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Easy Access to Aliphatic Sulfonamides using Sulfamoyl Chlorides under Visible Light Activation

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TITLE:

Easy Access to Aliphatic Sulfonamides using Sulfamoyl Chlorides Under Visible Light Activation

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KEYWORDS:

Blue-light activation, radical, H-atom donor, late-stage functionalization, commercial reagents, hydrofunctionalization, electron-deficient alkenes.

SUMMARY:

Presented here is a protocol for the easy synthesis of aliphatic sulfonamides using sulfamoyl chlorides, $(TMS)_3SiH$ and Eosin Y under blue-light irradiation.

ABSTRACT:

Sulfonamides are prevalent motifs in marketed drugs and natural products. Their synthesis represents a great interest to the pharmaceutical industry, due to their unique biological properties. Recently, several methods for the synthesis of aryl sulfonamides have been developed, but little effort has focused on developing one-step methodologies to access sulfonamides flanked by two alkyl groups. This protocol describes a practical and facile method for the net hydrosulfamoylation of electron-deficient alkenes using sulfamoyl chlorides as radical precursors under blue-light activation. This practical and cost-effective methodology is performed in the presence of the metal-free photocatalyst Eosin Y and uses light as a clean and traceless energy source. The procedure is scalable, displays a broad functional group tolerance, and can be applied for late-stage functionalization. All reagents used in this protocol are commercially available. Simple reaction set-up, the absence of work-up and easy purification, demonstrate the convenience of this protocol. The reaction is best applied to electron-deficient alkenes.

INTRODUCTION:

Over the recent decades, sulfonamides featured in a broad range of biologically active molecules and are common motifs in pharmaceuticals and agrochemicals[1,2]. Initially employed for

antibacterial purposes[3,4], the application of this motif in drug discovery has been extended to numerous diseases including cancer, CNS disorders, diabetes, dementia and HIV[5-11]. Sulfonamides stand out as metabolically stable bioisosteres of carboxylic acids and carboxamides, with the N-H pKa being tunable by varying substitution patterns[12-15].

Traditionally, sulfonamides are synthesized by substitution of a sulfonyl chloride with an amine[16,17]. The synthesis of sulfonyl chlorides often relies on a multi-step procedure employing harsh conditions, such as strong oxidants. Whilst milder one-step protocols for the installation of sulfonyl chloride intermediates have been developed[18,19], the design of a single-step transformation to access sulphonamides is highly desirable.

In the last decades, powerful strategies have been developed for the synthesis of (hetero)aryl sulfonamides, using transition metals, photoredox catalysis or organic catalysts[20-34]. Nevertheless, the one-step synthesis of aliphatic analogues remains underexplored[35-40]. A notable exception is the electrochemical oxidative coupling of amines and thiols, reported by Noël and co-workers[41]. We were interested in a complementary late-stage functionalization strategy, allowing the direct attachment of commercially available sulfamoyl chlorides onto inexpensive olefins to afford products of net hydrosulfamoylation under visible light activation. Specifically, this process requires an in situ generated sulfamoyl radical, and a suitable hydrogen atom donor.

Preliminary studies indicated that the direct single electron reduction of dimethylsulfamoyl chloride (E_{red} = -1.59 V versus saturated calomel electrode (SCE) in MeCN)[42] is more challenging than for methanesulfonyl chloride (E_{red} = -1.30 V versus SCE in MeCN)[43], an observation encouraging the identification of an alternative mode of activation to generate sulfamoyl radicals. Inspired by Chatgilialoglu's work in 1988[44], we believed that tris(trimethylsilyl)silane can act both as a silyl radical source capable of activating sulfamoyl chlorides, and as the hydrogen atom donor. Blue light irradiation is essential for this reaction to proceed, while Eosin Y is beneficial but not essential.

This practical and cost-effective one-step method tolerates numerous functional groups, thereby allowing access to a broad range of novel alkylsulfonamides including complex sulfonamide-containing cyclobutyl-spirooxindoles that are all valuable building blocks for drug discovery. As part of the challenges faced by industries aiming at avoiding operationally complex, over-engineered, and costly processes, this transformation is not sensitive to oxygen or moisture, uses a metal free photocatalyst, and is operationally simple. Furthermore, the use of blue light as an initiator for this chemical transformation makes this protocol green and sustainable.

