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A convenient high yield synthetic route leading to 2,9-diacyl-1,10-phenanthrolines has been developed. The reaction of bis-amide **1** with 2-pyridyllithium, 6-bromo-2-pyridyllithium or 2-thienyllithium led to the diacyl compounds **5**, **6** and **7**, respectively. Attempts to prepare **8** by intramolecular coupling of **6** or by treatment of **1** with dilithio analogue **9b** were unsuccessful. Treatment of **1** with butyllithium or aryllithium reagents led to **10a**, **10b** and **10c**.

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Introduction

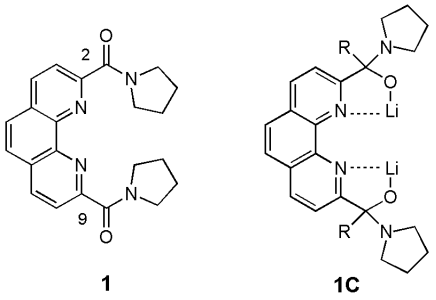
The literature dealing with 1,10-phenanthroline and its derivatives is quite extensive. The synthesis and application of these chemotypes is compiled in several recent reviews [1-4]. These molecules are important because of their chelating properties and historically their utility was in the area of analytical chemistry for the analysis of metal cationic species. Taylor-made 1,10-phenanthrolines, usually as metallic complexes, have been extensively investigated in supramolecular chemistry, molecular recognition studies, catalysts for substitution reactions, oxidative cleavages of DNA, sensing agents in ion-selective electrodes and as ionophores.

The direct addition of alkyllithium or aryllithium reagents to the 2- or 2, 9-positions of 1,10-phenanthroline leads to the 2-substituted- [5,6] or 2,9-disubstituted-1,10-phenanthrolines [7-9] after oxidative workup. Couplings of halo substituted -1,10-phenanthrolines using palladium (0) catalysis [10] or Suzuki methodology [11] have led to various 2,9-diaryl-1,10-phenanthrolines.

On the other hand, no direct methodology for the formation of 2,9-diacyl-1,10-phenanthrolines has been reported. The goal of this research was the development of a convenient synthetic pathway to 2,9-diacyl-1,10-phenanthrolines with additional N-coordination sites in the distal side chains. These diones could be reduced or further functionalized at the carbonyl group to lead to other 1,10-phenanthroline derivatives.

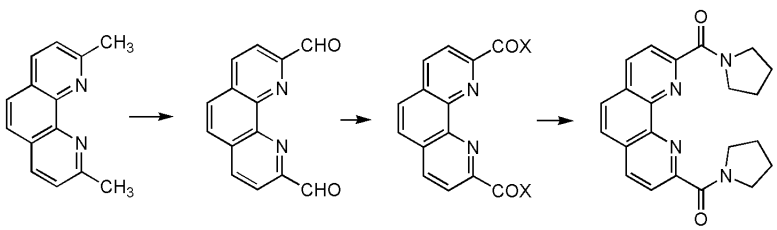
Results and Discussion.

The bis-amide **1** was selected as the precursor for the desired 2,9-diacyl-1,10-phenanthrolines. The sequential addition of an organolithium reagent (RLi) at low temperature to **1** would be expected to lead to a stable complex **1C** (-OLi coordination with the ring nitrogen's) which on aqueous workup would afford the 2,9-diacyl analogues. One notes the similarity to the stabilization exhibited by the *N*-methoxy-*N*-methyl group in the RLi additions to Weinreb amides (-OLi coordination with the O of the OCH_3 group) in the Weinreb ketone synthesis [12].



