Green Chemistry

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ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C6GC01027J

Journal Name

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

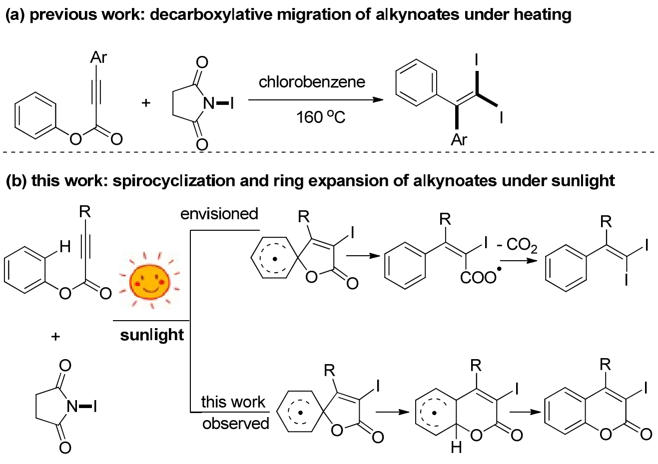
Sunlight-promoted cyclization versus decarboxylation in reaction of alkynoates with *N*-iodosuccinimide: an easy access to 3-iodocoumarins

Shengyang Ni,[a] Jia Cao,[b,c] Haibo Mei,[a] Jianlin Han,*[a] Shuhua Li*[b] and Yi Pan*[a]

A sunlight-initiated radical process of aryl alkynoates has been achieved by using *N*-iodosuccinimide as iodine source without use of any catalyst or additive. Experimental, x-ray analysis, and computational studies indicate that the reaction under sunlight tends to proceed through iodination, spirocyclization and ring expansion to form the kinetically controlled product. The sunlight-driven reaction provides a green pathway to especially valuable 3-halocoumarins derivatives.

Photoredox catalysis has been demonstrated to be powerful and straightforward tools for carbon-carbon and carbon-heteroatom bonds formation to assemble molecules with wide range of structural varieties.[1] The last decade has witnessed significant achievements in the area of photocatalysis used in synthesis of natural products and enantioselective catalysis.[2] As an abundant, renewable and simple accessible light source, sunlight can be applied in light activated reactions, therefore bodes well for the development of green synthetic methods.[3,4] In 2008, Yoon group developed an efficient Ru-catalyzed [2+2] enone cycloaddition reaction using the ambient sunlight.[5] Recently, elegant works by Wang[6] and Hashmi[7] have shown the possibility of radical alkynylation coupling reaction driven by sunlight in the presence of hypervalent iodine reagent or gold catalyst. Additionally, Jiao have demonstrated the sunlight-promoted aerobic oxidation of benzyl halides in the presence of $Ru(bpy)_3Cl_2$.[8] In the recent years, the demand in the development of green organic methodologies is at an all-time high. In this regard, the sunlight-driven organic reactions without use of any catalyst or additive represent a topic of great interests.

Aryl alkynoate has become an attractive and powerful organic intermediate in organic synthesis. It is mainly due to the easy introduction of several functional groups into acetylene bond motif in aryl alkynoates.[9] Furthermore, cascade intramolecular cyclization of aryl alkynoates renders this intermediate more attractive because of the application in preparation of substituted heterocycles.[10-12] Recently, we developed an iodination triggered cascade radical decarboxylative migration reaction of alkynoates giving 1,1-diiodoalkenes at 160 °C (Scheme 1a).[13a] In a continuation of our work on cascade reaction of alkynoates and inspired by these elegant sunlight irradiation works,[5-8] we envisioned that the decarboxylative migration of alkynoates could proceed under sunlight condition instead of high temperature (Scheme 1b). However, the product 1,1-diiodoalkenes under sunlight were not observed. Considering that sunlight-irradiation at room temperature is mild condition, the process might proceed through ring expansion to form 3-halocoumarins product[14] (Scheme 1b). Herein, we report the first example of sunlight-driven catalyst-free cascade radical iodination and cyclization of alkynoates with *N*-iodosuccinimide (NIS) at room



Scheme 1 Reaction of aryl alkynoates.

