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A new approach to the 1,10-phenanthroline core

Giorgio Chelucci,* Daniele Addis and Salvatore Baldino

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

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Abstract—A protocol for the synthesis of substituted 1,10-phenanthrolines is reported. The phenanthroline scaffold has been obtained constructing the central cycle starting from two pyridine rings. The method is hinged upon the intramolecular coupling of *cis*-1,2-di(2-bromo-3-pyridyl)ethenes that are in turn obtained from the Wittig reaction of 2-bromonicotinaldehydes with phosphonium salts prepared from 2-bromo-3-(bromomethyl)pyridines. Yields up to 75% have been obtained.

1,10-Phenanthroline is the parent of an important class of chelating agents that form a multitude of coordination compounds with various metal ions.[1] Most of the work on 1,10-phenanthroline derivatives has been prompted by the intense current interest in their redox and photoredox properties, biological activity and supramolecular chemistry.[2] Moreover, they have proven utility as ligands in metal complexes for catalysis.[3]

Substituted 1,10-phenanthrolines are most commonly synthesized modifying the existing framework by electrophilic or nucleophilic aromatic substitutions, or by de novo construction of the heterocycle. Since the 1,10-phenanthroline scaffold can be considered as a tricyclic molecule in which two pyridine rings are fused to a central benzene ring, two major schemes can be envisaged for its synthesis. One could start with a proper substituted central ring and build up two pyridine moieties in a single step or in sequence via the formation of an intermediate quinoline. Alternatively, the 1,10-phenanthroline framework could be constructed making the central cycle from pyridines. The first approach has been widely utilized,[4] whereas there is no report on the second one.

Continuing our interest on the 1,10-phenanthroline chemistry,[5] we have undertaken a study of methods to realize the synthesis of the 1,10-phenanthroline core starting from pyridines. This goal could be accomplished following two main strategies (Scheme 1). In the former approach (*Z*)-1,2-di(2-substituted-3-pyridyl)ethene **2** could be prepared from two pyridines and next the two pyridine rings in **2** could be coupled at their 2-substituted positions. In the latter approach one could synthesize 3,3′-disubstituted 2,2′-bipyridine **3** and then elaborate the substituents on the pyridine rings in order to form the central cycle (Scheme 1).

Herein, we report the first synthesis of substituted phenanthrolines from pyridines tackling this problem according to the former approach. To verify the feasibility of this project we needed a proper *cis*-ethene, the simpler of which, namely, (*Z*)-1,2-di(2-bromo-3-pyridyl)ethene **2a**, was prepared with high yield (94%) and stereoselectivity (cis/trans = 92/8) from the Wittig reaction of 2-bromonicotinaldehyde **6a**[6] with phosphonium salt **7a** derived from 2-bromo-3-bromomethylpyridine[7] (1.2 equiv of **7a**, 2.2 equiv of KOBu^t, THF, room temperature, 18 h) (Scheme 2).

With the ethene **2a** in hand, the intramolecular coupling of the two pyridines with a number nickel(0)- and palladium(0)-based catalytic systems used with success for intermolecular homocoupling of 2-halopyridines[8–12] was initially evaluated (Table 1). Among them, only $Pd(PPh_3)_4$ in the presence of $(Me_3Sn)_2$ afforded the desired phenanthroline **1a**, but in low yield (22%) because a relevant amount of (*Z*)-1,2-di(3-pyridyl)ethene (66% yield) was formed by debromination of **2a**.

Next, copper-based systems used for reductive coupling of aromatic halides were examined.[13] The use of

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* Corresponding author. Tel.: +39 079 229539; fax: +39 079 229559; e-mail: chelucci@uniss.it

