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A photoredox-neutral Smiles rearrangement of 2-aryloxybenzoic acids†

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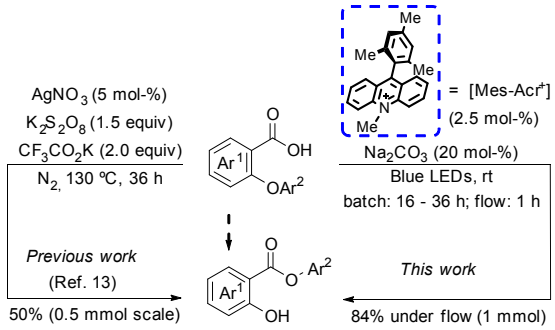
We report on the use of visible-light photoredox catalysis for the radical Smiles rearrangement of 2-aryloxybenzoic acids to obtain aryl salicylates. The method is free of noble metals, operationally simple and the reaction can be run under mild batch or flow conditions. Being a redox neutral process, no stoichiometric oxidants or reductants are needed.

Introduction

Salicylic acid is a natural product that plays an important role in plant defence against pathogens, and regulates many other functions in plants.[1] Among a variety of bioactive salicylate derivatives, we can find phenyl salicylate, which is used in medicine under the name of Salol and as a pro-drug with low gastric irritation.[2] The capacity of this compound to absorb in the region of 290-325 nm, make it useful as a UV filter in the manufacture of paints, adhesives, waxes, varnishes and other materials.[3] This compound is also a key precursor for salicylamides (Salol reaction)[4] and cyclic salicylate acetals.[5] These applications make Salol derivatives attractive targets to develop efficient routes for their preparation.

A convenient approach to obtain aryl salicylates involves the modular Ullman coupling of easily available 2-halobenzoic acids with phenols, followed by the Smiles rearrangement. This latter rearrangement has found widespread applications in organic synthesis, mainly through an intramolecular nucleophilic aromatic substitution.[6] Originally, this rearrangement was developed under ionic conditions and, consequently, the *ipso*-attack onto the aromatic ring was significantly accelerated by the presence of electron-withdrawing groups at *orto*/*para* positions. Different varieties of the ionic rearrangement have been developed, including the Truce-Smiles[7] and the Ugi-Smiles[8] versions. The group of Speckamp was the first to develop a radical version for the Smiles rearrangement.[9] Later on, several research groups have exploited this radical version in diverse elegant transformations, where the presence of activating substituents in the migrating unit is not required.[10]



Scheme 1. Smiles rearrangement of 2-aryloxybenzoic acids

The first radical Smiles rearrangement of 2-aryloxybenzoic acids was already reported in 1972, but only one example was described and UV-light ($\lambda > 280$ nm) was used as a promoter.[11] Importantly, it is also documented that upon exposure to UV-irradiation, phenyl salicylate undergoes photodegradation (oxidation and Fries rearrangement), limiting the synthetic utility of this method.[12] To the best of our knowledge, the next study on this reactivity was published very recently by Hossina and Jana, while exploring the silver catalyzed oxidation of 2-aryloxybenzoic acids.[13] The reaction was conducted at 130 °C, and instead of the expected decarboxylative dibenzofuran formation, a Smiles rearrangement was observed to provide aryl-2-hydroxybenzoates (Scheme 1). Mechanistic studies suggested that oxidation of the carboxylate produces a carboxyl radical that attacks intramolecularly the *ipso*-carbon of the aryl ether, followed by 1,5-aryl migration and finally hydrogen abstraction from the solvent (CH_3CN).

