One-Flow Syntheses of Unsymmetrical Sulfamides and *N*-Substituted Sulfamate Esters

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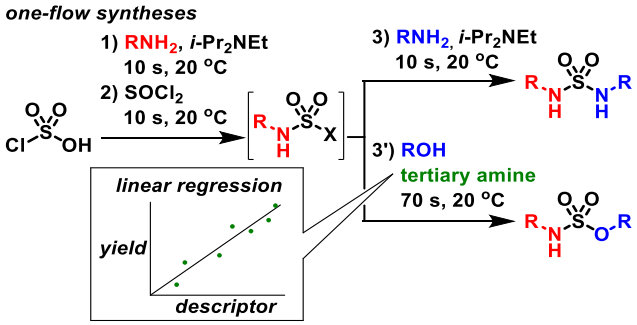


ABSTRACT: We developed one-flow syntheses of unsymmetrical sulfamides and *N*-substituted sulfamate esters by changing a nucleophile and a tertiary amine from inexpensive and commercially available chlorosulfonic acid. In the synthesis of *N*-substituted sulfamate esters, an unexpected symmetrical sulfite formation was suppressed by changing the tertiary amine. The effect of tertiary amines was proposed using linear regression. Our approach rapidly (≤ 90 s) provides desired products containing acidic and/or basic labile groups without tedious purification under mild (20 °C) conditions.

Unsymmetrical sulfamides and *N*-substituted sulfamate esters **A** are important as drugs and drug candidates.[1] Conventional synthetic approaches via sulfamoyl chloride **D** from sulfuryl chloride (**B**) or via sulfamic acid **H** from either chlorosulfonic acid (**F**) or isocyanate **G** usually require multiple steps, extensive periods of reaction time, high temperatures, and acidic conditions that are incompatible with acid-labile functional groups (Scheme 1a).[2,3] In addition, **D** presents a thermal hazard during purification by distillation.[4]

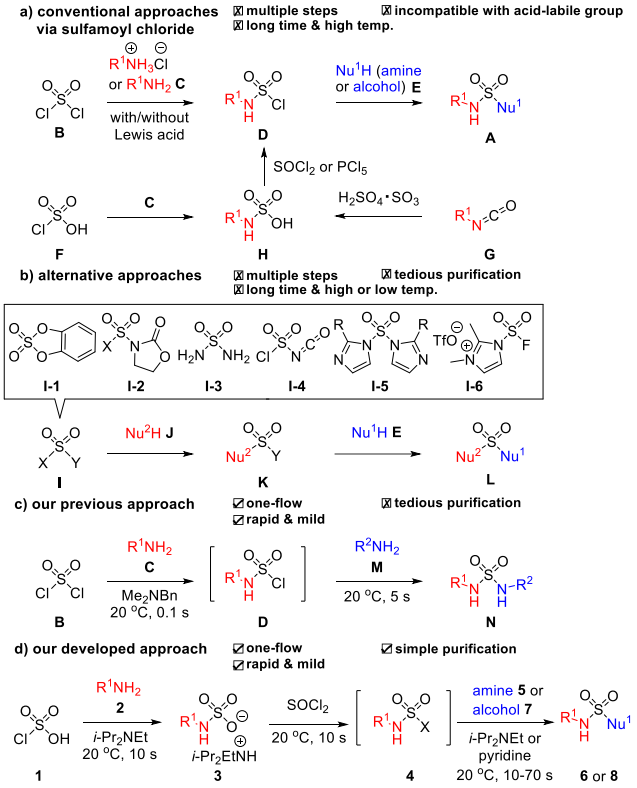
In order to avoid these problems, alternative approaches via **I** with two leaving groups and **K** with one leaving group have been developed (Scheme 1b). The former approach uses catechol sulfate **I-1**,[5] halogenosulfonyloxazolidinone **I-2**,[4,6] sulfamide **I-3**,[7] chlorosulfonyl isocyanate **I-4**,[8] sulfuryldiimidazole analogue (R = H or Me) **I-5**,[9] or fluorosulfuryl imidazolium salt **I-6**.[10] The latter approach uses an activated intermediate with triphenylphosphine ditriflate **K-1**.[11] In addition, *N*-hydroxy arenesulfonamide *O*-derivative[12] was also used as the precursor for the synthesis of **L**.[13] However, these approaches also require multiple steps,[5-12] tedious purification,[5-12] extensive periods of reaction time,[5,9-12] and either high or low temperatures.[5-7,9-11]

