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Paper

An Alternative Synthesis of Bipyrenol: A High-Yield Oxidative Coupling Reaction of a Pyrene Derivative with Cu(BF₄)₂·nH₂O

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Abstract An alternative synthesis has been developed with the objective of extending the applications of bipyrenol in mind. The key reaction involves the oxidative coupling of 2-hydroxypyrene menthyl carbonate to afford the corresponding pyrene dimer. In marked contrast to our previous method, i.e., the oxidation of 2-hydroxypyrene, the revised method is a clean and high-yielding reaction. By optimizing the reaction conditions, the yield of the alternative synthesis is increased to 88%.

Key words BINOL, bipyrenol, copper(II) tetrafluoroborate, oxidative coupling, pyrene

1,1'-Bi-2-naphthol 1 (BINOL) (Figure 1) and structurally similar axially chiral molecules have opened new doors in chemistry.¹ Many chemical modifications aimed at enhancing the properties of BINOLs, which are dependent on their chiral structures, have been reported. Among them, the expansion of the π -system of BINOL is frequently used because large polycyclic aromatic hydrocarbons (PAHs) increase the chiral space of a molecule, i.e., replacing the naphthalene of $\mathbf{1}$ with π -expanded PAHs such as phenanthrene,² anthracene,³ and chrysene.⁴ Along with these advances, we are interested in the photophysical properties of chiral molecules, i.e., emission from chiral molecules, known as circularly polarized luminescence (CPL).⁵ However, the quantum yields (Φ) of reported axially chiral molecules are not sufficient for inducing CPL in advanced materials, e.g., the Φ of **1** is merely 0.04.⁶ With these findings as background, we previously reported pyrene-based axially chiral molecules, 1,1'-bi-2-pyrenols 2 (bipyrenols) (Figure 1), and their enhanced photophysical properties.⁶

In our previous report, we adopted a classic synthetic method, i.e., the oxidative coupling reaction of 2-pyrenol





with FeCl₃ in MeNO₂/EtOH.⁶ One of the advantages of our synthetic strategy and/or the chemistry of **2** is the simple optical resolution, i.e., the diastereomixture of the corresponding menthyl carbonate is easily separated by SiO_2 column chromatography.

As far as we know, the same procedure was not applicable to the optical resolution of **1**. We speculated that an expanded π -system would enhance the differences in physical properties attributable to the differences in stereochemistry. In the case of **1**, the revised reaction scheme *Route B* of Scheme 1, namely, carbonate formation and the subsequent coupling reaction, seemed convenient. We adopted this strategy in our previous report. However, the oxidation of the carbonate with FeCl₃ was unsuccessful. Considering the

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wide application of bipyrenol **2**, in this study, we have developed a simple and high-yielding alternative synthesis of **2**.

Although many revised synthetic methods were reported after the first synthesis of **1** by oxidative coupling using metals such as FeCl₃,⁷ including a solid-state reaction with FeCl₃ known as the Toda reaction,⁸ the revised Toda reaction using microwave irradiation,⁹ CuCl₂/amine,¹⁰ H₂O₂/Au/SrTiO₃,¹¹ and phenyliodine(III) bis(trifluoroacetate) (PIFA)/BF₃·Et₂O,¹² and an organometallic method using the Suzuki–Miyaura coupling,¹³ our synthetic study on structurally well-defined oligopyrenes, in which the syntheses were carried out with Cu^{II}(BF₄)₂·nH₂O,¹⁴ gave us a hint toward the alternative synthesis of **2**. This oligomerization proceeded smoothly under mild conditions to give higher oligomers of 1,3-pyrenylenes, and the reaction mixture was clean and not contaminated with tarry products often found in oxidation reactions.

