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A Streamlined Synthesis for 2,3-Dihydroxyterephthalamides

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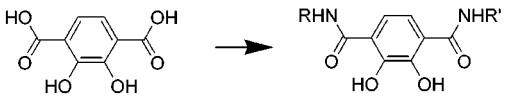
ABSTRACT



2,3-Dihydroxyterephthalamides have been synthesized through a route that avoids the protection and deprotection of the phenol groups. The procedure allows for symmetric and unsymmetric amide linkages. This synthetic sequence significantly decreases the time and cost of preparation and increases the overall yield of this class of metal chelators.

Catecholate ligands incorporating a variety of electron-withdrawing substituents have been extensively investigated for their extraordinarily high affinity for high oxidation state metals.[1−5] Catecholamides (CAM) are commonly found in nature in siderophores, a class of bacterially secreted ligands that function to sequester and acquire Fe(III) from the environment.[6] The siderophore enterobactin has an Fe(III) stability constant of 10^{49}, the highest known for any aqueous ferric complex, due to the three catecholamides suspended from its trilactone backbone.[7]

While the catecholate anion itself is highly sensitive to oxidation, amide substitution reduces this sensitivity. Catechol derivatives containing two carbonyl substituents, e.g., the carboxamido-2,3-dihydroxyterephthalates (CAMC) and the 2,3-dihydroxyterephthalamides (TAM), display higher Fe(III) affinity, are harder to oxidize, and are more acidic than the CAM.[8,9] The increased acidity of CAMC and TAM relative to other catecholates broadens their utility because they can fully complex Fe(III) in lower pH solutions. These properties prompted successful investigations of catecholamide ligands as in vivo decorporation agents for Pu(IV) and the in vitro stability of complexes with Ce(IV), a Pu(IV) analogue.[10−12] In addition, the two amide-linked substituents can be modified to tailor the solubility of the ligand and allow several ligands to be linked together to maximize the chelate effect. Herein we report a shorter synthetic route to the TAMs that decreases the time, cost, and hazards associated with the synthesis.

The typical TAM synthesis[8,9,13] involves six steps (Scheme 1) in an overall 30% yield: carboxylation of catechol to form **2**, conversion of the carboxylic acids to methyl esters **3**,

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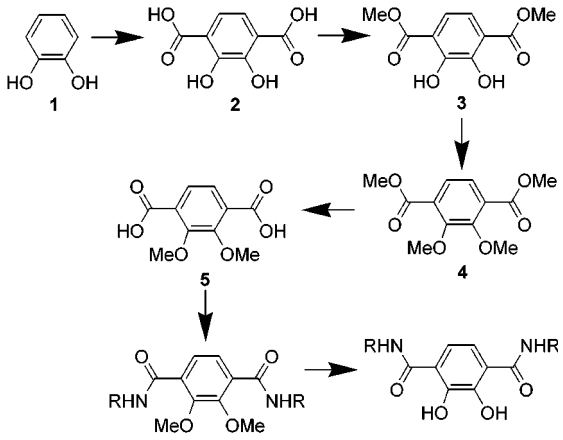
Scheme 1

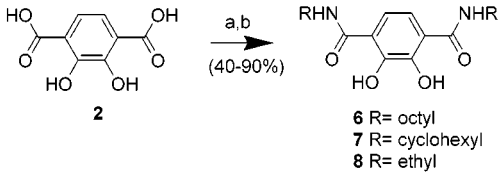


methyl or benzyl protection of the catecholate oxygens **4**, saponification of the esters to provide **5**, activation to the acid chloride, coupling with the desired amine, and deprotection of the catecholate oxygens to yield the desired TAM. The CAMC synthesis differs in that it requires the saponification of only one ester of **4** followed by amide bond formation and hydroxyl deprotection.

The more efficient synthesis reported here for TAMs does not require protection of the phenolic oxygens; the direct activation of 2,3-dihydroxyterephthalic acid **2** with $SOCl_2$ is followed by reaction with an amine. By avoiding the protecting group the number of synthetic steps are reduced from seven to three. This eliminates two steps involving the hazardous reagents dimethyl sulfate and BBr_3, decreases the synthetic time from approximately 9 to 2 days, increases the overall yield to 75%, and decreases the cost for alkyl TAMs 10-fold. This synthetic sequence also broadens the diversity of available TAMs since deprotection of methyl ether protecting groups with BBr_3 is incompatible with certain functional groups that might be desired in the amide side chains. Finally, this procedure has been adapted to allow for the preparation of CAMC ligands and the installation of two *different* amides, generating a much wider range of compounds.