PROTOCOL:

CAUTION: All chemicals used in this protocol must be handled with care. Please carefully read the material safety data sheets (MSDS) of solvents and reagents used in this protocol. $(TMS)_3SiH$, dimethylsulfamoyl chloride, MeCN, EtOAc and silica have been shown to be toxic, corrosive, irritant, cancerogenic and flammable. Standard lab safety measures are relevant for the handling

of those chemicals. All manipulations must be performed in a ventilated laboratory fume hood and the use of appropriate personal protective equipment (PPE), including lab coat, safety glasses, and nitrile gloves is compulsory.

1. Hydrosulfamoylation of electron-deficient alkenes

1.1. Add a magnetic stir bar to a 7 mL vial.

1.2. Weigh out 73.5 mg of *N*-phenylacrylamide (0.50 mmol, 1.0 equiv) and 1.7 mg of photocatalyst Eosin Y (0.0025 mmol, 0.5 mol%) and add both to the same vial.

1.3. Sequentially add 3.0 mL of MeCN, 309 µL of $(TMS)_3SiH$ (1.0 mmol, 2.0 equiv) and 1.25 mmol of sulfamoyl chloride (2.5 equiv) with a syringe. Cap the vial with a screw cap.

1.4. Place the vial in the photobox equipped with an 18 W blue LED lamp (λ = 450 nm) and a fan.

1.5. Stir the emulsion vigorously at 1,000 rpm for 4 h.

2. Monitoring of the starting material conversion by thin-layer chromatography (TLC)

2.1. Dissolve 1 mg of *N*-phenylacrylamide in 1 mL of Dichloromethane (DCM). Sample this solution on the TLC plate (left and middle spot).

2.2. Sample a 50 µL aliquot of the reaction mixture and transfer it to a 1.5 mL vial containing 50 µL of DCM. Sample this solution on the TLC plate (middle and right spot).

2.3. Add a solvent mixture of pentane and ethyl acetate (eluent: 80:20 pentane/ethyl acetate) to a TLC chamber.

2.4. Run the TLC plate in the chamber until the solvent front is at 0.5 cm distance of the top of the plate.

2.5. Remove the plate from the chamber, dry it under air and expose the plate to UV light (λ = 254 nm) under a lamp (*Rf* values: Starting material = 0.4; Product = 0.2).

3. Workup and purification

3.1. Transfer the reaction mixture to a 25 mL round-bottom flask and concentrate the mixture under reduced pressure using a rotary evaporator (150 rpm; until 20 mbar) equipped with a water bath, heated to 40 °C to obtain a crude oil.

3.2. Condition a silica column (pore size 60 Å, 230–400 mesh particle size, 12 g) by passing 60 mL of pentane through the column via a syringe.

3.3. Dilute the crude oil in 2 mL of DCM and transfer the solution onto the column.

3.4. Run a gradient elution on the automated column (EtOAc in pentane 0/100 to 100/0 over 20 min) and monitor by UV-VIS (254 nm) to elute the compounds.

3.5. Collect the fractions in test tubes and monitor the collected fractions by TLC (see section 2).

3.6. Sample aliquots of the collected fractions on a TLC plate.

3.7. Run the TLC plate in the chamber until the solvent front has almost reached the top of the plate and compare the *Rf* values (see step 2.5).

3.8. Collect the desired fractions as determined by TLC analysis and concentrate the solution under reduced pressure on a rotary evaporator (150 rpm; until 20 mbar) equipped with a water bath heated to 40 °C.

3.9. Dissolve 5 mg of the product in 0.6 mL $CDCl_3$ and add this solution to a nuclear magnetic resonance spectroscopy (NMR) tube.

