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DMAP-Catalyzed [2 + 4] Cycloadditions of Allenoates with *N*-Acyldiazenes: Direct Method to 1,3,4-Oxadiazine Derivatives

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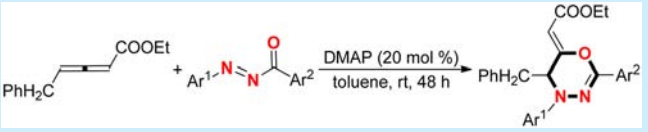
Supporting Information

ABSTRACT: An efficient DMAP-catalyzed [2 + 4] cycloaddition of allenoates and *N*-acyldiazenes is reported. The reaction involved embedding three heteroatoms into a six-membered ring and generated 1,3,4-oxadiazine derivatives in moderate to good yields.



Heterocyclic skeletons are found in many naturally occurring compounds used in medicinal chemistry.[1] 1,3,4-Oxadiazine is one of the most important frameworks for a variety of bioactive molecules (Figure 1).[2] Although many platforms for the synthesis of various heterocycles have been developed, only a few reports have concerned the synthesis of 1,3,4-oxadiazines, particularly via intermolecular cyclizations.[3] For this reason, the assessment of facile protocols for the efficient generation of 1,3,4-oxadiazines still poses a considerable challenge.

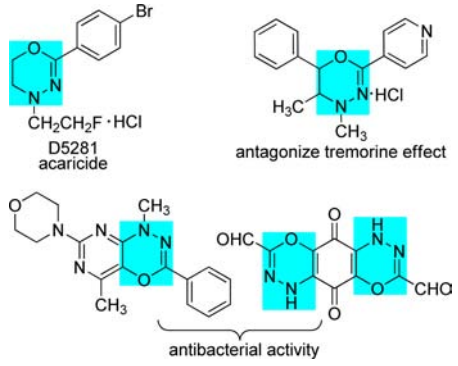
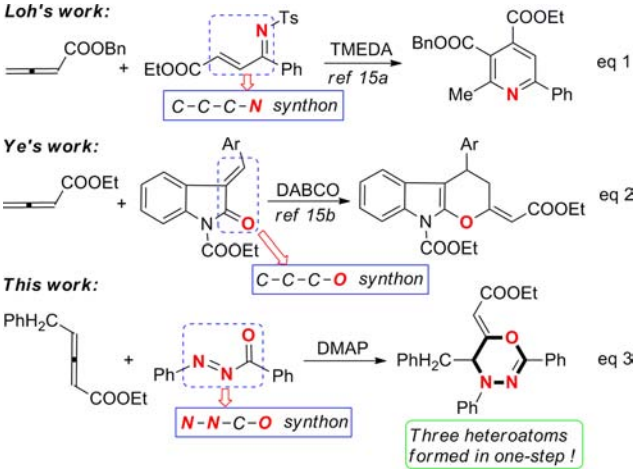


Figure 1. Selected examples of biologically active molecules containing a 1,3,4-oxadiazine skeleton.

Cyclization is an effective synthetic strategy, and it has been widely used to construct cyclic compounds. Most of the cyclizations can proceed in metallo- and organocatalytic systems. During the past decades, organic base-catalyzed intermolecular cycloaddition, especially for allenoate-based cycloaddition, has been proven as an efficient and environmentally benign method to afford cyclic products from easily available starting materials.[4] Accordingly, the electrophiles,[5] including alkenes,[6] imines,[7] aldehydes,[8] azomethine imines,[9] ylides,[10] and aziridines,[11] reacted with allenoates to form a wide range of carbo- and heterocycles. To continue to explore other organic base-promoted cycloadditions, the expansion of the scope of electrophile for constructing new heterocycles is highly desirable.

Recently, a desulfonylative [3 + 2] cycloaddition of allylic carbonates with arylazosulfones to pyrazoles in the presence of tertiary phosphine was developed.[12] In continuation of work on the pursuit of other annulations, *N*-acyldiazenes, an important class of diazene with distinctive reactivity, which were often used in carbene-catalyzed cycloadditions with ketenes[13] and aldehydes,[14] have received more attention. To the best of our knowledge, few papers have reported the use of *N*-acyldiazenes in organic base-catalyzed cycloadditions. Unlike reported [2 + 4] cycloadditions using α,β-unsaturated imines, ketones or aldehydes as electrophiles with only one heteroatom in the six-membered ring (Scheme 1, eqs 1 and 2),[15] the synthesis of three heteroatoms in a six-membered ring in one step is rare, especially for organic base-catalyzed annulations. Herein, a DMAP-catalyzed [2 + 4] cycloaddition

