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1,3-Dipolar Cycloadditions of 4-Acetoxy Allenoates: Access to 2,3-Dihydropyrazoles, 2,3-Dihydroisoxazoles, and Indolizines

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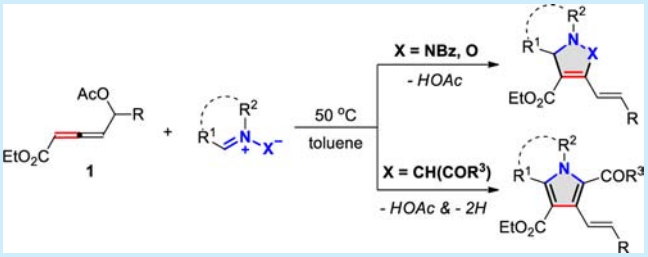
Supporting Information

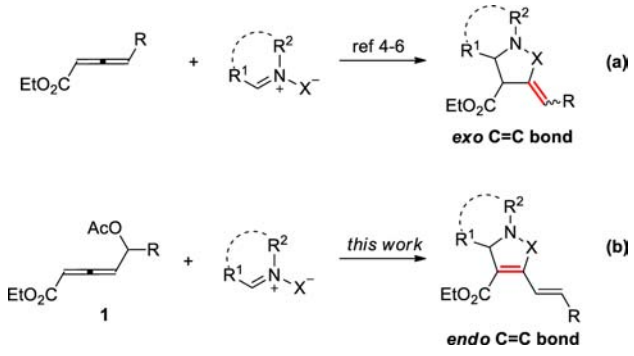
ABSTRACT: The thermal 1,3-dipolar cycloadditions of 4-acetoxyallenoates **1** with various dipoles have been reported. When azomethine imines and nitrones are used as the 1,3-dipole partner, the corresponding reactions afford 2,3-dihydropyrazole and 2,3-dihydroisoxazole derivatives, respectively. These reactions might proceed via a thermal 1,3-dipolar cycloaddition and the subsequent elimination of HOAc. In addition, allenoates **1** react well with in situ generated azomethine ylides in which a similar cycloaddition pathway is followed by oxidative aromatization to give indolizine derivatives.



Because of their biological significance and wide synthetic utility, the development of efficient and simple methods for the synthesis of *N*-heterocycles has attracted considerable attention. Among a variety of reported methods, the time-proven 1,3-dipolar cycloadditions represent one of the most powerful and straightforward tools.[1] In this context, the cycloadditions that employed electron-rich allenes as the dipolarophile partner have been extensively investigated, wherein allenes exhibit divergent reactivity due to their two similar cumulative C═C bonds.[2] Interestingly, electron-poor ones, 2,3-allenoates, have been recognized as a nice 1,3-dipole synthon with the aid of Lewis base catalysts, which are highly reactive toward the 1,3-dipolar-type cycloadditions with electron-poor alkenes and imines.[3] Additionally, the capability of allenoates as the dipolarophile partner for the 1,3-dipolar cycloadditions is self-evident[4−6] and features exclusive participation of the internal C═C bond of allenoate in the event of 1,3-dipolar cycloaddition, thus affording products bearing an *exo*-cyclic C═C bond unit (Scheme 1a). Only a few thermal 1,3-dipolar cycloadditions of allenoates gave the products with an *endo*-cyclic C═C bond.[7] As a complement, we herein report the cycloadditions of 4-acetoxyallenoates **1** with various 1,3-dipoles, including azomethine imines and nitrones as well as azomethine ylides (Scheme 1b). Importantly, the installation of an acetate group at the C4-position of allenoate **1** appears to facilitate these cycloadditions via the subsequent elimination of one molecule of HOAc, rendering mild reaction conditions and a different array of target structures (Scheme 1b).

As a part of our continuous efforts on the Lewis base catalyzed transformations of acetoxy-modified allenoates[8] and inspired by the recent reports of phosphine-catalyzed annulations of

Scheme 1. Allenoates as the Dipolarophile in Thermal 1,3-Dipolar Cycloadditions



allenoates with 1,3-dipoles,[9] we attempted to conduct the reaction of allenoate **1a** and azomethine imine **2a** in the presence of PPh_3 (20 mol %) and Cs_2CO_3 (1.2 equiv) in toluene at room temperature (Scheme 2, entry 1). Disappointingly, no reaction was observed. To our delight, a cycloaddition between **1a** and **2a** was triggered through simple elevation of the reaction temperature (50 °C), delivering 2,3-dihydropyrazole **3aa** in 77% isolated yield (Scheme 2, entry 2). The structural assignment was initially supported by NMR and HRMS and later corroborated by X-ray crystallography[10] of product **3fa** (vide infra). However, we were surprised to find that, without PPh_3 catalyst, the reaction was more successful and product **3aa** was obtained in 89% yield (Scheme 2, entry 3). Base additive Cs_2CO_3

