Silyl Radical-Mediated Activation of Sulfamoyl Chlorides Enables Direct Access to Aliphatic Sulfonamides from Alkenes

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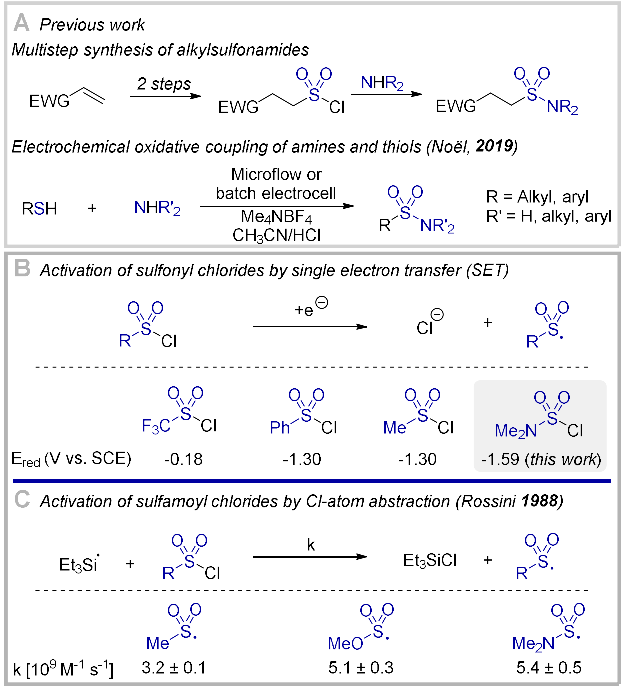
Supporting Information Placeholder

ABSTRACT: Single electron reduction is more challenging for sulfamoyl chlorides than sulfonyl chlorides. However, sulfamoyl and sulfonyl chlorides can be easily activated by Cl-atom abstraction by a silyl radical with similar rates. This later mode of activation was therefore selected to access aliphatic sulfonamides applying a single-step hydrosulfamoylation using inexpensive olefins, tris(trimethylsilyl)silane and photocatalyst Eosin Y. This late-stage functionalization protocol generates molecules as complex as sulfonamide-containing cyclobutyl-spirooxindoles for direct use in medicinal chemistry.

Since the discovery of the antibacterial drug Prontosil in the late 30's, the application of sulfonamides in medicinal chemistry has been extended to treat diseases such as cancer, CNS disorder, diabetes and dementia.[1] Due to their distinct physicochemical properties, sulfonamides have been used extensively as bioisosteres of carboxylic acids and carboxamides.[2] Also, the possibility of fine-tuning pK_a values through modification of the sulfonamide NH-substituent, has made them powerful functionalities to improve on drug potency and efficacy.[2a,3] Traditional approaches towards sulfonamides consist of reacting sulfonyl chlorides with amines.[4] More recently, alternative procedures have been developed to access (hetero)arylsulfonamides.[5] For example, Willis and co-workers developed a Cu-catalyzed protocol allowing the attachment of SO_2N-functionality to (hetero)aryl and alkenyl boronic acids using DABSO, a surrogate reagent for SO_2.[6] In the same year, a photosensitized nickel catalyzed cross-coupling between *N*-(hetero)aryl sulfonamide and *N*-(hetero)aryl bromides was reported by MacMillan and co-workers providing a broad range of arylsulfonamide motifs.[7] Methods to access alkylsulfonamides have also appeared due to the increasing demand from the pharmaceutical sector for C(sp[3])-rich molecules.[8] Most syntheses reported to date require a multiple reactions sequence, whereby an alkene is converted to a thioether or thioester, oxidized to a sulfonyl chloride, and subjected to amination.[9] This sequence suffers from limited functional group tolerance due to the harsh reaction conditions applied in the steps involved. To overcome these challenges, Noël and co-workers recently described the electrochemical oxidative coupling between alkyl thiols and amines (Scheme 1A).[10]

