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Visible-light-induced dearomative spirocyclization of *N*-benzylacrylamides toward perfluorinated azaspirocyclic cyclohexadienones

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ABSTRACT

A feasible approach to 2-azaspirocyclic cyclohexadienones *via* visible-light-induced perfluoroalkylation cyclization of *N*-benzylacrylamides was reported. Using R_f–X (X = I or Br) as the R_f radical source, the reaction underwent a cascade radical addition/dearomative cyclization process by Ir photocatalyst, leading to various 2-azaspiro[4.5]deca-6,9-diene-3,8-diones bearing perfluorinated groups including CF_3, *n*-C_3F_7, *n*-C_4F_9, *n*-C_6F_{13}, *n*-C_8F_{17}, *n*-$C_{10}F_{21}$, CH_2CF_2 and CF_2CO_2Et.

Introduction

Azaspirocycles skeletons proved to be the indispensable synthetic intermediates in the synthesis of pharmaceutical active molecules,[1] such as HIV-1 protease inhibitors,[2] annosqualine[3] and antiarthritic agents.[4] Remarkably, the introduction of fluorinated groups into organic molecules has also found widespread use in medicinal chemistry.[5] Recently, dearomative cyclization of the functionalized phenols and alkoxyarenes have emerged as a highly efficient method for the synthesis of the azaspirocycles compounds.[6–8] Thus, making good use of appropriate aromatic compounds to construct the fluorine-containing spiroheterocyclic systems through a dearomative cyclization reaction has also attracted increasing attentions over the past years.[8] For example, in 2014, Wang's group reported a dearomative cyclization reaction to construct trifluoromethylated 2-azaspiro[4.5] decanes through intramolecular trifluoromethylation of *N*-benzylacrylamide (Scheme 1, Eq. (1)).[8a] In 2016, Dolbier Jr's group developed a photoredox-catalyzed intramolecular difluoromethylation of *N*-benzylacrylamides coupled with the dearomative spirocyclization to afford CF_2H-containing 2-azaspiro[4.5]deca-6,9-diene-3,8-diones (Eq. (1)).[8b] Besides, the synthesis of various 1-azaspiro[4.5]decanes bearing a CF_3- or CF_2- group has also been reported by Xia's and Zhu's group (Eq. (2)).[8c,d] However, these achievements are mainly limited to the incorporation of the CF_3 or CF_2 moieties, and only one example leading to perfluorinated azaspiro[4.5]decanes using $C_4F_9SO_2Cl$ as the perfluorine source have been demonstrated in Dolbier's work.[8b] In addition, in general the fluorinated reagents used like Togni's reagent or R_fSO_2Cl are comparably expensive. Therefore, searching for other more commercial and multiple fluorine reagents is still in high demand by synthetic chemists. Actually, perfluoroalkyl iodides or bromines are much more commercially available, and have low cost than Togni's reagent in large scale productions.[9,10] Apparently, using perfluoroalkyl iodides or bromines as the fluorine sources is beneficial to develop practical access to perfluorinated azaspirocyclic compounds.

In recent years, visible-light-induced photoredox catalysis has attracted many researchers' attentions for the merits such as ease of operation cost-effectiveness, thereby serving as a powerful tool for the preparation of diverse important compounds under mild conditions.[11] With our ongoing studies on perfluoroalkylation by photoredox catalysis,[12] we herein want to demonstrate a visible-light-induced dearomatizing spirocyclization of *N*-benzylacrylamides using perfluoroalkyl iodides or bromides as the R_f radical precursors, allowing for the preparation of functional 2-azaspiro

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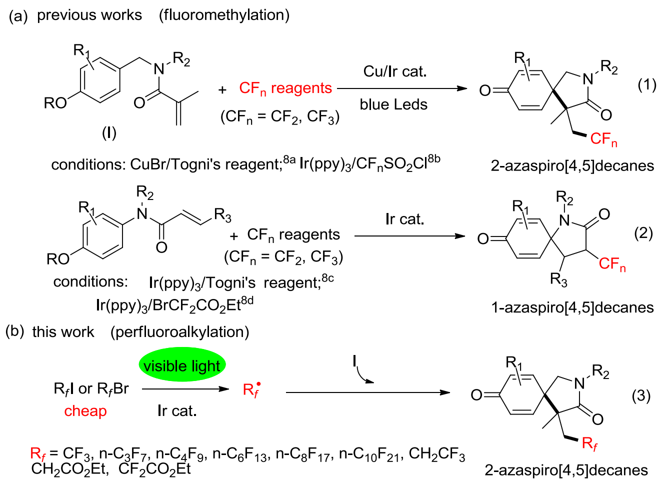


Scheme 1. Dearomative cyclization of acrylamides leading to fluorinated azaspirocyclic cyclohexadienones.

