RSC Advances

ROYAL SOCIETY OF CHEMISTRY

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Cite this: RSC Adv., 2019, 9, 12365

Novel asymmetric photodimerization reaction of coumarin derivatives bearing a chiral 2oxazolidinone auxiliary†

Kennosuke Itoh, ^[b] ^{*ab} Fumiya Odate,^c Takuma Karikomi,^d Keishi Obe,^e Tsutomu Miyamori,^f Hideaki Kamiya,^f Kenji Yoza,^g Kenichiro Nagai, ^[b] ^b Hideaki Fujii, ^[b] ^{*ab} Hiroyuki Suga ^[b] ^{*f} and Ken Tokunaga ^[b] ^{*h}

Received 31st January 2019 Accepted 10th April 2019

DOI: 10.1039/c9ra00822e

rsc.li/rsc-advances

A novel asymmetric photodimerization reaction of coumarin derivatives bearing the (S)-4-benzyl-2oxazolidinone auxiliary provides only the *syn*-head-to-tail (*syn*-HT) dimer with moderate diastereoselectivity (up to 75 : 25). The mechanism of complete *syn*-HT selectivity and moderate diastereoselectivity is proposed based on the result of density functional theory (DFT) calculation. The benzyl group of the (S)-4-benzyl-2-oxazolidinone auxiliary in combination with a Lewis acid exerts effective diastereofacial shielding of the reaction site.

The photodimerization reactions of coumarin derivatives have been recognized as attractive photochemical transformation reactions in terms of their photophysical properties as well as their photochemical properties, from the theoretical point of view.1 Recently, photodimerization reactions of coumarins have become increasingly important in several progressive research areas, e.g., drug delivery by the use of coumarin-modified mesoporous silica MCM-41^{2a} and the use of coumarinmodified polymeric nanoparticles,^{2b,2c} chemical biology,^{2d} 3D cell culture,^{2e} photopatterning of ion gels,^{2f} reversible twodata storage,2g nanolithography,2h photon optical polyoxometalate-containing materials,2i single-chain nanoparticles,^{2j} gelators,^{2k} and optically active polymers.^{2l} Although [2 + 2] photodimerization reactions of coumarin derivatives are useful photochemical reactions, difficulties in controlling headto-head (HH)/head-to-tail (HT), syn/anti, enantio- and diastereoselectivity of the reactions in solution have prevented further improvement of the usefulness and understanding of the reaction. To overcome these issues, several methodologies for syn/anti and HH/HT selective [2 + 2] photodimerization reactions of coumarins in solution have been developed, e.g., Lewis acid catalysis,3 supramolecular photocatalysis accomplished by the use of cyclodextrins,4a hydrazine derivatives,4b bisurea macrocycles,^{4c} cucurbit[8]uril,^{4d} taco-type host-guest complexes4e and self-assembled monolayers of coumarin derivatives on gold.4f For an enantioselective reaction, Tanaka and Fujiwara reported outstanding results of an asymmetric photodimerization of simple coumarin by the use of TADDOL derivatives which gave an anti-HT dimer with excellent enantiomeric excess (up to 96% ee).⁵ However, to the best of our knowledge, the methodology to synthesis a syn-HT dimer in a diastereoselective manner has vet to be demonstrated.6 Herein, we report a novel asymmetric [2 + 2] photodimerization of chiral coumarin-3-carboxamide which gives only syn-HT dimers along with moderate diastereoselectivity.

We initially conducted [2 + 2] photodimerization reactions of (*S*)-4-phenyl-3-(2-oxo-2*H*-chromene-3-carbonyl)-2-oxazolidinone (**1A**) in acetone, resulting in recovery of **1A** without any desired dimers, which could be caused by the incredibly poor solubility of **1A** (Table 1). Next, we tried to use (*S*)-4-isopropyl-3-(2-oxo-2*H*-chromene-3-carbonyl)-2-oxazolidinone (**1B**), which gave **2BE** and **2BF** as an inseparable mixture with good yield and the ratio of **2BE** to **2BF** as 55 : 45. X-ray crystallographic analysis provided a structure of 50 : 50 diastereomeric mixture of **2BE** and **2BF**, which revealed that the reaction had progressed in a *syn*- and HT-selective manner (Fig. 1). We also used (*S*)-4-benzyl-3-(2-oxo-2*H*-chromene-3-carbonyl)-2-oxazolidinone (**1C**) (entry 3) instead of **1B**.

