One Ring to Rule Them All: Demonstrating the Synthetic Capabilities of 7-bromoquinolin-2*(1H)*-one in the Synthesis of 1,2-dihydro-2-oxo-7 quinolinecarboxylic Acid and its Ellagic Acid Conjugate

Margaret L. Steward, Sara E. S. Martin

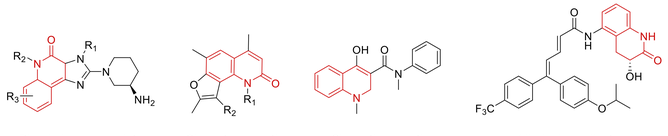
Department of Chemistry, The College of Wooster, Wooster, OH

Abstract

Quinolinones are medically relevant molecules often found in pharmaceutical agents. Ample research has been conducted on many analogues of quinoline-2*(1H)*-one analogues, though the 7-substituted isomer of this system is understudied. Herein this work, a multi-step synthesis is conceived and developed to demonstrate the potential of this understudied analogue in synthesizing larger biologically active molecules. The synthesis prepares 7-bromoquinolin-2*(1H)*-one (**1**), 7-bromo-1-methyl-2(1*H*)-quinolinone (**2**), 1,2-dihydro-2-oxo-7 quinolinecarboxylic acid (**3**), and its ellagic acid conjugate (**4**). Molecules **1** and **2** were successfully attained, while the synthesis of the carboxylic acid was inconclusive.

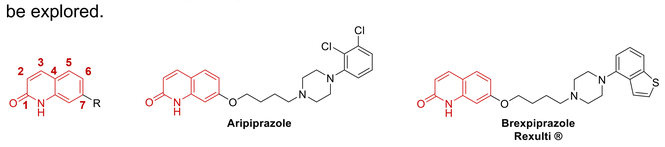
Background and Motivation

Quinolinones have many medicinal applications due to their biological properties (anti-bacterial, anti-inflammation, anti-proliferative, etc.). Drugs containing this motif are prescribed for a wide variety of illnesses.



Blood glucose regulator | **Chemotherapeutic** | **Chemotherapeutic** | **Allodynia medication**

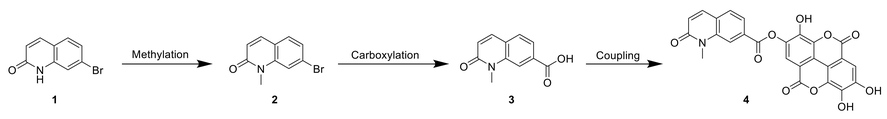
Relatively minimal research has been conducted on the 7-substituted analogue of quinoline-2*(1H)*-ones due to challenges in selective substitution. Few examples of on-the-market drugs using this structure include aripiprazole and brexpiprazole, an anti-depressant commercially called Rexulti®. With promising biological activity, further research into 7-substituted quinolinones should be explored.



Aripiprazole | **Brexpiprazole Rexulti ®**

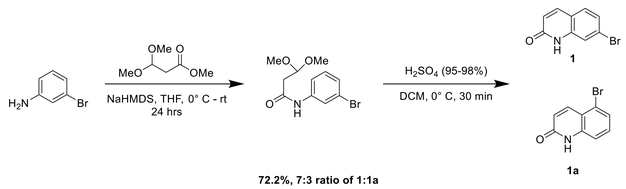
Research Goals

A multi-step synthesis was designed to synthesize 7-bromo-2*(1H)*-one (**1**) starting material, methylation to **2**, functionalization to **3**, and coupling to **4**. Molecule **4** is an appropriate example of a potentially biologically active large molecule using the 7-substituted quinolinone framework. All citations shown on this poster represent the literature precedent for the respective reactions.



Synthesizing 7-bromoquinolin-2(1H)-one (*1*)

Synthesis of **1** via an acylation-cyclization pathway resulted in an isomeric mixture of **1** and **1a.** No further purification methods were pursued for simplicity and proof of concept for the project.



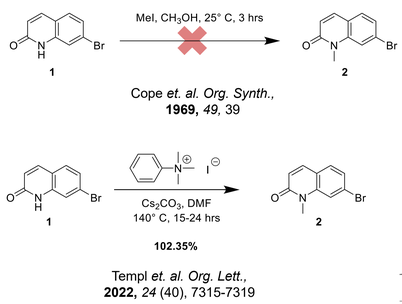
72.2%, 7:3 ratio of 1:1a

Ausec et. al., *Results Chem.*, **2025**, *14*, 102089

Zaugg *et. al. Org. Process Res. Dev.*, **2017,** *21* (7), 1003-1011

Methylation of Brominated Quinolinone (*2*)

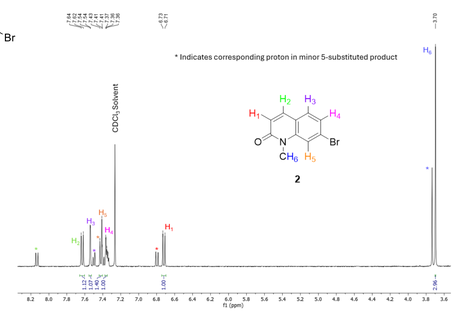
Two distinct routes to **2** were attempted. The Templ et. al. procedure was successful.