Micro-flow technology allows precise control of both the reaction time on a short scale (< 1 s) via rapid mixing and reaction temperature via high mass-transfer efficiency.[14] Recently, we reported a rapid, mild, and one-flow synthesis of unsymmetrical sulfamides **N** from **B** (Scheme 1c).[15] However, this approach required somewhat tedious purification due to competitive undesired reactions.

Here, we report a one-flow syntheses of unsymmetrical sulfamides **6** and *N*-substituted sulfamate esters **8** via sulfamic acid salts **3** and active intermediates **4** from inexpensive and commercially available chlorosulfonic acid (**1**) in the presence of tertiary amines (Scheme 1d). This process enabled a high-yielding synthesis of **6** via simple purification (aqueous work-up and/or preparative TLC), and when an unexpected side reaction was observed during the synthesis of **8** from **4**, it was suppressed simply by changing the tertiary amine. The effects of tertiary amines were discussed through linear regression.

We speculated that the first introduction of amine **2** against chlorosulfonic acid (**1**) would proceed smoothly under mild conditions (Scheme 1d). On the other hand, examinations into the activation of sulfamic acid salts **3** and the second introduction of amine **5** against **4** were necessary because a conventional activation of sulfamic acid salts **3** using phosphorus pentachloride or thionyl chloride requires high temperature and an extensive amount of reaction time.[3] Commercially available *N*-cyclohexyl sulfamic acid salts **3a** and $BnNH_2$ (**5a**) were used as model substrates for examining the second introduction (Scheme 2). The thionyl chloride was used as an activator of **3a**, and the amounts of *i*-Pr_2NEt and solvents were examined under micro-flow conditions. As a result, the use of 1.1 equiv. of *i*-Pr_2NEt and CH_2Cl_2 rapidly (20 s) afforded the desired **6a** in 92-

Scheme 1. Synthetic approaches to unsymmetrical sulfamides and *N*-substituted sulfamate esters.

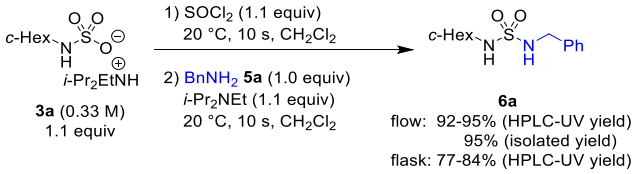


Bn = benzyl; Tf = trifluoromethanesulfonyl

95% HPLC-UV yields under mild (20 °C) conditions from three independent experiments. Also, sufficiently pure **6a** was obtained in 95% isolated yield after a simple aqueous work-up (for details, see supporting information, Table S1). In order to verify the importance of the micro-flow conditions, comparable batch conditions were examined (Scheme 2). Although the reagents were added quickly and the reaction mixture was vigorously stirred, reproducible results were not obtained (77-84%). Observed yields under batch conditions were *ca*. 10% lower than those under flow conditions (for details, see supporting information Table S2). *In addition, this reaction involves the generation of toxic gases such as sulfur dioxide and hydrogen chloride, and, therefore, scale-up syntheses should not be performed under batch conditions.*

