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Direct synthesis of 6-sulfonylated phenanthridines via silver-catalyzed radical sulfonylation-cyclization of 2-isocyanobiphenyls

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ABSTRACT

A convenient and straightforward synthesis of 6-sulfonylated phenanthridines via silver-catalyzed sequential radical insertion, cyclization and aromatization of 2-isocyanobiphenyls is reported. The protocol does not require a phenanthridine scaffold as a substrate and presents a highly regioselective synthesis of 6-alkyl/arylsulfonyl phenanthridines. The protocol utilizes readily available and easy to handle sodium sulfinates as sulfonating agents and potassium persulfate as an oxidant to afford good to excellent yields of the desired products in a one-pot operation at room temperature.

Sulfur-containing fragments are useful building blocks of numerous natural products, bioactive molecules and organic materials, thus C-S bond formation is an important step in various synthetic sequences [1,2]. Particularly, sulfonylated heterocycles constitute an important class of compounds that feature in many natural products, pharmaceuticals and biologically active compounds [3]. Heterocycles containing a sulfonyl group have found a wide range of applications in medicinal chemistry [4], organic synthesis [3b,3d] and material science [5]. Consequently, the development of more convenient and efficient methods for the introduction of a sulfonyl group into heterocycles has attracted considerable attention of synthetic chemists [6]. In general, sulfonylated heterocycles have been synthesized mainly in two ways:

(i) By the cyclization of various pre-sulfonated substrates [7] and
(ii) The sulfonation of already prepared heterocycles [8].

The phenanthridines heterocyclic scaffold is the basic constituent of many natural products, bioactive alkaloids, pharmaceuticals and functional materials [9]. In particular, C-6 diversely substituted phenanthridines have shown a variety of good biological activities [10], hence numerous methods are available for their synthesis [11]. Following the elegant approach of Nanni and coworkers [12], a general strategy involving sequential radical addition, cyclization and aromatization of 2-isocyanobiphenyls has emerged for the synthesis of 6-subsituted phenanthridines. In this method various alkyl [13], aryl [14], haloalkyl [14a,15], acyl [16], P-cenered [17], silyl [18], and S-centered radicals have been utilized to access a wide range of 6-substituted phenanthridines [11]. As regards the sulfur–containing functionalities, only 6-sulfenyl and 6-thiocyanatophenanthridines have been synthesized via radical sulfonylation-cyclization cascade reaction of 2-isocyanobiphenyls. (Scheme 1a) [19a–d]. However, a few 6-sulfonylated phenanthridines have been synthesized by the reaction of phenanthridine 5-oxide with sulfonic acid chloride and potassium cyanide in 13–31% yields [19e].

In view of the above discussion and our recent work on practical synthetic routes involving radicals [19d,20], we envisaged the insertion of sulfonyl radicals into isocyanides followed by cyclization and aromatization cascade to give 6-sulfonylated phenanthridines (Scheme 1b).

In order to realize our envisaged, synthetic strategy and optimize the reaction conditions, we began the investigation with the silver-catalyzed reaction of isocyanobiphenyl **1a** sodium sulfinate **2a**, using $K_2S_2O_8$ as an oxidant in DMF at room temperature (Table 1). 6-sulfonylated phenanthridine **3a** was obtained in an excellent yield of 86% in just 2 h. Next, different organic and inorganic oxidants, such as *tert*-butyl hydroperoxide (TBHP),

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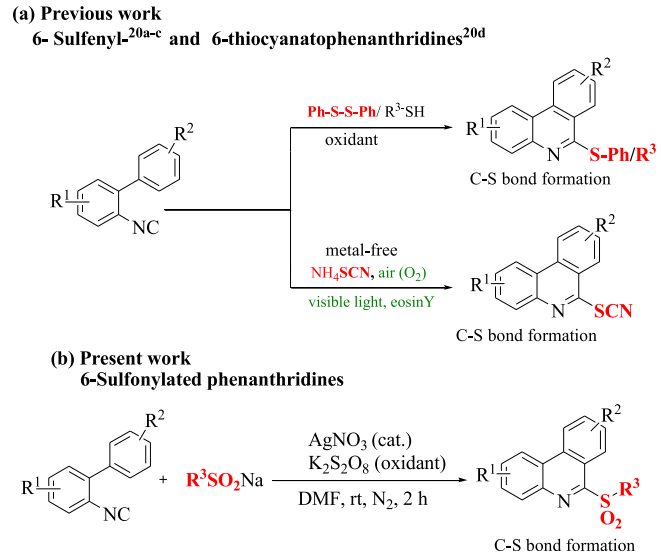


