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Time-Economical Radical Cascade Cyclization/Haloazidation of 1,6-Enynes: Construction of Highly Functional Succinimide Derivatives

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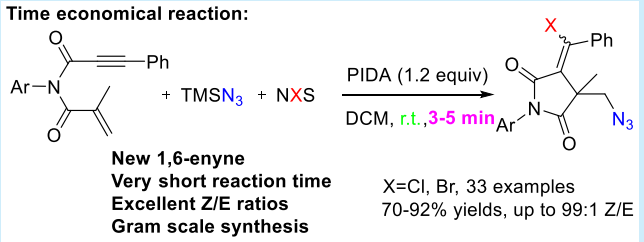
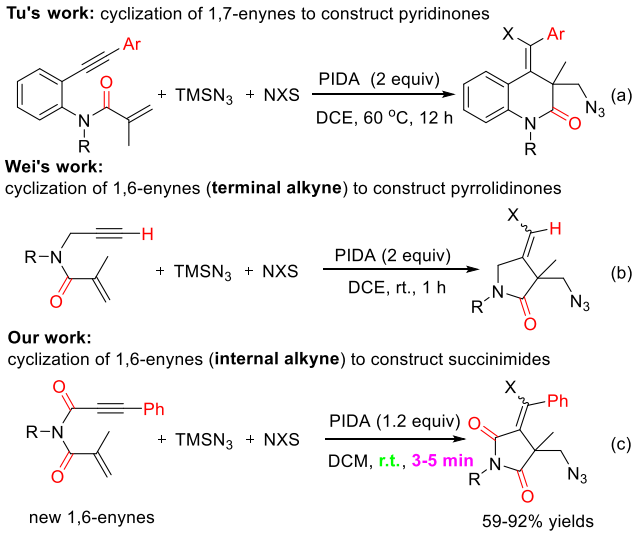
ABSTRACT: A "time-economical" radical cascade cyclization/haloazidation of 1,6-enynes provides a direct approach to access highly functional succinimide compounds. Moderate to excellent yields along with excellent *Z*/*E* ratio were obtained under the reaction features of broad substrate scope, good functional group tolerance, and mild reaction conditions.



Succinimide is one of the most important five-membered N-containing motifs, which widely exists in a large number of products with biological and pharmaceutical activities.[1] Indeed, some succinimide derivatives can be employed as drug candidates.[2−4] For example, the promotion effect of succinimide on amyloid fibrillation of hen egg white lysozyme was revealed by Liu and co-workers,[3] which indicated that the compounds with a succinimide scaffold have the potential role in treating a series of neurodegenerative diseases. In addition, Obniska and Kaminski[4] reported that the succinimide derivatives appear to possess anticonvulsant activity. Driven by their bioactive significance, several efficient strategies for the synthesis of these motifs have been well-established.[5] Despite the obtained achievements, a practicable approach to access the highly functional succinimide derivatives is still highly desirable.

Recently, the transition-metal-catalyzed[6] cyclization and radical cascade cyclization[7,8] employing 1,*n*-enynes as agents have emerged as versatile methodologies for building five- or six-membered carbocycles and heterocycle compounds, for which radical cascade cyclizations of 1,*n*-enynes especially draw more attention owing to their ability to construct various functional cycles by adjusting the versatile radical precursor.[7,8] In addition, halogen and azide groups are significantly useful motifs due to their unique reactivity and generally easy to vary functionalities.[9] Since 2015, Valiulin,[10] Chen,[11] and Leforestier's groups[12] subsequently disclosed a 1,2-chloroazidation radical reaction of various olefins, presenting several approach to access products containing halogen and azide groups. In 2016, Wang et al.[8b] achieved the metal-free radical cascade cyclization/iodoazidation of 1,7-enynes to prepare pyridinone compounds containing iodine and azide group (Scheme 1a). In 2018, Wei's group[8d] reported a mild radical haloazidation of 1,6-enynes to construct the functional 2-pyrrolidinones bearing halogen and azide groups (Scheme 1b). Moreover, chemists often consider several economic factors (such as atom economy,[13] step economy,[14] redox economy,[15] and pot economy[16]) in the field of organic synthesis, whereas we propose that time economy is equally important. We herein report a "time-economical" radial cascade cyclization/haloazidation of new 1,6-enynes to furnish highly functional succinimide derivatives (Scheme 1c).