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[a] School of Chemistry and Chemical Engineering, State Key laboratory of Coordination Chemistry, Nanjing University, Nanjing, 210093, China. Email: hanjl@nju.edu.cn, yipan@nju.edu.cn
[b] Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing, 210093, China. Email: shuhua@nju.edu.cn.
[c] Shaanxi Key Laboratory of Chemical Reaction Engineering College of Chemistry & Chemical engineering, Yan'an University, Yan'an, 716000, China.

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for compounds **3** and **4a**, x-ray analysis of **3j**, computational details, copies of ^1H NMR and ^{13}C NMR spectra.]. See DOI: 10.1039/x0xx00000x

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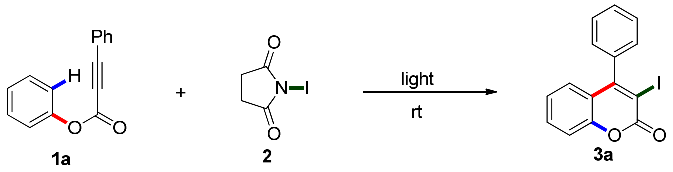
temperature (Scheme 1b). This reaction could be carried out without use of any oxidant or photocatalyst under simple conditions by using NIS as iodine precursor,[15] affording 3-iodocoumarins as products.

To probe the feasibility of this hypothesis, we initiated our studies with phenyl 3-phenylpropiolate **1a** as a model coupling partner and NIS **2** as iodine source for the cyclization reaction at room temperature. We were gratified to find that when a solution of **1a** and NIS (2.0 equiv) in CH_2Cl_2 was exposed to blue LEDs, a cyclization reaction occurred smoothly without use of any photocatalyst and the expected adduct was isolated in 80% yield (entry 1, Table 1). The scan of solvent found that no improvements were obtained when the reaction was conducted in acetone, THF, DMF and methanol (entries 2-4, 6). The result presented in entry 5 clearly suggested that acetonitrile was the solvent of best choice, giving the desired product **3a** in nearly quantitative yield (96%). Subsequently, the light sources, such white LED and fluorescent lamp, were scanned, which gave no better results (entries 7 and 8). From an environmental and practical point of view, we were intrigued to use abundant sunlight for activating this chemical transformation. Pleasingly, the reaction under sunlight could complete within 6 h with excellent chemical yield (90%, entry 9). In sharp contrast, blue LEDs irradiated reaction resulted in dramatically lower yield when the reaction was stopped at 6 h (52%, entry 10), and no reaction happened when the reaction was performed in the dark (entry 11). Inspired by this result, the attempts to improve the efficiency of this reaction were done through the variation of NIS loading amount, reaction concentration and time. These results clearly showed that using of 1.5 equiv of NIS, 2.5 mL of acetonitrile for 6 h was the best choice (up to 98% yield, entries 12-16). Finally, we would like to mention here the attempts to use other iodine sources, including TBAI, TBSI and I_2, however, all of these iodine sources did not lead to improved chemical yields (entries 17-19).

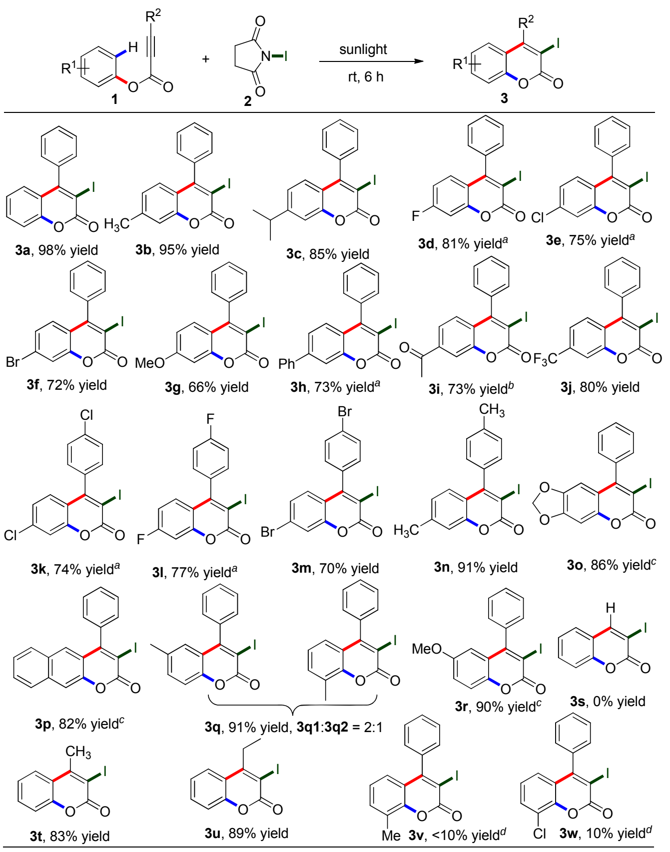
With the optimized reaction conditions in hand our next goal was the evaluation of potential generality of aryl alkynoates **1** in this sunlight-driven cyclization reaction. As illustrated in Table 2, a variety of alkynoates that bear *para*-substitution on the aromatic ring of ester moiety can be applied to give the 3-iodocoumarin with good to excellent yields (**3b**-**3j**, 66-95% yield). The electronegativity of substituted groups showed some effect on the efficiency of the reaction. Generally, the substrates with electron-donating groups on ester moiety (**3b**-**3c**) could work well to afford the desired product within 6 h. The reactions needed longer time to consume the starting material containing electron-withdrawing groups (fluoro **1d**, chloro **1e**, phenyl **1h** and acetyl **1i**), to give lower chemical yields. Similar trends were observed in the reactions of substrates bearing substituted phenylpropiolates (**1k**-**1n**), giving rise to coumarin derivatives (**3k**-**3n**) in 70-91% yields. In order to investigate the regioselectivity of the cyclization, we turned our attention to