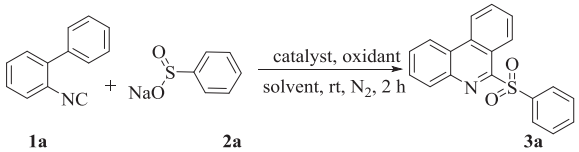
Scheme 1. Cyclization of 2-isocyanobiphenyls triggered by sulfur-centered radicals.

di-*tert*-butyl peroxide (DTBP), and $(NH_4)_2S_2O_8$ were tested in place of $K_2S_2O_8$, but among them $K_2S_2O_8$ was found to be the best (Table 1, entries 1–4). The optimum amount of the oxidant was found to be 2 equiv because on decreasing the amount, the yield was considerably decreased, while on increasing the amount no change in the yield was observed (Table 1 entries 12 and 13). Among the tested catalysts $AgNO_3$ proved to be the best and gave a maximum yield of the desired product **3a** (Table 1, entries 1vs 5–10). In the absence of a catalyst, the yield was poor (Table 1, Entry 11). Subsequently, quantitative catalyst loading was optimized (Table 1, entry 1 vs 14 and 15), which indicated that the silver catalyst played a key role in the reaction and its optimum amount required was 15 mol%. The screening of various solvents showed DMF to the best among DMSO, EtOH, CH_3NO_2, THF, CH_3CN, and toluene (Table 1, entries 16–21). The reaction was quenched on addition of a well known radical scavenger TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl) (4 equiv) at the beginning, which indicates that a radical intermediate is involved in the reaction (Table 1, entry 22).

Employing the optimized reaction conditions, we explored the generality and scope of the protocol across a wide range of 2-isocyanobiphenyls **1** and sodium sulfinates **2** incorporating various functionalities, such as CH_3, CH_3O, F, Cl and CF_3. The reaction shows splendid tolerance for both electron donating and electron-withdrawing groups and the substrates produce the desired 6-sulfonylated phenanthridines **3** in good to excellent yields irrespective of differences in their electronic and steric properties (Table 2). 2-Isocyanobiphenyls **1** and sodium sulfinates **2** bearing an electron-donating group in their aromatic rings appeared to react faster and afford slightly higher yields of the corresponding 6-sulfonylated phenanthridines **3** in comparison to those having an electron-withdrawing group (**3b-g** and **3n** vs **3i–l** and **3o**). Notably, aliphatic and alicyclic sulfinates also work well under the present reaction conditions (Table 2 entries **3h** and **3m**). We also investigated the regioselectivity of the present cyclization using a 2-isocyanobiphenyl bearing a *m*-methoxy group and found that a mixture of two regioisomers **3p** and **3p′** was formed in a ratio of 3:1, respectively (Table 2).

On the basis of the above observations and the literature precedents [14b,15a,19b,20e,20f,22], a plausible radical insertion, cyclization and aromatization mechanism is proposed in

Table 1
Optimization of reaction conditions.[a]



Entry	Solvent	Catalyst (mol%)	Oxidant (equiv)	Yield (%)[b]
1	DMF	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	86
2	DMF	$AgNO_3$ (15)	TBHP (2)	35
3	DMF	$AgNO_3$ (15)	DTBP (2)	44
4	DMF	$AgNO_3$ (15)	$(NH_4)_2S_2O_8$ (2)	62
5	DMF	Fe_2O_3 (15)	$K_2S_2O_8$ (2)	53
6	DMF	CuI (15)	$K_2S_2O_8$ (2)	30
7	DMF	$FeCl_3$ (15)	$K_2S_2O_8$ (2)	75
8	DMF	AgOAc (15)	$K_2S_2O_8$ (2)	42
9	DMF	CuCl (15)	$K_2S_2O_8$ (2)	28
10	DMF	$Cu(OAc)_2$ (15)	$K_2S_2O_8$ (2)	55
11	DMF	–	$K_2S_2O_8$ (2)	26
12	DMF	$AgNO_3$ (15)	$K_2S_2O_8$ (1)	68
13	DMF	$AgNO_3$(15)	$K_2S_2O_8$ (3)	86
14	DMF	$AgNO_3$ (10)	$K_2S_2O_8$ (2)	67
15	DMF	$AgNO_3$ (20)	$K_2S_2O_8$ (2)	86
16	DMSO	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	82
17	EtOH	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	25
18	CH_3NO_2	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	18
19	THF	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	–
20	CH_3CN	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	–
21	Toluene	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	–
22	DMF	$AgNO_3$ (15)	$K_2S_2O_8$ (2)	Traces[c]

[a] Reaction conditions: A mixture of 2-isocyanobiphenyl **1a** (0.25 mmol), sodium sulfinate **2a** (0.25 mmol), catalyst, and $K_2S_2O_8$ (1–3 equiv) in solvent (3 mL) was stirred for 2 h under N_2.
[b] Yield of isolated product **3a** after column chromatography.
[c] Reaction was quenched on addition of TEMPO (4 equiv) at the beginning.