Pergamon

Tetrahedron Letters 41 (2000) 10277–10280

TETRAHEDRON LETTERS

First synthesis of dioxadithiaporphycene with a benzene ring fused onto the double bond

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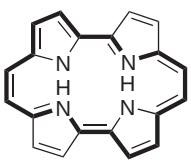
Received 15 August 2000; revised 13 October 2000; accepted 19 October 2000

Abstract

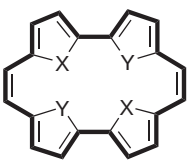
Dioxadithiaporphycenes **5** and **5′** were synthesized by using the Suzuki cross-coupling and McMurry coupling reactions as the key steps. This approach provided an access to the first dioxadithiaporphycene derivative **15** with a benzene ring fused onto the double bond. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: porphyrins and analogues; coupling reactions; furans; thiophenes.

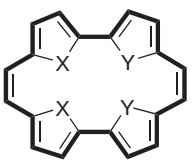
Porphycene (**1**), a planar and aromatic nitrogen-containing [18]annulene, was first synthesized in 1986 by Vogel and co-workers.[1] It possesses an N_4 coordination site and porphyrin-like properties. Some expanded porphycene derivatives are known as promising candidates for photodynamic therapy (PDT) in cancer treatment.[2] In recent years, numerous attempts have been made, with great success, to synthesize novel hetero-atom bridged annulenes related to porphyrin ring systems.[3] Replacement of pyrrole units by other heterocycles is an attractive approach. For example, tetraoxaporphycene (**2**),[4] tetrathiaporphycene (**3**)[5] and dithiaporphycene isomers (**4** and **4′**)[6] have been synthesized via reductive dimerization of the corresponding dialdehydes under the McMurry coupling conditions using low-valent titanium.[7] We report here on the first synthesis of dioxadithiaporphycenes **5** and **5′** and the benzo derivative **15** possessing a benzene ring fused onto the double bond. The Suzuki cross-coupling[8] and McMurry coupling reactions are the key steps in these syntheses.



1: porphycene



2: X = Y = O
3: X = Y = S
4: X = NH, Y = S
5: X = O, Y = S



4': X = NH, Y = S
5': X = O, Y = S

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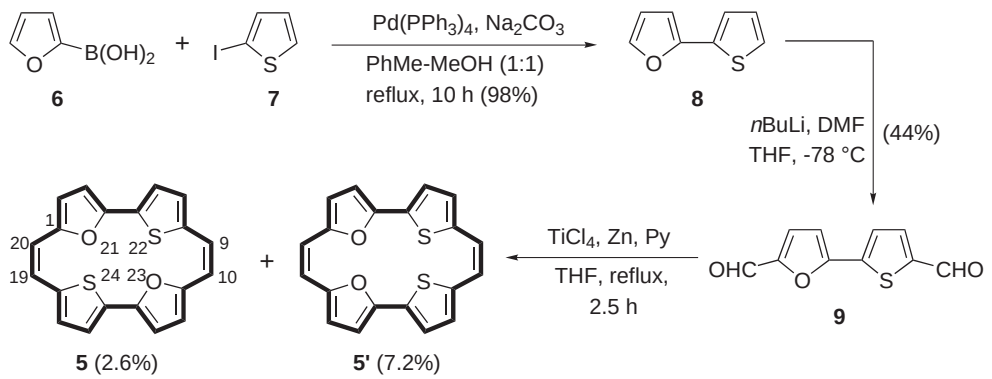
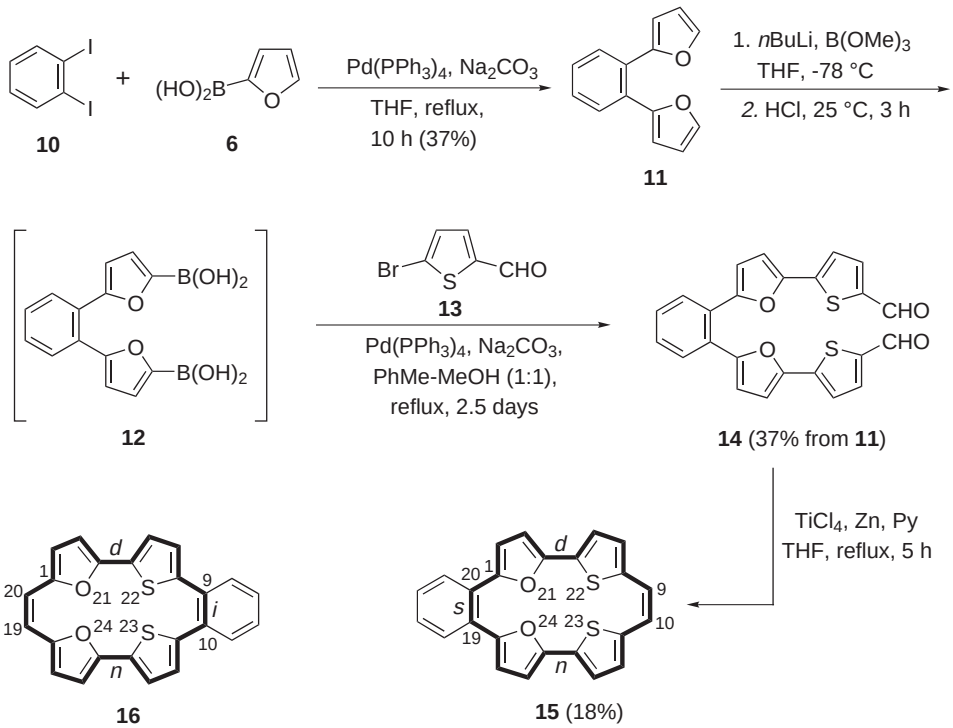
PII: S0040-4039(00)01846-3

