Two Rings to Rule Them All: Developing a Novel Synthesis for Exclusively 7-Substituted Coumarins

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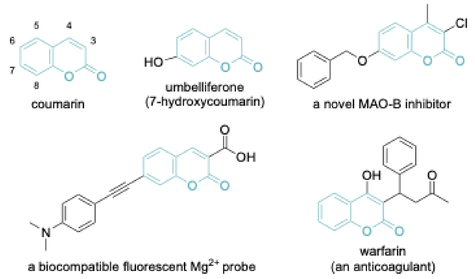
Abstract

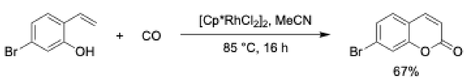
Coumarins (2*H*-1-benzopyran-2-ones) are a class of molecules with a plethora of applications in fluorescence, pharmaceuticals, and fragrances. Exclusively 7-substituted coumarins in particular show potential as innovative treatments for cancers and neurodegenerative diseases, but no selective and accessible synthesis for them has been discovered. The Martin lab seeks to apply a novel two-step pathway to the synthesis of 7-substituted coumarins. The first reaction struggles with extremely poor yields and is difficult to monitor via ^{1}H NMR, which has hampered experimentation with the second step in the past. Utilizing qualitative GC-MS to aid with spectral identification opened the door to exploring different reaction conditions to improve an unfavorable equilibrium and increase yields. Yields of the intermediate ester were increased from near 0% to 43% for both substrates examined, 3-bromophenol (**1**) and 3-methoxyphenol (**2**).

Background & Significance

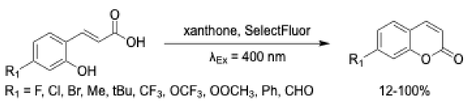
Coumarin is a privileged scaffold present in a diverse and widely applicable class of naturally occurring and synthetic compounds. Synthetic coumarins are utilized as selective fluorophores for metal ions in biological settings, anti-inflammatory drugs, anticancer drugs, biocompatible fluorescent probes, and anticoagulants. Exclusively 7-substituted coumarins in particular have potential as novel monoamine oxidase B inhibitors for Alzheimer's and ALS treatment.



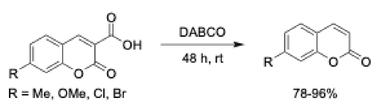
Some syntheses for exclusively 7-substituted coumarins exist, but those that do tend to have major drawbacks.



Gulías, *et al. Org. Process Res. Dev.* **2019**, 1669.
Expensive catalyst, limited scope, toxic gas

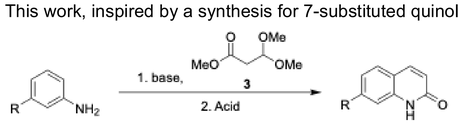


Zhao, *et al. Org. Biomol. Chem.* **2021**, 568.
Expensive equipment



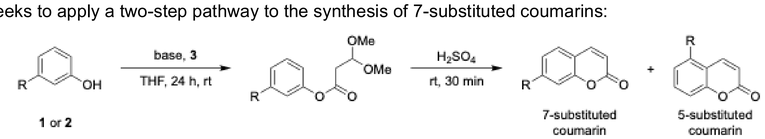
Wang, *et al. Green Chem.* **2023**, 3040.
Requires a coumarin to be synthesized in a previous step

This work, inspired by a synthesis for 7-substituted quinolinones:



Zaugg, *et al. Org. Process Res. Dev.* **2017**, 1003.

Seeks to apply a two-step pathway to the synthesis of 7-substituted coumarins:

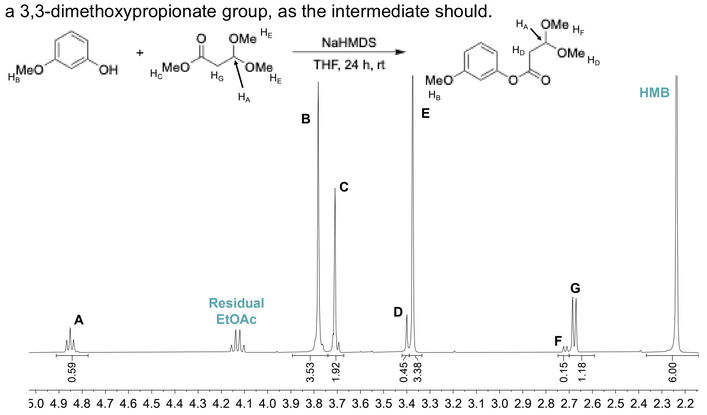


Challenges:
- Difficult to isolate intermediate
- Unclear which NMR signals belonged to the intermediate
- Roughly 0% yields for all past research