1 **1C**

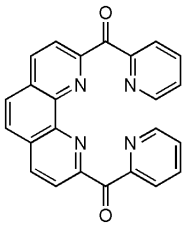
The synthesis of **1** was readily accomplished commencing from commercially available 2,9-dimethyl-1,10-phenanthroline **2**. The oxidation of **2** by selenium dioxide afforded 1,10-phenanthroline-2,9-dicarbaldehyde **3** [13,14]. Subsequent oxidation of this dialdehyde with nitric acid led to 1,10-phenanthroline-2,9-dicarboxylic acid **4a** [13], which was converted, into 1,10-phenanthroline-2,9-dicarbonyl chloride **4b** on treatment with thionyl chloride [15]. Treatment of **4b** with pyrrolidine readily afforded the bis-amide **1** in excellent yield.



2 **3** **4**a, X = OH
b, X = Cl **1**

Of particular note is the ^{13}C nmr spectrum of **1**, which exhibits four discrete absorptions for the CH_2 groups of the pyrrolidine moiety attributable to the syn and anti relationship of these carbons (restricted rotation) relative to the carbonyl group of the amide.

Treatment of the bis-amide **1** with 2-lithiopyridine, prepared from 2-bromopyridine by transmetallation using butyllithium [16-18] and conducted at –78 °C in dry THF, led to an excellent yield of the desired product **5** (86%). In a similar manner, 2-bromo-6-lithiopyridine (prepared in ether from 2,6-dibromopyridine on treatment at –78 °C with butylithium [16,19-20]) on treatment with bis-amide **1** afforded **6** in a quantitative yield. Treatment of **1** with 2-thienyllithium readily afforded **7** in excellent yield.



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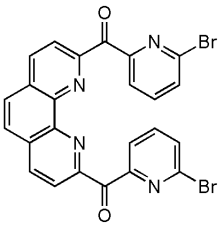

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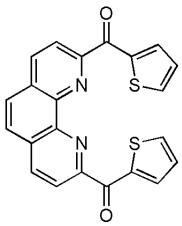

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Symmetrically functionalized bis-heterocylics have been prepared in good yields utilizing the homocoupling of halopyridines to form 2,2'-bipyridines using palladium diacetate as a catalyst in the presence of a phase transfer catalyst and a base in aqueous DMF [21]. In our hands, the coupling of 2-bromopyridine under these conditions afforded 2,2'-bipyridine. However, an attempt to utilize this methodology for the intramolecular coupling of **6** to **8** under these conditions was unsuccessful and only starting material could be isolated.

One other attempt to prepare **8** was also unsuccessful. Treatment of **9a** with butyllithium at –78 °C has been reported to afford **9b** [16,22,23], whose treatment with dimethylformamide afforded **9c**. On the other hand, treatment of the bis-lithio derivative **9b** with bis-amide **1** led to a crude product with a complex ^1H nmr spectrum which did not indicate the presence of **8**.

Alkyl and aryl ketones can also be readily prepared by reaction of bis-amide **1** with the appropriate alkyl-or aryl-organolithium reagent. Treatment of bis-amide **1** with butyllithium, phenyllithium or 4-lithioanisole (prepared by treatment of 4-bromoanisole with butyllithium) led to excellent yields of **10a**, **10b** and **10c**, respectively.

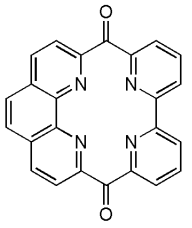
In summary, we have demonstrated that 2,9-diacyl-1,10-phenanthrolines can be readily synthesized by treatment of bis-amide **1** with alkyl-, aryl- or heteroaryl organolithium reagents in excellent yields. This procedure should be adaptable to the preparation of numerous ketones of this substitution type.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were obtained on a Bruker ARX-500 pulsed spectrometer. The ^1H nmr shifts are reported in δ (ppm) relative to TMS as an internal standard. The ^{13}C nmr chemical shifts are reported in δ values relative to the solvent ($CDCl_3$ 77.0 ppm and DMSO-d_6 39.5 ppm). The organolithium reagents 2-thienyllithium (1 *M* in THF), phenyllithium (1.9 *M* in cyclohexane-ether) and butyllithium (1.6 *M* in hexanes) were purchased from Aldrich. The 2-bromopyridine, 2,6-dibrompyridine, 6,6'-dibromo-2,2-dipyridyl and 4-bromoanisole were also supplied by Aldrich. The 2,9-dimethyl-1,10-phenanthroline is available commercially from a number of suppliers such as Aldrich, GFS and Acros. The THF was freshly distilled from Na metal prior to use.