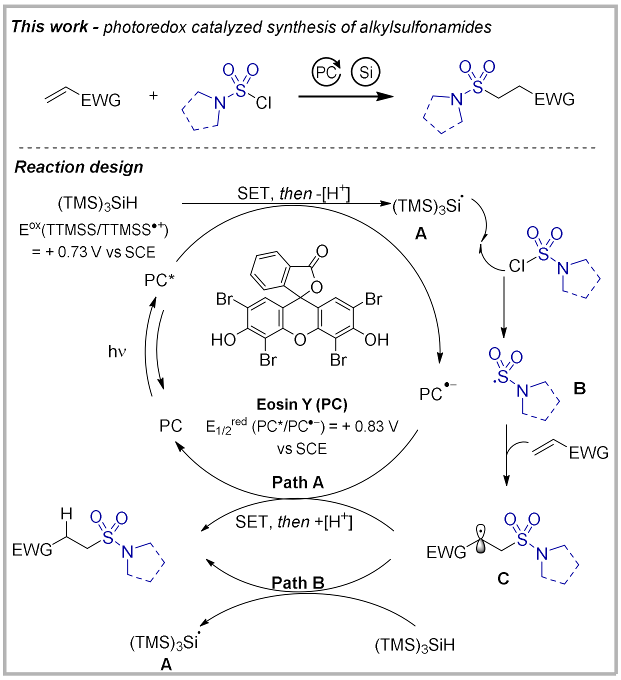
The aim of this study was to provide facile access to alkylsulfonamides from inexpensive feedstock olefins applying a single-step hydrosulfamoylation with sulfamoyl chlorides, many being commercially available.[11] This late-stage functionalization process was viewed as advantageous to accelerate access to diverse chemical libraries for immediate impact on drug discovery.



Scheme 1. A. Synthesis of alkylsulfonamides. B. Activation of sulfonyl chlorides by single electron transfer (SET). C. Activation of sulfamoyl chlorides by Cl-atom abstraction. EWG = electron-withdrawing group.

Photoredox catalysis has gained considerable interest for the functionalization of C(sp[3])-centers.[12] These advances include the generation of sulfonyl radicals from sulfonyl chlorides for subsequent addition to alkenes.[13] The success of these transformations relies on a redox matching between the excited state of the photocatalyst and the sulfonyl chloride. Fluoroalkyl, alkyl as well as (hetero)aryl sulfonyl chlorides have been successfully activated by single electron reduction.[13,14] However, the generation of sulfamoyl radicals from sulfamoyl chlorides remains underexplored.[13c,e,15]

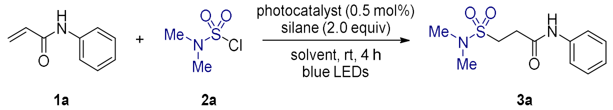
Preliminary work indicated that the direct single electron reduction of dimethylsulfamoyl chloride (E_{red} = -1.59 V vs. saturated calomel electrode (SCE) in MeCN)[16] is more challenging than for methanesulfonyl chloride (Scheme 1B). An alternative pathway for the generation of sulfamoyl radical is therefore desirable. Electron Paramagnetic Resonance (EPR) studies conducted by Rossini and co-workers, demonstrated in 1988 that dimethylsulfamoyl and methylsulfonyl radicals can be generated *via* direct Cl-atom abstraction by a silyl radical with similar reaction rates (~ 10^9 M^{-1} s^{-1}) (Scheme 1C).[17] With this knowledge, we designed a mechanistic scenario enabling hydrosulfamoylation of alkenes, whereby a silyl radical formed by photoredox catalysis would abstract a Cl-atom from a sulfamoyl chloride to afford a sulfamoyl radical, which could add to an alkene (Scheme 2).[18] Upon light irradiation, photocatalyst Eosin Y (PC) should produce excited triplet state PC* that could undergo single-electron transfer (SET) [$E_{1/2}^{red}$ (PC*/PC$^{\bullet-}$) = + 0.83 V versus saturated calomel electrode (SCE)][12b] with tris(trimethylsilyl)silane (TTMSS) [E^{ox} (TTMSS/TTMSS$^{\bullet+}$) = + 0.73 V vs SCE][18d] to generate the Si-centered radical **A** upon loss of a proton. Radical **A** would abstract the Cl-atom from sulfamoyl chloride affording sulfamoyl radical **B** that could undergo regioselective Giese addition to the alkene leading to the C-centered radical **C**. A single electron reduction event would afford the hydrosulfamoylated product and concomitantly regenerate Eosin Y (Scheme 2, Path A). An alternative photoinitiation-radical chain propagation pathway involving direct H-atom abstraction from TTMSS is also possible (Scheme 2, Path B).



