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A concise synthesis of tunable fluorescent 1,3-dihydroisobenzofuran derivatives as new fluorophores

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ABSTRACT

A convenient potassium *tert*-butoxide catalyzed addition–elimination reaction has been achieved using *exo*-cyclic enol ethers and aryl aldehydes as the starting materials. The transition-metal free reaction proceeded smoothly to afford 1,3-dihydroisobenzofuran derivatives with good to excellent yields. More importantly, the resulting products were discovered as novel fluorophores with good fluorescence properties and remarkable Stokes shifts. Changing the nature of the substituents in 1,3-dihydroisobenzofurans derivatives allowed the maximum emission wavelengths to be tuned between 438 and 597 nm and the Stokes shifts varied between 63 and 166 nm. In particular, derivative **C27** containing a piperidyl and a cyano group showed the maximum emission wavelength of 597 nm and a Stokes shift of 166 nm.

1. Introduction

Fluorescent molecules have recently attracted significant attention because of their extensive applications in the dyeing industry and in various fields of research [1–3]. Efficient, high-yield strategies to synthesize fluorescent scaffolds are therefore quite desirable [4–7], particularly methods of generating “smart” fluorophores with tunable fluorescent emission [8–23]. These fluorescent scaffolds typically have a core with extended π-conjugated aryl-(hetero)aryl motifs. Extending such π-conjugated systems by introducing a vinyl or aromatic group can yield high-emission fluorophores that are particularly useful for bioimaging [24–31].

Despite significant progress in this area, efficiently generating small useful organic fluorophores in biological applications remains a challenge. One class of compounds with substantial potential as tunable fluorophores are 1,3-dihydroisobenzofuran derivatives, a new type of vinylogous analogues of benzalphthalide [32], which can be served as a potential medical intermediate. Little is known about how the structure of these derivatives influences their fluorescence, which is a crucial question since it is possible that substituting the 1,3-dihydroisobenzofuran core may generate a diverse library of fluorophores with large Stokes shifts.

Synthesis of 1,3-dihydroisobenzofuran derivatives requires functionalizing benzylic methylene, which typically relies on reactions catalyzed by transition metal salts or complexes [33–38]. This functionalization has also been achieved using metal-free catalysts such as diphenyl phosphate [39], MsOH [40], chiral phosphoric acids [41] and ammonium salts [42,43], in which oxidant was usually needed. Another alternative is direct benzylic C–H activation by photoredox catalysis [44]. We recently reported a novel method for synthesizing a new type of 1,3-dihydroisobenzofuran derivatives **C** by reacting *exo*-cyclic enol ethers with imines in the presence of stoichiometric potassium *tert*-butoxide (*t*-BuOK, 1.2 equivalent) [45].

Here we improve on that approach by reacting *exo*-cyclic enol ethers with aldehydes directly, instead of with imines, in the presence of a catalytic amount of *t*-BuOK (20 mol%). This method is much more efficient because it does not require the preparation of imines from aldehydes and it does not release amine as a by-product. More importantly, this approach allows the concise generation of structurally diverse 1,3-dihydroisobenzofuran derivatives as novel fluorophores with fluorescence emission wavelengths varying from 438 to 597 nm and remarkable Stokes shifts of up to 166 nm.

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2. Results and discussion

2.1. Reaction optimization

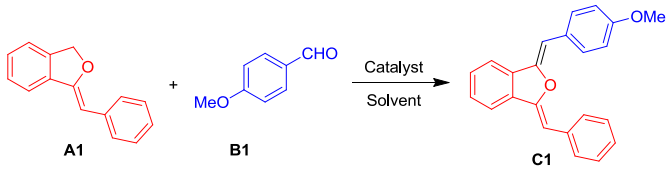
As shown in Table 1, we used (*Z*)-1-benzylidene-1,3-dihydroisobenzofuran (**A1**) and 4-methoxybenzaldehyde (**B1**) as the model substrates to investigate the reaction of *exo*-cyclic enol ether with aldehyde. Firstly, we screened several kinds of bases for the reaction of **A1** and **B1** in DMF, and found that the reaction proceeded to afford the product **C1** after 10 h in 46% yield at 80 °C in the presence of 20 mol% *t*-BuOK (entry 1). Other bases such as KHMDS and KOH also gave similar results, but NaH gave only 24% yield (entries 2–4). When DBU and K_2CO_3 were used, no reaction was observed due to the weak basicity (entries 5 and 6). Interestingly, adding 18-crown-6 (30 mol%) to the reaction substantially increased the yield of **C1** to 80% after only 4.5 h at 80 °C (entry 7). Increasing the reaction temperature to 110 °C led to a complete reaction with 82% yield within 2 h (entry 8). The effect of organic solvents was also examined, and it is noteworthy that DMSO used in the reaction of *exo*-cyclic enol ethers with imines was ineffective in the reaction of *exo*-cyclic enol ethers with aldehydes and product **C1** was not detected (entry 9). The reactions in THF or toluene gave substantially decreased yields and the reactions in acetonitrile or dichloroethane (DCE) led to no desired product (entries 10–13). The amount of catalyst proved crucial to the reaction of **A1** with **B1**, and **C1** was not generated when the amount of *t*-BuOK was decreased to 10 mol% (entry 14).

