Acyl Radicals from Aromatic Carboxylic Acids by Means of Visible-Light Photoredox Catalysis

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Abstract: Simple and abundant carboxylic acids have been used as acyl radical precursor by means of visible-light photoredox catalysis. By the transient generation of a reactive anhydride intermediate, this redox-neutral approach offers a mild and rapid entry to high-value heterocyclic compounds without the need of UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides.

Carboxylic acids are abundant and inexpensive starting materials readily available in great structural diversity. For this reason, continuous efforts have been made to engage this class of compounds in novel catalytic organic transformations. In more recent years, visible-light photoredox catalysis has emerged as a benign and powerful tool in organic synthesis, and novel strategies targeting carboxylic acids as building blocks have been developed. Those methods rely on photo-induced oxidation of carboxylates to generate, after CO₂ extrusion, reactive alkyl radical intermediates (Scheme 1a). Capitalizing upon the high synthetic potential of visible-light photoredox catalysis, we questioned whether carboxylic acids might be used for the generation of acyl radicals by single-electron reduction (Scheme 1b). This would offer an unprecedented synthetic method that extends beyond the existing routes to access acyl radicals, which are often characterized by harsh conditions (UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides) or the need of pre-generated acyl radical precursors such as telluroesters, selenoesters, and thioesters.

We envisioned that transient mixed anhydride intermediates, obtained from simple carboxylic acids in the presence of dimethyl dicarbonate (DMDC), could be engaged as oxidative quenchers of a photocatalyst to generate the desired acyl radical species, along with CO₂ and methanoate as the only byproducts. This would provide carboxylic acids with orthogonal redox reactivity under mild photocatalytic conditions and a novel entry to a broader spectrum of accessible products.

At the onset of our investigation, we tested our idea for the formation of 3,3-disubstituted 2-oxindoles by 1,2-acylation of alkenes (Scheme 1c). The 3,3-disubstituted 2-oxindoles containing the carbonyl functionality are common structural motifs in pharmaceutical and bioactive natural products, and represent versatile intermediates in organic synthesis.

Consequently, in the last few years, the development of efficient synthetic methods for the synthesis of 3,3-disubstituted 2-oxindoles has received increased interest. Among these, 1,2-acylation of methacrylamides has emerged as a particularly interesting approach. However, the use of stoichiometric amounts of external oxidants, high temperature, or high-energy UV light represent considerable disadvantages of the procedures.

Herein we report the first redox-neutral approach for the mild visible-light-mediated tandem acylationlation of olefines using carboxylic acids as an acyl radical source. We first explored the proposed acylation reaction using benzoic acid 1a and N-methyl-N-phenylmethacrylamide 2a as the model substrates in the presence of the photocatalyst, DMDC, and 2,6-lutidine under visible-light irradiation (Table 1). We were pleased to find that the strongly reducing fac-Ir(ppy)₃ provided the desired product 3a in excellent yield (entry 1). In contrast, much weaker reductants such as [Ir(ppy)₃(dtb bpy)]⁺ and [Ru(bpy)₃]⁺ were unable to promote the reaction (Supporting Information, Table S1, entries 1 and...
However, when aliphatic carboxylic acids were used. Instead of DMDC over 6 h (Method A). [c] Method A using 2.5 mol% of fac-Ir(ppy), over 14 h. [d] Reaction performed with 2.5 mol% of fac-Ir(ppy), 3 equiv of Boc$_2$O and 1 equiv of MgCl$_2$ over 48 h (Method B). [e] 4 equiv of Boc$_2$O were used. [f] Reaction carried out with Method A on 1 mmol scale; reaction time = 10 h. [g] See the Supporting Information for details.

We next turned to evaluate the scope of the olefin (Table 3). A range of methacrylates successfully gave access to the corresponding products in good to excellent yields (74–95%). Differently N-substituted phenylmethylcarbamate could be used without loss of efficiency (3t, 3u).

Table 1: Selected optimization studies.$^{[a]}$

| Entry | fac-ir(ppy)$_{[b]}$ [mol%] | DMDC [equiv] | 2,6-lutidine [equiv] | Solvent | Yield [%]$^{[c]}$ |
|-------|-----------------------------|--------------|-------------------|--------|------------------|
| 1     | 1                           | 4            | 2                 | DMA    | >95              |
| 2$^{[e]}$ | 0.5                         | 3            | 0.5               | DMF    | >95              |
| 3$^{[b]}$ | 0.5                         | 3            | 0.5               | DMF    | <5               |
| 4$^{[a,f]}$ | 0.5                         | 3            | 0.5               | DMF    | 88               |

[a] Reactions performed on 0.1 mmol scale using 2 equiv of 1a. [b] Determined by 1H NMR using 2,5-dimethylfuran as internal standard. [c] Performed with 1.5 equiv of 1a; [2a], 0.05 M. [d] Reaction time = 6 h; [e] Reaction performed with 3 equiv of Boc$_2$O instead of DMDC; [f] Addition of 1 equiv of MgCl$_2$. DMA = N,N-dimethylformamide; DMF = N,N-dimethylacetamide.

