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A Visible-Light-Driven, Metal-free Route to Aromatic Amides via Radical Arylation of Isonitriles

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Abstract. The photochemical metal-free carboamidation of aryl radicals has been exploited for the preparation of aromatic amides, including hetero- and polyaromatic derivatives, under visible light irradiation of arylazo sulfones in the presence of isocyanides in aqueous acetonitrile. The process was useful for the smooth preparation of the antidepressant moclobemide.

Keywords: benzamides; metal-free arylation; aryl radicals; visible light; arylazo sulfones.

Due to the widespread presence of the arylamide moiety in both natural- and non-natural bioactive compounds[1,2] including anticancer,[3] antiviral agent[4] and antidepressant,[5] the introduction of the amide group onto an aromatic ring is a challenge in organic synthesis.[6]

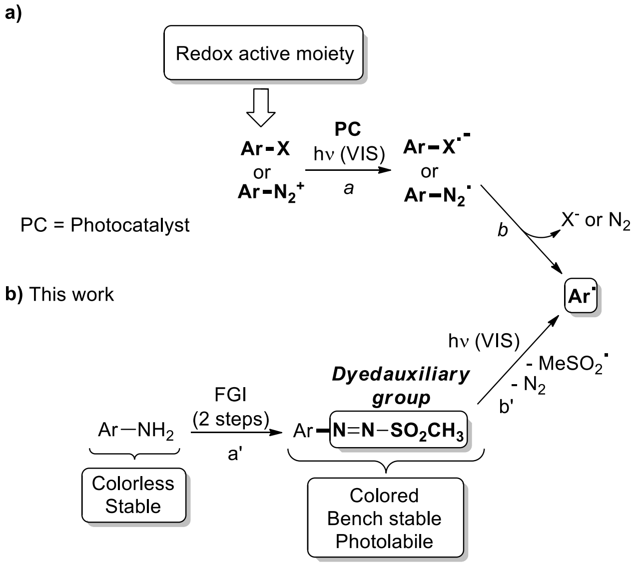
Apart from the activation of aromatic acids (or their derivatives) in the presence of amines under either homogeneous[7] or heterogeneous[8] conditions, other approaches are based on the formation of an Ar-C bond, such as the transition metal catalyzed aminocarbonylation of (hetero)aryl halides (mainly iodides),[9] and sulfonates.[10] More recently, the metal-free coupling of aryl diazonium salts with isonitriles has been described by the groups of Grimaud[11a] and Zhu.[11b] In the proposed mechanism, an aryl radical was thermally generated and then trapped by the isocyanide to form an aryl imidoyl radical[11b] that, in turn, underwent single electron transfer (SET) reaction and hydration of the resulting imidoyl cation.[11b]

Excellent results were obtained with arenediazonium salts bearing electron withdrawing substituents,[11] and in one case a strategy involving the in situ formation of the diazonium salts have been tested.[11a]

Aryl radicals could be also generated under visible light photoredox catalyzed reactions of arene diazonium salts ($Ar\text{-}N_2^+$)[12] or aryl halides (mainly iodides, Ar-I).[13] The aromatics underwent here a photocatalyzed SET and the desired $Ar^{\bullet}$ were formed upon fragmentation of the Ar-N bond in $ArN_2^{\bullet}$ or of the Ar-I bond in $ArI^{\bullet -}$ (Scheme 1a, paths a, b).[14]

The presence of a redox active moiety is mandatory to allow the SET between the photoexcited catalyst (PC*, in the role of reductant) and the starting substrate.[15] Despite the impressive advancements reported in this field, to the best of our knowledge, a photoredox carboamidation process of aromatics is still limited.[16]

We recently introduced a new class of substrates namely arylazo sulfones as suitable precursors of aryl radicals[17] under visible light irradiation. Such compounds could be smoothly prepared in two steps (Scheme 1b, paths a') starting from colorless and stable anilines, via diazotization and treatment of the obtained diazonium salt with sodium methanesulfinate (see experimental section and supporting information for further details). The amino group is then converted into a colored, bench stable but yet photolabile moiety ($-N_2SO_2CH_3$).[17] We propose now that such structural motif that imparts both color and photoreactivity is dubbed as *dyedauxiliary group,* in analogy to the electro-auxiliary groups.[14] Arylazo sulfones were recently applied to the metal- and photocatalyst-free synthesis of (hetero)biaryls.[17] We thus reasoned that arylazo sulfones are the ideal substrates to develop an uncatalyzed, metal-free radical route to benzamides, via arylation of isonitriles (Scheme 1b).

