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Efficient synthesis of *N*-oxysulfonyl formamidines via thionyl chloride-promoted reaction of sulfamates with formamides

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Supporting Information: Experimental synthetic details, ^{1}H and ^{13}C NMR spectra for all new compounds. This material can be found via the "Supplementary Content" section of this article's webpage."

ABSTRACT

N-oxysulfonyl formamidine derivatives have been efficiently synthesized under mild conditions through direct condensation of various sulfamates and formamides in the presence of thionyl chloride. The scope of this reaction was investigated, and a plausible mechanism was

proposed. The resulting *N*-oxysulfonyl formamidines can be converted to sulfamates via appropriate deprotection.

GRAPHICAL ABSTRACT

KEYWORDS: deprotection, formamidine, sulfamate, thionyl chloride

Introduction

Amidines are important intermediates in diverse functional group transformations,[1] including as auxiliaries in asymmetric synthesis,[2] as protecting groups for primary amines,[3] and as nitrogen-based nucleophiles.[4] Amidines have been used widely in medicinal chemistry,[5] coordination chemistry,[6] and supramolecular chemistry[7] because of their structural characteristics. They also occur in many bioactive natural products,[8] and *N*-sulfonyl formamidines in particular are attractive because of their wide range of pharmaceutical and biological properties.[9] Traditional methods for preparing *N*-sulfonylformamidines have been supplemented[10] and recent efforts have led to the updating and improvement of traditional processes as well as construction of the structurally diverse group of amidines.[11]

In contrast to the extensive literature on *N*-sulfonyl amidine synthesis, the preparation of *N*-oxysulfonyl amidines has been largely ignored.[12] In continuation of our previous work on

synthesis of *N*-sulfonyl amidines,[13] we undertook studies to develop a simple, efficient synthesis of *N*-oxysulfonyl formamidines (**3**) under mild conditions. To the best of our knowledge, this is the first report of the direct transformation of sulfamates into *N*-oxysulfonyl amidines.

Results and Discussion

We initially selected phenyl sulfamate **1a** and DMF **2a** as model substrates in order to investigate reaction conditions (**Table 1**). Treatment of **1a** with **2a** in the presence of 1.0 equiv of phosphoryl chloride in chloroform at 60°C afforded the desired oxysulfonyl formamidine **3a** in 54% isolated yield (entry 1). Screening of acid chlorides showed that $SOCl_2$ gave **3a** in 58% yield (entry 2), while oxalyl chloride gave lower yield (entry 3). The desired amidine product was obtained in chloroform in highest yield, as well as in 1, 2-dichloroethane (DCE), dichloromethane (DCM) and chlorobenzene at lower yields (entries 4–6). Increasing the reaction temperature to 70°C reduced yield slightly (entry 7), which we attributed to sulfamate decomposition. Therefore, we repeated the reaction at 40°C, but were surprised to obtain even lower yield of 46% (entry 8). Using DMF in slight excess improved the yield of **3a** (entry 9), with 1.5 equiv DMF giving the desired amidine in 85% yield (entry 10). There is no further influence on reaction yield when the amount of DMF was increased to 2.0 equiv (entry 11). In contrast, when DMF was used as the solvent, only a trace amount of desired product was obtained (entry 12). Therefore, 1.5 equiv was found to be the ideal amount of 2**a**. Exposure to air did not affect the reaction (entry 13), while removal of the chlorinating agent blocked the reaction completely (entry 14).

With the optimized conditions in hand (**Table 1**, entry 10), we examined reactions between various types of sulfamate **1** and formamide **2**. Aryl sulfamate derivatives bearing electron-donating or -withdrawing groups such as methyl, *tert*-butyl, methoxy, chloro, bromo or fluoro

groups reacted smoothly with DMF to give the corresponding products **3a-3e** in 85-90% yield (**Table 2**, entries 1-5). The sulfamate ester derived from 4-hydroxyazobenzene was transformed into the corresponding amidine **3f** in 92% yield (entry 6). To our satisfaction, an array of formamides proved to be suitable reaction partners, including *N*,*N*-diethylformamide, *N*,*N*-diisopropylformamide, *N*-methyl-*N*-phenylformamide, *N*-formyl-piperidine, and 4-formylmorpholine. These substrates furnished the corresponding sulfonylamidines **3g -3l** in good yield (entries 7-12). In contrast, sulfamate esters derived from benzyl or pentyl alcohol generated the desired *N*-oxysulfonyl amidines in low respective yields of 22% and 30% (entries 13 and 14); in addition, the product mixture contained [(dimethylamino)methylene]sulfamic acid[14] in nearly 50% yield. IR spectroscopy showed very strong C = N and S = O vibrations, and ^{1}H NMR revealed $(CH_3)_2N$ signals and two downfield-shifted singlet peaks corresponding to -N = CH proton and H-N + proton (see Supporting Information). We attribute this result to hydrolysis of the electron-rich *N*-alkoxy sulfonyl formamidine under these acidic conditions. Consistent with this idea, the electron-deficient substrate 2,2,2-trichloroethyl sulfamate ($TcesNH_2$) generated amidine **3o** in 92% yield (entry 15). These results suggest that the electronic properties of the alkyl significantly affect reaction outcomes. Notably, no reaction occurred between **1a** and *N*-phenyl formamide **2g** under the conditions we tested (entry 16).

