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Lewis Acid-Catalyzed Nucleophilic Substitutions of Benzylic Alcohols with Sulfamides

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Abstract: Nucleophilic substitutions of benzylic alcohols with sulfamides were achieved using an FeCl₃ Lewis acid catalyst in MeNO₂. It was necessary to adjust the reaction conditions to obtain efficient yields depending on the stability of the carbocation intermediates. The reaction could easily be performed, and it was revealed that a variety of diarylmethanols and benzylic alcohols were applicable to the reaction, irrespective of the type and position of the substituents. The sulfamide moieties were easily deprotected and converted into amine groups.

Sulfamides are important functional groups in organic chemistry, and they are used in various fields.^[1] For example, the hydrogen-bond donating ability of sulfamides has been utilized for the development of chiral auxiliaries^[2] and organocatalyses.^[3] Sulfamides are also used as radical precursors for C-C bondforming reactions by heterodimerization^[4] and as useful directing groups for C-H amination.^[5] Because sulfamide moieties are considered as bioisosteres of amides, ureas, carbamates, and sulfonamides, they are frequently found in biologically active compounds.^[6] Furthermore, sulfamides are utilized in functional molecules with self-assembling properties.^[7] Thus, until now, numerous efforts have been devoted to developing an efficient method to produce sulfamides (Scheme 1). Classically, the transamination of amines with H₂NSO₂NH₂ (Scheme 1, (a))^[1b,6b,8] and the amination of amines with sulfamoyl chloride (Scheme 1, (b))^[1b,6b,9] have been carried out for this purpose. However, these methods often have problems with reaction efficiency and the toxicity of hydrogen chloride as a byproduct. Recently, the synthesis of unsymmetrical sulfamides using sulfamoyl fluorides has been reported.^[10] Alternatively, several useful sulfurylcontaining reagents bearing designed leaving groups have been developed for amination reactions to synthesize sulfamides (Scheme 1, (c)).^[11] To provide symmetrical N,N'-disubstituted sulfamides, amination with SO₂/I₂^[7d] or DABCO·(SO₂)₂/I₂,^[12] which reduced the difficulty of handling harmful SO2 gas, has also been reported (Scheme 1, (d)). In addition, the transitionmetal catalyzed coupling reaction (Scheme 1, (e)),^[13] reductive amination of aldehydes,^[14] and 1,2-diamination of alkenes^[15] have also been performed for the synthesis of sulfamides.



(a) Transamination with NH2SO2NH2[refs 1b,6b,8]

$$\begin{array}{c} \mathsf{H}_2\mathsf{NSO}_2\mathsf{NH}_2 \\ \xrightarrow{\mathsf{H}_2\mathsf{NSO}_2\mathsf{NH}_2} \\ \mathsf{R}^1\mathsf{NH}_2 \xrightarrow{\mathsf{O}_2} \\ \mathsf{R}^1\mathsf{NH}_2 \\ \xrightarrow{\mathsf{NH}_2} \end{array}$$

(b) Amination with sulfamoyl chloride^[refs 1b,6b,9, see also 10]

$$\stackrel{O_2}{\underset{R^3}{\overset{Cl}{\xrightarrow{}} S^2 \times N^2}} \stackrel{R^2}{\underset{R^3}{\overset{R^3}{\xrightarrow{}}}} \stackrel{R^1}{\underset{R^3}{\overset{N^2}{\underset{R^3}{\xrightarrow{}} N^2}}} \stackrel{O_2}{\underset{R^3}{\overset{O_2}{\underset{R^3}{\xrightarrow{}}}}}$$

R

(c) Amination with sulfuryl-containing reagents[ref 11]

$$R^{1}-NH_{2} \xrightarrow{LG^{-S} N^{-}R^{2}}_{LG = leaving group} R^{1}N_{H}^{-S} N^{-}R^{2}$$

(d) Amination with SO₂/I₂ or DABCO · (SO₂)₂/I₂^[refs 7d,12]

$$R^{1} \cdot NH_{2} \xrightarrow{SO_{2}/I_{2} \text{ or}} R^{1} \cdot NH_{2} \xrightarrow{O_{2}} R^{1} \cdot NH_{2} \xrightarrow{O_{2}} R^{1} \cdot NH_{2} \cdot NH_{2}$$

(e) Transition-metal catalyzed coupling reaction[ref 13]

$$R^{1} X \xrightarrow{\text{transition-metal (cat)}}_{X = \text{halogen, B(OH)}_{2}} R^{1} R^{1} R^{1} R^{2} R^{1} R^{2} R^{2}$$

Scheme 1. Previously reported sulfamidation.

In recent years, nucleophilic substitutions of alcohols catalyzed by Lewis acids or Brønsted acids have gained increasing attention as methods with high atom efficiency and environmental friendliness (Scheme 2, (a)).^[16] A number of nucleophiles have been applied to the reaction system, and useful characteristic reactions have been reported. Although there are many reports on the nucleophilic substitutions of alcohols using sulfonamides as a nucleophile,^[17–19] there are few reported examples of the application of sulfamides for such a reaction. As such, we have conducted research on Lewis acid-

catalyzed nucleophilic substitutions of diarylmethanols with several nucleophiles.^[17q,20] Herein, we report the first practical nucleophilic substitution of benzylic alcohols with sulfamides catalyzed by Lewis acids (Scheme 2, (b)).