3.10. Run a ^{1}H NMR and a ^{13}C NMR and compare the spectra with the information listed below.

REPRESENTATIVE RESULTS:

The sequence produced the desired hydrosulfamoylated product with 83% yield (106 mg, 0.41 mmol) as an off-white solid. The structure and purity can be assessed by ^{1}H and ^{13}C NMR spectra (**Figure 1**, **Figure 2**). More specifically, in the ^{1}H and ^{13}C NMR, disappearance of two characteristic alkene peaks and appearance of two aliphatic peaks, are characteristic for the addition of dimethyl sulfamoyl chloride to the alkene. High-resolution mass spectrometry (HRMS) of the product also confirmed the formation of the desired product.

3-(*N*,*N*-dimethylsulfamoyl)-*N*-phenylpropanamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.29 (dd, J = 7.9 Hz, 2H), 7.09 (dd, J = 7.4 Hz, 1H), 3.35 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.87 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 137.9, 129.1, 124.6, 120.0, 43.5, 37.5, 30.5; **HRMS** (ESI-TOF) calculated for $C_{11}H_{15}O_3N_2{}^{32}S$ $[M-H]^-$: 255.0809; found 255.0806; **IR (neat)** 1681, 1619, 1551, 1491, 1443, 1336, 1314, 1258, 1186, 1147, 952, 760, 742, 684; **m.p.**: 120–122 °C.

A wide range of novel aliphatic sulfonamides can be prepared using this methodology in good to high yields[42]. Each compound has been fully characterized by ^{1}H, ^{13}C NMR, as well as HRMS, IR and melting point[42]. Note that vigorous stirring is required, due to the use of $(TMS)_3SiH$, which is not miscible in MeCN. Depending on the substrate, the completion of the reaction could be monitored visually as at this point, the mixture becomes homogenous. A color change was observed upon addition of dimethylsulfamoyl chloride. No degradation of the product was observed when the reaction time was extended to 72 h.

FIGURE LEGENDS:

Figure 1: ^{1}H NMR spectra of 1a and 3a ($CDCl_3$, 400 MHz). This figure has been modified from Gouverneur and co-workers[42].

Figure 2: ^{13}C NMR spectra of 1a and 3a ($CDCl_3$, 101 MHz). This figure has been modified from Gouverneur and co-workers[42].

Figure 3: Suggested mechanism for the hydrosulfamoylation of alkenes. This figure has been modified from Gouverneur and co-workers[42].

Figure 4: Substrate scope of sulfamoyl chlorides and alkenes. Reaction conditions: alkene **1** (0.5 mmol), sulfamoyl chloride **2** (1.25 mmol), $(TMS)_3SiH$ (1.0 mmol), Eosin Y (0.5 mol%), MeCN (3.0 mL), blue LED irradiation (λ_{max} = 470 nm), room temperature. [a] 16 h reaction time. [b] Scale-up experiment performed on 30.8 mmol (5.0 g) of benzyl acrylate. [c] The diastereomers were separated by silica flash column chromatography. [d] The minor isomer was not isolated. [e] Only traces of the hydrosulfamoylated product was observed. This figure has been modified from Gouverneur and co-workers[42].

DISCUSSION:

This operationally simple protocol uses commercially available substrates. Nitrogen atmosphere as well as strict water-free conditions are not required for the reaction to proceed in high yields, demonstrating the ease of this protocol. These reactions are often complete within 4 h at room temperature, although some less reactive sulfamoyl chlorides required additional time.

The absence of work-up and the ease of the purification step by silica column chromatography, make this protocol operationally and economically attractive. Interestingly, a fluctuation of the temperature (depending on the distance between the vial and the lamp) did not impact the outcome of the reaction. We noticed that a high purity of the sulfamoyl chlorides was crucial for this transformation to proceed in good yield.

Aiming at broadening the scope, the reactivity of the sulfamoyl radical was investigated towards a range of alkenes of different electronic profiles. As shown previously, the sulfamoyl radical can be added efficiently to electron-deficient alkenes; nevertheless, no conversion was observed with styrenes and unactivated alkenes. Current investigations for the compatibility of these substrates under our reaction conditions is ongoing. Furthermore, sulfonyl chlorides have shown to be reactive under similar reaction conditions[45].

