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Efficient synthesis of organic sulfonic acid derivatives containing dithiocarbamate side chains

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ABSTRACT

An efficient method for the synthesis of organic sulfonic acid potassiums containing dithiocarbamate side chains was developed through the reaction of amines, carbon disulfide and sultones in the presence of K_3PO_4 in water at room temperature. The organic sulfonic acid potassium derivatives are easily transformed into the corresponding organic sulfonic acids, which were further reacted with amines to afford the important organic sulfonamides containing dithiocarbamate side chains.

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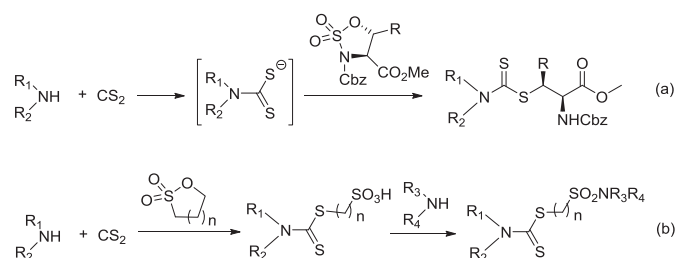
1. Introduction

Sulfonic acid and sulfonic amide are two kinds of important functional groups in medicinal chemistry,^{1,2} which widely present in biologically active natural products and medicinally valuable compounds.^{3,4} Therefore, the introduction of both kinds of groups is one of the most commonly used strategies for the lead optimization process in order to improve the desired biological and physical properties of a potential compounds.⁵

Recent years, dithiocarbamate derivatives have been received considerable attentions because of its important biological activities, such as anesthetic,⁶ anti-HIV,⁷ mono glyceride lipase inhibitors,⁸ anti-tumor agents.⁹ Therefore, many kinds of dithiocarbamate derivatives have been synthesized.¹⁰ However, to the best of our knowledge, it is no report on the direct synthesis of organic sulfonic acid derivatives containing dithiocarbamate side chain. Our group has developed several efficient methodologies for the synthesis of different kinds of dithiocarbamate esters,¹¹ from which some potent anticancer compounds were discovered.¹² As the requirement of our work, we urgently hope to develop an efficient method for the synthesis of organic sulfonic acid derivatives containing dithiocarbamate side chains.

Recently, Varma et al. have reported an efficient one-pot methodology for the synthesis of unnatural α -amino acids containing the dithiocarbamate side chains through the nucleophilic

ring opening of sulfamidates by in situ generated dithiocarbamate anion (Scheme 1, a).¹³ Inspired by their work, we envisioned that if replacing the sulfamidates with sultones, the organic sulfonic acid salts containing dithiocarbamate side chains should be formed in one-pot, from which the corresponding sulfonic acid derivatives, such as sulfonic acids, sulfonamides should be easily obtained (Scheme 1, b).



Scheme 1. Synthetic strategy toward sulfonic acid derivatives containing dithiocarbamate side chains.

2. Results and discussion

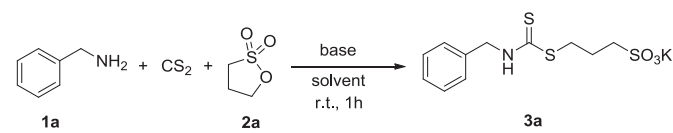
In order to examine the possibility, we initially carried out the reaction of benzylamine (**1a**), carbon disulfide with γ -sultone (**2a**) in the presence of Al_2O_3 at room temperature under solvent free conditions.¹⁴ To our delight, the desired product (**3a**) was obtained in 38% yield (Table 1, entry 1). Encouraged by this result, various solvents and bases were screened to optimize the reaction

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Table 1
Optimization of the reaction conditions for the formation of **3a**^a



Entry	Base	Solvent	Yield(%) ^b
1 ^{c,d}	—	—	38
2 ^c	—	EtOAc	35
3 ^c	—	MeOH	58
4	NaHCO ₃	MeOH	75
5	NaHCO ₃	EtOH	70
6	K ₃ PO ₄	Acetone	80
7	K ₂ CO ₃	Acetone	83
8	K ₂ CO ₃	H ₂ O	89
9	K ₃ PO ₄	H ₂ O	95
10	TEA	H ₂ O	85

^a Reaction conditions: **1a** (5 mmol, 1 equiv), K₃PO₄ (1 equiv), CS₂ (1.5 equiv) in water (5 mL) at rt for 10 min, then added **2a** (1 equiv).

^b Isolated yield.

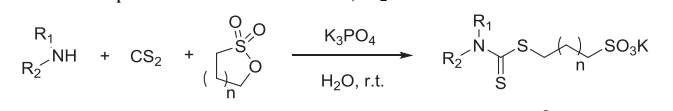
^c No base participated.

