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Cerium photocatalyzed radical smiles rearrangement of 2-aryloxybenzoic acids†

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We report herein a cerium photocatalyzed aryl migration from an aryl ether to a carboxylic acid group through radical-Smiles rearrangement. This operationally simple protocol utilizes inexpensive CeCl_3 as a photocatalyst and converted a variety of 2-aryloxybenzoic acids into aryl-2-hydroxybenzoates in good yields.

Introduction

In synthetic organic chemistry, rearrangement reactions offer a unique path to atom-economic synthesis.¹ In this vein, the Smiles rearrangement and its variants² have been found widespread synthetic applications in organic synthesis originally through an intramolecular nucleophilic aromatic *ipso* substitution.³ Typically the aromatic substrates are activated by electron-withdrawing groups at the *ortho* or *para* positions. Initially these reactions were explored in ionic reaction conditions and later was transposed into radical chemistry by Speckamp.⁴ However, the importance of radical-Smiles rearrangement has been realized recently.⁵ The radical Smiles rearrangement allows not only the formal migration of aryl and other unsaturated C–C bonds but is also capable of breaking various $\text{C}(\text{sp}^2)\text{-X}$ ($\text{X} = \text{S}, \text{O}, \text{N}, \text{C}$) bonds.⁶ Different from ionic reaction conditions, the presence of electron-withdrawing groups is not essential in radical Smiles rearrangement.

Various strategies have been developed for aryl-migration.⁶ Notably, aryl migration from an aryl ether through C–O bond cleavage to form a carboxyl ester is rare. In 1955 DeTar and Hlynsky first observed this migration through thermal decomposition of 2-phenoxybenzoyl peroxide.⁷ In 1972 Yang and co-workers reported the first example of radical Smiles rearrangement of 2-aryloxybenzoic acids using UV-irradiation ($\lambda > 280 \text{ nm}$) as a promoter.⁸ In 2016, Hossian and Jana reported silver-catalyzed carboxyl radical-assisted 1,5-aryl migration from 2-aryloxybenzoic acids at 130°C in the presence of stoichiometric amounts of oxidant and base to afford aryl-2-hydroxybenzoates (Fig. 1).⁹

In recent years, visible light driven photocatalysis has emerged as a sustainable synthetic tool in organic chemistry to generate a variety of radical entities from organic molecules.¹⁰ However, the employment of expensive and toxic metal catalysts (Ru

and Ir) in photoredox catalysis is a major concern especially for the synthesis of pharmaceutical compounds, particularly on a large scale. Therefore, the use of cheaper and more sustainable photocatalysts is a good alternative.¹¹ In 2017, independently two groups reported visible light driven efficient aryl migration from an aryl ether to a carboxylic acid group to form an ester.¹² This reaction was catalyzed by perylenediimide (PDI) and the Fukuzumi photocatalyst ($\text{Mes-Acr}^+ = \text{PC}$) and displays a broad substrate scope. Very recently Ye and co-workers¹³ reported dual *N*-heterocyclic carbene/photocatalyzed aryl migration of 2-aryloxy benzaldehydes *via in situ* formation of 2-aryloxy benzoic acids which further participate in radical smiles rearrangement. However, all the reported methods require stoichiometric amounts of oxidant or expensive photocatalysts. An operationally simple and inexpensive method for the efficient aryl migration of 2-aryloxy benzoic acids is still desirable. Although recently, it was found that employing inexpensive chemicals in the visible light photocatalysis is a robust alternative to generate carbon radicals under mild reaction conditions.¹⁴ In particular CeCl_3 was recently discovered to be a ligand-to-metal charge transfer (LMCT) activation manifold to trigger the generation of oxygen centered radicals from alcohols and carboxylic acids.¹⁴ In continuation of our research interest on visible light driven cerium photocatalysis,¹⁵ we herein report a mild protocol for the 1,5-aryl migration of 2-aryloxy benzoic acids using 10 mol% CeCl_3 .

