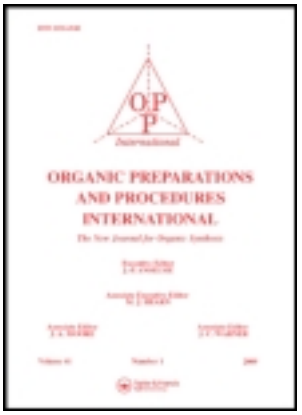

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Improved Synthesis of 2,9-Dichloro-1,10-phenanthroline

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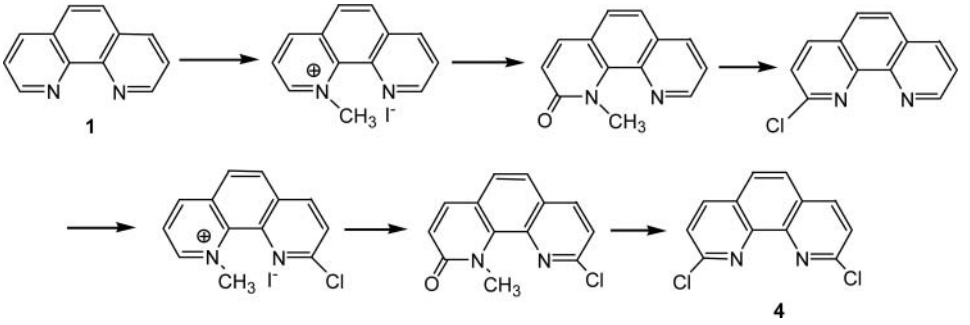
1,10-Phenanthroline is a classic ligand that plays an important role in coordination chemistry and continues to be of considerable interest as a versatile starting material in organic, inorganic and supramolecular chemistry.[1,2] As for 1,10-phenanthroline derivatives, most of the recent work has been prompted by the intense current interest in their molecular recognition, photophysical, catalysis, redox properties and cleavages of DNA.[3–5] Thus, a simple and convenient access to 1,10-phenanthroline building blocks appears of importance. Surprisingly, the functionalization of the 2,9-positions of 1,10-phenanthroline ligand appears to be relatively rare. Among these derivatives, 2,9-dihalo-1,10-phenanthrolines are the most versatile starting materials of particular importance as they can be used either directly for metal-catalyzed cross-coupling reactions to form additional derivatives or for the preparation of the 2,9-diamino,[6] 2,9-dialkoxy[7] and 2,9-diacetyl[8] analogues.

The synthesis of 2,9-dichloro-1,10-phenanthroline (**4**) has been reported by two groups. The conventional method (*Route 1, Scheme 1*) leads to **4** in six steps and in low overall yields (44%) from 1,10-phenanthroline (**1**).[9,10] Compound **4** has also been obtained in a three-step sequence (*Route 2, Scheme 2*) from **1**.[11,12] Compound **2** was obtained in 88% yield by



Scheme 1

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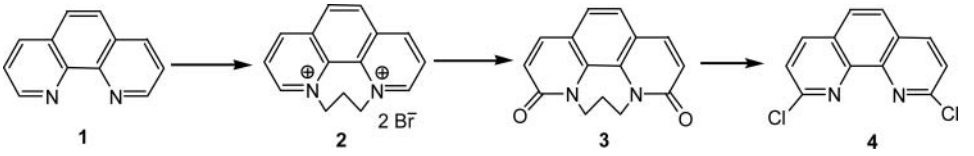
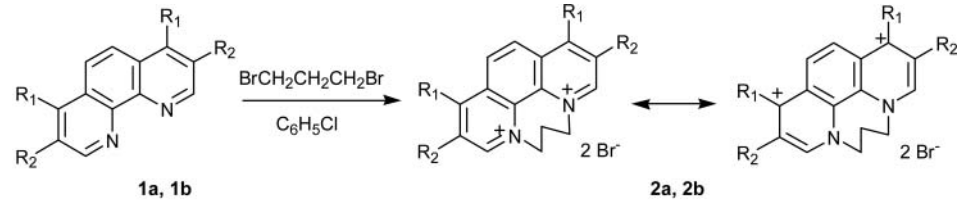
alkylation of 1,10-phenanthroline with 1,3-dibromopropane in nitrobenzene and it was subsequently converted in 35% yield to the *N,N′*-annelated dione **3** using $[K_3Fe(CN)_6]$ in basic aqueous solution. 2,9-Dichloro-1,10-phenanthroline (**4**) was then prepared in high yield (88%) by reaction of **3** with PCl_5 and $POCl_3$ at 110°C; however, the overall yields were also very low (27%) from 1,10-phenanthroline, largely due to the poor yields in the conversion of **2** to **3**. This paper reports an improved synthesis of 2,9-dichloro-1,10-phenanthroline (**4**) in 67% overall yield based on the *Route 2*.