Substrate **5**, used as reference compound in our previous photochemistry, was prepared by the carbonate reaction of 2-pyrenol **4** with (–)-menthyl chloroformate.⁶ The oxidation reaction of **5** was carried out under various conditions, as listed in Table 1. First, an oxidation reaction used for the synthesis of pyrene oligomers was employed (Table 1, entry 1),¹⁴ i.e., treatment of an excess amount of $Cu^{II}(BF_4)_2 \cdot nH_2O$ in boiling butyronitrile afforded the desired dimerized diastereomixture, *dia*-**6**, in 64% yield. As was mentioned in the Introduction, many Cu^{II} salts have been used for the synthesis of **1**. Hence, Cu^{II} salts including $CuCl_2$, $CuBr_2$, $Cu(OAc)_2 \cdot H_2O$, and $CuSO_4 \cdot 5H_2O$ were examined for the synthesis of *dia*-**6**. However, all of these Cu^{II} salts induced decomposition (Table 1, entries 2–5). We also exam-

Table 1 Oxidative Coupling Reaction of 5 Affording dia-6

Entry	Reagent	Equiv	Solvent	Yield of <i>dia-6 (%)</i>
1	Cu ^{II} (BF ₄) ₂ ·nH ₂ O	6ª	butyronitrile	64
2	CuCl ₂	6	butyronitrile	dec. ^b
3	CuBr ₂	6	butyronitrile	dec. ^b
4	Cu(OAc) ₂ ·H ₂ O	6	butyronitrile	dec. ^b
5	CuSO ₄ ·5H ₂ O	6	butyronitrile	dec. ^b
6	FeCl ₃	6	butyronitrile	dec. ^b
7	Cu [∥] (BF ₄) ₂ ·nH ₂ O	5ª	butyronitrile	85
8	Cu [∥] (BF ₄) ₂ ·nH ₂ O	4ª	butyronitrile	90
9	Cu [∥] (BF ₄) ₂ ·nH ₂ O	4ª	MeCN	88
10	Cu [∥] (BF ₄) ₂ ·nH ₂ O	4ª	EtOH	_c

^a Because of the high hygroscopicity of commercially available

 $Cu(BF_4)_2$ ·nH₂O, it was too difficult to weigh the reagent accurately.

^b Decomposition occurred and *dia*-**6** was not available in any quantity.

^c No reaction occurred.

ined the Fe^{III} salt used in our previous study for the preparation of *rac*-**2** (Table 1, entry 6). However, decomposition was also observed.

In the experiments in Table 1 (entries 7 and 8), the stoichiometry of $Cu^{II}(BF_4)_2 \cdot nH_2O$ was examined. We found that approximately four equivalents of $Cu^{II}(BF_4)_2 \cdot nH_2O$ were suitable for the reaction.¹⁵

Because of the limited solubility of the pyrene oligomers, we used butyronitrile, the best solvent in our previous study,¹⁴ because this coordinative solvent has unique polarity attributable to the lipophilic propyl group and the



Scheme 1 Two synthetic routes for **2**. *Route A*: previously reported route; *Route B*: an alternative route introduced in this study. *Reagents and conditions*: (a) (i) *tert*-butyl chloride, AlCl₃, CH_2Cl_2 ; (ii) [Irl(OMe)cod]₂, 4,4'-di-*tert*-butyl-2,2'-bipyridyl, bis(pinacolato)diboron, cyclohexane; (iii) H₂O₂, KOH; (b) FeCl₃/EtOH, reflux; (c) (–)-menthyl chloroformate, Et₃N, toluene, r.t.; (d) SiO₂ flash chromatography; (e) KOH, EtOH/H₂O (4:1), reflux; (f) oxidative coupling reaction. The conditions are summarized in Table 1.

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polar/coordinative nitrile group. However, the high cost of butyronitrile forced us to explore more cost-efficient solvents. EtOH, as used in the synthesis of *rac*-**2**, did not induce the reaction. Acetonitrile gave the best result, i.e., *dia*-**6** was obtained in 88% yield. Currently, the conditions listed in entry 9 (Table 1) are the best. The obtained *dia*-**6** was separated into the corresponding diastereomers and subsequent hydrolysis afforded optically pure **2**.

In all the reactions using $Cu^{II}(BF_4)_2 \cdot nH_2O$, the reaction mixtures contained dark yellow products that could be easily separated from *dia*-**6** by SiO₂ column chromatography.

