Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue





Cite this: *Org. Biomol. Chem.*, 2018, **16**, 9143

Received 1st October 2018,
Accepted 8th November 2018

DOI: 10.1039/c8ob02450b

rsc.li/obc

# A new synthetic route to 5,6,11,12-tetraarylethynyltetracenes†

Kei Kitamura,[a] Kenta Asahina,[a] Yusaku Nagai,[a] Keshu Zhang,[a] Shogo Nomura,[b] Katsunori Tanaka [b,c] and Toshiyuki Hamura *[a]

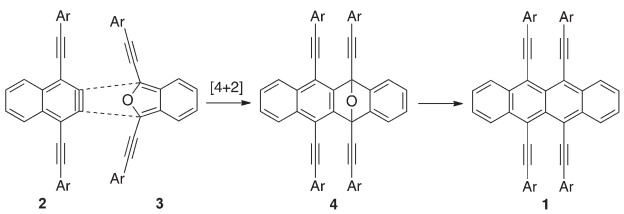
**A new synthetic route to 5,6,11,12-tetrakis(arylethynyl)tetracenes, π-extended rubrenes, was developed *via* [4 + 2] cycloadditions of dialkynylisobenzofuran and 1,4-naphthoquinone. Introduction of arylethynyl groups by double nucleophilic additions to tetracenequinone gave sterically congested (arylethynyl)tetracenes after reductive aromatization. The photophysical properties of the newly prepared π-conjugated molecules are also evaluated.**

We previously reported a preparation of 5,6,11,12-tetraarylethynyltetracene **1**, a new class of π-extended rubrenes, *via* [4 + 2] cycloaddition of dialkynylnaphthalyne **2** and dialkynylisobenzofuran **3** (Scheme 1).[1,2] In this reaction, two alkynyl groups on the naphthalyne **2** can lower the LUMO energy, allowing the practical construction of the sterically overcrowded structure through their efficient HOMO–LUMO interaction.

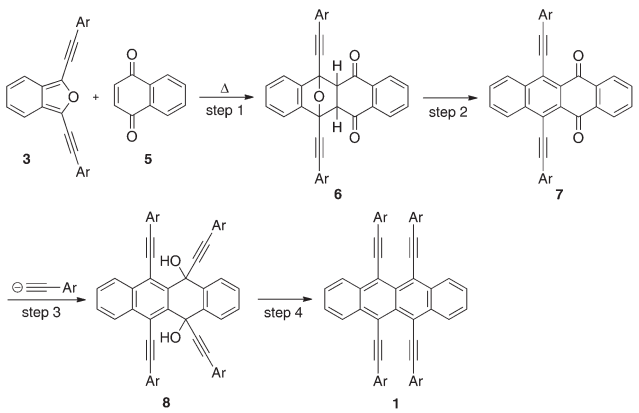
This approach, however, has a problem in that the yield of the aromatization (**4** → **1**) is low or moderate owing to the unexpected reactivities derived from the closely located *peri*-ethynyl groups in epoxytetracene **4** under the acidic conditions.[3]

To solve this problem, we focused on developing a new synthetic route to π-extended rubrene **1** using dialkynylisobenzofuran **3** as a reactive platform.[4,5] Our second approach consists of four-step syntheses, which is depicted in Scheme 2.[6] In the first step, the [4 + 2] cycloaddition of dialkynylisobenzofuran **3** and 1,4-naphthoquinone (**5**) gives the cycloadduct **6**, which is converted to the tetracenequinone **7** by aromatization (step 2). Subsequent introduction of two alkynyl groups by double nucleophilic additions of alkynyl anions (step 3), and reductive aromatization of the resulting diol **8** would produce the target compound **1** (step 4). Along these lines, we now report an efficient synthetic access to π-extended rubrenes possessing various arylethynyl groups at the *peri*-positions. Moreover, photophysical properties of the newly prepared poly-ethynylated tetracenes are evaluated. Also described is the application of the parent compound **1a** to a cellular imaging agent.

