Tetrahedron Letters 59 (2018) 3258–3261

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Redox-neutral C–H cyanation of tetrahydroisoquinolines under photoredox catalysis

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ARTICLE INFO

Article history:
Received 8 May 2018
Revised 4 July 2018
Accepted 10 July 2018
Available online 10 July 2018

Keywords:
Cyanation
C–H functionalization
Redox-neutral
Photoredox catalysis
Tetrahydroisoquinoline

ABSTRACT

Redox-neutral cyanation of C–H bond adjacent to a nitrogen atom was achieved by using the combination of a photoredox catalyst and *p*-toluenesulfonyl cyanide. The reaction of tetrahydroisoquinolines proceeded smoothly, affording the corresponding cyanated products selectively in good to high yield. Although the reaction rate became slower in the case of the substrates having electron-withdrawing groups, high yields were achieved by elongating the reaction time. Although the yields were only moderate, the reaction conditions were also applicable to *N*,*N*-dialkylanilines.

The cyano group, which can be found in various pharmaceutical compounds, is an important and useful functional group in organic synthesis, since it can be easily transformed to other functional groups [1]. Thus, the introduction of a cyano group as a C1 unit into an organic framework has been well studied. Among various cyanide compounds, α-amino nitrile derivatives are representative as a substructure of bioactive molecules and synthetic intermediates of α-amino carbonyl compounds and 1,2-diamines [2]. The addition of a cyanide anion to an imine, so-called Strecker reaction, is the most reliable method for the preparation of the α-amino nitrile derivatives [3].

C–H functionalization is a current topic to materialize environmentally benign synthesis by reduction of wastes and reaction steps in organic synthesis [4,5]. To date, oxidative C–H cyanation of amine compounds via iminium cation intermediates has been actively investigated. A pioneering work of C–H cyanation of *N*,*N*-dialkylanilines using a ruthenium catalyst was reported by Murahashi and coworkers [6]. Followingly, a variety of oxidative C–H cyanation reactions of amines were developed with transition metal catalysts including copper and iron salts [7]. In addition, simple combinations of oxidants and cyanide sources were also applicable to oxidative C–H cyanation [8]. On the other hand, recent progress of photoredox catalysis enables direct functionalization of C–H bonds [9]. In this context, direct C–H cyanation of amines has been achieved under photoredox catalysis with a terminal oxidant and a cyanide ion equivalent [10].

Among various C–H functionalizations under photoredox catalysis, a redox-neutral approach has attracted much attention [11], and there are many reports including C–C bond formation reactions via radical-radical coupling [11b]. However, redox neutral C–H cyanation of amines is surprisingly rare even for a benchmark test substrates such as tetrahydroisoquinoline (THIQ) derivatives, which are one of the fundamental framework of various bioactive compounds [12]. In 2011, Inoue and coworkers reported an elegant work on the C–H cyanation using a photoexcited benzophenone and *p*-toluenesulfonyl cyanide (TsCN), in which the reaction would proceed via hydrogen atom transfer from a substrate to the oxygen radical derived from benzophenone, followed by the attack of the resulting carbon radical to TsCN [13].

We recently disclosed a redox neutral C–C bond-forming reaction between THIQs and activated alkyl bromides under photoredox catalysis and the photo-mediated C–H fluorination and trifluoromethylation [14]. As part of our research project on photochemical C–H functionalization, we planned to investigate redox-neutral C–H cyanation of amine compounds. To design redox neutral system for C–H cyanation, we employed TsCN as an electrophilic cyanide source [15]. TsCN is usually utilized as a radical trapping cyanide source, and it reacts with a carbon radical to generate the corresponding cyanide compound together with a sulfonyl radical. Considering the electronic property of TsCN, we assumed that TsCN itself could accept one electron from a photoredox catalyst (*vide infra*) [16]. In this report, we demonstrate the

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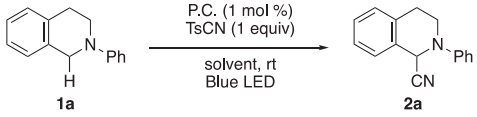
https://doi.org/10.1016/j.tetlet.2018.07.030
0040-4039/

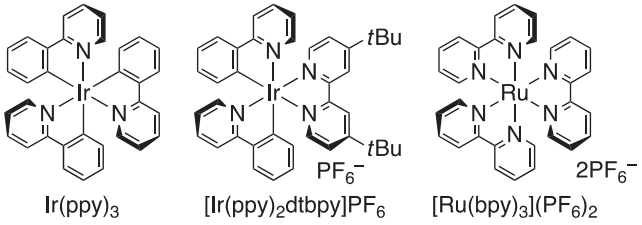
redox neutral C–H cyanation of THIQ derivatives and two *N*,*N*-dialkylaniline derivatives.