Results and discussions

At first, we initiated our study utilizing 2-phenoxybenzoic acid (**1a**) as a model substrate and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as an oxidant. A

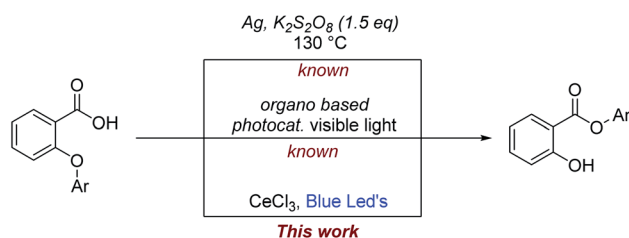


Fig. 1 Known reports for 1,5-aryl migration of 2-aryloxybenzoic acids.

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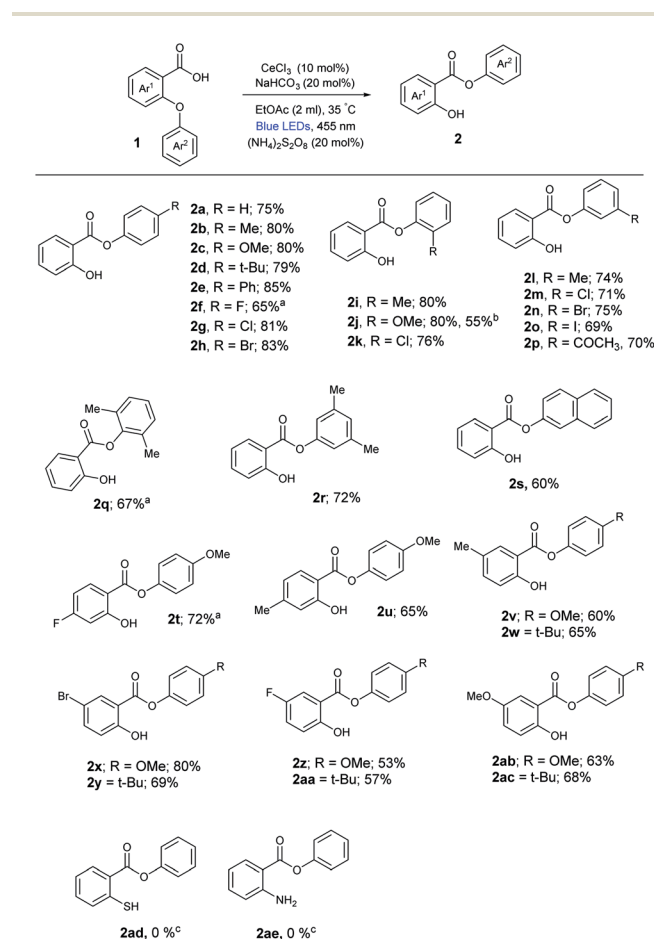
variety of reaction parameters were tested during the optimization of the reaction (Table 1). We were pleased to find that the efficient aryl migration from an aryl ether to a carboxylic acid group takes place at 35 °C, upon continuous irradiation with blue LEDs (455 nm) under cerium photocatalysis. Employing 10 mol% CeCl₃ as the photocatalyst and 20 mol% (NH₄)₂S₂O₈ as an oxidant in the presence of NaHCO₃ (10 mol%) in EtOAc gave compound **2a** in 75% isolated yield after 30 h (Table 1, entry 1). The reaction using CeCl₃·7H₂O and (t-Bu₄N)₂Ce^{IV}Cl₆ as a photocatalyst slightly reduced the yield of the reaction (Table 1, entry 2 and 3), while the conversion to **2a** decreased upon use of Ce(SO₄)₂·4H₂O (Table 1, entry 4). When NaHCO₃ was replaced by Cs₂CO₃, **2a** was afforded in 40% yield (Table 1, entry 5), while other bases such as Na₂CO₃, K₃PO₄ led to drastic reduction in the yield (Table 1, entry 6–7). The reaction was performed in absence of base afforded **2a** in 25% yield (Table 1, entry 8). The reaction worked with similar efficiency in CH₃CN (Table 1, entry 9), while other solvents such as THF, DCM and dioxane afforded **2a** in moderate yield (Table 1, entry 10–12). Employing O₂ balloon instead of (NH₄)₂S₂O₈ afford **2a** in 68% (Table 1, entry 13).¹⁶ Also, it was observed that the yields were less reproducible and varied about 15% upon using air as an oxidant (Table 1, entry 14). Irradiation with green LEDs did not lead to any product formation. Additionally, controlled experiments indicated that catalytic amount of the cerium salt, oxidant and light irradiation were necessary for the reaction to occur (Table 1, entries 16 and 17).