^aLaboratory of Medicinal Chemistry, School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan. E-mail: itok@pharm.kitasato-u.ac.jp ^bMedicinal Research Laboratories, School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

^cApplied Chemistry and Chemical Engineering Program, Graduate School, Kogakuin University, 2665-1 Nakano, Hachioji, Tokyo 192-0015, Japan

^dDepartment of Applied Chemistry, Faculty of Engineering, Kogakuin University, 2665-1 Nakano, Hachioji, Tokyo 192-0015, Japan

^eDepartment of Applied Chemistry, School of Advanced Engineering, Kogakuin University, 2665-1 Nakano, Hachioji, Tokyo 192-0015, Japan

¹Department of Materials Chemistry, Faculty of Engineering, Shinshu University, 4-17-1 Wakasato, Nagano 380-8553, Japan

⁸Bruker Japan, 3-9, Moriya-cho, Kanagawa-ku, Yokohama 221-0022, Japan

^hDivision of Liberal Arts, Center for Promotion of Higher Education, Kogakuin University, 2665-1 Nakano, Hachioji, Tokyo 192-0015, Japan

[†] Electronic supplementary information (ESI) available: Materials, experimental details, and characterization data. CCDC 1552472 (**1C**), 1885142 (**2BE** + **2BF**), 1484443 (**2CE**) and 1552473 (**2CF**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra00822e

As a result, solubility of the chiral coumarin and the diastereomeric ratio of dimers were improved to give 2CE and 2CF with the ratio of 63 : 37 in 99% yield. Photodimer 2CE and 2CF were separable. syn-HT structures of 2CE and 2CF were also successfully determined by X-ray crystallographic analyses. When the reaction was carried out in toluene (entry 4), syn-HT 2CE and syn-HT 2CF were obtained in excellent yield with the same diastereomeric ratio as the reaction in acetone (entry 3 versus entry 4). The yield of syn-HT 2CE and syn-HT 2CF was decreased by the use of $\alpha_1\alpha_2\alpha_3$ -trifluorotoluene (CF₃C₆H₅) as a reaction solvent, which was probably due to low solubility of 1C in CF₃C₆H₅ (entry 5). Solubility enhancement of 1C had a good impact on increasing the reaction rate by the use of CH₂Cl₂, CHCl₃ and CH₃CN as reaction solvents, but decreased the diastereoselectivity as compared to the reaction in toluene (entries 6-8 versus entries 3 and 4). As far as we know, there is only one example of a non-photochemical reaction, which is the highly diastereoselective 1,3-dipolar cycloaddition reaction, by the use of a chiral oxazolidinone-functionalized substrate in the absence of Lewis acid as reported by Sibi and co-workers.7 We were intrigued by induction of moderate diastereoselectivity in the absence of a chelating agent Lewis acid. Therefore, we tried to add Lewis acid in an effort to improve diastereoselectivity by utilizing a chelation control agent.8 Regarding a role for the Lewis acid in [2 + 2] photodimerization reactions, Lewis and coworkers reported the [2 + 2] photodimerization reaction of Paper



Fig. 1 ORTEP drawing of photodimers: the inclusion of chloroform was observed in *syn*-HT 2CE.

achiral coumarin in the presence of $BF_3 \cdot OEt_2$ to give the *syn*-HT dimer as a single product.³ In the search for a good chelating Lewis acid for 3-acyl-2-oxazolidinone derivatives, we tested $Zn(ClO_4)_2 \cdot 6H_2O$ for the reaction of **1B** (entry 9).⁹ A non-coordination solvent toluene was used for the reaction. As a result, the reaction of **1B** was inhibited by the addition of Zn(II) salt to give **2BE** and **2BF** with recovery of **1B** (entry 9).

Interestingly, the reaction of **1C** in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ in toluene proceeded to achieve an improvement of yields and diastereomeric ratio of *syn*-HT dimers (**2CE** : **2CF** = 75 : 25, entry 10). The use of acetone as a reaction solvent and $Zn(ClO_4)_2 \cdot 6H_2O$ as a Lewis acid diminished the yield of *syn*-HT **2CE** and *syn*-HT **2CF** (entry 11). The reaction of **1C** in the presence of $BF_3 \cdot OEt_2$ in toluene showed a slightly improved diastereomeric ratio in comparison with the reaction

Table 1 [2 + 2] Photodimerization reactions of chiral coumarin-3-carboxamidesa = (a + 2) = (a + 2)

