Organic LETTERS

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Stereoselective Synthesis of (2*Z*)-2,4-Dienamides via NBS-Mediated Allyloxyl Addition–Claisen Rearrangement–Dehydrobromination Cascade Reaction of Ynsulfonamides

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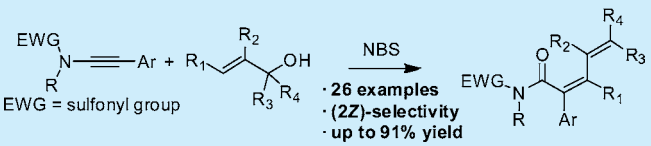
Supporting Information

ABSTRACT: An NBS-promoted allyloxyl addition–Claisen rearrangement–dehydrobromination cascade reaction has been developed. More than 20 substituted alkynylsulfonamides were reacted with allyl alcohols to generate (2*Z*)-2,4-dienamides in moderate to high yields. A mechanistic model has been proposed to account for the overall reaction sequence including the stereochemical outcome. Theoretical calculations suggested that a [3,3] sigmatropic rearrangement be the rate-limiting step.



Ynamides have become increasingly popular synthons in modern organic synthesis,[1] and various efficient synthetic methods have been established for these compounds.[2] Due to the better balance between the reactivity and stability issues, ynamides have proved to be good alternatives for the more conventional ynamines,[3] whose sensitivity toward hydrolysis coupled with its high reactivity makes them less accessible in diversity. In contrast, ynamides are relatively easy to handle and are accessible through a variety of stereoselective transformations.[4]

Many acyclic and cyclic compounds such as benzofurans,[5] enamides,[6] carbolines,[7] and oxazoles[8] have been synthesized from ynamides. A common feature of these reactions lies in the utilization of transition-metal catalysts[9] (Figure 1a). For example,

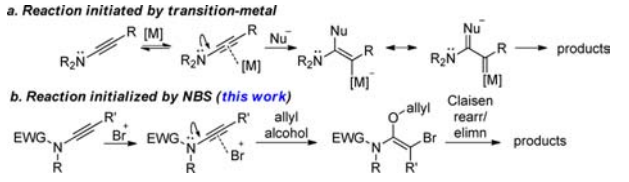
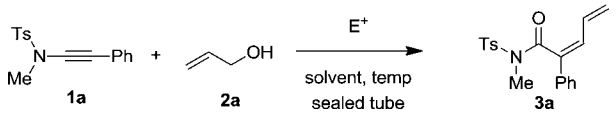


Figure 1. Reactions of ynamides/ynsulfonamides in different activation modes.

over the past decade, gold-catalyzed reactions have attracted considerable attention due to the strong π acidity of gold catalysts and the associated activation of unsaturated C–C bonds toward nucleophilic attack.[10] It should be highly desirable to investigate nontransition-metal activation modes for the carbon–carbon triple bond embedded in the ynamides. In terms of the latter modes, Hsung's group reported in 2002 a novel PNBSA-catalyzed asymmetric Claisen rearrangement[11] starting from chiral ynamides and Cao developed a carbocation-induced synthesis of 2-amidobenzofurans from ynamides and

Table 1. Optimization of the Reaction Conditions[a]



entry	E^+	solvent	temp (°C)	time (h)	yield[b] (%)
1	NBS	MeCN	80	8	53
2	NBS	MeCN	100	8	91
3	NBS	MeCN	110	8	84
4	NBS	THF	100	8	36
5	NBS	1,4-dioxane	100	8	42
6	NBS	MePh	100	8	messy
7	NBS	DCE	100	8	89
8	NBS	DMF	100	8	29
9	NBS	CCl_4	100	8	NR
10[c]	NBS	MeCN	100	8	88
11	NIS	MeCN	100	16	52
12	NCS	MeCN	100	24	NR
13	I_2	MeCN	100	16	43

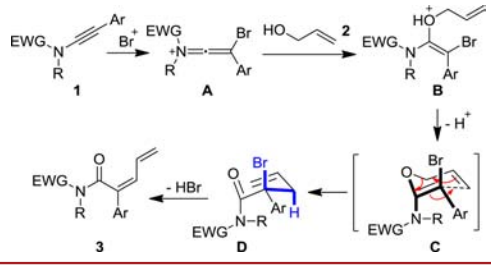
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), E^+ (1.05 equiv), solvent (2 mL), sealed tube. [b]Isolated yield. [c]NBS (2 equiv). E^+ = an electrophilic activator. NR = no reaction.

diarylmethanols in 2013.[12] More recently, Maulide's group realized a Brønsted acid catalyzed [3,3]-sigmatropic rearrangement[13] and Zhu disclosed a carbocation-initiated cycloisomerization using ynamides.[14] In these cases, either a proton[11,13a] or a carbocation[12,14] induced the initial electrophilic addition to the carbon–carbon triple bond and the subsequent transformations. Inspired by these excellent pieces of work, we sought to explore, with ynsulfonamides, whether