2,9-Bis(pyrolidin-1-yl)carbonyl-1,10-Phenanthroline (**1**).

Pyrrolidine (18.65 g, 262 mmols) was slowly added to a suspension of 1,10-phenanthroline-2,9-dicarbonyl chloride (8.0 g, 26.2 mmol) in dry CH_2Cl_2 (250 mL) at room temperature under an atmosphere of dry N_2. All of the dicarbonyl chloride dissolved and a yellow solution formed. This solution was stirred at room temperature for 24 hours, poured into a saturated aqueous $NaHCO_3$ solution (200 mL) and extracted twice with $CHCl_3$. The combined organic extracts were washed with water, dried over sodium sulfate, filtered to remove the drying agent and the solvent evaporated to yield **1** as an amorphous nearly white solid (8.32 g, 85%). Beautiful needles could be obtained on recrystallization from toluene, mp 224–225 °C; ^1H nmr ($CDCl_3$): δ 8.35 (d, *J* = 8.3 Hz, 2H), 8.24 (d, *J* = 8.3 Hz, 2H), 7.86 (s, 2H), 4.18 (t, *J* = 6.4 Hz, 4H), 3.79 (t, *J* = 6.5 Hz, 4H), 2.0 (m, 8H); ^{13}C nmr



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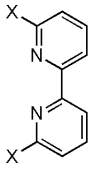
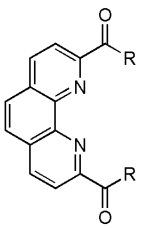


9a, X = Br
b, X = Li
c, X = CHO



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a, R = $(CH_2)_3CH_3$
b, R = C_6H_5
c, R = 4-$OCH_3C_6H_4$

($CDCl_3$): δ 166.0, 154.1, 144.3, 136.9, 129.3, 127.3, 123.4, 49.1, 47.1, 26.7, 24.0.

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57. H, 5.92; N, 14.96. Found: C, 70.47; H, 5.72; N, 15.08.

2,9-Bis(2-pyridylcarbonyl)-1,10-phenanthroline (**5**).

A solution of 2-bromopyridine (0.462 g, 2.92 mmols) in dry THF (25 mL) was cooled to –78 °C, under an atmosphere of dry N_2. A solution of butyllithium (1.6 *M* in hexanes) (2.0 mL, 3.21 mmol) was dropped slowly over a period of 15 minutes. The resulting dark yellow solution was stirred at –78 °C for 30 minutes. A solution of the bis-amide **1** (0.50 g, 1.33 mmol) in THF (22 mL) was slowly added to this pyridyllithium solution. The resulting deep purple solution was stirred at –78 °C for 2 h, warmed to ambient temperature and was quenched with a saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with EtOAc (2 × 40 mL), the combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield an orange-brown solid (0.52 g, 99%). This solid was washed with ether and methanol to afford a reddish-brown solid (0.45 g, 86%) which on heating in acetonitrile and collection of the insoluble material yielded a light tan product, mp 273–275 °C (dec); ^{1}H nmr (DMSO-d_6): δ 8.74 (d, *J* = 8.2 Hz, 2H), 8.65 (d, *J* = 4.9 Hz, 2H), 8.68 (d, *J* = 8.2 Hz, 2H), 8.22 (m, 4H), 7.88 (dt, *J* = 1.6, 7.8 Hz, 2H), 7.63 (m, 2H); ^{13}C nmr ($CDCl_3$): δ 191.7, 154.2, 153.7, 149.4, 145.2, 137.1, 136.3 130.3, 128.3, 127.1, 126.2, 123.5.

Anal. Calcd. for $C_{24}H_{14}N_4O_2$: C, 73.84, H, 3.61, N, 14.35. Found: 73.62, H, 3.42, N, 14.25.

