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Vinyldiazo Compounds as 3-Carbon Radical Acceptors: Synthesis of 4-Fluoroacridines via Visible-Light-Promoted Cascade Radical Cyclization

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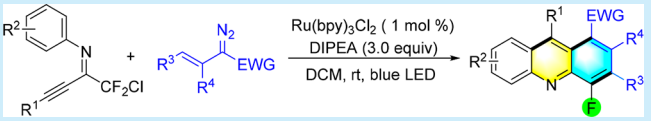
ABSTRACT: Vinyldiazo reagents were developed as the radical acceptors in a visible-light-promoted sequential radical cyclization reaction, providing a mechanistically distinct pathway to achieve (3 + 3) cyclization. Using N-aryl chlorodifluoromethyl alkynyl ketoimines as the radical precursors, the reaction allows the introduction of a fluorine atom to the acridine skeleton during the construction of both the pyridine and benzene motifs from acyclic building blocks. The resulting 4-fluoroacridines exhibited pronounced fluorescent properties in the solid state.



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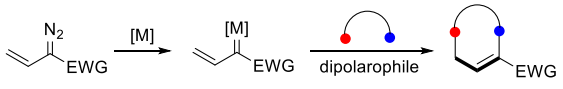
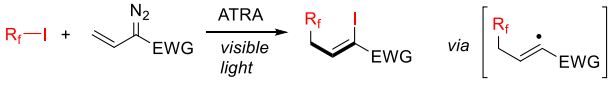
Stable vinyldiazo compounds are versatile synthons in organic synthesis and have been widely used in the construction of carbo- or heterocyclic rings of various sizes.[1] The decomposition of vinyldiazo compounds by transition metals forms electrophilic metallo-vinylcarbenes that commonly serve as 3-carbon building units for (3 + *n*) cyclization (Scheme 1a).[2] Alternatively, vinyldiazo compounds can work as nucleophiles to undergo cycloadditions with electrophilic π-bond motifs via a noncarbene route.[3] Whereas most of these cycloaddition reactions rely on dipoles as the key intermediates, the use of vinyldiazo compounds in a radical cyclization reaction has been less exploited despite its attractiveness.[4] Recently, our group reported a visible-light-promoted radical 1,3-addition of perfluoroalkyl iodides to vinyldiazoacetates under external photocatalyst and additive-free conditions.[5] The reaction proceeds through a radical propagation pathway, in which the vinyl radicals generated by the addition of $R_f^•$ to vinyldiazoacetates were terminated by iodine atom transfer (Scheme 1b). To further explore the synthetic utility of vinyldiazo species in radical reactions, we envisaged that the trap of vinyl radicals by unsaturated systems might lead to the discovery of new strategies for (3 + 3) cyclization via fundamentally distinct routes (Scheme 1c).

Scheme 1. Reactions of Vinyldiazo Compounds

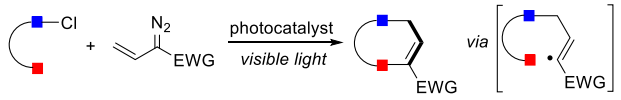
a) Transition metal-catalyzed (3+n) cycloaddition of vinyldizao compounds



b) 1,3-Atom transfer radical addition (ATRA) of R_fI to vinyldizao compounds



c) Carbocycles synthesis *via* radical addition to vinyldizao reagents (***not known***)



Acridines have been applied in industry as pigments and dyes for a long time.[6] Acridine derivatives exhibit considerable biological and pharmaceutical activities, such as anticancer, antibacterial, and antimalarial.[7] They have also found applications in materials science as organic semiconductor materials and fluorescent sensors.[8] Consequently, the development of efficient methods for the construction of this compound class has been a significant task in heterocyclic chemistry. Ring closures of suitable precursors to form the pyridine skeleton are the most widely applied methods for the preparation of acridines.[9] Transition-metal-catalyzed benzannulation of quinoline derivatives has also been reported.[10] However, a facile method to access diversely substituted acridines via cascade ring closures, allowing the formation of both pyridine and benzene motifs from acyclic building blocks, is still underdeveloped.

