Decarboxylative Cyanation of Aliphatic Carboxylic Acids *via* Visible-Light Flavin Photocatalysis

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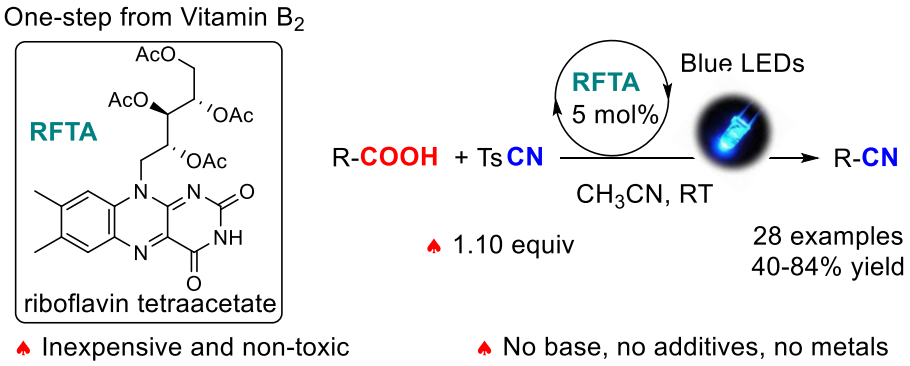
Supporting Information Placeholder



ABSTRACT: An operationally simple method is disclosed for the decarboxylative cyanation of aliphatic carboxylic acids at room temperature. Riboflavin tetraacetate, an inexpensive organic photocatalyst, promotes the oxidation of carboxylic acids upon visible-light activation. After decarboxylation, the generated radicals are trapped by TsCN, yielding the desired nitriles without any further additive, in a redox-neutral process. Importantly, this protocol can be adapted to flow conditions.

Aliphatic nitriles are highly versatile building blocks because they can be easily transformed into different carboxyl derivatives, amines, ketones, aldehydes, iminoethers (Pinner reaction) and a variety of heterocyclic scaffolds in medicinal chemistry.[1] In addition, nitrile-containing compounds have found important applications in pharmaceuticals, as illustrated in Figure 1.[2] Consequently, the development of practical protocols for the synthesis of such compounds has attracted considerable attention.

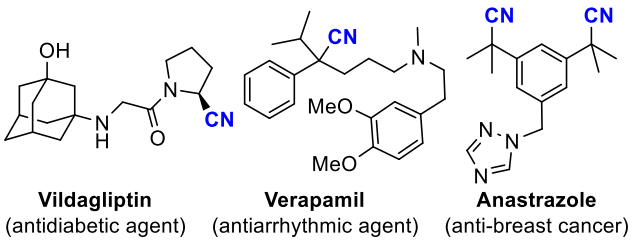
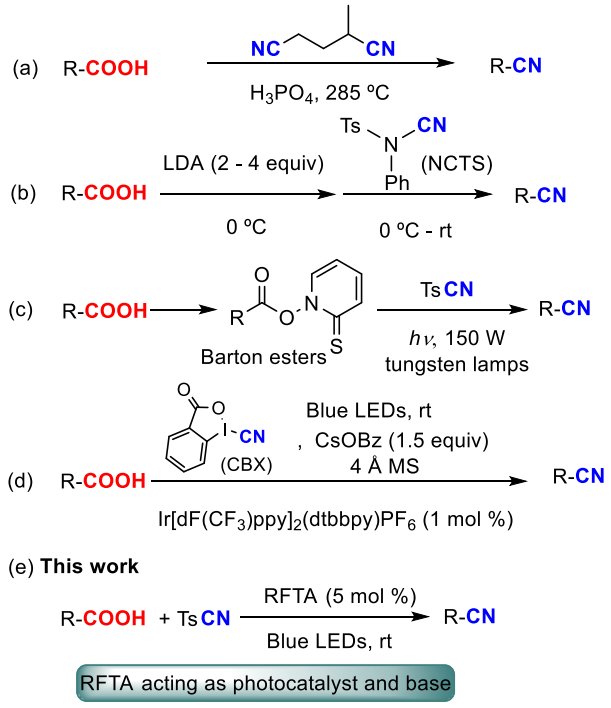


Figure 1. Selected bioactive aliphatic nitriles.