2,9-Bis(6-bromopyridin-2-ylcarbonyl)-1,10-phenanthroline (**6**).

A solution of 2,6-dibromopyridine (0.7 g, 2.95 mmols) in dry Et_2O (50 mL) was cooled to –78 °C under an atmosphere of dry N_2. A solution of *n*-BuLi (1.6 *M* in hexanes) (1.90 mL, 3.0 mmol) was dropped slowly over the period of 15 min. The resulting light yellow solution was stirred at –78 °C for 75 min. A solution of the bis-amide **1** (0.52 g, 1.39 mmol) in dry THF (25 mL) was slowly added to this 2-bromo-6-lithiopyridine solution. The resulting deep purple solution was stirred at –78 °C for 2 h, warmed to ambient temperature and was quenched with saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with EtOAc (2 × 40 mL), combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield a yellow solid (0.75 g, 98%). This solid was washed with EtOAc to give a light fawn colored powder (0.64 g, 84%), mp 238–240 °C; ^{1}H nmr ($CDCl_3$): δ 8.53 (d, *J* = 8.1 Hz, 2H), 8.46 (m, 4H), 7.99 (s, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H); ^{1}H nmr (DMSO-d_6): δ 8.79 (d, *J* = 8.3 Hz, 2H), 8.40 (d, *J* = 8.3 Hz, 2H), 8.25 (m, 4H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 2H); ^{13}C nmr (DMSO-d_6): δ 190.6, 154.3, 153.0, 144.2, 140.8, 139.5, 137.8, 131.0, 130.3, 128.7, 125.5, 123.0,

Anal. Calcd for $C_{24}H_{12}Br_2N_4O_2$: C, 52.58; H, 2.21, N, 10.22. Found: C, 52.34, H, 2.24, N, 10.17.

2,9-Bis(2-thienylcarbonyl)-1,10-phenanthroline (**7**).

A solution of the bis-amide **1**(1.0 g, 2.67 mmols) in dry THF (75 mL) was cooled to –78 °C under an atmosphere of dry N_2. A solution of 2-thienyllithium (1 *M* in THF) (5.9 mL, 5.68 mmol) was slowly added over the period of 20 minutes. The resulting deep purple solution was stirred at –78 °C for 3 hours, warmed to ambient temperature and was quenched with a saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with EtOAc (2 × 50 mL), the combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield a dark reddish-brown solid (1.06 g, 99%). Filtration through a small plug of silica with $CHCl_3$ elution afforded yellow crystals (0.86 g, 80%), mp 240–241 °C (recrystallized from $CHCl_3$); ^{1}H nmr (DMSO-d_6): δ 8.86 (dd, *J* = 1.0, 3.8 Hz, 2H), 8.80 (d, *J* = 8.3 Hz, 2H), 8.43 (d, *J* = 8.3 Hz, 2H), 8.26 (s, 2H), 8.07 (dd, *J* = 1.0, 4.0 Hz, 2H), 7.08 (m, 2H); ^{13}C nmr ($CDCl_3$): δ 184.1, 154.2, 145.4, 141.7, 138.5, 137.2, 135.7, 130.6, 128.4, 128.3, 123.0.

Anal. Calcd for $C_{22}H_{12}N_2O_2S_2$: C, 65.98, H, 3.02, N, 7.00. Found: C, 65.87, H, 2.83, N, 6.96.

2,9-Dipentanoyl-1,10-phenanthroline (**10a**).