(a) General equation for dehydrative nucleophilic substitutions[ref 16]

$$R^{2} \xrightarrow{\text{Brønsted acid}} R^{2} \xrightarrow{\text{Brønsted acid}} R^{2} \xrightarrow{\text{H}^{2}} H_{2}O$$

(b) This study; sulfamidation of benzylic alcohols

Lewis acid



Scheme 2. Related previous study (a) and present study (b)

To optimize the reaction conditions, we examined the effects of different Lewis acids and reaction temperatures on the nucleophilic substitution of benzhydrol (1a) with H2NSO2NMe2 (3) in MeNO₂ as a model reaction (Table 1). First, we carried out the reaction at different temperatures in the presence of SnBr₄, which was previously revealed to function as an efficient Lewis acid catalyst in the reactions of diarylmethanols with various nucleophiles (entries 1-4).^[17q,20] When the reaction was conducted at room temperature, some of the starting material 1a and the homoether generated from 2 molecules of 1a remained after 2 h, and the desired product 2a was produced in 55% yield (entry 1). However, when the reaction time was increased to 24 h, the reaction proceeded almost completely to afford 2a in 95% yield (entry 2). When the reaction temperature was increased to 50 and 80 °C, the reaction proceeded smoothly for 2 h to afford 2a in high yields in both cases (entries 3 and 4). Next, the reaction was examined in the presence of other tin salts, namely SnBr₂, SnCl₄, and SnCl₂, and other representative Lewis acids, namely InCl₃ and Yb(OTf)₃, at 50 °C for 2 h (entries 5-9). The reaction using SnCl₄ yielded almost the same result as the reaction using SnBr4 (entry 6). For the reactions using SnBr2 and InCl₃, the yields of 2a were slightly lower than those of the reactions using SnBr₄ and SnCl₄ (entries 5 and 8, respectively). In contrast, the reactions using SnCl₂ and Yb(OTf)₃ did not proceed well, and the corresponding yields of 2a were moderate (entries 7 and 9, respectively). Because FeCl₃ has been used as an efficient Lewis acid catalyst for nucleophilic substitutions,[21] we also carried out the reaction using FeCl₃ (entry 10). In this case, we obtained a good result that was comparable to those of SnBr₄ and SnCl₄. Ultimately, SnBr₄, SnCl₄, and FeCl₃ were determined to be efficient catalysts for the reaction. Considering the catalyst availability, we decided to use FeCl₃ for the subsequent examinations.



H ₂ NSO ₂ NMe ₂ (3 ; 1.5 equiv) Ph Lewis acid (5 mol %) Ph O ₂								
Ph	OH Me 1a ^t	MeNO ₂ (0.1 M) temp., time		Ph N ^S NMe ₂ H 2a				
Entry	Lewis acid	Temp [°C]	Time [h]	Yield of 2a [%] ^[a]				
1 ^[b]	SnBr ₄	rt	2	55				
2	î 🔰	rt	24	95				
3	†	50	2	94				
4	t 🔪	80	2	96				
5	SnBr ₂	50	2	89				
6	SnCl ₄	50	2	93				
7	SnCl ₂	50	2	42				
8	InCl₃	50	2	88				
9	Yb(OTf) ₃	50	2	31				
10	FeCl ₃	50	2	92				

Table 1. Examination of different Lewis acids in the nucleophilic substitution of

benzhvdrol (1a) with sulfamide 3

[a] Isolated yield. [b] **1a:2a**:homoether [bis(diphenyl)methyl ether] = 10:68:22 as determined by ¹H NMR spectroscopic analysis.

In order to explore the scope and limitations of the reaction, we conducted the sulfamidation of a series of diarylmethanols 1a-1n with H₂NSO₂NMe₂ (3) under the optimized reaction conditions (50 °C, 2 h) (Table 2). The reactions of 1b-1d, each bearing a Me-group on the aromatic ring of the substrates, produced the desired sulfamides 2b-2d, respectively, in high yields, similar to the case of 1a, regardless of the position of the substituent (entries 2-4 versus entry 1). For the reaction of 1e, it was anticipated that the diarylmethyl cation intermediate would be stabilized by the electron-donating property of the MeO-group and that the reactivity would be increased. Therefore, the reaction was carried out at room temperature, and the starting material was consumed immediately. However, a complex mixture was obtained (entry 5). To control the reactivity, we lowered the reaction temperature to 0 °C, and good yields were obtained in the reactions of 1e and 1g (entries 6 and 8, respectively). However, the reaction of 1f, which contained a MeO group in the meta-position, at room temperature for 24 h was somewhat complicated, and a moderate yield was obtained (entry 7). In contrast, in the reactions of 1h-1j bearing Cl substituents on the phenyl ring, it was found that a higher reaction temperature was necessary to enhance the reactivity (entries 9-12). The reaction of 1h at 50 °C was not completed even after 24 h, and 2h was obtained in 58% yield (entry 9). However, a high yield of 2h was obtained after 2 h when the reaction temperature was increased to 80 °C (entry 10). Similarly, the reactions of 1i and 1j at 80 °C for 2 h afforded high yields of the corresponding products (entries 11 and 12, respectively). The reaction of 1k bearing an ester group afforded a high yield of the product within a reaction time of 24 h (entry 13). However, no reaction occurred when 11, bearing a CN group, was used, even when the temperature and reaction time