Traditionally aliphatic nitriles have been prepared by nucleophilic substitution of primary alkyl halides, dehydration of primary amides, or dehydration of aldoximes.[3] More recently, hydrocyanation of olefins[4] and activation of weak Csp^3-H bonds (using metal catalysis[5] or HAT catalysis[6]) have become attractive alternatives, because of the readily available starting materials. Another interesting approach is the decarboxylative cyanation of carboxylic acids. Biomass-derived carboxylic acids are inexpensive starting materials, generally stable and non-toxic, that can be transformed into high-value chemicals after extrusion of CO_2.[7] In this context, the acid catalyzed exchange of an carboxylic acid with α-methylglutaronitrile at very high temperatures was one of the first successful protocols (**Scheme 1a**).[8] Very recently, the treatment of carboxylic acids with an excess of strong bases and electrophilic cyanating reagents proved to be successful for a range of substrates at low temperatures (**Scheme 1b**).[9] In 1991 Barton reported the first practical decarboxylative cyanation of the so-called Barton esters and excess of sulfonyl cyanides, under visible light irradiation at room temperature (**Scheme 1c**).[10] Despite being effective, Barton`s method still requires an additional step to prepare the ester from carboxylic acids. Direct decarboxylative cyanation offers better step- and atom economy. Substantial development in photoredox catalysis over the past decade enable previously unreachable transformations.[11] The Waser`s group reported the first di-

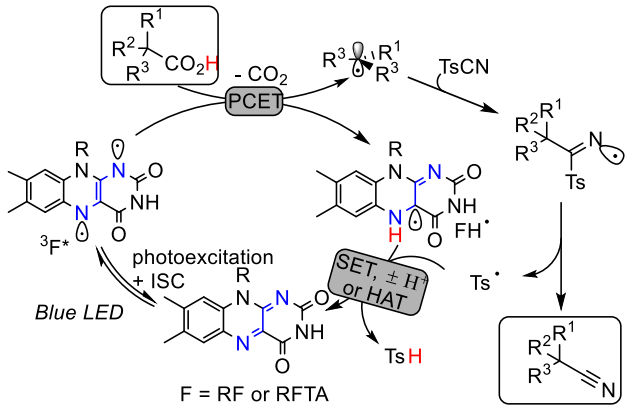
rect photocatalytic decarboxylative cyanation of aliphatic carboxylic acids at room temperature, using cyanobenziodoxolone (CBX) as cyanating reagent.[12] The above mentioned methodology is better suited for *α*-amino or *α*-oxo carboxylic acids and requires the use of an expensive iridium catalyst, in the presence of stoichiometric amounts of cesium benzoate and molecular sieves (**Scheme 1d**). In order to develop a more cost-effective protocol, we decided to explore organic photocatalysts for this visible-light promoted decarboxylative cyanation. We were particularly attracted by riboflavin (RF or vitamin B_2), a natural compound that is industrially produced by fermentation,[13] being inexpensive and non-toxic. Importantly, RF is responsible of the redox activity of hundreds of flavo-enzymes. Upon irradiation with visible light irradiation (λ_{max} ~ 450 nm), RF exhibits a moderate luminescence (λ_{max} ~ 510 nm), being. both, the singlet (2.48 eV) and the triplet state (2.17 eV) highly oxidizing.[14] The photocatalyst is generally involved in oxidations where molecular oxygen is used to regenerate the catalyst (aerobic transformations);[15] but is also able to generate singlet oxygen from its triplet state,[16] allowing energy transfer processes,[17] or even be used as reductant in organic synthesis.[18] In continuing our investigations of photocatalytic decarboxylative functionalization of carboxylic acids,[19] we present herein our results on the visible-light promoted decarboxylative cyanation, using riboflavin tetraacetate (RFTA) as photocatalyst and TsCN as cyanating reagent, in the absence of base or any other additive (**Scheme 1e**).