A plausible mechanism of the hydrosulfamoylation of electron-deficient alkenes is depicted in **Figure 3**. Upon irradiation with light, the generated excited triplet state Eosin Y* [$E_{1/2}^{red}$ ($PC^*/PC^{\bullet-}$) = + 0.83 V versus saturated calomel electrode (SCE)] should readily oxidize tris(trimethylsilyl)silane (TTMSS) [E^{ox} ($TTMSS/TTMSS^{\bullet+}$) = + 0.73 V versus SCE] via single-electron transfer (SET). Upon loss of a proton, silyl radical **A** is generated, which subsequently abstracts a chlorine-atom from the sulfamoyl chloride to generate sulfamoyl radical **B**. The latter radical **B**

undergoes regioselective Giese addition to the alkene, whereby the C-centered radical **C** is formed. The desired hydrosulfamoylated product is finally obtained upon single-electron reduction and protonation (Path A). In this event, the photocatalyst returns to its native oxidation state. A chain propagation reaction mechanism, involving a direct H-atom abstraction from TTMSS is also viable (Path B).

This protocol tolerates a wide range of functional groups, such as esters, amides, carboxylic acids, amines, ethers, halides, nitro and nitriles (**Figure 4**: **3a**–**3ah**). The successful introduction of primary, secondary as well as tertiary sulfonamides allowed access to a broad range of novel alkylsulfonamides (**3a**–**3ao**). Linear terminal alkenes (**3p**–**3w**), gem-disubstituted alkenes (**3x**,**y**), and a representative electron-deficient alkyne (**3ab**) are all suitable substrates. Cyclobutenes respond well to hydrosulfamoylation generating highly desirable 1,2-disubstituted sulfonamide-containing cyclobutanes (**3z**,**3aa**) or cyclobutyl-spirooxindoles (**3af**–**3ah**), all valuable building blocks for drug discovery. The diastereoisomers formed, are easily separable by flash column chromatography. Late-stage functionalization of biologically active molecules was also successful (**3ad, 3ae**). The scalability of this transformation was demonstrated, providing a short and safe synthetic route to access **3w**. We noted competitive desulfonylation with *N*-benzylmaleimide (**3ac**).

As an economic and efficient protocol, this protocol could have practical significance for the introduction of aliphatic sulfonamides in complex natural products and biologically active molecules, in both academic laboratory and industry laboratories.

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DISCLOSURES:

The authors have nothing to disclose.

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Figure

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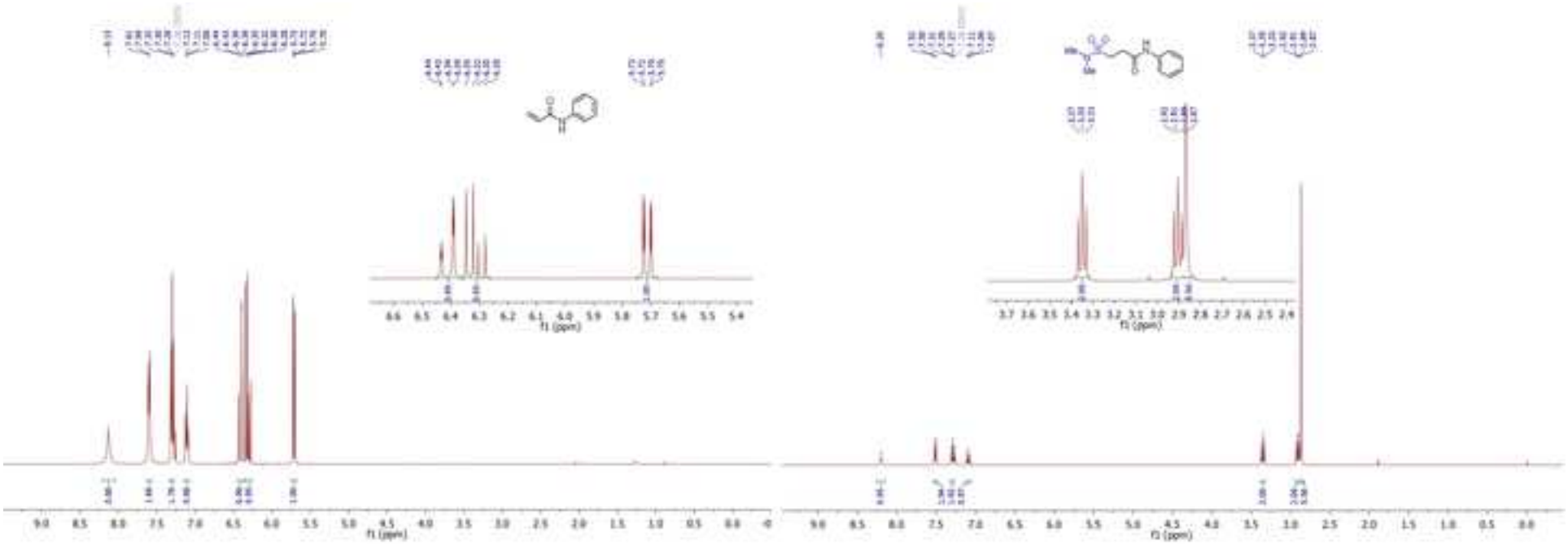

