Reactivity of Enyne-Allenes Generated via an Alder-Ene Reaction

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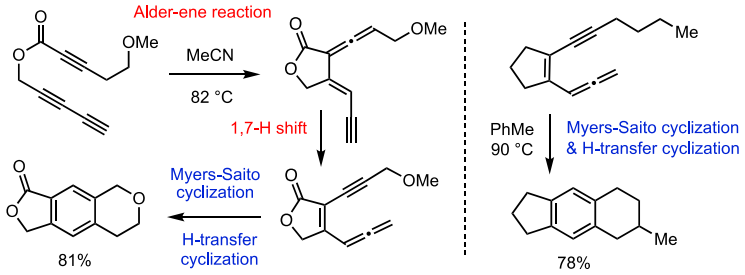
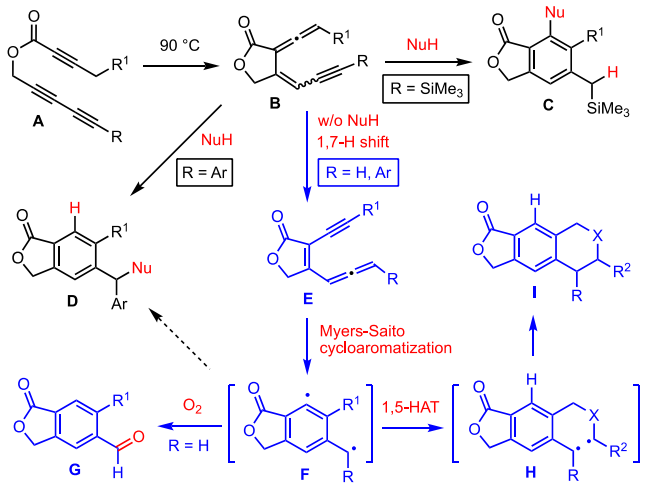


ABSTRACT: Tandem transformations of 1,3-diynyl propiolate derivatives are described. The Alder-ene reaction generates an enyne-allene, which undergoes a formal 1,7-H shift or a Diels-Alder reaction depending on the substituent on the alkyne. Terminal or aryl-substituted alkyne promotes a 1,7-H shift to generate a new enyne-allene, which undergoes a Myers-Saito cycloaromatization followed by a 1,5-H transfer-mediated cyclization to form highly functionalized benzo-fused 6-membered cycles. The reactivity of the preformed enyne-allene show comparable reactivity profiles.

The Myers-Saito cycloaromatization refers to the cyclization of enyne-allene to form an arene-based 1,4-σπ-diradical.[1,2] Certain anticancer natural products such as neocarzinostatin chromophore[3] contain a masked warhead functionality for enyne-allene formation as functionality relies on this aromatization process for their biological mode of action. Enyne-allene-containing molecules' anticancer activity and unique structure spurred extensive mechanistic[4] and synthetic[5,6] studies. In our investigation of the thermal reaction of ester-tethered triyne **A** in the presence of a nucleophile, we obtained benzannulation product **C** (Scheme 1).[7] We believe this novel benzannulation occurs via the Alder-ene reaction to form enyne-allene[8] **B** followed by a 1,4-addition of nucleophile. However, if the enyne-allene **B** contains an aryl substituent (R = Ar), nucleophile trapping occurs in the opposite mode to generate an isomeric product **D**. The different modes of nucleophile trapping to form products **C** and **D** suggest that the enyne-allene **B** with a silyl group undergoes preferential 1,4-addition with a nucleophile, whereas with an aryl substituent, a formal 1,7-H shift[9] becomes favorable to form a different enyne-allene **E**. The Myers-Saito cycloaromatization of **E** forms **F**, which can reveal a zwitterionic[10] reactivity to give **D**. A diradical reactivity of **F** gives aldehyde **G** after capturing O_2 or tricycle **I** via 1,5-hydrogen transfer to form **H** followed by a ring-closure.

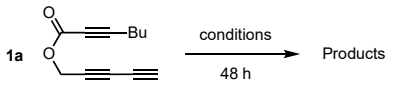
The substituent-dependent change in product distribution prompted us to investigate the Myers-Saito cyclization reactions of enyne-allenes **E** with and without nucleophiles. The role of the substituent is crucial for the enyne-allene **B** to undergo a formal 1,7-H shift to generate a new enyne-allene **F**.[9] Interestingly, products derived from the Myers-Saito cyclization of **B** have not been observed.

