Tetrahedron Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Potassium iodide-mediated radical arylsulfonylation/1,2-carbon migration sequences for the synthesis of β-sulfonated cyclic ketones

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ARTICLE INFO

Article history:
Received 12 July 2018
Revised 25 August 2018
Accepted 11 September 2018
Available online xxxx

Keywords:
Sulfonation
1,2-Carbon migration
Radical process
Alkenylcyclobutanols
β-Sulfonated cyclic ketones

ABSTRACT

Potassium iodide-mediated radical sulfonylation/1,2-carbon migration sequences of alkenylcyclobutanols has been developed. The reaction was effectively accelerated using potassium iodide as a catalyst under mild reaction conditions without other metal oxidant. This approach is environmentally benign by use of shelf-stable arylsulfonyl hydrazides as arylsulfonyl radical precursor and water as solvent. This approach offers a facile way to prepare β-sulfonated cyclic ketone derivatives.

The sulfone moiety serves as valuable building blocks for the synthesis of a large number of biologically active compounds and pharmaceuticals [1]. Therefore, the development of novel and practical methods for the installation of sulfonyl group into organic frameworks has been a subject of intense study [2]. The addition of sulfonyl radicals to unsaturated carbon-carbon bonds represents a general route to synthesis of sulfone compounds. Recently, sulfonyl hydrazides have emerged as valuable sulfonyl radical sources via various oxidation processes [3]. Compared to other sulfonylation reagents [4] including sulfonyl halides, sulfinic selenides, and sulfinates, sulfonyl hydrazides are regarded as favorable sulfonyl radical precursors due to its stability for air and moisture, high reactivity, and eco-friendly byproducts. Recently, several groups reported the syntnesis of β-funtionalized ketones by radical addition and 1,2-carbon migration sequences of allylic alcohol derivatives with various radicals including acyl, aryl, phosphoryl, difluoromethyl, trifluoromethyl, and amine radicals [5]. Narasaka and co-workers reported an oxidative sulfonylation reaction and pinacol-type rearrangement of 1-vinyl cyclic alcohols with sodium 2-naphthalenesulfinate promoted by cerium (IV) tetrabutylammonium nitrate [6]. However, there are some imperfections to the previous work, such as narrow substrates scope and use of metal oxidant. We envisioned the transformation of the alkenylcyclobutanols to the β-sulfonated cyclopentanones by transition metal-free sulfonylation/1,2-alkyl migration sequence with sulfonyl hydrazides as sulfonyl radical source.

In connection with our ongoing research program related to redox reaction and ring closure sequences, we recently reported the intramolecular redox reaction via C–H bond functionalization [7] and radical addition reaction to alkenes with several radical sources under redox conditions [5c–5g]. Herein, we report potassium iodode catalyzed oxidative sulfonylation and 1,2-alkyl migration of alkenylcyclobutanol derivatives.

To determine suitable reaction conditions for the catalytic radical arylsulfonylation/1,2-alkyl migration sequences of alkenylcyclobutanol derivatives, we examined the copper-catalyzed radical arylsulfonylation of 1-(1-phenylvinyl)cyclobutanol (**1a**) with p-toluenesulfonyl hydrazide (**2a**) as arylsulfonyl radical source. Treatment of 1-(1-phenylvinyl)cyclobutanol (**1a**) with p-toluenesulfonyl hydrazide (**2a**) and 20 mol % of copper salts in water at 80 °C gave the radical addition/1,2-alkyl migration product **3a** in low yields (Table 1, entries 1–2). Various iodide ion catalysts, such as tetrabutylammonium iodide (TBAI), sodium iodide, and potassium iodide were screened (Table 1, entries 5–7), potassium iodide was the most efficient catalyst for this transformation (Table 1, entry 5). A survey of the reaction media indicated that common solvents, such as acetonitrile, ethyl acetate, DMF, DMSO, and co-solvents of acetonitrile and water were also tested, which did not give improved results (Table 1, entries 6–11). To our delight, the addition of 18-crown-6 as an additive significantly improved the yield to 90% (Table 1, entry 12). In the absence of potassium iodide, no reaction occurred (Table 1, entry 13).

