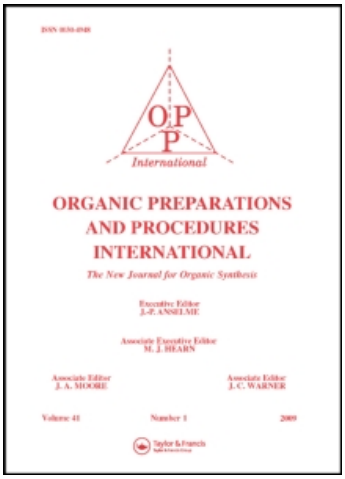

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IMPROVED SYNTHESIS OF 2-CHLORO- AND 2, 9-DICHLORO-1, 10-PHENANTHROLINES

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OPPI BRIEFS

IMPROVED SYNTHESIS OF 2-CHLORO- AND 2,9-DICHLORO-1,10-PHENANTHROLINES

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(06/28/07)

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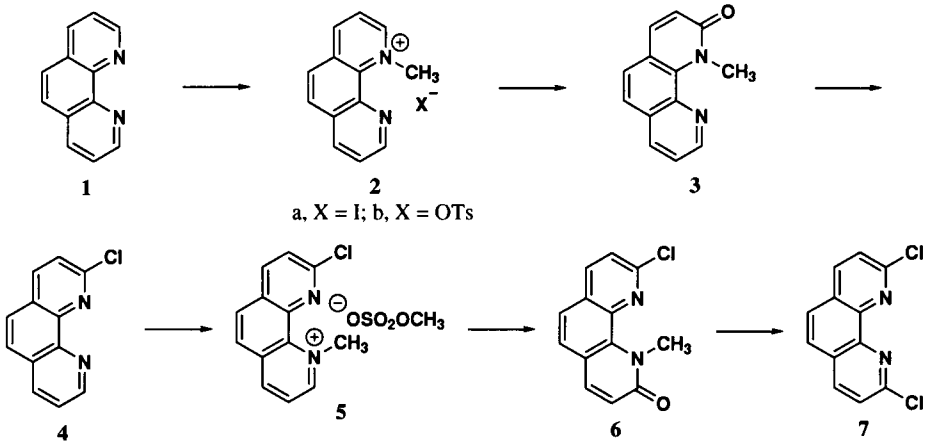
The 1,10-phenanthrolines and substituted analogues are quite important mainly due to their metal chelating properties.[1] Taylor-made 1,10-phenanthrolines (usually as their metal complexes) have been investigated in the areas of molecular recognition, catalysis, cleavages of DNA, sensing agents and as ionophores. The synthesis of a number of substituted 1,10-phenanthrolines such as 2-iodo,[2] 2-alkoxy[3], 2-hydrazino,[4] 2-amino,[5] 2-bromo[6] and the 2,9-dichloro (**7**)[7] analogues commence from **4**. Analogue **7** finds use as a starting material for the preparation of the 2,9-diodo,[2] 2,9-diamino,[5] 2,9-diacetyl,[8] and the 2,9-dialkoxy[5] analogues. These derivatives have been utilized in a wide variety of subsequent transformations. The *Scheme* below outlines improved procedures for the synthesis of 2-chloro- and 2,9-dichloro-1,10-phenanthroline (**4** and **7**), quite adaptable to the preparation of multi gram amounts.



Synthesis of 2-Chloro- and 2,9-Dichloro-1, 10-Phenanthrolines

Scheme 1

The original preparation of 2-chloro-1,10-phenanthroline (**4**) involved treatment of 1,10-phenanthroline (**1**) with methyl iodide to form the corresponding iodide salt (**2a**), which on treatment with aqueous NaOH and $K_3Fe(CN)_6$ afforded **3** which on heating for 6-8 h with $POCl_3$ and PCl_5 yielded **4**.[9] The experimental details for this procedure have been reported.[10] The use of the iodide salt (**2a**) presents solubility problems in the addition-oxidation step due to its low solubility in water. In addition, the formation of molecular iodine from oxidation of iodide anion leads to the desired product **3** as a brown material or in some cases with a distinct purple coloration. The low solubility of the iodide salt does not allow large scale synthesis of intermediate **3.** We found that treatment of 1,10-phenanthroline hydrate (**1**) with methyl *p*-toluenesulfonate in refluxing acetonitrile as solvent, followed by quenching in THF, led to the tosylate salt **2b** in quantitative yield. This salt (**2b**) is extremely water soluble and the addition-oxidation sequence using aqueous NaOH and $K_3Fe(CN)_6$ can be performed on a large scale for the preparation of 1-methyl-1,10-phenanthrolin-2(1*H*)-one (**3**) in high yields and purity. One might note that a prior attempt to convert **2b** into **3** with MnO_2 in THF was unsuccessful.[11]