As outlined in Scheme 1,[9] dialdehyde **9** possessing both furan and thiophene rings is required for synthesis of [20]annulenes **5** and **5′** through the McMurry coupling reaction. We attempted two cross-coupling procedures, both catalyzed by Pd(0), in the formation of the 2,2′-furanthiophene **8**. The Stille cross-coupling[10] of 2-(tributylstannyl)furan with 2-iodothiophene (**7**) in the presence of 5 mol% $Pd(PPh_3)_4$ (toluene, reflux, 26 h) gave compound **8**. However, complete removal of the tributyltin by-product from **8** by column chromatography proved difficult. Therefore, the Suzuki cross-coupling of 2-furanboronic acid (**6**)[11] with **7** was adopted. Refluxing a solution of **6** and **7** in mixed toluene and methanol (1:1) in the presence of 20 mol% $Pd(PPh_3)_4$ and Na_2CO_3 (4 equiv.) provided **8** in 98% yield. Compound **8** was then deprotonated by using 2.2 equiv. of *n*BuLi in THF at −78°C to give the 5,5′-dilithiated species which reacted with DMF to furnish 5,5′-diformyl-2,2′-furanthiophene (**9**) in 44% yield. Reductive dimerization of **9** was carried out under the conditions reported for porphycene synthesis.[1a,12] A THF solution of dialdehyde **9** (0.014 M final concentration) was slowly added to a slurry of the titanium reagent generated from 10 equiv. of $TiCl_4$ and 20 equiv. of activated zinc dust in THF containing 0.1 equiv. of pyridine followed by heating at reflux for 2.5 h. Two lower molecular weight compounds, 21,23-dioxa-22,24-dithiaporphycene (**5**) and 21,24-dioxa-22,23-dithiaporphycene (**5′**), were isolated in 2.6 and 7.2% yield, respectively.[13] Their structures were assigned based on ^{1}H NMR data. For compound **5**, the two olefinic protons on the same double bond are chemically non-equivalent with a coupling constant of ca. 13 Hz. In contrast, the adjacent olefinic protons in compound **5′** are chemically equivalent and they appear as singlet peaks at δ 6.63 and 5.78 ppm, respectively. We assume that the formation of **5′** began with an intermolecular coupling of formyl groups on the furan rings in **9** because of the relatively small size of oxygen compared to sulfur. This is then followed by an intramolecular carbonyl coupling on the side of the thiophene rings. We believe this is the reason why the distorted and less stable isomer **5′** was formed preferentially over **5**.



Scheme 1.

