused pyridines **7** were accessible from the corresponding cyclopentanone (Scheme 1b).[3−5] Nevertheless, the regioselectivity of this intermolecular sequence depends on the substitution pattern of the triazine derivative **5**. Although preformed enamines are usually employed, the one-pot procedure starting from the corresponding amine and ketone was also successful in certain cases.[2c,6] To the best of our knowledge, however, the intramolecular version of this powerful enamine-promoted domino *ih*DA/*r*DA reaction remains elusive despite the opportunity to elicit novel annulation processes.

At the onset of the following research program, we desired to capitalize on the accessibility of vinyl-triazine derivatives **4** through an S_NAr reaction between readily available 3-sulfonyl-triazines **2** and vinyl Grignard nucleophiles (Scheme 1a). Then, we reasoned that a Michael addition reaction of ketones **8** to vinyl-triazine derivatives **4** would furnish suitable ketone-triazine precursors, en route to intramolecular domino *ih*DA/*r*DA reactions via transient enamine intermediate **9** (Scheme 1c). We believe this approach would afford salient features. First of all, the regioselectivity control through *trans*-annular constraints would lead eventually to a complementary accessibility to [2,3]-fused pyridines **10**[7] (versus [3,4]-homologues **7** with the intermolecular version). Next, although the 1,4-conjugated addition reaction to alkene-substituted heterocyles has recently emerged as an innovative synthetic

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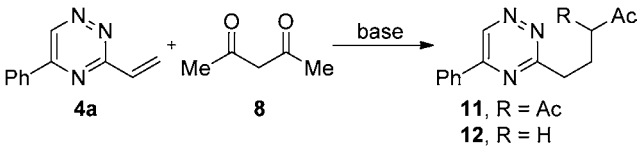
strategy,[8] the application to vinyl-triazine derivatives **4** remains almost unknown.[9] A reactivity investigation must then be undertaken. We are pleased to report here the achievement of the first Michael addition-*ih*DA/*r*DA sequence to furnish [2,3]-fused pyridine derivatives **10** in a one-pot synthesis.

As a model Michael process, we studied the 1,4-addition reaction of acetylacetone **8** to 5-phenyl-3-vinyl-1,2,4-triazine **4a** in the presence of amine bases (Table 1). A rapid survey of

Table 1. Michael Addition Reaction to 3-Vinyl-1,2,4-Triazine 4a[a]



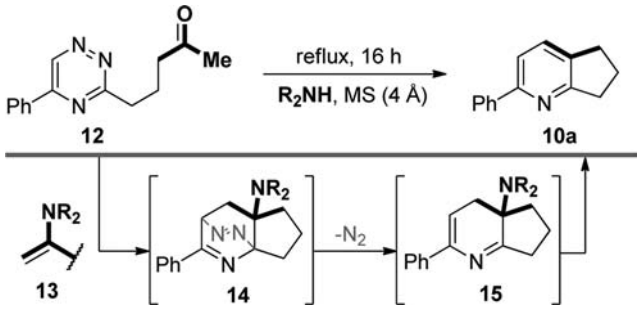
entry	solvent	base (mol %)	product	yield (%)[b]
1	toluene	Et_3N (20)	–	–
2	MeOH	Et_3N (20)	**11**	30(39)[c]
3	MeOH	DIPEA (20)	**11**	38
4	MeOH	Et_3N (50)	**12**	82[d]
5	^{t}BuOH	Et_3N (50)	**11**	16

[a]Reaction conditions: 3-vinyl-1,2,4-triazine **4a** (1 equiv), base (20−50 mol %), acetylacetone **8** (2 equiv), solvent (0.2 M), reflux, 12 h. [b]Isolated yield after column chromatography. [c]After 24 h. [d]No reaction took place at room temperature.