Scheme 2: Photoredox-catalyzed hydrosulfamoylation of electron-deficient alkenes. EWG = electron-withdrawing group. PC = photocatalyst. Si = tris(trimethylsilyl)silane.

A range of experiments revealed that treatment of *N*-phenylacrylamide **1a** with Eosin Y (0.5 mol%), $(TMS)_3SiH$, dimethylsulfamoyl chloride **2a** and MeCN as solvent under blue LED irradiation (λ_{max} = 470 nm), afforded the desired hydrosulfamoylated product **3a** isolated in 83% yield (Table 1, entry 1). A lower efficiency was observed when using different catalyst loadings or solvents (Table 1, entries 2-5). Notably, employment of silanes other than $(TMS)_3SiH$ failed to produce **3a** (Table 1, entries 6-7).[18a,d,g] Iridium-based $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$: Ir(III)*/Ir(II) = +1.21V vs. SCE in MeCN) and ruthenium-based ($Ru(bpy)_3(PF_6)_2$: Ru(II)*/Ru(I) = +0.77V vs. SCE in MeCN) photocatalysts were found to be suitable

Table 1. Range of experiments for the hydrosulfamoylation of alkenes.[a]

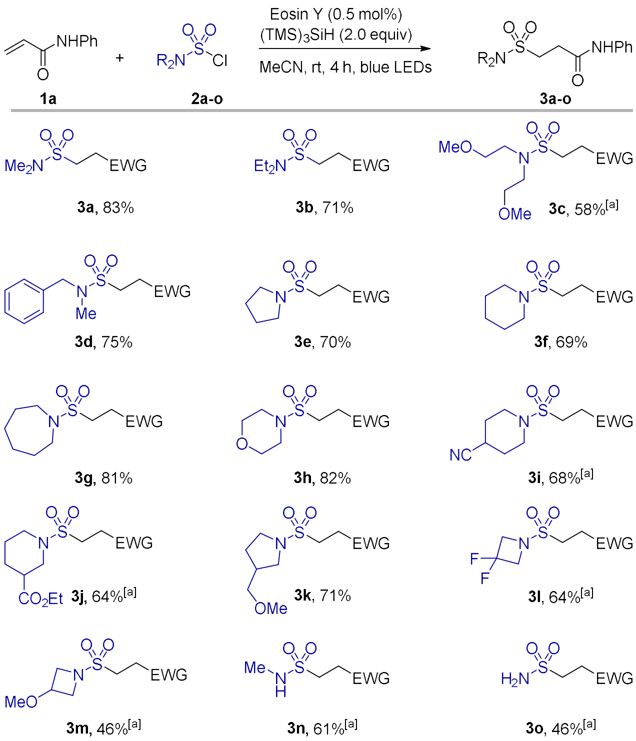


entry	photocatalyst	silane	solvent	yield [%]
1	Eosin Y	$(TMS)_3SiH$	MeCN	83
2[b]	Eosin Y	$(TMS)_3SiH$	MeCN	69
3[c]	Eosin Y	$(TMS)_3SiH$	MeCN	73
4	Eosin Y	$(TMS)_3SiH$	DCE	14
5	Eosin Y	$(TMS)_3SiH$	DMF	45
6	Eosin Y	Et_3SiH	MeCN	0
7	Eosin Y	Ph_3SiH	MeCN	0
8	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	$(TMS)_3SiH$	MeCN	88
9	$Ru(bpy)_3(PF_6)_2$	$(TMS)_3SiH$	MeCN	74
10	Eosin Y	-	MeCN	0
11[d]	Eosin Y	$(TMS)_3SiH$	MeCN	0
12	-	$(TMS)_3SiH$	MeCN	0[e]
13[f]	Eosin Y	$(TMS)_3SiH$	MeCN	0[g]
14[h]	Eosin Y	$(TMS)_3SiH$	MeCN	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), photocatalyst (0.5 mol%), silane (1.0 mmol), solvent (3.0 mL) under blue light (λ_{max} = 470 nm) irradiation for 4 h. Yields of isolated products. [b] 1 mol% of Eosin Y was used. [c] 0.1 mol% of Eosin Y was used. [d] Reaction performed in the dark. [e] After 16 h, 80% of **3a** was