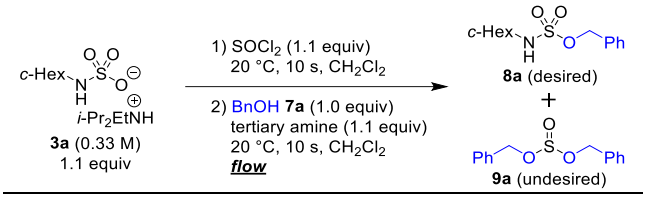
We examined the introduction of BnOH (**7a**) against **3a** (Table 1). The ratios of **7a**, **8a**, and **9a** were determined via ^{1}H NMR analysis. Unexpectedly, the desired sulfamate ester **8a** was obtained in a low ratio (30%), and the formation of undesired symmetrical sulfite **9a** (29%) was observed in the presence of *i*-Pr$_2$NEt as a tertiary amine (entry 14). We examined 17 tertiary amines to improve the selectivity of **8a** (entries 1-13, 15-18). As a result, the use of pyridine afforded the highest yield (82%, entry 15). In order to clarify the effects that the basicity and the steric hindrance of tertiary amines would exert on selectivity, we constructed two linear regression models reflecting differences in the ratio of **8a** and p*K*a of conjugated acid (p*K*aH)[16] and the percent buried volume (%V_{bur}, determined by DFT calculation, for details, see supporting information Table S4)[17] of tertiary amines (Figure 1). The first model (Figure 1a) was constructed using only data from 14 tertiary aliphatic amines (entries 1-14). The second model (Figure 1b), however, was constructed using all data from 18 tertiary amines

Scheme 2. Comparison between flow and flask conditions for synthesis of unsymmetrical sulfamide 6a



c-Hex = cyclohexyl; Ph = phenyl.

Table 1. Examination of tertiary amines for the synthesis of *N*-cyclohexyl sulfamate ester



entry	tertiary amine	p*K*aH	%V_{bur}	^{1}H NMR ratio		
				8a	**9a**	**7a**
tertiary aliphatic amines						
1	NMM	7.4[16a]	0.639	71	10	9
2	*N*-ethylmorpholine	7.7[16a]	0.692	51	19	12
3	DABCO	8.8[16b]	0.632	81	3	12
4	Me$_2$NBn	8.9[16c]	0.641	77	8	7
5	Et$_2$NBn	9.5[16c]	0.744	38	19	24
6	Me$_2$N*n*-Bu	10.0[16c]	0.664	71	12	5
7	Me$_2$NEt	10.0[16c]	0.601	69	14	3
8	*N*-methylpiperidine	10.1[16c]	0.646	57	19	6
9	MeNEt$_2$	10.3[16c]	0.657	54	19	8
10	Me$_2$N*i*-Pr	10.3[16c]	0.658	54	18	10
11	*N*-ethylpiperidine	10.4[16c]	0.699	44	23	9
12	*N*-methylpyrrolidine	10.5[16c]	0.614	65	13	10
13	Et$_3$N	10.7[16c]	0.715	39	24	13
14	*i*-Pr$_2$NEt	11.4[16b]	0.815	30	29	12
tertiary amines consisting of sp^2-hybridized nitrogen atom						
15	pyridine	5.2[16d]	0.436	82	0	18
16	2,6-lutidine	6.7[16d]	0.560	75	10	5
17	NMI	7.0[16c]	0.406	81	7	4
18	DMAP	9.7[16b]	0.433	44	22	12

NMM = *N*-methylmorpholine; DABCO = 1,4-diazabicyclo[2.2.2]octane; NMI = *N*-methylimidazole; DMAP = 4-dimethylaminopyridine; Bu = butyl.

(entries 1-18). The first model afforded relatively high prediction accuracy (R^2 = 0.77, MSE = 52.2) and indicated that the ratio of **8a** becomes higher as the %V_{bur} and p*K*aH becomes lower (Figure 1a). The second model showed a tendency similar to the first model, but the prediction accuracy was lower (R^2 = 0.59, MSE = 109). We speculated that two chemical descriptors (%V_{bur} and p*K*aH) was insufficient to accurately represent the