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were 80 °C and 24 h, respectively. This result might have occurred because the carbocation intermediate was destabilized by the strong electron-withdrawing nature of the CN group (entry 14). The reactions of **1m** and **1n**, which contained naphthyl rings, proceeded smoothly at 50 °C for 2 h to produce **2m** and **2n**, respectively, in high yields, regardless of the position of the substituent (entries 15 and 16, respectively).

Table 2. Sulfamidation of a series of diaryImethanols 1 with H2NSO2NMe2 (3)

	Ar FeC	1.5 equiv) ₃ (5 mol %)	Ar O ₂	
	Ar OH MeN	IO ₂ (0.1 M) mp., time	Ar N ^S T H 2	Me ₂
Entry	Ar	Temp [°C]	Time [h]	Yield [%] ^[a]
1 ^[b]	Ph (a)	50	2	92
2	$o\operatorname{-MeC}_{6}\operatorname{H}_{4}(\mathbf{b})$	50	2	98
3	m-MeC ₆ H ₄ (c)	50	2	89
4	$p-MeC_6H_4$ (d)	50	2	88
5	$o-MeOC_6H_4$ (e)	rt	0.25	ND ^[c]
6	↑	0	0.5	76 ^[d]
7	<i>m</i> -MeOC ₆ H ₄ (f)	rt	24	34 ^[d]
8	p-MeOC ₆ H ₄ (g)	0	0.5	93
9	$o\text{-CIC}_6\text{H}_4$ (h)	50	24	58
10	↑	80	2	93
11	<i>m</i> -CIC ₆ H ₄ (i)	80	2	87
12	<i>p</i> -ClC ₆ H₄ (j)	80	2	94
13	p-EtO ₂ CC ₆ H ₄ (k)	80	24	98
14	<i>р</i> -NCC ₆ H ₄ (I)	80	24	NR ^[e]
15	α-Np (m)	50	2	82 ^[d]
16	β-Np (n)	50	2	88

[a] Isolated yield. [b] Same as in Table 1, entry 10. [c] Not determined. [d] Recrystallization yield. [e] No reaction.

To further expand the scope of the substrates, various benzylic alcohols, instead of diarylmethanols, were applied to the reaction (Scheme 3). When the reactions of benzylic alcohols **5a–5c** having alkyl substituents at C-1position were examined, it was found that the reactions were strongly influenced by the steric effect of the substituents. The reaction of **5a**, bearing a linear alkyl substituent, at 50 °C for 2 h produced **6a** in 95% yield, while it is reported that treatment of **5a** under a Lewis acid catalyst gave styrene as a major product and several unidentified products.^[22] In contrast, the reactions of **5b** and **5c**, bearing branched alkyl substituents, afforded moderate and negligible yields, respectively, along with the unidentified products^[17a,22], a small amount of the corresponding starting materials, and homoethers, under different conditions; this result



could be attributed to the steric repulsion exerted by the

functional groups. The reactivities of hetero-atoms containing

cyclic benzylic alcohols, 5d and 5e, were found to be high; the

corresponding reactions performed at 0 °C afforded high yields

Scheme 3. Sulfamidation of various benzylic alcohols 5 with H2NSO2NMe2 (3).

In order to establish the selective synthesis of Nmonosubstituted sulfamide 7 and N,N'-disubstituted sulfamide 8, we examined the reaction upon changing the nucleophile from H₂NSO₂NMe₂ (3) to H₂NSO₂NH₂ (9), with the results listed in Table 3. When the reaction of 1a with 1.5 equiv of 9 was carried out at room temperature, it was found that the reaction was faster than that using 3 (see: Table 2, entry 1). Moreover, the reaction was completed in 1 h and afforded 7 and 8 in 70% and 30% yield, respectively (entry 1). To preferentially synthesize 7 instead of 8, we increased the amount of nucleophile 9 from 1.5 to 3 equiv. The reaction was performed at a concentration of 0.03 M due to the poor solubility of 9 in 0.1 M MeNO2. The reactivity was relatively unchanged by the increase in reactant concentration, and the desired product 7 was preferentially obtained in 81% yield (entry 2). Upon lowering the reaction temperature to 0 °C, it was found that the reactivity decreased and prolonging the reaction time was necessary. In this case, the ratio of 7 to 8 was almost the same as that in entry 2 (entry 3). When the reaction was carried out with an increase in the amount of nucleophile 9 to 5.0 equiv at room temperature, the chemoselectivity was improved, and the desired monosubstituted sulfamide 7 was produced in 89% yield (entry 4). Notably, the reaction was applicable for the 1-g scale (please refer to the experimental section). In contrast, when the same reaction was carried out using 0.5 equiv of 9 to selectively synthesize 8, the reaction at room temperature produced 7 and 8 in 18% and 80% yield, respectively (entry 5). However, when the aforementioned reaction was carried out at 50 °C, a slightly complex mixture was produced, and the yield of 8 was lower than that of the same reaction at room temperature (entry 6).

