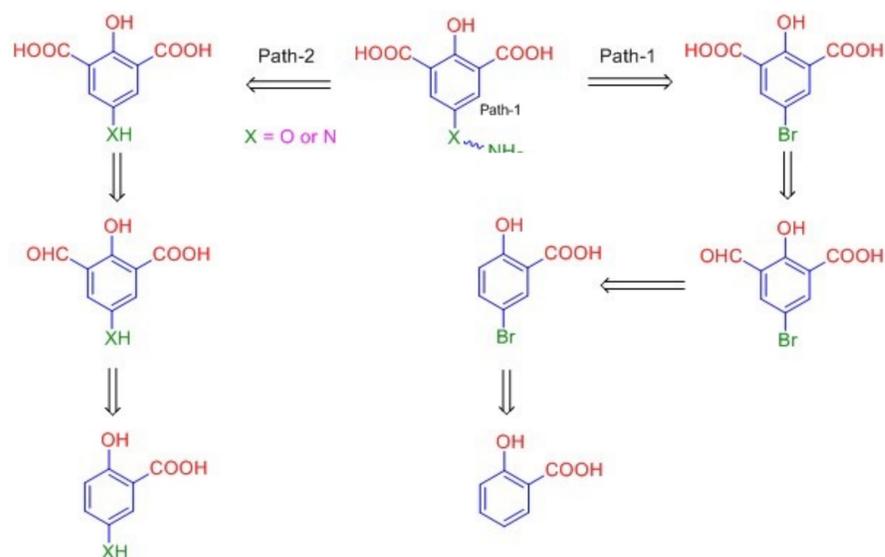


Abstract

Many modern medical diagnostics rely on magnetic nanoparticles as imaging and delivery agents, and magnetic nanoparticles can also be used for hyperthermic therapy. Iron nanoparticles are preferable because they are less toxic than gadolinium agents, and because ultrasmall iron oxide particles can serve as both positive and negative imaging agents. Biocompatibility of the nanoparticles is conferred by a layer of organic coating, for which polymers such as polyethylene glycol or biopolymers such as Dextran are commonly used. The coating serves to protect the iron from additional oxidation, or from taking part in other chemical reactions inside the body. The drawback in using macromolecular coating is in its excessive size which substantially reduces the resulting nanocomposite's magnetic response, mobility and penetrating properties in the vascular system. This project seeks to synthesize a non-polymeric small molecule which will coordinate to the iron oxide particle surface, and be less bulky than traditional coatings. It is the goal of this project to develop such a molecule that also has a linker to an amino group, which will allow for coupling to therapeutic agents, allowing the nanoconjugate to act as a drug delivery system. Our small molecule is based on salicylic acid equipped with an additional carboxyl group in the 3' position, to assure strong coordination to the nanoparticle surface, and a linker in the 5' position, to provide steric repulsive effect. Coordination complexes of both salicylic acid and of our small molecule product with metal cations are also studied herein, as this will provide insight into the interaction between the small molecule and the nanoparticle surface.

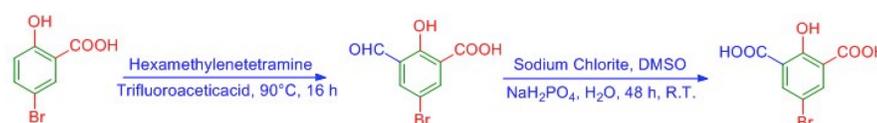
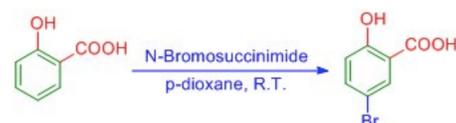
Retrosynthetic pathways



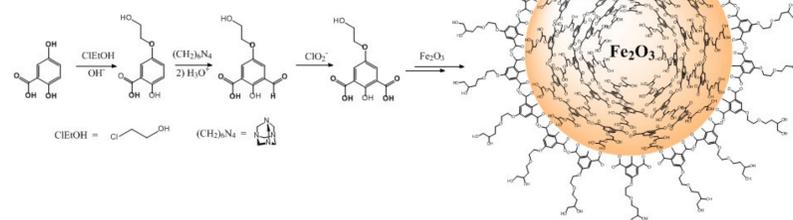
Overview

Two distinct chemical pathways to the final product have been explored, both of which show promise as sources of the target molecule in viable yield.

