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Aromatic Chlorosulfonylation by Photoredox Catalysis

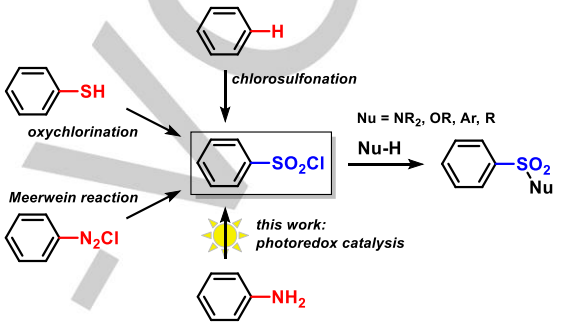
Michal Májek,[a] Michael Neumeier,[a] and Axel Jacobi von Wangelin[a],*

In memory of Prof. Marta Sališová

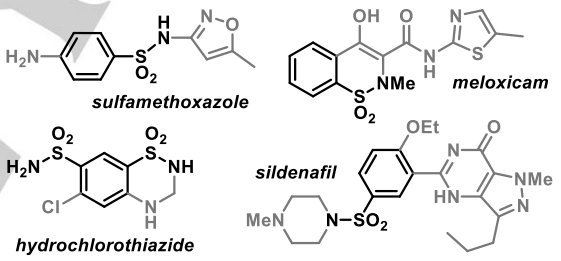
Abstract: Visible light photoredox catalysis enables the efficient synthesis of arenesulfonyl chlorides from anilines. The new protocol involves the convenient *in situ* preparations of arenediazonium salts (from anilines) and the reactive gases SO_2 and HCl (from aqueous thionyl chloride). The photocatalytic chlorosulfonylation operates at mild conditions (room temp., acetonitrile/water) with low catalyst loading (0.5 mol% $Ru(bpy)_3Cl_2$). Various functional groups are being tolerated (e.g. halides, azide, nitro, CF_3, SF_5, esters, heteroarenes). Theoretical and experimental studies support a photoredox catalysis mechanism (Φ 0.027).

Introduction

Sulfonyl chlorides constitute key intermediates in the preparation of numerous organosulfur compounds such as sulfones, sulfonates, and sulfonamides (Scheme 1).[1] Industrial processes via sulfonyl chlorides include the manufacture of fine chemicals, herbicides, pharmaceuticals, and dyes.[1] 17 of the 200 most frequently prescribed drugs in the U.S. contained sulfonamide linkages (Scheme 2).[2] Sulfonylations of alcohols and amines are among the five most widely applied reactions in pharmaceutical research endeavours.[2] Sulfonyl chlorides are also used in functional group protection strategies[3] and the activation of unreactive entities[4] (reactive esters such as triflates, tosylates, mesylates) and the chemical identification of amines (Hinsberg test).[5] Many protocols for the construction of the arenesulfonyl chloride function have been reported (Scheme 1). The direct chlorosulfonation with $ClSO_3H$ has a wide range of applications with simple aromatic substrates but exhibits severe limitations with highly functionalized arenes, when harsh conditions are required, or low regioselectivity is observed.[6] Sulfonyl chlorides can be obtained from the parent sulfonic acids with mild chlorination reagents (e.g. cyanuric chloride) but the preparation of sulfonic acids is governed by the same criteria as the chlorosulfonation.[7] Oxidative chlorinations of thiols allow the preparation of acid-sensitive sulfonyl chlorides. Various combinations of chlorinating agents and oxidant can be used (e.g. aqueous Cl_2, NaOCl/HCl, TMSCl/KNO_3, oxone/KCl or H_2O_2/$SOCl_2$).[8] These methods require the facile access to thiophenols, e.g. by reduction of sulfonyl chlorides or from arenediazonium salts and thiourea (or similar sulfur sources).[9] The first synthesis of arenesulfonyl chlorides from arenediazonium salts by Meerwein was a variation of the Sandmeyer reaction.[10] The protocol was performed in aqueous solution with SO_2 gas and gave mostly low to moderate yields. Arenediazonium salts exhibit very low solubility under these conditions which results in the formation of thick aqueous slurries that exhibit high hazard potential due to poor mixing, local overheating, and run-away reactions. The addition of organic co-solvents afforded slightly improved yields (~50%) but explosive run-away reactions were still observed.[11]



Scheme 1. Methods of preparation of arenesulfonyl chlorides.