Cope *et. al. Org. Synth.*, **1969,** *49*, 39

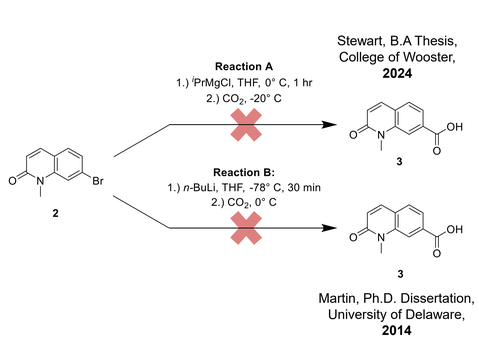
102.35%

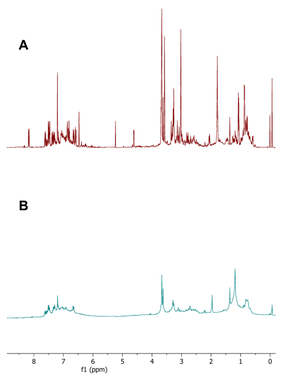
Templ *et. al. Org. Lett.*, **2022,** *24* (40), 7315-7319



Carboxylic Acid Functionalization (*3*)

Two routes to install a carboxylic acid at the 7-position (**3**) were attempted with inconclusive results. Characterization via ^{1}H NMR, ^{13}C NMR and TLC data suggest but do not confirm the presence of **3.**





Acknowledgements

I would like to thank from the bottom of my heart:

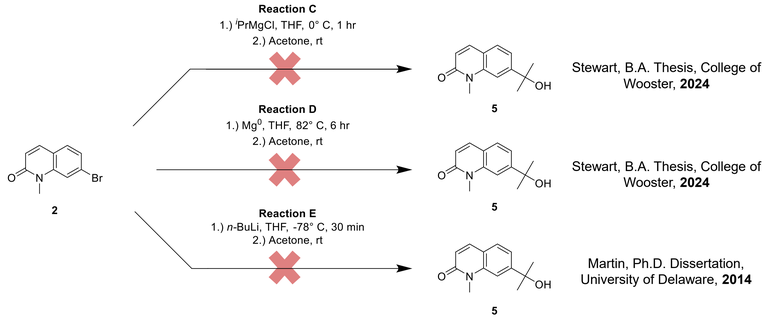
- Dr. Sara Martin
- The faculty and staff of the College of Wooster Chemistry Department
- Copeland Funding
- The Barry Goldwater Scholarship Foundation
- My labmates Edith Michelle-Aboa and Juniper Partee
- All my friends (especially those who safety buddied me…)
- My family, for always picking up the phone

MRI CHE-1626088

ACS Wooster Section

Carboxylation Troubleshooting

Control experiments using acetone were used to probe intermediate formation. Three distinct routes to produce **5** were attempted.



Characterization of Reaction D yielded identical results to that of the starting material. Both the ^{i}PrMgCl and *n*-BuLi routes yielded inconclusive ^{1}HNMR and TLC data, suggesting a new product was formed whose identity is unclear.

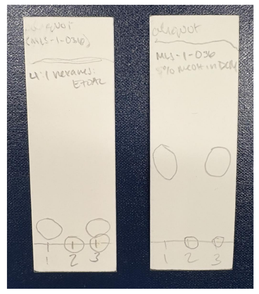
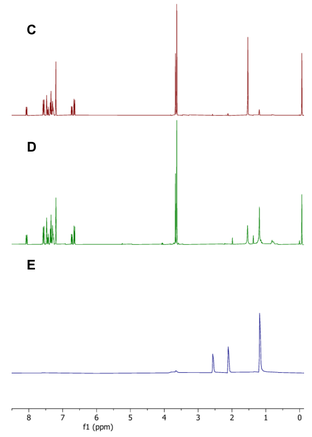


Figure 1. TLC plate data from *n*-BuLi acetone control (**E**) in 4:1 hexanes:ethyl acetate (left) and 5% methanol in dichloromethane (right). This shows the polarity difference between the starting material (Lane 1) and product (Lane 2).

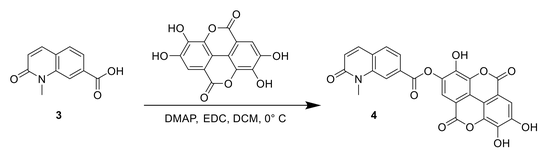


Conclusions

- **1** was synthesized at a larger scale (36 mmol) than previously reported in the Martin Group
- **2** was synthesized with moderate reagants
- Synthesis of **3** inconclusive, but characterization (TLC and ^{1}H NMR) of the ^{i}PrMgCl and *n*-BuLi routes suggests a new product was created

Future Work

- Further characterization of the compounds using GC-MS, IR, and other analytical techniques
- Repeat the experiments to synthesize **3** on a larger scale
- If 3 is successfully synthesized, carrying the multi-step synthesis forward to produce the ellagic acid coupling product **4** due to its potential biological activity



Stewart, B.A Thesis, College of Wooster, **2024**