Received: June 29, 2015
Published: August 13, 2015

DOI: 10.1021/acs.orglett.5b01859
Org. Lett. 2015, 17, 3994–3997

Scheme 1. Proposed Mechanism for the Formation of 3

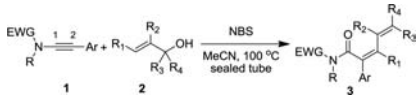


or not *N*-bromosuccinimide (NBS) or a similar species could mediate an allyloxyl addition−Claisen rearrangement−dehydrobromination cascade reaction (Figure 1b).

Ynsulfonamides (such as **1a**) were selected as the substrates due to their enhanced nucleophilicity over lactam- or oxazolidinone-containing ynamides as well as feasibility in synthesis, crystallization, and handling. These substrates were prepared via copper-mediated[1c,15] amidation of bromoalkynes according to Hsung's protocol. The reaction of **1a** with **2a** (2 equiv) was first carried out in the presence of NBS (1.05 equiv) in MeCN at 80 °C. Indeed, the allyloxyl addition−Claisen rearrangement−dehydrobromination cascade reaction was effected in a highly stereoselective manner upon the activation of the carbon−carbon triple bond with NBS and (2*Z*)-2,4-dienamide **3a** was generated in 53% yield as a single product (Table 1, entry 1). The (*Z*) configuration of a newly generated *α*,*β*-carbon−carbon double bond was confirmed by the NOESY analysis of **3a**, **3g**, and **3p**, in which the correlations between the specified protons were observed (see Supporting Information). The yield of **3a** was improved to 91% when the reaction mixture was heated at 100 °C (entry 2). However, raising the reaction temperature to 110 °C resulted in a drop in the yield of the diene product along with an increase in byproduct formation (entry 3). The solvent effects were next investigated, and MeCN was found to be superior to any other solvents tested (including THF, 1,4-dioxane, MePh, DCE, DMF, and CCl_4) at the same temperature (entries 2, 4−9). An increase of the NBS amount from 1.05 to 2 equiv failed to produce any beneficial effect (entry 10). Among the electrophilic activators investigated, NBS performed much better than NIS or I_2 (entries 11 and 13), while NCS failed to promote the reaction (entry 12).

A possible mechanism for the above reaction is depicted in Scheme 1. Nucleophilic attack of ynsulfonamide **1** on the

Table 2. Scope of the Current Cascade Reaction[a]



entry	ynamide **1**	alcohol **2**	product	**3** (%)[b]	entry	ynamide **1**	alcohol **2**	product	**3** (%)[b]
1	**1a**	**2a**	**3a**	91 84[c]	16	**1p**	**2a**	**3p**	80
2	**1b**	**2a**	**3b**	82	17	**1q**	**2a**	**3q**	61
3	**1c**	**2a**	**3c**	85	18	**1r**	**2a**	**3r**	85
4	**1d**	**2a**	**3d**	83	19	**1s**	**2a**	**3s**	41
5	**1e**	**2a**	**3e**	82	20	**1t**	**2a**	**3t**	79
6	**1f**	**2a**	**3f**	81	21	**1u**	**2a**	**3u**	27
7	**1g**	**2a**	**3g**	81[d]	22[i]	**1v**	**2a**	**3v**	trace
8[e]	**1h**	**2a**	**3h**	68	23	**1a**	**2b**	**3w**	69
9	**1i**	**2a**	**3i**	67[f]	24	**1a**	**2c**	**3x**	74
10[g]	**1j**	**2a**	**3j**	78	25	**1a**	**2d**	**3y**	31[j]
11	**1k**	**2a**	**3k**	73	26	**1h**	**2e**	**3z**	62
12	**1l**	**2a**	**3l**	76[h]					
13	**1m**	**2a**	**3m**	72					
14	**1n**	**2a**	**3n**	64					
15	**1o**	**2a**	**3o**	81					

[a]Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), NBS (1.05 equiv), MeCN (2 mL), 100 °C, sealed tube. [b]Isolated yield of **3**. [c]Use of **1a** (1 mmol). [d]*Z*/*E* = 7:1; ratio was determined by using ^{1}H and ^{13}C NMR. [e]Mbs = 4-MeO-benzenesulfonyl. [f]*Z*/*E* = 17:1. [g]Bs = benzenesulfonyl. [h]*Z*/*E* = 12:1. [i]An allyloxyl addition product was obtained (21%). [j]*Z*/*E* = 1:1.