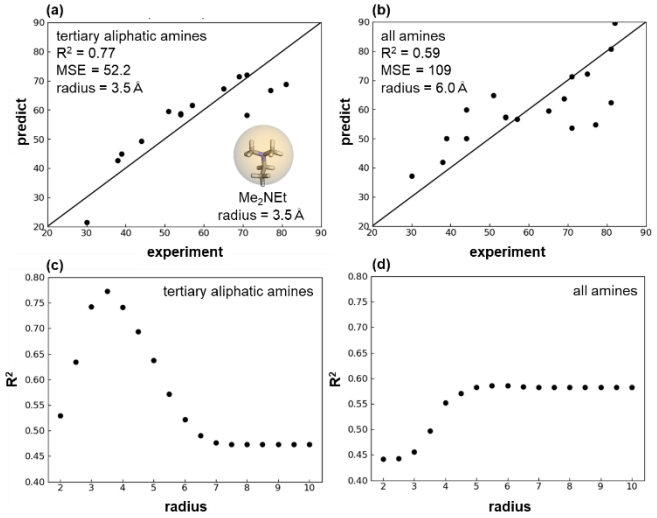


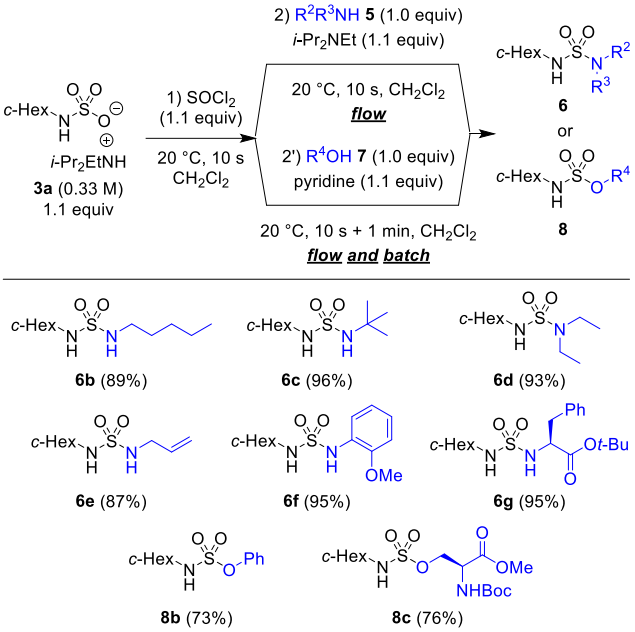
Figure 1. (a) Linear regression between the ratio of **8a** and 14 tertiary aliphatic amines (%V_{bur} and p*K*aH). The structure of Me_2NEt and a sphere (radius = 3.5 Å) centered on its nitrogen atom is shown for reference. (b) Linear regression between the ratio of **8a** and all 18 amines (%V_{bur} and p*K*aH). (c) Relationship between the coefficient of determination (R^2) and the radius of %V_{bur} for 14 tertiary aliphatic amines. (d) Relationship between the coefficient of determination (R^2) and the radius of %V_{bur} for all 18 tertiary amines. MSE = mean squared error.

relationship between the ratios of **8a** and the employed tertiary amines. In particular, these descriptors did not seem to well represent the differences in electrophilicity between *in situ* generated sulfonyl ammonium salts and sulfonyl imidazolium/pyridinium salts. Interestingly, the first regression model afforded the highest prediction accuracy when the radius of %V_{bur} was 3.5 Å (Figure 1c). It is conceivable that selectivity would be more sensitive to the steric hindrance that originates from inside the sphere (radius ≤ 3.5 Å) centered on the nitrogen atom of tertiary aliphatic amines compared with that from outside the sphere (radius > 3.5 Å). The valid radius (3.5 Å) was likely influenced by the steric bulkiness of an electrophile. On the other hand, in the case of the second model, the prediction accuracy increased as the radius of %V_{bur} increased from *ca*. 2.5 to *ca*. 6 Å and converged from 7 Å (Figure 1d), although the exact reason remains unclear.

We examined the scope of the nucleophiles in the introduction of amine **5** or alcohol **7** against **3a** (Scheme 3). When amylamine (**5b**) and *t*-$BuNH_2$ (**5c**) were used, the desired sulfamides **6b** and **6c** were obtained in high to excellent yields (89 and 96%). The use of Et_2NH (**5d**), allylamine (**5e**), aniline **5f**, and amino acid **5g** also afforded **6d-g** in high to excellent yields (87-95%). It should be noted that the simple aqueous work-up afforded sufficiently pure **6b-6g**. The use of alcohols such as phenol (**7b**) and Boc-Ser-OMe (**7c**) afforded **8b** and **8c** in good yields (73 and 76%).

