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Efficient Synthesis of 4,7-Diamino Substituted 1,10-Phenanthroline-2,9-dicarboxamides

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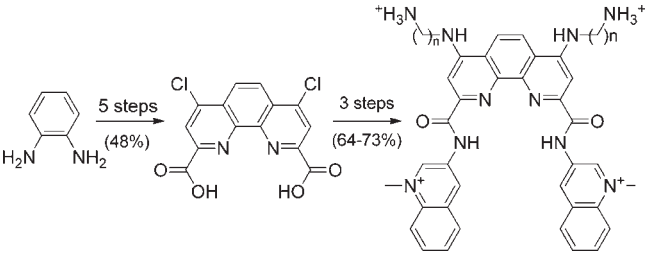
ABSTRACT



A convenient and high-yielding multigram synthesis of the versatile intermediate 4,7-dichloro-1,10-phenanthroline-2,9-dicarboxylic acid is described. The intermediate is further efficiently derivatized to 4,7-diamino-1,10-phenanthroline-2,9-dicarboxamides with potential G-quadruplex stabilizing effects.

Phenanthrolines are powerful bidentate metal chelators with numerous applications for example in supramolecular chemistry,[1] as ligands in transition metal catalyzed reactions,[2] in luminescent sensors,[3] and in photosensitizers for solar cells.[3−5] Particularly 1,10-phenanthroline-2,9-dicarboxylic acid and its derivatives have recently found uses in these and other areas.[6−13] Phenanthroline also serves as the scaffold for several potent stabilizers of DNA G-quadruplexes,[14−17] which can be formed in the telomeric chromosome terminals and in many gene promoter regions and are currently receiving much attention as potential targets for anticancer drug development.[18−21] A notable example are the highly potent bisquinolinium dicarboxamide Phen-DC3 (Figure 1).[14]

Based on the hypothesis that the improved metal chelating properties of 4,7-diamino substituted phenanthrolines would improve G-quadruplex interaction, we designed

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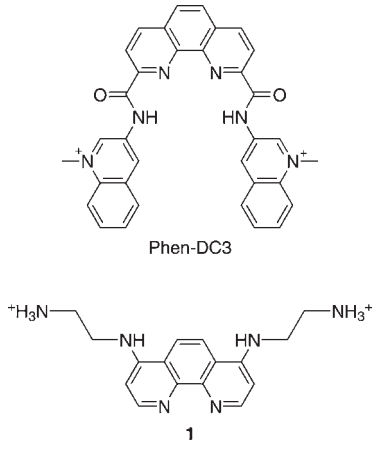


Figure 1. Previously reported G-quadruplex ligands.[14,17]

and evaluated **1** and similar compounds, which indeed possessed appreciable G-quadruplex stabilizing properties (Figure 1).[17] We wished to explore the G-quadruplex stabilizing properties of hybrids of these two structures, i.e. phenanthroline-2,9-dicarboxamide (Phen-DC) structures carrying 4,7-diamino substituents (**2**, Figure 2), with the aim to further increase the G-quadruplex interaction and obtain selectivity for specific G-quadruplex structures.

