ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2016, 52, 10918

Received 24th July 2016,
Accepted 12th August 2016

DOI: 10.1039/c6cc06111g

www.rsc.org/chemcomm

Metal-free C–H sulfonamidation of pyrroles by visible light photoredox catalysis†

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We report a one-step procedure for the preparation of *N*-(2-pyrrole)-sulfonamides from sulfonamides and pyrroles. The reaction uses visible light, an acridinium dye as photocatalyst and oxygen as the terminal oxidant for the oxidative C–N bond formation; structures of several reaction products were confirmed by X-ray structure analysis. The reaction is selective for pyrroles, due to the available oxidation power of the photocatalyst and the required stability of the carbocation intermediate under the reaction conditions.

Sulfonamides are an important class of organic compounds[1,2] finding applications in medicinal chemistry *e.g.* as Janus kinase (JAK) inhibitors for treating psoriasis and other inflammatory skin disorders,[3] HCV NS5B polymerase inhibitors for the treatment of hepatitis C virus,[4] and GPAT (glycerol 3-phosphate acyltransferase) inhibitors.[5] The heterocyclic sulfonamide drug rosuvastatin (Fig. 1), a HMG-CoA reductase inhibitor, was among the worldwide most sold pharmaceuticals in 2011[6] and 2013.[7]

Typical C–H sulfonamidation methods require transition metals[8,9] as for example the palladium-catalyzed intermolecular coupling of aryl chlorides and sulfonamides under microwave irradiation (Scheme 1a),[10] the palladium-catalyzed intramolecular sulfonamidation of imines,[11] the iridium-catalyzed reactions of arenes[12,13] and heteroarenes with sulfonyl azides (Scheme 1b),[14] and the copper-mediated C–H sulfonamidation, which requires stoichiometric amounts of copper.[15] Another approach is the sulfonamidation of indoles by stoichiometric amounts of iodine.[16–18] In 2008 Moeller *et al.* developed an intramolecular sulfonamidation of alkenes by electrochemical oxidation of electron-rich double bonds and subsequent C–N bond formation with a sulfonamide anion[19–22] and in 2013 Nicewicz *et al.* published the catalytic anti-Markovnikov intramolecular hydroamination following a similar concept. They oxidized the alkene with the organic photocatalyst 9-mesityl-10-methylacridinium[23] followed by an intramolecular reaction with the sulfonamide.[24–26] Recently, Nicewicz and co-workers extended this method to a site-selective C–H amination by oxidizing electron-rich aromatics with an acridinium dye and subsequent reaction with amines.[27]

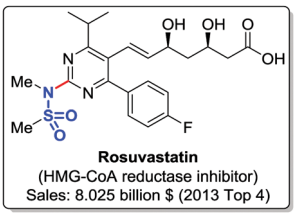
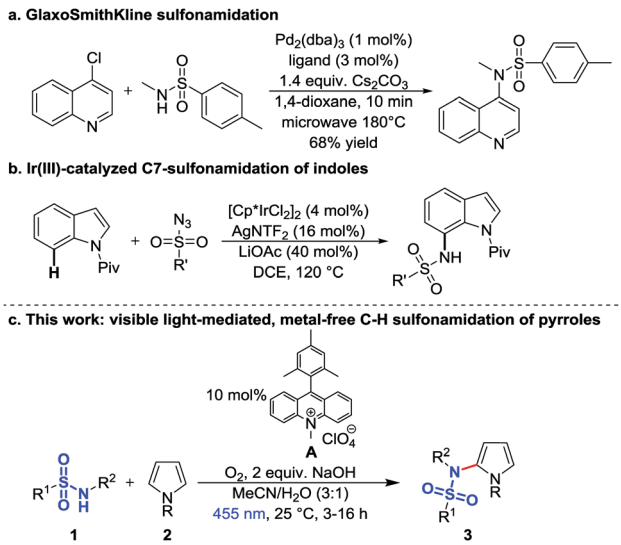


Fig. 1 The sulfonamide drug rosuvastatin.



Scheme 1 Transition metal-catalyzed and photocatalytic reactions for C–H sulfonamidations.

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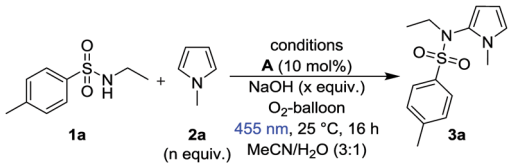
† Electronic supplementary information (ESI) available: Procedures, synthesis, spectroscopic, and crystallographic data. CCDC 1494732–1494736. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc06111g

‡ Both authors contribute equally to this work.

