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Synthesis of new fluorescent molecules having an aggregation-induced emission property derived from 4-fluoroisoxazoles

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Abstract

Fluorescent molecules based on a fluorinated isoxazole scaffold were provided for the synthetic methods and their photochemical properties. Simple 3,5-diarylisoxazoles led to increasing the fluorescent intensity and exhibited a redshift in the emission intensity by introducing a fluorine atom. α-Fluorinated boron ketoiminates (F-BKIs) derived from a ring opening reaction of 4-fluoroisoxazoles were also synthesized and exhibited a highly fluorescent luminescence as a new aggregation-induced emission (AIE) fluorophore.

Keywords

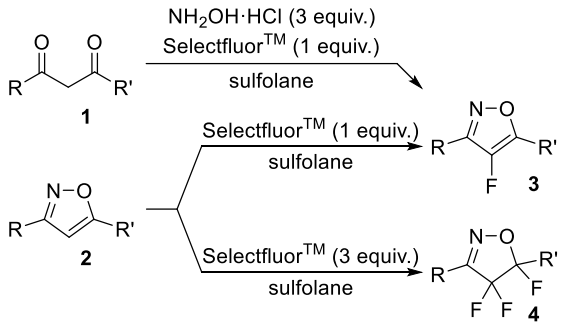
Fluorescence probe; Aggregation-induced emission; 4-Fluoroisoxazoles; Boron ketoiminates; α-fluorinated boron ketoiminates

Introduction

Fluorescence bio-probes based on conventional organic dyes are used for enzyme activity measurement and bio-imaging system, and especially give great results in the field of clinical diagnostic agents.[1-7] Most of the fluorescence bio-probes are mainly excited with near-ultraviolet ray and blue light ray, and they involve fluorescein, rhodamine, or 7-amino-4-methylcoumarin (7-AMC) scaffolds as convenient fluorophores in the molecules. Although these fluorophores usually exhibit strong fluorescence in the dilute solution, most of their emissions are partially or completely quenched in the solid states or in the highly concentrated solution by aggregation-caused quenching (ACQ) on account of the formation of delocalized excitons or excimers.[8] However, several molecules can exhibit strong emission when a molecular aggregate occurs in poor solvents or in the solid state. This property is called aggregation-induced emission (AIE) and has attracted much attention in the field of fluorescence bio-probes.[9-14] This is meaning that the AIE property that has weak fluorescence or non-fluorescence in a dilute solution but exhibits strong fluorescence in an aggregation state gives new photo functions to the bio-probes. For example, it is presumed that prion disease, which is caused by the accumulation of prion protein aggregates in the brain, plays an important role in the pathophysiological mechanism of prion protein-polymerized oligomers. However, since prion protein oligomers cannot be visualized with conventional fluorescent probes, the use of AIE fluorescent probes

are prospected for analyzing the causal relationship between prion diseases and prion proteins.

On the other hand, many fluorinated 6-membered heteroaromatic derivatives find applications in a wide variety of drugs and plant protective materials and, consequently, there are several examples of the synthesis of fluorinated 6-membered heteroaromatic rings by selective fluorination strategies.[15-27] However, selective fluorination of 5-membered heteroaromatic systems are rare and, in particular, there are only a few reports concerning the synthesis of fluorinated 5-membered heteroaromatic systems that have two heteroatoms, such as pyrazoles[28,29], isoxaoles[30] and thiazoles[31,32]. We recently reported selective fluorination of isoxazoles to give mono-fluorinated isoxazoles (**3**) or tri-fluorinated isoxazolines (**4**) in moderate to good yields (Scheme 1).[33] In addition, we also reported the reaction proceeded smoothly by starting with 1,3-diketones (**1**) to give **3** in excellent yields as one-pot reaction.



Scheme 1: Selective fluorination of isoxazoles and one-pot synthesis of 4-fluoroisoxazoles.