The conversion of **3** to 2-chloro-1,10-phenanthroline (**4**) has been reported using $POCl_3$ and PCl_5 at reflux for 8 hours.[7] We found that this reaction can be carried out by treatment of **3** with $POCl_3$ at reflux for 3 hours leading to good yields of **4** which is much more easily purified to afford a colorless product. It might be noted that a recent two-step preparation of **4,** in which 1,10-phenanthroline is treated with hydrogen peroxide in acetic acid followed by phosphorous oxychloride in DMF, leads to a lower yield and the scale is smaller.[12] With relatively large quantities of **4** available, we then focused on the conversion of **4** to 2,9-dichloro-1,10-phenanthroline (**7**). The preparation of 9-chloro-1-methyl-1,10-phenanthrolinium methylsulfate (**5**) was easily accomplished by treatment of **4** with dimethyl sulfate at 120-125°C for 2 h.[13] The conversion of **5** to **6** can readily be performed in high yield and purity by treatment with aqueous NaOH-$K_3Fe(CN)_6$. The conversion of **6** to **7** (as in the conversion of **3** to **4**) can be carried out using only $POCl_3$ at reflux for 4-5 h in good yields. The crude product, suitable for most purposes, was obtained in 82% yield. Crystallization from toluene, with addition of silica gel to absorb some colored impurities, led to pure **7** as colorless needles.

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EXPERIMENTAL SECTION

The 1,10-phenanthroline hydrate was purchased from GFS Chemicals, Inc. or Alfa Aesar. Methyl *p*-toluenesulfonate, dimethyl sulfate, phosphorus oxychloride and potassium ferricyanide were purchased from Acros Organics. Melting points were determined using a Mel-Temp II apparatus and are uncorrected. The ^1H and ^{13}C nmr data were recorded on a Varian Inova 500 or a Bruker ARX 500 instrument using TMS as an internal standard.

1-methyl-1,10-phenanthrolinium Tosylate (2b).- To a solution of 1,10-phenanthroline hydrate (**1**, 15.1 g, 0.076 mol) in acetonitrile (45 mL) in a round bottom flask equipped with a spin bar, drying tube and a condenser, was added methyl *p*-toluenesulfonate (28.4 g, 23 mL, 0.15 mol) and the reaction setup was purged with nitrogen gas. The mixture was refluxed for 3 h during which time the white salt precipitated and the liquid developed a distinct pinkish coloration. The cooled suspension was poured into THF (250 mL) and the mixture stored in the freezer overnight. The solid was collected, washed with additional THF and dried to afford 29.0 g (100%) of the tosylate salt. Crystallization of a small amount from ethanol led to beautiful colorless crystals, mp. 171-173°C. ^{1}H NMR (DMSO-d_6): δ 9.57 (d, J = 6.0 Hz, 1H), 9.39 (d, J = 8.0 Hz, 1H), 9.31 (dd, J = 1.5, 4.0 Hz, 1H), 8.80 (dd, J = 2.0, 8.5 Hz, 1H), 8.40 (m, 3H), 8.06 (dd, J = 4.5, 8.5 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 5.28 (s, 3H), 2.70 (s, 3H).
Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N, 7.64.
Found: C, 65.48; H, 4.94; N, 7.65.

1-Methyl-1,10-phenanthrolin-2(1*H*)-one (3).- Solutions of the tosylate salt (**2b**, 25.9 g, 0.07 mol) and of NaOH (50.0 g, 1.25 mol) were each dissolved in water (250 mL) and both placed into addition funnels. Then a solution of potassium ferricyanide (50.0 g, 0.15 mol) in water (250 mL) was placed in a beaker equipped with a spin bar and cooled in an ice bath. The simultaneous dropwise additions of first the NaOH solution then of the tosylate solution were commenced and were complete over a period of 15-20 min. An immediate yellow precipitate formed and the reaction mixture was kept at room temperature for 0.5 h. The flocculent product was collected and washed repeatedly with cold water to afford an off-white solid. This solid was air dried overnight (15.4 g) and was then heated in $CHCl_3$ (100 mL) to afford a yellow solution along with some insoluble material. Sodium sulfate (3 g) was added and the mixture was filtered to afford a yellow filtrate which on evaporation led to the desired product **3** (14.7 g, 96%), mp. 116-118°C, *lit.*[1] mp. 121°C. ^{1}H NMR ($CDCl_3$): δ 8.93 (dd, J = 2.0, 4.0 Hz, 1H), 8.17 (dd, J = 1.5, 8.0 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.56 (m, 2H), 7.50 (dd, J = 4.0, 8.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 4.49 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 164.2, 140.1, 147.1, 139.1, 137.9, 136.1, 130.1, 126.7, 122.4, 122.2, 121.9, 120.4, 37.8.

