One-pot Tandem Synthesis of a Coumarin/Naphthoquinone Monoimine-based Oxazabicycle and Its Fluorescence Redox-switching Properties

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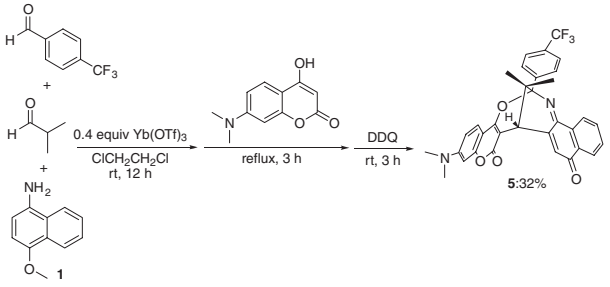
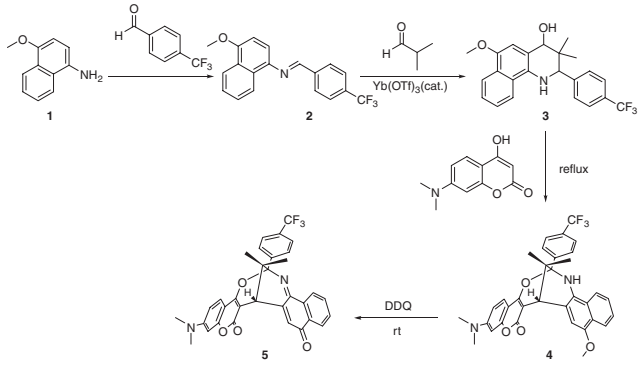
A coumarin/naphthoquinone monoimine-fused oxazabicyclic derivative was designed, synthesized, and characterized in a one-pot tandem reaction and its fluorescence redox switch properties were investigated. The coumarin emission of the synthesized oxazabicycle is completely quenched by the naphthoquinone monoimine moiety, the corresponding reduced aminonaphthalenol resulted in a moderate increase of the emission intensity. The reduced aminonaphthalenol can be reverted to the original nonfluorescence compound via DDQ oxidation. A reversible, fluorescence switch that can be chemically turned ON and OFF through the control of the redox state of the naphthoquinone monoimine moiety is demonstrated.

Fluorescent switching systems find wide use in probes for the determination of local environmental redox properties and also can function as bio-sensor elements to study electron- and energy-transfer mechanisms.[1] Typical organic chemical and electrochemical fluorescent switches are designed by covalently connecting a fluorophore (the donor) and an active redox switch (the acceptor) with a conjugated or unconjugated spacer.[2] The fluorescence emission of the donors can be reversibly quenched depending upon the oxidation state of the acceptors. Although many variables may influence the electronic communication between the fluorophore and the redox quencher, the structural rigidity of the spacer represents one of the major factors in controlling the fluorescence quenching efficiency of a donor-acceptor system.[3] While various redox switch systems using naphthoquinone as the active redox switch have been reported in the literature, little information is known for the acceptor properties of the structurally related quinone imine. Recently, we developed a one-pot tandem reaction for efficient preparation of structurally rigid oxazabicycles.[4] Here, we report our effort in the design and synthesis of a molecule by connecting a coumarin fluorophore with a potential quinone imine quencher through a nonconjugating, highly rigid heterobicyclic ring. Chemical interconversion between the coumarin donor and the quinone imine acceptor of the prepared oxazabicycle was explored by UV–vis spectroscopy, X-ray diffraction analysis, and fluorescence measurements.

Scheme 1 describes the one-pot tandem preparation of the designed oxazabicyclic compound **5**. It was realized by first mixing 4-methoxynaphthalen-1-amine (**1**) with *p*-trifluoromethylbenzaldehyde, isobutyraldehyde and 0.4 equiv of $Yb(OTf)_3$ in 1,2-dichloroethane at room temperature overnight, follow by the addition of 7-dimethylamino-4-hydroxycoumarin and subsequently refluxing for 3 h. After cooling down to room temperature, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was added and the mixture was stirred for 3 h. The oxazabicycle **5** was obtained in an overall yield of 32%. The proposed reaction intermediates are depicted in Scheme 2. It involved the $Yb(OTf)_3$-catalyzed condensation of **1** and *p*-trifluoromethylbenzaldehyde to afford the imine **2**, followed by coupling with isobutyraldehyde to give the cyclized aminoalcohol **3**.[5] The subsequent coupling of **3** with 7-dimethylamino-4-hydroxycoumarin under reflux conditions yielded the cyclized oxazabicycle **4**.[6] Final oxidation of **4** with DDQ afforded the target naphthoquinone monoimine **5**. The heterobicyclic structure was elucidated by X-ray crystallography. Figure 1 shows an ORTEP diagram of oxazabicycle **5**,[7] which clearly reveals a rigid bicyclo[3.3.1] skeleton, along with coumarin and naphthoquinone monoimine moieties. It is noteworthy that the bond formation for this one-pot construction of the bicyclic skeleton was highly efficient and atom-economical, with a total mass loss of only 54 g mol^{-1} from four components in four steps, that is, a sequential release of two molecules of water, one equivalent molecule of hydrogen and one equivalent molecule of methane.



