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N-Iodosuccinimide-Promoted Cascade Trifunctionalization of Alkynoates: Access to 1,1-Diiodoalkenes

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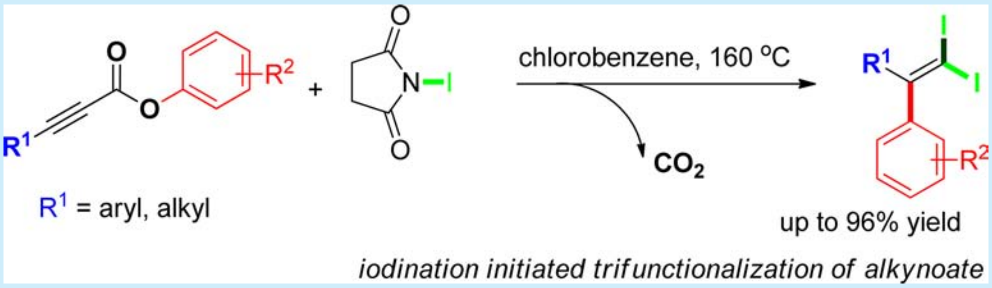
S *Supporting Information*



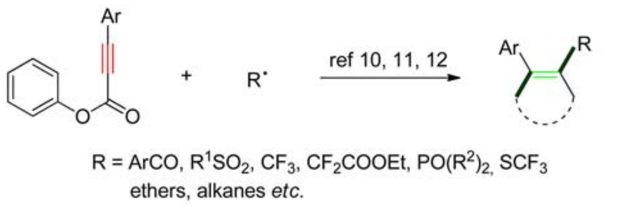
ABSTRACT: An efficient cascade trifunctioalization reaction of alkynoates with *N*-iodosuccinimide has been developed which proceeds through iodination, aryl migration, decarboxylation, and second iodination. This reaction represents an example of 1,1-difunctionalization of the acetylene bond and also provides a new strategy for the preparation of 1,1-diiodoalkenes.

1,1-Dihaloalkenes belong to an important class of building blocks in synthetic chemistry[1] and have been employed for a wide range of reactions, including metal-catalyzed cross-coupling,[2] construction of complex heterocycles,[3] and other useful conversions.[4] Furthermore, such a structure motif is found to exist in some natural products isolated from marine sponges.[5] Because of the high reactivity and versatility of iodides, 1,1-diiodoalkene intermediates more easily to undergo selective bond-forming reactions in organic synthesis and photochemistry.[6] Consequently, the development of new methods for the preparation of 1,1-diiodoalkenes is of great demand.[7]

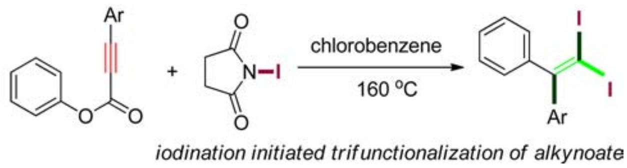
Functionalization of aryl alkynoates has become an attractive and powerful tool in organic synthesis, mainly because of the existence of the valuable acetylene bond motif in aryl alkynoates, which makes it easily derived from several functional groups.[8,9] Furthermore, cascade intramolecular cyclization of aryl alkynoates renders this organic synthetic intermediate more attractive due to the easy construction of substituted heterocycles. In recent years, many approaches have been explored on difunctionalization reactions of alkynoates which generate new bonds as well as introduction of additional functional groups (Scheme 1a). Cascade radical functionalization of alkynoates and followed by intramolecular cyclization with *o*-C(sp^2) on the aromatic moiety afforded varieties of functionalized coumarins.[10] Several radical coupling partners, such as α-keto acids,[10a] ethyl bromodifluoroacetate,[10b] diorganyl diselenides,[10d] Togni's reagent,[10e] dialkyl *H*-phosphonates,[10f] 2-oxoacetic acids,[10g] aldehydes,[10j] $AgSCF_3$, AgSCN,[10k] and others have been used for this transformation.