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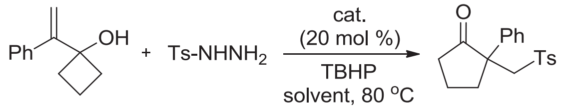
https://doi.org/10.1016/j.tetlet.2018.09.027
0040-4039/

Table1
Optimization of the reaction conditions.[a]



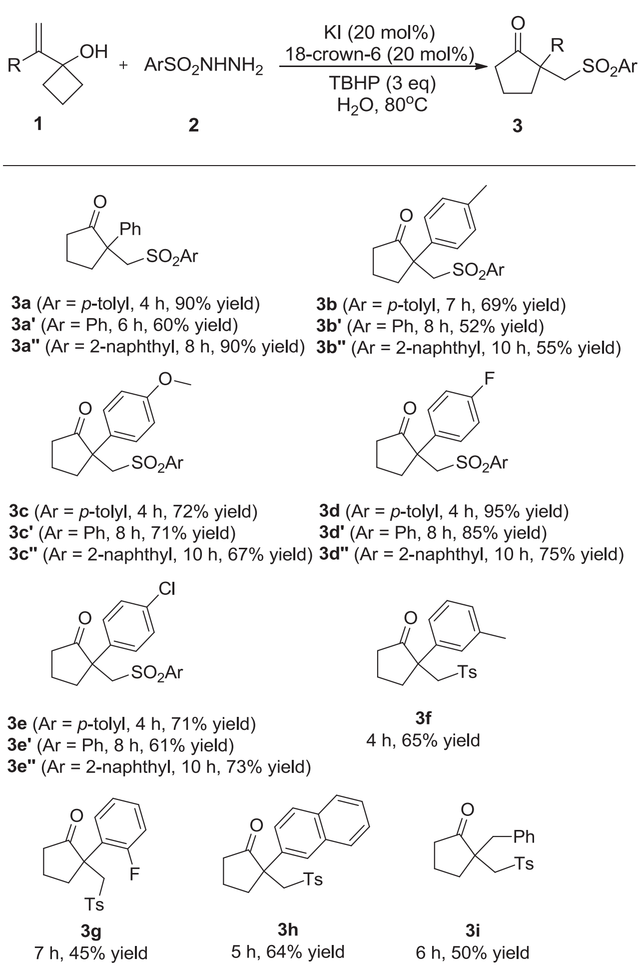
1a **2a** **3a**

Entry	Cat.	Solvent	Time (h)	Yield (%)[b]
1	CuBr	H_2O	5	5
2	$CuCl_2$	H_2O	5	13
3	TBAI	H_2O	5	45
4	NaI	H_2O	4	45
5	KI	H_2O	5	67
6	KI	CH_3CN	5	46
7	KI	EtOAc	6	23
8	KI	DMF	6	trace
9	KI	DMSO	6	trace
10	KI	$CH_3CN:H_2O$ (2:1)	5	50
11	KI	$CH_3CN:H_2O$ (1:2)	5	48
12[c]	KI	H_2O	4	90
13[d]	–	H_2O	4	trace
14[e]	KI	H_2O	4	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (0.04 mmol), TBHP (0.6 mmol) in solvent (3.0 mL) at 80 °C.
[b] Isolated yield.
[c] 18-crown-6 (0.04 mmol) was added.
[d] Without catalyst.
[e] TEMPO (3 equiv) was added.