reaction conditions revealed that the use of methanol versus toluene both favored the 1,4-addition process and addressed the solubility issue of starting material **4a** (entries 1−2). Protic assistance seems to increase the electrophilic character of the Michael acceptor through a hydrogen bond activation. In the presence of 20 mol % of triethylamine in refluxing methanol for 12 or 24 h, the corresponding diacetyl-adduct **11** was obtained albeit in moderate 30−39% yields (entry 2). The use of a sterically more hindered Hünig base (entry 3), in order to prevent any parasitic addition events to the alkene pendant, did not improve the reaction efficiency. Eventually, we were delighted to observe that an increased amount of triethylamine (50 mol %) led to a complete transformation of triazine **4a** into the corresponding monoacetyl product **12** with a good 82% yield (entry 4). In line with previous observations by Canac and Lubineau under different conditions,[10] we believe that the formation of this unexpected compound **12** results from the initial tandem 1,4-conjugated addition−protonation reaction of acetylacetone **8** to the alkene pendant of **4a** followed by a retro-Claisen condensation onto intermediate **11**. The acetyl elimination is likely triggered by nucleophilic attack of nonencumbered methanol, since no product **12** formation occurred in *tert*-butanol (diketone **11** was isolated instead, entry 5). Considering the much lower yield of compound **11** observed in *tert*-butanol, it is assumed that the deacetylation event drives the reaction to completion by interrupting the otherwise thermodynamically controlled 1,4-addition of acetylacetone **8**. In connection with the following study (*vide infra*), we also investigated an enamine-promoted process. Unfortunately, preliminary investigations in the presence of secondary amines such as pyrrolidine, with either the acetylacetone **8** or the acetone as nucleophiles, led to a mixture of products revealing the competitive 1,4-addition reaction of the amines to **4a**.

With keto-triazine **12** in hand, we attempted the synthesis of [2,3]-fused pyridine **10a** upon the influence of secondary amines ($\mathbf{R_2NH}$) (Table 2). In order to develop a user-friendly

Table 2. Optimization of the *ih*DA/*r*DA Sequence



entry	R_2NH (equiv)	coacid (equiv)	toluene (M)	product	yield (%)[a]
1	pyrrolidine (3)	–	0.1	**15**	60
2	pyrrolidine (3)	AcOH (3)	0.1	**10a**	22
3	pyrrolidine (3)	AcOH (3)	0.2	**10a**	28
4	pyrrolidine (3)	AcOH (3)	0.5	**10a**	62[b]
5	pyrrolidine (3)	AcOH (3)	1.0	**10a**	56
6	pyrrolidine (1)	AcOH (3)	0.5	**10a**	27
7	pyrrolidine (1)	AcOH (1)	0.5	**10a**	39
8	pyrrolidine (3)	PhCOOH (3)	0.5	**10a**	55
9	pyrrolidine (3)	PivOH (3)	0.5	**10a**	54
10	pyrrolidine (3)	APTS (3)	0.5	**10a**	43
11	2-Mepyrrolidine (3)	AcOH (3)	0.5	**10a**	45
12	proline (3)	AcOH (3)	0.5[c,d]	**10a**	28
13	prolinol (3)	AcOH (3)	0.5	**10a**	22
14	pyrrolidine (3)	AcOH (3)	MeOH (0.5)[e]	**10a**	34

[a]Isolated yield after column chromatography. [b]35% yield without molecular sieves. [c]Toluene/DMF (2:1), at 125 °C. [d]No product formation without acetic acid additive. [e]MeOH was used instead of toluene, and MS (3 Å) was used.

protocol, we tackled the challenging *in situ* formation of enamine reagent **13** in the presence of molecular sieves following Boger's protocol.[6] Nonetheless, one has to take into account the requisite preferential reaction of the kinetic-enamine **13**, versus the thermodynamic one, in order to achieve the unprecedented intramolecular domino *ih*DA-*r*DA sequence (**14** to **15**). The subsequent amine eliminative-rearomatization reaction would then lead to pyridine **10a**. Making use of pyrrolidine (3 equiv) in refluxing toluene, we observed a complete transformation of ketone **12** (entry 1, Table 2) into dihydropyridine **15** with a 60% yield without providing the expected pyridine **10a**. Accordingly, the intramolecular domino *ih*DA/*r*DA reaction upon *in situ* enamine **13** formation was established but the elimination of the secondary amine did not occur. Carrying out the reaction under more drastic conditions (up to 200 °C), by means of microwave heating, led to the recovery of starting material.[5c] This issue is indeed a known bottleneck of the *ih*DA-*r*DA sequence and depends on the topology of the intermediate compounds. In the literature, the elimination step was successfully achieved by means of diamine assistance,[5] performing oxidative eliminations,[4e] or making use of coacids.[3−5] As diamine assistance was unsuccessful in our case, we assumed that the coacid strategy would suit our system best by facilitating the amine R_2N-elimination upon the

