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Visible-Light Photocatalysed Cyanation of Benzylic C–H Bonds

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Abstract: Visible light-driven single-electron transfer-based direct cyanation of benzylic C-H bond with non-toxic *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) has been proposed using 4CzIPN, a widely used and affordable substitute for metal catalysts. The aforementioned method offers broad functional group tolerance, extensive substrate scope, excellent yields, and mild reaction conditions. This green and sustainable photocatalytic hydrogen atom transfer method can be applicable for the diversified functionalization of a variety of native C–H bonds.

Keywords: visible light, photocatalyst, 4CzIPN, cyanation, SET.

INTRODUCTION

THE cyano-group is an important structural motif[1] found in various bioactive and pharmaceutical drugs. The art and practice of synthesis have been revolutionised by the frequent use of the cyanation process in recent years to provide streamlined approaches towards synthetically valuable synthons[2–4] and sophisticated structural features seen in pharmaceuticals and natural products.[5–7] In organic synthesis arylacetonitriles serve as versatile intermediates because of their ability to undergo a wide range of functional group transformations. By virtue of their acidity,[8] the methylene protons are reactive towards electrophiles, but the cyano group can be readily converted into amides, amines, ketones, and acids,[9,10] among other functions. Heterocycles can also be built using the arylacetonitrile motif as a building block.[11] Substituted arylacetonitriles are well-known synthetic intermediates, but more recently, they have been also found in a number of medicinally active compounds.[12–14] There are various commercially available pharmaceutical drugs containing cyano-groups such as anastrozole, letrozole, cilomilast, bicalutamide, periciazine, rilpivirine, etc. (Figure 1).[14,15]

A number of research groups recently focused particularly on the potential for developing novel artificial approaches using visible light.[16–19] This is to enable the development of environmentally friendly and sustainable processes for organic synthesis. Visible light, or solar energy, is a clean, controllable, and unlimited energy source.[20] A number of innovative researchers[21,22] have focused on the conversion of solar energy into chemical energy for chemical reactions.

They have also devised a potentially effective technique for employing photoredox catalysts to initiate single electron transfer (SET) endeavours.[23,24] The application of metal-free organic dyes, specifically eosin Y, fluorescein, rose bengal, nile red, perylene, 4CzIPN and rhodamine B, has gained considerable interest as a superior substitute to transition metal photoredox catalysts. These dyes excel transition metal complexes in visible-light-promoted organic reactions involving SET[25–27] including both economically and environmentally. These organic dyes fulfil the fundamental requirements of green chemistry by

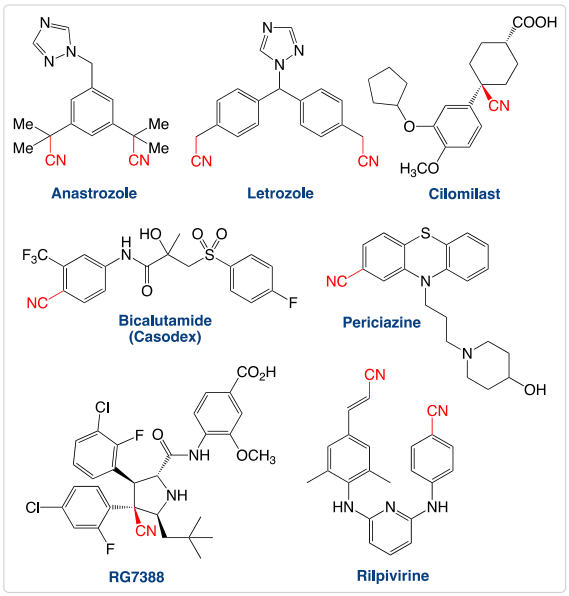


Figure 1. Chemical structure of some biologically active arylacetonitrile derivatives.