Scheme 2

First, we focused on improving the yield of the conversion of **2** to **3**. An efficient method for the preparation of N,N′-annelated dione **3** from **2** using potassium *tert*-butoxide and *tert*-butanol (with air as the oxidizing agent) gave better than twice the yields obtained with the existing synthesis (79% vs. 35%). Second, we found that the conversion of 1,10-phenanthroline (**1**) to **2**, which had been reported using a large excess of 1,3-dibromopropane in nitrobenzene in 88% yield, can be carried out in chlorobenzene in quantitative yields. Finally, 2,9-dichloro-1,10-phenanthroline (**4**) was obtained in high yield (85%) by reaction of **3** with PCl_5 and $POCl_3$.

In order to explore the scope of this method for the synthesis of substituted 2,9-dichloro-1,10-phenanthrolines, a number of 3,8- or 4,7-disubsitituted phenanthroline have been used as starting materials for the synthesis of corresponding derivatives. However, only *N,N′*-annelated compounds bearing Me groups at 3,8- or 4,7-positions could be obtained (*Scheme 3*). Electron-withdrawing substituents such as halo groups at 3,8- or 4,7-positions of 1,10-phenanthroline could not be converted to the corresponding *N,N′*-annelated compounds presumably because of the diminished reactivity of the nitrogens caused by electron-withdrawing groups. Attempts to convert **2a** and **2b** into the corresponding *N,N′*-annelated diones under these conditions were unsuccessful because the stabilized tautomeric structures predominate.



a) $R_1 = CH_3$, $R_2 = H$; b) $R_1 = CH_3$, $R_2 = CH_3$

Scheme 3

We have developed an efficient process for the preparation of 2,9-dichloro-1,10-phenanthroline in three steps from 1,10-phenanthroline in 67% yield. 2,9-Dibromo-1,10-phenanthroline was also obtained by this method in 81% yield from **3**. Moreover, 2,9-diodo-1,10-phenanthroline could be obtained by reaction of **4** with conc. aqueous hydriodic acid.[13] We believe that this procedure will provide a more practical alternative to the existing methods for the synthesis of 2,9-dihalo-1,10-phenanthrolines.

Experimental Section

All reagents and solvents were of reagent grade and used without further purification unless otherwise specified. 4,7-Dimethyl-1,10-phenanthroline and 3,4,7,8-tetramethyl-1,10-phenanthroline were purchased from Aladdin Reagent Co. Ltd. The 1,10-phenanthroline hydrate and other reagents were purchased from Sinopharm Chemical Reagent Co. Ltd. Melting points (mps) were determined on a WRS-1B digital melting point apparatus and are uncorrected.[1]H NMR spectra were obtained on a 300 MHz Varian Mercury VX-300 in $CDCl_3$ or D_2O with TMS as internal standard. Ultrasound-promoted reactions were carried out in a common ultrasonic laboratory cleaner (JN-5200D).

Compound 2

A mixture of 1,10-phenanthroline monohydrate (10.00 g, 50.5 mmol) in chlorobenzene (80 mL) was heated at 70°C with magnetic stirring. To the hot colorless solution, 1,3-dibromopropane (51 g, 253 mmol) was added dropwise over 15 minutes, and then the temperature was raised to 120°C. During the course of the reaction, a yellow powder precipitated from the reaction mixture. After 4 h, the mixture was allowed to cool to room temperature and the yellow powder was collected, washed with petroleum ether and dried *in vacuo* to yield compound **2** (19.30 g, 100%), mp. >300°C. ^{1}H NMR (D_2O): δ 9.50 (dd, J = 1.2 and 5.8 Hz, 2H), 9.28 (dd, J = 1.2 and 8.6 Hz, 2H), 8.41 (s, 2H), 8.37 (d, J = 2.7, 2H), 4.99 (t, J = 7.0 Hz, 4H), 3.27 (q, J = 6.7 Hz, 2H).