Scheme 3 shows the [4 + 2] cycloaddition of dialkynylisobenzofuran. Upon mixing of isobenzofuran **3a** and naphthoquinone **5** ($CH_2Cl_2$, r.t.), a new spot corresponding to the cycloadduct **6a** was observed by TLC. Further reaction at the same temperature, however, did not completely consume the start-



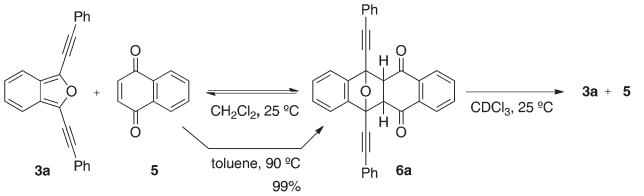

**Scheme 1** The first syntheses of π-extended rubrenes **1** *via* [4 + 2] cycloaddition of naphthalyne and isobenzofuran.




**Scheme 2** New synthetic route to π-extended rubrenes **1**.

[a]*Department of Applied Chemistry for Environment, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan. E-mail: thamura@kwansei.ac.jp*
[b]*Biofunctional Synthetic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan*
[c]*Biofunctional Chemistry Laboratory, Kazan Federal University, 18 Kremlyovskaya street, Kazan 420008, Russia*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02450b




**Scheme 3** [4 + 2] cycloaddition between isobenzofuran **3a** and 1,4-naphthoquinone (**5**).

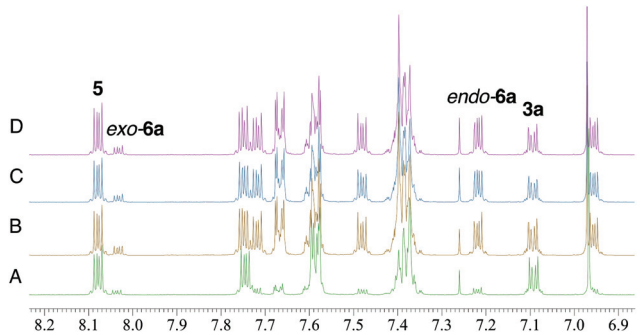
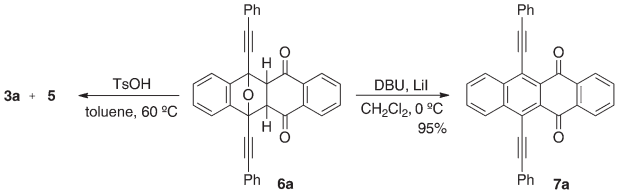



**Fig. 1** [4 + 2] cycloaddition between isobenzofuran **3a** and 1,4-naphthoquinone (**5**) monitored by NMR. (a) A: 5 min, B: 2 h, C: 7 h, D: 15 h.

ing materials **3a** and **5**, indicating their equilibrium with the cycloadduct **6a**. Indeed, $^1$H NMR analysis revealed that the cycloadduct **6a** including *endo*- and *exo*-isomers was readily formed after dissolving the isobenzofuran **3a** and naphthoquinone **5** in $CDCl_3$ at room temperature (see A in Fig. 1). After 7 h, the ratio of **3a**, **5**, *exo*-**6a**, and *endo*-**6a** almost became constant (see D in Fig. 1). The stereochemistry of the *exo*-**6a** and *endo*-**6a** was tentatively assigned by consideration of the chemical shift of each methine proton.[7]

After further study of this [4 + 2] cycloaddition, we were pleased to find that the solvent choice is crucial to produce the high yield of the cycloadduct **6a**: when the above-mentioned reaction was performed in toluene at 90 °C, the [4 + 2] cycloadduct **6a** gradually precipitated from the solution due to its low solubility in toluene, affording the essentially pure product **6a** almost in quantitative yield (Scheme 3). Interestingly, the *endo* isomer **6a** was solely produced under these conditions. By dissolving in $CDCl_3$ (25 °C, 26 h), the cycloadduct **6a** again underwent cycloreversion to give the dialkynylisobenzofuran **3a** and 1,4-naphthoquinone (**5**).[8]

Scheme 4 shows the conversion of the [4 + 2] cycloadduct **6a** to tetracenequinone **7a**. Upon heating of cycloadduct **6a** in the presence of TsOH at 60 °C, the cycloreversion occurred quickly, and the aromatized product **7a** was not obtained at all.[9,10] On the other hand, treatment of the cycloadduct **6a** with LiI and DBU at low temperature ($CH_2Cl_2$, 0 °C)[11] underwent the clean aromatization without invoking the cycloreversion to give the tetracenequinone **7a** in 95% yield.