having an extensive amount of potential for applications in visible-light-mediated chemical synthesis.[28–31] In recent years several synthetic methods for cyanation[32] including visible-light photocatalysis has emerged as a viable method for incorporating the cyanomethyl group into target molecules with advantages like high efficiency, moderate reaction conditions, energy-saving potential, and ease of use.[33]

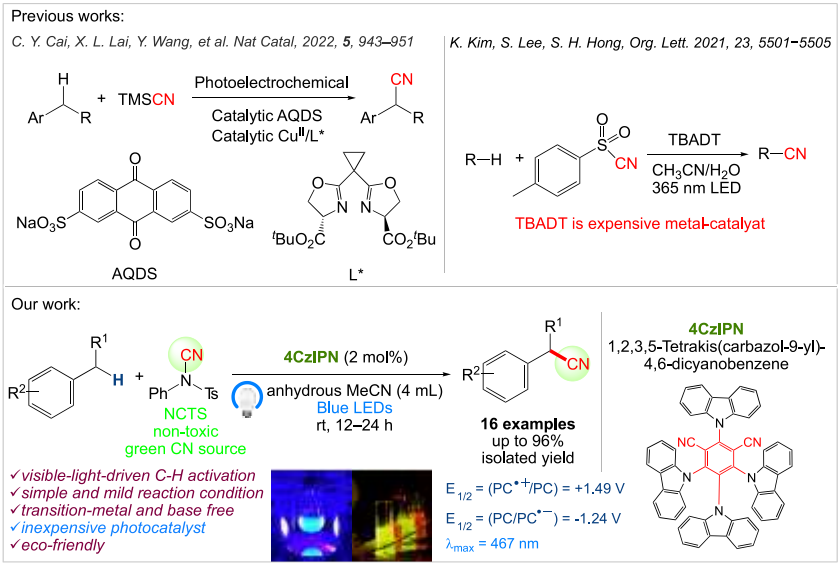
Developments in photocatalysis over the past decade have made transformations that were previously not feasible.[24,30,31,34,35] Therefore, continuing our research towards developing environmentally benign synthesis[36,37] herein we report a simple, visible light irradiated, efficient green protocol for cyanation of benzylic C–H bond via an benzylic radical initiation without the need of external oxidants or hydrogen atom abstractors. (Scheme 1).

EXPERIMENTAL

All materials used are commercially available and were purchased from Merck and Pubchem, further used without any additional purification. Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX (400 MHz and 100 MHz) FT spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ ppm).

General Procedure for the Preparation of Products (3a–p)

The reactions were carried out in a 10 mL glass vial, equipped with a rubber septum and a magnetic stirrer. Substituted benzene (0.2 mmol) (**1a**), *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) (1.3 equiv) (**2**), and 4-CzIPN (2 mol%), were dissolved in MeCN (4mL) and the mixture was irradiated with a 45W blue-LED under an air atmosphere at 12–24 h at rt. After completion of the reaction (monitored by TLC), the reaction crude was placed into a separatory funnel, water (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. Finally, the products (3a–p) were isolated by column chromatography (silica gel, eluent: 8 : 2 hexanes/ethyl acetate).



Scheme 1. Visible-light photocatalysed cyanation of benzylic C–H bonds.