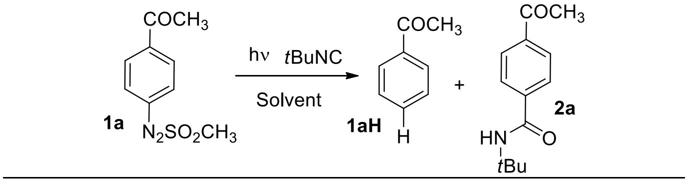


Scheme 1. a) Visible light photoredox generation of aryl radicals from redox active Ar-X; b) Photocatalyst-free, visible light generation of aryl radicals from arylazo sulfones bearing a dyedauxiliary group.

With this aim, the photoreactivity of a model compound, 1-(methylsulfonyl)-2-(4-acetylphenyl)diazene **1a** was tested in the presence of *tert*-butyl isocyanide and the results are depicted in Table 1. Early experiments were carried out in a solar simulator equipped with a 500 W Xenon lamp. Irradiation in non-anhydrous CH_2Cl_2 (entry 1) led exclusively to the photoreduced acetophenone **1aH**. Shifting to ethyl acetate, **1aH** was again observed in small amounts, along with traces of the desired benzamide **2a** (entry 2).

Similar results were obtained in neat acetonitrile, **1aH** remaining predominant, along with a 6% yield of **2a** (entry 3). However, when replacing part of the organic solvent with water, the yield of acetophenone **1aH** was halved, in favor of **2a** that became the major product though obtained in a low yield (20%, entry 4). Less satisfactory results were observed in acetone/water 9:1 mixture (entry 5). Doubling the concentration of **1a** resulted in a lowering of the arylation efficiency (**2a** isolated in only 5% yield, entry 6). Gratifyingly, the addition of 2 equiv. of a buffering agent ($NaHCO_3$) to the reaction mixture resulted in a significant increase of the benzamide yield, though the amount of **1aH** was still significant (entry 7). Higher amounts of isocyanide (up to 5 equiv., 0.5 M) gave **2a** in 51% yield (entry 8). We then investigated the role of the light source. Low pressure Hg lamps emitting in the UV region (310 and 366 nm, entries 9,10) were used, and **2a** was obtained in 44% and 33% yield, respectively.

Table 1. Optimization of the reaction conditions. [a]