Scheme 2. Top-selling pharmaceuticals containing arenesulfonamide linkages

We aimed to develop a photoredox-catalyzed chlorosulfonylation reaction which is driven by visible light in the presence of a photocatalyst and operates in standard reaction vessels under mild conditions. We wished to use organic solvents and avoid the handling of hazardous materials but rather embed the *in situ* generation of all reagents from available starting materials within an overall one-pot reaction protocol (Scheme 3). The use of the irritating and toxic gas SO_2 is impractical under lab-scale conditions. The common solid and liquid surrogates (i.e. sulfite salts, sulfolene, amine-SO_2 adducts, thionyl chloride) are easier to handle and less hazardous.[12] For our purpose, the use of $SOCl_2$ was especially suitable as it is a commercially available liquid, it is soluble in organic solvents, and undergoes rapid hydrolysis by addition of equimolar amounts of water to release two building blocks for the construction of the sulfonyl chloride moiety: SO_2 and HCl.[13] The aromatic electrophile should be generated by diazotization of abundantly available anilines under similar conditions. Polar organic solvents such as acetonitrile exhibit high solubility of anilines, arenediazonium salts, SO_2 and HCl, are miscible with minor amounts of water (for *in situ* hydrolysis of $SOCl_2$) and therefore warrant a homogeneous reaction without the limitations of earlier reports.[11],[14]

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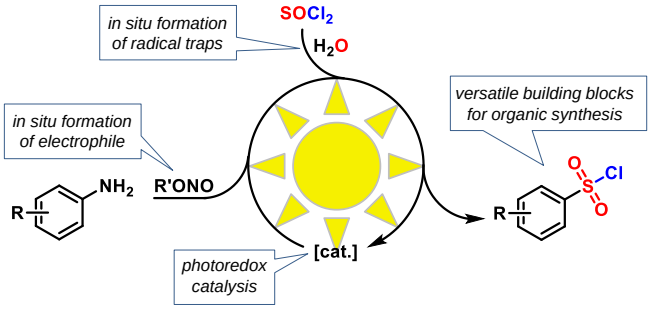
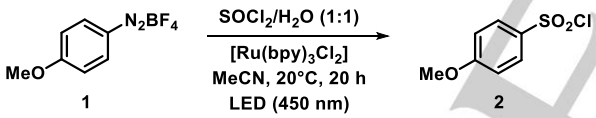


Scheme 3. Concept of photoredox-catalyzed chlorosulfonylation and *in situ* preparation of reagents.

Results and discussion

We initially focused on the development of the photoredox-catalyzed chlorosulfonylation of arenediazonium salts by SO_2 and HCl, with the latter two being formed *in situ* from equimolar $SOCl_2$/water in acetonitrile. The model substrate 4-anisole-diazonium tetrafluoroborate (**1**) was chosen since electron-rich arenediazonium salts were unreactive in a recently reported Meerwein protocol.[13] Optimization of the chlorosulfonylation of **1** in the presence of 0.5 mol% of the photocatalyst tris(2,2'-bipyridine)ruthenium(II)dichloride and blue light afforded 4-anisole-sulfonyl chloride (**2**) in excellent yield (Table 1).[15]

Table 1. Selected optimization experiments.[a]