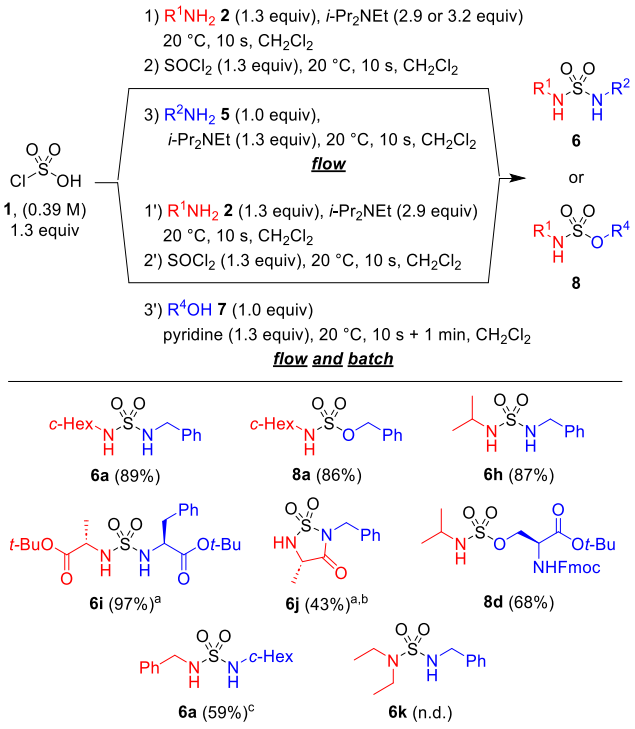
We examined the one-flow syntheses of **6a** and **8a** from readily and commercially available chlorosulfonic acid (**1**), as shown in Scheme 4 (for details of the optimization of the amounts of reagents, see supporting information Tables S6 and S7). As a result, the desired **6a** and **8a** were obtained in high to excellent yields (89 and 86%) with sufficient purity after a simple purification. We further investigated the substrate scope and derivatization. The use of *i*-$PrNH_2$ (**2b**) and $BnNH_2$ (**5a**) afforded the desired **6h** in high yield (87%). The use of acid-labile H-Ala-O*t*-Bu (**2c**) and H-Phe-O*t*-Bu (**5g**) afforded **6i** in excellent yield (97%). We carried out sulfahydantoin synthesis

Scheme 3. Examination of the substrate scope for the syntheses of 6 and 8.



t-Bu = *tert*-butyl; Boc = *tert*-butoxycarbonyl.

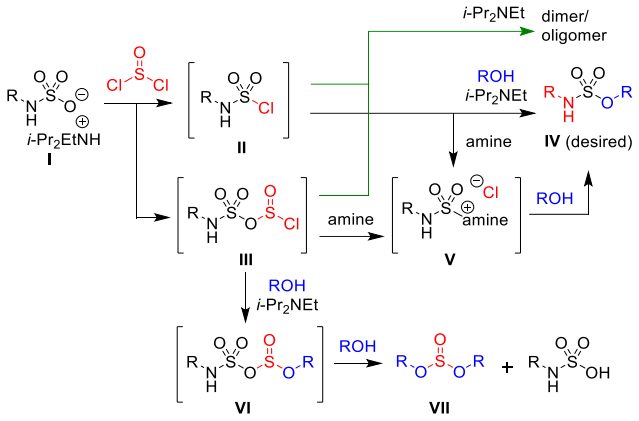
Scheme 4. One-flow syntheses of 6 and 8 from 1.