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Table 3. Examination of the reaction conditions of the selective synthesis of N-

diphenylmethyl sulfamide 7 and N,N'-Bis(diphenylmethyl)sulfamide 8

Entry	n [equiv]	Temp [°C]	Time [h]	Yield of 7 [%] ^[a]	Yield of 8 [%] ^[a]
1	1.5	rt	1	70	30
2 ^[b]	3.0	rt	2	81	15
3 ^[b]	3.0	0	24	83	13
4 ^[b]	5.0	rt	2	89	7
5	0.5	rt	24	18	80
6	0.5	50	24	18	59

[a] Isolated yield. [b] The reaction concentration was 0.03 M.

To demonstrate the versatility of the reactions presented herein, we attempted to deprotect the sulfamides to produce the corresponding amines (Scheme 4). In accordance with the literature procedure,^[14d] sulfamide **2a** was refluxed in a 5% H₂O–pyridine solvent for 24 h to be converted into amine **9** in near quantitative yield (Scheme 4, (1)). In a similar way, *N*,*N*-bis(diphenylmethyl)sulfamide **8** could also be converted to amine **9** in near quantitative yield (Scheme 4, (2)).



Scheme 4. Deprotection of sulfamides into the amines.

It is well established that the nucleophilic substitutions of alcohols, catalyzed by Lewis acids or Brønsted acids, proceed via carbocations following the S_N1 mechanism.^[16] However, we found that the reaction proceeded with difficulty for steric hindered substrates, such as **6c**. Thus, to verify the reaction pattern, we carried out the reaction using enantiopure (*R*)-**5a** as a starting substrate (Scheme 5, (1)), for which the product **6a** was obtained in 94% yield as a racemate; therefore, the reaction was found to follow S_N1 mechanism in this case as well. In addition, the homoether was reacted to give the sulfamide **2a** in 95% yield (Scheme 5, (2)), thus confirming the homoether as an intermediate, as observed by TLC analysis.



Scheme 5. Investigation for the reaction pattern and the intermediate.

Based on the above-mentioned results, a plausible catalytic pathway is shown in Scheme 6. Activation of the hydroxy group of **1a** by coordination with FeCl₃ in step (i) affords int-i. In step (ii), int-ii is generated, along with dehydroxylation. Although there is an equilibrium between int-ii and homoether, int-ii is regenerated from the homoether via re-activation of FeCl₃. Finally, nucleophile **3** reacts with int-ii to afford the desired sulfamide **2a**.



Scheme 6. Plausible catalytic reaction pathway.

Conclusion

In conclusion, we performed the sulfamidation of benzylic alcohols catalyzed by FeCl₃, a Lewis acid, using nucleophilic substitution reactions for the first time. A series of diarylmethanols and several benzylic alcohols were examined for the reaction, and it was revealed that this protocol could be applied to a broad range of substrates. This reaction can be easily performed without requiring the preparation of a reagent. The sulfamide moieties were converted into amine groups via a facile procedure. Further studies are now in progress in our laboratory to expand the substrate scope of this reaction and to develop useful materials using this protocol.

Experimental Section

General Information. ¹H and ¹³C NMR spectra were recorded with chloroform (in chloroform-d) or DMSO (in dimethylsulfoxide-d) as the internal standard. Electrospray ionization mass (ESI-MS) spectra were

recorded on a Bruker microTOFII-SHIY3 mass spectrometer (Bruker, Billerica, MA) using the positive mode ESI-TOF method for acetonitrile solutions and sodium formate as the reference. Thin layer chromatography was performed on a Wakogel B5F. All reactions were carried out under a nitrogen atmosphere in dried glassware. FeCl₃, SnCl₂, and H₂NSO₂NMe₂ (**3**) were purchased from Wako Pure Chemical Industries Ltd. MeNO₂ were purchased from Wako Pure Chemical Industries Ltd. and Kishida Chemical Co., Ltd. SnCl₄ (1.0 M in CH₂Cl₂), InCl₃, Yb(OTf)₃, and H₂NSO₂NH₂ (**9**) were purchased from Sigma-Aldrich. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

Typical Procedure for the Sulfamidation of Benzhydrol (1a) with $H_2NSO_2NMe_2$ (3) (Table 2, entry 1). $H_2NSO_2NMe_2$ (3) (50.5 mg, 0.41 mmol) and benzhydrol (1a) (50.0 mg, 0.27 mmol) were successively added to a solution of FeCl₃ (2.2 mg, 14 mmol) in MeNO₂ (2.7 mL) at room temperature. The whole mixture was stirred for 2 h at 50 °C, and then the mixture was guenched with H_2O at 0 °C and diluted with CH_2Cl_2 . The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na₂SO₄. After the filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography on silica (toluene/EtOAc = 50/1) twice to afford 2a (72.8 mg, 92% yield) as a white solid.