Scheme 1. Radical Haloazidation of Enynes to Construct Heterocycle Compounds



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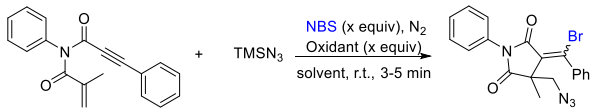
Our initial efforts focused on the optimization of reaction conditions by employing *N*-phenyl-*N*-(3-phenylpropioloyl)-methacrylamide **1a** to react with azidotrimethylsilane **2** and *N*-bromosuccinimide (NBS) in the reaction media at room temperature under a N_2 atmosphere (Table 1). As shown in

Table 1. Reaction Optimization of 1a with 2[a]



1a 2 3aa

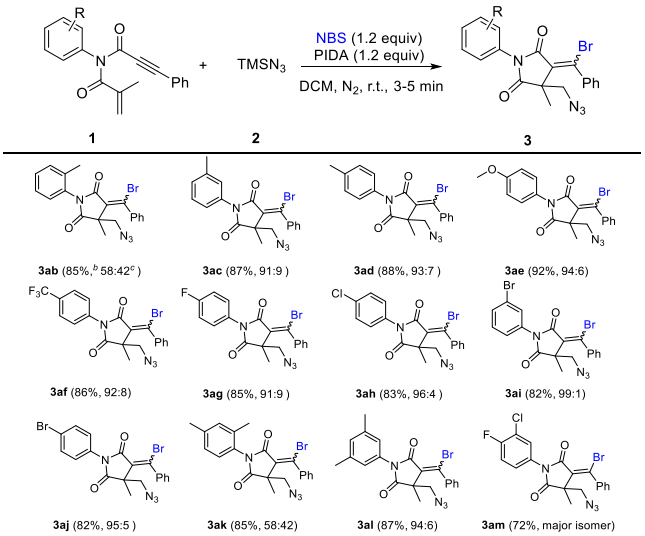
entry	oxidant (*x* equiv)	solvent	Br source (*x* equiv)	yield[b] (%)	*Z*/*E* ratio
1		DCM	NBS (1.2)	45	93:7
2		DCE	NBS (1.2)	40	93:7
3		CH_3CN	NBS (1.2)	38	93:7
4		EtOH	NBS (1.2)	23	93:7
5		DMF	NBS (1.2)	trace	93:7
6		THF	NBS (1.2)	trace	93:7
7		1,4-dioxane	NBS (1.2)	trace	93:7
8	TBHP (1.0)	DCM	NBS (1.2)	60	93:7
9	TBPB (1.0)	DCM	NBS (1.2)	68	93:7
10	BPO (1.0)	DCM	NBS (1.2)	NR	ND
11	H_2O_2 (1.0)	DCM	NBS (1.2)	NR	ND
12	DTBP (1.0)	DCM	NBS (1.2)	NR	ND
13	PIDA (1.0)	DCM	NBS (1.2)	85	93:7
14	PIDA (1.2)	DCM	NBS (1.2)	90	93:7
15	PIDA (1.5)	DCM	NBS (1.2)	87	93:7
16	PIDA (2.0)	DCM	NBS (1.2)	83	93:7
17	PIDA (1.2)	DCM	NBS (1.0)	75	93:7
18	PIDA (1.2)	DCM	NBS (1.5)	89	93:7
19	PIDA (1.2)	DCM	NBS (2.0)	88	93:7
20	PIDA (1.2)	DCM	NBS (1.2)	82[c]	93:7
21	PIDA (1.2)	DCM	NBS (1.2)	75[d]	93:7
22	PIDA (1.2)	DCM	NBS (1.2)	51[e]	93:7

[a]Reaction conditions: **1a** (0.20 mmol), $TMSN_3$ (0.24 mmol), and the oxidant were combined with NBS in solvent (2.0 mL) for 3−5 min (monitored reactions by TLC) under a nitrogen atmosphere. [b]Isolated yields. [c]Reaction at 40 °C. [d]Reaction at 50 °C. [e]Under air.