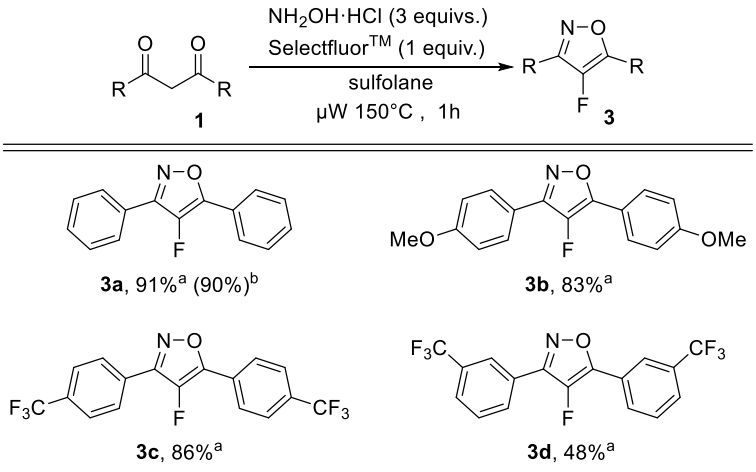
As part of a wider research program aimed at the applications of fluorinated 5-membered heteroaromatic systems, in this paper, we report the fluorescent luminescence characteristics of 4-fluoroisoxazoles and, the synthesis of α-fluorinated boron ketoiminates (F-BKIs) and their photochemical properties.

Results and Discussion

Synthesis and optical properties of 4-fluorinated isoxazoles

Although there are a huge number of fluorescent molecules, the fluorescent probes involving isoxazole scaffold are rare. Even if that were the case, those fluorescent probes are also including other fluorophores such as styryl-, anthranyl-, or pyrenyl-group in the molecules. We recently reported the synthesis of 4-fluoroisoxazoles (**3**), and 3,5-diaryl 4-fluoroisoxazoles are essentially planar structures in the previous paper.[33] These results suggest that **3** might have a potential ability as a fluorophore. Therefore, 3,5-diaryl 4-fluoroisoxazoles (**3**) were synthesized from 1,3-diketones (**1**) treating with Selectfluor™ and $NH_2OH \cdot HCl$ by microwave (μW) irradiation according to the previous method (Table 1). Since **3b** and **3c** have exhibited fluorescent properties by irradiation with a UV lamp, we measured further photochemical properties (Fig 1.). It is interesting that introducing a fluorine atom into the isoxazole scaffold led to increasing the fluorescent intensity and exhibited a redshift in the emission intensity.

Table 1: One-pot reaction for the synthesis of 3,5-disubstituted 4-fluoroisoxazoles (**3**).



[a]Isolated yield.
[b]Isolated yield by using conventional heating (oil bath) at 150°C for 1h.

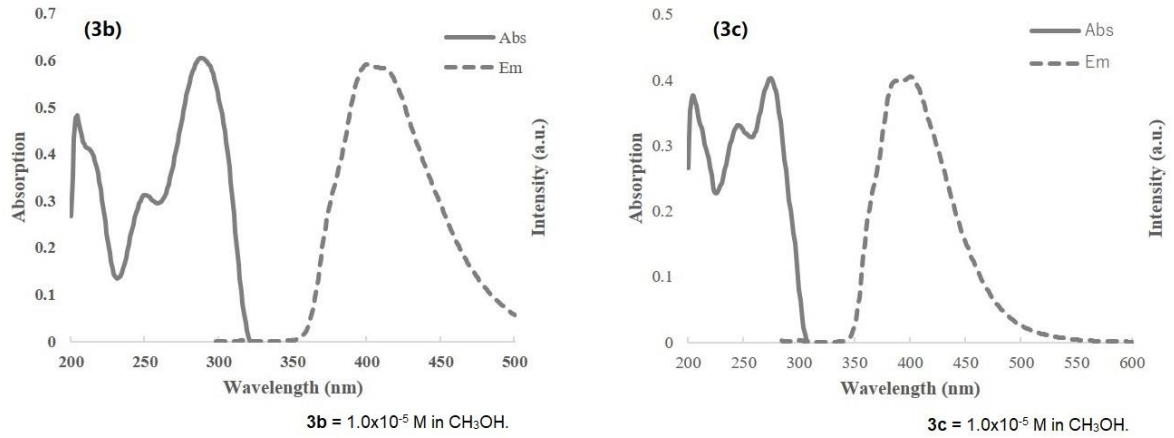
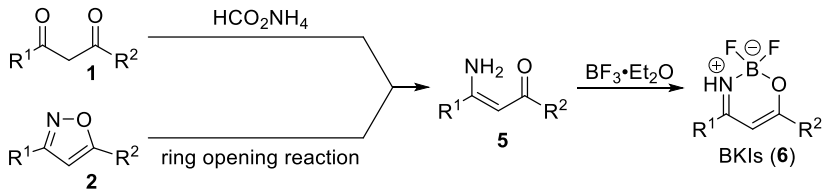


Figure 1: UV/Vis and FL spectra of compounds **3b** and **3c**.