Although these colored materials were trace products, our interest in π -expanded quinoidal molecules¹⁶ prompted us to perform careful isolation and analysis of these products. The colored products were further separated into several products and two of them were characterized as compounds **7** and **8** (Figure 2), i.e., **7** and **8** were formed by the direct oxidation of substrate **5**. This quinone formation might reflect the high reactivity of pyrene. In the synthesis of bianthracenol, the formation of quinone was also reported, however, the origin of the quinoidal oxygen is the hydroxy group of anthracenol.¹⁷



Figure 2 Molecular structures of quinoidal molecules 7 and 8 formed in the oxidation reactions

In conclusion, upon rearranging the order of the reaction in the synthesis of **2**, we found an easy synthesis of *dia*-**6**. The availability of stable carbonate **5** under the ambient conditions spared us the trouble of handling unstable π -expanded phenol **4**. This could induce the clean and high-yield formation of *dia*-**6**. We were also interested in the formation of pyrene-based quinones, such as **7** and **8**. Because the π -expanded quinones showed potential as component molecules for advanced materials, exploration of the selective synthesis of quinones from **5** and/or *dia*-**6** should be interesting. Our revised synthetic method may well contribute to the application of bipyrenol **2** in various fields of chemistry, including asymmetric synthesis, molecular recognition, and advanced materials, and could be used in the synthesis of new π -expanded axially chiral molecules. The synthesis of the menthyl carbonate of 4-tert-butylpyrene-2-ol 5 was conducted in accordance with a reported method.⁶ The following reagents were used as received: Cu(BF₄)₂·nH₂O (Sigma-Aldrich Co.) and EtOH (Wako Pure Chemical Industries, Ltd.). The following reagents were used after purification: butyronitrile (Tokyo Chemical Industry Co., Ltd., distilled over CaH₂ under N₂) and MeCN (Wako Pure Chemical Industries, Ltd., distilled over CaH₂ under N₂). Silica gel thin layer chromatography (Merck & Co., Inc.) was performed using Silica Gel 60 F254 Aluminium Sheet from Merck Co. Ltd. Column chromatography was performed using Neutral Silica Gel 60N (spherical, 40-50 mm) from Kanto Chemical Co., Inc as the silica gel. The ¹H NMR spectra were recorded on a Bruker Avance III 500 (500 MHz for ¹H) spectrometer in CDCl₃ (Acros Organics Co., Inc.) with TMS as the internal standard. Infrared spectra were recorded on a Shimadzu FTIR-8400 instrument using KBr pellet and/or liquid film techniques in the range of 500 to 4000 cm⁻¹. The absorption spectra were recorded on a Shimadzu UV-3600 using spectrophotometric-grade CH₂Cl₂ (reagent grade, treated with sulfuric acid). Atmospheric pressure chemical ionization (APCI) mass spectra were recorded on a Bruker micrOTOF II SDT1. Other experimental details, including spectroscopic studies, were reported previously.¹⁸

Synthesis of the Diastereomixture of 6 (dia-6) (Table 1, Entry 9)

Dry MeCN (200 mL) was introduced into a 300 mL three-necked flask and purged with N₂. Against the stream of N₂, compound **5** (1.00 g, 2.2 mmol) and Cu(BF₄)₂·nH₂O (2.07 g, 8.77 mmol) were added. The reaction mixture was refluxed under an inert atmosphere. After 3 h, TLC analysis showed the disappearance of **5** and the formation of new products attributable to **6** [R_f = 0.45 and 0.40 for the two diastereomers; SiO₂ eluted with a mixed solvent of *n*-hexane/toluene (2:3)]. The mixture was cooled and the solvent was removed under reduced pressure. The residue was suspended in CHCl₃ and this mixture was passed through a short SiO₂ column eluted with CHCl₃ to remove inorganic salts. The obtained crude product was further purified through another SiO₂ column with a mixed solvent of *n*-hexane/toluene (2:3) as eluent to give diastereomixture *dia*-**6** (0.88 g, 88%). The eluent was exchanged with a mixed solvent of *n*-hexane/toluene (1:4) to give trace amounts of colored products (*vide infra*).