2. Control experiments performed in the absence of the photocatalyst, the dicarbonate or the light source completely impeded any reactivity (Supporting Information, Table S1, entries 4–6). Fine tuning of the reaction conditions provided the desired product quantitatively while also decreasing reaction time and catalyst loading (Table 1, entry 2, Method A). When di-tert-butyl dicarbonate (Boc$_2$O) was used instead of DMDC to correspond the corresponding mixed anhydride, only traces of product 3a were found (entry 3). However, upon Lewis acid activation of Boc$_2$O with the addition of MgCl$_2$, the product was obtained in high yield (entry 4).$^{[11]}$

With the optimized conditions in hand (Method A), we examined the scope of the acid component.

As shown in Table 2, the reaction proceeds in good to excellent yield with a broad range of benzoic acids bearing different substituents in the para-, meta-, and ortho-position as well as carboxylic acids with extended aromatic systems (3a–3n). Ortho- and para-methyl, as well as para-hydroxy and para-trifluoromethyl benzoic acid, performed poorly under the optimized conditions, and fast conversion of these acids into the corresponding unreactive methyl esters was observed.$^{[12]}$ However, they could be efficiently employed (3e–3g, 3m) by replacing DMDC with Boc$_2$O together with the use of 1 equiv of MgCl$_2$ and 2.5 mol% of fac-ir(ppy)$_2$ over 48 h (Method B).$^{[13]}$ Electron-rich carboxylic acids, expected to be more difficult to reduce, can also serve to generate acyl radicals by simply increasing catalyst loading and reaction time (3d, 3i–k). Notably, carboxylic acids bearing free hydroxy and amino groups smoothly furnished oxindoles 3g and 3j as carbonate and carbamate derivatives, providing an efficient and mild acylation/protection procedure in one-pot. Heteroaromatic substrates such as 2-thiophene, 2-furoic, nicotinic, and 1-methylindole-2-carboxylic acid proved to be valuable reaction partners, generating products 3o–3r in moderate to good yields. Isothiocyanic acid could also be employed as a substrate furnishing product 3s by a consecutive difunctionalization. Furthermore, the optimized method was successfully applied to five-fold scale-up of the reaction providing product 3a in excellent yield (97%).$^{[14]}$ 2-Oxo-2-phenylacetic acid was also tolerated as a substrate, giving 3a in 30% yield.$^{[15]}$ However, when aliphatic carboxylic acids such as 1-phenylecypentanecarboxylic acid, 2-methoxy-2-phenylacetic acid, and N-Boc-glycine were employed under the optimized conditions, no formation of the corresponding products was observed.$^{[16]}$

We next turned to evaluate the scope of the olefin (Table 3). A range of methacrylates successfully gave access to the corresponding products in good to excellent yields (74–95%). Differently N-substituted phenylmethylcarbamate could be used without loss of efficiency (3t, 3u).
Substrates bearing electron-donating groups reacted smoothly and furnished the products in excellent yields (3w, 3y). Electron poor substrates reacted slower under the optimized conditions, and higher catalyst loading and reaction times were needed to obtain good yields (3v, 3x).

To showcase the generality and synthetic utility of this method, we sought to employ a range of olefins beyond methacrylamides (Scheme 2).

Pleasantly, we found that the procedure can be applied to styrene-type substrates 4a–c to readily build high molecular complexity accessing diverse heterocyclic motifs 5a–c in promising yields (Scheme 2).

A further demonstration of the synthetic value of the method is given by the straightforward preparation of compound 6, which features the hexahydropyrrolo[2,3-h]indole unit found in many natural products (Scheme 3).[17]

A plausible reaction mechanism (Figure 1a) begins with the photoexcitation of fac-Ir(ppy)₃ (depicted as IrIII in fac-[Ir(ppy)₃]⁺), which is a strong reductant (E1/2 (IrIV/IrIII) = −1.73 V vs SCE).[12] Single-electron reduction of mixed anhydride 1 in the presence of DMDC under basic conditions by fac-Ir(ppy)₃ (ppy), provides fac-Ir(ppy)₃ (ppy), and radical anion 11 that, after fragmentation, delivers acyl radical 111 along with CO₂ and methanoate. Subsequently, acyl radical 111 undergoes selective radical addition to olefin 2 giving radical intermediate 11V. Upon intramolecular cyclization, intermediate 11V is oxidized by fac-Ir(ppy)₃ (ppy), providing final product 3 along with the ground-state of the photocatalyst. To verify the proposed role of 11 in the catalytic cycle, we reacted isolated mixed anhydride 7 (E1/2 (red) = −1.74 V vs SCE) with olefin 2a in the presence of the photocatalyst under visible-light (Figure 1b) and as expected, smooth conversion into product 3a was observed. Furthermore, a series of Stern–Volmer fluorescence quenching studies clearly revealed that 7 is the only molecular entity in the reaction mixture that efficiently quenches fac-Ir(ppy)₃ (ppy).[15] Together, these experiments strongly support the proposed mechanism delineated in Figure 1a.

In conclusion, we have developed an operationally convenient visible-light photocatalytic tandem acylarylation of olefins using available aromatic carboxylic acids as starting material. The protocol presents a mild and energy-efficient system which offers a viable method for the generation of acyl radicals and their employment in C–C bonding reactions.

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Keywords: acyl radicals · acylarylation · carboxylic acids · oxidoles · photoredox catalysis

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