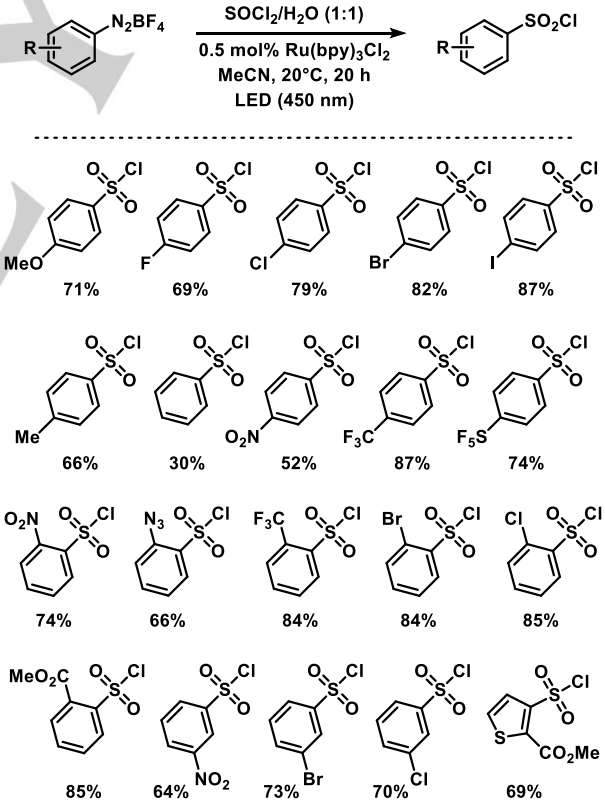


entry	c[1] in M	equiv. $SOCl_2/H_2O$	mol% [cat.]	Yield [%]
1	0.17	5	5	18
2	0.17	5	1	29
3	0.17	5	0.5	48
4	0.17	10	0.5	16
5	0.67	2.5	0.5	69
6	**0.67**	**5**	**0.5**	**96 (83)[b]**
7	1	5	0.5	95
8[c]	0.17	5	2.5	5
9[d]	0.67	5	0.5	<1
10	0.67	5	-	<2

[a] General procedure: A solution of 4-anisolediazonium tetrafluoroborate (**1**, 0.5 mmol), $SOCl_2$/water (1/1), and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ in acetonitrile was irradiated with a blue LED (450 nm, 3.8 W) for 20 h at 20°C. Yields of **2** were determined after aqueous quench and phase separation by GC-FID vs. 1-dodecanenitrile; [b] *in situ* formation of diazonium salt from 4-methoxy-aniline and 1.1 equiv. *i*-amyl nitrite; [c] Eosin Y·Na_2 instead of $Ru(bpy)_3Cl_2$, green LED (535 nm); [d] dark reaction.

With higher catalyst concentrations, hydrodefunctionalization was observed (entries 1, 2).[16] Higher excess amounts of $SOCl_2/H_2O$ led to low yields, possibly due to the strongly acidic conditions and/or the interference of single-electron transfer (SET) with SO_2 (entry 4). Interestingly, the reaction could also be performed in combination with the *in situ* generation of the anisolediazonium salt in a one-pot procedure (entry 6, in parentheses). The use of eosin Y, with similar redox properties,[17] resulted in very low conversion (entry 8) which is a consequence of dye protonation to the photo-inactive state.[18]

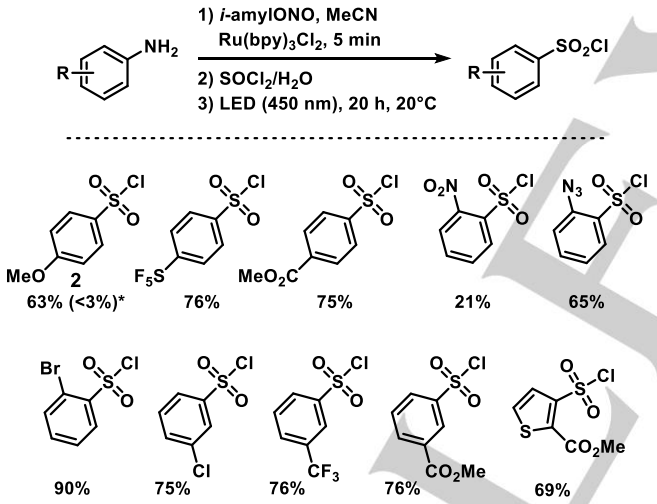
A set of 20 arenediazonium salts were then subjected to the optimized reaction conditions (Scheme 4, isolated yields are given).[15] It is important to note that the arenesulfonyl chlorides are volatile compounds so that precautions have to be taken when isolating the products. The GC yields of all products were >80%. The conditions exhibited exceptionally high functional groups tolerance; substrates with halide, azide, ester, nitro, CF_3, SF_5, and thiophene substituents were cleanly reacted. This protocol is a significant expansion of earlier methods which were not applicable to electron-rich and halide-bearing arene-diazonium salts, respectively.[10],[11],[13] However, pyridine-bearing substrates gave complex product mixtures which is in accord with the generally low stability of pyridinediazonium salts.[19]



Scheme 4. Photocatalytic chlorosulfonylation of arenediazonium tetrafluoro-borates (isolated yields are given, all GC yields >80%).