Table 1 Optimization of the reaction conditions.[a]



Entry	NIS (equiv)	Light source	Time (h)	Solvent (mL)	Yield (%)[b]
1	2.0	Blue LED	24	DCM (2.0)	80
2	2.0	Blue LED	24	Acetone (2.0)	83
3	2.0	Blue LED	24	DMF (2.0)	21
4	2.0	Blue LED	24	THF (2.0)	63
5	2.0	Blue LED	24	MeCN (2.0)	96
6	2.0	Blue LED	24	MeOH (2.0)	54
7	2.0	White LED	24	MeCN (2.0)	90
8	2.0	Fluorescent lamp	24	MeCN (2.0)	78
9	2.0	Sunlight	6	MeCN (2.0)	90
10	2.0	Blue LED	6	MeCN (2.0)	52
11	2.0	--	6	MeCN (2.0)	NR[c]
12	1.5	Sunlight	6	MeCN (2.0)	97
13	2.5	Sunlight	6	MeCN (2.0)	83
14	1.5	Sunlight	6	MeCN (1.5)	95
15	1.5	Sunlight	6	MeCN (2.5)	98
16	1.5	Sunlight	4	MeCN (2.5)	84
17	1.5	Sunlight	6	MeCN (2.5)	NR[d]
18	1.5	Sunlight	6	MeCN (2.5)	Trace[e]
19	1.5	Sunlight	6	MeCN (2.5)	25[f]

[a] Reaction conditions: **1a** (0.2 mmol), NIS, solvent, under air. [b] Isolated yield. [c] The reaction vial was packed with aluminium foil in the dark. [d] TBAI was used. [e] TBSI was used. [f] I_2 was used.



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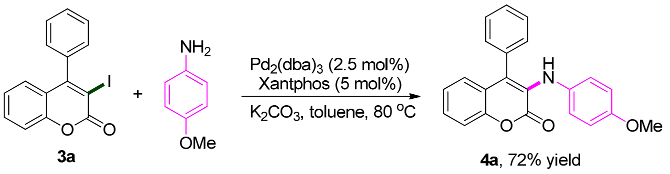
Scheme 2 Substrate scope of the sunlight-driven reaction. (Reaction conditions: **1** (0.2 mmol), NIS **2** (0.3 mmol), acetonitrile (2.5 mL), at room temperature, under air for 6 h. Isolated yield based on **1**. [a] 12 h. [b] 18 h. [c] Only one isomer was found which was determined by ^{1}H NMR. [d] 24 h)