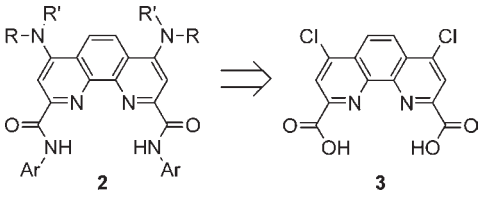
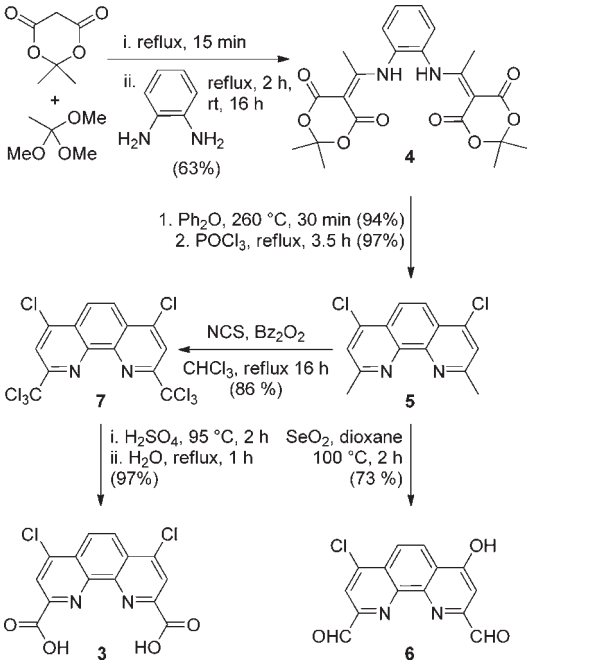


Figure 2. Target hybrid structures (**2**) and the central intermediate **3**.

Considering the importance of the phenanthroline scaffold, there are surprisingly few reports of 4,7-diamino-1, 10-phenanthrolines,[17,22−34] and 4,7-diamino substituted phenanthroline-2,9-dicarboxylates or -dicarboxamides have not previously been described. We therefore set out to develop a route to access these compound classes. As all 4,7-diaminophenanthrolines reported hitherto have been synthesized via the corresponding 4,7-dichlorophenanthroline,[17,22−34] we assumed that these compound classes would be accessible via **3** by amide coupling and nucleophilic aromatic substitution (Figure 2).

Intermediate **3** was synthesized via **5** as outlined in Scheme 1. The synthesis of **5** has been described previously, but only in relatively poor yields and involving steps that require two or more weeks to complete.[25,35] We found that **5** could be efficiently prepared by condensation of Meldrum's acid, trimethyl orthoacetate, and *ortho*-phenylenediamine to **4** followed by thermal cyclization−decarboxylation and treatment with refluxing phosphoryl chloride.[25,36,37]

Scheme 1. Synthesis of the central intermediate **3**



Conversion of 2,9-dimethyl-1,10-phenanthroline to its corresponding dicarboxylic acid has previously been achieved by oxidation with SeO_2 to the dialdehyde, followed by oxidation with nitric acid.[38] Oxidation of **5** with SeO_2 in 1,4-dioxane did not afford the desired dialdehyde as the major product, but rather the unsymmetrical partially hydrolyzed bis-aldehyde **6** in good yields. Further hydrolysis of the second chloro-substituent is probably

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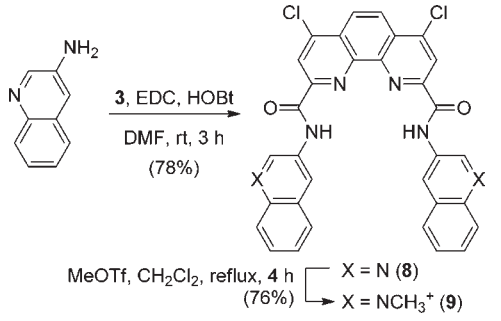
arrested by increased electron density. Although **6** was not the desired product from the reaction, it provides a useful entry into unsymmetrical 4,7-disubstitued phenanthroline-2,9-dicarboxylate derivatives.

2,9-Dimethyl-1,10-phenanthroline has also been oxidized by NCS promoted radical chlorination in refluxing CCl_4 to the corresponding bis-trichloromethyl compound, followed by hydrolysis and esterification by H_2SO_4 and MeOH.[38,39] We were reluctant to adopt this method due to the established health hazards and ozone depleting properties of CCl_4. Gratifyingly, chlorination of **5** could be performed in $CHCl_3$ to produce compound **7** in high yields. The reaction proceeded efficiently in commercial $CHCl_3$ stabilized by the free radical scavenger 1-amylene. Hydrolysis of the trichloromethyl groups was achieved by treatment with concentrated sulfuric acid followed by reflux in water to give **3** in quantitative yield.