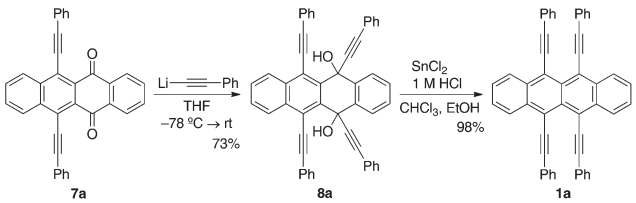



**Scheme 4** Aromatization of cycloadduct **6a** to tetracenequinone **7a**.

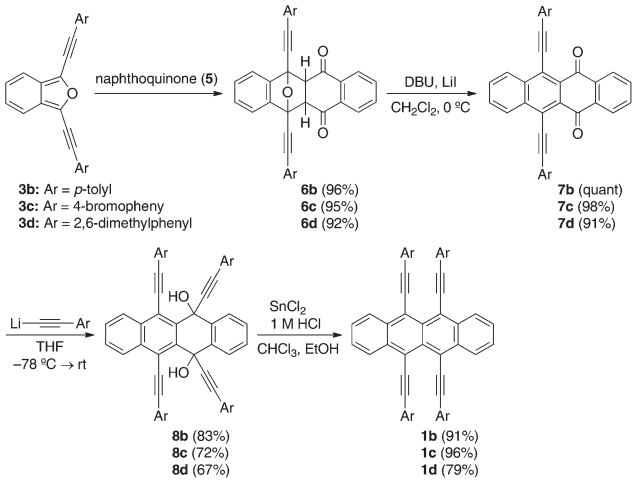
Further transformation of the tetracenequinone **7a** to π-extended rubrene **1a** was achieved through double nucleophilic additions of phenylethynyllithium, followed by $Sn^{II}$-mediated reductive aromatization (Scheme 5). Importantly, the nucleophilic addition of alkynyllithium to **7a** occurred cleanly by warming the reaction mixture to room temperature, in spite of the high steric hindrance between incoming nucleophile and proximal alkynyl groups.

In a similar manner, the substituted derivatives **1b** and **1c**, having four *p*-tolylethynyl or (4-bromophenyl)ethynyl groups at both *peri*-positions, were efficiently synthesized by this four-step sequence including the tetracenequinones **7b** and **7c** as key intermediates (Scheme 6).

It should be noted that the developed method has high synthetic potential in that the sterically congested derivative **1d**




**Scheme 5** Transformation of tetracenequinone **7a** to π-extended rubrene **1a**.




**Scheme 6** Preparation of π-extended rubrenes **1b–1d**.

possessing four 2,6-xylylethynyl groups on the tetracene core was easily accessible in good yield. This is a sharp contrast from our previous method by acid-promoted aromatization of the epoxy tetracene **4d** (Ar: 2,6-xylyl), where the product **1d** was obtained in poor yield, and a sizable amount of furan (structure not shown) was produced.[1]

To evaluate the photophysical properties, UV–Vis spectra of π-extended rubrenes **1a–1d** were measured in chloroform (Fig. 2). The π-extended rubrene **1a** has its absorption maximum at 640 nm, which was greatly red-shifted over 100 nm from that of the parent rubrene, indicating effective π-extension by the existence of four phenylethynyl groups on the tetracene core. The π-extended rubrenes **1b** and **1c** with *para*-substitution denoted the similar tendency of **1a**, whereas the absorption maximum of the sterically congested derivative **1d** was slightly blue-shifted (623 nm).