Scheme 1. Reactions of Alkynoates

(a) previous reported difunctionalization of alkynoates



(b) this work: trifunctionalization of alkynoates



On the other hand, alkynoates could undergo transition-metal-catalyzed oxidative *ipso*-cyclization reaction to afford azaspiro[4.5]trienones derivatives.[11] Further, we and other groups have developed the cascade oxidative difunctionalization reactions of alkynoates leading to substituted olefins.[12] Other types of difunctionalizations of alkynoates, such as [2 + 2]-cycloaddition with ketene silyl acetals affording functionalized

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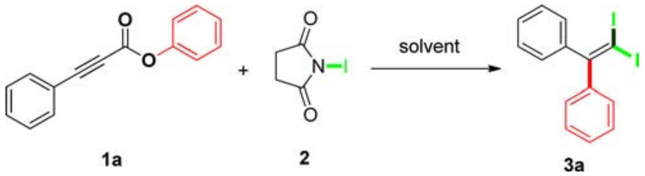
cyclobutenediones, have also been reported.[13] However, to the best of our knowledge, trifunctionalization of alkynoates has never been explored until now. There have been few examples on halogenation initiating cascade functionalization of alkynoates.[11a] Herein, we report an unprecedented iodination-triggered cascade radical trifunctionalization reaction of alkynoates, which proceeds through the sequence of iodination, aryl migration, decarboxylation, and second iodination (Scheme 1b). This reaction could be carried out under simple conditions with readily available *N*-iodosuccinimide (NIS) as the iodine precursor,[14] affording 1,1-diiodoalkenes as products. Furthermore, this process demonstrates a multistep radical reaction for trifunctionalization of alkynoates and also represents a strategy of the 1,1-difunctionalization of acetylene bonds.

Initial studies focused on investigating the cascade reaction of phenyl alkynoates **1a** and 3.0 equiv of *N*-iodosuccinimide **2** with dichloroethane as the solvent. We were pleased that the reaction proceeded at 120 °C, affording the desired 1,1-diiodoalkenes product **3a** in 21% chemical yield (entry 1, Table 1). When the solvent was switched to toluene (entry 2) or 1,4-dioxane (entry 5), no obvious improvement was found on the reaction outcome. On the other hand, no reaction was found when the DMSO or DMF was used as solvent (entries 3 and 4). A slightly higher chemical yield was obtained when the reaction was performed in chlorobenzene (32%, entry 6). Continuing the search for optimized conditions, we found that the reaction efficiency can be noticeably improved by increasing the reaction temperature (entries 7 and 8), affording product **3a** with up to 68% yield. The concentration also has an obvious effect on the reaction, and the results showed that 2.5 mL of chlorobenzene was the best choice (0.08 mol/L, entries 9 and 10). We then investigated the effect of the loading amount of NIS. Interestingly, decreasing the NIS substrate loading to 2.0 equiv afforded the best reaction outcome, and the highest yield was obtained (79%, entry 11). Further attempts to improve the yield by varying the reaction time were not successful (entries 14 and 15). Finally, other iodine reagents, such as iodine (entry 16) and the nucleophilic iodine reagent TBAI (entry 17), were used for this reaction instead of NIS, and the results clearly suggested that NIS should be considered as the best choice.

Table 1. Optimization of the Reaction Conditions[a]