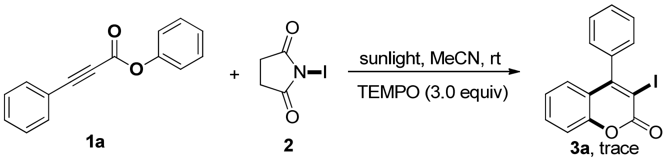
meta-substituted aryl phenylpropiolates. For substrates **1q-1r** with *meta*-substituents, the reactions proceeded very well with excellent yields as well as obvious regioselectivity. Especially, in the case of **1r** with *meta*-OMe, almost one isomer was observed (**3r**, >10:1 ratio). It is interesting to note that benzodioxole and naphthyl groups had no clear impact on the reactivity or regioselectivity, and the transformations afforded the expected site-selective products with 86% and 82% yield respectively (**3k-3l**). Aliphatic substrates, with methyl (**1t**) and ethyl-substituted acetylenic acid (**1u**), also could work rather well affording excellent yields within 6 h (**3t-3u**, 83-89%). However, no desired product was observed when phenyl propiolate **1s** was used as substrate. Finally, the substrates with *ortho*-methyl and chloro on the benzene ring of ester moiety were examined, however, almost no desired product **3v** and **3w** were found even the reaction time was prolonged to 24 h. It is mainly because that the steric hindrance of *ortho*-substituent makes the spirocyclization step difficult.

To highlight the utility of this cyclization reaction, we decided to demonstrate some further methodological potential of these derivatives **3** in the synthesis of the cores of pharmacologically active molecules. Hartwig amination of 3-iodocoumarin **3a** with *p*-anisidine catalyzed by $Pd_2(dba)_3$ and Xantphos afforded the corresponding 3-(4-methoxyphenylamino)-4-phenyl-coumarin[16] **4a** in 72% yield (Scheme 3).



Scheme 3 Transformation of **3a**.

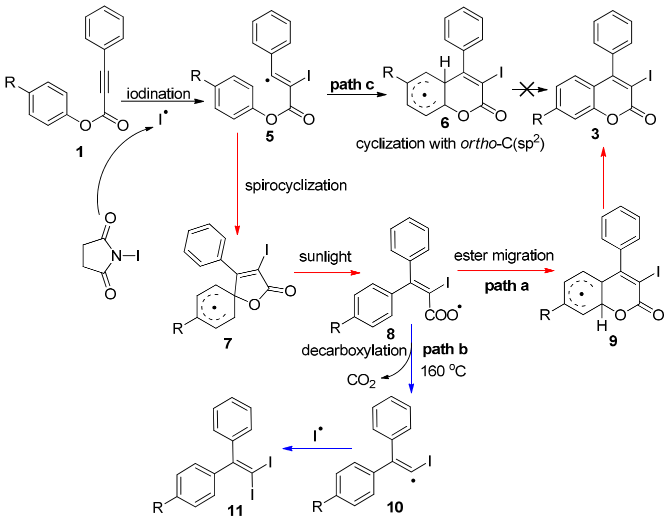
To get insight into the reaction mechanism, a control intermediate-trapping experiment with the addition of the radical-trapping reagents 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was carried out (Scheme 4). The formation of desired product **3a** was suppressed (see SI), and the result indicates that the transformation may proceed via a radical course.



Scheme 4 Mechanism Study.

To confirm the chemical structure of the product, the X-ray analysis of **3j** was performed (see SI). The product **3j** is 3-iodo-4-phenyl-7-(trifluoromethyl)-2*H*-chromen-2-one instead of 3-iodo-4-phenyl-6-(trifluoromethyl)-2*H*-chromen-2-one. This result clearly discloses that the migration of the ester moiety happens in this process.

Based on our experimental observation and previous reports,[10-14] we then investigated the possible reaction mechanism for this reaction (Scheme 5). Initially, the iodine radical is generated from NIS under the sunlight irradiation. Then the addition of the iodine radical to the C–C triple bond of alkynoate **1** leads to the intermediate **5**. Subsequently, the intermediate **5** proceeds through an intramolecular spirocyclization to form the intermediate **7**, which undergoes the cleavage of C–O bond to give the carboxyl radical **8**. Along path a, the cyclization of intermediate **8** generates the compound **9**. The deprotonation of **9** by NIS would give the product **3**. As reported,[13] along an alternative path b, intermediate **8** can also convert into the intermediate **10** by releasing a CO_2 molecule. Finally, the intermediate **10** reacts with NIS to form the final 1,1-diiodoalkene product **11**. Interestingly, **11** was not detected under the current sunlight irradiation experimental condition.



Scheme 5 Proposed mechanism.

