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Chemoselective synthesis of aryl carboxamido sulfonic acid derivatives

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ABSTRACT

A one-pot two-step synthetic strategy for the preparation of aryl carboxamido sulfonic acid derivatives was developed. The synthesis started from *m*-(chlorosulfonyl)benzoyl chloride, which was reacted with amines, alcohols, thiols, or sodium azide and catalytic activator at rt to give the corresponding sulfonic acid derivatives in good yields. The short reaction times and the one-pot chemoselective nature of the procedure diminished undesired side reactions and enhanced the efficiency of the reaction. In cases of electron-donor and electron-deficient substituted carboxanilides, piperidine was successfully incorporated at sulfur to obtain the corresponding sulfonamides in yields of 46% (4-nitroaniline) to nearly quantitative (4-methoxyaniline). The optimized conditions were applied to the preparation of diarylsulfonamides, sulfonic esters, thiosulfonates, and a sulfonyl azide, which are very important and key structures in modern organic synthesis. Furthermore, the method has been successfully used in the preparation of inhibitors of isocitrate dehydrogenase mutants, which are closely related to tumorigenesis.

1. Introduction

Sulfonic acid derivatives are very useful pharmaceutical compounds, exhibiting a wide range of biological activities such as antimicrobial, anti-cancer, anti-inflammatory, and antiviral functions.[1–3] The sulfonamide group is considered a transition-state mimic of peptide hydrolysis and is therefore used in the design of potent and irreversible protease inhibitors.[4] A large number of structurally novel sulfonamide derivatives showed remarkable inhibitory activities against quite significant proteases such as matrix metalloproteases, tumor necrosis factor-α converting enzyme (TACE), and HIV protease, and the resulting loss of protease activity invited research into small molecule treatments for cancer, arthritis, and acquired immunodeficiency syndrome (AIDS).[5] Recently, Hamachi and co-workers described an application of sulfonic esters in site-specific protein labeling and biofunctional imaging.[6–9] The tremendous utility of sulfonylated molecules necessitates their rapid and effective synthesis, particularly with a view to synthesize molecular libraries.

Numerous sulfonamide syntheses have been developed. A one-pot reaction of sulfinic acid salts (prepared by reacting organometallic reagents and sulfur dioxide) with *N*-chlorobenzotriazole can be used to synthesize sulfonamides.[10] Ruano et al. recently reported a one-pot two-step oxidative method to convert methyl sulfinates and a range of amines into the corresponding sulfonamides, using *m*-CPBA.[11] Caddick and co-workers reported a synthesis of sulfonamides from various pyridinium sulfonates using the activating reagent triphenylphosphine ditriflate.[12] The last method provided high yields and tolerated a variety of functional groups.

The sulfonylation of amines with sulfonyl chlorides in the presence of base is one of the most important methods of sulfonamide preparation because of its high efficiency and simplicity.[2,13] However, this method is limited by the formation of undesired disulfonamides and by the hydrolytic decomposition of highly active sulfonyl chlorides.[14] Recently, the direct conversion of a sulfonic acid to a sulfonamide was achieved using 2,4,6-trichloro-1,3,5-triazine to form the reactive sulfonyl chloride intermediate.[15,16] Mersharm and co-workers used copper(II) oxide to efficiently catalyze the transformation of sulfonyl chlorides to sulfonamides and sulfonic esters in the absence of base in good yields.[17] Although the moisture sensitivity, harsh preparative conditions, and disulfonamide side reactions of sulfonyl chlorides considerably restrict their use in sulfonamide syntheses, their high reactivity with primary amines makes them attractive for the development of new, mild, and straightforward synthetic methods.

m-(Chlorosulfonyl)benzoyl chloride (CSBC) bears two highly reactive functional groups, an acyl chloride, and a sulfonyl chloride. It is an ideal building block for the simple bi-directional expansion of the

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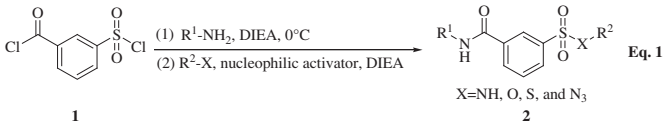
structural complexity of substituted arylsulfonyl compounds (Scheme 1). Owing to the differential reactivities of its acyl and sulfonyl chlorides, CSBC chemoselectively reacts at the more reactive acyl chloride, followed by sulfonyl coupling to give diverse carboxamido sulfonic acid derivatives in two distinct steps.[18] Even though the acyl and sulfonyl chloride groups participate in two sequential coupling reactions for the introduction of different substituents, the high reactivity of each functional group can easily lead to decomposition in the presence of base during the reaction. In addition, the subsequent flash column chromatography leads to the decomposition of unreacted sulfonyl chloride intermediates, and thereby, reduces the reaction yield and contaminates the desired product with byproducts such as sulfonic acids. Furthermore, the reactivity of CSBC with other nucleophiles such as alcohols, thiols, and azides has rarely been assessed. Therefore, a concise synthetic strategy is needed to facilitate the construction of structurally related molecular libraries. This report describes the development of a one-pot two-step strategy for the synthesis of aryl carboxamido sulfonic acid derivatives that is shorter and more efficient than currently known procedures.



1 2

Scheme 1. General scheme for the one-pot synthesis of carboxamido sulfonic acid derivatives.