We have previously reported a highly functionalized difluoromethyl radical precursor,[11] namely N-aryl chlorodifluoromethyl alkynyl ketoimine (Scheme 2, compound **1**), which is readily prepared from ClF_2CO_2H, CCl_4, and aniline followed by a Sonogashira coupling with terminal alkyne.[12] Its reaction with alkenes provides a facile method for the synthesis of *gem*-difluorinated fused quinolines by visible light photo-

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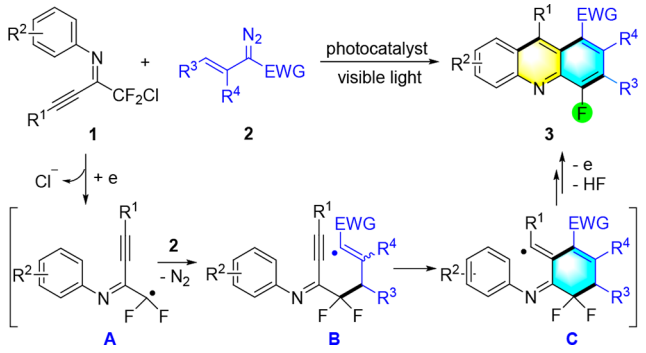
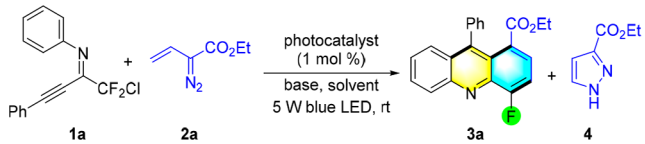
Scheme 2. Synthesis of 4-Fluoroacridines via Cascade Radical Cyclization



redox catalysis. We envisioned that the use of vinyldiazo reagents to replace alkenes as the radical acceptors would lead to 4-fluoroacridines. The working mechanism is shown in Scheme 2. The addition of difluoromethyl radical **A** to vinyldiazo compounds generates vinyl radical **B**, which undergoes addition to C−C triplet bond of ketoimine **1** intramolecularly to give vinyl radical **C**. The intramolecular homolytic aromatic substitution (HAS) of radical **C**, followed by single electron oxidation and elimination of HF would produce 4-fluoroacridine **3**. Due to the higher bond dissociation energy (BDE) of C−Cl bond, the termination of vinyl radical **B** by a halogen atom transfer can be suppressed. However enticing this proposal might appear, it was conceived to have two major challenges: (1) How will initial radical **A** be generated if less reactive C−Cl was used? (2) If photocatalyst was employed to generate radical **A**, how will the background pyrazole formation mediated by light or base be suppressed?[13] Here, we report the results of our research.

In our previous report on radical 1,3-addition of perfluoroalkyl iodides to vinyldiazoacetates, the initial R_f radical was generated by forming a radical pair complex between R_fI and triplet free vinylcarbene.[5] However, the direct generation of *gem*-difluoromethyl **A** in the absence of photocatalyst is less like due to the high dissociation energy of C−Cl bond. As expected, when the MeCN solution of alkynyl ketoimine **1a** and ethyl vinyldiazoacetate **2a** was irradiated with a 5 W blue LED at room temperature, no desired 4-fluoroacridine **3a** was detected, while the conversion of **2a** to pyrazole was found as the major background reaction (Table 1, entry 1). Therefore, we investigated the reaction using $Ru(bpy)_3Cl_2$ as the photocatalyst and $^nBu_3N/K_2CO_3$ as the bases, which are the optimal conditions of our previous report for the radical cyclization of **1a** with alkenes. Although the addition of photocatalyst and base favored the light-mediated pyrazole formation, we observed the generation of **3a** in 37% yield (Table 1, entry 2). Increasing the amounts of **2a** to 2.5 equiv led to **3a** in 49% yield, despite the yield of pyrazole **4** increasing to 94% (Table 1, entry 3). The use of $^nBu_3N$ as the sole base afforded **3a** in 58% yield, while the replacement of $^nBu_3N$ by inorganic base K_2CO_3 shut down the reaction completely (Table 1, entries 4 and 5). NEt_3 and $^iPr_2NEt$ gave better yields compared with $^nBu_3N$ (Table 1, entries 6 and 7). Several photocatalysts, such as $Ru(phen)_3Cl_2$, $Ir(ppy)_3$, $Ir(dfppy)_3$, and Eosin Y, were examined, but they were all less efficient than $Ru(bpy)_3Cl_2$ (Table 1, entries 8−11). Further inspection of the reaction conditions revealed that dichloromethane (DCM) was the best solvent for the reaction,

Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst	base (equiv)	solvent	3 (%)[b]	4 (%)[b]
1[c]	none	none	MeCN	NR	39
2[c]	$Ru(bpy)_3Cl_2$	$^nBu_3N$ (0.2)/K_2CO_3 (2)	MeCN	37	55
3	$Ru(bpy)_3Cl_2$	$^nBu_3N$ (0.2)/K_2CO_3 (2)	MeCN	49	94
4	$Ru(bpy)_3Cl_2$	$^nBu_3N$ (3)	MeCN	58	83
5	$Ru(bpy)_3Cl_2$	K_2CO_3 (3)	MeCN	NR	122
6	$Ru(bpy)_3Cl_2$	Et_3N (3)	MeCN	65	80
7	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	MeCN	71	76
8	$Ru(phen)_3Cl_2$	$^iPr_2NEt$ (3)	MeCN	67	83
9	$Ir(ppy)_3$	$^iPr_2NEt$ (3)	MeCN	56	89
10	$Ir(dFppy)_3$	$^iPr_2NEt$ (3)	MeCN	55	92
11	Eosin Y	$^iPr_2NEt$ (3)	MeCN	60	83
12	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	DMSO	57	96
13	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	DMF	43	106
14	**$Ru(bpy)_3Cl_2$**	**$^iPr_2NEt$ (3)**	**DCM**	**83**	**70**
15	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	DCE	74	76
16	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	toluene	11	119
17[c,d]	$Ru(bpy)_3Cl_2$	$^iPr_2NEt$ (3)	DCM	69	41

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), base, photocatalyst, and solvent (1.5 mL) under the irradiation of a 5 W blue LED at room temperature for 18 h. [b]Yields of **3a** and **4** were determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]1.5 equiv of **2a**. [d]5 mmol scale reaction, and **2a** was added in three portions.

whereas more polar solvents such as DMSO and DMF and less polar toluene were found to be unfavorable (Table 1, entries 12−16). In a gram scale reaction, adding 1.5 equiv of **2a** in 3 portions over the course of the reaction produces **3a** in the yield of 69%, and byproduct pyrazole **4** could be minimized to 41% yield (Table 1, entry 17).

With the optimized conditions in hand (Table 1, entry 14), the generality of this cascade radical cyclization reaction for the synthesis of 4-fluoroacridine was explored using a variety of alkynyl ketoimines **1b−1s** and ethyl vinyldiazoacetate **2a** (Scheme 3). Initially, the effects of the substitutents at the *para*-position of phenyl ring connected to the C−C triple bond were evaluated. Substrates bearing methyl, halogen, and phenyl groups worked well, affording the desired products **3a−3f** in 71−79% yields. The reaction became sluggish when strong electron-withdrawing nitro and electron-donating methoxy groups were introduced (**3g** and **3h**). The presence of a methyl group at the *meta*-position and a fluoro group at the *ortho*-position had no apparent effect on the reaction. When R^1 was a 1-naphthyl and 3-thienyl group, the corresponding 4-fluoroacridines **3k** and **3l** were obtained in the yields of 73 and 78%, respectively. It is worth mentioning that 9-cyclopropyl-4-fluoroacridine **3m** could be prepared by this radical transformation. In addition, a terminal alkyne motif also survived (**3n**), and no side product from radical addition to the terminal C≡C bond was detected. Alkynyl ketoimines bearing a substituent on the phenyl ring attached to the nitrogen atom all reacted efficiently with **2a** to give 7-bromoacridine **3o**, 7-