Scheme 1. Decarboxylative cyanation of aliphatic carboxylic acids.



The vast majority of photocatalytic decarboxylative functionalizations of carboxylic acids use stoichiometric bases to facilitate the oxidation of the corresponding carboxylate. However, the Gilmour group has recently reported that cinnamic acids[17] and biaryl carboxylic acids[15b] can be photooxidized using catalytic amounts of RF without any other base. More recently, MacMillan`s group reported that riboflavin tetrabuyrate has a better performance at pH 3.5 for the decarboxylative alkylation of peptides at the C-terminal carboxylic acid site.[20] Inspired by these results, we decided to develop a protocol in which a riboflavin derivative acts as base and photocatalyst in the decarboxylative cyanation of aliphatic carboxylic acids, avoiding the use of stoichiometric bases. Mechanistically, we anticipated that upon irradiation with visible light (λ_{max} ~ 450 nm) and after rapid intersystem crossing, the long-lived triplet-excited state of flavin would be oxidant enough (E_{red} = + 1.50 V *vs* SCE) to undergo single-electron oxidation of aliphatic carboxylates [E_{red} from + 1.0 V to + 1.50 V vs SCE]. Importantly, the flavin moiety can also act as a base (pK_a of RFH$^{\bullet}$ = 8.3), favoring the deprotonation of carboxylic acid prior to its single electron oxidation, or in a proton coupled electron transfer (PCET). After rapid decarboxylation of the aliphatic acyloxyl radical (k ~ 10^9 s^{-1}),[21] the generated radical is intercepted by Ts-CN, affording the desired nitrile and *p*-toluenesulfonyl radical (Ts$^{\bullet}$), like in the Barton nitrile transfer (Scheme 1c). The latter radical could be reduced by the hydroflavin radical [E_{red} (Ts$^{\bullet}$/Ts^{-}) = - 0.50 V[22] *vs* SCE; E_{red} (RF/RFH$^{\bullet}$) = - 0.60 V[23] *vs* SCE], regenerating the photocatalyst and producing TsH after protonation, in a redox-neutral process. Alternatively, *p*-toluenesulfonyl radical could abstract a hydrogen atom (HAT) from FH$^{\bullet}$ to turn-over the photocatalyst (**Scheme 2**).

Scheme 2. Plausible mechanism.



