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Preparation of 6-Difluoromethylphosphonated Phenanthridines by Visible-Light-Driven Radical Cyclization of 2-Isocyanobiphenyls

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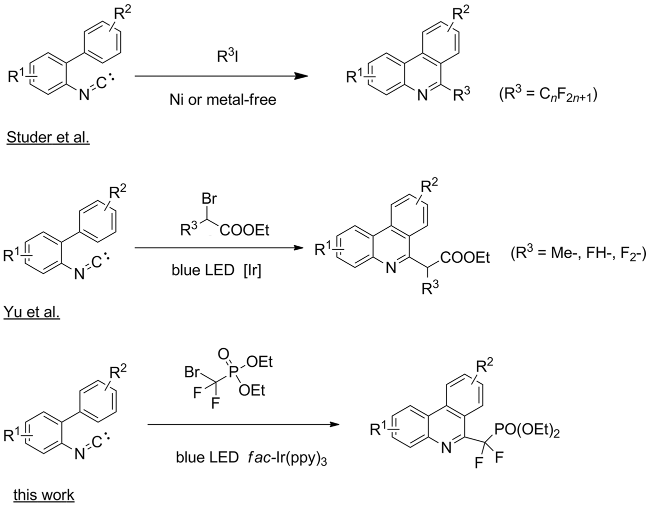
A protocol to obtain a variety of 6-difluoromethylenephosphonated phenanthridines through a radical cyclization process was explored. These reactions, performed with the use of diethyl bromodifluoromethylphosphonate as a radical resource and 2-isocyanobiphenyls as radical acceptors, were smoothly triggered by visible-light photocatalysis. Electron-withdrawing and electron-donating groups were well tolerated, and the target molecules were obtained in excellent to moderate yields.

Introduction

Fluorinated molecules are privileged and important, and they have attracted considerable attention because of their wide applications in our modern life involving materials, medicines, and agrochemicals.[1] Over recent decades, substantial efforts have been devoted to developing new synthetic methods for compounds bearing a difluoromethylene group.[2] In particular, the synthesis of difluoromethylenephosphonated compounds (DFMPCs) has drawn the interest of many chemists in very recent years,[3] because DFMPCs are found in a number of different types of drugs and are associated with a diverse range of biological activities.[4,5]

Visible light is a clean, inexpensive, and "almost infinitely" available source of energy.[6] In this regard, driving chemical reactions by visible light highly fulfills the increasing demand for energy conservation. Recently, we reported a room-temperature visible-light-driven protocol for the C–H difluoromethylenephosphonation of arenes and heteroarenes.[3e] In continuation of our interest in utilizing visible light to drive useful organic reactions, we focused our attention on the difluoromethylenephosphonation of phenanthridines.

The phenanthridine core has caught the attention of many pharmaceutical and synthetic chemists because it is associated with bioactivity and applications in natural products synthesis.[7] Although there are various ways to prepare the phenanthridine core,[8] and the isocyanide insertion reaction is always a simple and direct route.[9] The isocyanide insertion reaction usually proceeds through a radical procedure.[10] Both transition-metal catalysis[11–14] and visible-light photocatalysis[15] can induce the reaction effectively. For example, Studer and co-workers used $FeCl_3$,[14a] AgOAc,[12a] and $NiCl_2$[16] as initiators to synthesize 6-aroyl-, 6-phosphorylated, and 6-trifluoromethylphenanthridines, respectively. The Yu group achieved the synthesis of 6-trifluoromethyl-,[17] 6-alkylated,[15a] and mono- and difluoromethylated[15b] phenanthridines by using visible light. In spite of the promising progress achieved in recent years, few studies have paid attention to the synthesis of difluoromethylenephosphonated (DFMP) phenanthridines.



Scheme 1. Preparation of 6-substituted phenanthridines by isocyanide insertion reactions.

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We demonstrated that the phosphonodifluoromethyl (PDFM) radical can be generated from commercially available diethyl bromodifluoromethylphosphonate under visible-light photocatalytic conditions.[3e] However, attempts to direct the addition of the PDFM radical to phenanthridine produced DFMP phenanthridines in low yields (<5%). The synthesis strategy was therefore modified to an isocyanide insertion reaction by using bromodifluoromethylphosphonate as a radical precursor. Herein, we report the synthesis of DFMP phenanthridines by reaction of 2-isocyanobiphenyls with bromodifluoromethylphosphonate under visible-light irradiation (Scheme 1).

