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One-pot synthesis of *N*-acyl-substituted sulfamides from chlorosulfonyl isocyanate via the Burgess-type intermediates ☆

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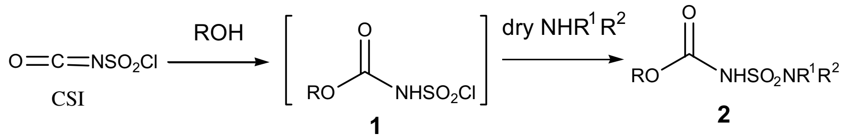
Abstract—The title *N*-alkoxycarbonyl- or *N*-aryloxycarbonyl-substituted sulfamides were synthesised in one-pot in efficient yields from chlorosulfonyl isocyanate (CSI), alcohols and aqueous (or dry) amines via the corresponding water-resistant intermediates, carboxysulfamoylammonium salts (Burgess-type reagents), which were generated in situ by the deactivation of the corresponding water-sensitive *N*-(chlorosulfonyl)carbamates with tertiary amines.

Alcohols or phenols react with chlorosulfonyl isocyanate (CSI) to form alkyl or aryl *N*-(chlorosulfonyl)carbamates **1**,[1,2] which react with amines containing reactive hydrogen to give stable *N*-alkoxy or *N*-aryloxycarbonyl sulfamides **2** (Scheme 1).[2,3] On the other hand, methyl *N*-(chlorosulfonyl)carbamate (**4**) is converted with triethylamine to afford an inner salt of methyl *N*-(triethylammoniumsulfonyl)carbamate (**5**, Burgess reagent).[4] The Burgess and related reagents react with several substrates to give valuable compounds.[4–6] The reaction of an isolated Burgess-like reagent, *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (**6**), with amines was reported.[6] However, the one-pot reaction using the Burgess and related reagents, which are prepared from CSI and alcohols in situ, with amines containing reactive hydrogen to give *N*-alkoxy or *N*-aryloxycarbonyl sulfamides **2** (Scheme 2) has not been reported. We found a new one-pot synthesis of the title *N*-acyl-substituted sulfamides **2** via the Burgess-type intermediates **3**, which were prepared in situ by the reaction of *N*-(chlorosulfonyl)carbamates **1** with tertiary amines (Scheme 2).[7] We describe here the preliminary results of the one-pot reactions to afford the title *N*-acyl-substituted sulfamides **2** via intermediates **3**. The representative results are summarized in Table 1. General procedure and spectral data are described in the Supplementary information.

First, we investigated the conditions of the one-pot reactions to give *N*-acyl-substituted sulfamides **2a** and **2b** by using isopropanol as a substrate. CSI was added dropwise to a solution of isopropanol in toluene at 0 °C. After stirring for 30 min, pyridine was added dropwise thereto. After stirring for 60 min, aqueous ammonia or



Scheme 1. The conventional process.

Keywords: Sulfamides; Chlorosulfonyl isocyanate; Burgess reagent.
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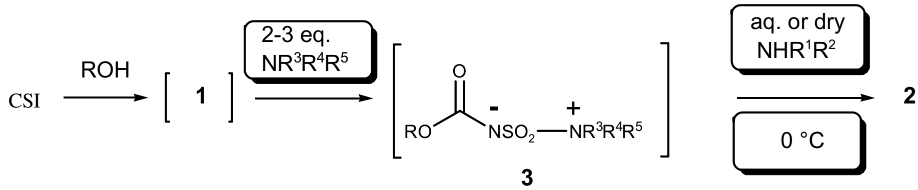
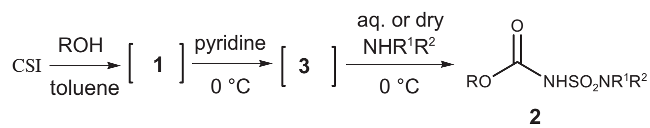


Scheme 2. Our new process.

Table 1. One-pot synthesis of *N*-acyl-substituted sulfamide via the Burgess-type intermediates



Entry	R	R^1	R^2	Product	Yield (%)[a]
1	*i*-Pr	H	H	**2a**	90
2[b]	*i*-Pr	H	H	**2a**	88
3[c]	*i*-Pr	H	H	**2a**	2
4[d]	*i*-Pr	H	H	**2a**	86
5[e]	*i*-Pr	H	H	**2a**	83
6[f]	*i*-Pr	H	H	**2a**	73
7	*i*-Pr	Me	H	**2b**	93
8[c]	*i*-Pr	Me	H	**2b**	7
9[g]	*i*-Pr	Me	H	**2b**	93
10[h]	*i*-Pr	Me	H	**2b**	88
11[i]	*i*-Pr	Me	H	**2b**	22
12[b]	*i*-Pr	Et	Et	**2c**	98
13[b,c]	*i*-Pr	Et	Et	**2c**	98
14[b]	*i*-Pr	Bn	Bn	**2d**	76
15[b]	*i*-Pr	1-Adamantyl	H	**2e**	45
16[b]	*i*-Pr	Ph	H	**2f**	97
17	*n*-Bu	H	H	**2g**	94
18	*n*-Bu	Me	H	**2h**	92
19	*t*-Bu	H	H	**2i**	94
20	*t*-Bu	Me	H	**2j**	97
21	1-Adamantyl	H	H	**2k**	92
22	1-Adamantyl	Me	H	**2l**	91
23	Ph	H	H	**2m**	67
24	Ph	Me	H	**2n**	27
25	4-Methoxyphenyl	H	H	**2o**	54
26	4-Methoxyphenyl	Me	H	**2p**	24