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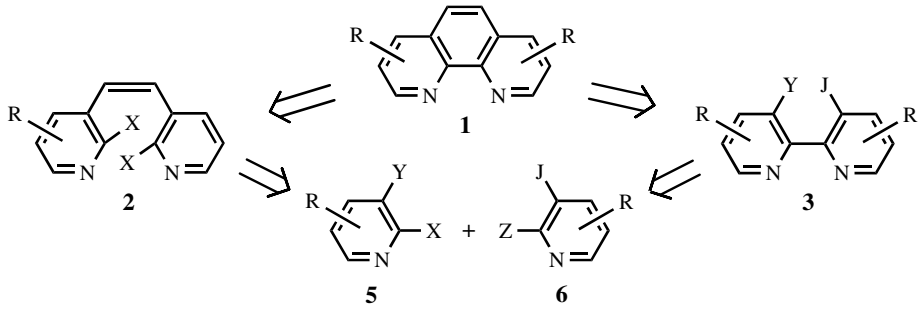
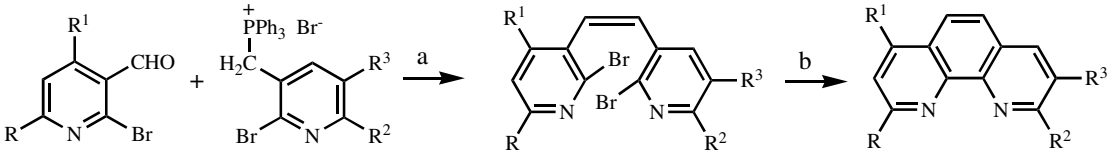


Scheme 1.



6a: R= R^1= H
6b: R= Me, R^1=H
6c: R= R^1= Me

7a: R^2= R^3= H
7b: R^2= Me, R^3= H
7c: R^2-R^3= -CH=CH-CH=CH-

1a, **2a**: R= R^1= R^2= R^3= H
1b, **2b**: R= Me, R^1=H, R^2= R^3= H
1c, **2c**: R= R^2= Me, R^1= R^3= H
1d, **2d**: R= R^1= Me, R^2= R^3= H
1e, **2e**: R= Me, R^1= H, R^2-R^3= -CH=CH-CH=CH-
1f, **2f**: R= R^1= Me, R^2-R^3= -CH=CH-CH=CH-

Scheme 2. Reagents and conditions: (a) **7** (1.2 equiv), KOBu^t (2.2 equiv), THF, rt, 18–60 h, 32–97%; (b) Cu, DMF or NMP, reflux, Table 1.

Table 1. Intramolecular coupling of **2a**

Reagent	Procedure[a]	Solvent	Temperature (°C)	Reaction time (h)	Yield of **1a** (%)
$NiCl_2$, Zn, PPh_3	A	DMF	Reflux	24	0
$Ni(CO)_2(PPh_3)_2$	B	Toluene/DMF	70	24	0
$Pd(PPh_3)_4$, $(Me_3Sn)_2$	C	Dioxane	80–100	24	22
$Pd(OAc)_2$, Bu_4NBr	D	DMF	115	48	0
Pd/C, HCOONa	E	H_2O	Reflux	168	0
CuTC	F	NMP	70	48	0
Cu	G	DMF	Reflux	5	67

[a] Procedure A: $NiCl_2 \cdot 6H_2O$ (0.5 mmol), PPh_3 (2 mmol) and Zn powder (0.5 mmol) in DMF (2.5 mL) were heated at 60 °C for 1 h under argon, then **2a** (0.55 mmol) was added and the mixture was heated at 70 °C.
Procedure B: **2a** (0.5 mmol) and $Ni(CO)_2(PPh_3)_2$ (0.0135 mmol) in toluene/DMF = 1/1 (1.5 mL) were heated at 70 °C under argon.
Procedure C: **2a** (0.5 mmol), $Pd(PPh_3)_4$, (0.05 mmol) and $(Me_3Sn)_2$ (0.6 mmol) in dioxane (2 mL) were heated in a sealed tube.
Procedure D: **2a** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), Bu_4NBr (0.25 mmol) and K_2CO_3 (0.5 mmol) in DMF (1 mL) were stirred under argon at 115 °C for few minutes, then isopropanol (0.5 mmol) was added and heating was continued.
Procedure E: **2a** (0.5 mmol), 10% Pd/C (3 mg), HCOONa (0.062 mmol), $BnNEt_3Cl$ (0.0062 mmol) in H_2O (1.6 mL) and 10 M NaOH (0.45 ml) were heated under reflux for 7 d.
Procedure F: **2a** (0.5 mmol) and copper(I) thiophene-2-carboxylate (CuTC) (1.5 mmol) in NMP (2 mL) were heated 70 °C under argon.
Procedure G: **2a** (0.5 mmol) and Cu (3.0 mmol) in DMF (2 mL) were heated under reflux under argon.

copper(I) thiophene-2-carboxylate (CuTC) failed,[14] whereas more profitable was the application to our substrate of the classical Ullmann coupling.[13] Thus, phenanthroline **1a** was obtained in 67% yield by heating under reflux **2a** with copper powder in DMF for 5 h.