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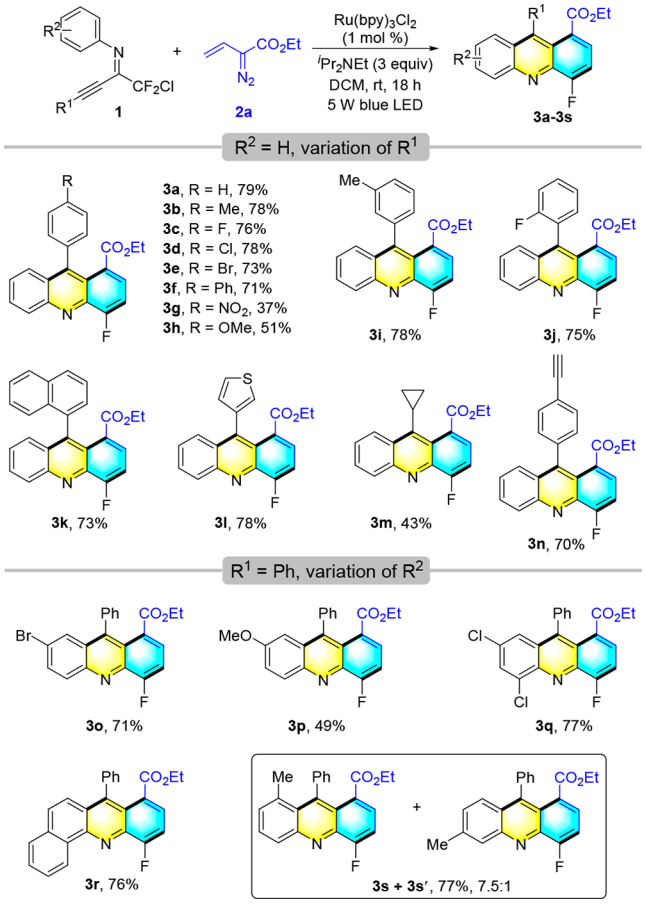
Scheme 3. Substrate Scope of Alkynyl Ketoimine 1[a]

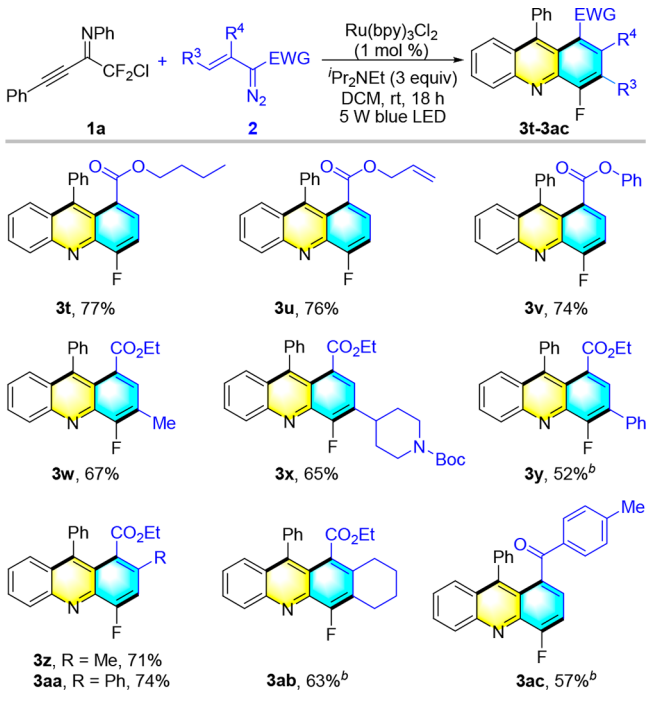


[a]Reaction conditions: alkynyl ketoimine **1** (0.2 mmol), ethyl vinyldiazoacetate **2a** (0.5 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), and $^iPr_2NEt$ (0.6 mmol) in 1.5 mL of DCM under the irradiation of a 5 W blue LED at room temperature for 18 h. Isolated yields.