For the current synthesis, compound **2** was activated with an excess of $SOCl_2$ in refluxing dioxane for 6 h (Scheme 2). Although a variety of organic solvents were used successfully, the use of dioxane ensures the removal of excess $SOCl_2$ during evaporation. Coupling the crude acid chloride **6** with octylamine, cyclohexylamine, or ethylamine followed by extraction with 1 M HCl and recrystallization yields the pure product in 40−90% yield, depending on the hydrophobicity of the product.

Scheme 2[a]



[a] (a) $SOCl_2$, dioxane, reflux; (b) NH_2R, TEA.

Activation of the dicarboxylic acid **2** with $SOCl_2$ was proposed on the basis of previous work on the $SOCl_2$ activation of 2,3-dihydroxybenzoic acid, for which there was originally some confusion about the product composition.[14−16] The product was first reported as 2,3-dihydroxybenzoyl chloride **9** on the basis of the previously reported formation of 2,4-dihydroxybenzoyl chloride **11**,[17] although characterization was limited to a melting point of 84 °C for the sublimed crystals (Figure 1). However it was later shown

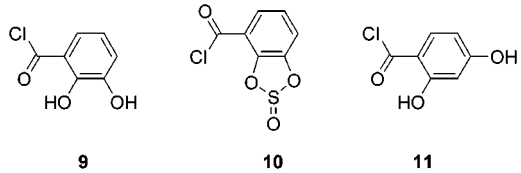


Figure 1. Phenolic acid chlorides **9**−**11** that have been described in the literature. What was originally reported as **9**, on the basis of analogy to **11**, was later shown to be **10**.

that the phenol groups react to form a sulfite ester, a convenient and effective in situ protecting group.[16] The resulting sublimed crystals of 2,3-dioxosulfinylbenzoyl chloride **10** were characterized by melting point and elemental analysis. This acid chloride has been useful for several syntheses requiring the installation of a catecholamide.[18−22] The formation of the catecholate sulfinic anhydride is also precedented; the synthesis of 1,2-dioxosulfinyl benzene from the reaction of catechol with $SOCl_2$ has been reported.[23,24]

The key intermediate for making the symmetric TAMs is the product of the reaction between **2** and $SOCl_2$. By analogy to **10** and **11**, both 2,3-dihydroxyterephthaloyl chloride **12** and 2,3-dioxosufinylterephthaloyl chloride **13** could be considered as products (Figure 2). One product isolated from refluxing dioxane exhibits a singlet in the ^1H NMR spectrum at ca. 8 ppm. We assign this as the labile intermediate **13**. The decomposition of **13** via loss of SO_2 to form the less reactive phenol acid chloride **12** can be monitored by ^1H

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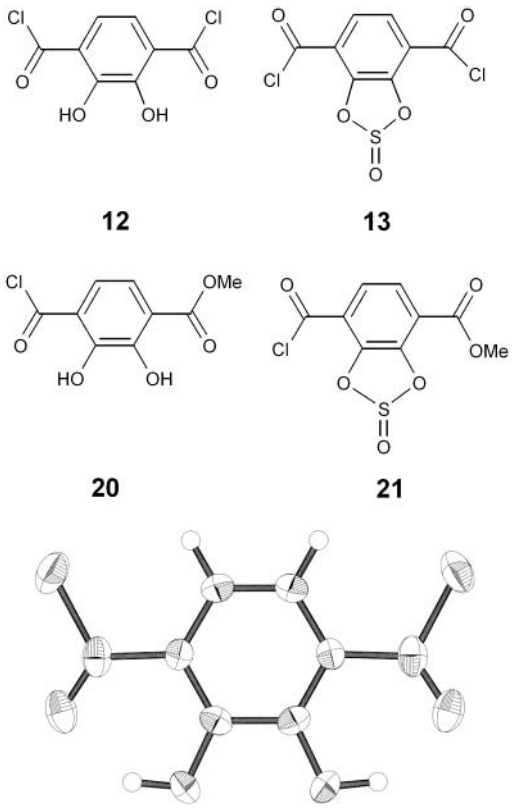
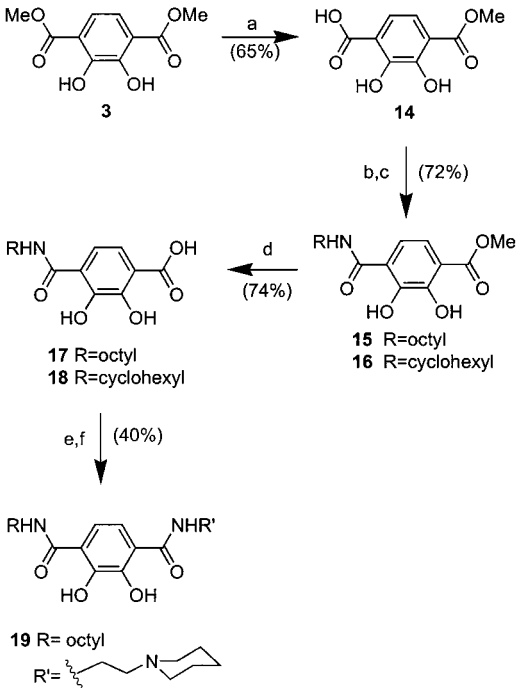