2-Chloro-1,10-phenanthroline (4).- Phosphorus oxychloride (65 mL, 106.9 g, 0.70 mol) was added to 1-methyl-1,10-phenanthrolin-2(1*H*)-one (**3**, 13.7 g, 0.065 mol) contained in a round-bottom flask equipped with a magnetic spin bar and condenser connected to a silicone oil bubbler. The resultant mixture was heated in an oil bath at reflux for 3 h. The excess phosphorus oxychloride was removed from the dark solution under water aspirator pressure and cold water was added to the residue. Aqueous ammonium hydroxide was then added (about pH 8) and the resultant oil quickly solidified to yield a brown solid. The solid was collected and dried to yield a tan solid (9.7 g). The filtrate was extracted with chloroform (2 x 20 mL) and concentration on the rotary evaporator led to additional product (0.2 g, total 9.9 g, 70%). The crude material was heated in chloroform (50 mL) and some dark insoluble material was removed by filtration. The

solvent was removed by rotary evaporation to afford a light tan solid (9.8 g, 70%). The ^{1}H NMR of this material showed only trace contamination. A small amount of this crude material was heated in acetonitrile to yield a yellowish-brown solution. Silica gel was added to the refluxing solution and the brown impurities were absorbed on the silica gel. Removal of the silica gel and concentration of the solution gave nearly white fluffy crystals of the 2-chloro-1,10-phenanthroline (**4**), mp. 127-128°C; *lit.* mp.[9] 129-130°C. ^{1}H NMR ($CDCl_3$): δ 9.22 (dd, J = 1.5, 4.0 Hz, 1H), 8.26 (dd, J = 2.0, 8.5 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.65 (dd, J = 4.5, 8.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H). ^{1}H NMR (DMSO-d_6): δ 9.12 (dd, J = 1.7, 4.1 Hz, 1H), 8.57 (d, J = 9.4 Hz, 1H), 8.53 (dd, J = 1.7, 8.0 Hz, 1H), 8.05 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 4.3, 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 151.3, 150.7, 146.0, 145.0, 138.7, 136.0, 129.0, 127.2, 126.9, 125.7, 124.2, 123.4.

9-Chloro-1-methyl-1,10-phenanthrolinium Methylsulfate (5).- A mixture of 2-chloro-1,10-phenanthroline (**4**, 10 g, 0.046 mol) and dimethyl sulfate (66.5 g, 50 mL, 0.52 mol) was placed in a small round bottom flask equipped with a condenser and spin bar. The system was purged with N_2 and the brown solution was heated in an oil bath held at 120-125°C for 2.5 h. The mixture was cooled to room temperature, added to THF (250 mL) and the mixture placed in the freezer overnight. The solid was collected, washed with THF and dried to yield a tan solid (13.7 g, 86%). A small portion was recrystallized from ethanol to yield pale yellow crystals; mp. 223-225°C; *lit.*[7] mp. 208°C. ^{1}H NMR (DMSO-d_6): δ 9.60 (d, J = 6.0 Hz, 1H), 9.42 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 8.5 Hz, 1H), 8.47 (m, 3H), 8.17 (d, J = 8.5 Hz, 1H), 5.21 (s, 3H), 3.70 (s, 3H).