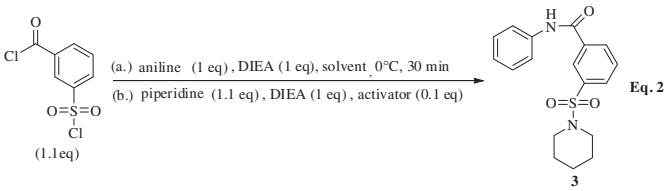
2. Results and discussion

2.1. Optimization of a one-pot, two-step synthesis of carboxamido sulfonamides

Making use of the well-known difference in reactivity between acyl chlorides and sulfonyl chlorides,[18] CSBC **1** was reacted with two different nucleophiles in a one-pot strategy to give the desired, disubstituted products **2** (Scheme 1). In the presence of *N*,*N*-diisopropylethylamine (DIEA), primary amines reacted chemoselectively with the more reactive acid chloride, leaving the sulfonyl chloride untouched. Subsequently, without quenching or work-up processes, the second nucleophile was added, along with a catalytic amount of nucleophilic activator (4-dimethylaminopyridine (DMAP), trimethylamine, or pyridine) and 1 equiv of DIEA. Compared to the one-pot synthesis, disubstituted sulfonamides could also be obtained in two individual steps; however, the average yield of the two-step procedure was generally about 60%.[18] Carboxamido sulfonamides, sulfonic esters, thiosulfonates, and sulfonic azides could also be synthesized using this one-pot strategy.

A variety of solvent/nucleophilic activator combinations were screened to optimize the reaction conditions (Scheme 1 and Table 1). In the model study, aniline (1 equiv) was used as the initial nucleophile to form the amide bond with the highly reactive acid chloride; then, the resulting intermediate was treated with piperidine (1.1 equiv) in the presence of a nucleophilic activator (0.1 equiv) to give the disubstituted product (Eq. 2 in Table 1). Using *N*,*N*-dimethylformamide (DMF) as the reaction solvent resulted in the decomposition of *m*-(chlorosulfonyl)benzoyl chloride (entries 1 and 2).[19] The use of solvents such as dichloromethane (DCM), acetonitrile (ACN), or tetrahydrofuran (THF) overcame this problem. In the preparation of sulfonic esters, the absence of catalytic activator resulted in no distinguishable product formation after 24 h. Referring to Table 1, DMAP in DCM as well as TMA·HCl in THF showed good catalytic ability in the formation of sulfonamide **2**. By contrast, the use of ACN instead of DCM or THF in the presence of different catalysts resulted in lower yields and prolonged reaction times (entries 5 and 6). Therefore, considering organic solubility and reaction efficiency, the use of a catalytic amount of DMAP in dichloromethane promised general applicability in the synthesis of diverse sulfonic acid derivatives.

Table 1
Optimization of reaction conditions for the one-pot synthesis of sulfonamides



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Entries	Solvent	Activator	Time[a] (h)	Isolated yield (%)
1	DMF	DMAP	—	Decomposed
2	DMF	TMA·HCl	—	Decomposed
3	DCM	DMAP	1	87
4	DCM	TMA·HCl	24	20
5	ACN	DMAP	24	48
6	ACN	TMA·HCl	24	43
7	THF	DMAP	24	67
8	THF	TMA·HCl	1	87

TMA·HCl:trimethylamine hydrochloride.
DIEA: *N*,*N*-diispropylethylamine.
[a] Reaction time in the second step.

2.2. R^1-group substituent effects in the syntheses of sulfonamides

A series of substituted anilines bearing electron-withdrawing and electron-donating groups (**4a**–**4l**, Table 2) were used to examine the reactivity in the first coupling step, after which the corresponding sulfonamides were formed using piperidine. Anilines substituted with chlorine, bromine, or iodine (at the *ortho*, *meta*, and *para* positions in **4a**–**4e**) did not obviously affect the production of the desired products **5a**–**5e**. Despite the presence of electron-withdrawing nitro group, a moderate yield (77%) was obtained with *m*-nitroaniline (**4f**), in which the amino group is apparently less affected by resonance effect. However, in the case of 4-nitroaniline (**4g**), nitro substitution at the *para* position considerably diminished the nucleophilicity of the amino group and thereby lowered the reaction yield (46%, entry 7). In the case of 2,4-dinitroaniline (**4h**), the yield of **5h** after 20 h was 5%. The reaction yield improved to 40% after the addition of a half equivalent of pyridine (entry 8). The secondary amine *N*-ethyl-2,4-dinitroaniline (**4i**) was expected to be more reactive than dinitroaniline **4h** because of the electron-donating nature of the *N*-ethyl group; however, the steric hinderance due to the ethyl group diminished the reactivity of the amine and resulted in no product formation (entry 9). As expected, the yields of 4-methoxyl (**4j**) and 2,4,6-trimethyl (**4k**) substituted anilines were almost quantitative; these findings are rationalized by consideration of the strongly electron-donating group(s) (entries 10 and 11). The fused 2-aminonaphthalene could also serve as a nucleophile in the reaction with **1**, giving a moderate yield (72%, entry 12). The applicability of diverse R^1 substituents in the developed one-pot synthetic strategy greatly expands the structural variability possible in the synthesis of sulfonamides.

2.3. Applicability of the one-pot, two-step preparation for carboxamido sulfonamides, sulfonic esters, thiosulfonates, and a sulfonyl azide

To expand the utility of this method in organic synthesis, the preparation of sulfonamides, sulfonic esters, thiosulfonates, and sulfonyl azides was attempted. In addition to piperidine, primary aliphatic amine **6a** and pyrrolidine **6b** were successfully employed