Based on these synthetic studies, we attempted to react some biologically active sulfamates[15] with DMF under standard conditions (Scheme 1). Chiral topiramate (**1k**) and estrone sulfamate (**1l**) reacted smoothly, generating the desired products in good yield

To gain insight into the reaction mechanism, we performed several control experiments (Scheme 2). We treated **1a** with the commercially available Vilsmeier reagent (**VR**) chloromethylenedimethyliminium chloride and obtained 60% of the desired **3a** under standard

reaction conditions (Scheme 2, *eq*. 1). Repeating the reaction with 1.0 equiv of **VR** and 0.5 equiv of DMF increased yield to 83% (Scheme 2, *eq*. 2). These results indicate that efficient reaction depends on the presence of a small amount of DMF, which may participate in the mechanism. Performing the reaction at room temperature led to **3a** in 46% yield (Scheme 2, *eq*. 3).

On the basis of our synthetic and mechanistic studies as well as the literature,[16], [17] we propose a possible mechanism for the dehydroxylation reaction (Scheme 3). Initially, thionyl chloride generates highly electrophilic active complex **I** from DMF, and removal of sulfur dioxide reversibly converts **I** to Velsmeier reagent **II**, which acts as a Lewis acid to attack DMF and form more stable complex **III.** (A chlorotropic tautomerization can occur via carbocation rearrangement.) Then, sulfamate **1** reacts via kinetically controlled path A with highly active complex **I**, via path B with Velsmeier reagent **II**, or via thermodynamically controlled path C with complex **III** to generate the final product **3**.

Sulfamates are important functional groups in medicinal chemistry and drug development,[18] and sulfamates are targets normally the amido (NH_2) group must be protected during drug discovery.[19] Therefore we wanted to know whether we could recover sulfamates efficiently from our *N*-oxysulfonyl amidines. When we reacted N-oxysulfonyl amidines with hydrazine hydrate in ethanol under mild reaction conditions, we selectively removed the formamidine functionality, recovering the sulfamates in good to excellent yields (**Table 3**).

Experimental

General procedure for preparing N-oxysulfonylformamidine

A mixture of phenyl sulfamate **1** (2.0 mmol, 1.0 equiv), formamide **2** (3.0 mmol, 1.5 equiv) and thionyl chloride (2.0 mmol, 1.0 equiv) in $CHCl_3$ (2.0ml) was stirred at 60 ^oC for the indicated

reaction time (see **Table 2**). The reaction mixture was cooled down to room temperature and evaporated under vacuum. The resulting residue was purified by silica gel column chromatography to give the desired product **3.**

(E)-phenyl((dimethylamino)methylene)sulfamate **(3a)**:[12a] White solid, m.p.: 67–68°C; ^{1}H NMR (400MHz , $CDCl_3$): δ 7.93 (s, 1H), 7.33-7.18 (m, 5H), 3.06 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100MHz , $CDCl_3$): δ 160.7, 150.6, 129.4, 126.4, 122.2, 41.5, 35.6; HRMS calcd. for $C_9H_{12}N_2NaO_3S$ $[M + Na]^+$; 251.0466; found 251.0464.

General procedure for the deprotection of N-Oxysulfonyl formamidines

Hydrazine monohydrate (500mg, 10 mmol) was added at room temperature to a stirred mixture of the appropriate N-oxysulfonyl formamidine **3** (1.0 mmol) in ethanol (5 mL). The reaction mixture was stirred for 1~2 h and the solvents were removed. Water and ethyl acetate (20mL) were then added, the phases were separated, and the water phase was additionally extracted with ethyl acetate (2 x 10mL). The organic phases were combined, dried with anhydrous Na_2SO_4 and filtered, the solvents were removed and purified by silica gel column chromatography to give the product **1**in good to excellent yield (see **Table 3**).