9-chloro-1-methyl-1,10-phenanthrolin-2(1*H*)-one (6).- The 9-chloro-1-methyl-1,10-phenanthrolinium methylsulfate (**5**, 13.7 g, 0.04 mol) and NaOH (30.0 g, 0.75 mol) were each dissolved in water (200 mL) and both placed into addition funnels. The potassium ferricyanide (45 g, 0.14 mol) was dissolved in water (200 mL) in a beaker equipped with a spin bar and cooled in an ice bath. The dropwise simultaneous addition of first the NaOH solution then the salt solution was carried out over a period of 1 h. An immediate yellow precipitate formed and filled the beaker which made stirring difficult. The reaction mixture was kept at room temperature for 30 min., then the flocculent product was collected by filtration and washed repeatedly with cold water to afford a tan solid. This solid was air dried overnight to yield a hard crunchy tan solid, which was then heated in $CHCl_3$ (50 mL) to afford a brown solution along with some insoluble material. Sodium sulfate (3 g) was added and the mixture was filtered to afford a brown filtrate. Concentration of the filtrate led to the desired product **6** (9.2 g, 93%). Some of this material was crystallized from benzene to afford a light tan solid (which retained benzene), mp. 146-148°C; *lit.*[7] 153-154°C. A white solid could be obtained by dissolving the crude material in hot acetonitrile and stirring with silica gel. Removal of the silica gel by filtration and evaporation of the solvent led to an off-white product, mp. 150-151°C. Beautiful long colorless needles could be obtained by recrystallization from toluene or acetonitrile. ^{1}H NMR ($CDCl_3$): δ 8.14 (d, 8.5 Hz, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.59 (m, 2H), 7.49 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 9.5 Hz, 1H), 4.44 (s, 3H). ^{1}H

NMR ($CDCl_3$): [crystallized from benzene] δ 8.14 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 9 Hz, 1H), 7.58 (m, 2H), 7.48 (d, J = 8.5 Hz, 1H), 7.36 (s, benzene), 6.93 (d, J = 9.5 Hz, 1H), 4.43 (s, 3H). ^{13}C NMR ($CDCl_3$): [crystallized from benzene] δ 164.1, 147.5, 139.3, 138.1, 139.0, 137.0, 129.0, 128.7 (benzene), 127.5, 123.4, 123.2, 122.1, 121.5, 37.5.

2,9-Dichloro-1,10-phenanthroline (7).- A mixture of 9-chloro-1-methyl-1,10-phenanthrolin-2(1*H*)-one (**6**, 8.8 g, 0.036 mol) and $POCl_3$ (20 mL, 32.9 g, 0.21 mol) was heated at reflux for 5 h. The resultant red-brown solution was cooled and the $POCl_3$ removed under reduced pressure of the water aspirator. Ice water (75 mL) was added to the residual black solid and aqueous ammonium hydroxide to pH 8. The olive colored solid was collected, washed with cold water and dried (8.1 g). This solid was heated in chloroform (250 mL), some insoluble material was removed by filtration and the filtrate was evaporated to afford 7.5 g (82%, >96% purity *via* ^1H nmr analysis) of **7** as a yellow-brown solid. For further purification, 1.0 g of this sample was heated in boiling toluene (150 mL) and a small amount of insoluble (less than 30 mg) was removed by filtration. The hot filtrate was treated with silica gel (which absorbed the color), the silica gel was removed by filtration and the filtrate was concentrated to 75 mL. The beautiful white crystals were collected to afford pure **7** (0.8 g, 80% recovery), mp. 238-240°C; *lit.*[5] mp. 234.5-235.5°C. ^1H NMR ($CDCl_3$): δ 8.22 (d, J = 8.5 Hz, 2H), 7.83 (s, 2H), 7.64 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 152.1, 145.1, 138.9, 127.9, 126.4, 125.1.

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FERRIC CHLORIDE-CATALYZED REDUCTIVE HALOGENATION OF CARBONYL COMPOUNDS TO BROMIDES AND IODIDES

Submitted by (06/15/07)

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The direct replacement of the hydroxy group by halogen is a well-known method for the synthesis of aralkyl halides.[1] Other methods such as bromodecarboxylation of carboxylates of Ag (I), Hg (II), Pb (IV) and Tl (I) with bromine[2] or, less frequently, the photocatalyzed side-chain halogenation of alkylarenes have also been reported.[3] Iodoalkanes are usually obtained by halogen exchange from an alkyl chloride or bromide.[4] However, the direct conversion of carbonyl compounds into organic halides has remained largely unexplored. Corre and co-workers[5] described the reductive bromination of aromatic carbonyl compounds using trimethylamine-borane complex (TMAB) and bromine, however, with a strong electron-withdrawing substituent on the benzene ring, the amount of bromination was low. The direct synthesis of benzyl halides from aromatic aldehydes using alkylboron dibromides[6] or a combination of chlorotrimethylsilane (TMSCl), 1,1,3,3-tetramethyldisiloxane (TMDS) and either LiBr or NaI[7] has been reported, but these methods failed with ketones. In our studies for the direct conversion of carbonyl compounds into the halides, it was found that $FeCl_3$ is a versatile catalyst for the synthesis of organic chlorides.[8] Herein we report the $FeCl_3$ catalyzed one-flask conversion of