

UV Light Induced Direct Synthesis of Phenanthrene Derivatives from a Linear 3-Aryl-N-(arylsulfonyl) Propiolamides

Ming Chen, Chao Yang, Yanpei Wang, Dazhi Li, and Wujiong Xia*

State Key Lab of Urban Water Resource and Environment, Shenzhen Graduate School, Harbin Institute of Technology, Harbin 150080, China

Supporting Information

ABSTRACT: A novel photochemical approach for the synthesis of phenanthrene derivatives from linear 3-aryl-*N*-(arylsulfonyl) propiolamides via a tandem radical Smiles rearrangement/C—S bonding/Mallory reaction is disclosed. The control experiment results and isolation of the key intermediates give further insight into the reaction mechanism. Gram scale reaction using a flow reactor demonstrated the synthetic potential applications of our protocol.

mong the UV light-induced cyclization reactions, the oxidative photocyclization of stilbene is of great interest owing to its preeminent reactivity in photochemistry. Moreover, stilbene derivatives that contain heteroatoms or large conjugated systems on aryl moieties could also undergo the same reaction to give corresponding products. This typical reaction is known as the Mallory reaction and has been extensively investigated for the synthesis of polycyclic aromatic hydrocarbons (PAHs) and other exceptional molecular structures ^{3,4} (Scheme 1a). Relevant

Scheme 1. Previous Work and Our Discovery

reaction mechanisms have been widely studied⁵ and clearly declared: upon irradiation, the intermediate *trans*-4a,4b-dihydrophenanthrene was formed, which then could be oxidized to phenanthrenes or transformed into other different products through elimination or rearrangement. Despite enormous achievements in photochemistry over the past years, ^{3,4,6} stilbenes utilized in the Mallory reaction still, in most cases, require advance preparation. Furthermore, compounds comprising a less active C≡C bond were rarely reported to participate in this classical reaction.⁷

Recently, our group reported a visible-light induced cascade reaction initiated by CF3 radical addition to the C-C double bond of *N*-(arylsulfonyl)acrylamines and afforded two products: α -arylamines and oxindoles (Scheme 1b). Inspired by this strategy, we synthesized a derivative compound, 3-aryl-N-(arylsulfonyl) proiolamide, by replacement of the unsaturated C=C bond with C≡C bond that directly tethered to an aromatic ring. Unfortunately, no expected amine or oxindole products were detected when it was subjected to the similar reaction conditions. However, when the substrate was exposed to UV light, we serendipitously discovered a new approach to efficient synthesis of various phenanthrene derivatives from linear, easily made N-(arylsulfonyl)proiolamides via a radical Smiles rearrangement / C-S bonding/Mallory reaction cascade (Scheme 1c). Herein we present what we have achieved regarding this unique and interesting new reaction.

Our initial discovery was made by subjecting N-methyl-3phenyl-N-(phenylsulfonyl) propiolamide 1a to the irradiation of a high-pressure mercury lamp with a Pyrex filter in acetonitrile (5 mM) under air. After 4 h, compound 1b was isolated as a major product in 60% yield along with 15% of phenanthrene A as a side product (Table 1, entry 1), in which the structures were characterized by 1D and 2D NMR spectra. It is of interest to point out that the isothiazolone S,S-dioxide framework contained in the product 1b is quite a popular element in many chemically bioactive motifs (Figure 1).¹⁰ For example, saccharin is bestknown as the oldest sweetener, 11 whose scaffold has drawn much attention in medicinal chemistry and has been identified as a key pharmacophore of biologically active compounds. 10 In addition, modified saccharin compounds have demonstrated extensive application in enzyme inhibitors (Figure 1). 10b,12 However, the traditional methods to construct the five-member structure are rare and tedious, ^{10b,13} thus limiting their utility in synthesis. Therefore, we were intrigued to optimize the reaction conditions.