Entry	Coumarin	Solvent	Additive	Time/h	Yield ^{<i>b</i>} /%	Diastereomeric ratio ^c
1	1A	Acetone	No	48	0	-(2AE):-(2AF)
2	1B	Acetone	No	48	83	55 (2BE) : 45 (2BF)
3	1C	Acetone	No	48	99	63 (2CE) : 37 (2CF)
4	1C	Toluene	No	48	90	63 (2CE) : 7 (2CF)
5	1C	$CF_3C_6H_5$	No	48	56	59 (2CE) : 41 (2CF)
6	1C	CH_2Cl_2	No	24	95	61 (2CE) : 39 (2CF)
7	1C	$CHCl_3$	No	24	96	58 (2CE) : 42 (2CF)
8	1C	CH ₃ CN	No	24	92	53 (2CE) : 47 (2CF)
9	1B	Toluene	$Zn(ClO_4)_2 \cdot 6H_2O$	96	24^d	70 (2BE) : 30 (2BF)
10	1C	Toluene	$Zn(ClO_4)_2 \cdot 6H_2O$	48	92	75 (2CE) : 25 (2CF)
11	1C	Acetone	$Zn(ClO_4)_2 \cdot 6H_2O$	48	72	75 (2CE) : 25 (2CF)
12	1C	Toluene	$BF_3 \cdot OEt_2$	48	90	70 (2CE) : 30 (2CF)
13	1C	Toluene	$Mg(ClO_4)_2$	48	72	69 (2CE) : 31 (2CF)
14	1C	Toluene	$Ni(ClO_4)_2 \cdot 6H_2O$	48	75	67 (2CE) : 33 (2CF)
15	1C	Toluene	$Co(ClO_4)_2 \cdot 6H_2O$	48	51	70 (2CE) : 30 (2CF)
16	1C	Toluene	$Cu(ClO_4)_2 \cdot 6H_2O$	48	42	71 (2CE) : 29 (2CF)
17	1C	Toluene	$Fe(ClO_4)_2 \cdot xH_2O$	48	77	72 (2CE) : 28 (2CF)
18	1D	Toluene	$Zn(ClO_4)_2 \cdot 6H_2O$	96	0	-(2DE):-(2CF)

^{*a*} The external irradiation was directed toward the Pyrex test tube with a working distance of 1 cm. All reactions were degassed by argon bubbling for 15 min prior to irradiation. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR. ^{*d*} Recovery of **1B** in 52%.



Scheme 1 Optimized structures of 1C (S $_0$ and T $_1$) and 2C (S $_0$).

in the absence of $BF_3 \cdot OEt_2$ (**2CE** : **2CF** = 70 : 30, entry 12). Other metal perchlorates such as Mg, Ni, Co, Cu and Fe slightly improved the **2CE** : **2CF** ratio (entries 13–17). To improve

solubility of the chiral coumarin, we prepared **1D** having three hydrophobic phenyl groups and used this compound for the photodimerization reaction. However, undesired photodecomposition of **1D** occurred (entry 18). Interestingly, no reaction was induced when the reaction of **1C** was performed in the presence of a stoichiometric amount of $Zn(ClO_4)_2 \cdot 6H_2O$ as well as BF₃·OEt₂. This phenomenon might suggest that the ratio of the metal complex of **1C** and metal-free **1C** in solution is important for the reaction to progress.^{3,10}

To gain insight into the mechanism of complete *syn*-HT selectivity and moderate diastereoselectivity, we optimized the structure of **1C** in toluene using DFT calculations (Scheme 1).¹¹ All calculations were performed using the B3LYP hybrid functional and a basis set (6-311G**) level of theory with Gaussian 16. The solvent effect of toluene was modeled *via* the polarizable continuum model using the integral equation formalism variant (IEFPCM). Three conformers **1CX**, **1CY** and **1CZ** were generated which are energetically closed.¹² We revealed that the order of the change in energy among three conformers was **1CX** (S₀) < **1CZ** (S₀) < **1CY** (S₀). The crystal structure of **1C** was similar to **1CZ**, which indicates that the major conformer involved in the [2 + 2] photodimerization would be changed between the solution and the crystalline states.¹³

Energies of photodimers *syn*-HH, *anti*-HH and *anti*-HT in toluene were also optimized by DFT calculation (B3LYP/6-311G^{**}) to explain the exclusive formation of *syn*-HT dimer, which would be induced predominantly by accommodating the (*S*)-4-benzyl-2-oxazolidinone auxiliary in a favorable direction with a special allowance in the TS (Fig. 2).¹⁴ Structures of **2CX** and **2CY** were found to correspond to the structures of the cycloadducts *syn*-HT **2CE** and *syn*-HT **2CF**, respectively. It must be noted that **2CZ** is the major diastereomer with a different conformation from that of **2CY**. Thus, the order of the change in energy for photodimers was **2CZ** < **2CX** < **2CY**. There was not much difference in energy between **2CX** and **2CZ**. Time-dependent DFT (TD-DFT) calculations showed that HOMO \rightarrow



Fig. 2 Exclusive formation of syn-HT dimers caused by the steric hindrance between two chiral coumarins.