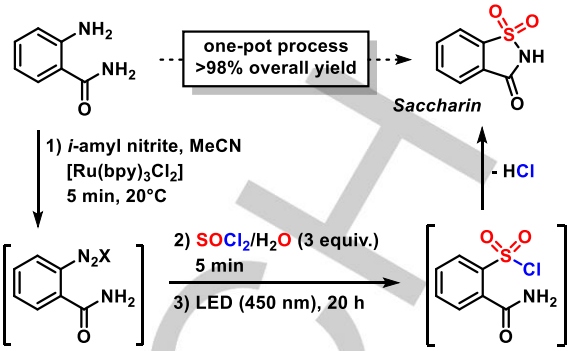
The high stability of the formed arenesulfonyl chlorides toward further photocatalytic single-electron transfer is remarkable in view of their significant electrophilicity and the redox potential of excited $[Ru(bpy)_3]^{2+}$.[20] Prolonged reaction times showed only very slight erosion of the yields of the arenesulfonyl chlorides by hydrodechlorosulfonylation. For example, 4-anisolesulfonyl chloride (**2**) slowly underwent defunctionalization under the photocatalytic reaction conditions with less than 5% of anisole being formed from **2** after 30 h.[15] Similarly high chemoselectivity was observed with the 4-iodo derivative which was not susceptible to reductive SET-activation under photocatalysis conditions.[21]

We then combined the standard procedure with the generation of arenediazonium salts under the reaction conditions.[22] The resultant three-step one-pot protocol involves the *in situ* preparation of all three components (arenediazonium salt, SO_2 and HCl) and their photoredox-catalyzed reaction to give arenesulfonyl chlorides (Scheme 5).[15] Interestingly, most of the one-pot reactions starting from anilines gave higher yields than the corresponding protocols starting from arenediazonium salts (Scheme 4). The low yield of the 2-nitrobenzenesulfonyl chloride is due to a sluggish diazotation reaction between the deactivated 2-nitroaniline and the mild nitrosonium source *iso*-amylnitrite.



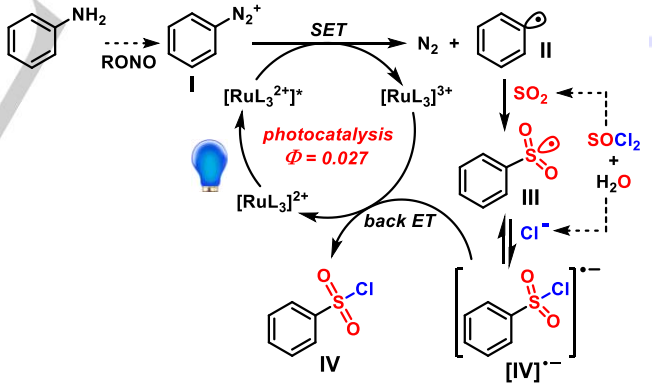
Scheme 5. Synthesis of chlorosulfonates from anilines by *in situ* diazotation-chlorosulfonation (isolated yields are given, all GC yields >80%; * reactions without catalyst and light, without catalyst with light, with catalyst without light afforded **2** in GC yields of <3%, respectively).

The great utility of arenesulfonyl chlorides for further chemical manipulation was probed with the synthesis of saccharin.[23] The photocatalytic chlorosulfonylation of 2-aminocarbonylbenzenediazonium tetrafluoroborate afforded saccharin as single isolable product in 70% yield after intramolecular sulfoxamidation. Surprisingly, a one-pot procedure starting from the commercial fluorescent label anthranilamide without isolation of the arenediazonium intermediate gave quantitative conversion to saccharin (>98% yield, Scheme 6).



Scheme 6. First photoredox-catalyzed one-pot synthesis of saccharin.