Conclusion

In conclusion, we have developed an efficient procedure for synthesizing *N*-oxysulfonyl formamidines under mild conditions. The reaction tolerates aromatic and electron-withdrawing aliphatic sulfamates, as well as biologically active sulfamates, and the desired products are generated in good to high yield. The resulting *N*-oxysulfonyl formamidines are easily converted into sulfamates by selectively removing the formamidine functionality using hydrazine hydrate in ethanol.

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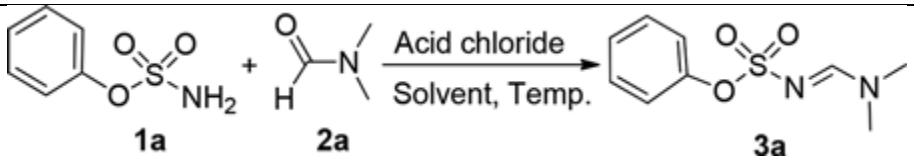
Table 1. Optimization of reaction conditions[a].



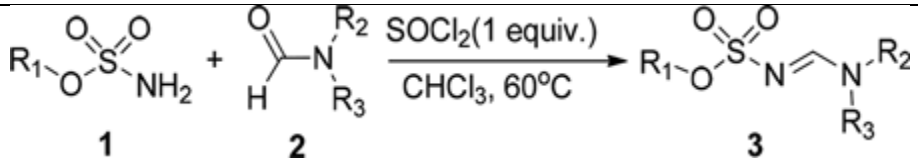
1a 2a 3a

Entry	Acid chloride	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$POCl_3$	$CHCl_3$	60	3	54
2	$SOCl_2$	$CHCl_3$	60	3	60
3	$(COCl)_2$	$CHCl_3$	60	3	56
4	$SOCl_2$	DCM	40	3	44
5	$SOCl_2$	DCE	60	3	50
6	$SOCl_2$	PhCl	60	3	21
7	$SOCl_2$	$CHCl_3$	70	2.5	53
8	$SOCl_2$	$CHCl_3$	40	6	46
9[c]	$SOCl_2$	$CHCl_3$	60	2	72
10[d]	**$SOCl_2$**	**$CHCl_3$**	**60**	**2**	**85**
11[e]	$SOCl_2$	$CHCl_3$	60	2	87
12	$SOCl_2$	DMF	60	5	trace
13[cf]	$SOCl_2$	$CHCl_3$	60	2	86

14[c]	–	$CHCl_3$	60	6	NR

[a]Reactions were performed with 2.0 mmol of phenyl sulfamate **1a** (1.0 equiv.) and 2.0 mmol acid chloride (1.0 equiv) in 2 mL of solvent, unless otherwise noted. [b]Isolated yield after column chromatography. [c]1.2 equiv of DMF was used. [d]1.5 equiv of DMF was used. [e]2.0 equiv of DMF was used. [f]The reaction was performed with the drying tube on top of the condenser.

Table 2. Preparation of N-oxysulfonyl formamidines[a].



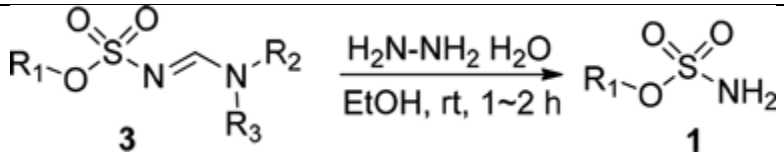
1 2 3

Entry	**1**	R_1	**2**	R_2, R_3	Time (h)	**3**	Yield (%)[b]
1	**1a**	C_6H_5	**2a**	Me, Me	2	**3a**	85
2	**1b**	4-$MeOC_6H_5$	**2a**	Me, Me	2	**3b**	87
3	**1c**	4-^{t}BuC6H5	**2a**	Me, Me	2	**3c**	90
4	**1d**	4-ClC_6H_5	**2a**	Me, Me	2	**3d**	85
5	**1e**	4-FC_6H_5	**2a**	Me, Me	3	**3e**	90
6	**1f**	4-azobenzene	**2a**	Me, Me	3	**3f**	92
7	**1a**	C_6H_5	**2b**	Et, Et	3	**3g**	77
8	**1g**	4-BrC_6H_5	**2b**	Et, Et	2	**3h**	76
9	**1a**	C_6H_5	**2c**	*i*-Pr, *i*-Pr	3	**3i**	88
10	**1a**	C_6H_5	**2d**	Me, Ph	5	**3j**	60
11	**1a**	C_6H_5	**2e**	$(CH_2)_5$	4	**3k**	85
12	**1a**	C_6H_5	**2f**	$(C_2H_4)_2O$	5	**3l**	63

