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Potassium *tert*-butoxide-mediated metal-free synthesis of sulfonamides from sodium sulfinates and *N*,*N*-disubstituted formamides

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ABSTRACT

By using formamides as amine sources, a novel and efficient KO-*t*-Bu mediated amination of sodium sulfinates has been developed. The reaction utilizes readily available starting materials under metal-free conditions, thus providing an alternative and attractive route to sulfonamides.

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Introduction

Sulfonamides are highly valuable structural motifs in numerous bioactive molecules, pharmaceuticals, and natural products. They exhibit a broad spectrum of biological activities and are employed extensively in various medicinal and pharmaceutical applications, for example, as antibacterials, anticonvulsants, HIV protease inhibitors, antitumor agents, and antifungal agents [1]. Therefore, considerable efforts have been devoted to develop a methodology for constructing sulfonamides during the past decade. Conventionally, sulfonamides can be synthesized by the nucleophilic substitution of amines to sulfonyl chlorides [2]. Compared to sulfonyl chlorides, sodium sulfinates can be considered better sulfonylation reagents because of their stability, low price and convenience of handling [3]. Recently, Jiang and co-workers reported an elegant $CuBr_2$-catalyzed oxidative synthesis of sulfonamides via the reaction of sodium sulfinates and amines with DMSO or O_2 [4]. This reaction can also be carried out under metal-free conditions [5]. These methods avoid prefunctionalization of the sulfonate component, thus resulting in greater step and atom economy (Scheme 1).

N,*N*-Disubstituted formamides are easy to handle, inexpensive, commercially available, rendering them ideal as amination reagents in organic reactions [6]. In 2012, Wan and co-workers developed a method for the synthesis of amides from aldehydes and *N*,*N*-disubstituted formamides under metal-free conditions [7]. Meanwhile, reactions of *N*,*N*-disubstituted formamides with alcohols [8] or acids [9], which furnished the corresponding amides under oxidative conditions, have been reported. In 2014, Pan and co-workers reported an elegant process for the copper-mediated synthesis of sulfonamides from thiols and formamides under air atmosphere [10]. In view of the above, we report herein a method for the formation of sulfonamides by oxidative amination of sodium sulfinates with *N*-substituted formamides. To the best of our knowledge, the synthesis of sulfonamides from sodium sulfinates and formamides has not been reported.

Results and discussion

We initially chose *N*,*N*-dimethylformamide **1a** and sodium *p*-tolylsulfinate **2a** as the substrates to test the reaction. As shown in Table 1, this reaction proceeded via a sequential two-step process. First, **1a** was added to a base in a solvent at 50 °C over 15 min. Next, a mixture of **2a** and an oxidant in a solvent was added dropwise at 50 °C. The mixture was stirred at 50 °C for 12 h. Various bases were tested for the proposed reaction using 2.0 equiv of *N*-iodosuccinimide (NIS) as the oxidant, in CH_3CN (Table 1, entries 1–9). The desired product **3a** was obtained in 68% yield when KO-*t*-Bu was used as the base (entry 9). Other bases such as KOH, K_2CO_3,

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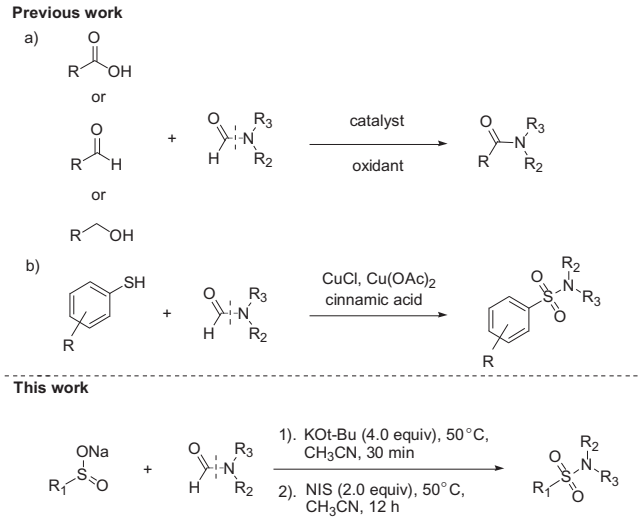


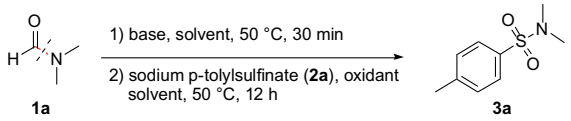
Scheme 1. Reported and designed routes for amination of sodium sulfinate.

