Understanding the Reactivity of 4(3*H*)-Quinazolinone Via *N*3-Alkylation

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Background

- The molecules of focus are 4(3*H*)-Quinazolinone and its derivatives (Figure 1).
- Quinazolinones are a privileged scaffold, meaning that it and its derivatives have a greater chance of being biologically active.[1]
- Different quinazolinones have already been discovered to provide diverse biological activities such as: anti-tumor agents, anti-viral, anti-bacterial, etc.[2]

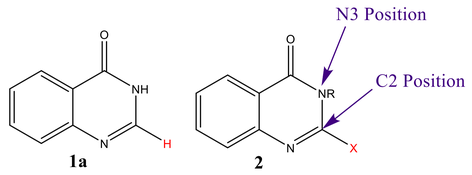
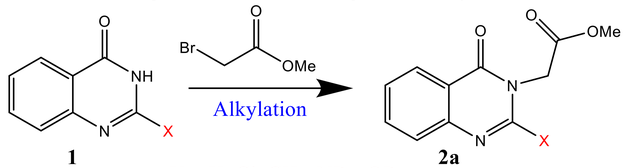


Figure 1. 4(3*H*)-Quinazolinone (**1a**) and derivatives that can be made by changing the substituent at the C2 position (**2**).

Project Goals/Methods

- Quinazolinone-containing compounds typically require multi-step synthesis to prepare.[3]
- This project aims to add to understanding of the reactivity of 4-quinazolinones.
- **Part 1**: Synthesis of *N*3-methyl acetate quinazolinone.



Explore C2 substituent affects on:

- The efficiency of *N*3-alkylation.
- The regioselectivity of *N*3-alkylation.[4]

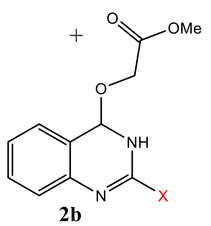


Figure 2. Exploration of C2 substituent effect on quinazolinone alkylation.

- **Part 2**: Synthesis of *N*3-alkylamino-4-quinazolinones.

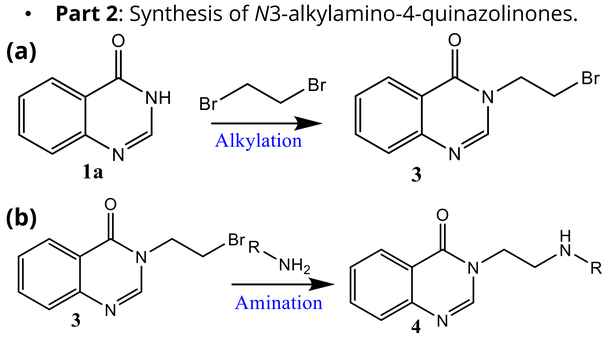


Figure 3. Two-step synthesis to prepare *N*3-alkylamino-4-quinazolinones.

Part 1 Results

- When X = Cl the reaction provided a good yield (Figure 4a).
- X = CH_3 did not result in a product when the base used was Na_2CO_3, but it worked when the base was switched to NaH (Figure 4b-c and e).
- X = diisopropylamine did not result in the desired product (Figure 4d).