With the optimal reaction conditions in hand, we investigated the scope of substrates for potassium iodide catalyzed radical arylsulfonylation/1,2-alkyl migration sequences of alkenylcyclobutanols 1 with arylsulfonyl hydrazides 2 in the presence of 20 mol % of potassium iodide and 18-crown-6 in water at 80 °C. As shown in Table 2, various alkenylcyclobutanols 1 with electron-donating or electron-withdrawing substituted-aryl and naphthyl groups furnished the corresponding ring expansion products with moderate to high yields (45–95%, Table 2, **3a**–**3h**). To further examine the scope of this reaction, a range of sulfonyl hydrazide derivatives **2**, such as benzenesulfonyl hydrazide and 2-naphthylsulfonyl hydrazide, were exposed to the optimal reaction conditions to react with 1-(1-arylvinyl)cyclobutanols 1. It was found that the corresponding products **3a**′–**3e**′ and **3a**″–**3e**″ were obtained in moderate to high yields (52–90%, Table 2). Notably, this potassium iodide-mediated radical sulfonation/1,2-carbon migration reaction with alkyl-substituted vinylcyclobutanol, 1-(3-phenylprop-1-en-2-yl)-cyclobutanol, gave 50% yield of desired product **3i** under the optimal reaction conditions. The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 1, when 1-(1-phenylvinyl)cyclobutanol (**1a**) with p-toluenesulfonyl hydrazide (**2a**) under the optimum reaction conditions, the reaction proceeded smoothly to afford the desired tosyl-substituted cyclopentanone **3a** on a gram scale with 88% yield (Scheme 1). To illustrate synthetic utility, we also carried out reductive removal of the sulfone group to afford cyclopentanone derivative 4 in moderate yield (Scheme 2).

Table 2
Substrate scope.[a,b]



3a (Ar = *p*-tolyl, 4 h, 90% yield)
3a' (Ar = Ph, 6 h, 60% yield)
3a'' (Ar = 2-naphthyl, 8 h, 90% yield)

3b (Ar = *p*-tolyl, 7 h, 69% yield)
3b' (Ar = Ph, 8 h, 52% yield)
3b'' (Ar = 2-naphthyl, 10 h, 55% yield)

3c (Ar = *p*-tolyl, 4 h, 72% yield)
3c' (Ar = Ph, 8 h, 71% yield)
3c'' (Ar = 2-naphthyl, 10 h, 67% yield)

3d (Ar = *p*-tolyl, 4 h, 95% yield)
3d' (Ar = Ph, 8 h, 85% yield)
3d'' (Ar = 2-naphthyl, 10 h, 75% yield)

3e (Ar = *p*-tolyl, 4 h, 71% yield)
3e' (Ar = Ph, 8 h, 61% yield)
3e'' (Ar = 2-naphthyl, 10 h, 73% yield)

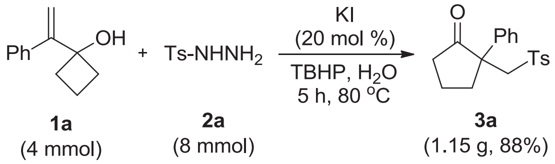
3f
4 h, 65% yield

3g
7 h, 45% yield

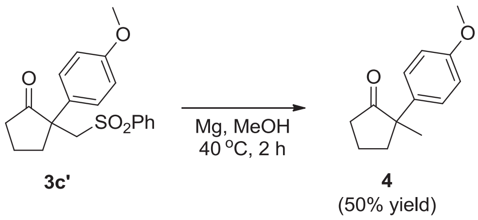
3h
5 h, 64% yield

3i
6 h, 50% yield

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), KI (0.04 mmol), 18-crown-6 (0.04 mmol), TBHP (0.6 mmol) in H_2O (3.0 mL) at 80 °C.
[b] Isolated yield.



Scheme 1. Gram scale sulfonation/1,2-alkyl migration of **1a**.



Scheme 2. Desulfonation of compound **3c**′.

To gain mechanistic insights into this transformation, some preliminary experiments were performed. The absence of potassium iodide as catalyst shut down the reactivity (Table 1, entry 13). A trace of the product was detected in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) (Table 1, entry 14). We propose the reaction mechanism shown in Fig. 1 based on our results and previously reported work [3,8]. Initially, potassium iodide interacts with TBHP to generate *tert*-butoxyl and *tert*-butylperoxy radicals which then react with arylsulfonyl hydrazide **2** to generate an arylsulfonyl radical I with the release of N2. Next, the arylsulfonyl radical **I** inserts to alkenylcyclobutanols **1**, yielding radical intermediate **II**, which is oxidized by the TBHP to afford the cation **III**. 1,2-Alkyl migration of cation **III** leads to a ring expansion that yields the product 3.