Organic Letters
Letter
pubs.acs.org/OrgLett

Synthesis of Azulen-1-yl Ketones via Oxidative Cleavage of C−C Multiple Bonds in *N*-Sulfonyl Enamides and 1-Alkynes under Air and Natural Sunlight

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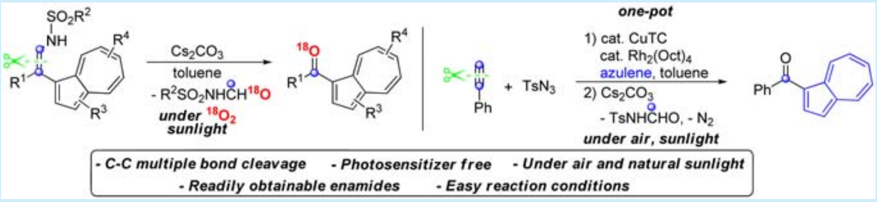
Supporting Information



ABSTRACT: A synthetic method to prepare azulen-1-yl ketones was developed via oxidative cleavage of the C−C double bond in the reaction of easily obtainable *N*-sulfonyl enamides with Cs_2CO_3 under air and natural sunlight and in the absence of a photosensitizer. Oxidative cleavage of C−C triple bonds was also demonstrated for the synthesis of azulen-1-yl ketones via a tandem Cu-catalyzed [3 + 2] cycloaddition, Rh-catalyzed arylation, photooxygenation, and ring-opening reaction in one pot under air and natural sunlight.

Azulenes, which are nonbenzenoid aromatic hydrocarbons and nonalternant isomers of naphthalene, are an important class of compounds because of their biological activities[1] and physicochemical properties.[2] Hence, the establishment of a new approach to prepare azulene and its derivatives from easily accessible starting materials is highly desirable.[3] In this regard, the introduction of new functional groups to the azulene ring and the transformation of previously present functional groups are required. The selective introduction of an acyl group to the azulene ring is particularly desirable because of such groups' electronic and electrochemical properties. Although Hafner and co-workers developed an azulene synthesis method,[4] the selective introduction of an acyl group to azulenes is limited by the unusual reactivity of azulene, which stems from its polarized π-electron system.[5] To date, the Vilsmeier−Haack reaction (eq 1, Scheme 1)[6a,b] and Friedel−Crafts acylation using an acid anhydride and an acyl chloride (eqs 2 and 3)[6c,e] have afforded azulen-1-yl ketones; however, these reactions suffer from low yields, diacylation, and poor functional-group compatibility. Moreover, because azulenes tend to decompose in the presence of oxidants, the oxidation of secondary alcohols derived from the reaction of azulen-1-yl metal with an aldehyde is not a suitable approach for the preparation of azulen-1-yl ketones. Thus, the development of new, convenient methods to prepare azulen-1-yl ketones is imperative.

Recently, the *N*-sulfonylaminoalkenylation of azulenes was developed *via* *N*-sulfonyl-1,2,3-triazoles from 1-alkynes and azides in a one-pot reaction.[7] Because the electronic structure of azulene enables cation stabilization via aromatization of the seven-membered ring,[3] we envisioned that the treatment of *N*-sulfonylaminoalkenyl azulene with a base would produce a tricyclic compound with an azulene skeleton. In addition, easy access to *N*-sulfonylaminoalkenylated azulenes from readily available alkynes, azides, and azulenes led us to investigate the cyclization of such azulenes.[7] Accordingly, various bases, including metal carbonates and phosphates, were examined to induce cyclization. However, to our surprise, when *N*-sulfonylaminoalkenyl azulene **1a** was treated with K_2CO_3 under air and natural sunlight, 1-benzoyl azulene (**2a**) was produced in 63% yield, together with 4-methylbenzenesulfonylformamide (**3a**) in 30% yield (eq 6). No cyclization product was observed in the reaction. The structure of **2a** was confirmed by X-ray crystallography (Figure 1).