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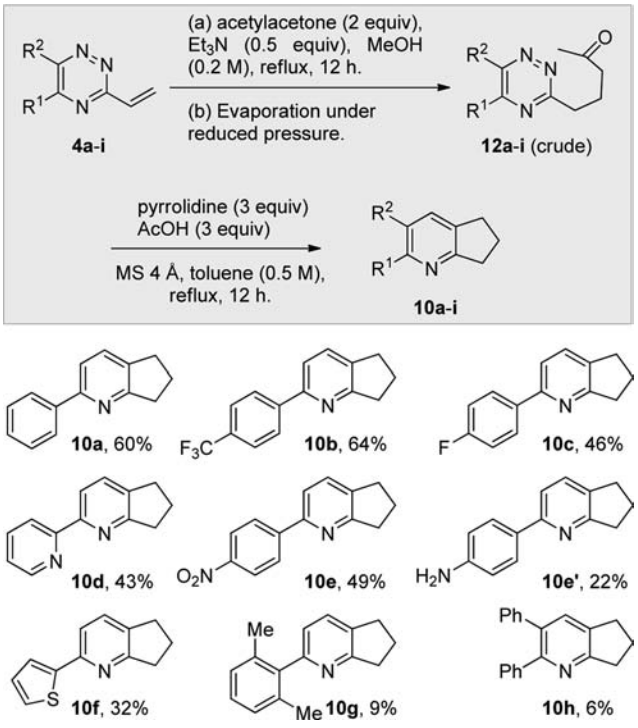
protonation event. We were very pleased to discover that a mixture of pyrrolidine and an excess of acetic acid introduced at the start of the reaction allowed the formation of pyridine **10a** albeit in a low 22% isolated yield (entry 2, Table 2). Worthy of note, this one-pot sequence completes the literature precedents, whereby the acid treatment is usually applied sequentially after completion of the cycloaddition step. Working in a more concentrated solution (entries 3−5, Table 2) improved the yields up to 62% at 0.5 M (entry 4, Table 2). The optimum was exceeded at 1 M concentration (56% yield, entry 5, Table 2) which led to some decomposition as evidenced by the ^{1}H NMR analysis of the crude reaction mixture. Attempts to decrease the amount of coacid or pyrrolidine gave lower yields (entries 6−7, Table 2). The examination of various additives showed that other carboxylic acids such as benzoic acid (55% yield, entry 8, Table 2) or the sterically hindered pivaloic acid (54% yield, entry 9, Table 2) did not improve the process. More acidic APTS appears more disadvantageous for the success of the reaction (43% yield, entry 10, Table 2). The use of α-substituted secondary amine promoters was detrimental to the process efficiency (22−45% yield, entries 11−13, Table 2).[11]

Subsequently, we envisaged a tandem Michael-*ih*DA/*r*DA sequence, having in mind that the first 1,4-conjugated addition step was favored in the presence of a protic solvent (see Table 1). Unfortunately, it turned out that the domino *ih*DA/*r*DA reaction occurred with only a 34% yield in methanol (entry 14, Table 2). Nonetheless, as described in Scheme 2, we carried out

Scheme 2. Scope and Limitations of the One-Pot Michael-*ih*DA/*r*DA Sequence



this novel strategy in a one-pot sequential fashion, namely by performing the Michael reaction (**4a** to **12**) with 50 mol % of triethylamine in refluxing methanol followed by a solvent evaporation under reduced pressure. Then, the domino *ih*DA/*r*DA reaction was achieved by the subsequent addition of pyrrolidine, acetic acid, and molecular sieves in toluene. Gratifyingly, this multistep sequence finally led to the corresponding product **10a** with an improved 60% overall yield from the corresponding vinyl-triazine **4a**. With this user-friendly protocol in hand, the scope of the one-pot Michael-*ih*DA/*r*DA process was explored for various 3-vinyl-1,2,4-triazine derivatives **4** (Scheme 2). This multistep sequence was performed from the vinylic starting materials **4b−d** and **4f** to provide novel fused-pyridines flanked at C6 by either substituted aryl rings (**10b−10c**), heterocyclic pyridine, or thiophene moieties (**10d**, **10f**) with reasonably good overall isolated yields ranging from 32% to 64%. The electron deficient 3-vinyl-1,2,4-triazine derivative **4e**, having a pendant 5-p$NO_2C_6H_5$, was nicely transformed into the corresponding pyridine derivative **10e** with 49% isolated yield. However, the pyridine analogue **10e′** featuring a 5-p$NH_2C_6H_5$ ring was also formed, as an unexpected product, with 22% isolated yield. Interestingly, this reduction reaction can be avoided by performing the reaction under an air atmosphere. This reductive phenomenon is not fully understood yet but shows that the transformation of functional groups is allowed. Although the synthesis of more sterically hindered products with either a 2,6-dimethylphenyl moiety **10g** or a 5,6-diphenylpyridine ring **10h** was practically possible, it occurred with modest 6−9% overall yields. Analysis of the crudes (**12g**, **12h**) showed that the Michael addition proceeded completely and that the *ih*DA is disfavored, probably due to steric repulsion in the formation of intermediate **14** featuring a 3D topology.