The obtained *dia*-**6** was separated by SiO_2 column chromatography again. As reported in our previous study, the product having a high R_f value is the (R)-isomer of menthyl carbonate and the product having a low R_f value is the (S)-isomer. The yields of both isomers were 44% (0.40 g, each). All of the spectroscopic data were identical with those reported previously.⁶ It should be emphasized again that the purity of the products was easily determined by ¹H NMR measurements because these diastereomers showed completely different spectra.

The collected colored compounds were separated by preparative thin-layer chromatography [SiO₂ eluted with a mixed solvent of *n*-hexane/CHCl₃ (1:20)]. We isolated two trace products **7** and **8** having R_f values of 0.25 and 0.28, respectively [SiO₂, *n*-hexane/toluene (2:3)]. Spectroscopic data are as follows.

Compound 7

¹H NMR (500 MHz, CDCl₃, TMS): δ = 8.51 (d, J = 7.3 Hz, 1 H), 8.43 (d, J = 7.3 Hz, 1 H), 7.81 (d, J = 7.3 Hz, 1 H), 7.77 (d, J = 7.3 Hz, 1 H), 7.51 (s, 1 H), 7.47 (s, 1 H), 4.65 (ddd, J = 10.7, 10.7, 4.4 Hz, 1 H), 2.24 (d, m, J = 12.0 Hz, 1 H), 2.13 (sept d, J = 6.9, 4.4 Hz, 1 H), 1.77–1.68 (m, 2 H), 1.55–1.50 (m, 1 H), 1.43 (s, 9 H), 1.21 (ddd, J = 12.0, 12.0, 12.0 Hz, 1 H), 1.10 (ddd, J = 12.0, 12.0, 3.5 Hz, 1 H), 0.975 (d, J = 6.3 Hz, 3 H), 0.95–0.85 (m, 2 H), 0.89 (d, J = 6.3 Hz, 3 H).

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To confirm this compound consists of 1,6-pyrenequinone, not 1,8-pyrenequinone, differential NOE and ${}^{1}H{}^{-1}H$ COSY experiments were carried out (see the Supporting Information).

UV/Vis (CH₂Cl₂, qualitative): λ_{max} (absorbance) = 465 (shoulder, 0.18), 447 (0.21) nm.

MS (APCI): m/z [M + H]⁺ calcd for C₃₁H₃₅O₅: 487.24; found: 487.3 (70%).

Compound 8

¹H NMR (500 MHz, CDCl₃, TMS): δ = 8.31 (d, *J* = 2.3 Hz, 1 H), 8.25 (d, *J* = 8.6 Hz, 1 H), 8.05 (d, *J* = 8.6 Hz, 1 H), 7.98 (d, *J* = 2.3 Hz, 1 H), 7.30 (s, 1 H), 6.81 (s, 1 H), 4.67 (ddd, *J* = 10.7, 10.7, 4.4 Hz, 1 H), 2.21 (d, m, *J* = 12.0 Hz, 1 H), 2.07 (sept d, *J* = 6.9, 4.4 Hz, 1 H), 1.77–1.70 (m, 2 H), 1.55–1.50 (m, 1 H), 1.43 (s, 9 H), 1.20 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1 H), 1.10 (ddd, *J* = 12.0, 12.0, 3.5 Hz, 1 H), 0.980 (d, *J* = 6.3 Hz, 3 H), 0.978 (d, *J* = 6.3 Hz, 3 H), 0.95–0.85 (m, 2 H), 0.88 (d, *J* = 6.3 Hz, 3 H).

UV/Vis (CH₂Cl₂, qualitative): λ_{max} (absorbance) = 435 (0.08), 400 (shoulder, s, 0.07), 364 (0.20), 347 (0.17), 330 (s, 0.08), 300 (s, 0.22), 289 (0.24) nm.

MS (APCI): m/z [M + H]⁺ calcd for C₃₁H₃₅O₅: 487.24; found: 487.3 (100%).

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Supporting Information

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