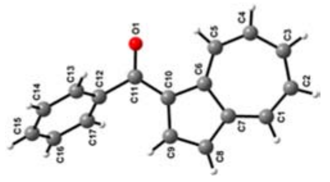


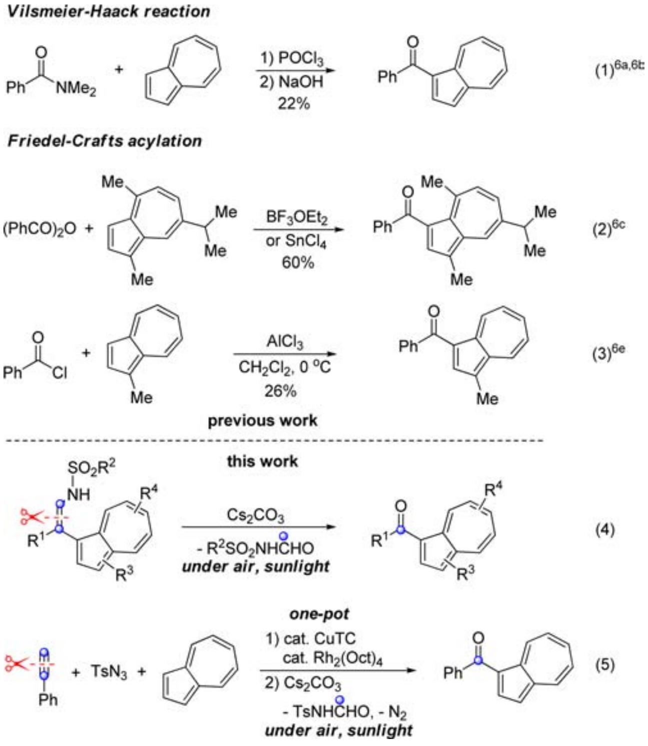
Figure 1. X-ray structure of 1-benzoyl azulene (**2a**).

We herein report a synthetic method for azulen-1-yl ketones via oxidative cleavage of the C−C double bond in *N*-sulfonyl enamides by the reaction of a wide range of enamides with Cs_2CO_3 under air and natural sunlight and in the absence of a photosensitizer (eq 4). In addition, the oxidative cleavage of C−

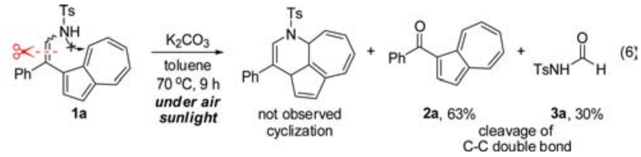
Received: September 3, 2015
Published: October 6, 2015

DOI: 10.1021/acs.orglett.5b02545
Org. Lett. 2015, 17, 5060−5063

Scheme 1. Methods To Synthesize Azulen-1-yl Ketones

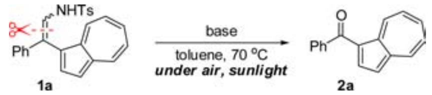


C triple bonds via the tandem Cu-catalyzed [3 + 2] cycloaddition, Rh-catalyzed arylation, photooxygenation, and ring-opening reaction starting from phenylacetylene is demonstrated for the one-pot synthesis of azulen-1-yl ketones (eq 5).



First, we intensively investigated the oxidative cleavage of the C−C double bond in *N*-sulfonyl enamides (Table 1). Although Li_2CO_3 and Na_2CO_3 were totally ineffective for the oxidative cleavage, the exposure of **1a** to Cs_2CO_3 in toluene at 70 °C for 5 h gave **2a** in 90% isolated yield (entry 4).[8] Because Vilsmeier−Haack reaction and Friedel−Crafts acylation using azulene generally produce a mixture of mono- and diacylated azulenes, the fact that the present reaction produces only a monoacylated product is noteworthy. Use of 4 Å molecular sieves did not affect the reaction efficiency and resulted in **2a** in 90% yield (entry 5). The reaction did not proceed under a nitrogen atmosphere (entry 6), whereas it produced the desired product **2a** in 90% yield under molecular oxygen (entry 7). Although the reaction was not totally ineffective in the presence of potassium phosphate dibasic and monobasic (K_2HPO_4 and KH_2PO_4, respectively), potassium phosphate tribasic (K_3PO_4) provided **2a** in 86% yield (entries 8−10).