Fluorescence spectra were also measured in chloroform (Fig. 3). The π-extended rubrenes **1a–1d** showed a fluorescent maximum peaking at around 690 nm, which were excited at their absorption maximum. A larger Stokes shift was observed in **1d** (1620 $cm^{-1}$) compared to that of **1a** (1200 $cm^{-1}$). The absolute fluorescent quantum yields of these π-extended derivatives were nearly 10%, which were lower than that of the parent rubrene.

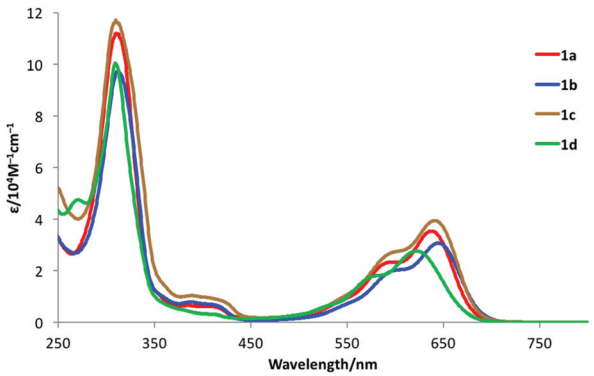



**Fig. 2** UV–Vis absorption spectra of π-extended rubrenes **1a–1d**.

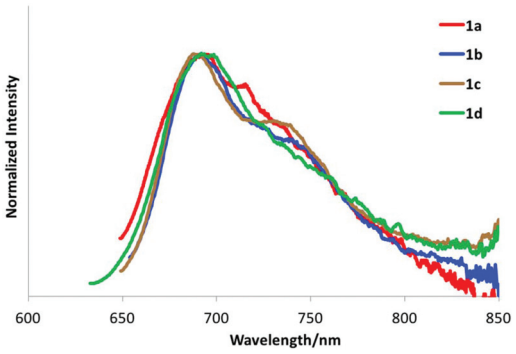



**Fig. 3** Fluorescence spectra of π-extended rubrenes **1a–1d**.

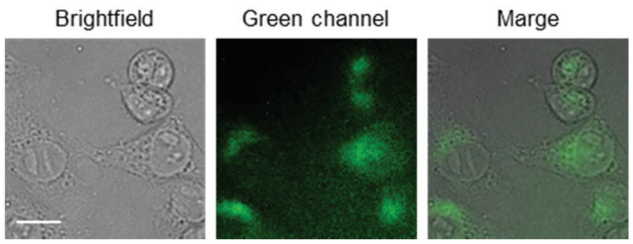



**Fig. 4** Fluorescence imaging of HeLaS3 cells by π-extended rubrene. The cells were treated with 100 μM of **1a** for 30 min at 37 °C and analyzed by fluorescence microscopy. Green channel: $\lambda_{em}$ = 620 nm, $\lambda_{ex}$ = 700 nm. Scale bar: 20 μm.

Finally, preliminary investigation of cellular imaging using π-extended rubrene was performed by treating the HeLa cells with **1a** for 30 min at 37 °C. Fluorescence signals from cells upon excitation at 620 nm indicate a future applicability of π-extended rubrene as a bioimaging probe (Fig. 4).

## Conclusions

In conclusion, [4 + 2] cycloaddition of dialkynylisobenzofuran and 1,4-naphthoquinone allowed rapid construction of alkynylated tetracenequinones, which were amenable to transformation *en route* to tetrakis(arylethynyl)tetracenes. Further studies on the application of these attractive π-conjugated molecules to organic electronics materials and fluorescent probes are underway in our laboratories.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP15H05840 in Middle Molecular Strategy and JST ACT-C Grant Number JPMJCR12YY, Japan.

## Notes and references

1 (*a*) K. Kitamura, K. Asahina, Y. Nagai, H. Sugiyama, H. Uekusa and T. Hamura, *Chem. – Eur. J.*, 2018, **24**, 14034–14038; (*b*) T. Hamura, *Patent JP* 2016169213, 2016.