The filtrate from the isolation of **2** may be re-used after addition of the appropriate amount of 1,3-dibromopropane.

Anal. Calcd for $C_{15}H_{14}Br_2N_2$: C, 47.15; H, 3.69; N, 7.33. Found: C, 47.02; H, 3.65; N, 7.41.

Compound 2a

In a similar manner to the synthesis of **2, 2a** was obtained in quantitative yield as a pale yellow solid form **1a**, mp. >300°C. ^{1}H NMR (D_2O): δ 9.34 (d, J = 6.0 Hz, 2H), 8.66 (s, 2H), 8.31 (d, J = 6.0 Hz, 2H), 4.98 (t, J = 6.6 Hz, 4H), 3.27 (q, J = 6.8 Hz, 2H), 3.13 (s, 6H).

Anal. Calcd for $C_{17}H_{18}Br_2N_2$: C, 49.78; H, 4.42; N, 6.83. Found: C, 49.86; H, 4.31; N, 6.87.

Compound 2b

In a similar manner to the synthesis of **2, 2b** was obtained in quantitative yield as a pale yellow solid form **1b**, mp. >300°C. ^{1}H NMR (D_2O): δ 9.18 (s, 2H), 8.53 (s, 2H), 4.85 (t, J = 6.4 Hz, 4H), 3.17 (q, J = 6.8 Hz, 2H), 2.91 (s, 6H), 2.62 (s, 6H).

Anal. Calcd for $C_{19}H_{22}Br_2N_2$: C, 52.08; H, 5.06; N, 6.39. Found: C, 52.11; H, 5.15; N, 6.29.

Compound 3

A suspension of **2** (7.64 g, 20 mmol) in *tert*-butanol (120 ml) was sonicated at room temperature for 15 minutes and heated at 40°C with stirring; then potassium *tert*-butoxide (8.96 g, 80 mmol) was added over 10 minutes. The mixture was allowed to react for 4 h, and then cooled to room temperature. The resulting precipitated solid was collected and dissolved in water (70 mL), and the solution was extracted with $CHCl_3$ (3 × 60 mL). The combined extracts were dried over $MgSO_4$ and evaporated to give 3.47 g of a brown solid which could use for next step without purification. The *tert*-butanol filtrate from above was evaporated to dryness, and the solid residue was purified by column chromatography on silica gel, eluted with dichloromethane to give 0.49 g of product; the overall yield is 3.96 g (79%), mp. > 300°C; *lit.*[11] mp. >320°C. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, J = 9.4 Hz, 2H), 7.36 (s, 2H), 6.80 (d, J = 9.4 Hz, 2H), 4.32 (t, J = 6.5Hz, 4H), 2.46 (q, J = 6.5Hz, 2H).

2,9-Dichloro-1,10-phenanthroline (4)

Compound **3** (6.60 g, 26.2 mmol) was suspended in $POCl_3$ (80 mL) and PCl_5 (10.88 g, 52.4 mmol) was added in one portion. The mixture was degassed and refluxed (110°C) under nitrogen atmosphere for 8 h. The excess $POCl_3$ was then distilled off under reduced pressure and the residual material was decomposed with cracked ice. The resulting suspension was neutralized to pH 8 with aqueous ammonia solution (30%) with cooling. The brown precipitate obtained and dried under vacuum, then recrystallized from methanol (300 mL) to afford compound **4** (5.54 g, 85%) as a yellow solid. mp. 238–240°C; *lit.*[9] mp. 238–240°C. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, J = 8.3 Hz, 2H), 7.83 (s, 2H), 7.65 (d, J = 8.3 Hz, 2H).

2,9-Dibromo-1,10-phenanthroline

Using $POBr_3$ and PBr_5 as brominating agent, in a process similar to that for the synthesis of **4,** 2,9-dibromo-1,10-phenanthroline was obtained in 81% yield as a yellow solid from **3**, mp. 248–250°C; *lit.*[6] mp. 248–249°C. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 2H), 7.83 (s, 2H), 7.79 (d, J = 8.4 Hz, 2H).

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