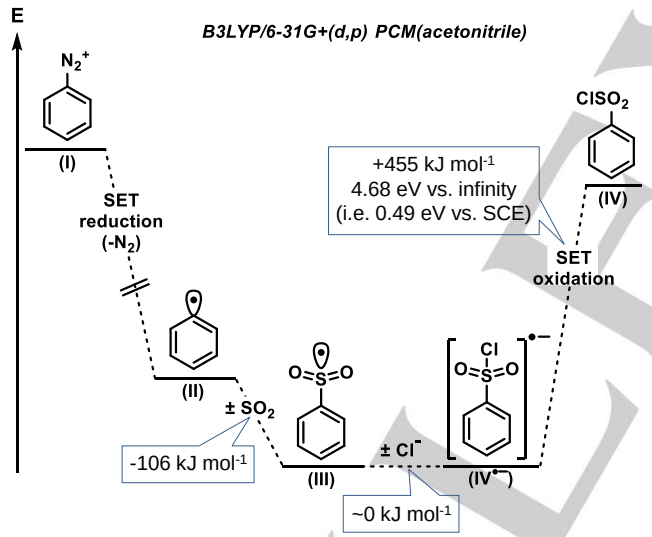
Based on our previous works on related photoredox-catalyzed reactions of arenediazonium salts,[17],[24] we have proposed a mechanism of this chlorosulfonation (Scheme 7): The arenediazonium salt **I** undergoes facile SET-reduction with the excited photocatalyst to the reactive aryl radical (**II**) which is rapidly trapped by the good *n*-donor SO_2. The resultant stabilized *S*-centered sulfonyl radical **III** reacts with chloride anion to give the radical anion $[\mathbf{IV}]^{\bullet-}$. Back-electron transfer with the oxidized form of the catalyst, $[Ru(bpy)_3]^{3+}$, affords the neutral arenesulfonyl chloride **IV**. Only with very unstable diazonium salts and/or at elevated temperatures, minor amounts of the aryl chloride were detected. Reductive activation of the arenesulfonyl chlorides does not occur under the reaction conditions. Nucleophilic substitution at the sulfonyl chloride was also not observed.



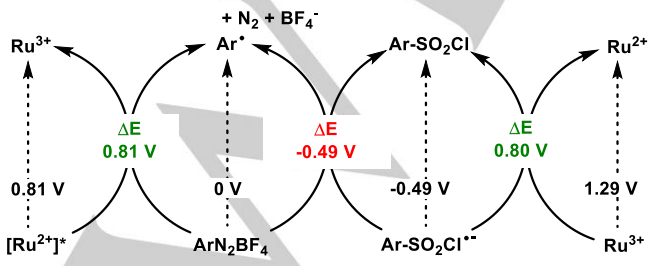
Scheme 7. Postulated reaction mechanism of the photoredox-catalyzed chlorosulfonylation. For quantum yield determination, see below and ESI.

DFT calculations were performed to rationalize the key steps of the proposed reaction mechanism (Scheme 8). These suggest a high thermodynamic driving force of the radical trapping of **II** with SO_2 to give arenesulfonyl radical **III** which is irreversible under the reaction conditions (stabilization greater than 100 kJ/mol). This is consistent with our observation that rapid aryl radical trapping proceeded with relatively low amounts of the trapping reagent SO_2 in comparison with literature reports of other electron-donor traps.[25] The competing pathway is H atom

abstraction from the solvent.[16] Moreover, the high stability of arenesulfonyl radicals vs. aryl radicals is also documented by the recent development of a photocatalytic sulfoxide synthesis by reaction of arylsulfenium ions with π-electron donors.[26] Our calculations show that the addition of the chloride anion onto the sulfur-centered radical **III** is energetically neutral and barrierless. Even if a slow back-electron transfer from the radical anion [**IV**]$^{\bullet-}$ to the catalyst would not impair the overall reaction selectivity. Both intermediates **III** and [**IV**]$^{\bullet-}$ are the global thermodynamic sinks of the reaction and do not undergo side reactions. The predicted redox potential of the couple **IV** / [**IV**]$^{\bullet-}$ is 0.49 V vs. SCE which is fully consistent with the experimental value.[27] We have analyzed the thermodynamics of the half-reactions of the redox couples present in the standard reaction mixture (Scheme 9). The excited catalyst [Ru^{2+}]* can easily reduce the arenediazonium salt in a highly exergonic process ($\Delta G = -zF\Delta E$). On the other hand, the radical anion [**IV**]$^{\bullet-}$ is not sufficiently reducing to convert the arenediazonium salt (ΔE -0.49 V). The only species capable of oxidation of [**IV**]$^{\bullet-}$ is the oxidized form of the photocatalyst [Ru^{3+}]. This back-electron transfer is required for a closed photocatalytic cycle. We have determined a reaction quantum yield of Φ = 2.7%[15] using a modified setup of the total photon flux counter by Riedle et al.,[28] which suggests that radical chain processes are not operating.