methoxyacridine **3p**, 5,7-dichloro acridine **3p**, and benzo[c]-acridine **3r** in good yields. A 7.5:1 mixture of two isomers **3s** and **3s′** was obtained in a total yield of 77% when a methyl group was present at the *meta*-position, which provided two nonequivalent sites for cyclization.

Next, we investigated the scope of vinyldiazo compounds, which would introduce different substitutents to the 1-, 2-, or 3-position of acridines (Scheme 4). As expected, the nature of the ester substituent has little impact on the reaction outcome. Replacing the ethyl in the ester motif of vinyldiazoacetate with *n*-butyl, allyl, and phenyl groups led to 4-fluoroacridines **3t**, **3u**, and **3v** in good yields (77, 76, and 74%, respectively). The use of vinyldiazoacetates substituted at the alkenyl moiety proved more challenging. In relation with the structure of the alkenyl moiety, some points are remarkable: (i) the reaction is more efficient for C*α*-substituted (**3z**, **3aa**) than for C*β*-substituted vinyldiazoacetates (**3w**, **3x**, and **3y**); (ii) the presence of a phenyl group at the C*β* position (**3y**) hampered the overall efficiency of the reaction, which disfavored the radical addition to the vinyl terminus of the vinyldiazoacetate; (iii) cyclic vinyldiazoacetate was also a suitable substrate for the reaction, producing cyclohexane-fused acridine **3ab** in the yield of 63%. Finally, we were delighted to find the electron-withdrawing group was not limited to the ester group, as exemplified by

Scheme 4. Photocatalytic Radical Cyclization of Alkynyl Ketoimine 1a with Various Vinyldiazo Compounds[a]



[a]All reactions were carried out under the conditions as described in Scheme 3. Isolated yields. [b]Vinyldiazo compounds were added in three portions.

reaction of vinyl diazoketone with **1a** to give 4-fluoroacridine **3ac**.

The large conjugated systems give the potential for these 4-fluoroacridines to show strong absorption and fluorescence emission peaks at the long wavelengths. The absorption and emission spectra of 4-fluoroacridines **3a**, **3h**, **3k**, **3l**, and **3r** in the solid state were shown in Figure 1a and 1b. Whereas all the synthesized 4-fluoroacridines are essentially nonfluorescent in solution, they showed fluorescence character under the

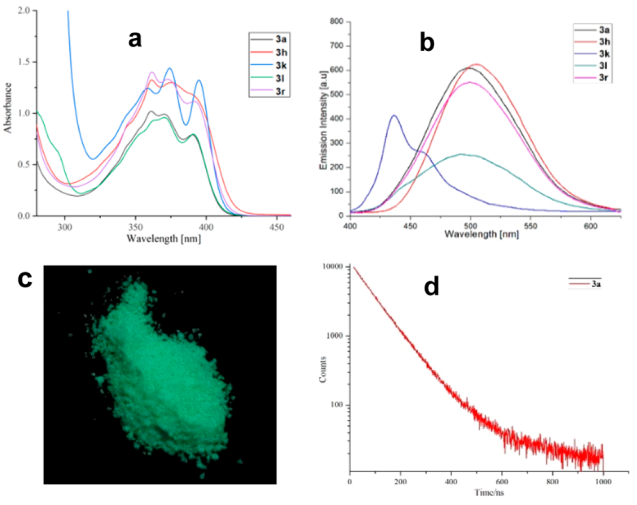


Figure 1. (a) Absorption spectra of **3a**, **3h**, **3k**, **3l**, and **3r**. (b) Fluorescence emission spectra of **3a**, **3h**, **3k**, **3l**, and **3r**. (c) Digital image of **3a** in solid state under UV irradiation (365 nm). (d) Fluorescence lifetime decay of **3a**.