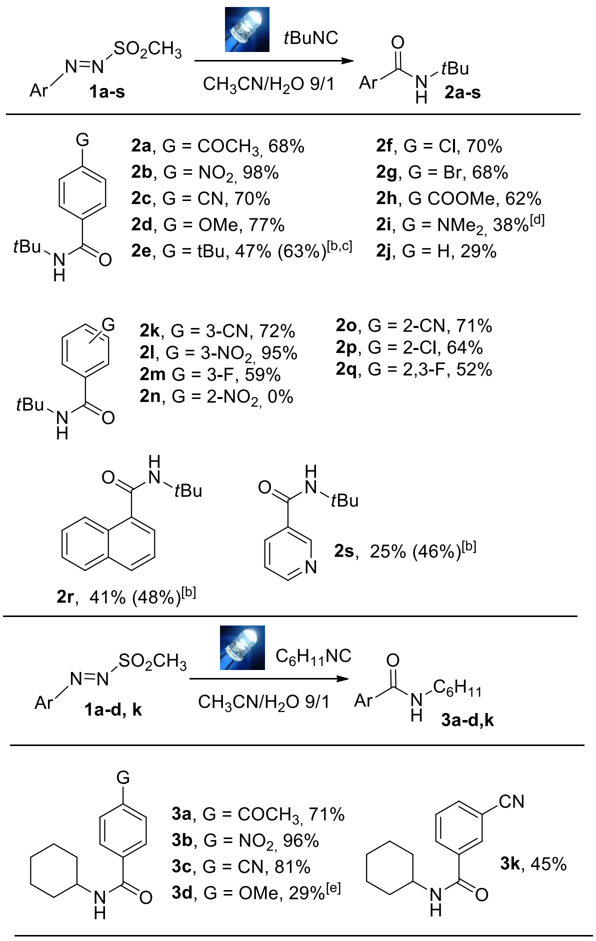
Entry	Solvent	Conditions	Products (% yield)
1	CH_2Cl_2	**1a** (1 mmol), *t*BuNC (4 equiv.) SolarBox[b]	**1aH**, 18
2	CH_3COOEt	**1a** (1 mmol), *t*BuNC (4 equiv.) SolarBox[b]	**1aH**, 4; **2a**, 3
3	CH_3CN	**1a** (1 mmol), *t*BuNC (4 equiv.) SolarBox[b]	**1aH**, 30; **2a**, 6
4	CH_3CN/H_2O 9:1	**1a** (1 mmol), *t*BuNC (4 equiv.) SolarBox[b]	**1aH**, 14; **2a**, 20
5	Acetone/H_2O 9:1	**1a** (1 mmol), *t*BuNC (4 equiv.) SolarBox[b]	**1aH**, 18; **2a**, 11
6	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (2 equiv) SolarBox[b]	**1aH**, 14; **2a**, 5
7	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (2 equiv.) $NaHCO_3$[c],SolarBox[b]	**1aH**, 20; **2a**, 27
8	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.) $NaHCO_3$[c],SolarBox[b]	**1aH**, 5; **2a**, 51
9	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.) $NaHCO_3$[c],366 nm[d]	**1aH**, 13; **2a**, 33
10	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.), $NaHCO_3$[c],310 nm[e]	**1aH**, 12; **2a**, 44
11	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.) $NaHCO_3$[c],410 nm[f]	**1aH**, 12; **2a**, 55
12	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.) $NaHCO_3$[c],450 nm[g]	**1aH**, 12; **2a**, 68
13[h]	CH_3CN/H_2O 9:1	**1a** (2 mmol), *t*BuNC (5 equiv.) $NaHCO_3$[c]	-
14	CH_3CN/H_2O 9:1	**1a** (2 mmol), $NaHCO_3$[c], 450 nm[g]	**1aH**, 60

[a] Reaction conditions. **1a** (1-2 mmol), tBuNC (2-5 equiv) in the chosen solvent (2 mL). A 100% consumption of **1a** was observed in all cases. [b]Irradiation was carried out by using a solar simulator equipped with a 500 W Xenon lamp, outdoor + IR filter. t_{irr} = 16 h. [c] 2 equiv. [d]15 W Hg phosphor coated lamp, t_{irr} = 24 h; [e]15 W Hg phosphor coated lamp, t_{irr} = 24 h; [f]1 W LED, λ_{em} = 410 nm, t_{irr} = 24 h; [g]1 W LED, λ_{em} = 450 nm, t_{irr} = 24 h. [h] Blank experiment in the absence of light.

Interestingly, when moving to visible light sources the arylated product was formed in satisfactory amounts, especially with a 1W 450 nm LED (entry 12). No arylation took place in the absence of light (entry 13). Finally, irradiation of **1a** in the absence of tBuNC exclusively led to **1aH** (entry 14).

The conditions described in entry 12 were thus adopted to investigate the synthetic scope of the reaction. A set of arylazo sulfones (**1a-s**) was then synthesized in variable yields (see supporting information for further details) and irradiated in the presence of *tert*-butyl isocyanide.

Table 2. Photochemical synthesis of *N*-alkyl arylamides **2,3**.[a]



[a] Reaction conditions: **1a-s** (0.1 M), isocyanide (0.5 M), NaHCO$_3$ (2 equiv.) in MeCN/H$_2$O 9/1 irradiated for 24 h (1 W LED, λ_{em} =450 nm). A 100% consumption of **1** was observed in all cases.