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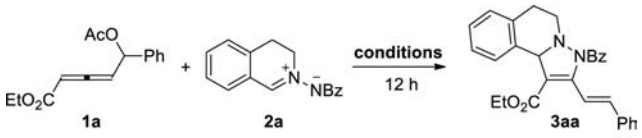
Scheme 2. Preliminary Results of the Reaction of 1a and 2a

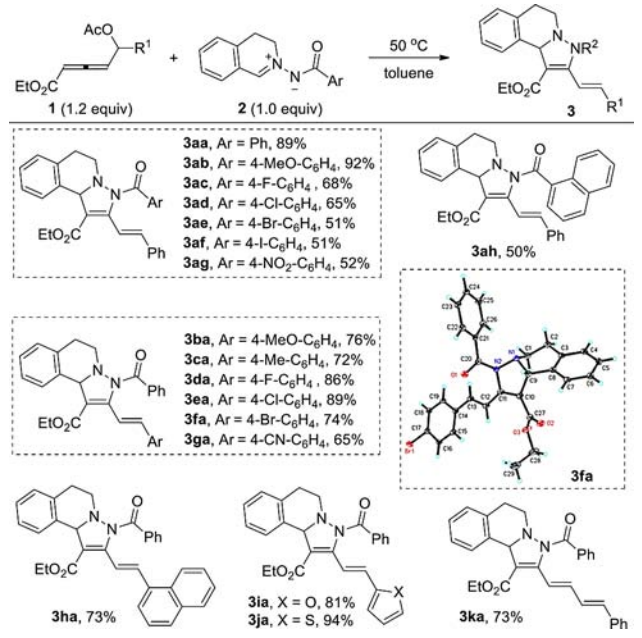


entry	conditions	yield (%)
1	20 mol % PPh_3, 1.2 equiv Cs_2CO_3, rt	< 5
2	20 mol % PPh_3, 1.2 equiv Cs_2CO_3, 50 °C	77
3	1.2 equiv Cs_2CO_3, 50 °C	89
4	50 °C	89

was also found not to be necessary at all, although HOAc was generated during the course of the reaction (Scheme 2, entry 4).

These promising results and the bioactive relevance of pyrazoloisoquinoline derivatives[11] led us to investigate the generality of this 1,3-dipolar cycloaddition. As shown in Scheme 3,

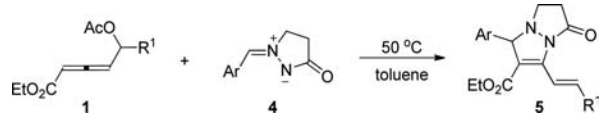
Scheme 3. 1,3-Dipolar Cycloadditions of Allenoates 1 and Azomethine Imines 2



the 1,3-dipolar cycloadditions of allenoates **1** and azomethine imines **2** were efficiently achieved with a considerably wide range of substrates. In terms of the imine partner, various benzoyl groups (**3aa**−**ah**), including 4-methoxybenzoyl, 4-halobenzoyl, and 4-cyanobenzoyl as well as 1-naphthoyl, could be well tolerated under the thermal cycloaddition conditions. The electron-donating substituents promoted the corresponding reactions more efficiently than those of the electron-withdrawing ones, which might arise from the difference of the nucleophilicity of nitrogen anion. On the other hand, the R^1 group of allenoates **1** also exhibited good tolerance. In addition to various phenyl substituents (**3ba**−**ha**), heteroaryl (**3ia** and **3ja**) and styryl (**3ka**) could be readily incorporated. It should be noted that no reactions were observed between **2a** and allenoates **1** with an alkyl R^1 substituent (not shown), demonstrating the limitation of this thermal 1,3-dipolar cycloaddition.

As a much more readily available 1,3-dipole, azomethine imines **4** are widely employed in the 1,3-dipolar cycloadditions. We were pleased to find that azomethine imines **4** also exhibited good activity toward 1,3-dipolar cycloaddition with allenoates **1**, and the results are summarized in Table 1. A wide range of aryl