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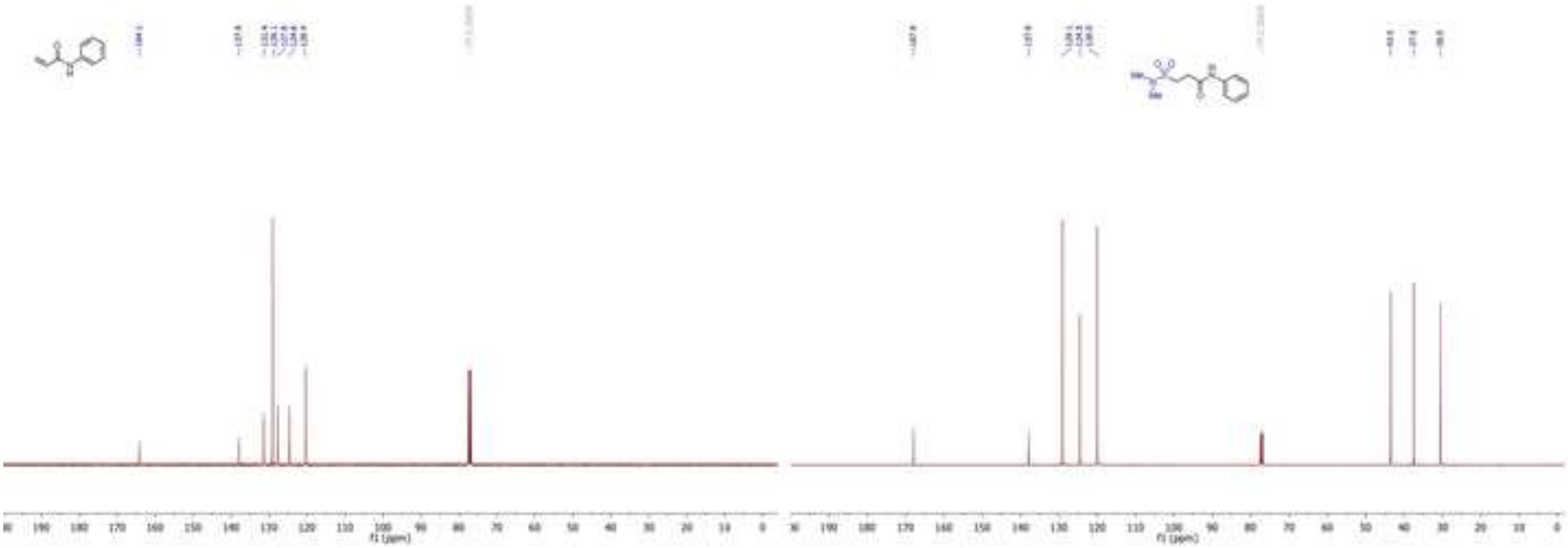