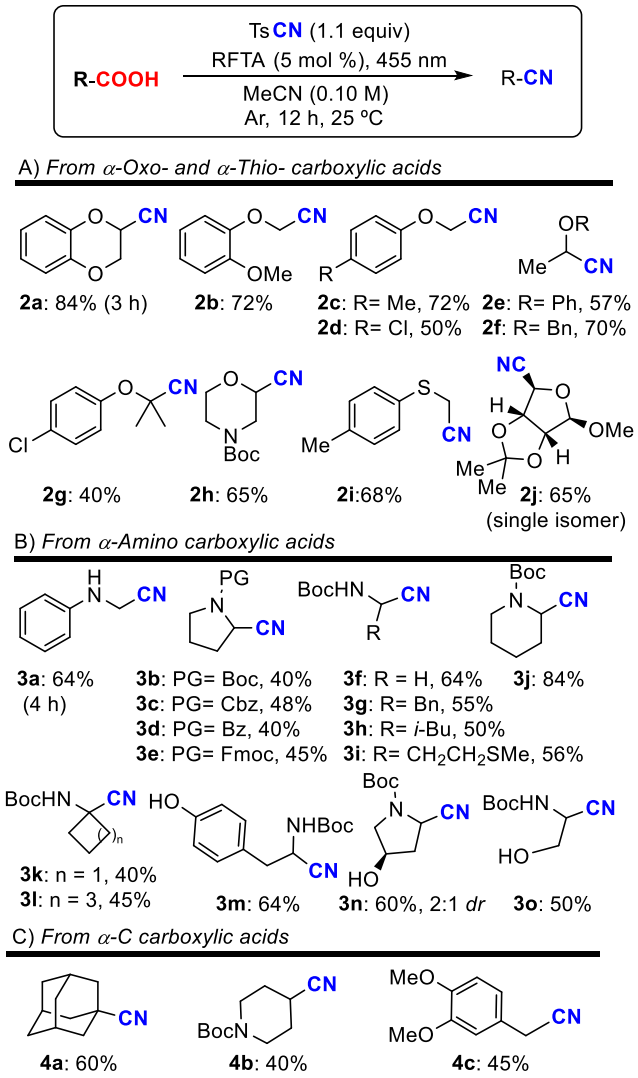
To optimize the photocatalytic decarboxylative cyanation we selected carboxylic acid **1a** as the model substrate (**Table S2**, in supporting information). When the reaction was conducted in degassed CH_3CN using RF as catalyst, under blue LED irradiation (λ_{max} 450 nm, 15 ± 2 mW/cm^2) over 12 h at room temperature, the expected nitrile **2a** was obtained in only 10% yield (entry 1). However, under identical conditions, the use of riboflavin tetraacetate (RFTA), readily available in one step from RF, allowed the formation of **2a** in excellent yield (entry 2). This result is consistent with the increased photostability, better solubility and more stable T_1 state of RFTA compare to RF, resulting in a more efficient oxidizing agent.[24] Although other solvent systems gave also good results for the model reaction, CH_3CN afforded the desired product consistently in higher yield (entries 3-5). Increasing the concentration of substrate (entry 6), decreasing the catalyst loading (entry 7) or running the reaction in the presence of air (entry 8) has a deleterious impact on the reaction. According to our mechanistic hypothesis, it is not surprising that the presence of O_2 from air interferes with the desired process. Encouraged by the previous results, we run the reaction over only 3 h and we were pleased to observed similar yields for product **2a** (entry 9). As expected, a base was not necessary in the present protocol. In fact, the addition of an organic base (entry 10) or an inorganic base (entry 11) had a negative

impact on the reaction. We also examined NaCN and TMSCN as cyanating reagents, but only traces of product **2a** were observed (entries 12 and 13). These experiments indicate that the carbocation pathway is no accessible without an external oxidant. Moreover, CBX also failed under our optimized conditions (entry 14). Control experiments revealed the need of photocatalyst and light for the success of the reaction (entries 15 and 16).

To evaluate the scope of the reaction under optimized conditions (**Scheme 3**), we first screened different α-oxo carboxylic acids. After decarboxylation, a catalytic steady generation of α-alkoxyalkyl radicals should be produced, which are nucleophilic enough (high-lying SOMO) to be trapped by electrophilic TsCN. We were pleased to observe than different primary (**2b-2d**), secondary (**2a**, **2e**) and tertiary (**2g**) α-aryloxy carboxylic acids gave the corresponding nitriles in moderate to good yields under the optimized conditions. Eventually, α-alkoxy carboxylic acids were also good substrates, affording nitriles **2f** and **2h** in good yields. Remarkably, α-thio nitrile **2i** was obtained in good yield under these reaction conditions, despite the many possibilities for parasitic reactivity (*e.g.*, further oxidation of the intermediate radical, homocoupling, H-atom abstraction, etc.). In addition, when a ribosic acid derivative was submitted to our standard conditions, nitrile **2j** was obtained as a single isomer with retention of configuration. After decarboxylation, the radical is stabilized by orbital interactions with both axial ring oxygen lone pair and adjacent σ* C-O bond (anomeric effect), and should react with TsCN from the less hindered convex face.[25] We also explored different natural and unnatural protected α-aminoacids in our decarboxylative cyanation protocol. It is worth mentioning that *N*-Boc α-aminonitriles are useful reductive carbolithiation precursors that can participate in inter- and intramolecular reactions with electrophiles, as has been elegantly exemplified in the synthesis of natural alkaloids.[26] Conventional *N*-protecting groups such as Boc, Cbz, Bz and Fmoc, were compatible with our reaction conditions, affording the corresponding proline nitriles (**3b-3e**) in moderate yields.[27] Other monoalkyl substituted α-aminoacids (products **3g-3j**), as well as less nucleophilic glycine derivatives (products **3a** and **3f**), gave the corresponding nitriles in synthetically useful yields. Quaternary *N*-Boc protected aminoacids were less reactive, affording compounds **3k** and **3l** in moderate yield. Interestingly, the tyrosine derivative with an easily oxidized phenol moiety, furnished product **3m** in good yield; likely by a selective PCET from the carboxyl group (more acidic than phenol) to the RFTA*. Moreover, free hydroxyl groups were well tolerated under our reaction conditions in secondary and primary alcohol moieties, obtaining products **3n** and **3o** in moderate to good yields. Finally, a few aliphatic carboxylic acids without heteroatoms in the α-position were also examined, furnishing nitriles **4a** to **4c** in moderate yields.