isolated. [f] no sulfamoyl chloride **2a** was added. [g] 74% of hydrosilylated product was isolated. [h] 4.0 equiv of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) were added. $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ = [4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine-N1,N1′]bis[3,5-difluoro-2-{5-(trifluoromethyl)-2-pyridinyl-N}phenyl-C]Iridium(III) hexafluorophosphate. $Ru(bpy)_3(PF_6)_2$ = Tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate.

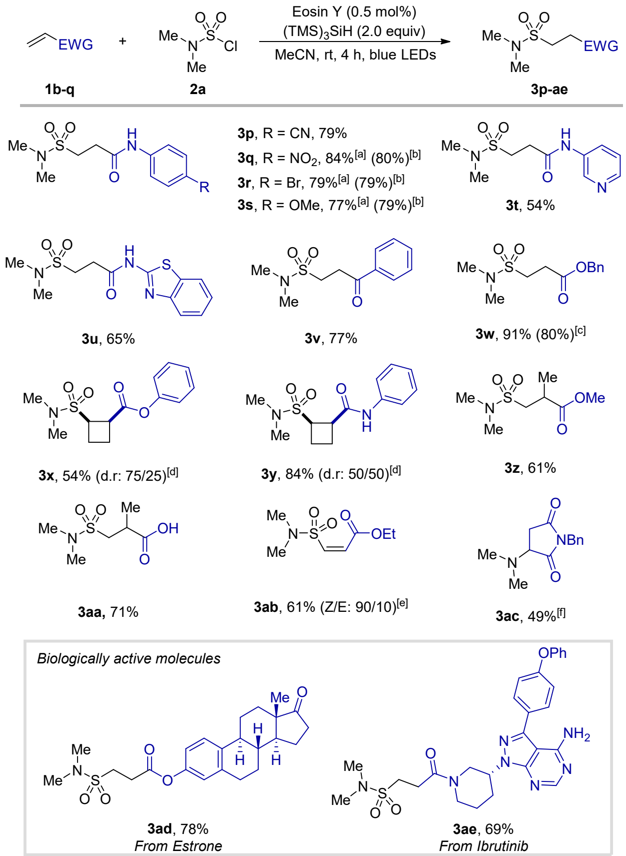
for this transformation (Table 1, entries 8-9).[12a] Eosin Y was retained for further studies due to economic and ecological considerations. Control experiments demonstrated that irradiation and $(TMS)_3SiH$ are essential for this transformation (Table 1, entries 10,11). The reaction can be performed without photocatalyst, although this process requires significantly longer reaction time (Table 1, entry 12; 16 hours instead of 4 hours). In absence of sulfamoyl chloride, the hydrosilylated product was isolated in good yield, demonstrating the ability of Eosin Y to generate a silyl radical from TTMSS (Table 1, entry 13).[19] Furthermore, full recovery of starting material was observed when the radical scavenger TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) was added to the standard reaction conditions (Table 1, entry 14). Finally, no deuterium incorporation was observed using MeCN-*d3* as solvent or by addition of excess MeOD, suggesting that TTMSS acts as a H-atom donor. $(TMS)_3SiCl$ was isolated as a side-product of the reaction, which is consistent with Cl-atom abstraction from the silyl radical. The results of the deuteration experiments and the observation that the reaction is possible in the absence of photocatalyst although more effective in its presence (Table 1, entry 12), advocate in favour of a photoinitiation-radical chain propagation pathway (Scheme 2, Path B).

