

A palladium-catalyzed synthesis of 2-alkylidene-pyrrolo[*c*]-1,4-dioxanes: synthesis of 3,4-(*cis*-1,2-dimethyl)ethylenedioxy pyrrole

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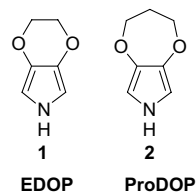
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Abstract—Palladium-catalyzed cyclization of ethyl-1-benzyl-3,4-dihydroxypyrrole-2,5-dicarboxylate with various propargylic carbonates rendered 2-alkylidene-pyrrolo[*c*]-1,4-dioxane derivatives with excellent yields. Further chemical manipulations of a selected compound led to 3,4-(*cis*-1,2-dimethyl)ethylenedioxy pyrrole in good yield.

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Heterocycle-based conjugated polymers, such as polypyrrole, polythiophene, polyfuran, and others, have received significant attention due to the wide range of electrical, electrochemical, and optical properties they display. The heteroatoms within a ring play an important role in controlling the properties of the polymers due to their intrinsic electron-donating or electron-withdrawing capabilities, along with other properties, which include hydrogen bonding and polarizability.¹ These polymers have been utilized in the applications as semiconductors for field-effect transistors^{2,3} and LEDs,^{4,5} as conductors for electrostatic charge dissipation and EMI shielding, and redox active materials for energy storage (batteries and supercapacitors) and electrochromic devices.⁶ Appending an alkylendioxy bridge across the 3- and 4-positions of pyrrole yields poly(3,4-alkylendioxy pyrrole) (PEDOP), which adds electron density to the aromatic ring, reducing both the monomer and polymer oxidation potentials and results in the formation of highly stable conducting states. Despite the importance of poly(alkylendioxy pyrroles), the routes for monomer synthesis are limited due to the intrinsic electron-rich property of pyrrole rendering the chemistry more difficult than the thiophene equivalent. Merz et al. first reported the synthesis of 3,4-ethylenedioxy pyrrole (EDOP, **1**), which included examples of noncyclic dialkoxypyrroles.⁷ The chemistry used was

similar to many dioxythiophene syntheses where the ring formation is completed via Williamson etherification. Subsequently, our group has reported the synthesis of a range of 3,4-alkylendioxy pyrroles, their derivatives, and their electrochemical studies.^{8–10} As reported, this route is practical for the synthesis of 3,4-alkylendioxy pyrroles equipped with less hindered substituents on the alkylendioxy bridge. Investigating the tailored properties of the polymers lead to a search for a route to produce a variety of derivatives that may have bulky or functionalized substituents. It is difficult to place substituents on the ethylenedioxy ring using the Williamson etherification method and low yields result.



Here we report an efficient route for the synthesis of substituted 3,4-ethylenedioxy pyrroles via palladium-catalyzed cyclization of a dihydroxypyrrole derivative with various propargylic carbonates as well as the synthesis of 3,4-[*cis*-1,2-dimethyl]ethylenedioxy pyrrole. It is well known that palladium reacts with propargylic carbonate to form an allenyl palladium complex in situ, which subsequently reacts with a heteroatomic nucleophile to give carbon–heteroatom bond formation.^{11–14} Sinou et al. published a series of papers on the synthesis

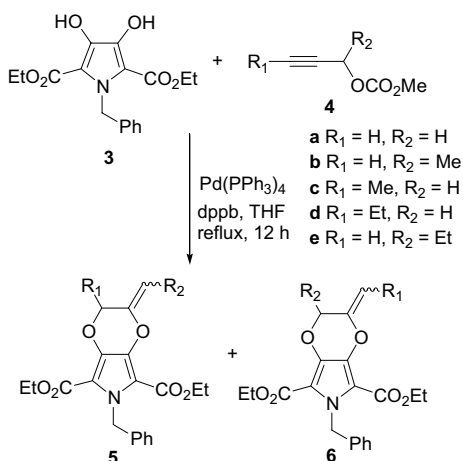
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of 2-alkylidene-1,4-benzodioxanes via palladium-catalyzed cyclization of a catechol and a propargylic carbonate.^{11–13} In our work, we predicted that the 3,4-dihydroxypyrrole derivative **3** may be used as a catechol equivalent to produce methylidene-1,4-pyrrolo[*c*]dioxane as shown in Scheme 1.

