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Synthesis of *N*-Sulfonylformamidines by *tert*-butyl Hydroperoxide–Promoted, metal-free, direct oxidative dehydrogenation of aliphatic amines

Ayijiamali Rouzi, Ruzeahong Hudabaierdi, Abudureheman Wusiman*

School of Chemistry and Chemical Engineering, Xinjiang Normal University, Urumqi, Xinjiang, 830054, PR China

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ABSTRACT

A direct and convenient metal-free method to prepare sulfonyl amidines in the presence of aqueous *tert*-butyl hydroperoxide (T-HYDRO) has been developed. Different tertiary and secondary amines were tested for compatibility with the oxidative conditions and could be coupled with sulfonyl azides to form the corresponding amidines in moderate to good yields.

1. Introduction

Amidines are interesting compounds because they have a unique structural motif, and are regarded as organic superbases,[1] as well as being key intermediates in the synthesis of heterocyclic compounds,[2] and versatile nitrogen ligands in metallocyclic complexes.[3] Amidines are also important in medicinal chemistry because they are found in many bioactive natural products[4] and have been identified as important pharmacophores.[5]

There are several well-known practical methods for the synthesis of *N*-sulfonyl formamidines[6] and recent efforts have been dedicated to the improvement of traditional protocols.[7] Among selected elegant examples, the Li group have reported two types of dehydrogenation of aliphatic tertiary amines: using sulfonyl azides in the presence of stoichiometric diethyl azodicarboxylate (DEAD)[7a] and CuCl–CCl_4[7b] catalytic systems (Scheme 1, eq a). He and co-workers have also reported the CuCl-catalyzed imidation of a tertiary amine using sulfonyl azides as the nitrogen source in the presence of benzyltriethylammonium chloride (TEBA)[7c] (Scheme 1, eq b). Wang and co-workers have developed a synthesis of sulfonyl amidines from tertiary amines and sulfonyl azides in the presence of a stoichiometric amount of $FeCl_3$,[7d] as well as an electrochemical approach[7e] (Scheme 1, eq c). Although tremendous efforts have been made,[6g] a milder and metal-free method for the synthesis of sulfonyl amidines is still in demand.

Various synthetic methodologies have been developed for activation/functionalization of the α, β-C(sp^3)–H bonds of amines. However, most of these procedures need a transition metal as the active catalyst.[8] Thus, the development of a new and efficient metal-free method for the simultaneous oxidative dehydrogenation and functionalization of amines remains a significant challenge. Based on our previous work on oxidation using *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant,[9] we investigated the use of TBHP for the oxidative dehydrogenation of amines. Herein, we describe a mild and simple T-HYDRO (TBHP 70 wt% in water)-promoted, catalyst-free direct functionalization of aliphatic amines with sulfonyl azides to produce sulfonyl formamidines (Scheme 1, eq d).

2. Results and discussion

Initially, we chose tosylazide (TsN_3) **1a** and triethylamine **2a** as standard substrates to optimize suitable conditions for this reaction (Table 1). To our delight, the reaction of **1a** (1.2 equiv.) with **2a** (1.0 equiv.) was performed smoothly in the presence of 2.0 equiv. of T-HYDRO in ethyl acetate (EtOAc) at 60 °C, and generated the desired

* Corresponding author.
E-mail address: arahman@xjnu.edu.cn (A. Wusiman).

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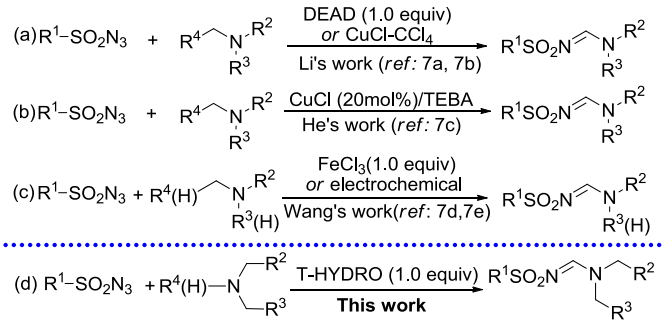
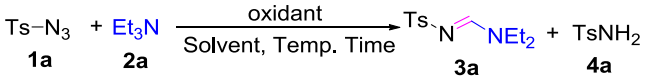


Scheme 1. Representative approaches for synthesis of N-sulfonylformamidines.