In recent times, visible-light promoted photoredox catalysis has emerged as a sustainable synthetic tool to generate radicals from carboxylic acids at room temperature.[14] However, the use of expensive and toxic nobel-metal-catalysts (Ru and Ir) is a major concern in the synthesis of bioactive compounds, especially on a large scale. Therefore, the use of cheaper and more sustainable organic photocatalysts is a good alternative.[15]

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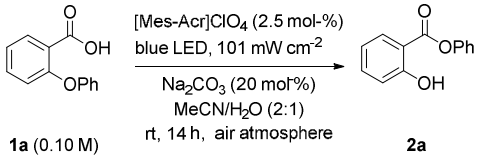
In this scenario, we planned the above mentioned transformation[16] with the inexpensive and commercially available Fukuzumi photocatalyst (Mes-Acr$^+$ = PC).[17] Given its high oxidation potential [$E_{1/2}$ (PC+*/PC$^\bullet$) = +2.12 V *vs* SCE], this photocatalyst allows the visible light promoted oxidation of carboxylic acids to generate carboxyl radicals.[18] Importantly, we reasoned that the phenoxyl radical obtained after the rearrangement could be able to oxidize the Mes-Acr$^\bullet$ radical [$E_{1/2}$(PC$^+$/PC$^\bullet$) = - 0.55 V *vs* SCE], enabling the turnover of the catalyst without using any stoichiometric oxidant (redox neutral process). Other salient features of this protocol are: (a) room temperature reaction, (b) substoichiometric amounts of base, (c) nobel-metal free, (d) reduced reaction times and scale-up using continuous flow conditions (Scheme 1).[19]

Results and discussion

To optimize the radical Smiles rearrangement, we used 2-phenoxybenzoic acid (**1a**) as a model substrate. After screening different conditions (Table 1), we obtained the best results (entry 1) using a 2:1 CH_3CN/H_2O as the solvent mixture, [**1a**] = 0.10 M, 20 mol-% of Na_2CO_3, 2.5 mol-% of Mes-Acr$^+$ and irradiation at room temperature over 14 h with blue LEDs (λ_{max}= 456 nm, 101 mWxcm^{-2}). Gratifyingly, inert atmosphere was not critical for the success of this reaction (entry 2). These conditions contrast with those reported by Li and coworkers,[19] where Ar atmosphere was required as well as an anhydrous media to complete the reaction in 26-48 h. In comparison, our protocol is operationally simpler, more robust and faster. Regarding the light source, we observed that one bulb of blue LEDs (12 x 1 W) was optimal (entries 1 and 3), while white light was slightly less efficient when LEDs were used (entry 4) and completely inefficient when a CFL was employed (entry 5).[20] Shorter times (entry 6), higher concentrations of substrate (entry 7), or other solvent mixtures (entries 8-10) also afforded compound **2a** in diminished yields. As expected, control experiments revealed that the presence of both, the photocatalyst and the visible-light, was essential for the success of the reaction (entries 11 and 12). However, the reaction worked even in the absence of Na_2CO_3, although in lower yield (entry 12). This result can be explained considering that the photoexcited catalyst [(Mes-Acr$^+$)*] is oxidant enough to remove one electron from acid **1a** ($E_{1/2}^{ox} = +2.04$ V *vs* SCE), but the carboxylate anion is a better reductive quencher ($E_{1/2}^{ox} = +1.77$ V *vs* SCE, Figure S13 in ESI).

Table 1. Optimization of the reaction conditions

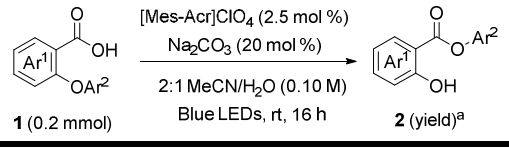


1a (0.10 M) **2a**

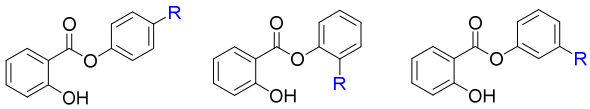
Entry	Deviation from above	Yield (%)[a]
1	None	88 (76)
2	Under argon[b]	85 (75)
3	Blue LEDs 2 bulbs (12 x 1 W)	89
4	White LED bulb (12 x 1 W)	71
5	CFL 18 W	0
6	8 h	74
7	[**1a**] = 0.18 M	70
8	In MeCN/H_2O (1:1)	63
9	In acetone/H_2O (2:1)	79
10	In *t*-BuOH/H_2O (2:1)	23
11	No photocatalyst	0
12	No light	0
13	Without Na_2CO_3	60

[a] GC yields using durene as internal standard, while in brackets yields determined for isolated pure products. [b] Using three cycles of freeze-pump-thaw. LED = Light Emitting Diode. CFL = Compact fluorescent lamp.