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irradiation of 365 nm UV light at room temperature. For example, compound **3a** is a faint yellow solid, which emits green fluorescence upon UV light irradiation (Figure 1c). In addition, the fluorescence lifetime of **3a** was measured as 95.15 ns using the time-correlated single-photo counting (TCSPC) technique (Figure 1d, for details, see the Supporting Information).

It is known that the excited state Ru^{2+}* can be reduced to Ru^{+} by accepting an electron from tertiary amine.[14] The luminescence quenching experiments demonstrated that $^{i}Pr_2NEt$ displayed luminescence quenching of the $[Ru(bpy)_3]^{2+}$* excited state (Figure 2a). On the contrary, a

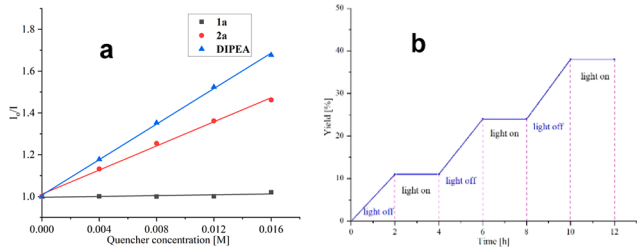

Figure 2. (a) Stern−Volmer plot. (b) Time profile of photocatalytic radical cyclization of **1a** and **2a**.

decrease in $[Ru(bpy)_3]^{2+}$* luminescence was not observed by adding substrates **1a** ($E_{1/2}^{red}$ = −1.24 V vs SCE, see Figure S6 in the Supporting Information), which indicates the oxidative quenching of $[Ru(bpy)_3]^{2+}$* by **1a** is less likely. Our previous report has demonstrated that vinyldiazo compounds present absorbance spectra in the visible region. Therefore, they were also potential reagents to quench the excited $[Ru(bpy)_3]^{2+}$*. However, the quenching ability of ethyl vinyldiazoacetate **2a** is lower than that of $^{i}Pr_2NEt$, seen by comparing the rates of slope, revealing the electron transfer between $[Ru((bpy)_3]^{2+}$* and $^{i}Pr_2NEt$ is still a major pathway to quench excited photocatalyst (for details, see Figures S1−S3 in the Supporting Information). The light "on/off" experiment disclosed that the present radical cyclization reaction proceeded via a photoredox catalytic mechanism, which is different from the radical-chain propagation pathway for the radical 1,3-addition of R_fI to vinyldiazo compounds (Figure 2b).[5] All of the results support that difluoromethyl radical **A** was generated by the single electron reduction of **1a** by $[Ru(bpy)_3]^{+}$ (See Scheme S1 in the Supporting Information for the complete mechanism).

In summary, vinyldiazo reagents were developed as the radical acceptors in a sequential radical cyclization reaction, which provided a mechanistically distinct pathway to achieve (3 + 3) cyclization. Using N-aryl chlorodifluoromethyl alkynyl ketoimines as the radical precursors, their reactions with vinyldiazo compounds by visible light photoredox catalysis afforded various 4-fluoroacridines in good yields. The reaction allows the introduction of a fluorine atom to the acridine skeleton during the construction of both the pyridine and benzene motifs from acyclic building blocks. Additionally, the synthesized compounds displayed a pronounced solid state fluorescence. Because the presence of fluorine atoms on the aromatic ring has been known to improve the thermal and chemical stability of the acridines,[15] we hope that this method can find practical applications in medicinal chemistry and materials science.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01204.

Experimental details, characterization data, and NMR spectra of all new products (PDF)

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Notes

The authors declare no competing financial interest.

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