RESULTS AND DISCUSSION

In order to realise our idea and optimise the reaction conditions, the key reaction of substituted benzene **1** and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) **2** with a catalytic amount of 4CzIPN in presence of solvent under irradiation with blue LEDs [45 W, λ_{max} = 467 nm] was carried out (Table 1). We were delighted to obtain the desired substituted product **3**, in 91 % yield (Table 1, entry 1). Then, the control experiments were carried out, which show that 4CzIPN and visible light source (blue LED) are essential for the reaction, because in the absence of any of the reagents/reaction parameters either the product was not detected or was formed in trace amounts (Table 1, entries 1 versus 10 and 11). Further running the reaction under green LEDs [45 W, λ_{max} = 518 nm], in presence of 4CzIPN and MeCN yield of the desired product become lower (Table 1, entry 12). On decreasing the amount of 4CzIPN from 2 mol% to 1 mol% the yield was considerably reduced (Table 1, entry 10), whereas the yield was not enhanced even on use of 3 mol% of 4CzIPN (Table 1, entry 11). By application of Eosin Y, Rhodamine-6G, Rose Bengal, 4-CzPN and 4DPAIPN the yield of product become very less under blue LED (λ_{max} = 467 nm) (Table 1, entries 2, 3,4, 5 and 6). When the reaction was performed under nitrogen atmosphere then only a trace of product formation was detected (Table 1, entry 15) as well as on quenching the reaction with 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (1.0 mmol) in standard state also gave the trace of product formation (Table 1, entry 16), showing that there may be radical intermediates involved in the reaction. Next, the reaction conditions were optimized with respect to anhydrous solvents used in the reaction. By using solvent DMF, DMSO and MeOH with 4CzIPN (2 mol%) results increase in yield of desired product (Table 1, entries 7, 8 and 9). MeCN was the best solvent in terms of the yield (Table 1, entry 1), hence it was used throughout the synthesis.

We then turned our focus to investigating the adaptability of different substrates or anticipated reaction conditions as we continued to search for the best reaction conditions for our model reaction (Table 2). The scope of the present protocol across a range of substituted benzene and *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) incorporating various substituents were studied. One important insight was that at the reaction conditions used, NCTS and substituted benzene with strong electron withdrawing groups as well as electron donating groups were well tolerated, and desired arylnitrile products were produced in good to excellent yields (Table 2).

However, it was observed that *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) and substituted benzene with

Table 1. Optimization of reaction conditions.[a]

Entry	Photocatalyst (PC) / mol%	Light source	Solvent	Yield / %[b]
1	4CzIPN (2 mol%)	467 nm	MeCN	91
2	Eosin Y (2 mol%)	467 nm	MeCN	38
3	Rhodamine-6G (2 mol%)	467 nm	MeCN	23
4	Rose Bengal (2 mol%)	467 nm	MeCN	28
5	4CzPN (2 mol%)	467 nm	MeCN	52
6	4DPAIPN (2 mol%)	467 nm	MeCN	55
7	4CzIPN (2 mol%)	467 nm	DMF	68
8	4CzIPN (2 mol%)	467 nm	DMSO	66
9	4CzIPN (2 mol%)	467 nm	MeOH	70
10	4CzIPN (1 mol%)	467 nm	MeCN	81
11	4CzIPN (3 mol%)	467 nm	MeCN	91
12	4CzIPN (2 mol%)	518 nm	MeCN	78
13	–	467 nm	MeCN	Trace[c]
14	4CzIPN (2 mol%)	467 nm	MeCN	0[d]
15	4CzIPN (2 mol%)	467 nm	MeCN	Trace[e]
16	4CzIPN (2 mol%)	467 nm	MeCN	Trace[f]

[a] Reaction conditions: 1-bromo-4-methylbenzene (1a) (0.2 mmol), NCTS (2) (1.3 equiv), PC (2 mol%), anhydrous MeCN (4 mL), 45 W blue LEDs, 12-24 h.

[b] Isolated yield of the product (3a).

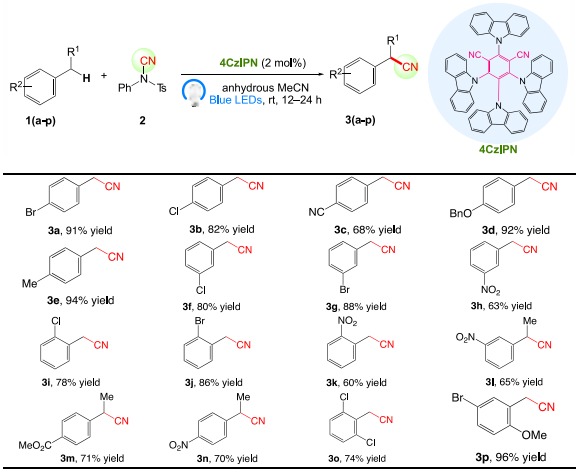
[c] No photocatalyst.