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Table 1. Optimization of the Conditions toward the Synthesis of $1b^a$

				yield (%) ^b	
entry	solvent	light source	time (h)	1b	A
1	MeCN	HP mercury lamp	4.0	60	15
2	MeCN	MP mercury lamp	2.5	70	10
3	MeCN	300 nm	1.5	73	<5
4	MeCN	350 nm	18	48	10
5	MeCN	180 nm	1.5	72	<5
6	$MeCN^c$	300 nm	1.5	73	<5
7	$MeCN^d$	300 nm	1.5	53	30
8	benzene	300 nm	2.0	67	13
9	CH_2CI_2	300 nm	2.0	69	10
10	THF	300 nm	3.0	55	25
11	toluene	300 nm	2.0	71	<5
12	MeOH	300 nm	3.5	40	12

^aReaction conditions: **1a** (0.2 mmol), solvent (anhydrous 40 mL), under air atmosphere. ^bIsolated yield. ^cUnder O_2 atmosphere. ^dUnder O_2 atmosphere.

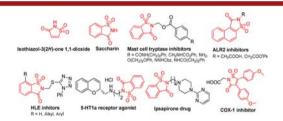


Figure 1. Representative bioactive isothiazolone 1,1-dioxide derivatives.

Screening of the light source revealed that 300 nm wavelength light afforded the best yield (Table 1, entries 1–5). Based on the optimal light source, a set of solvents were then examined, and acetonitrile was found to be the ideal medium (Table 1, entries 3, 8–12). Notably, the presence of oxygen could significantly affect the yield of the desired product. For example, when the reaction was performed under an air or oxygen atmosphere, the yield was higher than in the case of a nitrogen atmosphere (Table 1, entries 3, 6–7). In addition, we found that the reaction required a longer time to complete when the concentration of substrate 1a was higher; the relationship between the substrate concentration and reaction time for 1a to be completely consumed is displayed with a concentration—time curve, as shown in Figure 2, which revealed that the reaction time was in direct proportion to the substrate concentration.

With the optimal reaction conditions in hand, we then prepared a series of *N*-tosylpropiolamides and submitted them to the standard conditions; the results are listed in Scheme 2.

As shown in Scheme 2, both electron-donating and -with-drawing substituents were well tolerated under the reaction conditions. For example, the *p*-methyl, *p*-methoxyl, *p*-halo, *p*-CF₃, and *p*-phenyl substituted substrates could be smoothly converted into corresponding products in moderate to high yields (Scheme 2, 2b–7b). As a bonus, one of the products 2b was suitable for single X-ray diffraction analysis (Scheme 2). Notably, the reaction was sensitive to the position of the substituent, e.g., the *m*-substituted substrate 8a, affording regioisomers of 8b and 8b' in an approximate ratio of 4:3,

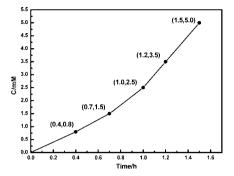


Figure 2. Concentration—time curve of 1a.

Scheme 2. Reaction Scope toward the Synthesis of Compound \mathbf{h}^a

^aReaction conditions: a (0.2 mmol), MeCN (anhydrous 40 mL) under air atmosphere; isolated yields are shown. ^bThe ratio is determined by GC.

while the F-substituted substrate 9a afforded the regioisomers of 9b and 9b' in a ratio of 3:1. However, the reaction of the *m*-CF₃ substituted substrate 10a showed high regioselectivity with 10b as the single isomeric product, which might be attributed to a strong steric effect of the CF₃ group. It is noteworthy that the *o*-substituted substrate could produce both an unsubstituted product 1b by elimination of the *o*-substituent and a desired *ortho*-substituted product (Scheme 2, 11b–13b), in which the formation of 1b was in agreement with the classical Mallory

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reaction. ^{1d} Moreover, we also tested a series of substrates bearing different substituents on the aromatic ring that were directly linked to the alkyne. All of these photocyclic cascade reactions proceeded efficiently and delivered the corresponding products in good yields (Scheme 2, 14b–17b).

