



Visible light induced hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide

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ARTICLE INFO

Keywords:

Oxindole
Alkene
Difluoromethylation
Phosphonium salt
Photoredox catalysis

ABSTRACT

A visible light induced hydrodifluoromethylation of alkenes derived from oxindoles with (difluoromethyl)triphenylphosphonium bromide was developed. This reaction delivers a series of previously unknown difluoromethylated oxindoles containing C–CF₂H quaternary centers in moderate to excellent yields. The resulting CF₂H-containing oxindoles are potentially useful in drug discovery.

1. Introduction

The indolin-2-one (oxindole) frame is commonly found in natural compounds as well as in biological active compounds [1]. Especially, the 3-substituted oxindoles are widely recognized as valuable synthetic intermediates [2]. On the other hand, the incorporation of fluorine atom(s) and fluorine-containing groups into organic molecules has a significant influence on the lipophilicity, metabolic stability, and bioavailability of compounds [3]. Given the biological importance of fluorinated functional groups and oxindole scaffolds, the fluorinated oxindoles have many applications in drug development [4]. Over the last decade, there has been continuous interest in the preparation of oxindoles bearing fluorinated functional groups at the 3-position. Up to now, numerous synthetic methods have been developed for the preparation fluorinated oxindoles, such as 3-fluoro-2-oxindoles [5], 3,3-difluoro-2-oxindoles [6], 3-trifluoromethyl-2-oxindoles [7], 3-difluoroalkyl-2-oxindoles [8], and 3-monofluoroalkyl-2-oxindoles [9].

The difluoromethyl moiety (CF₂H) is an intriguing structural motif that has special biological properties [10]. Additionally, it is proposed to act as a hydrogen bond donor and thus a surrogate for hydroxyl or thiol groups [11]. Recently, a variety of methods have been developed for the direct introduction of CF₂H into organic compounds [12,13]. However, the synthesis of difluoromethylated oxindoles remains limited. In 2014, the groups of Dolbier [14a], Wang [14b,c], and Tan [14d] independently reported the photoredox- or transition-metal-catalyzed radical difluoromethylation/cyclization of *N*-arylacrylamides for the construction of difluoromethylated oxindoles with different CF₂H

sources (Scheme 1a). Although these methods are efficient, the substrates are limited to the disubstituted terminal alkenes. Thus, the development of new synthetic methods of difluoromethylated oxindoles is highly desirable.

Very recently, our group disclosed that bromodifluoromethylphosphonium bromide was used as a CF₂H radical precursor for the difunctionalization-type difluoromethylation reactions of alkenes under visible light photoredox conditions [15]. To further extend the application of difluoromethylphosphonium salts, we became interested in the incorporation of CF₂H into oxindoles (Scheme 1b). This protocol affords a series of difluoromethylated oxindoles containing C–CF₂H quaternary centers, which are difficult to access by existing methods.

2. Results and discussion

We initiated our exploration by investigating the difluoromethylation of 3-(propan-2-ylidene)indolin-2-one (**1a**) with several difluoromethylphosphonium salts (**2a–d**) in the presence of Ir(ppy)₃ (3 mol%) under visible-light irradiation (Table 1). To our disappointment, no desired product was obtained using difluoromethylphosphonium salts **2a–c** (entries 1–3). In contrast, difluoromethylphosphonium bromide (**2d**) could promote this reaction, giving the difluoromethylated product **3a** in 33% yield (entry 4). We envisioned that the bromide anion probably acted as a reductive quencher in the catalytic cycle of this reaction. Thus, we investigated different additives, including tetra-*n*-butylammonium iodide (TBAI), diisopropylethylamine (DIPEA), NaI, and KI (entries 5–8). Among them, KI was