Scheme 2 Proposed mechanism for diastereofacial selectivity.

LUMO transition for each of the three conformers 1CX, 1CY and **1CZ** would be best described as a triplet excited state $[^{3}(\pi,\pi)^{*}]$ (T_1) for the carbon–carbon double bond of the reaction site with zero oscillator strength (Scheme 2). Therefore, it is suggested that the ground state (S_0) for each of the three conformers was excited to become a singlet state $[^{1}(\pi,\pi)^{*}]$ (S₁) followed by intersystem crossing (ISC) to generate T₁. Consequently, the order of the change in energy among T₁ of the three conformers was also calculated as 1CX $(T_1) < 1CZ (T_1) < 1CY (T_1)$. From the results mentioned above, the [2 + 2] photodimerization reaction would start from excitation of the most stable comformer 1CX (S₀) which preferentially generates $1CX(T_1)$ via ISC of a singlet excited state 1CX (S_1). The resulting triplet species 1CX (T_1) would be subjected to react with 1CX (S₀) in syn-HT fashion (discussed below) to give 2CX. The effect of the Lewis acid is unclear at the present time. However, we postulate that the Lewis acid could stabilize 1CX by a coordination in a bidentate fashion to prevent the conformational change to 1CY and 1CZ, which would be induced by a free rotation of the carbon-carbon single bond between the coumarin ring and the 2-oxazolidinone auxiliary.3,8,15,16 The moderate diastereoselectivity could be explained by the following process (also depicted in Scheme 2). Two carbonyl groups in the (S)-3-acyl-4-benzyl-2-oxazolidinone auxiliary could be oriented opposite each other to minimize the dipole moment and the electrostatic repulsion. To minimize steric repulsion caused between the benzyl group of the 2-oxazolidinone auxiliary and the carbonyl group of the coumarin ring, the conformational bias leads more favorably toward 1CX rather than 1CY and 1CZ. The carbonyl group including the 2-oxazolidinone ring would serve as a shielding group to prevent approach from the top side, thus affording 2CX, i.e., syn-HT 2CE (Scheme 3).

The reduction of the chiral oxazolidinone moiety was successfully proceeded to give triol **3**.¹⁷ Interestingly, the reduction of chroman-2-one moiety also concomitantly occured with the removal of chiral auxiliary affording **3** as a single diastereomer.¹⁸



Scheme 3 Removal of the chiral auxiliary with the reduction of chroman-2-one moiety.

In conclusion, we have developed a novel asymmetric photodimerization reaction of chiral coumarin-3-carboxamide which affords *syn*-HT dimer selectively with a moderate level of diastereoselectivity. Removal of chiral auxiliary was conducted to expand the applicability of the photodimer by the reduction using NaBH₄ in THF–H₂O. Further studies to elucidate the reaction mechanism and for application in the area of medicinal chemistry, drug delivery, and chemical biology are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI Grant numbers JP17K14550 and JP18K05111. The computation was mainly carried out using the computer facilities at Research Institute for Information Technology, Kyushu University. We gratefully thank Ms. Noriko Sato (the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy) for ¹H NMR analyses.

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- 13 See the ESI[†] for the crystal structure of **1A**.
- 14 See the ESI† for the experimental and the computational details and results.
- 15 A small extent of downfield-shifts for the H-4 and C-4 of the coumarin ring of **1C** was observed in the presence of $BF_3 \cdot OEt_2$ and $Zn(ClO_4)_2 \cdot 6H_2O$ (1 equiv.) by ¹H and ¹³C NMR spectroscopic analyses. Absorption of **1C** at 287 nm was enhanced slightly with an increasing amount of $Zn(ClO_4)_2 \cdot 6H_2O$. See the ESI† for the spectra.
- 16 The structure of **1C** ZnCl_2 complex was optimized by DFT calculation (B3LYP/6-311G) to show bidentate complexation of Zn(n) ion between the carbonyl oxygen of coumarin ring and the acyl oxygen of (*S*)-3-acyl-4-benzyl-2-oxazolidinone auxiliary. See the ESI† for the computational results.
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