Table 1. Cycloadditions of 1 with Azomethine Imines 4a



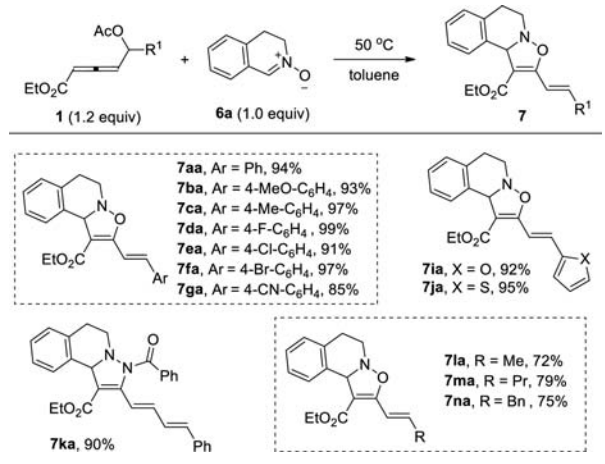
entry	1 (R^1)	4 (Ar)	5	yield[b] (%)
1	**1a** (Ph)	**4a** (Ph)	**5aa**	72
2	**1a**	**4b** (4-FC_6H_4)	**5ab**	64
3	**1a**	**4c** (4-ClC_6H_4)	**5ac**	53
4	**1a**	**4d** (4-MeC_6H_4)	**5ad**	53
5	**1a**	**4e** (4-$MeOC_6H_4$)	**5ae**	64
6	**1l** (Me)	**4f** (4-$NO_2C_6H_4$)	**5lf**	50
7	**1m** (Pr)	**4f**	**5mf**	51
8	**1n** (Bn)	**4f**	**5nf**	50

[a]Reaction conditions: **1** (0.24 mmol), **4** (0.2 mmol), toluene (2 mL), 50 °C. [b]Isolated yield.

groups with electron-donating or -withdrawing substituents of **4** could be tolerated, delivering the corresponding products **5aa**−**ae** in moderate yields (Table 1, entries 1−5). In sharp contrast to imines **2**, imine **4** smoothly underwent cycloadditions with the allenoates **1** bearing an alkyl R^1 substituent at the C4 position. Indeed, the reactions of imine **4f** with allenoates **1l**−**n** afforded the corresponding products **5lf**−**nf** in ca. 50% yields (Table 1, entries 6−8).

To further demonstrate the potential of allenoates **1** toward thermal cycloaddition, the reaction of **1a** with nitrone **6a** was conducted under the same conditions. We were delighted to find that the corresponding cycloaddition product **7aa** was isolated in 94% yield. As shown in Scheme 4, the cycloadditions of allenoates

Scheme 4. 1,3-Dipolar Cycloadditions of Allenoates 1 and Nitrone 6a



1 and nitrone **6a** exhibited high efficiency. Essentially quantitative isolated yields were obtained in the cases of allenoates **1b**−**k** with an aryl substituent. Allenoates **1l**−**n** with an alkyl R^1 substituent were also applicable, but in relatively lower efficiency, affording the corresponding products **7la**−**na** in 72−79% yields.

Compared to cyclic nitrone **6a**, acyclic nitrones **8a**−**c** were somewhat less reactive for the 1,3-dipolar cycloadditions with allenoates **1** (Scheme 5). The reaction of nitrone **8a** with

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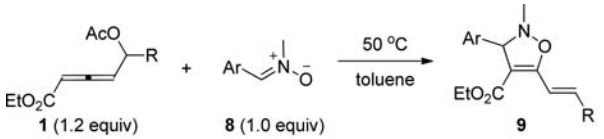
Scheme 5. 1,3-Dipolar Cycloadditions of Allenoates 1 and Nitrones 8

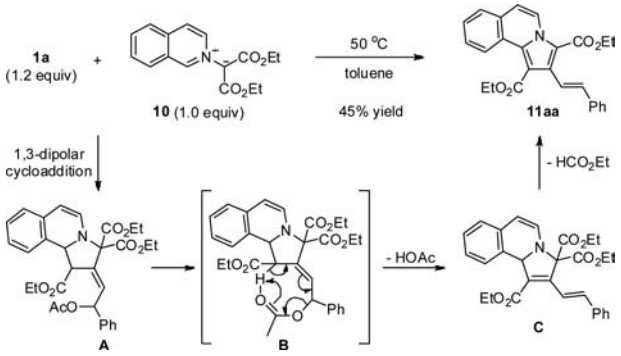


9aa (R = Ph, Ar = Ph): 85% yield
9ab (R = Ph, Ar = 4-MeO-C_6H_4): 79% yield
9ac (R = Ph, Ar = 4-Cl-C_6H_4): 76% yield
9la (R = Me, Ar = Ph): 62% yield
9oa (R = Bn, Ar = Ph): 60% yield

allenoate **1a** afforded the cycloaddition product **9aa** in 85% yield. For the cases of nitrones **8b** and **8c**, the yields of products **9ab** and **9ac** significantly dropped to 79% and 76%, respectively. Furthermore, acyclic nitrone **8a** also reacted with allenoates **1** with an alkyl R^1 substituent (**1l** and **1o**), delivering the corresponding products in moderate yields.