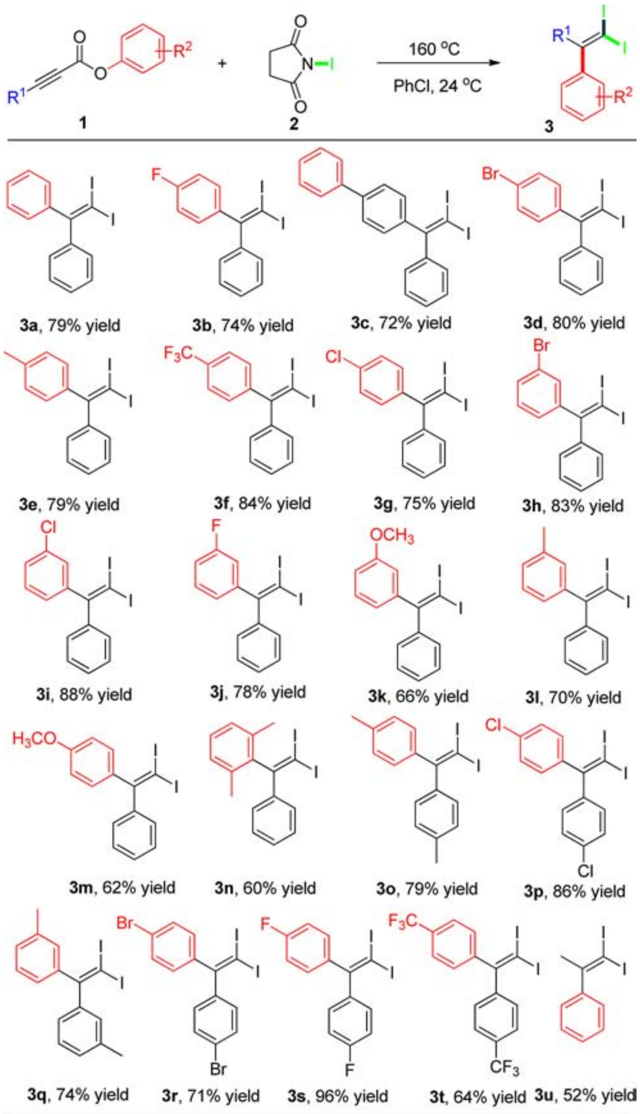


entry	solvent (mL)	NIS (equiv)	temp (°C)	time (h)	yield[b] (%)
1	DCE (2.0)	3.0	120	24	21
2	toluene (2.0)	3.0	120	24	23
3	DMF (2.0)	3.0	120	24	NR
4	DMSO (2.0)	3.0	120	24	NR
5	1,4-dioxane (2.0)	3.0	120	24	26
6	PhCl (2.0)	3.0	120	24	32
7	PhCl (2.0)	3.0	140	24	47
8	PhCl (2.0)	3.0	160	24	68
9	PhCl (1.5)	3.0	160	24	55
10	PhCl (2.5)	3.0	160	24	71
11	PhCl (2.5)	2.0	160	24	79
12	PhCl (2.5)	2.2	160	24	75
13	PhCl (2.5)	2.5	160	24	72
14	PhCl (2.5)	2.0	160	12	52
15	PhCl (2.5)	2.0	160	16	73
16	PhCl (2.5)	2.0	160	24	10[c]
17	PhCl (2.5)	2.0	160	24	NR[d]

[a] Reaction conditions: **1a** (0.2 mmol), NIS, solvent, under air. [b] Isolated yield based on **1a**. [c] I_2 was used. [d] TBAI was used.

The next objective of this study focused on exploration of the alkynoates' structural generality by using NIS as the coupling partner (Scheme 2). As shown in Scheme 2, aryl alkynoates bearing different substituents on the aromatic ring of the ester moiety, such as halo, phenyl, methyl, methoxyl, and trifluoromethyl groups, were well tolerated, affording the corresponding product in 60−88% isolated chemical yields (**3a**−**n**). Of particular interest was that the position of substituents on aromatic rings showed almost no effect on the reaction efficiency. Most of the reactions could proceed smoothly regardless of the electronic properties; even the

Scheme 2. Reaction Scope of Aryl Alkynoates with NIS[a,b]



[a] Reaction conditions: **1** (0.2 mmol), NIS **2** (0.4 mmol), chlorobenzene (2.5 mL) at 160 °C for 24 h. [b] Isolated yields.

substrates bearing strong electron-withdrawing groups were well tolerated in this system (4-fluorophenyl 3-phenylpropiolate **1b** and 4-(trifluoromethyl)phenyl 3-phenylpropiolate **1f**). We also presented an example of disubstituted substrate **1n** (2,6-dimethylphenyl 3-phenylpropiolate) containing two methyl groups in the *ortho*-position, which also gave rise to the expected product **3n** in 60% yield. We then carried out another series of experiments using the substrates with substituted phenylpropiolates under standard reaction conditions (**3o**−**t**). Pleasingly, starting compounds containing various substituents on the phenylpropiolates were acceptable, resulting in the expected product with up to 96% chemical yields (**3s**). Finally, an aliphatic substrate, with methyl-substituted acetylenic acid **1u** (phenyl but-2-ynoate), was examined in the current reaction. It also showed good applicability for this reaction to give the corresponding methyl, phenyl-substituted 1,1-diiodoalkene (**3u**) with a lower yield (52%).