Table 1 Optimization of the reaction conditions



Entry	Conditions	Yield[a] [%]
1	**A** (10 mol%), n = 20, x = 2, 3 h	98
2	**A** (10 mol%), n = 20, x = 2, 6 h	99
3	**A** (10 mol%), n = 20, x = 2	99
4	No photocatalyst, n = 20, x = 2	—
5	**A** (10 mol%), n = 20, x = 2, no light	—
6	No photocatalyst, n = 20, x = 2, no light	—
7	**A** (10 mol%), n = 20, x = 2, no base	—
8	**A** (10 mol%), n = 20, x = 2, no oxidant	16
9	**A** (10 mol%), n = 10, x = 2	99
10	**A** (10 mol%), n = 5, x = 2	95
11	**A** (5 mol%), n = 20, x = 2	83
12	**A** (10 mol%), n = 20, x = 1	40

[a] Determined by GC analysis with naphthalene as internal standard.

However, for the synthesis of many drug motifs an intermolecular sulfonamidation of heteroarenes would be useful. A particular interesting target structure in this respect is pyrrole due to its presence in many biologically important compounds[28–33] and active drugs, *e.g.* atorvastatin,[34] one of the best-selling drugs of the last years.[32,35,36] Based on previous results we have therefore developed a metal-free photocatalytic C–H sulfonamidation of pyrroles using blue light, the commercially available organic dye 9-mesityl-10-methylacridinium perchlorate (**A**) as photocatalyst, oxygen as the terminal oxidant and sodium hydroxide as base (Scheme 1c).

The reaction conditions were optimized by irradiating a mixture of *N*-ethyl-4-methylbenzene-1-sulfonamide (**1a**), *N*-methylpyrrole (**2a**), 9-mesityl-10-methylacridinium perchlorate (**A**), sodium hydroxide and oxygen with blue light at room temperature. Different catalysts, bases, oxidants, varying amounts of trapping reagent and different irradiation times were investigated (Table 1).

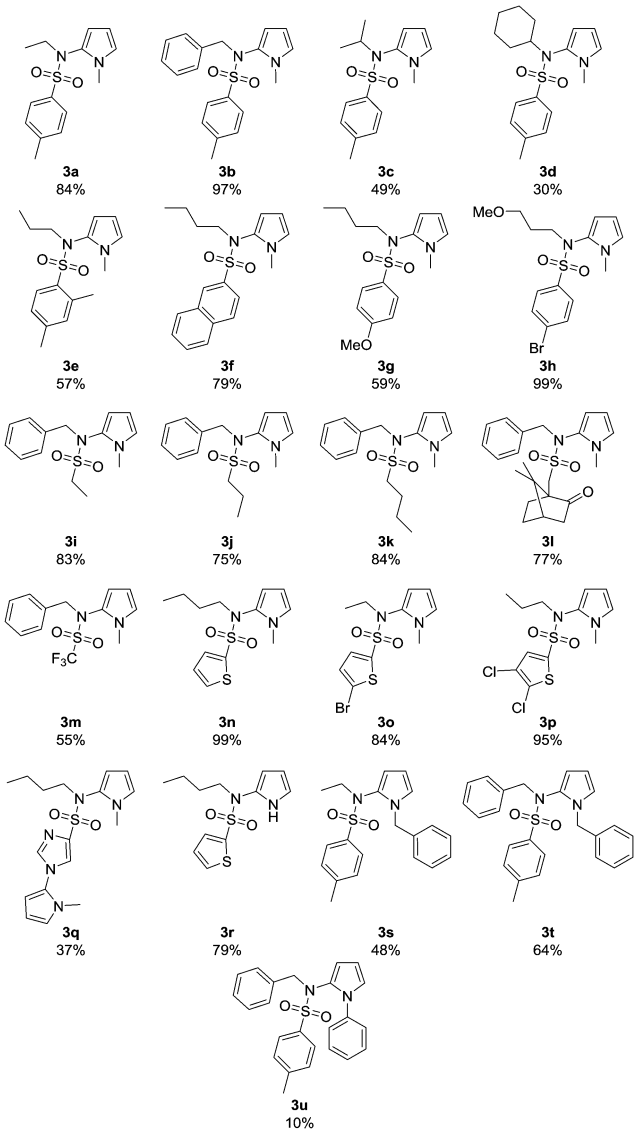
In a typical reaction mixture for the photocatalytic reaction, one equivalent of the sulfonamide **1a**, 20 equivalents of *N*-Me-pyrrole (**2a**), two equivalents of sodium hydroxide and 10 mol% of 9-mesityl-10-methylacridinium perchlorate (**A**) in a mixture of MeCN/H_2O (3 : 1) with an oxygen-balloon were used to give **3a** in 98% yield for 3 h and 99% yield for 6 and 16 hours, respectively, (Table 1, entries 1–3). The catalyst with tetrafluoroborate as counter ion is working equally good in the reaction. Control experiments without photocatalyst, light or base, confirmed that all components are necessary for product formation (Table 1, entries 4–7). Without oxygen balloon the yield dropped to 16% (Table 1, entry 8). The excess of the heteroarene **2a** can be reduced to 10 equiv. with still quantitative product yields and 5 equiv. giving 95% yield (Table 1, entries 9 and 10). A catalyst loading of 5 mol% gave 83% of **3a** and just one equivalent of sodium hydroxide decreased the yield to 40% (Table 1, entries 11 and 12). Nitrobenzene (18%) and ammonium persulfate are not suitable oxidants (see ESI,† Table S1, entries 1 and 2). The bases potassium hydroxide (45%), potassium phosphate (36%), potassium *tert*-butoxide (31%) and the weak bases potassium carbonate (13%), cesium carbonate (6%) and cesium fluoride (no product formation) are less efficient (see ESI,† Table S1, entries 3–8). Other photocatalysts like $Ru(bpy)_3Cl_2$[37] and eosin Y[38–40] were tried for the oxidation under various conditions, but no product formation occurred.