Scheme 1. Organic Base-Catalyzed Cycloadditions



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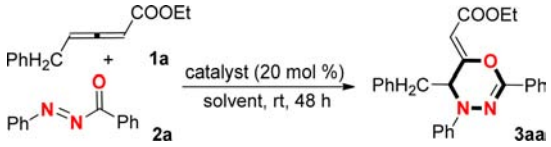
is reported using *N*-acyldiazenes as electrophiles to mix three heteroatoms in a six-membered ring and generate 1,3,4-oxadiazines (Scheme 1, eq 3).

The first investigation was conducted with benzyl allenoate (**1a**) and phenyl(phenyldiazenyl)methanone (**2a**) in the presence of 10 mol % of 4-(dimethylamino)pyridine (DMAP) as a catalyst (Table 1, entry 1). 1,3,4-Oxadiazine

Table 1. Optimization of Reaction Conditions[a]



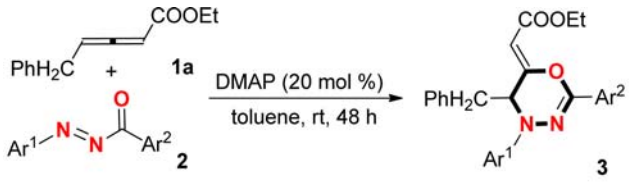
entry	catalyst	solvent	yield[b] (%)
1	DMAP	toluene	61[c]
2	DMAP	toluene	70
3	DMAP	toluene	71[d]
4	DMAP	toluene	63[e]
5	DMAP	toluene	60[f]
6	DMAP	acetone	65
7	DMAP	EtOAc	61
8	DMAP	CH_3CN	60
9	DMAP	CH_2Cl_2	58
10	DMAP	THF	56
11	DMAP	DMF	48
12	DMAP	DMSO	<10
13	pyridine	toluene	<5
14	DABCO	toluene	NR[g]
15	Et_3N	toluene	NR
16	DBU	toluene	ND[h]
17	Ph_3P	toluene	NR
18	$^nBu_3P$	toluene	NR

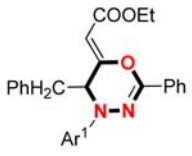
[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.20 mmol), catalyst (0.04 mmol, 20 mol %), solvent (2.0 mL), rt, 48 h. [b]Isolated yield. [c]10 mol % of DMAP. [d]30 mol % of DMAP. [e]At 0 °C. [f]At 80 °C. [g]NR = no reaction occurred. [h]ND = no desired product was detected.

derivative **3aa** was produced in 61% yield via a [2 + 4] cycloaddition pathway. The product yields increased to 70% and 71% after the amount of DMAP was increased to 20 and 30 mol %, respectively (Table 1, entries 2 and 3). Further examination of the reaction temperature indicated that room temperature is the best choice for this [2 + 4] cycloaddition (Table 1, entries 4 and 5). The solvent effect was also examined by screening toluene, acetone, EtOAc, CH_3CN, CH_2Cl_2, THF, DMF, and DMSO (Table 1, entries 6−12), of which toluene was found to be the most suitable medium. Other tertiary amines, such as pyridine, DABCO, Et_3N, and DBU, were also used as catalysts, giving either poor product yield or no reactions (Table 1, entries 13−16). Meanwhile, tertiary phosphine shut down the cycloaddition completely (Table 1, entries 17 and 18). Optimized reaction conditions were determined using 20 mol % of DMAP as a catalyst in toluene solution at room temperature for 48 h.

With the optimized conditions in hand, the scope of the reaction was expanded to other *N*-acyldiazenes (**2**), as illustrated in Scheme 2. The reactions preceded smoothly to give the desired 1,3,4-oxadiazines with good yields in most of the cases. For the monosubstituted Ar^1 groups, both electron-rich and electron-poor groups were compatible with these reaction conditions, and no obvious substitution effect was

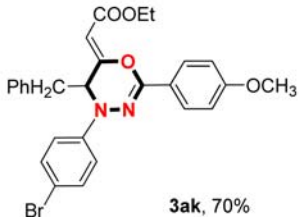
Scheme 2. DMAP-Catalyzed [2 + 4] Cycloadditions[a,b]