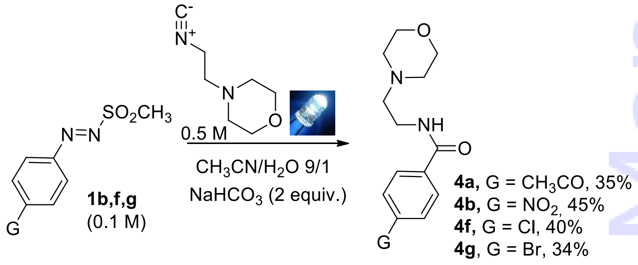
[b] a 1 W LED, λ_{em} = 410 nm was used

[c] 21% of *tert*-butylbenzene **1eH** was detected by means of GC analyses

[d] 15% of *N,N*-dimethylaniline **1iH** was detected by means of GC analyses

[e] 15% of anisole **1dH** was detected by means of GC analyses

As depicted in Table 2, para- substituted *N-tert*-butylbenzamides **2a-i** were mainly obtained in highly satisfactory amounts from the corresponding arylazo sulfones, except for aminoderivative **2i** isolated in 38% yield along with a significant amount of *N,N*-dimethylaniline **1iH** (15%). When using 4-*tert*-butylphenylazo sulfone **1e**, best results were obtained by using a 410 nm LED (*tert*-butylbenzene **1eH** was also found as side product). The parent phenylazo sulfone **1j** afforded the corresponding amide **2j** in a poor yield (29%). Ortho- and meta- substituted benzamides **2k-m,o-p** as well as 2,3-difluorobenzamide **2q** were isolated in satisfactory amounts, but the reaction was unsuccessful with 2-nitrophenylazo sulfone **2n**. Finally, 1-naphthyl (**2r**) and 3-pyridyl (**2s**) derivatives were likewise obtained in discrete yields (48 and 46% respectively) upon 410 nm LED irradiation. We then extended the scope of the reaction to other isocyanides. Arylation of cyclohexyl isocyanide took place efficiently when using electron poor substrates **1a-c**, and also 3-cyano derivative **3k** was isolated in a modest yield. On contrast, the synthesis of **3d** was not clean. The process was finally applied to the synthesis of the antidepressive moclobemide (**4f)** and its analogues (**4a,b** and **4g**)[18] (Scheme 2), that were obtained in discrete yields (34-45%) from the corresponding aromatic precursors and commercially available 2-morpholinoethyl isocyanide.

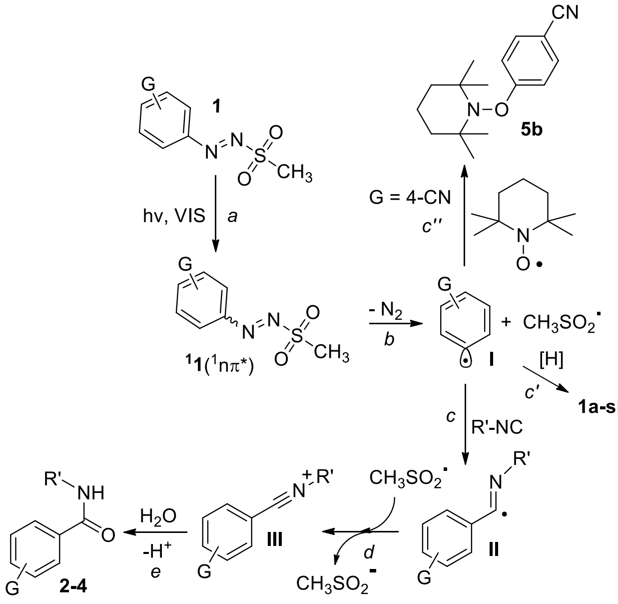


Scheme 2. Photochemical synthesis of moclobemide **4f** and its analogues **4a,b** and **4g**.