Indeed the reaction of the dihydroxypyrrole **3** with methyl propargylic carbonate **4a** in the presence of Pd(PPh₃)₄/dppb (1,4-bis(diphenylphosphino)butane), in THF at room temperature, gave the cyclized product methylidene-1,4-pyrrolo[*c*]dioxane **5a**, in 85% yield in 36 h. The use of another catalyst, Pd₂(dba)₃, under the similar reaction conditions brought comparable reaction times and yields. We observed a lower reactivity of **3** in comparison with catechol as explained by less nucleophilicity of the diol of **3** as the two neighboring ester groups withdraw electrons from the oxygen of the diol. When the system was heated to reflux (66 °C), the reaction proceeded much faster and was complete in 12 h.¹⁵ In order to evaluate substituent effects on the reaction rate, two substrates, 1-methylethynyl methyl carbonate (**4b**) and 3-methylethynyl methyl carbonate (**4c**), were prepared for comparison. The two compounds are structural isomers by location of a methyl group. When **4b** was employed in the reaction, it gave **6b** in excellent yield (98%) with trace amounts of **5b**. The reaction of **4c** gave **5c** in 95% yield with **6c** in trace amounts. Note, with these methyl substituents, **5c** and **6b** are the same compound. The size of the substituent was increased from methyl to ethyl using 3-ethylethynyl methyl carbonate (**4d**) and 1-ethylethynyl-methyl carbonate (**4e**). Again, the reaction with **4d** gave **5d** as a major product in 95% yield with **6d** as a minor product while the reaction of **4e** gave **6e** as a major product in 96% yield and **5e** as a minor product.

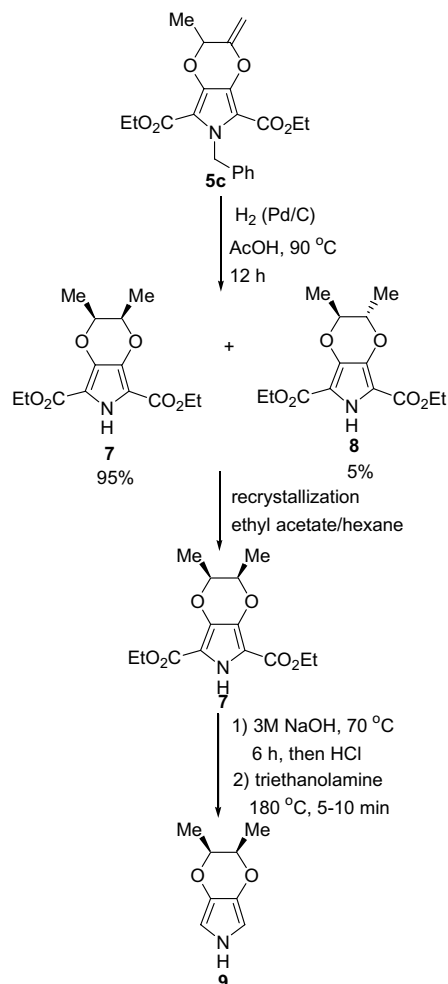
However, the regioselectivity was somewhat decreased to around 85:15 and no significant reaction rate difference between the two reactants was observed. To demonstrate the usefulness of the methodology developed here, compound **5c** was selected for further chemical manipulation.



Scheme 1.

One pot hydrogenation of the *exo*-vinylidene unit and catalytic hydrogen transfer debenzoylation of **5c** was carried out in the presence of a palladium catalyst as shown in Scheme 2 at 90 °C. The reaction smoothly afforded both saturated and debenzoylated **7** and **8** with **7** in 95% yield. As expected, hydrogenation took place predominantly on the less hindered side of the *exo*-vinylidene group to give the *cis*-product in a 95:5 ratio. The major product **7** was easily purified by recrystallization from a mixture of ethyl acetate diluted with hexane. The X-ray crystal structure of **7** confirmed the *cis* orientation of the two methyl groups on the dioxane ring where one methyl group (C7) was highly distorted from the dioxane plane as shown in Figure 1. It should also be noted that the pyrrole ring and two neighboring ester groups are in the same plane due to hydrogen bonding between the NH of the pyrrole and the carbonyl group.¹⁷

Hydrolysis and decarboxylation of **7** (Scheme 2) gave 3,4-[*cis*-1,2-dimethyl]ethylenedioxy-pyrrole **9** in 70% yield.¹⁰ Compound **9** was a pale yellow oil sensitive to decomposition by oxygen as with other alkylendioxy-pyrroles. All compounds were fully characterized and spectroscopic data for selected compounds is given.¹⁶



Scheme 2.