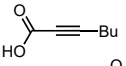
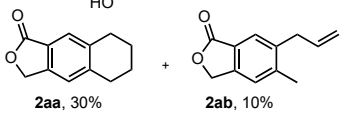
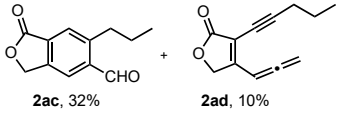
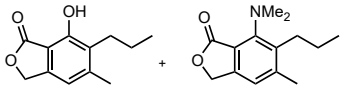
Scheme 1. Reactivity of in situ generated enyne-allenes



We commenced our exploration with 1,3-diynyl-2-heptynoate **1a** in toluene under reflux (Table 1), which mainly led to the cleavage of the ester providing 2-heptynoic acid as the major product along with uncharacterizable polymeric material (entry 1). A drastic change in the reaction profile was observed when the solvent was switched to CH_3CN. The reaction in undistilled CH_3CN generated product **2aa** (30%) was isolated along with **2ab** (10%) along with aldehyde **2ac** (32%) and unreacted enyne-allene **2ad** (10%) (entry 2). The formation of aldehyde **1bb** is the consequence of the trapping of the radical intermediate with molecular oxygen[11] and **2ad** is just a remaining intermediate. On the other hand, in freshly distilled CH_3CN, only two

Table 1. Solvent effect on the product distribution



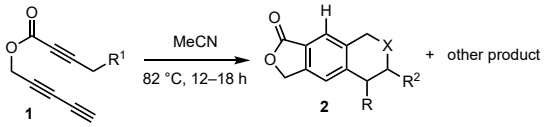
entry	solvent	temp (°C)	products / yield
1	PhMe	110	 87%
2	MeCN (undistilled)	82	 **2aa**, 30% + **2ab**, 10%;  **2ac**, 32% + **2ad**, 10%
3	MeCN (distilled)	82	**2aa**, 52% + **2ab**, 13%
4	DMF	110	 **2ae**, 35% + **2af**, 20%
5	DMSO	90	**2ae**, 60%
6	$ClCH_2CH_2Cl$	83	complex mixture

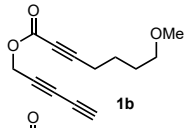
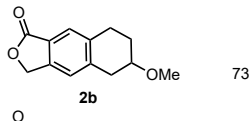
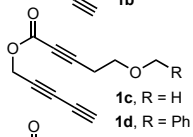
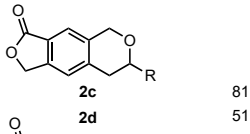
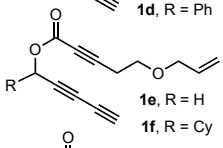
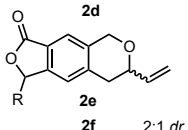
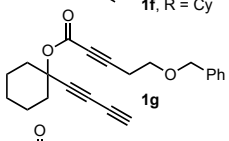
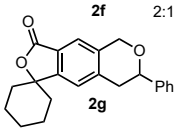
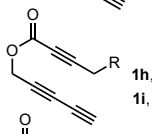
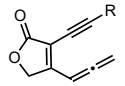
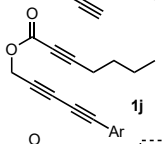
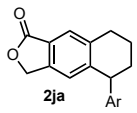
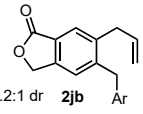
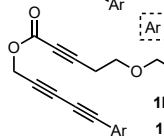
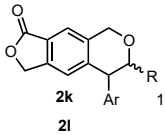
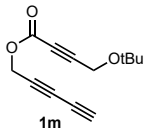
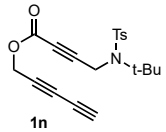
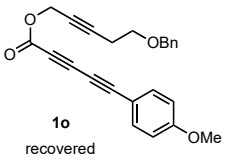
[a] Condition. [b] Isolated yields.