DOI: 10.1021/acs.orglett.5b01859
Org. Lett. 2015, 17, 3994−3997

bromine atom of NBS forms ketene iminium **A**, to which a nucleophilic addition of alcohol **2** takes place to afford **C** after loss of a proton. Intermediate **C** undergoes Claisen sigmatropic rearrangement leading to α-aryl-α-bromo-γ,δ-unsaturated amide **D**, which gives (2*Z*)-2,4-dienamide **3** upon elimination of a molecule of hydrogen bromide via a *trans*-coplanar conformation.

Next, the scope of this cascade reaction was investigated. An array of ynsulfonamides were subjected to the optimal reaction conditions (see Table 1, entry 2), and the results are summarized in Table 2. Ynsulfonamides bearing a sulfonyl group (such as Ts, Ms, Ns, Mbs, and Bs) on the nitrogen atom were converted smoothly into the corresponding conjugated dienamides in moderate to high yields when heated with allyl alcohol (**2a**) and NBS (entries 1−20). A series of substituents on the ynsulfonamide nitrogen atom (e.g., Me, ^{n}Bu, Bn, and Ph) and those on the phenyl ring within the Ar moiety (e.g., *p*-Cl, *p*-Me, *m*-Me, *o*-Cl, and *p*-OMe) were tolerated. In terms of the effect of the structural characteristics of ynsulfonamide **1** on the cascade reaction, both the presence of the less electron-withdrawing *p*-methoxy benzensulfonyl (Mbs) group on the nitrogen atom (entries 8 and 9) and the possession of a chloro substituent at the *para* or *ortho* position of the phenyl group attached to C-2 (entries 14 and 19) resulted in lower yields of the desired products. In the former case, the reactivity of ketene iminium **A** was presumably lowered with Mbs attached to the nitrogen; for the latter, the alkyne activation step was possibly affected adversely by the chlorine atom. Moreover, if the sulfonyl group was replaced by an acyclic or cyclic alkoxycarbonyl, the reaction efficiency dramatically decreased (entry 21) or essentially diminished (entry 22). In these two cases, higher reaction temperatures led only to the formation of complex mixtures. Finally, the reaction of ynsulfonamides (including **1a** and **1h**) with four substituted allyl alcohols (**2b**−**2e**) was investigated. The cascade reaction took place reasonably well with substituted allyl alcohols (**2b**, **2c**, and **2e**), although the dienamide products were obtained in moderate yields (entries 23, 24, and 26). Notably, the use of **2d** as the nucleophile led to the formation of the product **3y** in only 31% yield, probably due to the severe steric hindrance caused by the two germinal methyl groups in **2d** (entry 25).

The density functional theory was applied to gain insight into the reaction mechanism (Figure 2).[16] According to the calculation

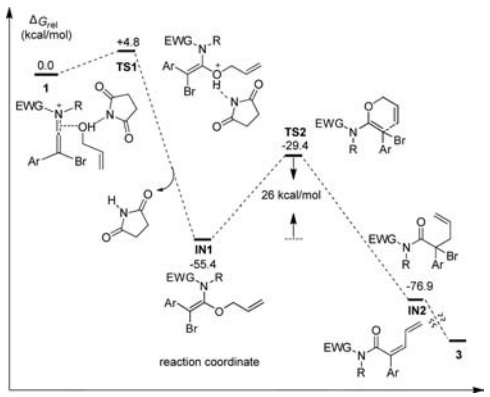


Figure 2. Free energy profile for the cascade reaction.

results, addition of allyl alcohol takes place to afford **IN1** and succinimide through the transition state **TS1** involving a C−O bond formation along with an O−H bond cleavage. The activation barrier is 4.8 kcal/mol for this step. Subsequent [3,3] sigmatropic rearrangement would generate **IN2** via a six-membered transition state (**TS2**), whose free energy of activation is calculated to be 26.0 kcal/mol. The higher barrier for **TS2** indicates that the second step is rate-limiting. Finally, dehydrobromination of **IN2** would give the final product **3**.

In summary, we have developed a cascade reaction that includes NBS-mediated addition of allyl alcohols to ynsulfonamides, Claisen rearrangement, and dehydrobromination, providing a simple and efficient route to (2*Z*)-2,4-dienamides, a type of useful intermediate in organic synthesis. A mechanistic model has been proposed to account for the overall reaction sequence including the stereochemical outcome. Theoretical calculations suggested that the [3,3] sigmatropic rearrangement should be the rate-limiting step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01859.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSFC (21272105; 21290180; 21302078), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1138), FRFCU (lzujbky-2013-ct02), and "111" Program of MOE for the financial support. We are grateful to Professor Ran Fang of Lanzhou University and to Professor Fayang Qiu of Guangzhou Institute of Biomedicine and Health for enlightening discussions.

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DOI: 10.1021/acs.orglett.5b01859
Org. Lett. 2015, 17, 3994−3997