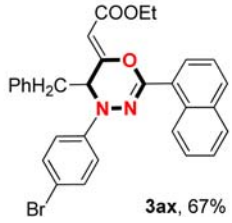


Ar^1 = Ph, **3aa**, 71%
Ar^1 = 4-MePh, **3ab**, 74%
Ar^1 = 4-ClPh, **3ac**, 70%
Ar^1 = 4-BrPh, **3ad**, 74%
Ar^1 = 4-NO_2Ph, **3ae**, 0%
Ar^1 = 2-ClPh, **3af**, < 5%
Ar^1 = 3-ClPh, **3ag**, 67%
Ar^1 = 2,4-$(Cl)_2$Ph, **3ah**, 77%
Ar^1 = 3,4-$(Cl)_2$Ph, **3ai**, 80%
Ar^1 = 3,5-$(Cl)_2$Ph, **3aj**, 60%

Ar^2 = 4-MeOPh, **3al**, 80%
Ar^2 = 4-MePh, **3am**, 46%
Ar^2 = 4-FPh, **3an**, 76%
Ar^2 = 4-ClPh, **3ao**, 71%
Ar^2 = 4-BrPh, **3ap**, 41%
Ar^2 = 4-NO_2Ph, **3aq**, 0%
Ar^2 = 2-MePh, **3ar**, 19%
Ar^2 = 3,4-$(MeO)_2$Ph, **3as**, 78%
Ar^2 = 3,5-$(MeO)_2$Ph, **3at**, 80%
Ar^2 = 3,4,5-$(MeO)_3$Ph, **3au**, 70%
Ar^2 = 2-furanyl, **3av**, 63%
Ar^2 = 1-naphthyl, **3aw**, 69%



3ak, 70%



3ax, 67%

[a]Reaction conditions: **1a** (0.30 mmol), **2** (0.20 mmol), DMAP (0.04 mmol), toluene (2.0 mL), rt, 48 h. [b]Isolated yield.

observed (**3aa**−**ad**,**ag**). For a NO_2-substituted diazene involved in the reaction, no desired product **3ae** was detected. Using **2f** with a Cl on the *ortho*-position of the Ar^1 group only afforded a trace amount of **3af**, and this was ascribed to the steric effect (**3af** vs **3ac** and **3ag**). Disubstituted Ar^1 groups were also tested, specifically 2,4-dichloro, 3,4-dichloro, and 3,5-dichloro, giving the corresponding products (**3ah**−**aj**) in 60−80% yields. Furthermore, changing substituents on the Ar^2 group in substrate **2** was also found to be suitable for the reaction, affording the desired products (**3ak**−**ap**) in moderate to good yields, except **3aq** and **3ar** due to their strong electron-withdrawing and steric effects, respectively. Substrates with two or three electron-rich groups, such as 3,4-dimethoxy, 3,5-dimethoxy, and 3,4,5-trimethoxy, reacted with **1a** to afford the corresponding products (**3as**−**au**) in 70−80% yields. For diazenes **2** having a heteroaromatic or naphthalen-1-yl group (Ar^2), the anticipated products (**3av**−**ax**) were isolated in 63−69% yields. The structure of **3al** was unambiguously confirmed by a single-crystal X-ray analysis.[16]

To further evaluate the scope of this reaction, other γ-substituent allenoates and active diazenes were examined, and the results are listed in Scheme 3. Allenoates with different γ-substituents, including methyl and ethyl penta-2,3-dienoates, reacted smoothly with various diazenes to produce the