[a] Isolated yield.
[b] Dry liquid amine containing active hydrogen (ammonia, diethylamine, dibenzylamine, 1-adamantanamine or aniline) was used.
[c] No tertiary amine was used (a conventional condition).
[d] Ethyl acetate was used as a solvent.
[e] Acetonitrile was used as a solvent.
[f] Dichloromethane was used as a solvent.
[g] Triethylamine was used.
[h] *N*-Methylmorpholine was used.
[i] 4-DMAP was used.

methylamine was added dropwise. An usual work-up gave the target compound **2a** or **2b** in 90% or 93% yield, respectively (Table 1, entries 1 and 7).

The use of aqueous amines (ammonia or methylamine) dramatically decreased the yields under the conventional condition, which used no tertiary amines (90 vs 2%; 93 vs 7%, Table 1, entries 1, 3, 7, 8) because isopropyl *N*-(chlorosulfonyl)carbamate **7** is extremely water sensitive. However, in our new process via the Burgess-type intermediates **3**, aqueous amines did not decrease the yields. For example, aqueous ammonia (90%) afforded similar yield comparing with dry liquid ammonia (88%) (Table 1, entries 1 and 2). Aqueous ammonia and methylamine solutions are more available and usable than neat amines because they are gaseous. The conventional reactions sometimes require cryogenic reaction temperatures because of the low boiling points of amines or high exothermic reaction heat. A cryogenic reaction temperature confines equipment and significantly increases the cost of production. Our new process allows the use of aqueous amines and requires no cryogenic temperature. Therefore, the present new process is more practical than the conventional one.

When dry diethylamine was used in both of our new process, which proceeded via the Burgess-type intermediates **3**, and the conventional one which used no tertiary amine, they afforded the target product **2c** in the same yield (Table 1, entries 12 vs 13).

Solvent, which does not react with CSI at 0 °C, must be chosen. Ethyl acetate (86%, Table 1, entry 4) and acetonitrile (83%, Table 1, entry 5) led to the lower yields than toluene (90%, Table 1, entry 1). Dichloromethane gave the target compound **2a** in 73% yield (Table 1, entry 6). Therefore, toluene was chosen as a reaction solvent.

Tertiary amines to afford the Burgess-type intermediates **3** influenced the yields for the reaction. When no tertiary amine was used (a conventional condition), aqueous methylamine gave the product **2b** in 7% yield (Table 1, entry 8). Pyridine (93%, Table 1, entry 7) and triethylamine (93%, Table 1, entry 9) are preferable. *N*-Methylmorpholine provided moderate yield (88%, Table 1, entry 10). 4-DMAP gave low yield (22%, Table 1, entry 11). Presumably this depends upon the reactivity and stability of the ammonium intermediates **3**.

The scope of alcohols as substrates is relatively broad. Primary, secondary and tertiary alcohols gave the target compounds **2** in high yields. Especially, bulky aliphatic alcohols such as *tert*-butanol (Table 1, entries 19 and 20) and 1-adamantyl alcohol (Table 1, entries 21 and 22) gave the target compounds in high yields (91–97%). Phenol and 4-methoxyphenol afforded the corresponding phenoxycarbonylsulfamides **2m** and **2o** in 67% and 54% yields, respectively (Table 1, entries 23 and 25), because of its lower nucleophilicity. In cases of preparing sulfamides **2n** and **2p** by using aqueous methylamine, yields were lower than 30% because of a side reaction replacing the phenoxy anion with methylamino group.

The scope of amines containing active hydrogen as substrates is relatively broad. Ammonia, primary and secondary amines gave the target compounds in high yields. Surprisingly, an aromatic amine such as aniline (Table 1, entry 16) gave the target compound **2f** in 97% yield, although the reported elemental reaction of aniline with Burgess-like reagent **6** at room temperature for 12 h gave *N*-[(*tert*-butoxycarbonyl)-*N*′-phenylsulfamide (**8**) in 50% yield.[6] A bulky aliphatic amine such as 1-adamantanamine (Table 1, entry 15) gave the target compound **2e** in 45% yield.

Further investigation on the generality of the present reaction is currently underway. On the other hand, compound **2i** is a raw material of the aminosulfamoyl-containing side chain[8] of the novel carbapenem antibiotic doripenem hydrate.[9] The title reaction was applied to a practical process for the synthesis of the side chain.[7] In addition, we already found that alcohols as the substrates can be changed into thiols[10] to afford the corresponding sulfamide derivatives as this study. These results of our further works will be reported separately.

In conclusion, we described a new one-pot process to produce *N*-acyl-substituted sulfamides **2** in the presence of water or in the absence of water in efficient yields from CSI, alcohols and aqueous or dry amines via the Burgess-type intermediates **3**, which are generated in situ by the reaction of *N*-(chlorosulfonyl)carbamates **1** with tertiary amines.

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