OPTIMIZING THE SYNTHESIS OF A THERANOSTIC RHODAMINE

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ABSTRACT

Current designs for small molecule theranostics, which serve both a diagnostic and therapeutic role, often involve dyes linked to therapeutic agents through a cleavable, traceless linker. In order to facilitate the separation of the dye from the therapeutic in response to a biological or chemical stimulus, linkers must incorporate elements of molecular logic, increasing their complexity and the overall bulk of the small molecule theranostic. By combining the self-immolative molecular logic of the linker into the structure of the dye itself, we hope to create a series of smaller, more atom-economical theranostics. Rhodamine dyes, which naturally possess aromatic rings with highly-tunable electron density, are promising candidates in this regard. Toward this end, we have synthesized a substituted rhodamine-precursor in 4 steps with a 25% overall yield, utilizing a highly-optimized radical bromination. Upon completion of the rhodamine scaffold, we hope to explore the kinetics of its "turn-on" fluorescence and self-immolative drug release.

INTRODUCTION

In small molecule theranostics, the focus is to integrate a type of diagnostic testing to observe the presence of a drug in the desired molecular target. This method provides a non-invasive technique in detecting things such as diseases.[1] In previous designs, linkers served the sole purpose of bridging the trigger and drug together and activating a cascade of disassembly reactions.[2] Our goal is to optimize the use of a linker by serving both it's original purpose, as well as providing a fluorescence response followed by a release of a drug. Rhodamine dyes have shown promising characteristics as a linker due to its electron rich ring which provides a mechanism of action for a fluorescent turn on and drug release. The synthesis of our desired rhodamine dye has yet to be studied. It is our hope, through this research, to be able to optimize the use of linkers and control the self-immolative effects of the dye which will improve the ways we analyze the effectiveness of drugs today.

SELF-IMMOLATION

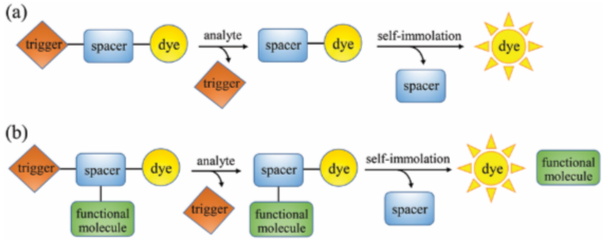


Figure 1. Previous designs for self-immolative molecules (*Chem. Soc. Rev.*, 2018, *47*, 6900)

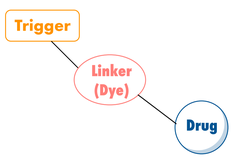


Figure 2. Illustration of basic self-immolative structure of proposed design

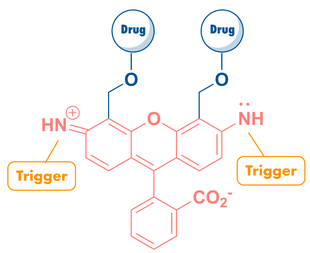


Figure 3. Illustration of self-immolative structure with desired rhodamine dye linker

MECHANISM OF "TURN ON" FLUORESCENCE & DRUG RELEASE

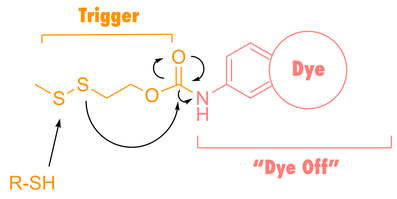


Figure 4. Mechanism to "turn on" fluorescent dye

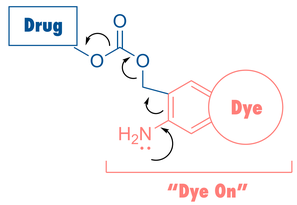
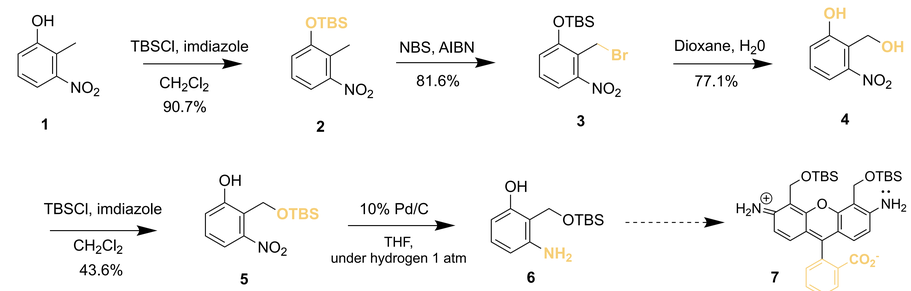


Figure 5. Mechanism of drug release

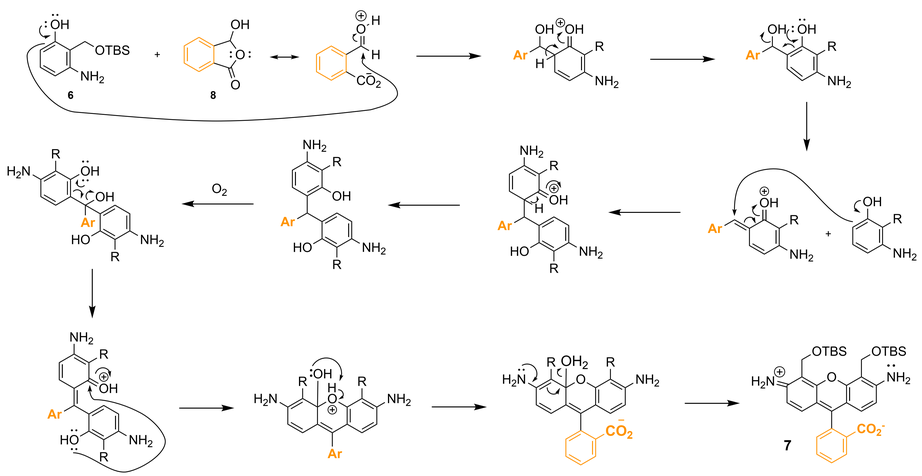
SYNTHESIS OF PROPOSED RHODAMINE DYE

Scheme 1. Synthesis of Rhodamine Dye[3,4]



PROPOSED MECHANISM OF DYE FORMATION

Scheme 2. Mechanism of Rhodamine Dye



OPTIMIZING REACTIONS

- Changed molar equivalents
- Used solvent system gradient
- Dissolved material in solvent, then inserted through side arm of flask
- Skipped addition of second protecting group and went straight to nitro reduction
- Utilized Prep TLC Technique

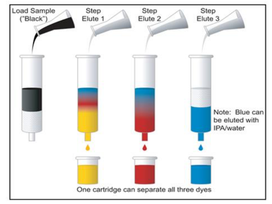


Figure 7. Solvent system gradient used for better separation. (Copyscape, 2018)

Figure 8. Material added through side arm of bomb flask. (CHEMGlass, 2020)

CONCLUSION

- Synthesized an advanced precursor of desired rhodamine dye
- Optimized the bromination step through modifying the way the starting material was added into the bomb flask

FUTURE DIRECTIONS

- Complete synthesis of rhodamine core
- Optimize nitro reduction & addition of second protecting group
- Use NMR and UV-Vis Spectroscopy to test the molecular logic and kinetics of the compound
- Study cell-based assays utilizing proposed rhodamine dye

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ACKNOWLEDGMENTS

- Dr. Herman Nikolayevskiy & the Nikolayevskiy Lab
- Dr. Mark Swanson & San Francisco State University
- Chemistry Department at the University of San Francisco