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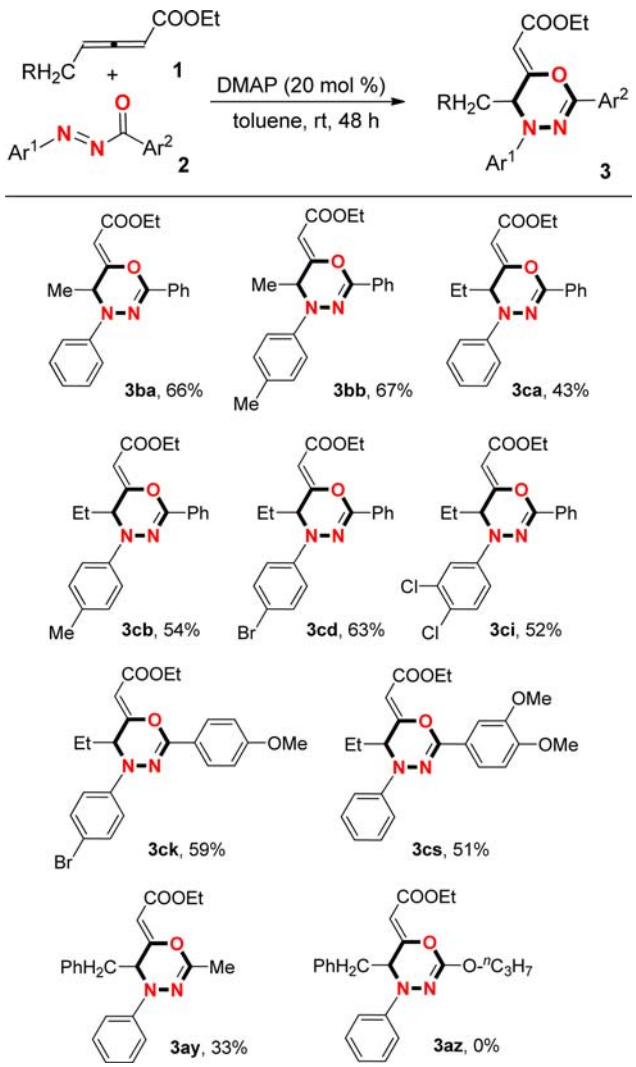
Scheme 3. Scope of Other γ-Substituent Allenoates and Active Diazenes[a,b]



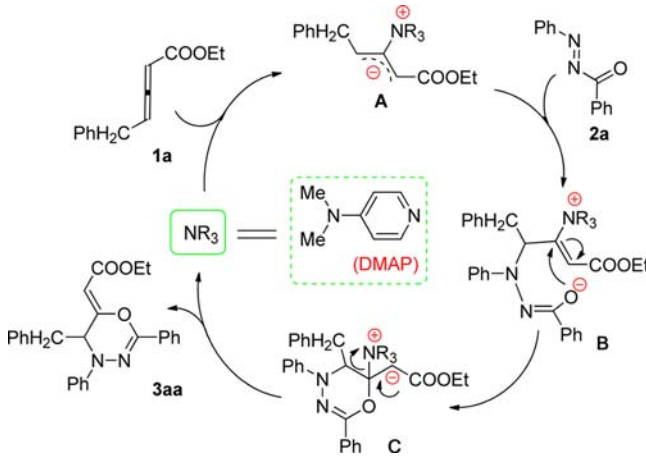
[a]Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol), DMAP (0.04 mmol), toluene (2.0 mL), rt, 48 h. [b]Isolated yield.

corresponding 1,3,4-oxadiazines in modest yields. *N*-Acetyldiazene is an effective electrophile. It reacted with **1a**, albeit producing **3ay** in only 33% yield. However, reaction with *N*-carbopropoxy-substituted diazene failed (**3az**).

A plausible mechanism was proposed for this [2 + 4] cyclization, as depicted in Scheme 4. The first step involves the activation of allene ester **1a** by DMAP to generate a zwitterionic intermediate **A**. Subsequent γ-nucleophilic attack of the electrophile **2a** provided **B**, which underwent intramolecular Michael addition of oxygen anion to carbon atom to produce intermediate **C**. Finally, the catalyst DMAP was eliminated, and the C=C double bond was regenerated, to afford the product **3aa**.

In summary, a direct synthetic method for the preparation of 1,3,4-oxadiazins via a DMAP-catalyzed [2 + 4] cycloaddition of allenoates with *N*-acyldiazenes is reported here. The reactions generated the corresponding products with good yields in most cases under simple and mild reaction conditions. This organic base-catalyzed one-step cycloaddition reaction generated three heteroatoms in a six-membered ring, providing new synthetic protocols for further heterocyclic

Scheme 4. Proposed Mechanism



synthesis. Further development of diazenes is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01237.

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Notes

The authors declare no competing financial interest.

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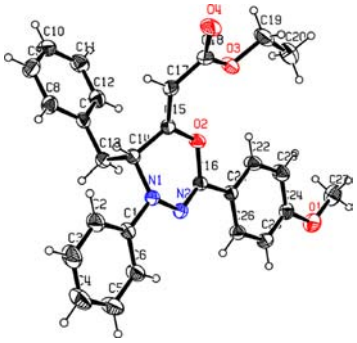
(16) The X-ray single crystal structure of **3al** is available from the Cambridge Crystallographic Data Centre (CCDC 1058288).



NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 was corrected on June 12, 2015.

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