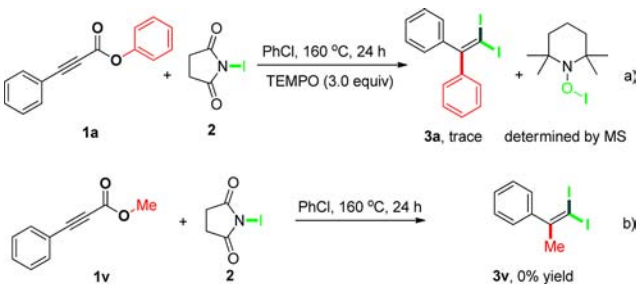
After NIS was examined in this reaction, we then turned our attention to other similar halo sources. Thus, the reactions using commercially available *N*-halosuccinimide substrates were carried out (Scheme 3). *N*-Bromosuccinimide (NBS) was found to react well with phenyl alkynoates under standard conditions, affording the expected 1,1-dibromoalkene product **4a** in 66% isolated yield, which was a little bit lower compared with the yield from NIS (**3a**, 79% yield). Unfortunately, no reaction was observed when *N*-chlorosuccinimide was used as chloro source, and most of the starting material **1a** was remained.

Scheme 3. Reaction of Aryl Alkynoates with NBS and NCS[a,b]

[a]Reaction conditions: **1a** (0.2 mmol), NBS or NCS (0.4 mmol), chlorobenzene (2.5 mL) at 160 °C for 24 h. [b]Isolated yields.

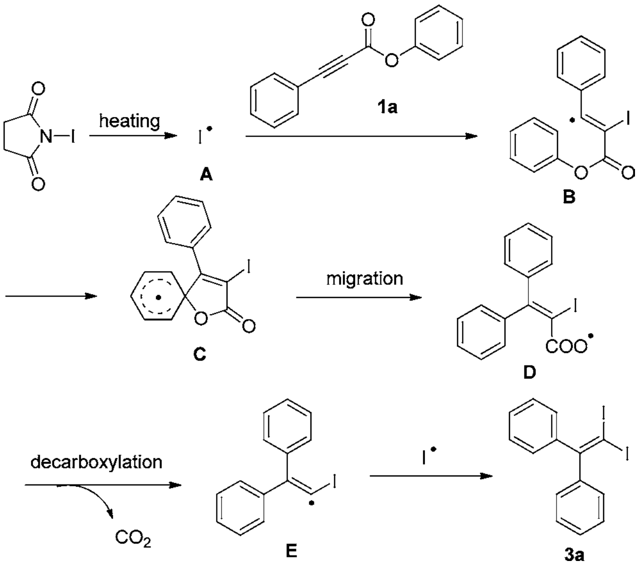
The final portion of this involved the elucidation of the observed reaction outcome and the proposal of the possible reaction mechanism. A control experiment of phenyl alkynoates **1a** and NIS **2** in the presence of the radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was carried out (Scheme 4a). As expected, the formation of desired product **3a** was suppressed, and only TEMPO−iodine adduct was observed (determined by ESI-MS analysis). The result indicates that the transformation may proceed via a radical course. Another experiment was conducted with methyl alkynoate **1v** as starting material under the standard conditions (Scheme 4b). No reaction was found, and almost all of the starting material **1v** was recovered. This result cleanly suggests that the migration proceeds through the cyclic transition state instead of direct group shift.

Scheme 4. Investigation of the Reaction Mechanism



On the basis of our experimental observations and previous reports,[12] we proposed a mechanistic pathway, as depicted in Scheme 5, for this cascade radical reaction. The first step of this reaction is the generation of iodine radical **A** from NIS under heating. The second step is the iodination of phenyl alkynoate **1a** through the iodine radical **A** addition to the C−C triple bond of alkynoate resulting in intermediate **B**. Subsequently, the intermediate **B** proceeds through intramolecular cyclization to afford the spiro intermediate **C**, which undergoes the aryl migration via cleavage of C−O bond to give the carboxyl radical **D**. Subsequent decarboxylation of carboxyl radical **D** generates intermediate **E** with release of CO_2. Finally, the intermediate alkene radical **E** reacts with iodine radical to complete the second iodination, affording the final 1,1-diiodoalkene product **3a**.

Scheme 5. Proposed Mechanism



In conclusion, we have developed an unprecedented NIS-promoted trifunctionalization reaction of aryl alkynoates under simple conditions. This reaction proceeds through the sequence of iodination, aryl migration, decarboxylation, and second iodination via one C−O and two C−C bond cleavages, along with one C−C bond and two C−I bond formations. The reaction tolerates a wide range of substrates affording the corresponding 1,1-diiodoalkene product in good to excellent yields. This reaction could be viewed as 1,1-difunctionalization of the acetylene bond, and it represents a new strategy for the preparation of 1,1-diiodoalkenes. Further studies on the reactions of aryl alkynoates with iodine radical are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03685.

Experimental procedures; full spectroscopic data for compounds **3** and **4a**; ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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