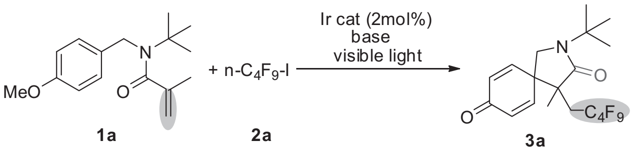
[4.5]deca-6,9-diene-3,8-diones bearing various perfluorinated groups such as CF_3, n-C_3F_7, n-C_4F_9, n-C_6F_{13}, n-C_8F_{17}, n-$C_{10}F_{21}$, CH_2CF_3, CF_2CO_2Et under mild reaction conditions (Scheme 1, Eq. (3)).

Results and discussion

Our preliminary investigation started from the model cyclization cascade between *N*-benzylacrylamides **1a** and perfluorobutyl iodide **2a** under visible-light irradiation from 5W blue LEDs (Table 1). A set of solvents were investigated initially, and it showed that when DMF (entry 1) was used as solvent, the desired perfluorinated-containing **3a** in 48% yields was generated in the presence of Ir catalyst (entry 1). Sequentially, a series of data indicated that the solvent, base and photocatalyst have important influence on the reactions (entries 2–6). Encouraged by this results, alternative bases were tested in attempting to improve the yield further. Unfortunately, the use of the K_3PO_4, CH_3CO_2Li, CH_3CO_2K and K_2HPO_4 gave lower yields (entries 7–10). After further screening, the K_2CO_3 turned out to be the optimal base among other inorganic bases (entry 11). In addition, the polarity of medium can be enhanced to stabilize the carbocation intermediate with the addition of water to the reaction mixture,[8b] which increased the yield to 65% (entry 12). Subsequently, the photocatalysts were also tried. However, when using $Ru(bpy)_3Cl_2$, $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and eosin Y as catalysts, no products were detected (entries 13–15). In order to indicate that visible light is necessary, one control experiment was also carried out for the cyclization. Expectedly, the reaction did not work in the darkness (entry 16).

With the optimized conditions possessed, we targeted to investigate the scope of substrate leading to perfluorinated azaspirocyclic cyclohexadienones (Scheme 2). Firstly, we investigated the compatibility of *N*-substituents of *N*-benzylacrylamides. Delightfully, the reaction conditions could tolerate a series of alkyl groups (e.g. *n*-Bu, *t*-Bu and i-Pr) on the N atom, thereby affording a series of perfluorinated 2-azaspiro[4.5]deca-6,9-diene-3,8-diones in moderate to good yield (**3a**–**3c**) through tandem cyclization/dearomatization process. Next, we continued to examine the substrate scope with a series of substituents on aromatic ring. Fortunately, we observed that the reactions of both Br and Cl at 3-position of aromatic ring proceeded smoothly to afford corresponding azaspirocyclic cyclohexadienone isomers in moderate yields, respectively (**3e**–**3f′**). Furthermore, in order to form a uni-

Table 1
Optimization of reaction conditions.[a]



Entry	Initiator	Base	Solvent	Yield **3a** (%)[b]
1	*fac*-$Ir(ppy)_3$	Li_2CO_3	DMF	48
2	*fac*-$Ir(ppy)_3$	Li_2CO_3	Dioxane	42
3	*fac*-$Ir(ppy)_3$	Li_2CO_3	DCE	32
4	*fac*-$Ir(ppy)_3$	Li_2CO_3	DMSO	27
5	*fac*-$Ir(ppy)_3$	Li_2CO_3	CH_3CN	46
6	*fac*-$Ir(ppy)_3$	Li_2CO_3	DMF/CH_3CN	35
7	*fac*-$Ir(ppy)_3$	K_3PO_4	DMF	40
8	*fac*-$Ir(ppy)_3$	CH_3COOLi	DMF	29
9	*fac*-$Ir(ppy)_3$	CH_3COOK	DMF	37
10	*fac*-$Ir(ppy)_3$	K_2HPO_4	DMF	38
11	*fac*-$Ir(ppy)_3$	K_2CO_3	DMF	54
12[c]	*fac*-$Ir(ppy)_3$	K_2CO_3	DMF	65
13	$Ru(bpy)_3Cl_2$	K_2CO_3	DMF	Trace
14	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2CO_3	DMF	Trace
15[d]	Eosin Y	K_2CO_3	DMF	Trace
16[e]	*fac*-$Ir(ppy)_3$	K_2CO_3	DMF	Trace

[a] Reaction conditions: **1a** (0.3 mmol), C_4F_9I (2 equiv), photocatalyst (2 mol%), base (3 equiv), and solvent (2 mL) were irradiated with a 5 W blue LEDs at room temperature for 18 h under N_2. DMF = *N,N*-dimethyl formamide, DCE = 1,2-dichloroethane, DMSO = dimethyl sulfoxide.

[b] Yield of the isolated product.

[c] 2 equiv. of water as additive.

[d] Using 5 mol% of photocatalyst.

[e] Under darkness.