Path 1



Path 2



Syntheses

Path 1

Salicylic acid was brominated by reaction with *N*-bromosuccinimide (78% yield), and then formylated by HMTA to give a light yellow fibrous solid in 65% yield. This was then oxidized by addition of sodium chlorite. The product, 5-bromo-3-carboxylsalicylic acid (BCSA) was an off-white solid in 62% yield.

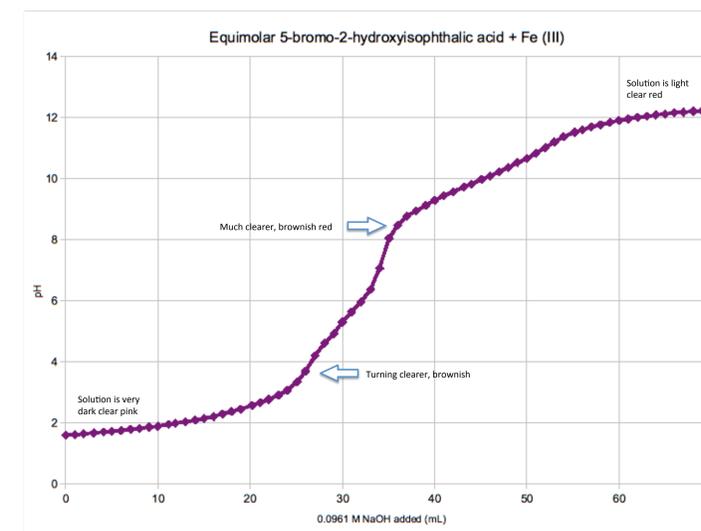
Path 2

2,5-dihydroxybenzoic acid was coupled to 2-chloroethanol in water under basic conditions, yielding 57% purified product. The product of the coupling was then reacted with an excess of HMTA (67% yield). The aldehyde was further oxidized to give a carboxylic acid (80% yield).

A brominated derivative of isophthalic acid was successfully synthesized from salicylic acid in three steps. This molecule is a precursor to similar structures that will act as coating for iron oxide nanoparticles. The structure of the acid was confirmed by ¹H NMR and MS.

A three step synthesis of a viable ligand for a magnetite/maghemite nanoparticle was demonstrated via Path 2, and its structure confirmed with ¹H NMR and MS. This ligand is moderately soluble in water, however, its solubility is greatly increased by addition of iron (III) chloride solution, indicating a non-covalent binding interaction between the two.

Titration of 5-bromo-3-carboxylsalicylic acid (BCSA) and iron (III) in solution together with sodium hydroxide indicated that the organic acid binds strongly to the iron (III) cation in solution. The iron remains soluble even at high pH when in solution with BCSA, which indicates that BCSA protects the aqueous iron from aggregating as solid iron hydroxide. It took approximately three molar equivalents of base to reach the equivalence point.



Conclusions and future work

The brominated derivative of isophthalic acid is a precursor to similar structures that will act as potential coating for magnetite nanoparticles. The structure of the organic acid was confirmed by ¹H NMR and MS. This derivative was shown to bind to iron (III) ions in solution at a range of pHs, however, it remains to be determined what the correct ratio of organic ligand:iron cation is. This value will be determined by quantitative spectrophotometric analysis of degree of product formation.

A similar isophthalic acid derivative with an ethanol tail was synthesized from 2,5-dihydroxybenzoic acid and had its structure confirmed with ¹H NMR and MS. This ligand will be reacted with ~5 nm iron oxide nanoparticles and tested as stabilizing agent in aqueous colloid solution.

References

- 1) William E. Smith. Formylation of Aromatic Compounds with Hexamethylenetetramine and Trifluoroacetic Acid J. Org. Chem., 37, No. 24, 4A (1972).
- 2) New Opportunities with the Duff Reaction Nicolas Masurier et al. Org. Chem. Vol. 73, No. 15, 5989-5992, 2008
- 3) Amino Acid Promoted CuI-Catalyzed C-N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. Hui Zhang, Qian Cai, and Dawei Ma, J. Org. Chem. 2005, 70, 5164-5173

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