Table 2. Substrate scope



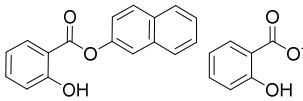
1 (0.2 mmol) **2** (yield)[a]



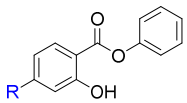
R = H, **2a** (75%)
R = Cl, **2b** (75%)
R = F, **2c** (70%)
R = Me, **2d** (85%)
R = OMe, **2e** (0%)[b]; (80%)[c]
R = NO_2, **2f** (0%)

R = Cl, **2g** (73%)
R = Me, **2h** (75%)
R = OMe, **2i** (58%)[b]; (75%)[c]
R = allyl, **2j** (75%)

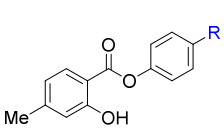
R = Cl, **2k** (60%)
R = OMe, **2l** (35%)[b] (70%)[c]



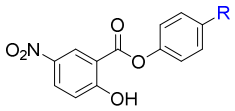
2m (80%)[d] **2n** (75%)[d]



R = Me, **2o** (75%)
R = Cl, **2p** (67%)[d]
R = Br, **2q** (60%)
R = OPh, **2r** (64%)



R = Me, **2s** (70%)
R = F, **2t** (60%)



R = H, **2u** (54%)
R = F, **2v** (67%)
R = Me, **2w** (56%)

[a] Unless otherwise noted, the reaction was performed using 2:1 CH_3CN/H_2O as solvent, without deoxygenation and during 16 h. Yields were determined for isolated pure products. [b] t = 60 h. [c] Run in 2:1 $(ClCH_2)_2/H_2O$, in combination with 10 mol-% of $(PhS)_2$, over 10 h. [d] Run in 2:1 $(ClCH_2)_2/H_2O$.

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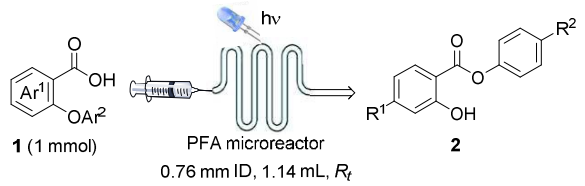
Having found these optimized conditions, we next evaluated the scope of the reaction with diverse substituted 2-aryloxybenzoic acids, which were prepared through Ullman cross-coupling of 2-halobenzoic derivatives with phenols (Table 2). Initially, we evaluated substrates with substituents introduced in the phenol component (**1a**-**1n**, Figure S2 in ESI). Products with electron-withdrawing substituents, such as chloro (**2b**, **2g**, **2k**) or fluoro (**2c**); or weak electron-donating groups, such as methyl (**2d**, **2h**), were obtained in good yields. Notably, the allylic functionality was well tolerated (product **2j**), without observing any oxidation or further modification. Noteworthy, nitro substrate **1f**, which is activated for ionic Smiles rearrangement through intramolecular S_NAr, failed to give **2f** under our reaction conditions. Moreover, substrates derived from 1- and 2-naphthols also gave the expected products (**2m**, **2n**) in good yields, but using 2:1 $(ClCH_2)_2/H_2O$ to improve the solubility of substrates. In contrast to the results obtained by Li and coworkers,[19] compounds derived from methoxy phenols (**1e**, **1i** and **1l**) were poor substrates under our optimized conditions. However, using $(PhS)_2$ as a HAT cocatalyst,[21] the corresponding products (**2e**, **2i** and **2l**) were obtained with significant higher yields and within shorter reaction times. On the other hand, diverse substituents in the benzoic acid component were well tolerated under our mild conditions, including alkyl groups (**2o**, **2s** and **2t**), halogens (**2p** and **2q**), phenoxy (**2r**) and nitro group (**2u**, **2v** and **2w**).