main products **2aa** (52%) and **2ab** (13%) were obtained (entry 3). Unexpectedly, in DMF at a higher temperature (110 °C), phenol derivative **2ae** (35%) and dimethylamine adduct **2af** (20%) were generated (entry 4). In DMSO, phenol derivative **2ae** (60%) was obtained as the sole product (entry 5), whereas a complex mixture was observed in dichloroethane (entry 6). Based on these results, we employed CH_3CN for the sequential reaction of the Alder-ene, 1,7-H shift (a deuterium-labeling pattern indicates that the 1,7-H shift occurs in a stepwise manner: see SI for details), Myers-Saito cycloaromatization, and 1,5-H transfer cyclization.[12]

With the optimized condition, we next explored the reaction with substrates containing additional substituents (Table 2). When heating **1b** containing a methoxy group at the carbon bearing the C–H bond undergoing 1,5-H transfer gave products **2b** with a 73% yield (entry 1). The reaction of **1c** and **1d** containing a methoxyethyl or benzyloxyethyl group generated the corresponding products **2c** (81%) and **2d** (51%), respectively (entries 2 and 3). Substrate **1e** containing an allyloxyethyl group provided **2e** (46%), whereas a similar substrate **1f** containing an extra cyclohexyl group in the tether gave a slightly increased yield of **2f** (53%, 2:1 *dr*) (entries 4 and 5). The introduction of a quaternary center on the ester tether in **1g** decreased the yield of **2g** to 36% (entry 6). The reaction of **1h** containing a propargylic triethylsilyl group generated **2h**, which did not undergo the Myers-Saito cyclization at 110 °C for an extended time (entry 7).[13] Similar behavior was observed with **1i** containing a CH_2OTHP group, and **2i** was isolated in 56% yield (entry 8).[13] Substrate **1j**, containing an aryl group on the terminal carbon of the diyne moiety, afforded **2ja** and **2jb** in a 60% yield with a 2.2:1 ratio (entry 9). Substrates **1k** and **1l** containing a benzyloxy or an allyloxy group provided improved yields

Table 2. Reaction scope with terminal and an aryl group containing 1,3-diynes



entry	substrate	product	yield (%)
1	 **1b**	 **2b**	73
2	 **1c**, R = H	 **2c**	81
3	**1d**, R = Ph	**2d**	51
4	 **1e**, R = H	 **2e**	46
5	**1f**, R = Cy	**2f** 2:1 *dr*	53
6	 **1g**	 **2g**	36
7	 **1h**, R = $SiEt_3$	 **2h**	73
8	**1i**, R = CH_2OTHP	**2i**	56
9	 **1j**	 **2ja** Ar 2.2:1 dr  **2jb** Ar	60
10	Ar = Ph-4-OMe;  **1k**, R = Ph	 **2k** Ar 1.7:1 *dr*	84
11	**1l**, R = Vinyl	**2l** 2:1 *dr*	72
	 **1m** decomposed	 **1n** recovered	 **1o** recovered

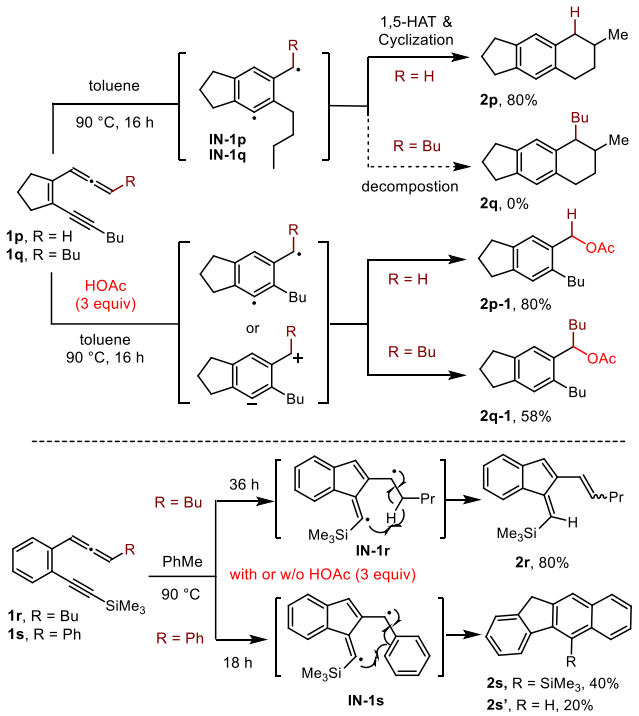
[a] Condition. [b] Isolated yields.

of products **2k** (84%, 1.7:1 *dr*) and **2l** (72%, 2:1 *dr*) (entries 10 and 11).[14] Substrate **1m** decomposed, whereas **1n** was recovered. Substrate **1o** containing a reversed ester linkage was recovered after heating at 150 °C in xylene for 18 h.