[d] Under dark condition.

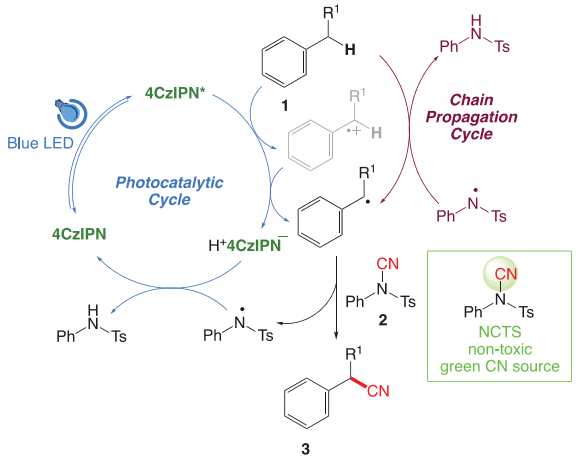
[e] Reaction was performed under nitrogen.

[f] Reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl(TEMPO) (1.0 mmol). Blue light (467 nm) and green light (518 nm).

Table 2. Scope of reaction.



Reaction conditions: Substituted benzene (1a–p) (0.2 mmol), NCTS (2) (1.3 equiv), 4CzIPN (2 mol%), anhydrous MeCN (4 mL), 45 W blue LEDs (467 nm), 12–24 h.



Scheme 2. Proposed mechanism for visible-light photocatalysed cyanation of benzylic C-H bonds.

electron-donating groups like methoxy and methyl at various positions exhibited improved reactivity and produced the corresponding products in good to excellent yields (**3e, 3d** and **3p**). On the other hand, substrate containing electron-withdrawing groups, such as bromo, chloro, cyano and nitro provided the corresponding products in moderate yields (**3a, 3b, 3f, 3g, 3i, 3j** and **3n**).

On the basis of the observed reactivity a plausible mechanistic pathway[38] is depicted in **Scheme 2**. Commercially available organic photocatalyst 4CzIPN has been shown to be a potent oxidant ($^{1/2}E$ = +1.35 V) while photoexcited. The photoredox 4CzIPN catalyst, activated by irradiation with blue LED (λ_{max} = 467 nm) acts as electrophile enables the abstraction of hydridic hydrogen from substituted benzene **1** to generate a nucleophilic carbon-centered radical, as previously reported.[32,39] This carbon radical is trapped by NCTS reagent **2** to generate the nitrile and a *N*-phenyl-*p*-toluenesulfonamide radical. This nitrile radical combines with carbon centered radical to give the desired product **3**. Further single electron reduction of *N*-phenyl-*p*-toluenesulfonamide radical by reduced 4CzIPN would regenerate the catalyst. The reaction between the reduced catalyst and *N*-phenyl-*p*-toluenesulfonamide radical is significantly slow so that the radical chain process operates dominantly.

CONCLUSION

In conclusion, employing NCTS as an electrophilic cyanating reagent and 4CzIPN as a catalyst, we have developed an organophotoredox catalyzed reaction that allows for the site-selective cyanation of benzylic C-H bonds in an array of alkyl arenes using a radical initiation mechanism affording structurally diverse benzyl cyanides with moderate to good yields. An effective late-stage benzylic C–H cyanation has given its impact on a range of therapeutic candidates and complex compounds, which is made possible in this synthetic protocol using wide range excellent compatibility with functional groups. Therefore, it is a superior substitute for the existing strategy for sustainable and environmentally friendly chemistry (better atom and step-economy). This approach is expected to facilitate the efficient benzylic C–H functionalization in complex compounds and advance the development of a library of benzylic cyanation of compounds that leads for medicinal research.

Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: https://doi.org/10.5562/cca4084.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from Adobe's web site.

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