Synthesis of boron ketoiminates and α-fluorinated boron ketoiminates

Boron ketoiminates (BKIs, **6**) are one of the new types of boron-chelating dye.[34-38] Their optical properties feature a large Stokes shift and high-molar absorption coefficient (*ε*) that are quite similar to the corresponding boron diketonates. Some groups reported about the synthetic methods and their properties of BKIs that can be easily synthesized from the corresponding 1,3-diketones (**1**) or from the corresponding isoxazoles (**2**) by ring opening reaction (Scheme 2).

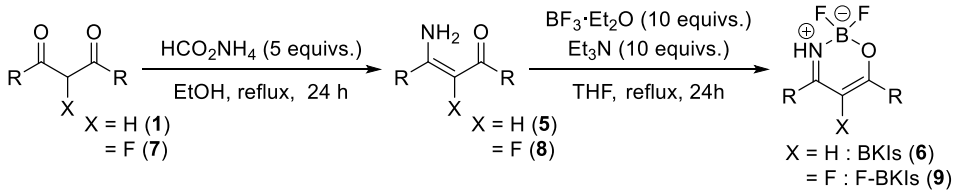


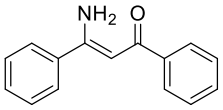
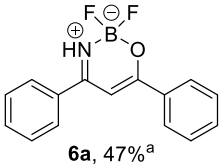
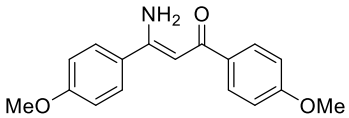
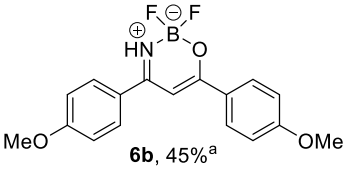
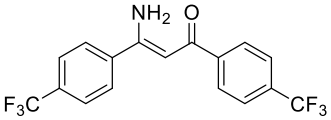
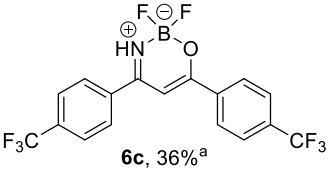
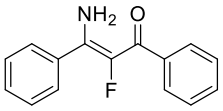
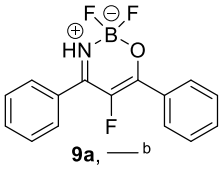
Scheme 2: Synthesis of BKIs (**6**) from 1,3-diketones (**1**) or isoxazoles (**2**).

Based on the above results, we attempted to introduce a fluorine atom into BKIs for the synthesis of α-fluorinated boron ketoiminates (F-BKIs, **9**) structure. First, 1,3-

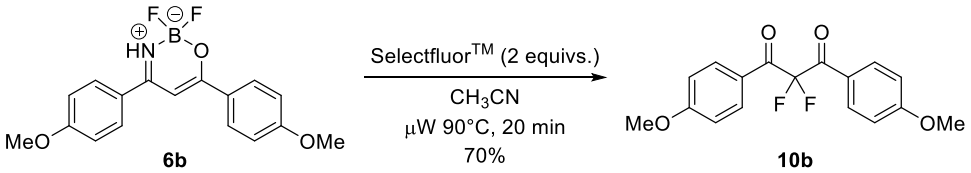
diketones (**1**) were treated with ammonium formate to give the corresponding enaminoketone (**5**) in high yields as shown in entries 1-3 (Table 2). Then, the synthesized **3** were treated with 10 equivs. of $BF_3{\cdot}Et_2O$ in anhydrous THF solution in the presence of an excess amount of Et_3N to give BKIs **6** in moderate yields. On the other hand, when the same condition was applied to the 2-fluoro-1,3-diphenylpropane-1,3-dione (**7a**), only a few enaminoketone **8a** was obtained (entry 4). Therefore, the subsequent reaction for giving α-fluorinated boron ketoiminates (F-BKIs, **9a**) had to be abandoned. Next, selective fluorination was conducted to **6b** for giving F-BKIs **9b**, but the attempt was failed and was only gave the corresponding α,α-difluoro-1,3-diketone **10b** in a 70% yield (Scheme 3).