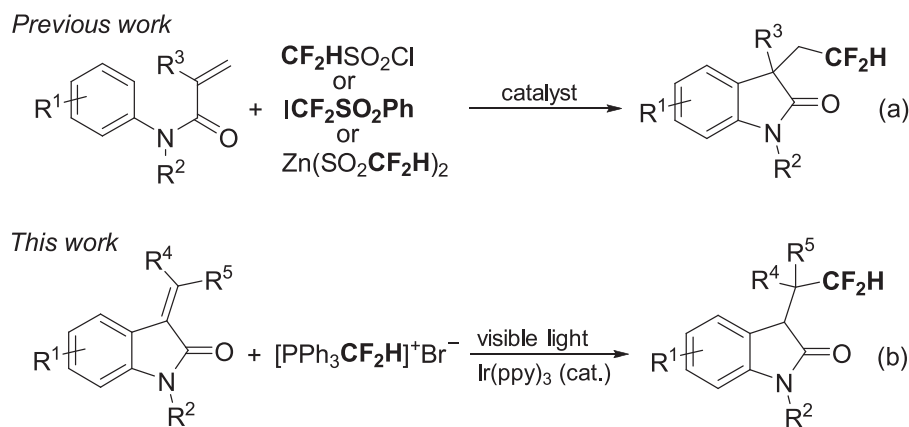
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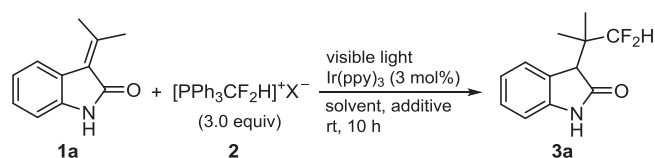
<https://doi.org/10.1016/j.jfluchem.2018.01.013>

Received 7 December 2017; Received in revised form 27 January 2018; Accepted 27 January 2018

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Scheme 1. Synthesis of difluoromethylated oxindoles.

Table 1
Optimization of reaction conditions.^a

Entry	2 (X)	Solvent	Additive	Yield (%) ^b
1	2a (PF ₆)	DMF	–	0
2	2b (BF ₄)	DMF	–	0
3	2c (OTf)	DMF	–	0
4	2d (Br)	DMF	–	33
5	2d (Br)	DMF	TBAI	72
6	2d (Br)	DMF	DIPEA	50
7	2d (Br)	DMF	NaI	75
8	2d (Br)	DMF	KI	77
9	2d (Br)	DCE	KI	84
10	2d (Br)	EA	KI	0
11	2d (Br)	THF	KI	89
12	2d (Br)	CH ₃ CN	KI	96
13 ^c	2d (Br)	CH ₃ CN	KI	71
14 ^d	2d (Br)	CH ₃ CN	KI	85
15 ^e	2d (Br)	CH ₃ CN	KI	0
16 ^f	2d (Br)	CH ₃ CN	KI	94
17 ^g	2d (Br)	CH ₃ CN	KI	0
18 ^h	2d (Br)	CH ₃ CN	KI	0

^a Reaction conditions: **1a** (0.2 mmol), difluoromethyltriphenylphosphonium salt (0.6 mmol), Ir(ppy)₃ (0.006 mmol), additive (0.4 mmol), solvent (2.0 mL), visible light, rt, under N₂.

^b Yields were determined by ¹⁹F NMR spectroscopy using fluorobenzene as an internal standard.

^c Difluoromethyltriphenylphosphonium bromide (0.4 mmol).

^d Ir(ppy)₃ (0.002 mmol) was added.

^e Without degassing.

^f H₂O (0.6 mmol) was added.

^g Without Ir(ppy)₃.

^h No light.

superior to other additives, affording **3a** in 77% yield (entry 8). Subsequent variation of the solvent led to the discovery that CH₃CN was an excellent solvent for this reaction (entries 9–12). Decreasing the amount of **2d** or Ir(ppy)₃ resulted in lower yields (entries 13 and 14). Notably, **1a** was not converted at all without the degassing of the reaction system, which signified that rigorous exclusion of oxygen is necessary for this reaction (entry 15). Furthermore, the presence of water did not affect the reaction (entry 16). Finally, the control experiments showed that both the photocatalyst and visible light were indispensable for this transformation (entries 17 and 18).

With the optimized reaction conditions in hand (Table 1, entry 12), the substrate scope of this transformation was investigated. As shown in Table 2, a series of oxindole-derived alkenes (**1b–o**) with different substituents and substitution patterns underwent the

hydrodifluoromethylation to afford the corresponding products (**3b–o**) in moderate to excellent yields. The substrates with either electron-donating (**1b** and **1c**) or electron-withdrawing substituents (**1d** and **1e**) were suitable substrates. Moreover, different halide substitutions on the oxindole ring (**1f–j**) were well tolerated, and the corresponding adducts were obtained in high yields. When compound **1k** with methyl as the *N*-protecting group was subjected to the reaction, slightly lower yield was obtained. Finally, this photocatalytic protocol presented herein was easily extended to other polysubstituted oxindole-derived alkenes (**1l–o**). The structure of these hydrodifluoromethylated products were confirmed by the X-ray crystallographic analysis of **3g** (see the Supporting information).

To gain insight into the reaction mechanism, the isotopic labeling experiments were conducted under standard reaction conditions. When

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