With the optimized conditions in hand, we explored the generality of this transformation on a range of sulfamoyl chlorides as well as electron-deficient alkenes (Schemes 3 and 4). Various functional groups, such as esters, amides, carboxylic acids, amines, ethers, halides, nitro and nitriles were tolerated, and products **3a-ae** were isolated in moderate to excellent yields. As shown in Scheme 3, we established that primary, secondary as well as tertiary sulfamoyl chlorides are suitable precursors for the hydrosulfamoylation of *N*-phenylacrylamide (**1a**). Dimethyl, diethyl and bis(2-methoxyethyl)sulfamoyl chloride (**2a**-**c**) allowed the introduction of linear sulfonamides in good yields. Benzylmethylsulfamoyl choride (**2d**) was successfully used for this transformation and afforded **3d** in 75% yield. The incorporation of cyclic sulfonamides including five-, six- and seven-membered rings afforded pyrrolidine, piperidine and azepane sulfonamides in good to excellent yields (**3e**-**g**). A sulfonamide containing a morpholine moiety was isolated in 82% yield (**3h**). Piperidine derivatives containing an ester and a nitrile, as well as a 3-methoxymethylpyrrolidine were compatible with this protocol allowing access to valuable building blocks containing vectors for further functionalization (**3i**-**k**). Furthermore, sulfamoyl chlorides containing small rings of pharmaceutical relevance, decorated with fluorine and methoxy substituents were also competent substrates (**3l**,**m**). Additionally, a secondary sulfonamide was obtained in moderate yield (**3n**). Sulfamoyl chloride proved to be a suitable reagent and afforded the primary sulfonamide in 46% yield (**3o**), a motif commonly used in bioactive molecules.[20]



Scheme 3. Substrate scope of sulfamoyl chlorides. Reaction conditions: alkene **1a** (0.5 mmol), **2a**-**o** (1.25 mmol), TTMSS (1.0 mmol), Eosin Y (0.5 mol%), MeCN (3.0 mL), blue LED irradiation (λ_{max} = 470 nm), room temperature, 4 h. Yields of isolated products. [a] 16 h reaction time. EWG = C(O)NHPh.

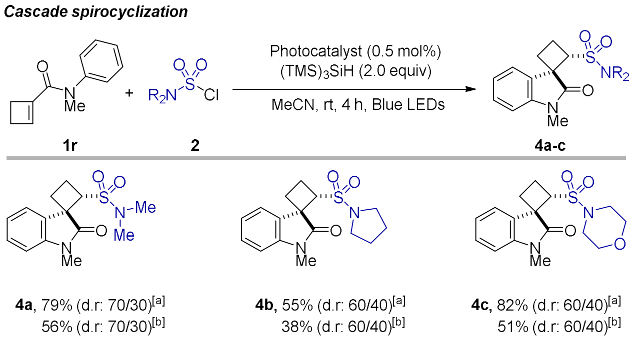
We next examined the scope of electron-deficient alkenes using dimethylsulfamoyl chloride (Scheme 4). A variety of *N*-phenylacrylamides bearing different substituents on the arene were initially surveyed. Both electron-withdrawing and -donating groups, such as halogen, nitro, nitrile and methoxy, were tolerated and afforded the desired products in good yields (**3p**-**s**). Notably, the reaction of substrates **1c**-**e** was significantly slower (16 hours reaction time). Photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 was more effective (4 hours reaction time). Heteroarenes, such as the pyridine derivative was converted to the hydrosulfamoylated product with no competitive C-H sulfamoylation (**3t**). Ketone and ester derivatives were transformed to the desired products in good yields (**3v**,**w**). Considering the high value of cyclobutane derivatives to medicinal chemists, we investigated the introduction of sulfonamide function into cyclobutenes.[21] Highly valuable *1,2*-disubstituted cyclobutanes were isolated in moderate yield and diastereomeric ratio (**3x**,**y**), a useful advance considering that radical functionalization of cyclobutenes remains underexplored; this is possibly due to their propensity to undergo 4π-electrocyclic ring opening as well as polymerization.[22] *Gem*-disubstituted alkenes afforded the hydrosulfamoylated products in good yield (**3z**,**aa**). A representative electron-deficient alkyne gave the desired hydrosulfamoylated alkene with high *Z*-selectivity (Z/E: 90/10) and good yield (**3ab**). We noted competitive desulfonylation with *N*-benzylmaleimide (**3ac**).[23] Unactivated and electron-rich alkenes do not react under our reaction conditions.[16]