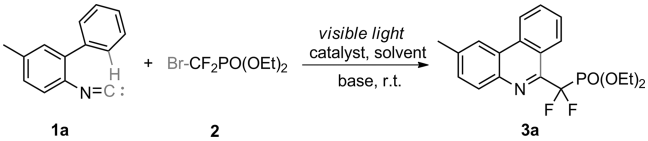
Results and Discussion

Initial studies focused on the difluoromethylenephosphonation of 2-isocyano-1,1′-biphenyl (**1a**) with diethyl bromodifluoromethylphosphonate (**2**) under visible-light irradiation [blue light-emitting diodes (LEDs), λ = 450 nm]. It was encouraging to see that the reaction of isocyanide **1a** with **2** in a dry CH_2Cl_2 solution containing tris[2-phenylpyridinato-C^2,*N*]iridium(III) [*fac*-Ir(ppy)$_3$] (1 mmol-%) as a photocatalyst and K_2HPO_4 (1.2 equiv.) as a base provided aimed product **3a** in 27% yield after 48 h of irradiation at room temperature (Table 1, entry 1). Several solvents such as CH_3CN, DMF, THF, and toluene were used to replace CH_2Cl_2 (Table 1, entries 2–5), and toluene was chosen as the ideal organic solvent for the reaction. With the best solvent in hand, different bases including K_2CO_3, Cs_2CO_3, KOAc, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and Et_3N were then tested (Table 1, entries 6–10). We were happy to see that the yield of **3a** improved to 84% in the presence of KOAc. Attempts to use other photocatalysts, such as Ru(bpy)$_3$Cl$_2$·6H$_2$O (bpy = 2,2′-bipyridyl) and eosin Y, were unsuccessful and resulted in almost no product (Table 1, entries 11 and 12). Diethyl bromodifluoromethylphosphonate (**2**) shows an irreversible reduction event at –0.84 V [vs. saturated calomel electrode (SCE)].[3e] Because the potentials of these photocatalysts in the excited state [e.g., –0.81 V for $Ru(bpy)_3^{3+} \rightarrow Ru(bpy)_3^{2+*}$][6c] are more positive than that of the *fac*-$Ir(ppy)_3^{+\bullet} \rightarrow$ *fac*-$Ir(ppy)_3^*$ couple (–1.73 V),[3e] the photoredox cycles are unfavorable in these cases. In addition, the amount of KOAc was carefully screened, and 2.0 equivalents KOAc provided the best yield of the target product (91%; Table 1, entries 8, 13–15). Control experiments indicated that both visible light and the photocatalyst were essential for the transformation.

With the optimized conditions in hand, we examined the substrate scope of this visible-light-driven PDFM radical isocyanide insertion reaction by employing various biarylisonitriles. As shown in Table 2, biarylisonitriles with cyclized aromatic rings substituted with either electron-withdrawing or electron-donating groups afforded the corresponding products (Table 2, entries 2–6 and 10) in good to moderate yields (51–96%). Nevertheless, substrates bearing electron-donating groups afforded better yields than those with electron-withdrawing substituents. For arylisonitriles bearing different substituents at the arene moiety containing the isocyanide, the yields were also good (Table 2, entries 7–9). The process appears to be general with the position of the methyl group on the arene ring bearing the isocyano group, as demonstrated by the efficient conversion of biarylisonitriles to the corresponding DFMP phenanthridines (Table 2, entries 1, 11, and 12). In addition, multisubstituted biarylisonitriles also worked well under the standard reaction conditions (Table 2, entries 1, 13–16), which highlights the potential of the method in organic synthesis.