13	**1h**	$C_6H_5CH_2$	**2a**	Me, Me	3	**33mm**	22[c]
14	**1i**	n-C_5H_9	**2a**	Me, Me	3	**3n**	30[c]
15	**1j**	Cl_3CCH_2	**2a**	Me, Me	2	**3o**	92
16	**1a**	C_6H_5	**2g**	H, Ph	5	**3p**	0

[a]Reactions were performed with 2.0 mmol of sulfamate **1** (1.0 equiv) and 3.0 mmol formamide **2** (1.5 equiv) in 2.0 mL of chloroform, unless otherwise noted. [b]Isolated yield after column chromatography. [c](Dimethylamino)methylene sulfamic acid was isolated in nearly 50% yield.

Table 3 Deprotection of *N*-oxysulfonyl formamidines[a].

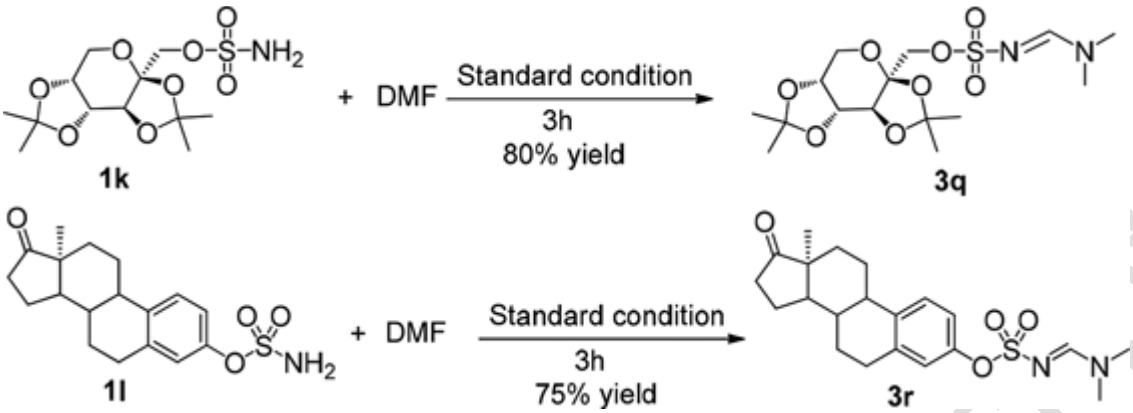


3 **1**

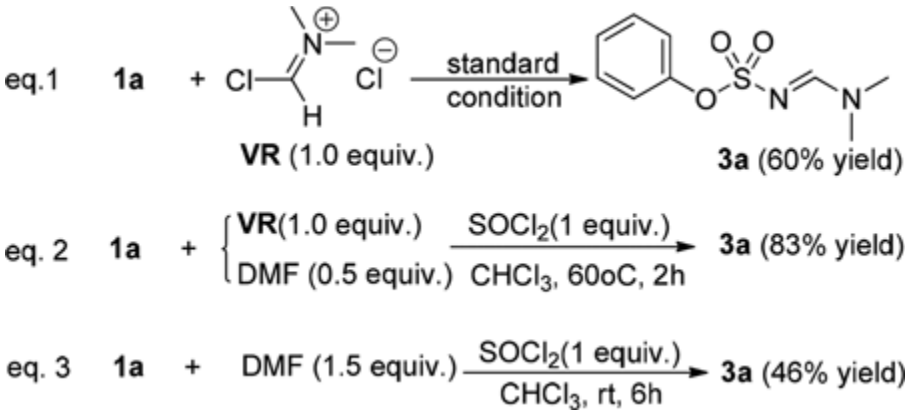
Entry	Formamidine (**3**)	Amidine (**1**)	Time (h)	Yield (%)[b]
1	**3a**	**1a**	1	89
2	**3c**	**1c**	1	91
3	**3g**	**1a**	1.5	93
4	**3i**	**1a**	2	85
5	**3k**	**1a**	2	96
6	**3l**	**1a**	2	83
7	**3o**	**1j**	1	89
8	**3q**	**1k**	1	90
9	**3r**	**1l**	1	85

[a]*N*-Sulfonylformamidine **3** (1.0 mmol), $N_2H_4 \cdot H_2O$ (10.0 mmol), EtOH (5mL). [b]Isolated yield.

Scheme 1. Reactions of topiramate and estrone sulfamate with DMF.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction mechanism.