Table 3. Reactions using continuous flow conditions[a]



Product	Yield (%)[b]	R_t (min)	Productivity (mmoL/h)	
			Batch[c]	Flow[d]
2a: R^1, R^2 = H, H	84	43	0.010	0.172
2b: R^1, R^2 = Cl, H	69	60	0.009	0.093
2o: R^1, R^2 = H, Me	70	60	0.009	0.097

[a]Run in 2:1 CH_3CN/H_2O (8 mL, 0.125 M), using 2.5 mol-% of Mes-Acr$^+$ and at a flow rate to achieve the residence time (R_t) reported. [b]Yields were determined for isolated pure products. [c] Data from Table 2. [d] see ESI for details.

To improve the practicability of our protocol, we considered to increase the scale of the reaction. Due to the light attenuation by the reaction media (Lambert-Beer law) and to maintain homogenous irradiation- particularly at large scales- the use of continuous flow reactors is currently one of the best solutions in photoredox catalysis.[22] After some experimentation (Figure S4 in ESI), we accomplished our reaction under flow conditions, obtaining similar yields but within about 1 h of residence time. A small increase in the concentration of substrate and the use of an appropriate PFA microreactor (0.76 mm internal diameter, 1.14 mL of V_R) allowed productivities of products **2a**, **2b** and **2o** at least ten times greater than under batch conditions (Table 3). This significant increase in productivity can be attributed to a better harvesting of the lamp irradiation and clearly it facilitates the scalability of the reaction

We performed some control experiments to gain insight into the reaction mechanism. As expected, the Smiles rearrangement of **1b** was not observed in the presence of radical scavengers such as 2,2,6,6-tetramethyl-piperidinyl-1-oxy (TEMPO) or butylated hydroxytoluene (BHT) (Scheme 2a). This observation is consistent with a free radical mechanism. In another control experiment, we submitted an equimolar mixture of **1b** and **1o** to the standard reaction conditions and the only products observed were **2b** and **2o** by ^{1}H-NMR and GC-MS (Scheme 2b). The absence of crossover products in this experiment supports the intramolecular character of this rearrangement. The lifetime of excited [Mes-Acr$^+$]* in CH_3CN/H_2O (2:1) was determined, in the presence of different concentrations of *in-situ* formed sodium salt of **1a**, using time-correlated single photon counting (TCSPC, Figure S11 in ESI). The emission of [Mes-Acr$^+$]* is clearly quenched by the salt of **1a**, as can be seen in the Stern-Volmer plot (Scheme 2c), indicating a SET between both species. Since both known singlet states of photocatalyst (LE^S or CT^S) are fluorescent, while the long-lived triplet states do not emit, this quenching of fluorescence might indicate that the reaction proceeds (at least partially) through a singlet excited state.[23] Importantly, from the same Stern-Volmer plot, we obtained a quenching constant rate (k_q = 5.3 x 10^9 M^{-1} s^{-1}) near the diffusion limit. In addition, we determined the photochemical quantum yield for the formation of **2a**, using two different light intensities. We obtained a uniform quantum yield (Φ_R) of about 1% for **2a** under our standard conditions (Scheme 2d). This low Φ_R is consistent with the long reaction times needed ($t_R \geq 16$ h) for most substrates and in combination with the fast quenching, indicates that efficient radical chain processes are very unlikely to promote the reaction.

Based on the above commented mechanistic studies, cyclic voltammetry measurements (Table S5 in ESI) and literature precedents, we propose a plausible mechanism for the photoinduced Smiles rearrangement of most substrates examined (illustrated for **1a** in Scheme 3). The photoexcited catalyst is oxidative enough to remove an electron from the corresponding benzoate of **1a** to obtain the corresponding carboxyl radical (ΔG = - 0.35 eV). Given the slow rate of decarboxylation of benzoyloxyl radicals (k = 2 x 10^6 s^{-1})[24] the *ipso* attack to the aryl ether moiety, followed by a 1,5-aryl migration, seems a reasonable pathway. Given the oxidation potential obtained for phenolate **2a** (Fig. S15 in ESI), the corresponding phenoxyl radical can easily oxidize Mes-Acr$^•$(ΔG = - 1.76 eV) , closing the catalytic cycle without requiring any external oxidant (redox neutral process).[25] The final proton transfer from **1a** to phenolate leads product **2a** and resets the carboxylate of **1a**.