On the basis of the experimental results, our previous work,[3e] and the reports of others on the mechanism of the isocyanide insertion reaction,[9e,14a,16] we speculate that the reaction takes place through electron transfer (ET) from the excited photoredox *fac*-Ir(ppy)$_3$ catalyst to bromodifluoromethylphosphonate, which leads to the generation of the PDFM radical. Addition of the PDFM radical to the isocyanide functionality in the 2-isocyanobiphenyl provides imidoyl radical **A**. Subsequently, intramolecular radical cyclization affords intermediate **B**, which goes on to generate deprotonated radical anion **C** with the aid of a base. Finally, electron transfer from radical anion **C** to *fac*-Ir^{IV}(ppy)$_3$ affords the desired DFMP product and regenerates the photocatalyst (Scheme 2).

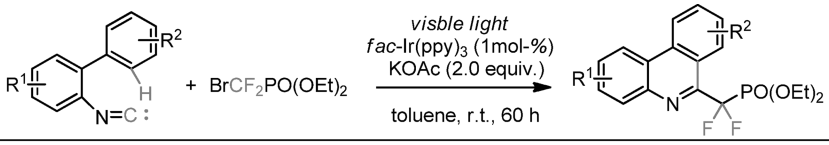
Table 1. Optimization of the reaction conditions.[a]

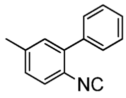
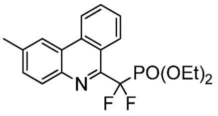
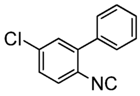
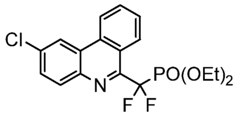
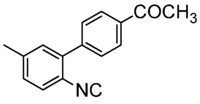
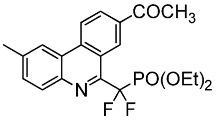
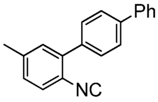
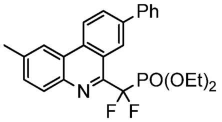
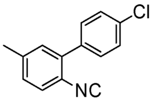
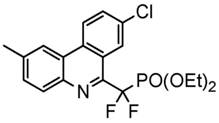
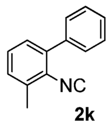
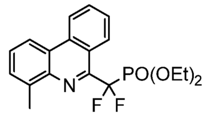
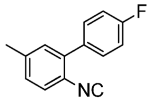
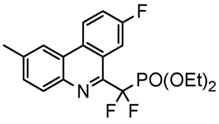
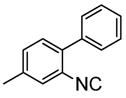
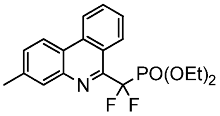
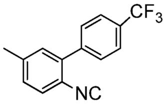
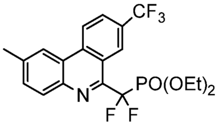
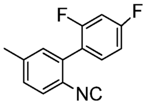
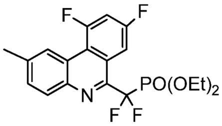
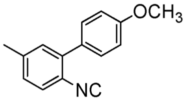
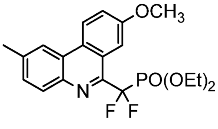
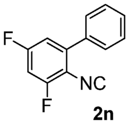
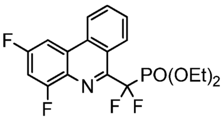
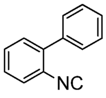
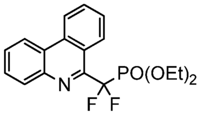
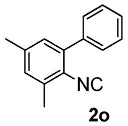
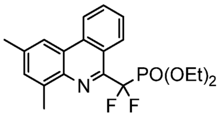
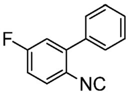
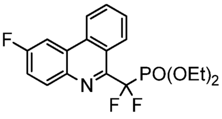
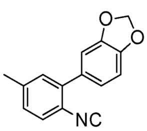
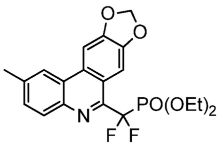