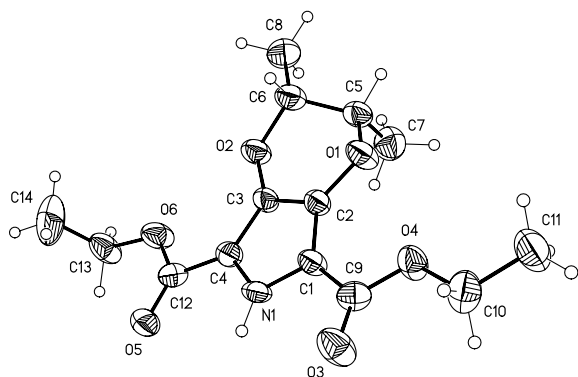


Figure 1. X-ray crystal structure of 7.

In conclusion, we have demonstrated a highly efficient route for synthesis of 2-alkylidenepyrrolo[*c*]-1,4-dioxane derivatives via a palladium-catalyzed cyclization of a dihydroxypyrrole derivative and propargylic carbonates. A selected intermediate **5c** was used to produce a monomer, 3,4-(*cis*-1,2-dimethyl)ethylenedioxyppyrrrole, potentially useful for producing an electroactive polymer.⁶

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15. A typical procedure for palladium-catalyzed cyclization is as follows. A mixture of the dihydroxypyrrole derivative **3** (0.5 g, 1.5 mmol) and the propargylic carbonate **4b** (0.2 g, 1.65 mmol) in THF was deoxygenated by bubbling with argon for 15 min. The solution prepared above was then added to a deoxygenated solution of Pd(PPh₃)₄ (47 mg, 4.0 × 10⁻² mmol) and dppb (71 mg, 0.16 mmol) in THF under argon. The reaction mixture was stirred at reflux for 12 h. After cooling to room temperature, the solvent was removed by rotary evaporation and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent.
16. Spectroscopic data of selected compounds; **7**. A colorless crystal; mp 132 °C; ¹H NMR (CDCl₃, 300 MHz) δ 8.60–8.40 (br, 1H), 4.35 (m, 6H), 1.39–1.30 (m, 12H); ¹³C NMR (CDCl₃, 75 MHz) 160.0, 135.0, 108.3, 74.0, 61.1, 14.7, 14.5; HMRS (FAB) calcd for C₁₈H₁₉NO₆ (MH⁺) 298.1291, found 298.1291; Anal. Calcd for C₁₈H₁₉NO₆: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.57; H, 6.50; N, 4.69. **9**. A pale yellow oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.15–7.05 (br, 1H), 6.16 (d, *J* = 3.0 Hz, 2H), 4.22 (q, *J* = 6.0 Hz, 2H), 1.28 (d, *J* = 6.0 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) 127.8, 98.4, 73.3, 14.2; HMRS (FAB) calcd for C₈H₁₁NO₂ (M⁺) 153.0790, found 153.0789; Anal. Calcd for C₈H₁₁NO₂: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.80; H, 7.20; N, 9.10.
17. Crystal data and structure refinement for **7**. Empirical formula, C₁₄H₁₉NO₆; formula weight, 297.30; temperature, 193(2) K; wavelength, 0.71073 Å; crystal system, orthorhombic; space group, *Pca*2(1); unit cell dimensions, *a* = 17.168(2) Å, *b* = 10.0901(7) Å, *c* = 17.348(2) Å, α = 90°, β = 90°, γ = 90°; volume, 3005.3(4) Å³; *Z*, 8; density (calculated), 1.314 Mg/m³; absorption coefficient, 0.103 mm⁻¹; *F*(000), 1264; crystal size, 0.34 × 0.22 × 0.17 mm³; theta range for data collection, 2.02–27.50°; index ranges, -22 ≤ *h* ≤ 22, -13 ≤ *k* ≤ 12, -22 ≤ *l* ≤ 22; reflections collected, 24671; independent reflections, 6880 [*R*(int) = 0.0470]; completeness to θ = 27.50°, 99.8%; absorption correction, empirical; max. and min. transmission, 0.9848 and 0.9687; refinement method, full-matrix least-squares on *F*²; data/restraints/parameters, 6880/1/439; goodness-of-fit on *F*², 1.033; final *R* indices [*I* > 2σ(*I*)], *R*1 = 0.0552, *wR*2 = 0.1361 [4152]; *R* indices (all data), *R*1 = 0.1068, *wR*2 = 0.1687, absolute structure parameter, -1(2); largest diff. peak and hole, 0.402 and -0.226 e Å⁻³. Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229566. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).