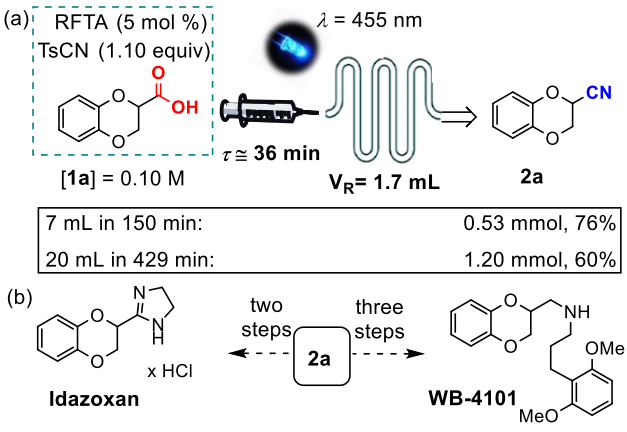
Considering the high molar absorption coefficient of RFTA (~13000 $M^{-1}cm^{-1}$) and its concentration in the reaction (0.005 M), approximately 90% of the light is absorbed after within the first 0.2 mm of the solution. This situation limits the scale of the reaction in batch and we decided to transfer the process to a continuous flow reactor.[28] After some optimization experiments in the microreactor (PFA tubes, 0.508 mm internal diameter, V = 1.70 mL), it was found that 36 min of residence time are sufficient to achieve full conversion of the starting material. Compound **2a** was obtained in a slightly diminished yield compare to batch conditions (76% *vs* 84%). These conditions allowed us to prepare 0.53 mmol in 150 min, but a diminished yield was obtained when the reaction was scaled up to 2 mmol (**Scheme 4a**).[29] Remarkably, 2-cyano-1,4-benzodioxan (**2a**) is a convenient synthetic precursor of Idazozan[30] and WB-4101,[31] selective antagonists of adrenoreceptors (**Scheme 4b**).

Scheme 3. Decarboxylative cyanation of carboxylic acids[a]