Entry	Catalyst	Base	Solvent	Yield [%]
1	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_2Cl_2	27
2	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_3CN	trace
3	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMF	52
4	*fac*-Ir(ppy)$_3$	K_2HPO_4	THF	59
5	*fac*-Ir(ppy)$_3$	K_2HPO_4	toluene	61
6	*fac*-Ir(ppy)$_3$	K_2CO_3	toluene	40
7	*fac*-Ir(ppy)$_3$	Cs_2CO_3	toluene	15
8	*fac*-Ir(ppy)$_3$	KOAc	toluene	84
9	*fac*-Ir(ppy)$_3$	DBU	toluene	13
10	*fac*-Ir(ppy)$_3$	Et_3N	toluene	20
11	eosin Y	KOAc	toluene	trace
12	Ru(bpy)$_3$Cl$_2$·6H$_2$O	KOAc	toluene	trace
13[b]	*fac*-Ir(ppy)$_3$	KOAc	toluene	83
14[c]	*fac*-Ir(ppy)$_3$	KOAc	toluene	91
15[d]	*fac*-Ir(ppy)$_3$	KOAc	toluene	65
16[e]	*fac*-Ir(ppy)$_3$	KOAc	toluene	n.r.[f]
17	–	KOAc	toluene	n.r.[f]

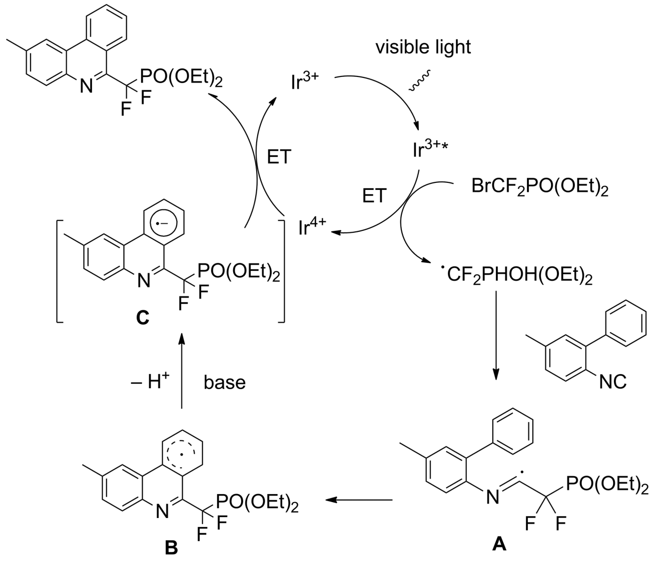
[a] Reaction conditions: A mixture of **1a** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), base (0.24 mmol, 1.2 equiv.), and photocatalyst (0.002 mmol, 1.0 mol-%) in dry solvent (2.0 mL) was irradiated with a 3 W blue LED lamp for 48 h. The reaction was conducted in a sealed tube full of Ar gas. [b] KOAc (1.6 equiv.). [c] KOAc (2.0 equiv.). [d] KOAc (2.4 equiv.). [e] No irradiation. [f] n.r.: no reaction.

Table 2. Scope of the arylisonitriles.[a]



Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1	 **2a**	 **3a**	91	9	 **2i**	 **3i**	67
2	 **2b**	 **3b**	55	10	 **2j**	 **3j**	85
3	 **2c**	 **3c**	69	11	 **2k**	 **3k**	87
4	 **2d**	 **3d**	70	12	 **2l**	 **3l**	86
5	 **2e**	 **3e**	51	13	 **2m**	 **3m**	74
6	 **2f**	 **3f**	96	14	 **2n**	 **3n**	69
7	 **2g**	 **3g**	83	15	 **2o**	 **30**	83
8	 **2h**	 **3h**	64	16	 **2p**	 **3p**	86

[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), KOAc (0.4 mmol, 2.0 equiv.) and *fac*-Ir(ppy)$_3$ (0.002 mmol, 1.0 mol-%) in dry toluene (2.0 mL) was irradiated with a blue LED lamp (3 W) for 60 h.



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, we disclosed a mild and straightforward way to prepare 6-difluoromethylenephosphonated (DFMP) phenanthridines through radical cyclization of 2-isocyanobiphenyls by using inexpensive and commercially available diethyl bromodifluoromethylphosphonate under visible-light irradiation. The present method is expected to offer a practical approach to DFMP phenanthridines, which is unlikely to be achieved by direct C–H difluoromethylenephosphonation of phenanthridines.

Acknowledgments

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