To emphasize the general applicability of allenoates **1** for the 1,3-dipolar cycloaddition, we finally extended the dipole partner to azomethine ylide **10**. Again, allenoate **1a** and azomethtine yilde **10** readily underwent dipolar cycloaddition to give pyrrolo[2,1-*a*]isoquinoline derivative **11aa** in 45% yield. In this process, one molecule each of HOAc and HCO_2Et were eliminated. Although the detailed mechanism was not clear at this stage, a plausible explanation for the formation of product **11aa** was presented in Scheme 6. Following the general

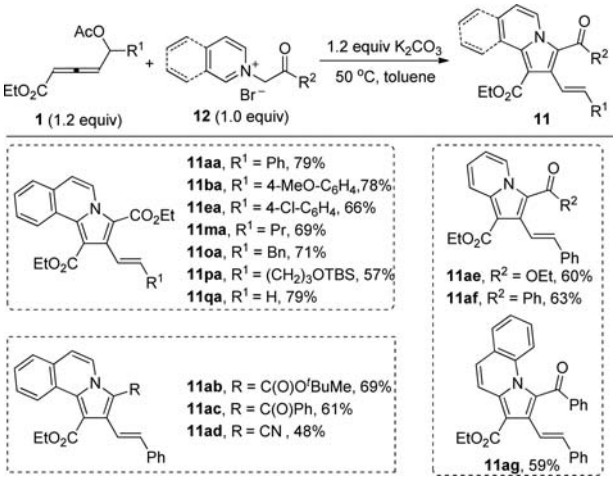
Scheme 6. 1,3-Dipolar Cycloaddition of Allenoate 1a and Azomethine Ylide 10



cycloaddition of allenoate and 1,3-dipole,[4−7] a similar cycloaddition adduct **A** was believed to be formed first. Likely due to its liable deprotonation of ester *α*-H and ready leaving character of allyl acetoxy, adduct **A** would eliminate one molecule of HOAc via transition state **B**, leading to the generation of intermediate **C**. These two steps might also be involved in the cycloaddition of allenoate **1** with azomethine or nitrone. Finally, intermediate **C** underwent the elimination of HCO_2Et to yield product **11aa**. The process of HCO_2Et elimination was similar to that of the 1,3-dipolar cycloaddition of azomethtine yilde and alkyne.[12]

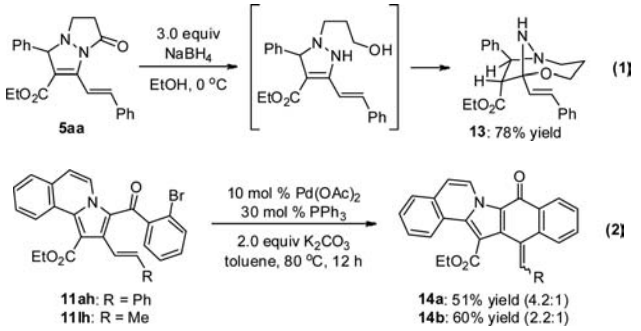
To our delight, the azomethine ylide involved cycloaddition with allenoate **1a** could be realized more efficiently using in situ generated azomethine ylide from the reaction of isoquinolinium derivative **12a** and K_2CO_3, delivering the same product **11aa** in 79% yield (Scheme 7). It was noteworthy to point out that this alternative cycloaddition exhibited wide substrate scope in terms of both allenoate **1** and azomethine ylide partners. Furthermore, this protocol could be successfully extended to pyridinium and

Scheme 7. 1,3-Dipolar Cycloadditions of Allenoates 1 and Pyridinium Derivatives 11 with the Aid of K_2CO_3



isoquinolinium derivatives, affording the corresponding products **11ae−af** in ca. 60% yields. For all of these cases, the formation of indolizines **11** would involve an additional aromatization step via air oxidation.

The synthetic utility of the cycloaddition products can be demonstrated by simple chemical manipulations. For instance, upon treatment of $NaBH_4$, cycloadition product **5aa** was readily converted into a novel NH-bridged bicycle **13** as a single isomer in 78% yield (eq 1). The formation of **13** might proceed via the reduction of pyrazolidinone and the subsequent intramolecular oxa-Michael addition. Moreover, using a common Heck reaction condition, novel large *π*-conjugated systems **14a** and **14b** were obtained from cycloaddition products **11ah** and **11lh**, respectively (eq 2).



In summary, we have established that 4-acetoxyallenoates **1** as a versatile dipolarophile are capable of undergoing 1,3-dipolar cycloaddition with various dipoles, including azomethine imine, nitrone, and azomethine ylide, affording the cycloaddition products with an endocyclic C═C bond. The wide array of target structures arose from the elimination of HOAc. Efforts are under way to realize the asymmetric variant using chiral metal complex catalysts and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02724.

Experimental procedures; spectral data for all novel compounds; NMR spectra of obtained compounds (PDF)
X-ray data of **3fa** (CIF)

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Notes

The authors declare no competing financial interest.

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