Next, we examined the reactivity of preformed enyne-allenes (Scheme 2). Treatment of terminal allene-containing enyne-allenes **1p** provided a good yield of the expected product **2p**, while a butyl-substituted allene-containing **1q** decomposed under the same conditions and product **2q** was not obtained. On the other hand, **1p** and **1q** lead to the formation of products **2p-1** and **2q-1**, re-

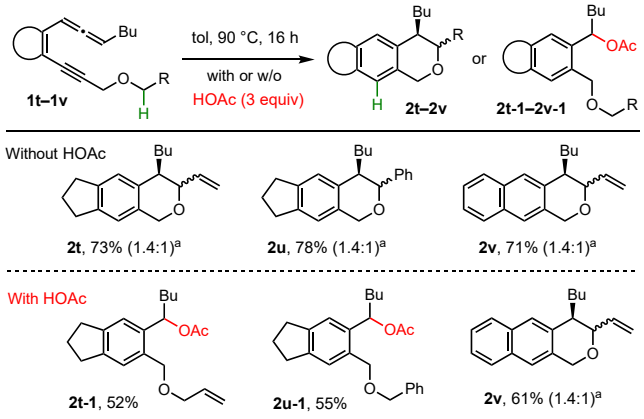
spectively, upon heating in the presence of AcOH (3 equiv). These results suggest that the substituent on the allene does not affect the Myers-Saito cyclization to form intermediates **IN-1p** and

Scheme 2. The effect of the allene substituent on the reactivity of enyne-allenes for radical and ionic reaction



IN-1q, but their trapping behaviors manifested by radical and ionic characters are significantly different. The enyne-allenes **1r** and **1s** provided products **2r** and **2s**, respectively, regardless of the presence or absence of AcOH. These reactions are assumed to proceed through the Schmittel cyclization[2b-d, 4h, 12e] involving **In-1r** and **In-1s,** although **2s** can be derived from a Diels-Alder reaction.

Table 3. The favorable ionic trapping mode of reaction of enyne-allenes over a radical mode



[a]Ratio of diastereomers.

We further explored the reactivity of enyne-allenes **1t–1v** that contain more active C–H bonds for 1,5-hydrogen transfer, which provided diradical-mediated ring-closure products **2t–2v** in 71–78% yields (Table 3). In the presence of AcOH (3 equiv), the reactions of **1t** and **1u** containing an allyl and benzyl ether, respectively, still favor acetoxy-trapping to generate products **2t-1** (52%) and **2u-1** (55%). In contrast, a benzene-tethered substrate **1v** prefers to undergo a radical-mediated cyclization to give **2v** in 61% yield. This indicates that the ionic versus radical reactivity of the intermediate generated from the Myers-Saito cyclization critically depends on the substituents of the σ,π-1,4-diradicals.

In summary, we explored the tandem transformation of 1,3-diynyl propiolate derivatives under thermal conditions. The overall process involves a sequence of Alder-ene reaction, formal 1,7-H shift, Myers-Saito cycloaromatization, 1,5-H translocation, and radical coupling to form a 6-membered ring fused to the newly formed arene moiety. The 1,7-H shift to form more stable isomeric enyne-allenes depends on the substituent of the alkyne moiety. If the alkyne moiety is terminal or contains an aryl substituent, the 1,7-H shift occurs, and the rearranged enyne-allenes efficiently undergo the Myers-Saito cycloaromatization to generate a σ,π-1,4-diradicals. Among possible pathways, a 1,5-H translocation promoted by the aryl σ-radical from a benzylic C–H to form π,π-1,6-diradical followed by annulation to form 6-membered rings including functionalized isochromane skeletons.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

This material is available free of charge at http://pubs.acs.org

General information, Experimental details, Characterization data of substrates and products, References, 1H&13C NMR spectra.

Accession codes

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Notes

The authors declare no competing financial interests.

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(14) The diastereomer conformation of **2k&2l** are assigned based on the *J* coupling constants between 2 methine units as described on the ^{1}H NMR spectra of these 2 entries in the Supporting infomation.