Scheme 1. One-pot tandem synthesis of **5**.



Scheme 2. Proposed reaction sequence of the one-pot tandem synthesis.

Having established the quick access of this oxazabicyclic derivative, we turned our attention toward investigating its redox properties. The readily available oxazabicycle **5** was swiftly converted to the aminonaphthalenol **6** by sodium borohydride reduction in methanol at room temperature. The resulting reduced **6** can be reverted to the original **5** via DDQ oxidation

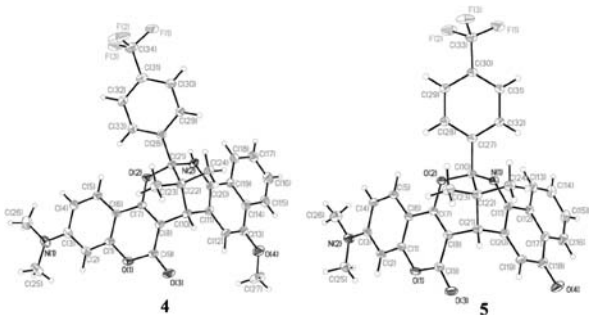
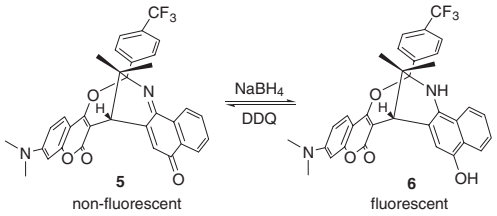


Figure 1. X-ray crystal structures of oxazabicycles **4** and **5**.



Scheme 3. Redox switching between **5** and **6**.

Table 1. Absorption parameters for **5** and **6** in methanol

Compound	λ_{max}/nm	log ε
5	204, 248, 360	4.35, 4.17, 4.01
6	206, 247, 348	4.57, 4.27, 4.05

(Scheme 3).[9] The structure of aminonaphthalenol **6** was indirectly confirmed by methylation of its hydroxy group with methyl iodide. The resultant methylated compound gave the exact same spectroscopic data as that of **4**, whose crystal structure is also depicted in Figure 1.[7]

Table 1 lists the absorption parameters for **5** and **6**.[9] As expected, no drastic absorbance changes of UV–vis spectra were observed after reduction. For the emission properties, the fluorescence of the coumarin derivative **5** was found to be completely quenched at room temperature. It is fully quenched in protic, aprotic polar and nonpolar solvents, therefore the quenching is not solvent-dependent. The quenching of intrinsic fluorescence emission of the coumarin excited state of **5** is probably due to collisionless intramolecular electron-transfer from the excited coumarin to the adjacent quinone imine acceptor.[8] However, instant fluorescence occurs upon reaction of the heterobicycle with a reducing agent. Addition of sodium borohydride to the oxazabicycle **5** in methanol caused reduction of naphthoquinone monoimine to the corresponding reduced form. Reduction of the naphthoquinone monoimine to aminonaphthalenol converts it from an electron-withdrawing group to an electron-donating group, resulting in a profound electronic change in the system, which subsequently leads to a change in the emission profile. Indeed, the reduced **6** was found to emit a moderate fluorescence emission with the quantum yield of 0.12 in toluene. Table 2 lists the fluorescence parameters and quantum yields of **6** in different solvents.[9] Note that the emission of **6** is solvent dependent. The fluorescence intensity increases as the solvent polarity decreases, along with the decrease of the Stoke's shifts. Although the relative emission intensity between the oxidized **5** and the reduced **6** is far from substantial, our studies have clearly demonstrated that

Table 2. Fluorescence parameters for compound **6** in different solvents

Solvent	λ_{ex}/nm	λ_{em}/nm	Stoke's shift /cm^{-1}	Φ_F
CH_3OH	329	379	4010	0.05
CH_3CN	345	411	4655	0.03
CH_2Cl_2	359	403	3041	0.09
Toluene	348	391	3160	0.12

the emission of the fluorophore of the two compounds can be controlled by the redox state of the naphthoquinone monoimine moiety, that is, the quinone imine, along with a suitable spacer connected to the fluorophore, can function as a quencher in a redox switch system just like its counterpart quinone.

In conclusion, an oxazabicycle-based fluorescence redox switch was efficiently synthesized in a one-pot tandem reaction. In this molecule, the fluorophore and the redox couple were fixed in a rigid, unconjugated heterobicyclic ring spacer. The emission properies of the oxazabicycle can be manipulated by external chemical stimuli, that is, by sodium borohydride reduction of naphthoquinone monoimine to give the reduced aminonaphthalenol, which can be reverted to the original nonfluorescence naphthoquinone monoimine via DDQ oxidation.

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7 Crystallographic data (excluding structure factors) for **4** and **5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-690748 and -707791, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033.

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9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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