Table 1 Optimization of the reaction conditions. **1a** (0.2 mmol), CeCl₃ (10 mol%), EtOAc (2 ml) at 35 °C, 455 nm blue LED for 24 h

Entry	Deviation from standard conditions	2a ^a (%)
1	None	80(75)^b
2	CeCl ₃ ·7H ₂ O instead of CeCl ₃	68
3	(t-Bu ₄ N) ₂ CeCl ₆ instead of CeCl ₃	60
4	Ce(SO ₄) ₂ ·4H ₂ O instead of CeCl ₃	35
5	Cs ₂ CO ₃ instead of NaHCO ₃	40
6	Na ₂ CO ₃ instead of NaHCO ₃	10
7	K ₃ PO ₄ instead of NaHCO ₃	23
8	With out NaHCO₃	25
9	CH ₃ CN instead of EtOAc	75
10	THF instead of EtOAc	33
11	DCM instead of EtOAc	23
12	Dioxane instead of EtOAc	50
13	O ₂ balloon instead of (NH ₄) ₂ S ₂ O ₈	68
14	Air instead of (NH ₄) ₂ S ₂ O ₈	55–70
15	Green Led's (530 nm)	0
16	Without light	0
17	With out CeCl ₃	Trace

^a NMR yields using trimethoxy benzene as internal standard. ^b Isolated yield.

With the optimized reaction conditions in hand, we evaluated the substrate scope of the reaction with diverse substituted 2-aryloxybenzoic acids, which were prepared through known literature protocols. As shown in Scheme 1, a broad range of 2-aryloxybenzoic acids were reacted in our reaction conditions afforded corresponding aryl-2-hydroxybenzoate derivatives in good yields. First, the electronic variation in the *para*-position of the Ar² ring was studied. The results indicated that electron-donating and withdrawing substituents such as Me (**1b**), methoxy (**1c**), *tert*-butyl (**1d**), phenyl (**1e**), fluoro (**1f**), chloro (**1g**) and bromo (**1h**) were all well tolerated, giving aryl-2-hydroxybenzoates (**2b–2h**) in 65–85% yield. Next, the electronic variation in the *ortho* and *meta*-substitution of the Ar² ring was investigated. Electron donating (Me, OMe) and withdrawing groups (Cl, Br, I, COCH₃) provided the corresponding aryl-2-hydroxybenzoates (**2i–2p**) in moderate to excellent yields (Scheme 1). Meanwhile employing *ortho/meta* substituted aryloxy benzoic acids (**1q, 1r**) afforded the products (**2q, 2r**) in good yields. Interestingly, substrate derived from 2-naphthol (**1s**) also furnished the migratory product (**2s**) in 60% yield. Next the substitution on Ar¹ ring was studied. Diverse electron donating and withdrawing groups provided the corresponding aryl-2-



Scheme 1 Cerium photocatalyzed 1,5-aryl migration of 2-aryloxybenzoic acids. Reaction conditions as given in Table 1 (entry 1). Isolated yields, average of at least two independent runs. ^a30 h reaction time. ^b80 h reaction time. ^c36 h reaction time.



hydroxybenzoates (**2t–2ac**) in moderate to good yields (Scheme 1). Unfortunately, the migratory event of the corresponding thioether (**1ad**) and aryl amine (**1ae**) failed in our reaction conditions. Further to demonstrate the potential application of our methodology, a gram-scale synthesis of acetyl free Guacetisal was carried out in our cerium photocatalysis. Performing the reaction with 4.1 mmol portion of **1j**, it could be converted to **2j** in 55% yield. This result indicated that the cerium photocatalyzed radical smiles rearrangement had great potential in practical organic synthesis.