In summary, we report here for the first time a one-pot sequential domino Michael-*ih*DA/*r*DA reaction using 3-vinyl-1,2,4-triazine as an unprecedented Michael acceptor. This sequence provides a novel access to functionalized [2,3]-fused pyridine derivatives via a unique intramolecular *ih*DA reaction of 1,2,4-triazines promoted by enamine intermediates. The extension of this novel one-pot annulation process to other substrates is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01487.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, p 507. (b) Lindsley, C. W.; Layton, M. E. In *Science of Synthesis*; Weinreb, S. M., Eds.; Thieme: Stuttgart, 2003; Vol. 17, p

DOI: 10.1021/acs.orglett.5b01487
Org. Lett. 2015, 17, 3154−3157

357. (c) Kumar, R.; Sirohi, T. S.; Singh, H.; Yadav, R.; Roy, R. K.; Chaudhary, A.; Pandeya, S. N. *Mini Rev. Med. Chem.* **2014**, *14*, 168.
(2) For reviews on *ih*DA/*r*DA reactions, see: (a) Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: London, 1987; Chapter 10, p 300. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (d) Raw, S. A.; Taylor, R. J. K. *Adv. Heterocycl. Chem.* **2010**, *100*, 76. (e) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (f) Knall, A.-C.; Slugovc, C. *Chem. Soc. Rev.* **2013**, *42*, 5131.
(3) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179. (b) Boger, D. L.; Panek, J. S.; Duff, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 5745 and references cited therein.
(4) For representative examples, see: (a) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1521. (b) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1791. (c) Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111. (d) Chenard, B. L.; Ronau, R. T.; Schulte, G. K. *J. Org. Chem.* **1988**, *53*, 5175. (e) Branowska, D. *Molecules* **2005**, *10*, 265. (f) Altuna-Urquijo, M.; Gehre, A.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **2009**, *65*, 975. (g) Gehre, A.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **2009**, *65*, 1115.
(5) (a) Sainz, Y. F.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086. (b) Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2004**, 508. (c) Bromley, W. J.; Gibson, M.; Lang, S.; Raw, S. A.; Whitwood, A. C.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 6004. (d) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 1249.
(6) Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895.
(7) (a) For an alternative domino ihDA/rDA reaction of 1,2,4-triazines to [2,3]-fused pyridines, see: Branowska, D.; Ostrowski, S.; Rykowski, A. *Chem. Pharm. Bull.* **2002**, *50*, 463. (b) For an alternative domino *ih*DA/*r*DA reaction of 1,2,3-triazines to [2,3]-fused pyridines, see: Anderson, E. D.; Duerfeldt, A. S.; Zhu, K.; Glinkerman, C. M.; Boger, D. L. *Org. Lett.* **2014**, *16*, 5084. (c) For an alternative synthesis to cyclopenta-[2,3]-fused pyridines, see: Borioni, A.; Del Giudice, M. R.; Mustazza, C.; Gatta, F. *J. Heterocycl. Chem.* **2000**, *37*, 799. Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194.
(8) For reviews, see: (a) Klumpp, D. A. *Synlett* **2012**, 1590. (b) Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831.
(9) Badarau, E.; Bugno, R.; Suzenet, F.; Bojarski, A. J.; Finaru, A. L.; Guillaumet, G. *Bioorg. Med. Chem.* **2010**, *18*, 1958.
(10) Rodrigues, F.; Canac, Y.; Lubineau, A. *Chem. Commun.* **2000**, 2049.
(11) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923.

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