The 1 Mmol-Scale Synthesis of 2a. $H_2NSO_2NMe_2$ (3) (186.2 mg, 1.50 mmol) and benzhydrol (1a) (184.5 mg, 1.00 mmol) were successively added to a solution of FeCl₃ (8.2 mg, 51 mmol) in MeNO₂ (10 mL) at room temperature. The whole mixture was stirred for 2 h at 50 °C, and then the mixture was quenched with H_2O at 0 °C and diluted with CH_2Cl_2 . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was dried over Na₂SO₄. After the filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (hexane/EtOAc = 9/1 to 4/1) to afford **2a** (281.8 mg, 97% yield) as a white solid.

Typical Procedure for the Sulfamidation of Benzhydrol (1a) with $H_2NSO_2NH_2$ (9) to Provide 7 (Table 3, entry 5). To a solution of FeCl₃ (1.6 mg, 9.9 mmol) in MeNO₂ (6.7 mL) at room temperature was successively added $H_2NSO_2NH_2$ (9) (96.5 mg, 1.00 mmol) and benzhydrol (1a) (36.7 mg, 0.20 mmol). The whole mixture was stirred for 2 h at room temperature, and then the mixture was quenched with H_2O at 0 °C and diluted with CH_2Cl_2 . The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na₂SO₄. After the filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography on silica (toluene/EtOAc = 4/1) to afford 7 (46.3 mg, 89% yield) as a white solid. The crude 8 was repurified by thin layer chromatography on silica (toluene/EtOAc = 50/1) twice to afford 8 (2.8 mg, 7% yield) as a white solid.

The 1 Gram-Scale Synthesis of 7. A 500-mL two-necked flask was charged with FeCl₃ (48.8 mg, 0.30 mmol) in MeNO₂ (15 mL + 5 mL + 5 mL rinse) and MeNO₂ (175 mL). Then, H₂NSO₂NH₂ (9) (2.88 g, 30.0 mmol) and benzhydrol (1a) (1.11 g, 6.00 mmol) were added to this mixture. The whole mixture was stirred for 2 h at room temperature, and then the mixture was quenched with H₂O at 0 °C and diluted with CH₂Cl₂. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄. After the filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (toluene/EtOAc = 3/1) to afford 7 (1.43 g, 91% yield) as a white solid.

Procedure for the Deprotection of Sulfamides into Amines (Scheme 4, (1)). According to the literature procedure,^[14d] a solution of **8a** (291.1 mg, 1.00 mmol) in 5% H₂O-pyridine (5.0 mL) was refluxed for 24 h. After the removal of pyridine by evaporation, the crude solid was dissolved in 1 M HCl and diluted with Et₂O. The solution was then back-extracted with Et₂O. The aqueous layer was basified with 6 M NaOH and extracted with Et₂O. The organic layer was dried over Na₂SO4, filtered, and concentrated *in vacuo* to afford amine **9** (183.0 mg, quantitative yield) without requiring further purification. ¹H NMR (CDCl₃) δ = 7.42–7.36 (m, 4H), 7.36–7.29 (m, 4H), 7.27–7.21 (m, 2H), 5.23 (s, 1H), 1.87 (br s, 2H) ppm. ¹³C NMR (CDCl₃) δ = 145.5, 128.4, 126.83, 126.80, 59.6 ppm.

[Analytical Data of Compounds 2a-2k, 2m, 2n, 6a, 6b, 6d, 6e, 7, and 8]

N-(diphenylmethyl)-N',N'-dimethylsulfuric diamide (2a) (Table 2, entry 1). White solid. (72.8 mg, 92% yield). M.p.: 118–119 °C. IR (KBr): \tilde{v}

= 3286, 1338, 1151 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.37–7.30 (m, 8H), 7.30–7.25 (m, 2H), 5.62 (d, J = 6.5 Hz, 1H), 5.03 (br s, 1H), 2.56 (s, 6H) ppm. ^{13}C NMR (CDCl₃) δ = 141.3, 128.7, 127.7, 127.4, 61.5, 37.5 ppm. HRMS calcd for C15H18N2O2S [M + Na]^+ 313.0981, found 313.0979.

 $\begin{array}{l} \textbf{N-[bis(2-methylphenyl]methyl]-N',N'-dimethylsulfuric diamide (2b)} \\ (Table 2, entry 2). White solid. (71.0 mg, 98% yield). M.p.: 142–144 °C. IR (KBr): <math>\tilde{v}$ = 3270, 1334, 1146 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.30–7.25 (m, 2H), 7.21–7.26 (m, 6H), 6.03 (d, *J* = 6.0 Hz, 1H), 4.61 (br s, 1H), 2.55 (s, 6H), 2.38 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 138.7, 136.1, 130.9, 127.7, 127.4, 125.9, 55.0, 37.5, 19.2 ppm. HRMS calcd for C₁₇H₂₂N₂O₂S [M + Na]⁺ 341.1294, found 341.1292. \end{array}