Table 1
Optimizing the condition for the formation of **3a**[a].



Entry	1a: 2a	Oxidant (eq.)	Solvent	Temp. (°C)	Time (h)	Yield of 3a (%)[b]
1	1.2: 1	T-HYDRO (2)	EtOAc	60	2	40
2	2.0: 1	T-HYDRO (2)	EtOAc	60	4	55
3	2.5: 1	T-HYDRO (2)	EtOAc	60	24	60
4	2.5: 1	T-HYDRO (2)	MeCN	60	24	55
5	2.5: 1	T-HYDRO (2)	$CHCl_3$	60	24	20
6	2.5: 1	T-HYDRO (2)	DCM	60	24	56
7	2.5: 1	T-HYDRO (2)	DCE	60	24	65
8	2.5: 1	T-HYDRO (2)	DCE	80	5	75
9	2.5: 1	T-HYDRO (3)	DCE	80	2	60
10	2.5: 1	T-HYDRO (1)	DCE	80	5	77
11[c]	2.5: 1	TBHP (1)	DCE	80	5	77
12	2.0: 1	T-HYDRO (1)	DCE	80	2.5	78
13	2.0: 1	DTBP (1)	DCE	80	8	8
14	2.0: 1	CHP (1)	DCE	80	5	63
15	2.0: 1	TBPB (1)	DCE	80	8	30
16	2.0: 1	BPO (1)	DCE	80	8	48
17	1.5: 1	T-HYDRO (1)	DCE	80	1	55
18	1: 3.0	T-HYDRO (1)	DCE	80	1	30
19	2.0: 1	–	DCE	80	12	6

[a] Reactions were performed in 2 mL of solvent in a sealed tube unless otherwise noted. [T-HYDRO]: TBHP, 70 wt% in water. [DTBP]: Di-*tert*-butylperoxide. [CHP]: Cumyl hydroperoxide. [TBPB]: *tert*-Butyl peroxybenzoate. [BPO]: Benzoyl peroxide.
[b] Isolated yield after column chromatography.
[c] TBHP 5.5 M in decane.

sulfonyl formamidine **3a** in 40% yield, while the tosylamide **4a** was also isolated as a byproduct in approximately 20% yield (entry 1). Therefore, we investigated the use of an excess of TsN_3. As expected, when the amount **1a** was increased from 1.2 to 2.0 and 2.5 equiv. the yield of **3a** was gradually increased to 55% and 60%, respectively and the yield of the isolated tosylamide **4a** to 40% (entries 2–3). Various solvents, including acetonitrile (MeCN), chloroform ($CHCl_3$), dichloromethane (DCM), and 1,2-dichloroethane (DCE) were screened (entries 4–7). The highest yield was observed with DCE (entry 7). A 75% yield was also obtained by raising the reaction temperature to 80 °C and shortening the reaction time from 24 to 5 h (entry 8). Surprisingly, when treated with 3.0 equiv. of T-HYDRO, **1a** was consumed in 2 h and the yield of **3a** decreased to 60% (entry 9). In contrast, the use of 1.0 equiv. of T-HYDRO generated a 77% yield of product (entry 10). The use of TBHP in decane instead of T-HYDRO gave a similar yield of the product (entry 11). Leaving the other conditions unchanged and decreasing the loading of TsN_3 to 2.0 equiv. resulted in the highest yield of 78% (entry 12). Further screening of different oxidants revealed no better results (entries 13–16). Moreover, the yield of **3a** showed an obvious decline when the amount of TsN_3 was decreased (entry 17). When the molar ratio of **1a**: **2a** was changed to from 2:1 to 1:3, the yield decreased (entry 18). Interestingly, a 6.0% yield of the desired sulfonyl amidine **3a** could be isolated in the absence of T-HYDRO (entry 19). Therefore, the optimal reaction conditions were determined to be treatment of sulfonylazide (**1**) with tertiary amine (**2**) in a 2:1 M ratio, with T-HYDRO (1.0 equiv.) as the oxidant, in DCE at 80 °C.