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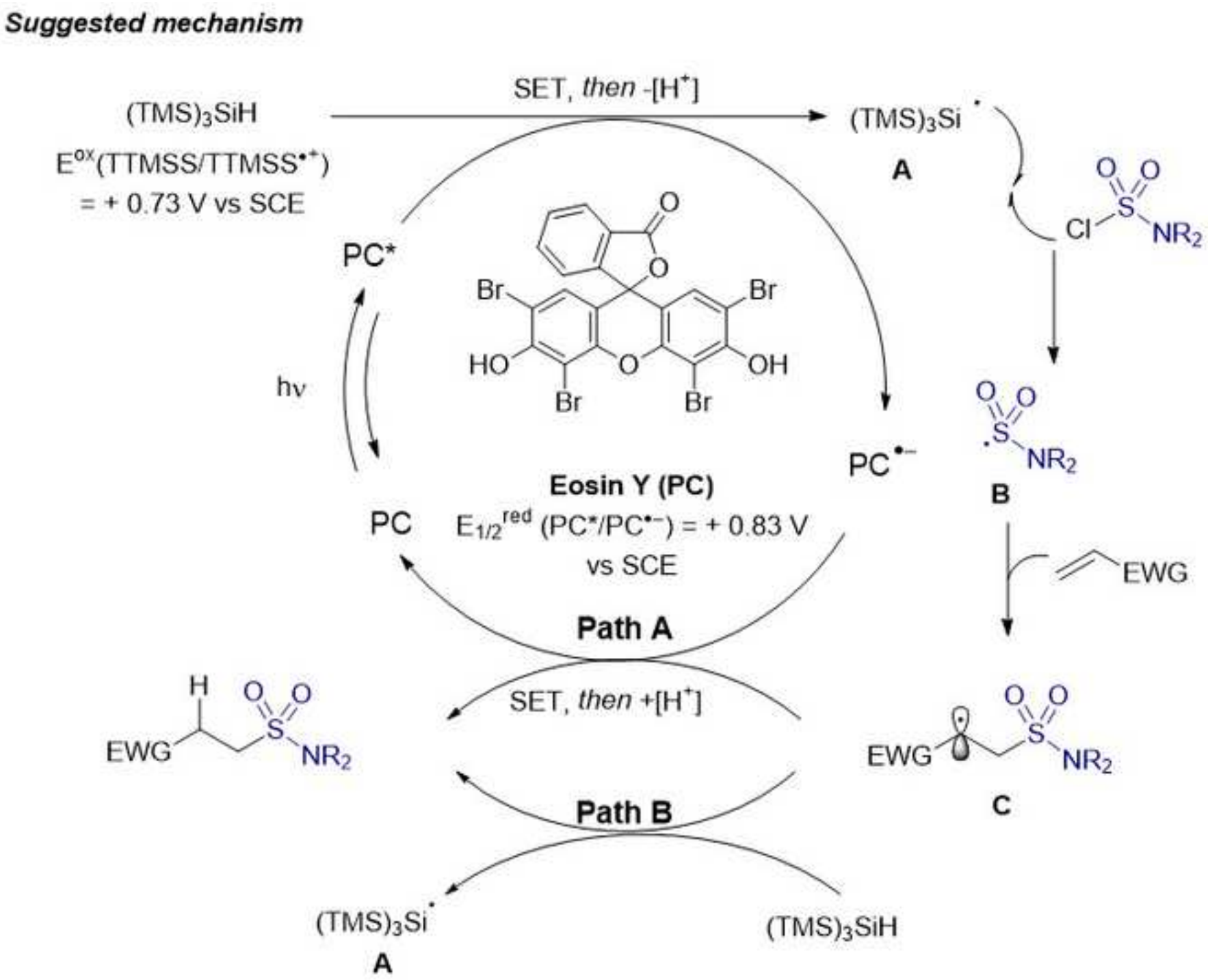