A solution of the bis-amide **1** (1.0 g, 2.67 mmols) in dry THF (75 mL) was cooled to –78 °C under an atmosphere of dry N_2. A solution of butyllithium (1.6 *M* in hexane) (3.55 mL, 5.68 mmols) was slowly added over the period of 20 minutes. The resulting deep purple solution was stirred at –78 °C for 3 hours, warmed to ambient temperature and was quenched with saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with EtOAc (2 × 50 mL), the combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield orange crystals (0.93 g, 100%). Filtration through a small plug of silica with elution by CH_2Cl_2, yielded light yellow crystals (0.80 g, 86%). Recrystallization from a small amount of EtOAc provided white crystals, mp 125–126 °C; ^{1}H nmr (DMSO-d_6): δ 8.65 (d, *J* = 8.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 8.15 (s, 2H), 3.50 (t, *J* = 7.5 Hz, 4H), 1.78 (m, 4H), 1.46 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 6H); ^{13}C nmr ($CDCl_3$): δ 202.5, 153.0, 145.2, 137.0, 130.7, 128.2, 120.5, 37.4, 26.4, 22.6, 13.9.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83, H, 6.94, H, 8.04. Found: C, 75.69, H, 6.79, N, 8.01.

2,9-Dibenzoyl-1,10-phenanthroline (**10b**).

A solution of the bis-amide **1** (0.68 g, 1.82 mmols) in dry THF (50 mL) was cooled to –78 °C under an atmosphere of dry N_2. A solution of phenyllithium (1.8 *M* in cyclohexane-ether) (2.22 mL, 4.0 mmol) was slowly added over a period of 20 minutes. The resulting purple solution was stirred at –78 °C for 2 hours, warmed to ambient temperature and was quenched with a saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with ethyl acetate (2 × 50 mL), the combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield a yellow-orange solid (0.70 g, 99%). Recrystalization from EtOAc afforded light yellow crystals (0.61 g, 86%), mp 196–197 °C; R_f = 0.40 ($CHCl_3$–MeOH, 98:2); ^{1}H nmr (DMSO-d_6): δ 8.80 (d, *J* = 8.3 Hz, 2H), 8.40 (m, 6H), 8.27 (s, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 4H); ^{13}C nmr (DMSO-d_6): δ 192.1, 154.2, 144.0, 137.9, 135.8, 133.0, 131.2, 130.0, 128.4, 128.1, 123.0.

Anal. Calcd for $C_{26}H_{16}N_2O_2$: C, 80.40; H, 4.15; N, 7.21. Found: C, 80.02; H, 3.80; N, 7.19.

2,9-Di-(4-methoxybenzoyl)-1,10-phenanthroline (**10c**).

A solution of butyllithium (1.6 *M* in hexane) (4.35 mL, 6.96 mmols) in dry Et_2O (50 mL) and under dry N_2 atmosphere was cooled to –78 °C. A solution of 4-bromoanisole (1.25 g, 6.7

mmol) in dry Et_2O (10 mL) was slowly added over a period of 15 minutes. The resulting solution was warmed to room temperature and was stirred for 2 hours. This 4-lithioanisole solution was slowly added to a pre-cooled (–78 °C) and stirred solution of the bis-amide **1** (1.0 g, 2.67 mmols) in dry THF (70 mL). The resulting deep purple solution was stirred at –78 °C for 3 hours, warmed to ambient temperature and was quenched with a saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with ethyl acetate (2 × 50 mL), the combined organic extracts were dried over sodium sulfate, the drying agent removed by filtration and the filtrate evaporated to yield orange crystals (1.20 g, 100%). Filtration through a small plug of silica, elution with $CHCl_3$, yielded a light yellow solid (1.0 g, 83%). Recrystallization from EtOAc provided very light pink crystals, m.p. 192–193 °C; ^{1}H NMR ($CDCl_3$); δ 8.67 (d, J = 8.7 Hz, 4H), 8.42 (m, 4H), 7.91 (s, 2H), 6.73 (d, J = 8.5 Hz, 4H), 3.78 (s, 6H); ^{13}C nmr ($CDCl_3$): δ 190.4, 163.4, 155.3, 144.9, 137.1, 134.5, 129.9, 129.4, 128.1, 123.2, 113.5, 55.2.

Anal. Calcd for $C_{28}H_{20}N_2O_4$: C, 74.99, H, 4.50, N, 6.25. Found: C, 74.87, H, 4.30, N, 6.26.

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