Table 2: Synthesis of enaminoketones (**3**) and BKIs (**4**).



entry	enaminoketone (**3**)	BKIs (**4**)
1	 **5a**, 96%[a]	 **6a**, 47%[a]
2	 **5b**, 79%[a]	 **6b**, 45%[a]
3	 **5c**, 75%[a]	 **6c**, 36%[a]
4	 **8a**, 15%[a]	 **9a**, —[b]

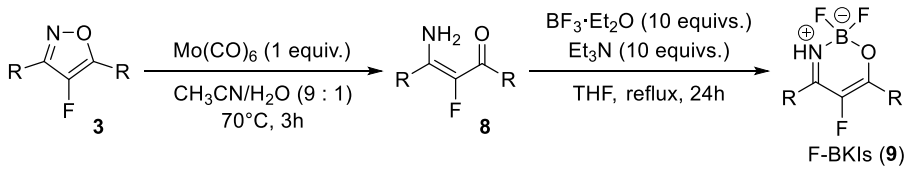
[a]Isolated yield. [b]The boron complexation process towards **8a** was not examined.

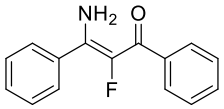
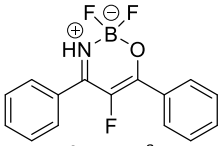
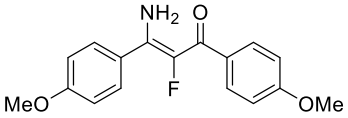
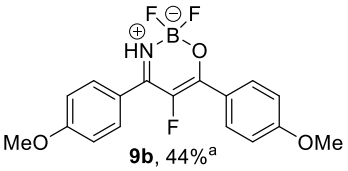
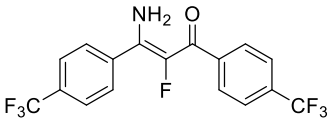
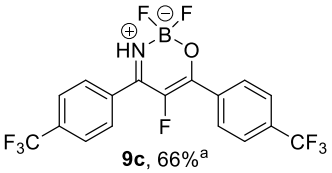


Scheme 3: Selective fluorination towards BKIs **6b**.

As an alternative method, a ring-opening reaction of isoxazoles was applied to the synthesis of F-BKIs **9**. It is well-known that the reductive cleavage of N–O bond in the isoxazole has been efficiently performed by using transition metals or their complexes to give the corresponding enaminoketones **5**.[35,37] Consequently, we examined several conditions for the ring opening of **3**, and it revealed that the use of $Mo(CO)_6$ as a metal complex for reductive cleavage of N–O bond gave the corresponding α-fluorinated enaminoketones **8** in moderate yields (Table 3). Then subsequent boron complexation process towards **8** that employed $BF_3 \cdot Et_2O$ and Et_3N gave the desired F-BKIs **9** in moderate to good yields.

Table 3: Ring opening reaction of 4-fluoroisoxazoles (**3**) followed by the synthesis of F-BKIs (**9**).