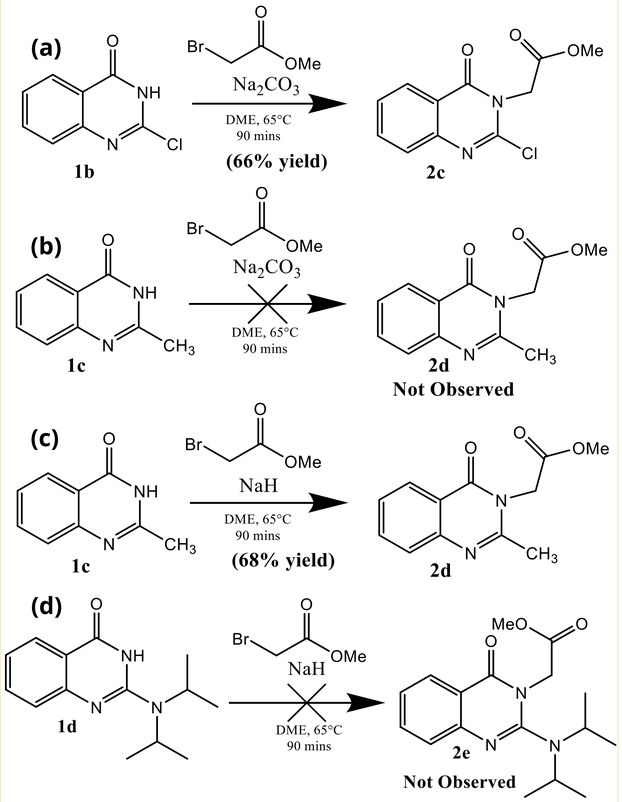


Figure 4. (a) Alkylation of C2-chloro-quinazolinone (**1b**). (b) and (c) Alkylation of C2-methyl quinazolinone (**1c**) using Na_2CO_3 or NaH as a base. (d) Alkylation of C2-diisopropylamine quinazolinone (**1d**). (e) H-NMR (in $CDCl_3$, 400 MHz) of **2d**.

Part 2 Results

- Alkylation of 4-quinazolinone with dibromoethane, followed by amination with either benzylamine or phenethylamine furnished *N*3-ethylamino-4-quinazolinones **4a** and **4b** in good yield (Figure 5).

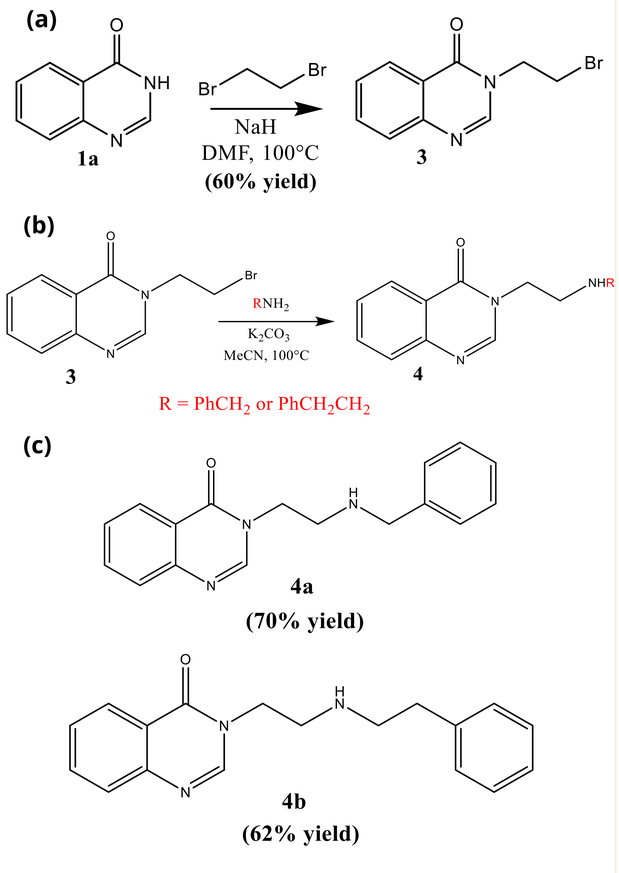


Figure 5. (a) Alkylation to form *N*3-ethylbromo quinazolinone (**3**). (b) Amination of **3** with a primary amine. (c) *N*3-alkylamino-4-quinazolinones synthesized (**4a** and **4b**). (d) H-NMR (in $CDCl_3$, 400 MHz) of **4a**.

Conclusions

Part 1:

- A strong base was required for *N*3-alkylation without an electron-withdrawing group at the C2 position.
- Electron-withdrawing groups at the C2 position facilitate *N*3-alkylation.
- Bulkier groups at the C2 position result in no product formation.
- Based on the NMR, no sign of *O*-alkylation was found.

Part 2:

- The alkylation reaction ran very smoothly and rarely produced side products.
- The amination also ran smoothly, but there is side reactivity. An elimination reaction product (alkene) was commonly found as a side product.

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