entries 1−7 of Table 1, moderate yields along with excellent *Z*/*E* ratios of the desired cycloaddition/bromoazidation product **3aa** were obtained in only 3−5 min using chlorinated solvents (dichloromethane (DCM), 1,2-dichloroethane (DCE), and polar solvents (acetonitrile, ethanol)) as reaction media, whereas poor reactivity was observed using basic solvents (dimethylformamide (DMF)) and ether solvents (tetrahydrofuran, 1,4-dioxane). To further improve the reaction efficiency, other parameters were systematically investigated in DCM. Due to the notable role in the generation of a radical, several oxidants were then screened to find their promoting effect in this cyclization (entries 8−13). For example, corresponding cascade reactions with an obvious increase in yields of product **3aa** smoothly proceeded with the addition of TBHP (60%, entry 8) or TBPB (68%, entry 9), whereas no reaction occurred in the presence of BPO, H_2O_2, or DTBP. To our delight, with the oxidation of phenyliodine diacetate (PIDA), the desired cycloadduct **3aa** was obtained with significantly improved yield (85%, entry 13). Obviously, the loading of oxidant had a certain influence on the reactivity of this tandem cycloaddition reaction, providing further improvement of yield to 90% with 1.2 equiv of PIDA (entry 14). However, more loading of PIDA was detrimental to the reaction, resulting in lower yield (entries 15 and 16). In addition, 1.2 equiv of a bromo source was always proven to be the optimized loading in this reaction after several investigations of bromo source loading (entry 14 vs entries 17−19). It was found that further increasing of the reaction temperature distinctly impaired the reactivity (entries 20 and 21), and it should be noted that the yield decreased significantly when the reaction was carried out in air (entry 22), which meant that neither high temperature nor air was suitable for this reaction. According to the above experiments, the optimal reaction system was confirmed as follows: reaction of 1,6-enyne **1a** with 1.2 equiv of azidotrimethylsilane **2** and 1.2 equiv of NBS was performed in DCM (2 mL) with 1.2 equiv of PIDA at room temperature under a N_2 atmosphere.

Based on the optimal reaction condition, we evaluated the scope and limitation of the cascade reaction using various N-substituted phenyl-*N*-(3-phenylpropioloyl)methacrylamides **1** along with azidotrimethylsilane **2** and NBS as an active partner. As indicated in Table 2, good to excellent yields with excellent

Table 2. Three-Component Bromoazidation of 1,6-Enynes[a]



[a]Reaction conditions: unless otherwise noted, **1** (0.20 mol), $TMSN_3$ (0.24 mmol), NBS (0.24 mmol), and PIDA (0.24 mol) in DCM (2.0 mL) at room temperature for 3−5 min (monitored reactions by TLC) under a nitrogen atmosphere. [b]Isolated yields. [c]Ratio of *Z*/*E* isomer is detected by ^1H NMR.

configurational selectivity (*Z*/*E* ratio) could be obtained in all cases. Notablely, the *Z*/*E* ratio of the reaction had an obvious steric effect. For example, by adjusting the position of substituent R from *ortho* to *para*, the *Z*/*E* ratio of the products was significantly increased (**3ad** vs **3ab**). The *ortho*-substituents appeared to play a crucial role in configurational selectivity when both *ortho*- and *para*-substituents existed in 1,6-enyne (**3ak** vs **3ab** and **3ad**), whereas *meta*-substituents were proven to be dispensable (**3ac** vs **3al**). In addition, the reaction was tolerated for *para*-substituents with various electronic properties, furnishing a series of cycloaddition/bromoazidation adducts in 82−92% yield along with excellent *Z*/*E* ratio (**3ad**−**3ah**, **3aj**). In general, it could be concluded that the electronic properties of the substituents have little effect on the reaction, and the yield of the reaction was good

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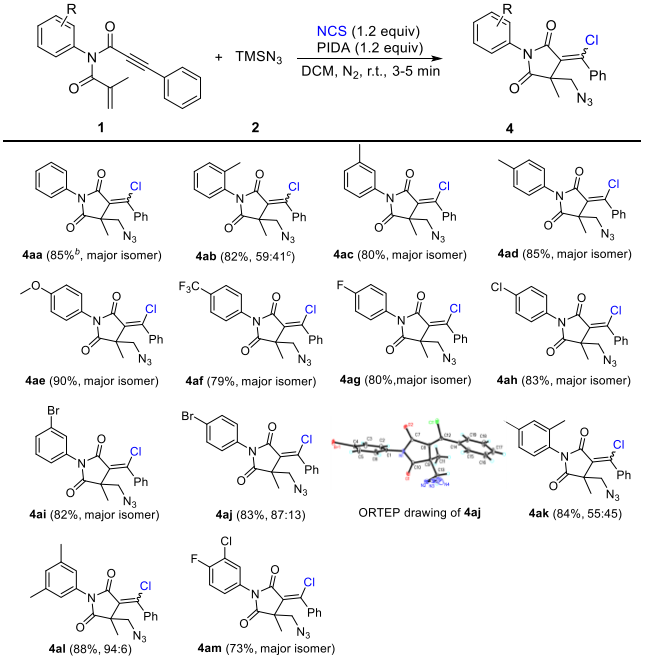
whether it was the electron-donating group (Me-, MeO-), the strong electron-withdrawing group (CF_3-, F-), or the weak electron-withdrawing group (Cl-, Br-) on the benzene ring.