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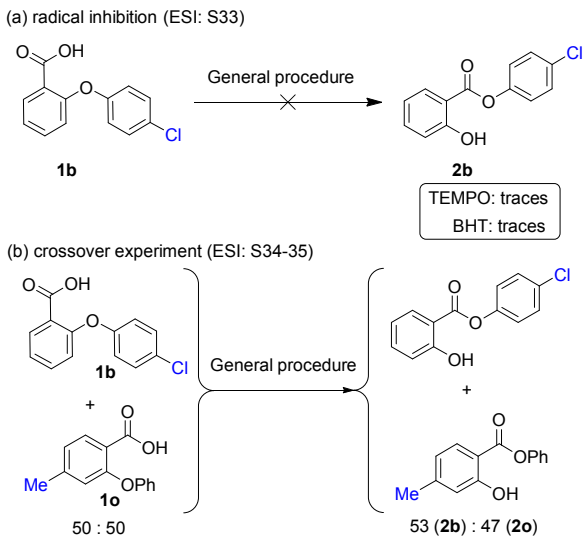
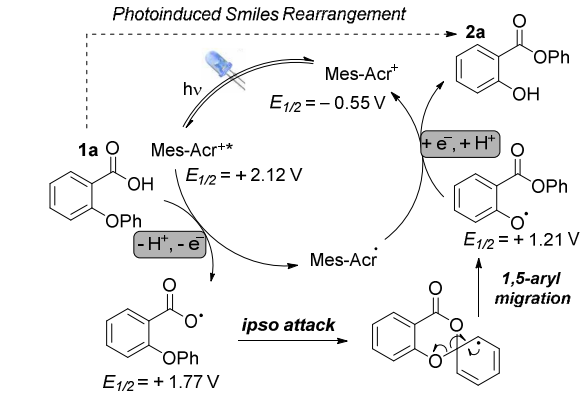


Scheme 2. Mechanistic studies



Scheme 3. Plausible mechanism.

As commented before, to obtain methoxy phenols **2e**, **2i** and **2l,** it was necessary to include $(PhS)_2$ as co-catalyst. We speculated that the higher oxidation potential of the corresponding phenoxyl radical of these substrates makes the driving force of the electron transfer (e.g. $\Delta G° = -2.25$ eV for 2e) greater than the reorganization energy (λ). According to the Marcus theory,[26] the rate of the expected electron transfer decreases in this inverted region, being faster the back electron transfer (BET) from Mes-Acr• to the corresponding benzoyloxyl radical.[27] As proposed by the group of Nicewicz,[21] we believe that *in-situ* generated $PhS^{\bullet}$ [from external $(PhS)_2$] is able to regenerate the Mes-Acr^+, competing with the BET previously mentioned. After protonation of PhS^-, PhSH can transfer a hydrogen atom to obtain the final product, as illustrated for **1e** in Figure S3 (ESI).

Conclusions

In conclusion, a new Smiles rearrangement of 2-aryloxybenzoic acids under mild visible-light activation conditions was presented. The method provides a convenient access to aryl salicylates with diverse substituents, using Mes-Acr^+ as photocatalyst, in the presence of air and water. For methoxylated derivatives, it was necessary to modify the procedure, adding $(PhS)_2$ as co-catalyst. In order to scale-up the reaction, it can also be run under flow conditions, achieving much better productivities. Importantly, the overall reaction proceeds in a redox neutral fashion, avoiding the need for stoichiometric additives. The mechanistic studies accomplished support the proposed working models.

Experimental section

See the ESI†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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27 Given that for most of the substrates this BET is highly exergonic (e.g.: for **1a**, ΔG_{BET} = -2.32 eV), should be located in the Marcus-inverted region, being thereby very slow. On the contrary, for methoxylated substrates this BET is less exergonic (e. g. : for **1e**, , ΔG_{BET} = -1.62 eV), and likely to be fast because should lie in the Marcus-normal region.