In order to explore the scope of this methodology to the synthesis of substituted phenanthrolines, a number of (*Z*)-1,2-di(2-bromo-3-pyridyl)ethenes **2b–f** were prepared by crossed Wittig reactions between 2-bromoaldehydes **6a–c** and phosphonium salts **7a–c** (1.2 equiv of **7**, 2.2 equiv of KOBu^t, THF, room temperature, 18–48 h) (Scheme 2). 2-Bromoaldehydes **6b**,**c** afforded the related ethenes in high yield and stereoselectivity: **2b** (94%, cis/trans = 93/7), **2c** (97%, cis/trans = 94/6) and **2e** (95%, cis/trans = 90/10). Whereas with the more sterically hindered 2-bromoaldehyde **6c**, the corresponding ethenes were isolated in lower yield: **2d** (88%, 61% conversion, cis/trans = 74/26) and **2f** (32%, cis/trans = 80/20).

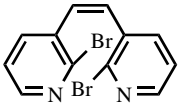
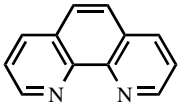
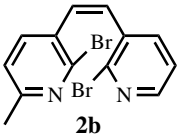
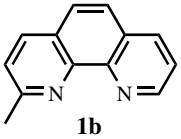
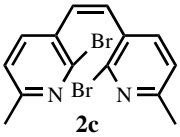
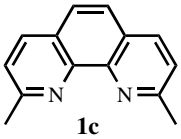
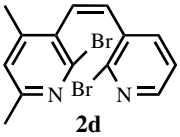
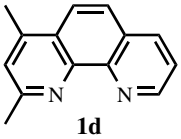
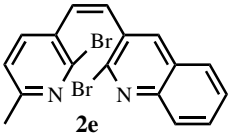
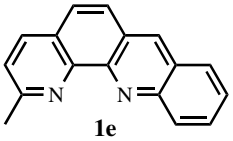
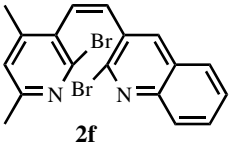
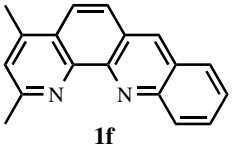
Aldehydes **6b** and **6c** were obtained by reduction of the 6-methyl- and 4,6-dimethyl-3-cyano-2-bromopyridine (DIBAL, CH_2Cl_2, −78 °C, 77 and 80%)[15] prepared in turn by bromination of the related commercially available 6-methyl- and 4,6-dimethyl-3-cyano-2-hydroxypyridine (Bu_4NBr, P_2O_5, toluene reflux, 4 h, 70% and 56%).[16] Phosphonium salts **7b** and **7c** were obtained (1.2 equiv of PPh_3, THF, reflux, 24 h, >87%) from the corresponding 2-bromo-3-bromomethyl-6-methylpyridine and 2-bromo-3-bromomethylquinoline,[17] respectively. The 2-bromo-3-bromomethyl-6-methylpyridine was accessible from the related bromoaldehyde **6b** via reduction ($NaBH_4$, MeOH, >90%) followed by bromination (CBr_4, PPh_3, CH_2Cl_2, −10 °C, 90%).[18]

Ethenes **2b–f** were submitted to intramolecular Ullmann coupling to give phenanthrolines **1b–f**.[19] Compounds **2b**,**c**,**e** were used as the obtained cis–trans mixture, whereas with **2d** and **2f** the pure cis-isomer was employed. The reactions were initially carried out in refluxing DMF, but a longer reaction time with respect to **1a** was required to obtain total conversion of the starting material (Table 2). Thus, the anulation was next performed in refluxing 1-methyl-2-pyrrolidinone (NMP). The rising of the temperature not only shorted the reaction time but also the yield was in some cases increased.

The yields of the intramolecular coupling were fairly good with alkylsubstituted phenanthrolines **2b–d** (59–75% yield), whereas a substantial reduction of the yield was observed with benzo-fused phenanthrolines **2e–f** (35–36%).