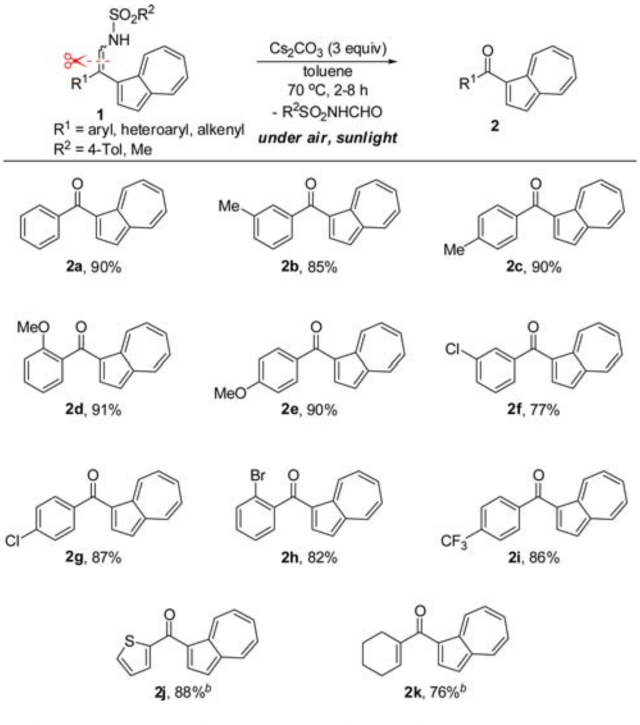
Table 1. Reaction Optimization[a]



entry	base	time (h)	yield (%)[b]
1	Li_2CO_3	20	0
2	Na_2CO_3	20	0
3	K_2CO_3	9	63 (30)[c]
4	Cs_2CO_3	5	92 (90)[d]
5[e]	Cs_2CO_3	5	90
6[f]	Cs_2CO_3	5	5
7[g]	Cs_2CO_3	3	90
8	K_3PO_4	5	86
9	K_2HPO_4	20	0
10	KH_2PO_4	20	0

[a] **1a** (0.2 mmol, 1 equiv) and base (3 equiv) were heated in toluene (1.0 mL) at 70 °C under air and natural sunlight. *Z*/*E* ratio of **1a** = 10:1. [b] NMR yield using CH_2Br_2 as an internal standard. [c] Isolated yield of *N*-tosylformamide (**3a**). [d] Isolated yield of **2a**. [e] 4 Å molecular sieves (20.0 mg) were used. [f] Under a N_2 atmosphere. [g] Under an O_2 atmosphere.

Scheme 2. Synthesis of Azulen-1-yl Ketones *via* the Oxidative Cleavage of the C−C Double Bond in Azulen-1-yl *N*-Sulfonyl Enamides[a]

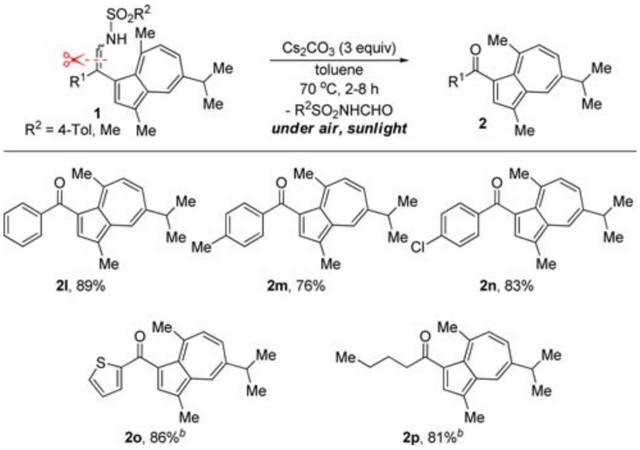


[a] **1** (0.2 mmol, 1 equiv) and Cs_2CO_3 (3 equiv) were heated in toluene (1.0 mL) at 70 °C under air and natural sunlight. [b] A mesyl group was used instead of a tosyl group.

Encouraged by these results, we explored the scope and limitation of the oxidative cleavage of the C−C double bond in azulen-1-yl *N*-sulfonyl enamides (Scheme 2). The electronic alteration of the substituents on the aryl ring of azulen-1-yl *N*-sulfonyl enamides **1** did not significantly affect the reaction efficiency. For example, azulen-1-yl *N*-tosyl enamides with electron-donating substituents such as 3- or 4-methyl and 2- or 4-methoxy groups on the aryl ring underwent the oxidative cleavage reaction under air and natural sunlight to give the corresponding azulen-1-yl ketones (**2b**−**2e**) in good to excellent yields ranging from 85% to 91%. Electron-withdrawing chloride or bromide groups were tolerated under the optimal reaction conditions, which enabled various synthetic transformations. Azulen-1-yl *N*-tosyl enamide **1i** with a 4-trifluoromethylphenyl group was applied to the present method and provided the desired product **2i** in 86% yield. The oxidative cleavage reaction using azulen-1-yl *N*-mesyl enamides with thiophen-2-yl and cyclohexen-1-yl groups proceeded, furnishing **2j** and **2k** in 88% and 76% yields, respectively.