To further emphasize the compatibility of this strategy, we then investigated the tolerance of other halogen sources by exchanging NBS with *N*-chlorosuccinimide (NCS) (Table 3).

Table 3. Three-Component Chloroazidation of 1,6-Enynes[a]

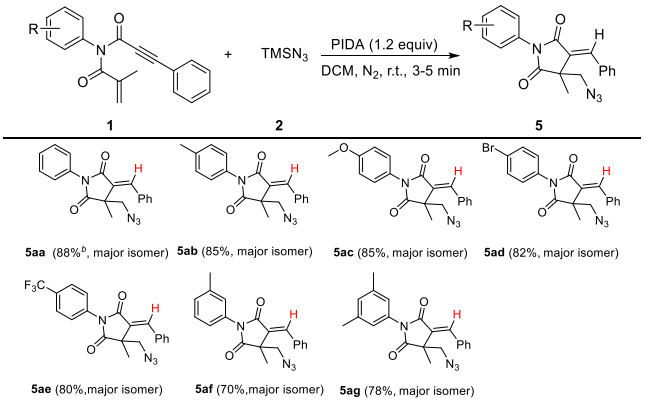


[a]Reaction conditions: unless otherwise noted, **1** (0.20 mmol), $TMSN_3$ (0.24 mmol), NCS (0.24 mmol), and PIDA (0.24 mmol) in DCM (2.0 mL) at room temperature for 3−5 min (monitored reactions by TLC) under a nitrogen atmosphere. [b]Isolated yields. [c]Ratio of *Z*/*E* isomer is detected by ^{1}H NMR.

When NCS was used as the halogen source, the chloroazidation reactions occurred smoothly and good to excellent yields (73−90%) were obtained with the *Z* isomer as the major product in almost all cases. Similar to that in the bromoazidation reaction, *ortho*-substituents have a significant effect on configurational selectivity of the desired product with an impaired *Z*/*E* ratio (**4ad** vs **4ak**). The *para*-substituents containing both electron-withdrawing and electron-donating R aryl groups were suitable for the chloroazidation, leading to the formation of the desired multifunctional succinimide compounds in 79−90% yield with excellent *Z*/*E* ratio (**4ad**−**4ah**, **4aj**). From the X-ray crystallography of product **4aj**, the configuration of the cycloadducts was established. Similar to synthetic compound **3**, the benzene ring of 1,6-enyne bearing different substituents, such as electron-donating (Me-, MeO-) and electron-withdrawing groups, had no significant effect on the yield of the reaction.

Moreover, without the addition of a halogen source, the cascade azidation/cyclization reaction of 1,6-enyne **1** and azidotrimethylsilane **2** also occurred smoothly (Table 4), affording the corresponding non-halogen multifunctional succinimide product **5** with good yields (80−88%) and excellent *Z*/*E* ratios. The R group containing both electron-withdrawing and electron-donating groups was compatible for the cascade reaction and had no obvious electronic effect on the reactivity.

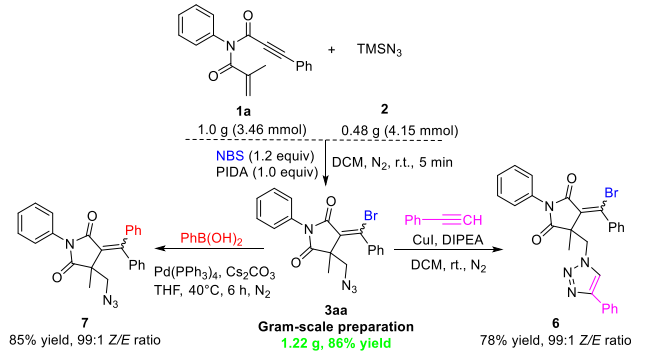
Table 4. Cycloaddition/Azidation Reaction of 1,6-Enyne[a]



[a]Reaction conditions: unless otherwise noted, **1** (0.20 mmol), **2** $TMSN_3$ (0.24 mmol), and PIDA (0.24 mmol) in DCM (2.0 mL) at room temperature for 3−5 min (monitored reactions by TLC) under a nitrogen atmosphere. [b]Isolated yields.