2 For related reviews, see: (*a*) M. M. Richter, *Chem. Rev.*, 2004, **104**, 3003–3036; (*b*) M. Bendikov, F. Wudl and D. F. Perepichka, *Chem. Rev.*, 2004, **104**, 4891–4946; (*c*) J. E. Anthony, *Angew. Chem.*, 2008, **120**, 460–492, (*Angew. Chem., Int. Ed.*, 2008, **47**, 452–483).

3 For related distorted π-crowded ethynylnaphthalene derivatives, see: (*a*) B. Bossenbroek, D. C. Sanders, H. M. Curry and H. Shechter, *J. Am. Chem. Soc.*, 1969, **91**, 371–379;

(*b*) H. A. Staab and J. Ipaktschi, *Chem. Ber.*, 1971, **104**, 1170–1181; (*c*) A. E. Jungk and G. M. J. Schmidt, *Chem. Ber.*, 1971, **104**, 3272–3288. See also: (*d*) R. A. Pascal, Jr., *Chem. Rev.*, 2006, **106**, 4809–4819.

4 (*a*) T. Hamura and R. Nakayama, *Chem. Lett.*, 2013, **42**, 1013–1015; (*b*) K. Asahina, S. Matsuoka, R. Nakayama and T. Hamura, *Org. Biomol. Chem.*, 2014, **12**, 9773–9776; (*c*) R. Kudo, K. Kitamura and T. Hamura, *Chem. Lett.*, 2017, **46**, 25–28.

5 For our synthetic application of isobenzofurans to polyacene derivatives, see: (*a*) S. Eda and T. Hamura, *Molecules*, 2015, **20**, 19449–19462; (*b*) R. Akita, K. Kawanishi and T. Hamura, *Org. Lett.*, 2015, **17**, 3094–3097; (*c*) S. Eda, F. Eguchi, H. Haneda and T. Hamura, *Chem. Commun.*, 2015, **51**, 5963–5966; (*d*) H. Haneda, S. Eda, M. Aratani and T. Hamura, *Org. Lett.*, 2014, **16**, 286–289.

6 For syntheses of substituted rubrene derivatives, see: (*a*) A. S. Paraskar, A. R. Reddy, A. Patra, Y. H. Wijsboom, O. Gidron, L. J. W. Shimon, G. Leitus and M. Bendikov, *Chem. – Eur. J.*, 2008, **14**, 10639–10647; (*b*) J. Zhang, S. Sarrafpour, T. E. Haas, P. Müller and S. W. Thomas, *J. Mater. Chem.*, 2012, **22**, 6182–6189.

7 For a related [4 + 2] cycloaddition of diphenylisobenzofuran with 1,4-naphthoquinone, and structural characterization of the *endo*/*exo*-cycloadducts, see: T. Wombacher, S. Foro and J. J. Schneider, *Eur. J. Org. Chem.*, 2016, 569–578. See also ref. 5*b* and 6.

8 The perfect *endo* selectivity observed in the [4 + 2] cycloaddition of isobenzofuran **3a** and naphthoquinone **5** is presumably due to the lower solubility of the *endo* cycloadduct **6a** in toluene than that of the *exo* cycloadduct **6a**. Therefore, the *endo* cycloadduct **6a** was selectively precipitated from the solution under the equilibrium between the starting materials and the cycloadducts. In a similar manner, the *endo* cycloadducts **6b–6d** were obtained as a single stereoisomer by precipitation owing to their poor solubility with EtOH or heptane. For details, see ESI.†

9 A similar approach for preparation of substituted rubrenes by using [4 + 2] cycloaddition of diarylisobenzofuran and naphthoquinone was developed, see: J. A. Dodge, J. D. Bain and A. R. Chamberlin, *J. Org. Chem.*, 1990, **55**, 4190–4198.

10 Under the acidic conditions, dialkynylisobenzofuran **3a** was gradually decomposed, which promoted the cycloreversion of the cycloadduct **6a**.

11 For related base-induced aromatization, see: (*a*) R. Polley and M. Hanack, *J. Org. Chem.*, 1995, **60**, 8278–8282; (*b*) S.-H. Chan, C.-Y. Yick and H. N. C. Wong, *Tetrahedron*, 2002, **58**, 9413–9422.