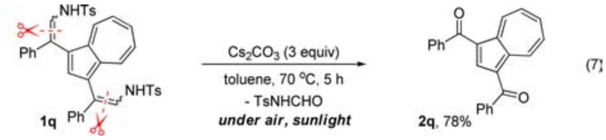
In addition, the C−C double bond in guaiazulen-3-yl *N*-tosyl enamides with phenyl, 4-tolyl, 4-chlorophenyl, and thiophen-2-yl groups was oxidatively cleaved and produced the guaiazulen-3-yl ketones (**2l**−**2o**) in good yields (Scheme 3). The oxidative cleavage reaction also proceeded in the reaction of guaiazulen-3-yl *N*-tosyl enamide **1p** with an *n*-butyl group with Cs_2CO_3 under air and natural sunlight.

Scheme 3. Synthesis of Guaiazulen-3-yl Ketones *via* the Oxidative Cleavage of the C−C Double Bond in Guaiazulen-3-yl *N*-Sulfonyl Enamides[a]



[a] **1** (0.2 mmol, 1 equiv) and Cs_2CO_3 (3 equiv) were heated in toluene (1.0 mL) at 70 °C under air and natural sunlight. [b] The mesyl group was used instead of the tosyl group.

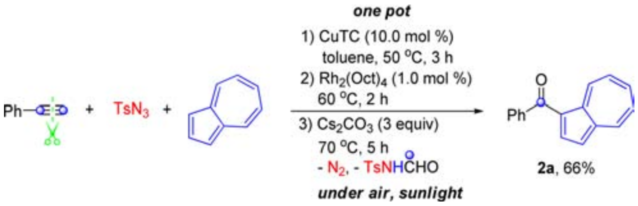
When the readily accessible 1,3-bis(*N*-tosylamino)alkenyl-substituted azulene **1q**[7] was treated with Cs_2CO_3 (3 equiv) under air and natural sunlight, the 2-fold oxidative cleavage reactions proceeded smoothly and 1,3-dibenzoylazulene **2q** was produced in 78% yield (eq 7).



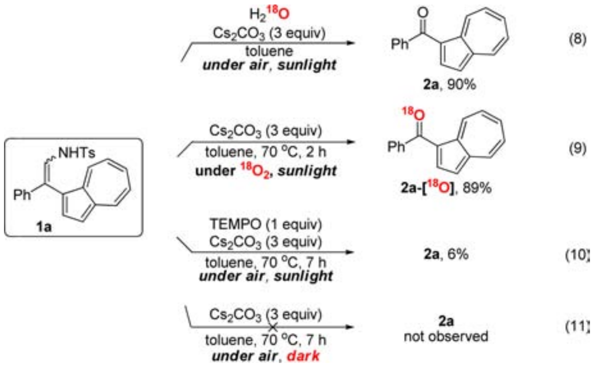
In general, a wide range of *N*-tosyl enamides were previously prepared from the reaction of azulene with triazoles.[7] Thus, we envisioned that the oxidative cleavage of the C−C triple bonds of 1-alkynes might occur via a tandem Cu-catalyzed [3 + 2] cycloaddition, Rh-catalyzed arylation, photooxygenation, and ring-opening reaction to produce azulen-1-yl ketones in one pot (Scheme 4). After phenylacetylene reacted with *N*-tosyl azide in the presence of copper(I) thiophene-2-carboxylate (CuTC, 10.0 mol %) in toluene, $Rh_2(Oct)_4$ (1.0 mol %) and azulene were added to the reaction mixture, which was subsequently treated with Cs_2CO_3, resulting in the formation of 1-benzoyl azulene **2a** in 66% yield in one pot.

Next, two isotopic labeling experiments were performed to examine the source of oxygen in the oxidative cleavage reaction (Scheme 5). Although *N*-sulfonyl enamide **1a** was treated with Cs_2CO_3 in toluene and $H_2{}^{18}O$ under air and natural sunlight, the corresponding ^{18}O-inserted-ketone was not observed (eq 8).