[a]Amino acid hydrochloride (1.0 or 1.3 equiv) was used as **2** and/or **5**, and *i*-Pr_2NEt (1.0 or 1.3 equiv) was used for trapping hydrogen chloride. [b]The cyclization using NaOH was carried out at room temperature for 1 h in $EtOH/H_2O$. [c]The yield was determined via HPLC-UV analysis. Fmoc = 9-fluorenylmethyloxycarbonyl. n.d. = not detected.

because this has garnered attention as bioactive compounds.[18] The desired **6j** was obtained in an acceptable yield (43%, 4 steps). The use of *i*-$PrNH_2$ (**2b**) and Fmoc-Ser-O*t*-Bu (**7d**) afforded **8d** in a good yield (68%). When the addition order of

Scheme 5. A plausible reaction mechanism



c-HexNH$_2$ (**2a**) and BnNH$_2$ (**5a**) was switched, the desired **6a** was obtained in a decreased yield (59%). It is conceivable that the *in situ* generated active intermediate, BnNH-SO$_2$-X **4b** is more acidic than *c*-HexNH-SO$_2$-X **4a**, and the undesired reaction (Scheme 5, dimer/oligomer formation from **II**/**III**) from **4b** occurred rapidly to decrease the yield. When the bulky Et$_2$NH (**5d**) and BnNH$_2$ (**5a**) were used, the desired **6k** was not obtained. Thus, we successfully developed the one-flow rapid (≤ 90 s), mild (20 °C), and simple purification syntheses of **6** and **8** by altering a nucleophile and a tertiary amine.

A plausible reaction mechanism appears in Scheme 5. Activation of the *i*-Pr$_2$NEt salts of sulfamic acid **I** with thionyl chloride generates intermediates **II**/**III**. The subsequent coupling between **II** and alcohol in the presence of *i*-Pr$_2$NEt affords the desired *N*-substituted sulfamate ester **IV**. On the other hand, the deprotonation of **II**/**III** and the following elimination of Cl$^-$ and/or SO$_2$, cause undesired dimerization/oligomerization in the presence of a base (green colored arrows).[19] As previously described, our regression models indicated that the use of less basic (lower p*K*aH) tertiary amines affords higher yields. This is reasonable because a less basic amine could avoid the undesired deprotonation of **II**/**III**. Another plausible undesired pathway includes double nucleophilic substitution at the thionyl group in **III** with ROH that generates an undesired symmetrical sulfite **VII** via **VI**. Our regression models indicated that the use of less bulky (%V_{bur}) tertiary amines would afford higher yields. We speculated that less bulky and nucleophilic amines would attack the sulfonyl group in **III** to generate ammonium salts **V** and lead to the desired **IV**. It is conceivable that the steric hindrance originating from inside a sphere (radius ≤ 3.5 Å) centered on the nitrogen atom of tertiary aliphatic amines would avoid this desired attack of the amine against **III**. It is also reasonable that less basic and nucleophilic pyridine would attack the sulfonyl group in **III** to afford the desired **IV** in the highest yield via pyridinium salts **V**.

In conclusion, we have demonstrated a rapid (≤ 90 s), mild (20 °C), and one-flow synthetic approach to unsymmetrical sulfamides and *N*-substituted sulfamate esters from inexpensive and commercially available chlorosulfonic acid with only the need to change the nucleophile and the tertiary amine. Unexpectedly, an undesired symmetrical sulfite formation was observed in the synthesis of *N*-substituted sulfamate ester. Our constructed linear regression models indicated that the use of tertiary amines with lower p*K*aH and %V_{bur} would afford higher yields. In addition, interestingly, the first regression model (Figure 1a) indicated the existence of a valid radius (3.5 Å) that is probably relevant to the steric hindrance around the sulfonyl group in electrophile **III**. The developed approach with simple purification (aqueous work-up and/or preparative TLC) afforded a variety of 14 unsymmetrical sulfamides and *N*-substituted sulfamate esters (43 to 97% yields) containing acidic and/or basic labile groups. This process could be valuable for accelerating drug discoveries based on unsymmetrical sulfamides and *N*-substituted sulfamate esters.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

A description of general experimental techniques, a detailed procedure for micro-flow and batch syntheses, computational details, and spectral data for all new compounds are available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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