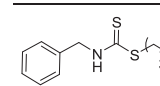
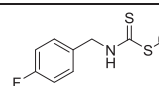
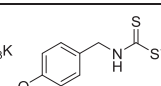
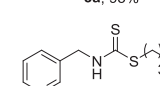
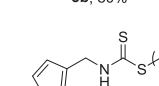
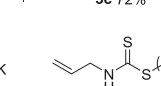
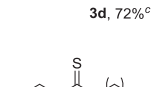
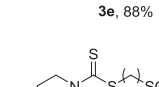
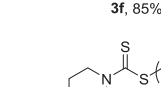
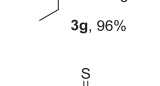
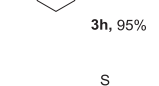
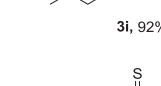
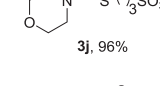
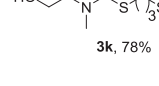
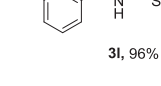
^d The reaction was performed in the solid phase of Al₂O₃.

conditions (Table 1). We were excited to find that the product **3a** could be obtained with a yield of up to 95%, using K₃PO₄ as base in water at room temperature (Table 1, entry 9).

With the optimized reaction conditions in hand, we set out to examine the substrate scope of this methodology (Table 2). A variety of amines (**2a**) were first allowed to react with carbon disulfide and γ -sultone (**2a**) under optimized reaction conditions. All the reactions were performed smoothly to give the desired products in good to excellent yields (**3a–3l**). Generally, the secondary amines provided the expected products in 92–96% yields (**3g–3j**). Much to our satisfaction, amines with different functional groups including double

Table 2
Substrate scope for the reaction of amines, CS₂ and sultones^{a,b}

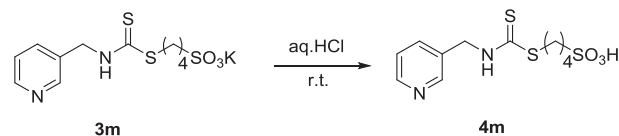


		
3a , 95%	3b , 80%	3c , 72%
		
3d , 72% ^c	3e , 88%	3f , 85%
		
3g , 96%	3h , 95%	3i , 92%
		
3j , 96%	3k , 78%	3l , 96%
		
3m , 73% ^c	3n , 98%	3o , 85%

^aReaction conditions: **1** (5 mmol, 1 equiv), K₃PO₄ (1 equiv), CS₂ (1.5 equiv) in water (5 mL) at r.t. for 10 min, then added **2** (1 equiv); ^bIsolated yield; ^creaction time was 3 h.

bond, hydroxyl, alkoxy, ester and heterocycle, were all well tolerated in this reaction conditions. Then, replacing the γ -sultone (**2a**) with δ -sultone (**2b**) to react with carbon disulfide and different amines and the expected products (**3m–3o**) were also obtained in 73–98% yields.

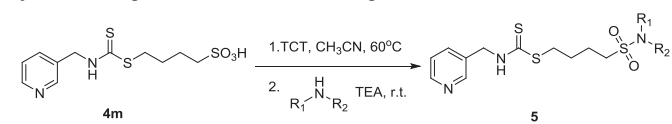
It is important to note that the organic sulfonic acid salts containing dithiocarbamate side chains (**3**) could be easily transformed into corresponding organic sulfonic acids. Such as compound **3m** was treated with 1 equiv HCl (aq, 1M) at room temperature to afford the corresponding sulfonic acid **4m** in quantitative yield (Scheme 2).

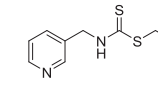
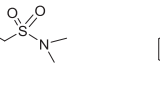
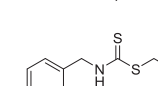
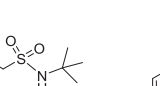
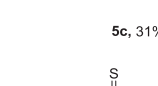

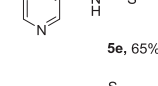
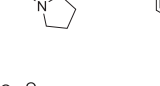
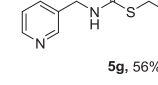
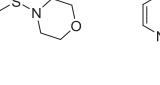


Scheme 2. Synthesis of compound **4m** from **3m**.

To further extend the application of this method, we next selected compound **4m** to react with various amines and hope to afford the more important organic sulfonamides containing dithiocarbamate side chains **5**. After screening the reaction conditions (See Supplementary data, Table 1), it was found that the reaction performed smoothly in the presence of 2,4,6-trichloro-1,3,5-triazine (TCT) using acetonitrile as solvent and triethylamine as base at 60 °C for 24 h. As shown in Table 3, the optimized reaction conditions were suitable for the different kinds of amines, including primary amines, secondary amines, ammonia, high steric hindrance *t*-butylamine and low reactivity imidazole, to afford the desired products **5a–5j** in moderate to good yields.

Table 3
Synthesis of organic sulfonamides containing dithiocarbamate side chains **5**^{a,b}



	
5a , 43% ^c	5b , 45%
	
5c , 31%	5d , 52%
	
5e , 65%	5f , 59%
	
5g , 56%	5h , 51%
	
5i , 54%	5j , 56% ^d

^aReaction conditions: **4m** (1 mmol, 1 equiv), TCT (0.6 equiv) in anhydrous CH₃CN (10 mL) at 60 °C for 24 h, then added amine (1.5 equiv), TEA (1.5 equiv) at r.t. for 1 h; ^bIsolated yield; ^camine is (CH₃)₂NH·HCl, TEA (3 equiv); ^donly NH₃·H₂O without TEA.

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