The scope of the reaction was explored using the optimized reaction conditions (Table 1, entry 3): various sulfonamides **1**, *N*-substituted pyrroles **2** (5–20 equiv.), 10 mol% 9-mesityl-10-methylacridinium perchlorate (**A**), blue light irradiation, oxygen as terminal oxidant, sodium hydroxide (2 equiv.) as base and acetonitrile/water (3 : 1) as solvent mixture. As depicted in Table 2, all expected products **3a–v** were obtained (yield 10–99%). *N*-Me-pyrrole (**2a**) reacted with various sulfonamides **1** in moderate to excellent yields of 30–99%. The R^1 moiety can be an aromatic group (toluene **3a–3d**, *m*-xylene **3e**, naphthalene **3f**, 4-methoxybenzene **3g**, and 4-bromo-benzene **3h**), an alkyl rest (primary alkyl chains **3i–3k**, the bulky 10-camphor **3l**, and trifluoromethane **3m**) or a heteroarene (thiophene derivatives **3n–3p**, and imidazole **3q**). The reaction with the imidazole sulfonamide **1q** resulted in two C–N bond formations (**3q**), as the base can deprotonate the imidazole moiety, which reacts with a second molecule **2a**. A benzyl-trifluorosulfonamide group was introduced to *N*-methylpyrrole in compound **3m** in 55% yield. The R^2 group was varied using different primary (**3a**, **3e–3h**, **3n–3q**) and secondary alkyl chains (**3c**, **3d**) and benzyl (**3b**, **3i–3m**). Electron donating or electron withdrawing substituents are generally well tolerated. The bromide and chloride substituents (**3h**, **3o**, **3p**) allow further synthetic modifications of the coupling products. Sulfonamides **1r–1t** with R^2 = phenyl are not converted as their anions are less nucleophilic. Several pyrrole derivatives, such as **2b**, *N*-benzylpyrrole (**2c**) and 1-phenylpyrrole (**2d**) led to the products **3r** (79%), **3s** (48%), **3t** (64%), and **3u** (10%), respectively. The molecular structures of compounds **3b–3d**, **3j**, and **3r** were confirmed by X-ray single crystal analysis (Fig. 2).

While a wide variety of *N*-alkyl sulfonamides can be used in the reaction, the scope of the heterocycle undergoing C–N arylation is limited. The sulfonamidation proceeds selectively with pyrroles; the reaction under identical conditions using furan, thiophene, indole, anisol or dimethoxybenzene does not yield the expected product and starting materials are re-isolated. In a reaction mixture with **2a** and furan (1 : 1), product **3a** is formed exclusively from **1a** in comparable yield to a reaction in absence of furan. This high specificity of the reaction can be explained by the limited oxidation power of the excited acridinium photocatalysts and the required sufficient stability of the heterocycle and its radical cation under the reaction conditions for a clean conversion with sulfonamide anions as nucleophiles.[41] The formation of specific aggregates can also not be excluded.