 $\begin{array}{l} \textbf{N-[bis(3-methylphenyl])methyl]-N',N'-dimethylsulfuric} & diamide (2c) \\ (Table 2, entry 3). White solid. (59.0 mg, 89% yield). M.p.: 86–88 °C. IR \\ (KBr): <math>\bar{v}$ = 3294, 1339, 1156 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.23 (t, *J* = 8.0 Hz, 2H), 7.17–7.06 (m, 6H), 5.54 (d, *J* = 7.0 Hz, 1H), 4.91 (br s, 1H), 2.56 (s, 6H), 2.34 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 141.4, 138.4, 128.5, 128.4, 128.0, 124.3, 61.5, 37.6, 21.4 ppm. HRMS calcd for C₁₇H₂₂N₂O₂S [M + Na]* 341.1294, found 341.1294. \\ \end{array}

 $\begin{array}{l} \textbf{N-[bis(4-methylphenyl])methyl]-N',N'-dimethylsulfuric diamide (2d)} \\ (Table 2, entry 4). White solid. (61.8 mg, 88% yield). M.p.: 134–135 °C. IR (KBr): <math>\bar{\nu}$ = 3288, 1339, 1154 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.20 (d, J = 8.0 Hz, 4H), 7.14 (d, J = 8.0 Hz, 4H), 5.56 (d, J = 7.0 Hz, 1H), 4.92 (br s, 1H), 2.57 (s, 6H), 2.33 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 138.6, 137.3, 129.3, 127.2, 61.1, 37.6, 21.0 ppm. HRMS calcd for C₁₇H₂₂N₂O₂S [M + Na]⁺ 341.1294, found 341.1294.

N-[bis(2-methoxyphenyl)methyl]-*N'*,*N'*-dimethylsulfuric diamide (2e) (Table 2, entry 6). White solid. (47.2 mg, 76% yield). M.p.: 144–145 °C. IR (KBr): \bar{v} = 3323, 1329, 1254, 1155 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.45 (dd, *J* = 1.5, 7.5 Hz, 2H), 7.21 (dt, *J* = 2.0, 8.0 Hz, 2H), 6.93 (dt, *J* = 1.5, 7.5 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 9.5 Hz, 1H), 5.85 (br d, *J* = 9.0 Hz, 1H), 3.80 (s, 6H), 2.61 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 156.4, 129.2, 128.7, 128.5, 120.3, 110.8, 55.3, 54.2, 37.7 ppm. HRMS calcd for C₁₇H₂₂N₂O₄S [M + Na]⁺ 373.1192, found 373.1203.

N-[bis(3-methoxyphenyl)methyl]-*N'*,*N'*-dimethylsulfuric diamide (2f) (Table 2, entry 7). White solid. (23.4 mg, 34% yield). M.p.: 114–116 °C. IR (KBr): \bar{v} = 3289, 1330, 1278, 1151, 1053 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.29–7.23 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.89–6.86 (dm, 2H), 6.81 (dd, *J* = 2.0, 8.0 Hz, 2H), 5.55 (d, *J* = 6.5 Hz, 1H), 4.88 (br s, 6H), 3.79 (s, 6H), 2.60 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 159.8, 142.8, 129.8, 119.6, 113.2, 113.0, 61.4, 55.2, 37.6 ppm. HRMS calcd for C₁₇H₂₂N₂O₄S [M + Na]^{*} 373.1192, found 373.1202.

N-[bis(4-methoxyphenyl]methyl]-N',N'-dimethylsulfuric diamide (2g) (Table 2, entry 8). White solid. (74.5 mg, 93% yield). M.p.: 120–122 °C. IR (KBr): \bar{v} = 3285, 1333, 1249, 1154, 1035 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.24–7.18 (m, 4H), 6.88–6.82 (m, 4H), 5.54 (d, *J* = 6.5 Hz, 1H), 4.90 (br s, 1H), 3.78 (s, 6H), 2.56 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 159.0, 133.8, 128.5, 113.9, 60.4, 55.2, 37.6 ppm. HRMS calcd for C₁₇H₂₂N₂O₄S [M + Na]* 373.1192, found 373.1197.

N-[bis(2-chlorophenyl)methyl]-N',N'-dimethylsulfuric diamide (2h) (Table 2, entry 10). White solid. (50.3 mg, 93% yield). M.p.: 144–145 °C. IR (KBr): \ddot{v} = 3294, 1343, 1150 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.44–7.36 (m, 4H), 7.31–7.22 (m, 4H), 6.39 (d, *J* = 7.0 Hz, 1H), 4.88 (br s, 1H), 2.75 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 137.4, 133.5, 130.1, 129.2, 129.1, 126.9, 55.9, 37.9 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₅H₁₆Cl₂N₂O₂S 381.0202, found 381.0205.