Scheme 4. Substrate scope of electron-deficient alkenes. Reaction conditions: alkene **1b**-**q** (0.5 mmol), **2a** (1.25 mmol), TTMSS (1.0 mmol), Eosin Y (0.5 mol%), MeCN (3.0 mL), blue LED irradiation (λ_{max} = 470 nm), room temperature, 4 h. Yields of isolated products. [a] 16 h reaction time. [b] [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 was used instead of Eosin Y and full conversion was observed within 4 hours. [c] Scale-up experiment performed on 30.8 mmol (5.0 g) of benzyl acrylate. [d] The diastereomers were separated by silica flash column chromatography. [e] The minor isomer was not isolated. [f] Only traces of the hydrosulfamoylated product was observed.

To further demonstrate the potential of this transformation to late-stage functionalization, we applied this methodology to the derivatization of alkene-containing biologically active molecules. A hydrosulfamoylated Estrone derivative was isolated in good yield (**3ad**). Furthermore, hydrosulfamoylation of Ibrutinib afforded **3ae** in good yield, with all functional groups other than the alkene remaining intact. The hydrosulfamoylation of benzyl acrylate **1i** was accomplished in one step on a 5 g scale affording **3w** in 80% yield (6.7 g), suggesting that this methodology could be applicable to large-scale batch production. Further transformations of **3w** included hydrolysis, reduction and amidation.[16]

We explored the possibility to build molecular complexity through intramolecular quaternization of the *α*-carbonyl radical intermediate.[24] *N*-Methyl-*N*-phenylcyclobutene carboxamide **1r** underwent a cascade spirocyclization to afford sulfonamide-containing cyclobutyl-spirooxindoles (**4a-c**). Both Eosin Y and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ were suitable photocatalysts, but the Ir photocatalyst gave higher yields. Linear, cyclic as well as heterocyclic sulfonamides were within reach albeit in low diastereoselectivity; these were easily separated affording valuable 3D-building blocks for medicinal chemistry (Scheme 5).[25]



Scheme 5. Substrate scope of sulfonamide-containing cyclobutylspirooxindoles. Reaction conditions: **1r** (0.5 mmol), **2** (1.25 mmol), TTMSS (1.0 mmol), photocatalyst (0.5 mol%), MeCN (3.0 mL), blue LED irradiation (λ_{max} = 470 nm), room temperature, 4 h. Yields of isolated products. Both diastereomers were separated by silica flash column chromatography. [a] $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ as photocatalyst. [b] Eosin Y as photocatalyst.

In conclusion, this study established that tris(trimethylsilyl)silane enables facile hydrosulfamoylation of alkenes by serving both as a silyl radical source capable of activating sulfamoyl chlorides, and as the hydrogen atom donor. This most practical and cost-effective methodology is performed in the presence of the organophotocatalyst Eosin Y. Numerous functional groups are tolerated allowing access to a broad range of novel alkylsulfonamides that are valuable building blocks for drug discovery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Data and materials availability: additional optimization, mechanistic data, cyclic voltammetry, experimental procedures and analytical data (^{1}H, ^{19}F, ^{13}C NMR, high resolution mass spectrometry) for all new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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