Next, we designed a scheme for synthesis of the first benzo porphycene analogue **15** by taking advantage of the Suzuki cross-coupling reaction (Scheme 2).[9] The commercially available 1,2-diiodobenzene (**10**) underwent double cross-coupling with 2-furanboronic acid (**6**)[11] to give **11** in 37% yield. Lithiation of the furan rings in **11** with *n*BuLi (3 equiv.) followed by reaction with $B(OMe)_3$ (6 equiv.) and acidic hydrolysis produced bis-boronic acid **12**. The latter compound is not stable after removal of solvent to dryness and was used, without purification,



Scheme 2.

for the second Suzuki cross-coupling with 5-bromothiophene-2-carboxaldehyde (**13**). Thus, dialdehyde **14** was synthesized in 37% yield from **11** in two steps. Intramolecular McMurry coupling within **14** in the presence of a slurry of the titanium reagent generated from 5 equiv. of $TiCl_4$ and 10 equiv. of activated zinc dust in THF containing 0.05 equiv. of pyridine (THF, reflux, 5 h) furnished benzo[*s*]21,24-dioxa-22,24-dithiaporphycene (**15**)[14] in 18% yield. As expected, the olefinic protons of **15** appear at δ 6.78 ppm as a singlet peak in the ^{1}H NMR spectrum.

We tried to synthesize benzo[*i*]21,24-dioxa-22,24-dithiaporphycene **16** with a benzene ring fused onto the C_9 and C_{10} positions. Unfortunately, the Suzuki cross-coupling of 1,2-diiodobenzene (**10**) with 2-thiopheneboronic acid failed to form the mono- and bis-coupled compounds. The severe steric interaction between the iodine and thiophene ring in the mono-coupled product may render its formation difficult via the reductive elimination step in the catalytic cycle.

In summary, we have developed a novel strategy for synthesis of the first benzo porphycene analogue **15**. Our approach takes advantage of the Suzuki cross-coupling to fuse a benzene ring onto the double bond. The synthetic scheme is flexible and should be useful for synthesis of related compounds. For example, replacement of 5-bromothiophene-2-carboxaldehyde (**13**) in Scheme 2 by 5-bromo-2-furaldehyde should lead to synthesis of benzo tetraoxaporphycene. Use of 2,3-bis{[(trifluoromethane)sulfonyl]oxy}naphthalene[15] for coupling with 2-furanboronic acid (**6**) in Scheme 2 should provide an access to 21,24-dioxa-22,24-dithiaporphycene fused with a naphthalene ring. Syntheses of these novel chromophores are underway in our laboratory.

Acknowledgements

We thank the Department of Chemistry, HKUST and the Research Grants Council of the Hong Kong Special Administrative Region, China (HKUST676/96P) for financial support.

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13. Spectroscopic data for **5**: IR (KBr) 2971, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, $J=3.42$ Hz, 2 H), 6.14 (d, $J=3.91$ Hz, 2 H), 5.62 (d, $J=3.42$ Hz, 2 H), 5.52 (d, $J=3.42$ Hz, 2 H), 5.34 (d, $J=13.19$ Hz, 2 H, olefinic), 4.95 (d, $J=12.69$ Hz, 2 H, olefinic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 151.6, 140.2, 134.9, 130.7, 122.5, 119.9, 114.9, 114.6, 106.8; MS (+CI) m/z (relative intensity) 348 (M^+, 100); HRMS (FAB+) m/z calcd for $C_{20}H_{12}O_2S_2$ (M^+) 348.0279, found 348.0288. For **5′**: IR (KBr) 2924, 2854, 1464, 1378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, $J=3.41$ Hz, 2 H), 6.91 (d, $J=3.42$ Hz, 2 H), 6.63 (s, 2 H, olefinic), 6.36 (d, $J=3.42$ Hz, 2 H), 6.23 (d, $J=3.41$ Hz, 2 H), 5.78 (s, 2 H, olefinic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 149.8, 141.5, 136.4, 129.3, 127.1, 125.8, 114.8, 112.0, 109.0; MS (+CI) m/z (relative intensity) 348 (M^+, 100); HRMS (FAB+) m/z calcd for $C_{20}H_{12}O_2S_2$ (M^+) 348.0279, found 348.0283.
14. Spectroscopic data for **15**: IR (neat) 2924, 2857, 1462, 1378 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.47 (AA′BB′, 2 H), 7.43–7.34 (AA′BB′, 2 H), 7.16 (d, $J=3.63$ Hz, 2 H), 6.90 (d, $J=3.66$ Hz, 2 H), 6.78 (s, 2 H, olefinic), 6.47 (s, 4 H, furan ring protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 149.5, 142.1, 137.8, 131.2, 129.5, 129.4, 128.6, 125.6, 124.7, 111.3, 107.1; MS (+CI) m/z (relative intensity) 399 (M+H$^+$, 100); HRMS (+FAB) calcd for $C_{24}H_{14}O_2S_2$ (M^+) 398.0435, found 398.0441.
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