 $\begin{array}{lll} \textbf{N-[bis(3-chlorophenyl])methyl]-N',N'-dimethylsulfuric} & diamide & (2i) \\ (Table 2, entry 11). White solid. (68.0 mg, 87% yield). M.p.: 115–117 °C. IR (KBr): <math display="inline">\bar{\nu}$ = 3269, 1337, 1150 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.32–7.26 (m, 6H), 7.22–7.18 (m, 2H), 5.55 (d, J = 7.5 Hz, 1H), 5.13 (br s, 1H), 2.59 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 142.6, 134.8, 130.2, 128.3, 127.4, 125.5, 60.6, 37.6 ppm. HRMS calcd for C1₅H1₆Cl₂N₂O₂S [M + Na]⁺ 381.0202, found 381.0201. \end{array}

 $\begin{array}{lll} \textbf{N-[bis(4-chlorophenyl])methyl]-N',N'-dimethylsulfuric} & diamide & (2j) \\ (Table 2, entry 12). White solid. (67.2 mg, 94% yield). M.p.: 164–166 °C. \\ IR (KBr): <math display="inline">\bar{\nu}$ = 3268, 1331, 1148 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.31 (d, J = 8.5 \\ Hz, 4H), 7.23 (d, J = 9.0 Hz, 4H), 5.55 (d, J = 7.0 Hz, 1H), 5.21 (br s, 1H), \\ 2.57 (s, 6H) ppm. ^{13}C NMR (CDCl₃) δ = 139.4, 133.8, 129.0, 128.7, 60.3, 37.6 ppm. HRMS calcd for C₁₅H₁₆Cl₂N₂O₂S [M + Na]⁺ 381.0202, found 381.0199. \end{array}

Diethyl 4,4'-[[(*N*,*N*-dimethylsulfamoyl)amino]methylene}dibenzoate (2k) (Table 2, entry 13). White solid. (68.1 mg, 98% yield). M.p.: 120–121 °C. IR (KBr): \bar{v} = 3268, 1329, 1279, 1150, 1109 cm⁻¹. ¹H NMR (CDCl₃) δ = 8.01 (d, *J* = 7.4 Hz, 4H), 7.38 (d, *J* = 8.5 Hz, 4H), 5.70 (d, *J* = 7.0 Hz, 1H), 5.29 (br s, 1H), 4.36 (q, *J* = 7.0 Hz, 4H), 2.57 (s, 6H), 1.37 (t, *J* = 7.0 Hz, 6H) ppm. ¹³C NMR (CDCl₃) δ = 166.0, 145.5, 130.1, 127.3, 61.11, 61.06, 37.6, 14.3 ppm. HRMS calcd for C₂₁H₂₆N₂O₆S [M + Na]^{*} 457.1404, found 457.1406.

 $\begin{array}{l} \textbf{N-[bis(naphthalen-1-yl]methyl]-N',N'-dimethylsulfuric diamide (2m)} \\ (Table 2, entry 15). White solid. (66.9 mg, 82% yield). M.p.: 233–236 °C. IR (KBr): <math display="inline">\tilde{\nu}$ = 3320, 1338, 1142 cm^{-1}. ¹H NMR (DMSO-d_6) δ = 8.41 (d, J = 9.0 Hz, 1H), 8.19–8.14 (m, 2H), 8.01–7.96 (m, 2H), 7.92–7.87 (m, 2H), 7.57–7.51 (m, 4H), 7.51–7.47 (m, 4H), 7.10 (d, J = 9.5 Hz, 1H), 2.46 (s, 6H) ppm. ^{13}C NMR (DMSO-d_6) δ = 137.2, 133.5, 130.3, 128.9, 128.3, 126.8, 125.9, 125.2, 122.8, 53.6, 37.4 ppm. HRMS calcd for C₂₃H₂₂N₂O₂S [M + Na]* 413.1294, found 413.1297. \\ \end{array}

N-[bis(naphthalen-2-yl)methyl]-*N*',*N*'-dimethylsulfuric diamide (2n) (Table 2, entry 16). White solid. (55.4 mg, 88% yield). M.p.: 169–170 °C. IR (KBr): $\tilde{\nu}$ = 3281, 1328, 1151 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.86–7.79 (m, 8H), 7.52–7.46 (m, 6H), 5.97 (d, *J* = 7.0 Hz, 1H), 5.28 (d, *J* = 7.0 Hz, 1H), 2.58 (s, 6H) ppm. ¹³C NMR (CDCl₃) δ = 138.6, 133.1, 132.8, 128.7, 128.0, 127.6, 126.4, 126.3, 126.2, 125.4, 61.7, 37.7 ppm. HRMS calcd for C₂₃H₂₂N₂O₂S [M + Na]⁺ 413.1294, found 413.1299.

N-(1-phenylethyl)-*N*',*N*'-dimethylsulfuric diamide (6a) (Scheme 3). colorless oil. (54.3 mg, 95% yield). IR (neat): $\tilde{v} = 3295$, 1327, 1150 cm⁻¹. ¹H NMR (CDCl₃) $\delta = 7.37$ -7.31 (m, 4H), 7.30-7.25 (m, 1H), 4.68 (br s, 1H), 4.51 (dq, *J* = 7.0, 6.5 Hz, 1H), 2.59 (s, 6H), 1.52 (d, *J* = 7.0 Hz, 3H) ppm. ¹³C NMR (CDCl₃) $\delta = 143.2$, 128.6, 127.6, 126.2, 53.9, 37.6, 23.9 ppm. HRMS calcd for C₁₀H₁₆N₂O₂S [M + Na]⁺ 251.0825, found 251.0826.