The photochemistry of arylazo sulfones was investigated in details by our research group.[17] In particular, the selective generation of aryl radicals and aryl cations has been demonstrated by simply tuning the irradiation wavelength (visible light for the former ones and UVA light for the latter ones). Accordingly, excitation of substrates **1a-s** at 450 or 410 nm promoted the substrate to its singlet nπ* excited state, which underwent homolysis of the N-S bond to give, after N$_2$ loss, aryl radicals **I** (Scheme 3, paths a, b) that were subsequently trapped by the chosen isocyanide to give imidoyl radical **II**. The chemistry of aryl radicals has been deeply studied in the past.[19] Thus, when generated in the presence of a hydrogen donor, homolytic hydrogen atom transfer (path c'). is favored (see Table 1, entry 14). However, under the optimized conditions, trapping of **I** by the isonitrile moiety took place faster than hydrogen abstraction, and reduced **1a-sH** were observed only as the minor products. Replacing part of the organic solvent having labile C-H bonds with water was beneficial for the process. Oxidation of **II**,[20] by a SET reaction has been reported as feasible[21] and we propose that methanesulfonyl radical acts here as oxidant in the formation of the nitrilium ion **III**[22] responsible for the formation of the desired benzamides **2-4** upon water addition (paths d, e).[23]

Methanesulfinic acid generated during the process,[17] can likewise act as hydrogen donor.[24] The presence of $NaHCO_3$, however, was probably able to prevent the formation of this acid and thus limiting the formation of products **1a-sH.**

In order to deepen the mechanism involved, the reaction of **1b** with *t*BuNC was conducted in the presence of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)[11b, 13d] as a radical trap. Notably, arylation was suppressed in favor of the formation of adduct **5b** (16% yield, path c").



Scheme 3.

The present work describes a visible light induced metal-free way to prepare aromatic amides starting from bench stable and easy synthesizable arylazo sulfones in aqueous organic solution. Notably, both the conditions used (e.g. the solvents and the excess of isocyanide employed) and the isolated yields of the arylamides are comparable with those described in analogous thermal processes involving diazonium salts.[11b] Contrary to what was observed with arenediazonium salts, however, the high compatibility of arylazo sulfones with tertiary amines allowed for the use of basic isocyanides such as 2-morpholinoethyl isocyanide, which has been exploited in the preparation of the antidepressant moclobemide and its analogues.

Experimental Section

Synthesis of arylazo sulfones 1a-s. Diazonium salts were prepared just before use from the corresponding anilines[25] and purified by dissolving in acetone and precipitation by adding cold diethyl ether. To a cooled (0 °C) suspension of the appropriate diazonium salt (1 equiv, 0.3 M) in CH_2Cl_2 was added sodium methanesulfinate (1 equiv. except where indicated see Supporting Information for further details) in one portion. The temperature was allowed to rise to room temperature and the suspension stirred overnight. The resulting mixture was then filtered and the solvent evaporated under vacuo from the resulting solution. The raw product was purified by dissolution in cold CH_2Cl_2 and precipitation by adding n-hexane.

General Procedure for the synthesis of benzamides 2-4. To a solution (5 mL) of aryl azosulfone **1a-s** (0.5 mmol, 0.1 M) and the isocyanide (2.5 mmol, 0.5 M) in MeCN−H_2O 9:1 The resulting solution was divided were in two portion and poured into two Pyrex vials. 2 Equiv. of $NaHCO_3$ were then added and the mixture purged for 2 min with nitrogen and irradiated at 450 nm for 24 h. The course of the reaction has been followed by both GC and HPLC analyses. The photolyzed solution was then concentrated and the crude residue purified by column chromatography (eluant, cyclohexane/ethyl acetate mixture).

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COMMUNICATION

A Visible-Light-Driven, Metal-free Route to Aromatic Amides via Radical Arylation of Isonitriles

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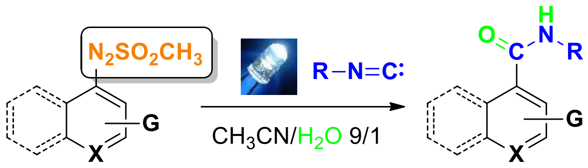

G = H, NMe_2, OMe, tBu, Cl, Br
CN, $COCH_3$, COOMe, NO_2
X = CH, N