2.2. Substrate scope

Next, we studied the scope of the reaction using a series of aldehydes and various *exo*-cyclic enol ethers (Table 2). The reaction was examined in DMF at 110 °C, using 20 mol% of *t*-BuOK as the catalyst and 30 mol% of 18-crown-6 as the additive. A series of benzaldehydes with *para*-substituted electron-donating groups, such as methoxy, methylthio, *t*-butyl and methyl groups, readily reacted with 1,3-dihydroisobenzofuran **A** to give the products **C1**–C**4** in moderate to high yields, and the methoxy group gave the best yield of 81%. The fact suggests that the stronger electron-donating ability of methoxy group contributes to the higher yield. Notably, when more strongly electron-donating *N*,*N*-dimethylamino, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl were used as the *para*-substituents of benzaldehyde, the reactions of **A** with them proceeded smoothly to afford the products **C5**–**C8** in excellent 88–99% yields. In contrast, 2-methoxy and 3,4-dimethoxy substituted benzaldehydes were tested in the reactions with **A**, only 52% and 53% yields were observed for the products **C9** and **C10**, respectively. Nevertheless, 2,4-dimethoxy benzaldehyde reacted with **A** to give product **C11** in 90% yield. The different yields between **C10** and **C11** reveals that the electron-donating ability in ortho-position is stronger than that in meta-position. It is noteworthy that benzaldehyde, benzaldehydes containing electron-withdrawing substituents, naphthaldehydes or alkylaldehydes were ineffective in this catalytic reaction.

Subsequently, we tested the reactions of a series of *exo*-cyclic enol ethers with 4-(dimethylamino)benzaldehyde. *Exo*-cyclic enol ethers in which R^2 was a phenyl ring *para*-substituted with electron-donating methoxy and methyl groups or electron-withdrawing chloro, trifluoromethyl, and cyano groups reacted well to afford the desired products **C12**–**C16** in 83–89% yields. If R^2 of *exo*-cyclic enol ethers was changed to 2-methoxyphenyl, 2-chlorophenyl, 3-chlorophenyl or 2-naphthyl, the reactions of *exo*-cyclic enol ethers with 4-(dimethylamino)benzaldehyde also proceeded smoothly to afford the products **C17**–**C20** in 75%–93% yields. Substituting the R^1 position of *exo*-cyclic enol ethers with methyl or chloro group gave products **C21** and **C22** in 89% and 98% yield, respectively. The *exo*-cyclic enol ether carrying two methoxy groups at R^1 and 4-methoxyphenyl at R^2 gave product **C23** in only 53% yield, while the *exo*-cyclic enol ether carrying a fluoro atom at R^1 and 4-fluorophenyl at R^2 afforded product **C24** in decreased 34% yield. Finally, we used 4-(piperidin-1-yl)benzaldehyde to react with the *exo*-cyclic enol ethers containing 4-hydroxymethylphenyl, 4-cyanophenyl at R^2 or a cyano group at R^1, the reactions produced **C25**–**C27** in 63–82% yields.

Table 1
Optimization of conditions for the reaction of **A1** with **B1**.[a]



Entry	catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	*t*-BuOK	DMF	80	10	46
2	KHMDS	DMF	80	10	44
3	KOH	DMF	80	10	43
4	NaH	DMF	80	10	24
5	DBU	DMF	80	10	n.d.
6	K_2CO_3	DMF	80	10	n.d.
7[c]	*t*-BuOK	DMF	80	4.5	80
8[c]	*t*-BuOK	DMF	110	2	82
9[c]	*t*-BuOK	DMSO	110	2	n.d.
10[c]	*t*-BuOK	THF	110	2	45
11[c]	*t*-BuOK	toluene	110	2	14
12[c]	*t*-BuOK	MeCN	110	2	n.d.
13[c]	*t*-BuOK	DCE	110	2	n.d.
14[d]	*t*-BuOK	DMF	110	10	n.d.

[a] Reaction conditions: **A1** (0.2 mmol), **B1** (0.3 mmol), catalyst (0.04 mmol), solvent (1.0 mL), unless otherwise noted.
[b] Determined by ^{1}H NMR using $PhSiMe_3$ as the internal standard.
[c] 30 mol% of 18-crown-6 was added.
[d] 10 mol% of *t*-BuOK and 15 mol% of 18-crown-6 were used, n.d. = not detected.

2.3. Reaction mechanism

Based on the experimental results, we proposed the reaction mechanism of *exo*-cyclic enol ethers **A** and aldehydes **B** (Scheme 1). First, deprotonation of exo-cyclic enol ethers **A** in the presence of *t*-BuOK affords intermediate **D**, which adds to aldehydes **B** to produce **E**. The oxygen anion **E** traps a proton, leading to the key intermediate **F**. Then, deprotonation of **F** gives **G** which undergoes an E2 elimination to afford the desired product **C**.

2.4. Photophysical properties

After the facile preparation of these 1,3-dihydroisobenzofuran derivatives, we then examined their photophysical properties. The UV absorption spectra of compounds **C1**–**C27** in dichloromethane are shown in Fig. 1. As shown in Fig. 1a–e, we can see that the maximum absorption wavelength of each product has little difference. In general, the products **C1**–**C4** and **C9**–**C11** bearing MeO, SMe, *t*-Bu or Me groups have similar absorption spectra and their absorption peaks are located around 380 nm in the range of 350 and 450 nm, which suggests that the above substituents possess the similar electron-donating ability. In contrast, when piperidyl, *N*,*N*-dimethyl, pyrrolidyl and morpholinyl were introduced to form products **C5**–**C8** and **C12**–**C27**, the absorption peaks are all red-shifted. The results are ascribed to the stronger electron-donating ability of N atom than O, S and C atoms. In particular,