 $\begin{array}{l} \textbf{N-[cyclohexyl(phenyl)methyl]-N',N'-dimethylsulfuric diamide (6b)} \\ (Scheme 3). White solid. (31.4 mg, 59% yield). M.p.: 93–94 °C. IR (KBr):$ $<math display="inline">\bar{\nu}$ = 3296, 1326, 1152 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.36–7.30 (m, 2H), 7.28–7.24 (m, 1H), 7.22–7.18 (m, 2H), 4.88 (br s, 1H), 4.07–4.01 (m, 1H), 2.45 (s, 6H), 2.04–1.97 (m, 1H), 1.81–1.75 (m, 1H), 1.69–1.51 (m, 3H), 1.39–1.32 (m, 1H), 1.26–0.99 (m, 4H), 0.97–0.87 (m, 1H) ppm. ¹³C NMR (CDCl₃) δ = 141.5, 128.3, 127.4, 127.2, 63.6, 44.0, 37.5, 29.9, 29.6, 26.1, 25.9 ppm. HRMS calcd for C₁₅H₂₄N₂O₂S [M + Na]* 319.1451, found 319.1451.

N-(3,4-dihydro-2H-chromen-4-yl)-N',N'-dimethylsulfuric diamide (6d) (Scheme 3). White solid. (57.4 mg, 86% yield). M.p.: 72–74 °C. IR (KBr): $\bar{\nu} = 3320, 1346, 1146$ cm⁻¹. ¹H NMR (CDCl₃) $\delta = 7.33$ (d, J = 7.5 Hz, 1H), 7.20–7.14 (m, 1H), 6.93–6.87 (m, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.57–4.43 (m, 2H), 4.29–4.22 (m, 1H), 4.21–4.15 (m, 1H), 2.85 (s, 6H), 2.25–2.14 (m, 2H) ppm. ¹³C NMR (CDCl₃) $\delta = 154.9, 129.6, 129.5, 121.1, 120.8, 117.2, 62.4, 47.9, 38.1, 29.6 ppm. HRMS calcd for C₁₁H₁₆N₂O₃S [M + Na]⁺ 279.0774, found 279.0763.$

N-(3,4-dihydro-2*H*-thiochromen-4-yl)-*N*',*N*'-dimethylsulfuric diamide (6e) (Scheme 3). colorless oil. (67.2 mg, 92% yield). IR (neat): $\bar{\nu}$ = 3300, 1332, 1143 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.34 (d, *J* = 7.5 Hz, 1H), 7.17–7.03 (m, 3H), 4.59 (s, 1H), 4.45 (br s, 1H), 7.23 (dt, *J* = 3.0, 12.5 Hz, 1H), 2.99–2.91 (m, 1H), 2.82 (s, 6H), 2.52–2.45 (m, 1H), 2.12–2.01 (m, 1H) ppm. ¹³C NMR (CDCl₃) δ = 133.4, 132.0, 130.5, 128.5, 126.9, 124.5, 51.3, 38.1, 28.6, 21.8 ppm. HRMS calcd for C₁₁H₁₆N₂O₂S₂ [M + Na]⁺ 295.0545, found 295.0539.

N-(diphenylmethyl)sulfuric diamide (7) (Table 3, entry 4). White solid. (46.3 mg, 89% yield). M.p.:144–145 °C. IR (KBr): \tilde{v} = 3347, 3266, 1331, 1163 cm⁻¹. ¹H NMR (DMSO-d₆) δ = 7.80 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.5 Hz, 2H), 6.61 (br s, 2H), 5.57 (d, *J* = 9.5 Hz, 1H) ppm. ¹³C NMR (DMSO-d₆) δ = 143.1, 128.2, 127.4, 126.8, 60.1 ppm. HRMS calcd for C₁₃H₁₄N₂O₂S [M + Na]⁺ 285.0668, found 285.0664.

N,*N*'-[bis(diphenylmethyl)]sulfuric diamide (8) (Table 3, entry 5). White solid. (34.2 mg, 80% yield). M.p.:160–161 °C. IR (KBr): \tilde{v} = 3296, 1322, 1146 cm⁻¹. ¹H NMR (CDCl₃) δ = 7.28–7.21 (m, 12H), 7.19–7.15 (m, 8H), 5.59 (d, *J* = 6.5 Hz, 2H), 4.90 (br d, *J* = 6.5 Hz, 2H) ppm. ¹³C NMR (CDCl₃) δ = 141.0, 128.7, 127.6, 127.2, 61.6 ppm. HRMS calcd for C₂₆H₂₄N₂O₂S [M + Na]* 451.1451, found 451.1458.

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Sulfamidation by nucleophilic substitution catalyzed by FeCl₃ H₂NSO₂NR¹R² FeCl₃ (5 mol %) S NR¹R² MeNO₂ (0.1 M) up to 98% yield

Key Topic: Sulfamidation Reaction

Sulfamidation of benzylic alcohols was achieved for the first time using nucleophilic substitutions catalyzed by FeCl₃, a Lewis acid. A variety of *N*-benzyl-substituted sulfamides were produced efficiently via this novel protocol.

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