To showcase the practicality and scalability of the strategy, a large-scale reaction and further transformation were carried out in our research (Scheme 2). The reaction on a gram scale (1.0 g of **1a**) proceeded successfully, furnishing corresponding succinimide adduct **3aa** in a satisfactory yield (86%). Due to the easily transformable reactivity of the azide group,[17] the cycloaddition of **3aa** with phenylacetylene was performed under the catalysis of cuprous iodide, furnishing the cycloadduct triazole compound **6** in 78% yield along with a 99:1 *Z*/*E* ratio. In the presence of catalyst $Pd(PPh_3)_4$, the coupling reaction of adduct **3aa** with phenylboronic acid occurred smoothly, providing the coupling product **7** in 85% yield.

Scheme 2. Gram-Scale Experiment and Further Transformation



We then proceeded with control experiments to obtain the reaction mechanistic insight into the formation of highly functional succinimide compounds (Scheme 3). The desired cyclization of **1a** was completely inhibited in the presence of 2.0 equiv of radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl or 2,6-di-*tert*-butyl-4-methylphenol under the standard conditions, which disclosed that the cascade reaction underwent a radical pathway. On the basis of the above experimental results and previous works,[7,8] we described a proposed mechanism for a radical cascade reaction (for example, **3aa**) in Scheme 3. The reaction was initiated by the ligand exchange between PIDA and $TMSN_3$, in which intermediate **A** can be easily obtained. Driven by the weak I−N bond of intermediate **A**, it subsequently underwent thermal homolytic cleavage to

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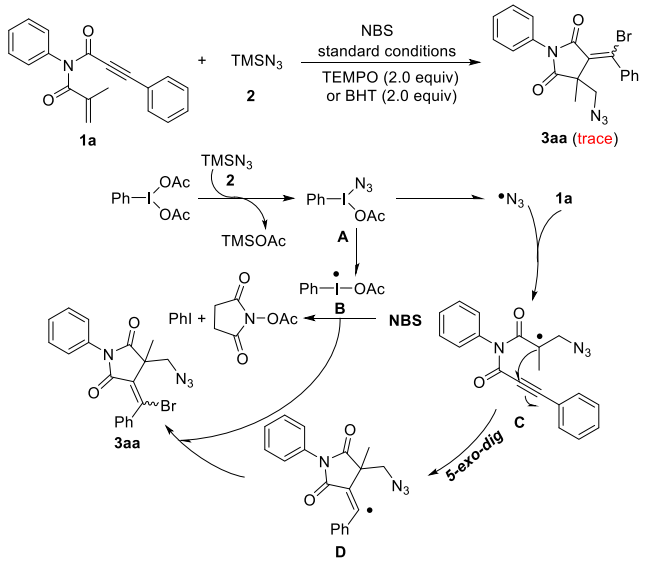
Scheme 3. Control Reaction and Proposed Reaction Mechanism



generate the azide radical along with the release of radical **B**. Then, the azide radical attacked the alkene moiety of 1,6-enyne **1a**, giving alkyl radical **C**. Radical **C** is transformed into radical intermediate **D** by way of 5-*exo*-*dig*. Finally, under the promotion of radical **B**, the bromine radical was released in situ from NBS, which combined radical **D** to deliver the desired product **3aa**.

In conclusion, we developed an efficient "time-economical" radical cascade cyclization/haloazidation of 1,6-enynes and $TMSN_3$ in the presence of different halogen sources to access the highly functional succinimide product containing halogen and an azide group in moderate to excellent yields with up to 99:1 *Z*/*E* ratio. Additional, the significant features of this process are large-scale synthesis and easy further transformation. Most importantly, the reaction time is very short (3−5 min), which is in line with the concept of green chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00682.

Experimental procedure, characterization data, NMR spectra and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1984640 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

We note that chlorinated azide (N_3Cl) is a dangerous species, which is generally produced by the inorganic reaction of chlorine gas with silver azide or the reaction of sodium hypochlorite with sodium azide in acetic acid. However, no method has been found for the synthesis of the species in organic reactions. Although we have carried out these reactions in our laboratories without any incidents, for safety concerns, one should pay careful attention not to deviate from the reaction conditions described in the Supporting Information of this paper.

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