Scheme 8. Thermodynamic reaction profile obtained from DFT calculations.



Scheme 9. Reaction potentials of the half-reactions (vs. SCE). Redox potentials of $Ru(bpy)_3Cl_2$ and arenediazonium salts were taken from ref. [15].

Conclusions

We have developed a methodology which allows efficient transformations of anilines to sulfonyl chlorides upon the sequential combination of *in situ* preparations of the three reagents arenediazonium salt, sulfur dioxide, and HCl with a photoredox-catalyzed three-component reaction. Equimolar thionyl chloride and water were employed as liquid sources of SO_2 and HCl; the mild nitrosonium reagent *i*-amyl nitrite afforded the arenediazonium intermediates. The three-component assembly of arenesulfonyl chlorides is driven by visible light in the presence of 0.5 mol% $Ru(bpy)_3Cl_2$ as photocatalyst at room temperature. The proposed mechanism has been corroborated by DFT calculations and photochemical studies. This method is another example of the potential of chemical synthesis at the interfaces of three distinct physical entities: visible light, a liquid and gaseous phase.[24b],[29] Future efforts in our group will aim at the development of related multi-component photocatalyses with easily available gaseous reagents.

Experimental Section

Full experimental details and characterization of compounds are provided in the Supporting Information.

General procedure for the chlorosulfonylation of arenediazonium tetrafluoroborates: A vial (6 mL) was charged with a magnetic stir bar, the arenediazonium salt (1.0 mmol), and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.5 mol%). The vial was sealed with an aluminium-capped septum. Acetonitrile (1.5 mL) was added and the solution was purged with N_2 for 5 min. Then, water (90 µL, 5.0 mmol) and thionyl chloride (0.36 mL, 5.0 mmol), were added (Careful! Exothermic reaction!). The solution was irradiated with an external LED (455 nm, 3.8 W) at 20°C. After 20 h, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by SiO_2 gel column chromatography in *n*-pentane/ethyl acetate.

General procedure for the chlorosulfonylation of anilines: A vial (6 mL) was charged with a magnetic stir bar, the parent aniline (1.0 mmol), and $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (3.7 mg, 0.5 mol%). The vial was sealed with an aluminium-capped septum. Acetonitrile (1.5 mL) was added and the solution was purged with N_2 for 5 min. *iso*-Amyl nitrite (0.16 mL, 1.2 mmol) was added and the reaction mixture was stirred for 5 min at 20°C. Then, water (90 µL, 5.0 mmol) and thionyl chloride (0.36 mL, 5.0 mmol) were added (Careful! Exothermic reaction!). The reaction was irradiated with an external LED (455 nm, 3.8 W) at 20°C. After 20 h, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by SiO_2 gel column chromatography in *n*-pentane/ethyl acetate.

Acknowledgements

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Keywords: photoredox catalysis • sulfonylation • aromatic substitution • photochemistry • ruthenium

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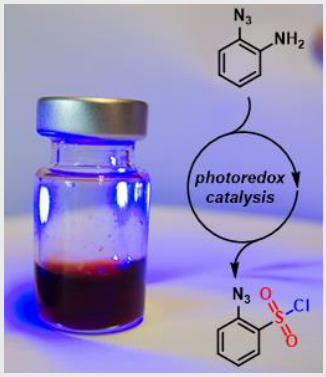
COMMUNICATION

A new method of chlorosulfonylation of anilines with visible light has been developed. The protocol combines the *in situ* generation of the three reactive reagents (arenediazonium salt, SO_2, and HCl) from readily available starting materials with the photoredox-catalyzed three-component addition to give diversely functionalized arene-sulfonyl chlorides.



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