Convenient Synthesis of Linear-extended Bipyridines Involving a Central Phenyl Linking Group

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Linear-extended bipyridines were synthesized via the Hantzsch dihydropyridine synthesis, subsequent oxidative aromatization with molecular oxygen in the presence of activated carbon, and decarboxylation. 4,4″-*p*-Terphenyldicarboxaldehyde was prepared by the Suzuki–Miyaura cross-coupling reaction.

Supramolecular chemistry is now widely studied from the aspect of synthesis of building blocks by molecular recognition and self-organization, based on noncovalent interaction.[1] These investigations lead to the design of artificial supramolecules, promising for the use in advanced technologies such as molecular machinery, molecular-based memory devices, and molecular imprinting. In these studies, 4,4′-bipyridine and its diquaternary derivatives, such as viologens have been intensively investigated owing to their redox, electrochemic properties, and their ability to form intra- and intermolecular charge-transfer complexes.

So far, much attention has been paid to derivatives of 4,4′-bipyridine,[2] however, "linear-extended" bipyridines[3] represented in the general formula (Figure 1) in which phenyl, biphenyl, or terphenyl is inserted between the two pyridine units, have not been investigated well, because convenient methods for their synthesis are limited. Fujita and his co-workers reported the synthesis of 1,4-bis(2,6-dimethyl-4-pyridyl)benzene via the Suzuki–Miyaura cross-coupling between 4-bromo-2,6-lutidine and 1,4-phenylenebisboronic acid in their supramolecular complexes using organic-pillared coordination cages.[4] However, by this method, synthesis of 4,4″-bis(2,6-dimethyl-4-pyridyl)-*p*-terphenyl is not facile because of the nonavailability of the corresponding coupling precursors or difficulty of their preparation. Here, we report a practical method for the synthesis of linear-extended bipyridines. The synthetic procedure is shown in Scheme 1.

The oxidation of Hantzsch 1,4-dihydropyridines **4**–**6**, which were easily synthesized by the reaction of dicarboxaldehydes **1**–**3**, β-ketoesters, and ammonia provided the corresponding pyridine esters **7**–**9**. Subsequent decarboxylation gave the desired pyridine derivatives **10**–**12**. To realize our strategy, the corresponding dicarboxaldehydes are required. 1,4-Benzenedicarboxaldehyde (**1**) and 4,4′-biphenyldicarboxaldehyde (**2**) are commercially available.

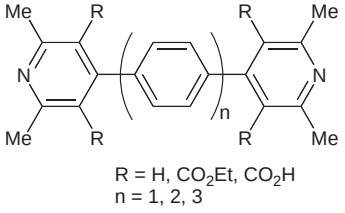
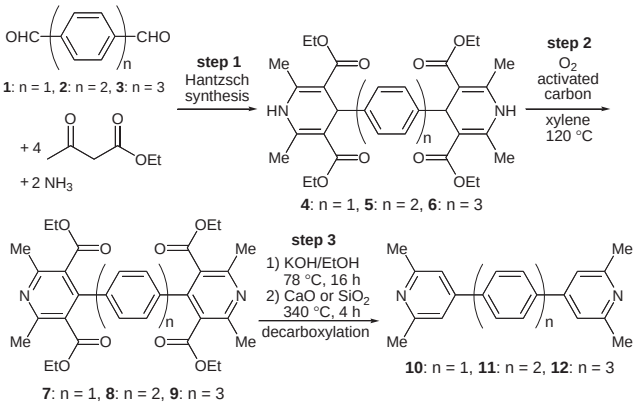
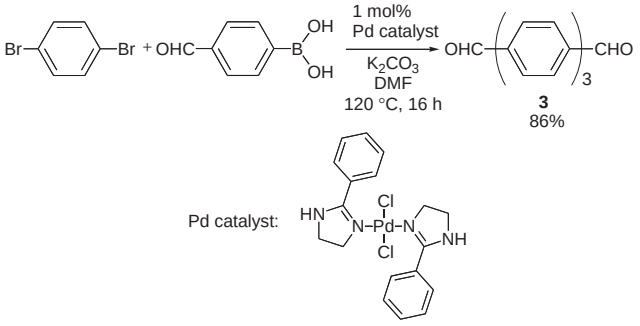


Figure 1. Linear-extended bipyridines.



Scheme 1. Synthesis of linear-extended bipyridines.



Scheme 2. Preparation of 4,4″-*p*-terphenyldicarboxaldehyde.

4,4″-*p*-Terphenyldicarboxaldehyde (**3**) was prepared via the Suzuki–Miyaura cross-coupling reaction (Scheme 2). Reaction of 1,4-dibromobenzene with 4-formylphenylboronic acid catalyzed by 2-phenylimidazoline–$PdCl_2$ complex[5] gave **3** in 86% yield.