With the optimized conditions in hand, the scope of the reaction was investigated as shown in Table 2. A wide range of sulfonyl azides and tertiary amines could be used in this reaction system under the optimized conditions. The phenylsulfonyl azides bearing electron-donating and electron-withdrawing groups reacted with triethylamine to afford the corresponding sulfonyl amidines in good to excellent yields (**3a**–**3j**). Moreover, having the substituted group at different positions on the phenyl ring had no obvious effect on the reaction. However, the strong electron-withdrawing nitro group gave a comparably lower yield of **3i**. 2-Naphthalenesulfonyl azide reacted slowly, but the desired product **3k** was obtained in a relatively high yield. Notably, the aliphatic sulfonylazides, benzylsulfonyl azide and butylsulfonyl azide, afforded the products **3l** and **3m** in nearly 40% isolated yields. In addition, the five membered heteroaromatic sulfonyl azide derivatives with one or two heteroatoms provided the corresponding amidines in good yields (**3n**–**3q**). Furthermore, the reaction of 3-pyridinesulfonyl azide with *tri*-propyl amine allowed the formation of the **3r** in 75% yield. To our satisfaction, an array of tertiary amines proved to be suitable reaction partners and afforded the corresponding coupling products **3s**–**3w** in good to moderate yields. For *tri*-*n*-octylamine, the yield of corresponding sulfonyl amidine **3u** was 47%, probably because of steric hindrance from the long alkyl group. Tertiary amines with different alkyl groups, *N,N*-diethylpropylamine and *N,N*-diethylbutylamine, were also investigated and two products (**3v/3a** and **3w/3a**) were obtained for each tertiary amine in good yields, and it was found that the reaction was more selective for the ethyl group giving a ratio for the two products of nearly 2:1. Cyclic amines were also used as substrates and *N*-ethyl piperidine produced the corresponding amidine **3x** in 45% isolated yield with a trace amount of product resulting from hydrogen abstraction from the cyclic α-carbon. Interestingly, when using *N*-methylpyrrolidine, the cyclic sulfonyl amidine **3y** was obtained predominantly. The aromatic tertiary amine *N,N*-diethyl aniline gave a relatively poor yield of **3z** with a mixture of E and Z configurations.

To gain further insight into the mechanism of the reaction, a series of control experiments were carried out (Scheme 2). First, tosylazide and T-HYDRO were reacted under the standard reaction conditions; however, neither sulfonamide nor 1,2-ditosyldiazene (TsN = NTs)[7c] were observed (Scheme 2, eq. 1). Then, butylated hydroxytoluene (BHT) as a radical scavenger[10] was added to the reaction mixture. When 1.0 or 2.0 equiv. BHT was used, the yields of product and sulfonamide decreased dramatically, and no products were obtained when 3.0 equiv. of BHT were used and the starting material **1a** was almost completely recovered (Scheme 2, eq. 2). From these results, we believe that a radical pathway is involved in the reaction process. In addition, we considered that the enamine may be the intermediate product, and to confirm this hypothesis, *N,N*-diethylethenamine was synthesized via the reaction of diethylamine with acetaldehyde using K_2CO_3 as the dehydrating agent,[11] followed by reaction with **1a** without further purification to give **3a** isolated in 45% yield (Scheme 2, eq. 3). Furthermore, the enamine intermediate was also successfully captured using (2,4-dinitrophenyl)hydrazine [see Electronic Supporting Information (ESI)]. However, the sulfonyl amidine could not be converted to the sulfonamide under the standard conditions (Scheme 2, eq. 4).