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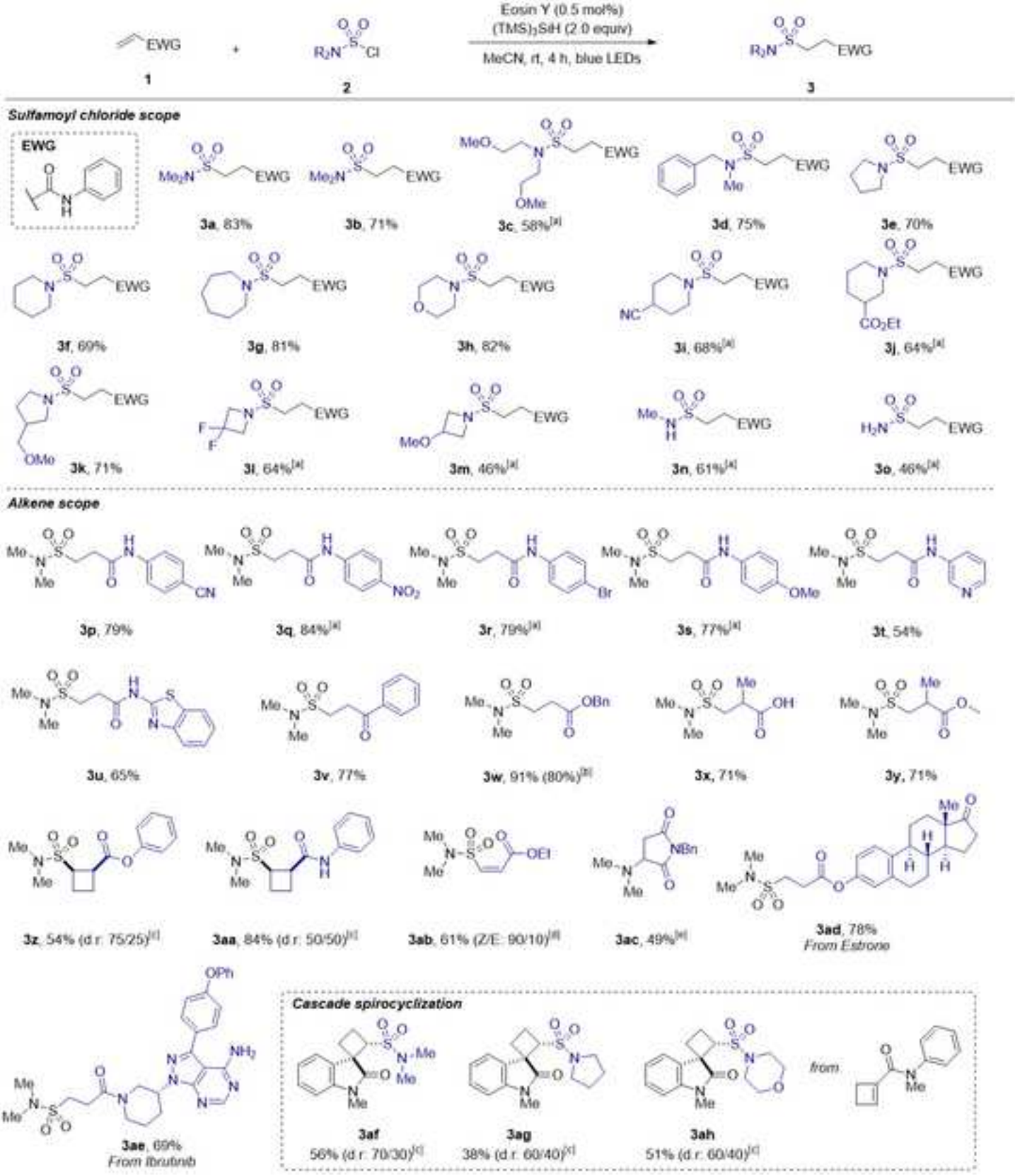