Figure 2. Reaction of **2** with $SOCl_2$ affords the labile intermediate **13** and the resultant **12**, which has been structurally characterized by X-ray crystallography (ORTEP). Thermal ellipsoids are drawn at the 50% probability level. Reaction of **14** with $SOCl_2$ also affords both **20** and **21**.

NMR spectroscopy, as the singlet at 8 ppm disappears and another appears at ca. 7.5 ppm. The starting compound **2** exhibits a singlet in the ^{1}H NMR spectrum at ca. 7.2 ppm. Sublimation of the resultant yellow solid yielded crystals suitable for X-ray diffraction.[25] This confirmed that the activated intermediate with a ^{1}H NMR signal at 7.5 is **12** and not an ester polymer formed from the reaction of the phenol oxygens with the acid chloride. As is seen with all TAMs in the solid state, the carbonyl is oriented such that the oxygen is hydrogen-bonded to the phenolic proton.[26] The stability of this chelate hydrogen bond possibly in part hinders the formation of a polymeric ester. An amine can be coupled with a mixture of **12** and **13** without a loss in yield, and the transitory protecting group is easily cleaved during the aqueous workup following the amine coupling.

This procedure was modified so a TAM with two different amide linkages can be prepared (Scheme 3). This methodology is demonstrated with the synthesis of ligand **19** and is general for most amides. Monosaponification of the dimethyl

Scheme 3. Two Different Amide Linkages Can Be Prepared with a Modification of This Procedure[a]



[a] (a) 1 equiv of $NaHCO_3$ aqueous, 70 °C; (b) $SOCl_2$, dioxane, reflux; (c) NH_2R, TEA, 0 °C; (d) 1 M KOH; (e) $SOCl_2$, dioxane, reflux; (f) 1-(2-aminoethyl)piperidine, 0 °C.

ester **3** with aqueous $NaHCO_3$ affords **14** in 70% yield. The acid chloride was prepared by treatment of **14** with $SOCl_2$ in refluxing dioxane. The crude acid chloride was then coupled to octylamine in the presence of TEA to yield **15**, which was converted to the acid **17** using degassed 1 M KOH. Halting the synthesis at this point provides the CAMC ligands. Finally, **17** was activated with $SOCl_2$ and treated with 1 equiv of 1-(2-ethylamino)piperidine to afford **19** in 40% yield. In general, it was found that installing the more hydrophobic of the two amides first eased the separation of the product from the excess amine. For monitoring the progress of any reaction, thin-layer chromatography was used with one of three solvent systems, 5:4:1 benzene/ethyl formate/formic acid, 5:4:1:1 ethyl acetate/acetone/methanol/water, or 4:3:1:1 ethyl acetate/acetic acid/methanol/water.

During the course of activating mono ester **14** with $SOCl_2$, one product is initially observed in the ^{1}H NMR spectrum that is tentatively assigned as **21**. As with **13**, the decomposition of this to the acid chloride **20** is observed (Figure 2). Sublimation of the resultant yellow solid affords a pure yellow powder, confirmed by elemental analysis as the acid chloride **20**.

In summary, a synthesis for 2,3-dihydroxyterephthalamides has been developed that obviates the need for protection of the catecholates. The synthesis has been adapted to permit the introduction of two different amide linkages and can be used for the synthesis of the CAMC ligands. These routes avoid the costly BBr_3 deprotection and shorten the synthesis

(25) $C_8H_4O_4Cl_2$: yellow tablet shaped crystal, size 0.50 × 0.14 × 0.05 mm^3, FW = 235.02, T = −109 °C, orthorhombic space group, *Pccn*, a = 13.781(3) Å, b = 4.835(1) Å, c = 13.241(3) Å, V = 882.3(8) Å^3, Z = 4, R = 0.050, Rw = 0.060, GOF = 1.79.

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of a symmetric TAM from 1 week to 1 day. This methodology could enable broad application in large-scale production of sequestering agents based on this class of ligands.

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Supporting Information Available: Full experimental details and characterization of all new compounds, including crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

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