Goals:
- Confidently identify intermediate in NMR and GC-MS
- Increase yields via changing reaction conditions and addition of molecular sieves

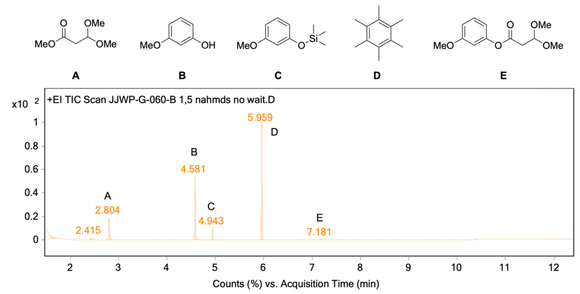
Identification of the Intermediate

Identifying the intermediate in NMR spectra proved to be consistently difficult. In prior work on this project, signals from a reactant, methyl 3,3-dimethoxypropionate, were originally identified as signals from the product. However, in some reactions, though a new set of peaks was observed that seemed to imply the presence of another molecule that contained a 3,3-dimethoxypropionate group, as the intermediate should.



Yields were determined based on the 2H doublet labeled E in the spectrum above, integrated against hexamethylbenzene as a quantitative standard.

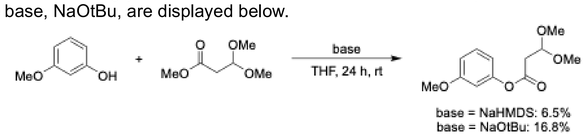
GC-MS analysis was unfruitful for identification or quantitation of the intermediate, but it did show that the phenol substrate was being protected by the $SiMe_3$ groups (C) of the NaHMDS base, potentially lowering yields.



Alternative bases were tested to determine if they might inhibit side product formation.

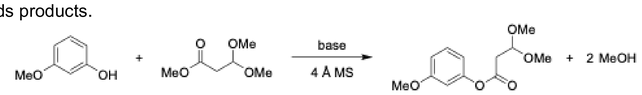
Alterations to Reaction Conditions

The results of the trials with stoichiometric alterations found that using excess base was important to maximizing yields of the intermediate. The results of experimentation with an alternate base, NaOtBu, are displayed below.



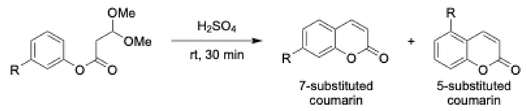
Application of Molecular Sieves

To improve the reaction equilibrium, powdered 4Å molecular sieves were added to absorb the methanol produced over the course of the reaction in an attempt to shift the equilibrium towards products.



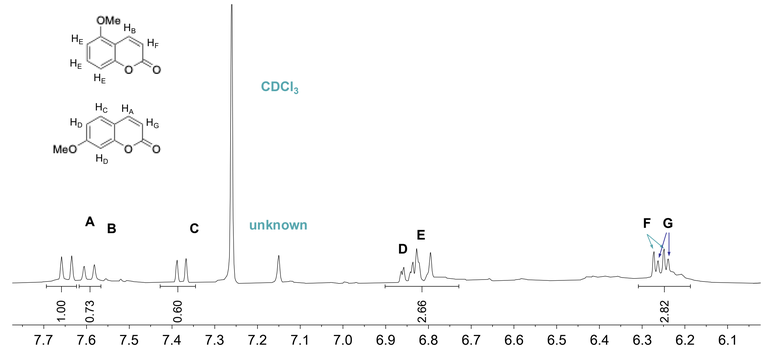
- If NaHMDS is used with sieves, yield improves from 6.5% to 23%
- If NaOtBu is used with sieves, yield improves from 16.8% to 43%
- When **1** is used as substrate instead of **2**, yields still reach a maximum of 43%

Attempts at Coumarin Synthesis



At a few points during experimentation, the reaction was scaled to 2.5 mmol and the second step of the synthesis was attempted.

Attempt #	Phenol	First step yield	Coumarin yield
1	3-Methoxy (**2**)	7.5%	1%
2	3-Bromo (**1**)	43%	0%
3	3-Methoxy (**2**)	43%	1%



Future Directions

Most early reactions experimenting with different conditions were run with a faulty workup that destroyed the desired product, so future variables to screen for should include:
- Reaction duration
- Temperature
- Amount of solvent (concentration of base)

The yield of the intermediate may also be able to be improved via a more optimized workup.

Exploring a wider range of substrates could improve yields of both synthetic steps and reveal critical information about the scope of the entire synthesis, with the context that 7-bromocoumarin has never been successfully synthesized and isolated with this synthesis.

Finally, molecular sieves may be applicable in the cyclization step as well, but an acid with a larger radius than H_2SO_4 would need to be used to avoid it being trapped in the sieves.

Acknowledgements

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