In 2004 Fukuzumi *et al.* reported an excited state reduction potential (E_{red}^*) of 1.88 *vs.* SCE (in PhCN)[23] for the charge transfer triplet (CT^T) state of 9-mesityl-10-methylacridinium. Verhoeven *et al.* stated E_{red}^* = 1.45 V *vs.* SCE (in MeCN) for the locally excited triplet (LE^T) state.[42] The dye has been very well

Table 2 Substrate scope (isolated yields)



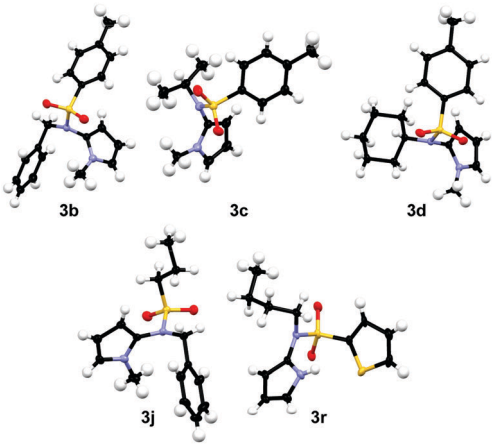


Fig. 2 Crystal structures of compounds **3b–3d**, **3j** and **3r**.

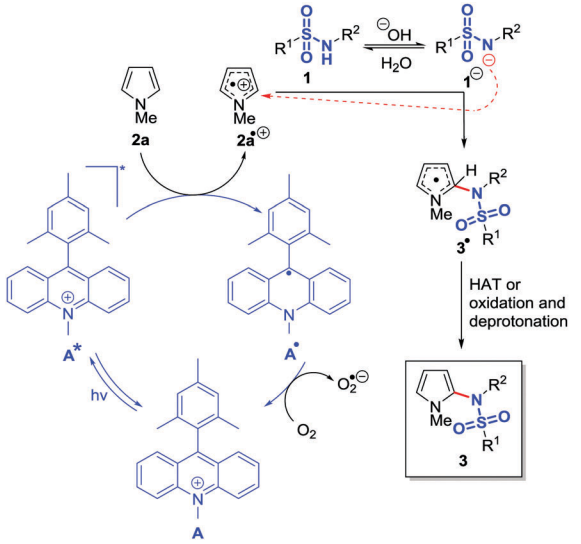


Fig. 3 Proposed catalytic cycle for the visible light-mediated C–H sulfonamidation of *N*-methylpyrrole (**2a**).

investigated in the last decade revealing a charge transfer singlet (CT^S) state with E_{red}^* = 2.08 V *vs.* SCE (in MeCN) and a locally excited singlet (LE^S) state with E_{red}^* = 2.18 V *vs.* SCE (in MeCN).[23,42–45] Nicewicz *et al.* used acridinium dyes to oxidize alkenes[24,46–50] and electron-rich arenes[27] to their corresponding radical cations and subsequently trapped them with suitable nucleophiles. Our proposed mechanism (Fig. 3) is based on the reported catalytic cycles and mechanistic investigations, and is supported by cyclic voltammetry measurements. Photocatalyst **A** is excited by blue light irradiation. *N*-Methylpyrrole (**2a**) has an oxidation potential of 1.20 V *vs.* SCE (in MeCN, see ESI†) and can be therefore easily oxidized by **A*** to $\mathbf{2a}^{\bullet+}$. Oxygen regenerates **A** resulting in the formation of superoxide $O_2^{\bullet-}$.[27,43,45,51]

Under the reaction conditions, sulfonamide **1** is partly deprotonated by sodium hydroxide and the resulting anion $\mathbf{1}^-$ reacts as nucleophile with the radical cation of **2a**. The process was studied in detail by Moeller *et al.* for the intramolecular reaction between radical cations of alkenes and sulfonamides.[19–22] Superoxide $O_2^{\bullet-}$ may abstract a hydrogen from $\mathbf{3}^\bullet$ yielding the desired product **3**.[27] Alternatively, oxidation and deprotonation steps may yield the product.

The excited state of the organic dye 9-mesityl-10-methylacridinium (**A**) is able to oxidize pyrroles to the corresponding radical cation, which is subsequently attacked by sulfonamide anion nucleophiles. Reoxidation and deprotonation or hydrogen atom transfer from the resulting radical intermediate results in products of an oxidative C–H sulfonamidation in the 2-position of pyrrole. The mild metal free photocatalytic oxidation protocol does not require prefunctionalized starting materials such as aryl halides or arylboronic acids or the use of less stable sulfonyl azides. A plausible reaction mechanism was proposed and is

supported by electrochemical investigations. The method may find use in the synthesis of functionalized *N*-pyrrole sulfonamides, which are interesting structures with potential pharmaceutical activity.

This work was supported by the German Science Foundation (DFG) (GRK 1626). A. M. thanks the Fonds der Chemischen Industrie for a scholarship. We thank Dr Rudolf Vasold for GC-MS measurements and Ms Regina Hoheisel for cyclic voltammetry measurements.

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