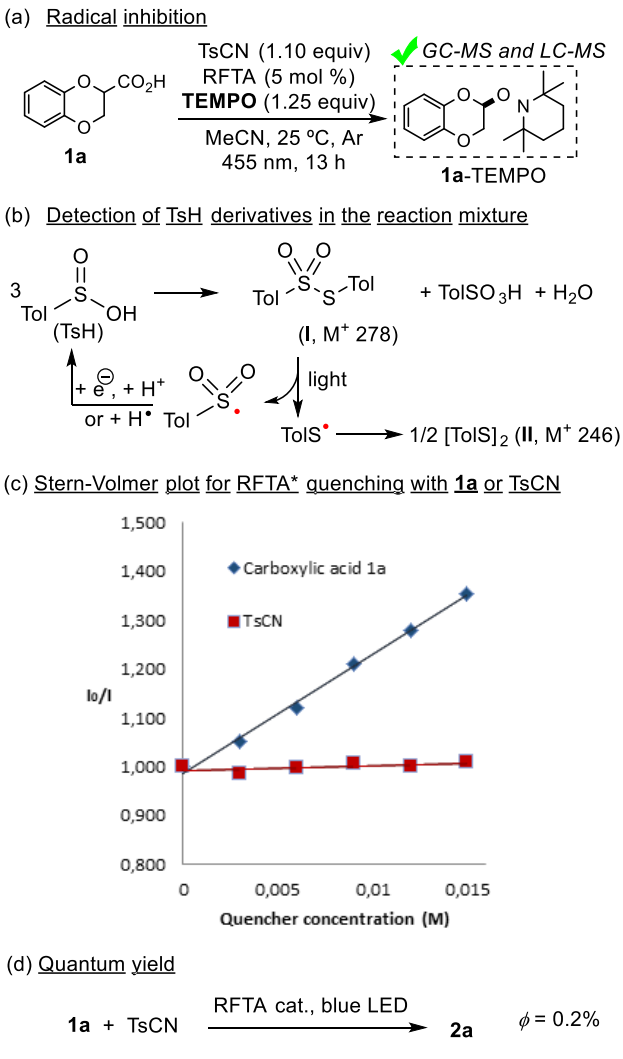
[a]Isolated yields are reported for reactions at 0.25 mmol scale.

Scheme 4. Formation of 2a under flow conditions and formal syntheses of Idazoxan and WB-4101



We conducted some control experiments to confirm the postulated reaction mechanism. The decarboxylative cyanation of **1a** was inhibited in the presence of TEMPO, observing the formation of **1a-TEMPO** by LC-MS (**Scheme 5a**). This result is in accordance with the intermediacy of radicals in the reaction. In the GC-MS of crude reaction mixtures we systematically observed peaks with m/z 278 and 246 that can be assigned to compounds **I** and **II**, formed after disproportionation of *p*-toluenesulfinic acid (TsH),[32] as indicated in **Scheme 5b**. Importantly, by-products **I** and **II** might also be involved in the oxidation of the hydroflavin radical to close the catalytic cycle of the studied reaction (**Scheme 2**). Moreover, as revealed in **Scheme 5c**, the emission intensity of RFTA* is not altered in the presence of TsCN, but is clearly diminished in the presence of carboxylic acid **1a**. This dynamic quenching of RFTA* by carboxylic acid **1a** supports the PCET to afford the corresponding acyloxy radical as a key step of the proposed mechanism. In addition, from the Stern-Volmer plot using lifetimes of excited RFTA* in the presence of increasing amounts of carboxylic acid **1a** (see SI), we determined that this quenching occurs at a rate near the diffusion limit (k_q = 3.5 x 10^9 $M^{-1}s^{-1}$). Finally, the quantum yield for the decarboxylative cyanation of **1a** was very low (**Scheme 5d**), which strongly suggest that a radical chain mechanism is very unlikely.

Scheme 5. Mechanistic studies



In summary, we have demonstrated that the decarboxylative cyanation of aliphatic carboxylic acids with TsCN can be efficiently promoted at room temperature, using inexpensive RFTA as photocatalyst and visible-light in the absence of additives. The protocol can be easily transferred from batch to flow conditions and a variety of functional groups is tolerated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, optimization studies, mechanistic experiments, characterization and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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(29) A similar 61% yield was obtained when the reaction was run at 2.0 mmol scale under batch conditions (see SI 18). Although the reaction mixture and the microreactor were carefully purged with N_2 before the process started, the collecting flask was open and after a prolonged time (> 150 min) the diffusion of O_2 into the reaction mixture might have a deleterious effect on the reaction yield. To scale up the reaction without a decrease in the yield it might be more appropriate to use a flow reactor of larger volume.

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