The efficiency of our cerium photocatalyzed 1,5-aryl migration of 2-aryloxybenzoic acids prompted us to conduct some preliminary mechanistic studies. As anticipated, ON/OFF experiments revealed that our reaction required continuous visible light irradiation to proceed (see ESI†). The inhibition of catalysis upon addition of TEMPO further indicates that the reaction proceeds *via* radical intermediates. Based on these experimental observations and the known literature reports we propose that the aryl migration proceeds *via* Ligand to Metal Charge Transfer (LMCT), which generates the key aromatic carboxy-radical. Given that decarboxylation of aromatic carboxyl radicals is slower than that of their aliphatic homologues,¹⁷ the generated aromatic carboxy-radical could be further trapped by the aryl ether substituent in an intramolecular fashion, and further reduction would generate the aryl-2-hydroxybenzoates (Scheme 2). The simplified mechanistic proposal is shown in Scheme 2. The putative Ce(III) species could be oxidized to Ce^{IV} ($E_{1/2}(\text{Ce}^{\text{III}}/\text{Ce}^{\text{IV}}) = 0.41 \text{ V vs. SCE in MeCN})^{14a}$ either by the phenoxy radical **E** or by the $(\text{NH}_4)_2\text{S}_2\text{O}_8$ ($E = 1.75 \text{ V vs. SCE}$).¹⁸ The coordination of the substrate forms complex **B**, which undergoes the photoinduced Ce–O(CO) homolytic cleavage regenerates the catalytically competent Ce(III) species (detected by UV spectroscopy, see ESI†) and the carboxy-radical **C**. A subsequent intramolecular *ipso* attack on the aryl ether moiety generates the cyclized intermediate **D**, followed by a aryl migration led to phenoxy radical intermediate **E**. Given the oxidation potential obtained for phenolate of **2a**,^{12a} the corresponding phenoxy radical can easily oxidize Ce(III) closing the catalytic cycle without requiring any external stoichiometric

oxidant. The final proton transfer from **1a** to phenolate leads to product **2a**.

Conclusions

In summary, we have developed a cerium photocatalyzed selective 1,5-aryl migration of 2-aryloxybenzoic acids through radical Smiles rearrangement. This operationally simple protocol utilizes inexpensive CeCl₃ as a photocatalyst and converted a variety of 2-aryloxybenzoic acids into aryl-2-hydroxybenzoates in absence of stoichiometric oxidant and base. Furthermore, we have applied our methodology for the gram scale synthesis of Guacetisal an important drug molecule in pharmaceutical industry.

Conflicts of interest

There are no conflicts to declare.

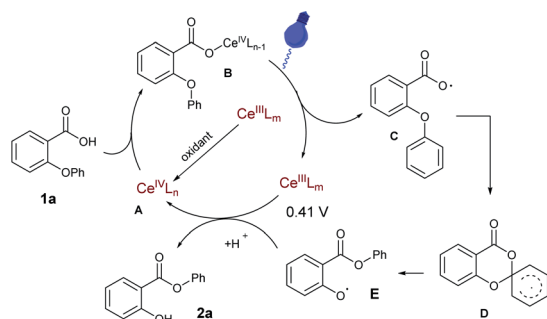
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Plausible reaction mechanism



Scheme 2 Plausible mechanism for 1,5-aryl migration of 2-aryloxybenzoic acids.



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