Coupling of 3-aminoquinoline to **3** using EDC and HOBt proceeded smoothly to afford **8** (Scheme 2). The quinolines were methylated using methyl triflate in analogy to a previously reported method to provide the triflate salt **9**.[14]

Scheme 2. Amide Coupling and *N*-Methylation



With the bis-carboxamide **8** in hand, we directed attention toward introduction of the 4,7-diamine substituents. It is previously observed that DMF can act as a source of dimethylamine by either thermal or base promoted decomposition.[28,40] Using aqueous ammonia in DMF with microwave heating, dimethylamine generated *in situ* was introduced in the 4,7-positions to provide **10** in high yield (Scheme 3).

Diamines were coupled to **8** by nucleophilic aromatic substitution under relatively mild conditions using excess diamine as solvent to afford **12a**–**b**, isolated in excellent yields as their HCl-salts (Scheme 3).

We expected the final *N*-methylation of **12a**–**b** to represent a challenge, as the 4-amino substituents greatly increase the nucleophilicity of the phenanthroline nitrogen atoms and the terminal primary amines would efficiently compete with the quinolines as methylation sites. Indeed, treatment of **12a** with methyl triflate with the same conditions

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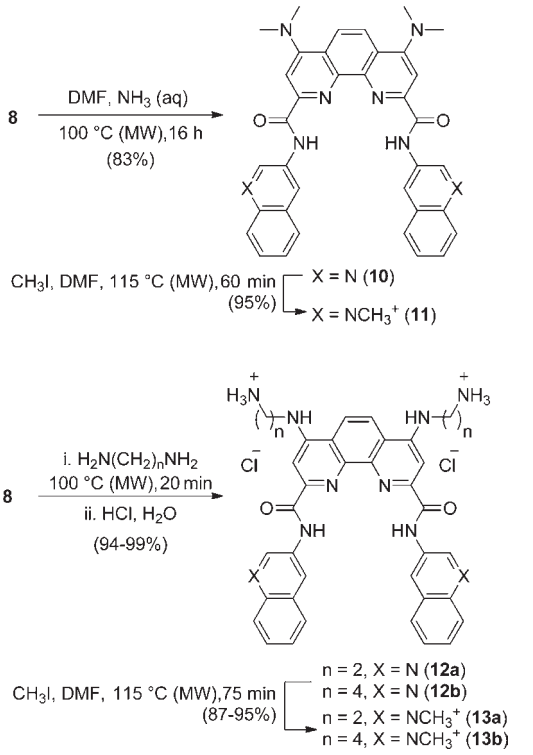
Scheme 3. Introduction of 4,7-Diamines and *N*-Methylation



as those used for **8** resulted in overmethylation and complex reaction mixtures. Anticipating that the hydrochloride salt would be sufficient to protect the terminal amines and that intramolecular hydrogen bonding with the amides would protect the phenanthroline nitrogen atoms, we proceeded to investigate milder methylation methods. We found that the quinolines of compounds **10** and **12a**–**b** were *N*-methylated with high selectivity by MeI in DMF with microwave heating to 115 °C for 60–75 min to provide the dimethylated products **11** and **13a**–**b** in excellent yields (Scheme 3).

In summary, we have developed a concise protocol for the multigram synthesis of **3**, a compound that we expect to be useful as a general intermediate to modified phenanthroline-2,9-dicarboxylates and carboxamides, compound classes that recently have found numerous interesting applications.[6–13] We furthermore describe the conversion of **3** to 4,7-diamino substituted phenanthroline-2,9-dicarboxamides (**11**, **13a**–**b**), which are expected to act as potent G-quadruplex ligands. The G-quadruplex interacting properties of the ligands described here and other analogues are currently being investigated in our laboratory.

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Supporting Information Available. Experimental procedures, temperature–time profiles for microwave experiments, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.