Scheme 4. Synthesis of Azulen-1-yl Ketones *via* the Oxidative Cleavage of the C−C Triple Bond of Phenylacetylene in One Pot

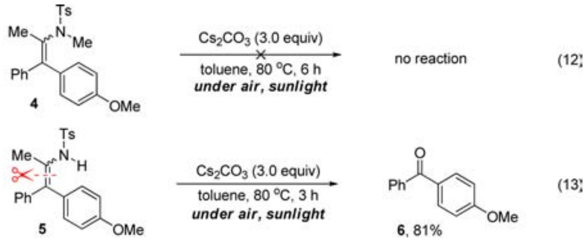


Scheme 5. Labeling and Radical Scavenger Experiments



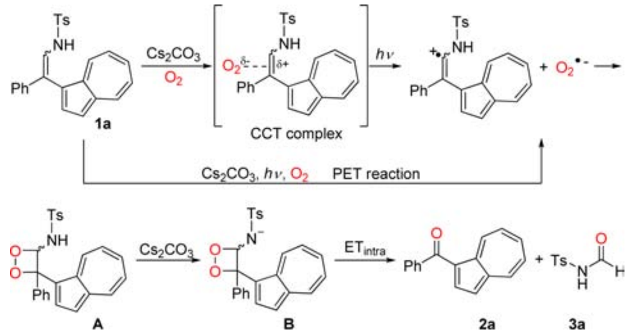
However, when the same reaction was performed under an $^{18}O_2$ atmosphere, the corresponding ^{18}O-inserted-ketone **2a**-[^{18}**O**] was produced in 89% yield (eq 9). These results indicate that oxygen in the oxidative cleavage reaction was obtained from molecular oxygen and that the dioxetane intermediate was involved in the reaction. When TEMPO (1 equiv) was added to the present reaction under air, azulen-1-yl ketone **2a** was only obtained in 6% yield, which indicates that radical species were involved in the reaction (eq 10). Moreover, the oxidative cleavage reaction did not proceed in the absence of light and under air, which suggests that natural sunlight is critical for a successful oxidative cleavage reaction (eq 11).

To elucidate the role of Cs_2CO_3 in the oxidative cleavage reaction, *N*-sulfonyl enamides **4** with a 3°-amine moiety and **5** with a 2°-amine moiety were used in the developed reaction. When *N*-sulfonyl enamide **4** was treated with Cs_2CO_3, the oxidative cleavage product **6** was not observed (eq 12). However, the C−C double bond in *N*-sulfonyl enamide **5** was smoothly cleaved with Cs_2CO_3 under the optimal reaction conditions and produced 4-methoxyphenyl phenyl ketone **6** in 81% yield (eq 13). These results indicate that the N−H proton is essential and that Cs_2CO_3 may initiate the oxidative cleavage reaction via the abstraction of the N−H proton.



Although the reaction mechanism has not been fully established at the present stage, a plausible reaction mechanism is illustrated in Scheme 6.[9] First, the alkene cation radical and

Scheme 6. A Plausible Mechanism



$O_2^{\bullet-}$ are produced by the excitation of the contact charge-transfer (CCT) complex and/or photoinduced electron transfer (PET) reaction of the C−C double bond in *N*-sulfonyl enamide **1a** with O_2. The subsequent [2 + 2] cycloaddition of the ion radical pairs produces dioxetane **A**. The oxidative cleavage reaction is initiated by the deprotonation of dioxetane **A** with a 2°-amine moiety by Cs_2CO_3, which induces the formation of *N*-sulfonyl amide anion **B**, which, in turn, readily decomposes to **2a** and **3a**. Further studies to demonstrate the reaction mechanism and applicability of the reaction to various enamides are under investigation.

In conclusion, we have developed a synthetic method to prepare azulen-1-yl ketones via an oxidative cleavage of the C−C double bond in *N*-sulfonyl enamides by the reaction of readily obtainable *N*-sulfonyl enamides with Cs_2CO_3 under air and natural sunlight and in the absence of a photosensitizer. An oxidative cleavage of C−C triple bonds was also demonstrated for the synthesis of azulen-1-yl ketone via the tandem Cu-catalyzed [3 + 2] cycloaddition, Rh-catalyzed arylation, photo-oxygenation, and ring-opening reaction in one pot under air and natural sunlight. Notably, the present method offers a wide range of azulen-1-yl ketones that are difficult to prepare using previously developed tools.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02545.

> Experimental procedures, characterization data, X-ray crystallography data (**2a**), and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (2011-0018355).

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