In conclusion, we have developed the first protocol for the synthesis of substituted 1,10-phenanthrolines from two pyridine rings with fairly good yields.[20] The method is hinged upon the Ullmann intramolecular coupling of *cis*-1,2-di(2-bromo-3-pyridyl)alkenes which are in turn

Table 2. Intramolecular coupling of (*Z*)-dipyridyl-alkenes **2** (Scheme 1)[a]

Alkene	Product	Reaction time (h)		Yield[b] (%)	
		DMF	NMP	DMF	NMP
 **2a**	 **1a**	5	—	67	—
 **2b**	 **1b**	18	9	75	76
 **2c**	 **1c**	120	30	32	59
 **2d**	 **1d**	40	—	24	62
 **2e**	 **1e**	40	26	24	36
 **2f**	 **1f**	—	14	—	35

[a] Reaction conditions: ethene (0.5 mmol) and Cu (3.0 mmol) in dry DMF or NMP (2 mL) were heated under reflux under argon.
[b] Isolated yields.

obtained from the Wittig reaction of 2-bromonicotinaldehydes with phosphonium salts prepared from 2-bromo-3-bromomethylpyridines. Further studies on this subject are currently in progress.

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19. All compounds showed satisfactory spectroscopic and analytical data. Phenanthrolines **1a**,[21] **1b**[22] and **1c**[23] are known compounds. 2,3-Dimethyl-1,10-phenanthroline (**1d**): mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (dd, 1H, $J = 4.2$, 1.5 Hz), 8.22 (dd, 1H, $J = 8.1$, 1.5 Hz), 7.96 (d, 1H, $J = 9.0$ Hz), 7.73 (d, 1H, $J = 9.0$ Hz), 7.59 (dd, 1H, $J = 8.1$, 4.2 Hz), 7.36 (s, 1H), 2.90 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 158.8, 150.1, 146.0, 145.3, 144.1, 135.8, 128.2, 126.2, 124.9, 124.7, 122.5, 122.3, 25.5, 18.9. 9-Methyl benzo[*b*][1,10]phenanthroline (**1e**): mp 63–65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.62 (dd, 1H, $J = 8.4$, 0.9 Hz), 8.09 (d, 1H, $J = 8.4$ Hz), 8.03 (d, 1H, $J = 7.5$ Hz), 7.88–7.82 (m, 1H), 7.79 (d, 1H, $J = 9.0$ Hz), 7.63 (d, 1H, $J = 9.0$ Hz), 7.66–7.59 (m, 1H), 7.54 (d, 1H, $J = 8.4$ Hz), 3.00 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.2, 148.2, 146.8, 146.2, 136.2, 135.7, 131.1, 129.8, 127.5, 127.3, 127.2, 126.9, 126.6, 126.0, 125.8, 124.1, 25.7. 7,9-Dimethyl benzo[*b*][1,10]phenanthroline (**1f**): mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.62 (d, 1H, $J = 8.7$ Hz), 8.04 (d, 1H, $J = 8.1$), 7.92–7.78 (m, 3H), 7.63 (t, 1H, $J = 7.5$ Hz), 7.40 (s, 1H), 2.95 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 158.6, 148.3, 147.1, 146.0, 144.3, 135.6, 131.2, 129.7, 127.5, 127.2, 126.7, 126.5, 125.6, 125.3, 121.9, 25.6, 19.1.
20. The number of steps needed to obtain phenanthrolines **1a**–**f** and the related overall yield from commercially available pyridine derivatives are reported. Phenanthroline **1a** was obtained in three steps (60%) from 2-bromonicotinaldehyde **6a** and in four steps (41%) from 2-bromo-3-methylpyridine. Phenanthroline **1b** was obtained in four steps (40%) from 2-hydroxy-6-methylnicotinonitrile and in four steps (46%) from 2-bromo-3-methylpyridine. Phenanthroline **1c** was obtained in four steps (31%) and in seven steps (16%) from 2-hydroxy-6-methylnicotinonitrile (this pyridine is the common starting material for both bromoaldehyde **6b** and phosphonium salt **7b**). Phenanthroline **1d** was obtained in four steps (25%) from 2-hydroxy-4,6-dimethylnicotinonitrile and in four steps (37%) from 2-bromo-3-methylpyridine. Phenanthroline **1e** was obtained in four steps (19%) and from 2-hydroxy-6-methylnicotinonitrile and in four steps (21%) from 2-chloroquinoline-3-carbaldehyde. Phenanthroline **1f** was obtained in four steps (5%) from 2-hydroxy-4,6-dimethylnicotinonitrile and in four steps (7%) from 2-chloroquinoline-3-carbaldehyde.
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