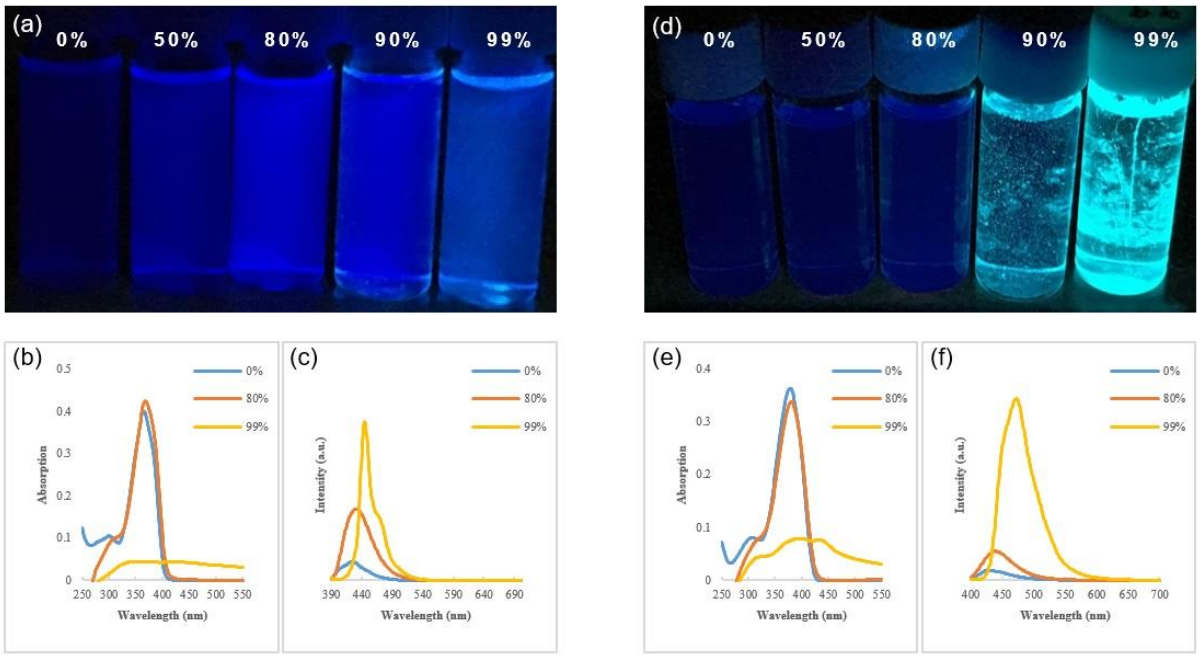
entry	α-F enaminoketone (**8**)	F-BKIs (**9**)
1	 **8a**, 61%[a]	 **9a**, 79%[a]
2	 **8b**, 41%[a]	 **9b**, 44%[a]
3	 **8c**, 41%[a]	 **9c**, 66%[a]

[a]Isolated yield.

Optical properties of boron ketoiminates and α-fluorinated boron ketoiminates

Chujo and his group have described that BKIs could be a promising structure for receiving AIE properties.[36] For the purpose of comparison with the photochemical properties of BKIs and F-BKIs, we measured the optical properties of **6** and **9**. As shown in Fig. 2, the UV/Vis absorptions spectra of **6b** and **9b** in THF were decreased by adding H_2O, and white precipitates have appeared in the samples accordingly as over 80% of water contents. On the other hand, the fluorescent luminescence (FL) of **6b** and **9b** exhibited an increase in the emission intensities along with the formation of white precipitates. Although the FL intensities had relatively low than the

corresponding BKIs, a similar tendency has also appeared in other F-BKIs (**9a** and **9c**). In other words, it was revealed that F-BKIs are exhibited AIE property.



(a-c) Photograph, UV/Vis and FL spectra of **6b** with solvent compositions of the THF/H_2O mixture upon excitation at 389 nm (1.0 x 10^{-5} M). (d-f) Photograph, UV/Vis and FL spectra of **9b** on solvent compositions of the THF/H_2O mixture upon excitation at 380 nm (1.0 x 10^{-5} M).

Figure 2: Photochemical properties comparisons of BKIs and F-BKIs.

Conclusion

In conclusion, we demonstrated that 3,5-diaryl-4-fluoroisoxazoles exhibited a fluorescent luminescence, while the emissions were not strong. It is interesting that introducing fluorine atom into the isoxazole scaffold led to increasing the fluorescent intensity and exhibited a redshift in the emission intensity. We achieved the first synthesis of α-fluorinated boron ketoiminates (F-BKIs) by applying a reductive

cleavage of N–O bond of α-fluorinated isoxazoles and clarified that F-BKIs were exhibited AIE property as well as BKI.

Experimental

See Supporting Information File for full experimental data.

Supporting Information

General procedures and analytical data, including copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra.

Supporting Information File 1:

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