In order to optimize the reaction conditions, *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) was selected as a test substrate (Table 1). Based on our previous work [14a], the initial reaction was carried out with $Ir(ppy)_3$ in MeCN (entry 1). As expected, product **2a** was obtained in 70% yield. To improve the reaction efficiency, various solvents were screened (entries 2–7). Other non-protic polar solvents generally afforded high yields of **2a**, and an almost quantitative yield (99%) was achieved when using DMA as the solvent (entry 4). In contrast to the preceding reports, less polar solvents, such as THF and CH_2Cl_2, were also applicable to this reaction (entries 6 and 7). Other Ir and Ru photoredox catalysts were examined, revealing that the desired product **2a** could be obtained, but $Ir(ppy)_3$ is superior to other catalysts (entries 8 and 9). The use of K_2HPO_4 as base decreased the reaction efficiency (entry 10), probably because of decomposition or isomerization of TsCN [17]. Control experiments suggest that a photoredox catalyst and light irradiation are essential for this reaction (entries 11 and 12).



Having established the optimized conditions, the generality of substituted THIQ derivatives were examined (Table 2). The substitution on the *N*-aryl ring did not affect the reaction efficiency. Thus THIQs with *ortho*-, *meta*- and *para*-tolyl groups were converted to the corresponding products in high yields (entries 1–3). Although electron-rich substrates were applicable to this cyanation reaction without difficulty (entries 4 and 5), electron-withdrawing groups somewhat retarded the reaction. Indeed, the yields of **2g** and **2h** were 55% and 43% NMR yields, when the reaction of **1g** and **1h** were operated under the standard conditions. To our delight, however, prolonged reaction time and an excess amount of TsCN (2.0 equiv) resulted in higher yields, and 78% of **2g** and 88% of **2h** were isolated, respectively (entries 6 and 7). In addition, 7-chloro-substituted THIQ **1i** could be applied to this reaction, providing the cyanation product in 71% yield (entry 8). Unfortunately, *N*-methyl- and *N*-Boc-THIQs did not provide the desired cyanation products under our reaction conditions, probably because of higher anodic peak potentials of these THIQs in comparison with those of *N*-Ar-THIQs.

Table 1
Optimization of the reaction conditions.[a]

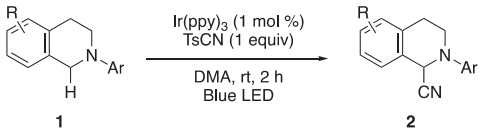


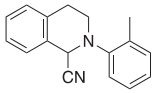
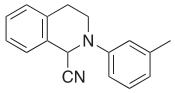
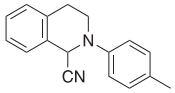
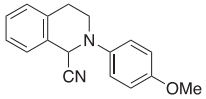
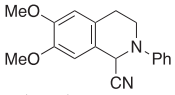
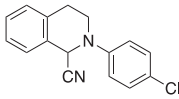
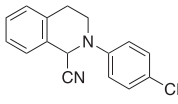
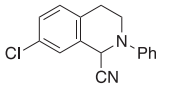
$Ir(ppy)_3$ $[Ir(ppy)_2dtbpy]PF_6$ $[Ru(bpy)_3](PF_6)_2$

Entry	Solvent	P. C.	Time (h)	Yield (%)[b]
1	MeCN	$Ir(ppy)_3$	2	70
2	DMSO	$Ir(ppy)_3$	2	73
3	DMF	$Ir(ppy)_3$	2	91
4	DMA	$Ir(ppy)_3$	2	99 (94)[c]
5	MeOH	$Ir(ppy)_3$	2	57
6	THF	$Ir(ppy)_3$	2	79
7	CH_2Cl_2	$Ir(ppy)_3$	2	86
8	DMA	$[Ir(ppy)_2dtbpy]PF_6$	2	90
9	DMA	$[Ru(bpy)_3](PF_6)_2$	2	67
10[d]	DMA	$Ir(ppy)_3$	4	43
11	DMA	–	2	0
12[e]	DMA	$Ir(ppy)_3$	2	0

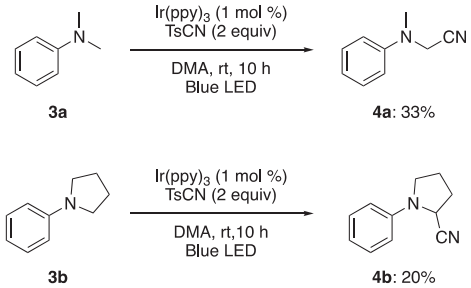
[a] The reactions were carried out with photoredox catalyst (P.C.) (1 mol %) and TsCN (1 equiv) on a 0.1 mmol scale, unless otherwise mentioned.
[b] Determined by ^1H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Isolated yield.
[d] Run with K_2HPO_4 (1 equiv).
[e] Run under the dark.

Table 2
Substrate scope of THIQs.[a]



Entry	Product		Yield (%)[b]
1		**2b**	89
2		**2c**	89
3		**2d**	97
4		**2e**	87
5		**2f**	82
6[c]		**2g**	78
7[c]		**2h**	83
8[c]		**2i**	71

[a] The reactions were carried out with $Ir(ppy)_3$ (1 mol %), TsCN (1 equiv) in DMA (1 mL) at room temperature for 2 h, unless otherwise mentioned.
[b] Isolated yield.
[c] Run with TsCN (2 equiv) for 10 h.



Scheme 1. Cyanation of *N*,*N*-dialkylanilines.