To understand the experimental observations, the free energy profiles of three possible reaction paths of **1a** are obtained with UB3LYP calculations. The obtained results are depicted in Figure 1 (for computational details, see SI). The optimized geometries of all the species along the reaction pathways are given in Fig S1 (see SI). The results indicate that the energy barrier of the rate-limiting step along path **c** is higher than those of path **a** and **b**. Hence, path **c** should be excluded. This result is in line with the experiment (no radical intermediate **6** was detected). For path **a** and path **b**, these two pathways are the same before the compound **8** is formed. The species **8** is converted into **9** along path **a** via the transition state $\mathbf{TS_{8\text{-}9}}$ (with a barrier of 8.83 kcal/mol), and converted into **10** and CO_2 along path **b** via $\mathbf{TS_{8\text{-}10}}$ (with a barrier of 11.93 kcal/mol), respectively. The formation of **10** and CO_2 is exothermic by 16.03 kcal/mol, and the formation of **9** is exothermic by 1.28 kcal/mol. Thus, the formation of the intermediate **9** is the kinetically controlled product. Once the species **9** is formed, its further deprotonation can easily lead to the formation of **3a**, which is the main product detected experimentally at room temperature. The experimental results suggest that the reaction may take place along pathway **a**.

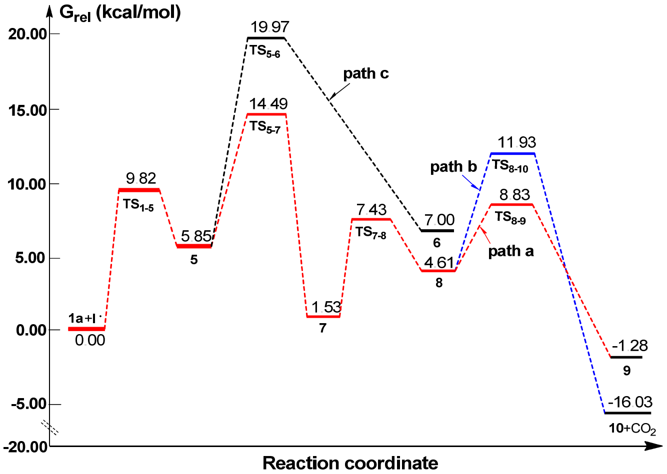


Fig. 1 Gibbs free energy profile for the reaction calculated in acetonitrile solution (The free energy barrier ΔG is relative to that of the reactant **1a** and iodine radical).

Conclusions

To conclude, a sunlight-driven catalyst-free cascade radical iodination and cyclization reaction of aryl alkynoates with *N*-iodosuccinimide as iodine source was reported. The reactions were carried out under convenient conditions via exposing the reaction mixture to the sun. Experimental, x-ray analysis, and computational studies indicate that the reaction under sunlight tends to proceed through iodination, spirocyclization and ring expansion to form the kinetically controlled product. The sunlight-driven reaction provides a green pathway to especially valuable 3-halocoumarins derivatives.

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21102071 and 21472082). The Jiangsu 333 program (for Pan) and Changzhou Jin-Feng-Huang program (for Han) are also acknowledged.

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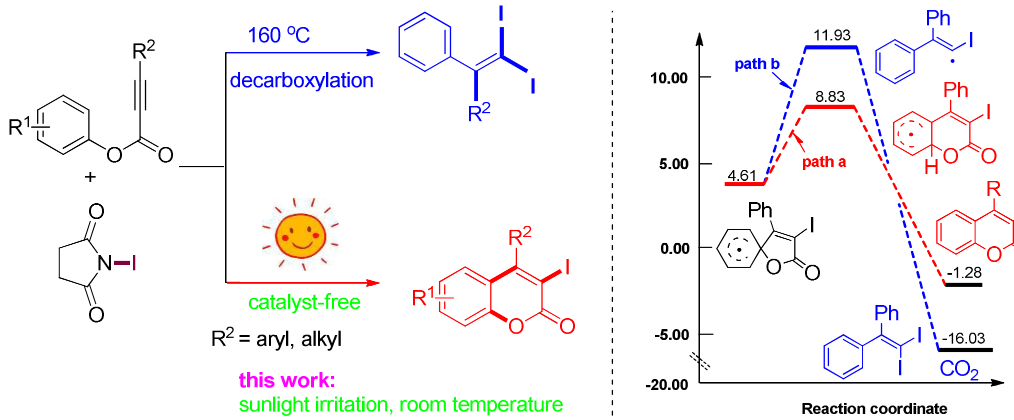

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