CH_3COONa, NaH, CH_3Ona, and C_2H_5ONa proved inactive (entries 1–7). The product yield was improved to 81% upon increasing the amount of KO-*t*-Bu to 4.0 equiv (entry 10). Screening of different solvents revealed that CH_3CN was the best medium for this conversion (entries 10–16). Extensive screening revealed that the reaction temperature affected the reaction, with lower yields obtained at 80 °C and 25 °C (entries 17 and 18). The yield of **3a** decreased to 65% in the presence of 1.0 equiv of NIS (entry 19). Attempts to use alternative oxidants such as I_2 and *N*-bromobutanimide (NBS) proved less efficient, affording **3a** in lower yields (entries 20 and 21).

This optimized protocol could be applied to the coupling of **1a** with a broad range of sodium sulfinates (Table 2). Sodium benzenesulfinate afforded the product in 85% yield (**3b**). *o*-Substituted sodium benzenesulfinates gave a lower yield, which might be explained by the steric hindrance at the *ortho*-position (**3c**). Halogen groups on the aromatic ring of the sodium benzenesulfinates were well tolerated in the reaction, affording the desired product in moderate yields (**3d**–**3g**). The reactions of sodium arenesulfinates bearing electron-donating or electron-withdrawing groups at the *para*-position of the aryl ring afforded the corresponding products **3h**–**3k** in good yields (65–85%). However, a much lower yield of sulfonamide **3l** was obtained when 4-nitro-substituted benzenesulfinate was used. 1-Naphthyl sodium sulfinate and 2-naphthyl sodium sulfinate were also suitable reactants for this reaction and gave the corresponding products **3n** and **3o** in 55% and 62% yield respectively. In addition, heterocyclic sodium sulfinates were tolerated in this reaction, and the desired products were obtained in moderate yields (**3p**–**3r**).

A series of formamides were also examined to expand the synthetic utility of the protocol (Table 3). *N*-Formylpiperidine was suitable for this transformation, giving products **4a** and **4b** in good yields. Various substituted sodium arenesulfinates were reacted with *N*-acetylmorpholine, and the desired sulfonamides **4c**–**4g** were obtained in satisfactory yields. *N*-Acetylmorpholine also smoothly react with sodium thiophene-2-sulfinate to form the corresponding sulfonamide **4h**. Sulfonamide **4i** was obtained in lower yield when *N*,*N*-diethylformamide was used, because of the larger steric hindrance on the nitrogen atom of the formamide. Moreover,

Table 1
Optimization of reaction conditions.[a]



1a **3a**

Entry	Base (equiv)	Oxidant	Solvent	Yield (%)
1	KOH (3.0)	NIS	CH_3CN	0
2	K_2CO_3 (3.0)	NIS	CH_3CN	0
3	CH_3COONa (3.0)	NIS	CH_3CN	0
4	HCOONa (3.0)	NIS	CH_3CN	Trace
5	NaH (3.0)	NIS	CH_3CN	Trace
6	CHONa (3.0)	NIS	CH_3CN	Trace
7	C_2H_5ONa (3.0)	NIS	CH_3CN	Trace
8	NaO-*t*-Bu (3.0)	NIS	CH_3CN	15
9	KO-*t*-Bu (3.0)	NIS	CH_3CN	68
10	**KO-*t*-Bu (4.0)**	**NIS**	**CH_3CN**	**81**
11	KO-*t*-Bu (4.0)	NIS	EtOH	36
12	KO-*t*-Bu (4.0)	NIS	PhMe	70
13	KO-*t*-Bu (4.0)	NIS	C_6H_5Cl	42
14	KO-*t*-Bu (4.0)	NIS	CH_2Cl_2	20
13	KO-*t*-Bu (4.0)	NIS	DCE	64
14	KO-*t*-Bu (4.0)	NIS	Xylene	Trace
15	KO-*t*-Bu (4.0)	NIS	CH_3OH	38
16	KO-*t*-Bu (4.0)	NIS	Isopropanol	27
17	KO-*t*-Bu (4.0)	NIS	CH_3CN	54[b]
18	KO-*t*-Bu (4.0)	NIS	CH_3CN	73[c]
19	KO-*t*-Bu (4.0)	NIS	CH_3CN	65[d]
20	KO-*t*-Bu (4.0)	I_2	CH_3CN	74
21	KO-*t*-Bu (4.0)	NBS	CH_3CN	51

[a] Reaction conditions: 1) **1a** (4.0 equiv), base (x equiv), solvent (2 mL), 50 °C, 30 min. 2) **2a** (1.0 mmol), oxidant (2.0 equiv), solvent (2 mL), 50 °C, 12 h, Schlenk tube under air.
[b] The mixture was stirred at 80 °C.
[c] The mixture was stirred at 25 °C.
[d] 1.0 equiv of NIS was used.

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