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
Acetonitrile	Sigma Aldrich	34851	for HPLC, ≥99.9%
Biotage			#
Black Polypropylene Screw Caps	Fisherbrand	15394789	-
Blue LED	HepatoChem	P201-18-2 450 nm 18W	-
Capillary tube	Sigma Aldrich	Z114960	volume 5-25 µL
Eosin Y	Sigma Aldrich	E4009	Dye content ~99 %
EtOAc	Sigma Aldrich	34858	for HPLC, ≥99.7%
GraceResolv LOK flash cartridge	Grace	5171343	
Magnetic stirring bar	Biotage	355543	-
N,N-Dimethylsulfamoyl chloride	Sigma Aldrich	D186252	-
N-Phenylacrylamide	Homemade	-	-
Pentane	Sigma Aldrich	34956	for HPLC, ≥99.0%
Photoredox Box	HepatoChem	HCK1006-01-016	-
TLC Silica gel 60 F_{254}	Merck	105554	aluminium sheets 20 x 20 cm
Tris(trimethylsilyl)silane	Combi-Blocks	QF-2110	-
Vial holder	HepatoChem	HCK1006-01-020	-
Vial screw glass 7ml	Samco	T101/V3	-

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Journal of Visualized Experiments

Dear Editor,

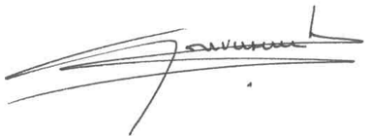
Manuscript number: JoVE61384
Title: "Easy Access to Aliphatic Sulfonamides using Sulfamoyl Chlorides under Visible Light Activation"
Corresponding Author: Professor Véronique Gouverneur

All authors appreciate the time taken by the editor for looking carefully at our manuscript titled "Easy Access to Aliphatic Sulfonamides using Sulfamoyl Chlorides under Visible Light Activation" by Sandrine M. Hell, Claudio F. Meyer, Andrés A. Trabanco, and Véronique Gouverneur.

For convenience, we have answered specifically to all points raised by the editor. An updated version of the manuscript has been uploaded.

We are looking forward to hearing from you.

Sincerely yours,



Modifications of the manuscript.

Line 1:
The title has been re-formatted as such: "EASY ACCESS TO ALIPHATIC SULFONAMIDES USING SULFAMOYL CHLORIDES UNDER VISIBLE LIGHT ACTIVATION".

Line 121,122:
The intensity of the UV lamp has been added: "2.5. Remove the plate from the chamber, dry it under air and expose the plate to UV light (λ = 254 nm) under a lamp (*Rf* values: Starting material = 0.4; Product = 0.2)."

Line 126-128:
The pressure and the speed of the rotary evaporator has been added: "3.1. Transfer the reaction mixture to a 25 mL round-bottom flask and concentrate the mixture under reduced pressure using a rotary evaporator (150 rpm; until 20 mbar) equipped with a water bath, heated to 40 °C to obtain a crude oil."

Line 130,131:
The column specification has been added: "3.2. Condition a silica column (pore size 60 Å, 230 – 400 mesh particle size, 12 g) by passing 60 mL of pentane through the column via a syringe."

Line 138:
The explanation on how to perform a TLC is described is section 2. Section 3.5 has been modified as follow: "3.5. Collect the fractions in test tubes and monitor the collected fractions by TLC (see section 2)."

Line 142,143:
The TLC plate has to be placed in the chamber until solvent front has almost reached the top. This information has been added as follow: "3.7. Run the TLC plate in the chamber until the solvent front has almost reached the top of the plate and compare the *Rf* values (see section 2.5)."

Line 145-147:
The pressure and the speed of the rotary evaporator has been added: "3.8. Collect the desired fractions as determined by TLC analysis and concentrate the solution under reduced pressure on a rotary evaporator (150 rpm; until 20 mbar) equipped with a water bath heated to 40 °C."

Line 149,150:
The definition of NMR is now specified: "3.9. Dissolve 5 mg of the product in 0.6 mL $CDCl_3$ and add this solution to a NMR (Nuclear Magnetic Resonance Spectroscopy) tube."

Line 152,153:
The definition of NMR has been specified above. The solvent in which the NMR has to be done was added: "3.10. Run a ^{1}H NMR and a ^{13}C NMR in $CDCl_3$ and compare the spectra with the information listed below."

Line 166:
"(Figure 4)" has been removed for clarity.

Line 184-190:
The labels [a-e] are describing important informations, which are dependent on the substrates. Those labels should stay as they are.

Line 213,214:
A sentence was added: "Furthermore, sulfonyl chlorides have shown to be reactive under similar reaction conditions.[45]"

References:
The journal names have been now spelt out (see manuscript).