Next, the substituent pattern on the N-atom was also examined. It was observed that all these substituents, in addition to the methyl group, were generally well tolerated under the reaction conditions and afforded the N-substituted products in moderate yields (18b-22b). A substrate containing polycyclic aromatic rings, e.g., 23a, effectively delivered product 23b in a moderate yield of 53% without its isomer. A rationale for the mechanistic selectivity was proposed in which the α -hydrogen of the naphthyl group was more inclined to be oxidized than the β hydrogen, thus leading to the single regioisomer adduct. The other naphthyl-group-containing substrate, 24a, gave the corresponding product 24b in 50% yield. To evaluate the efficiency of this photocyclic cascade reaction, we finally extended the substrate scope to a range of heteroaromatic compounds, and the expected products were obtained in satisfactory yields (Scheme 2, 25b-28b). In addition, we extended the substrate scope to the compound in which the sulfonyl group was replaced by a carbonyl group; however, no corresponding product was obtained under the reaction conditions.14

To gain further insight into this cascade reaction, substrates **29a** and **30a**, only containing one phenyl ring appended on either an alkyne or a sulfonyl group, were synthesized and subjected to the reaction conditions, but failed to form the corresponding products (Scheme 3, eq 1), which indicated that the both aromatic substituents were essential for the reaction.

Scheme 3. Control Experiment

During the investigation on the reaction of substrate 14a, besides the desired product 14b, an intermediate was also isolated in 42% yield which was characterized as compound 14c by shortening the reaction time to 0.3 h (Scheme 3, eq 2). We speculated that the product 14b was derived from the intermediate 14c via a typical Mallory reaction. To test our hypothesis, 14c was subsequently submitted to the standard conditions, which was completely converted into the product 14b within 1.0 h (Scheme 3, eq 3).

The conversion of **14a** to **14c** tuned by the reaction time further suggested the possibility of wider application of our protocol in the preparation of various isothiazol-3(2H)-one 1,1-dioxides, the key framework included in pharmaceutical compounds, such as COX-1 inhibitor (Figure 1). ¹⁵ Therefore, some of N-tosylpropiolamides were chosen for a scope study by submission to the standard reaction conditions by control of the

reaction time. As shown in Scheme 4, a variety of 4,5-diarylisothiazol-3(2H)-one 1,1-dioxides could be obtained smoothly in moderate to excellent yields.

Scheme 4. Photoinduced Synthesis of 4,5-Diarylisothiazol-3(2H)-one 1,1-Dioxides^a

^aReaction conditions: a (0.2 mmol), MeCN (anhydrous 40 mL), under air atmosphere, conversion and isolated yields are shown.

Based upon the above-mentioned results, the reaction mechanism was proposed as shown in Scheme 5. Under

Scheme 5. Reaction Mechanism of the Syntheses of Compounds b and c

irradiation with UV light, the alkyne group was excited to 1,2-biradicals, which initiates a radical Smiles rearrangement reaction to form the more stable 1,5-biradical intermediate III. Sequential C—S bonding via 1,5-biradical cyclization afforded the five-membered isothiazol-3(2H)-one 1,1-dioxide compound c. The final product b was obtained from compound c through the typical Mallory reaction.

To demonstrate the further synthetic utility of this protocol, we carried out the reactions on gram scale using *N*-methyl-3-phenyl-*N*-(phenylsulfonyl)propiolamide **1a** as the representative substrate with a flow reactor (Scheme 6). Using the optimal reaction conditions, the product **1b** was obtained in 70% yield.

In conclusion, we have discovered a novel tandem radical Smiles rearrangement/C–S bonding/Mallory reaction, which provides a direct access to the synthesis of isothiazolone *S*,*S*-dioxide containing phenanthrene derivatives from linear, easily made 3-aryl-*N*-(arylsulfonyl) propiolamides. Moreover, the

Scheme 6. Gram Scale Study with a Flow Reactor

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isolation of the key intermediates involved in the reaction process added more credence to the proposed mechanism. Finally, the gram scale reaction using a flow reactor further demonstrated the synthetically potential applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00878.

Crystallographic file for 2b (CIF)

Crystallographic file for 9b' (CIF)

Experimental procedures and ¹H and ¹³C NMR spectra for all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: xiawj@hit.edu.cn.

Notes

The authors declare no competing financial interest.

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