Hantzsch 1,4-dihydropyridines can be easily synthesized by thermal condensation of dialdehydes with β-ketoesters in the presence of ammonia. That is, treatment of dialdehydes **1**–**3** with ethyl acetoacetate and ammonia gave the corresponding Hantzsch 1,4-dihydropyridines that precipitated after cooling to room temperature. The resulting suspensions were filtered to afford Hantzsch 1,4-dihydropyridines **4**–**6** in 72–85% yield.

Then we focused our attention on conversion of 1,4-dihydropyridines to pyridines. So far, various oxidants were studied in the aromatization of 1,4-dihydropyridines.[6] However, most of those methods use hazardous oxidants and/or give low chemical yield.

We recently reported oxidative aromatization with molecular oxygen in the presence of activated carbon.[7] We found that activated carbon–O_2 system also exhibited high performance in the transformation of Hantzsch 1,4-dihydropyridines to the

Table 1. Synthesis of linear-extended bipyridines[a]

	Step 1		Step 2		Step 3
n	Time/h	Yield/%[b]	Time/h	Yield/%[b]	Yield/%[b]
1	48	84	48	92	63
2	96	72	16	92	42
3	72	85	24	92	43

[a]All reactions were carried out in gram scales. [b]Isolated yield.

corresponding pyridines. That is, Hantzsch 1,4-dihydropyridines were treated with 50 wt % activated carbon (available from Tokyo Chemical Industry Co., Ltd.) at 120 °C in xylene for 24 to 72 h to afford the corresponding pyridines **7**–**9** in 92% yield.[8] This simple process is not only environmentally friendly but also economical and operationally simple. Only oxygen and commercially available and inexpensive activated carbon are used. Neither metal oxides nor organic peroxides are required.

Having pyridine esters, we examined the following decarboxylation. Refluxing pyridine-3,5-dicarboxylates with aqueous KOH gave the corresponding potassium salts of pyridine carboxylic acid. After subsequent thermal decarboxylation, the desired products **10**–**12** were obtained in 42–63%. The reaction conditions and yields in each step of Scheme 1 are summarized in the Table 1.

It should be mentioned that the decarboxylation procedure of step 3 proceeds first by hydrolysis with KOH in EtOH, so intermediates for decarboxylation (actually, de-esterification) are potassium carboxylates then the carboxylic acids. In this step, the addition of CaO[9] or SiO_2 to the mixture under thermal conditions improved the yield of step 3, even though the yield is still moderate.

In summary, we have developed a convenient method for the synthesis of some linear-extended bipyridines. That is, the combination of Hantzsch dihydroxypyridine synthesis, then activated carbon-promoted oxidative aromatization using molecular oxygen followed by decarboxylation of Hantzsch pyridine esters afforded linear-extended bipyridines efficiently.[10–13]

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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10 **Typical procedure for the synthesis of Hantzsch 1,4-dihydropyridines:** In a 250-mL round-bottomed flask, 1,4-benzenedicarboxaldehyde (**1**) (1.34 g, 10 mmol), ethyl acetoacetate (5.21 g, 40 mmol), 25 wt % ammonia solution (2.00 g), and ethanol (20 mL) were charged and the mixture was heated to reflux (80 °C, oil bath temperature). After confirmation of the completion of the reaction by TLC, the mixture was cooled to room temperature. The solid product **4** was obtained by filtration, then washed with ethanol and dried in vacuum to give **4** as a pale yellow solid (4.88 g, 84%).
11 **Typical procedure for the oxidative aromatization of Hantzsch 1,4-dihydropyridines:** A mixture of 1,4-dihydropridine **4** (2.90 g, 5 mmol) and activated carbon (available from Tokyo Chemical Industry Co., Ltd.) (1.45 g) in xylene (20 mL) was placed in a 250-mL three-necked flask under an oxygen atmosphere and stirred at 120 °C. After confirmation of the completion of the reaction by TLC, the mixture was filtered using Celite. The filtrate was then concentrated, and product was isolated by silica-gel column chromatography to give the corresponding pyridine **7** as a pale yellow solid (2.65 g, 92%).
12 **Typical procedure for decarboxylation of pyridine esters:** A suspension of pyridine ester **7** (1.15 g, 2 mmol) in KOH solution (10 mL, 20 wt %) and ethanol (40 mL) was heated to reflux (80 °C, oil bath temperature) till a clear liquid was formed. After solvent was removed under vacuum, the dried residue was mixed with CaO (1.00 g) powder. After heating with stirring at a sand bath temperature of about 340 °C for 4 h, the mixture was cooled to room temperature. After extraction using $CHCl_3$, the precipitates were removed by filtration. The filtrate was concentrated, the crude product was purified by silica-gel column chromatography to afford product **10** as a white solid (363 mg, 63%).
13 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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