Synthesis of 2,*N*3-Disubstituted Quinazolin-4(3*H*)-ones

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INTRODUCTION

What is quinazolinone?

- Privileged organic scaffolds (Figure 1)
- Ubiquitous among biologically active medicinal targets.

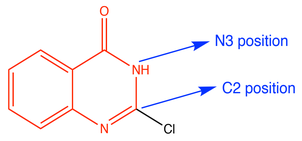

Figure 1: An example of C2 substituted quinazolinone with quinazolinone core in red

Why should we care?

- Quinazolinone's structure sets the foundational framework that can be chemically altered at the C2 and *N*3 position (Figure 1) to exhibit a wide array of biological effects such as anti-parasitic activity.
- The relatively stable, and alterable structure of the heterocyclic rings makes quinazolinone an ideal chemical scaffold for pharmaceutical development.

Project Goal:

Synthesize 2,*N*3-disubstituted quinazolin-4(3*H*)-ones and gain synthetic insights into the reactivity of 4(3*H*)-Quinazolinones.

APPROACH

PART I: Study the effects of different C2 substituents on quinazolinone *N*3 alkylation outcome using scheme shown in Figure 2.

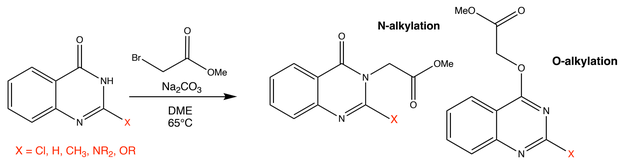

Figure 2: Reaction scheme to study the efficacy and regioselectivity of alkylation of varying C2 substituents of quinazolinones using methyl bromoacetate.

PART II: Study the synthesis of *N*3-alkylamino-4-quinazolinones from 4-hydroxyquinazoline (Figure 3).

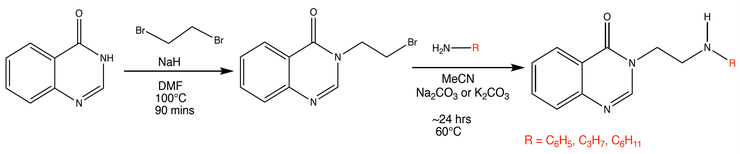

Figure 3: Two-step synthetic pathway featuring *N*3-alkylation followed by reaction with various 1° amines.

RESULTS

PART I Observations:

- When R = Cl, using Na_2CO_3 as the base resulted in a good yield (Figure 4a).
- *O*-alkylation product was not observed.
- When R=CH_3, using Na_2CO_3 did not form the expected product. Then, using a stronger base (NaH) resulted in a good yield of expected product (Figure 4b). H-NMR confirmed formation of product (Figure 4c).

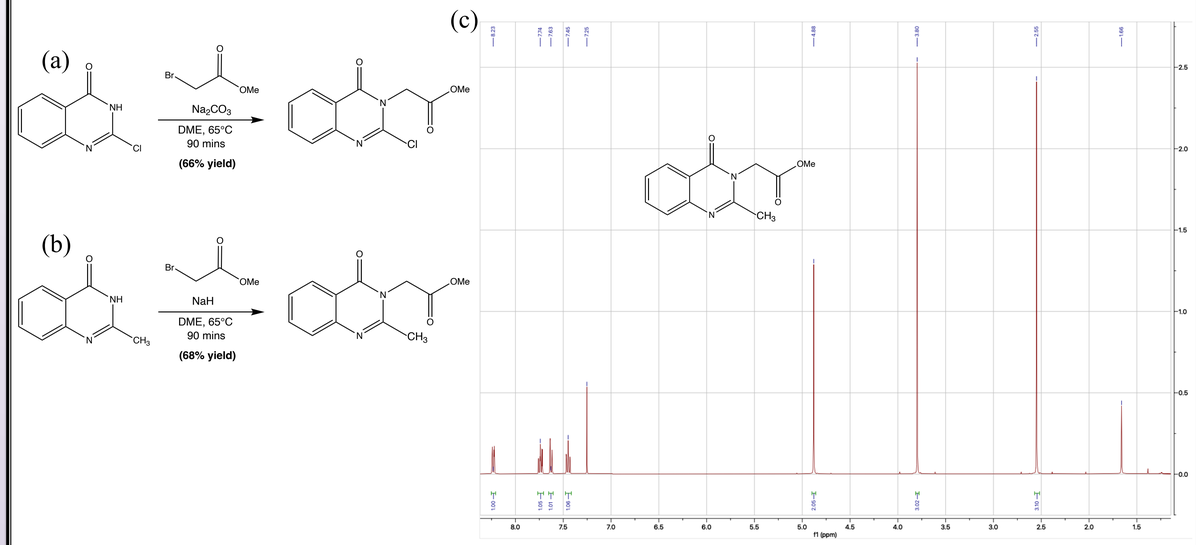

Figure 4: (a) Alkylation of C2-chloro-substituted quinazolinone. (b) Alkylation of C2-methyl-substituted quinazolinone. (c) H-NMR (in $CDCl_3$, 400 MHz) of the C2-chloro-*N*-alkylated product from part b.

PART II Observations:

- Synthesis of *N*3-ethylbromo-substituted quinazolinone proceeded smoothly in good yield. (Figure 5a)
- For subsequent amination using 1° amine RNH_2, when R=C_6H_5, a good yield was obtained (Figure 5b). H-NMR confirmed formation of product (Figure 5c).

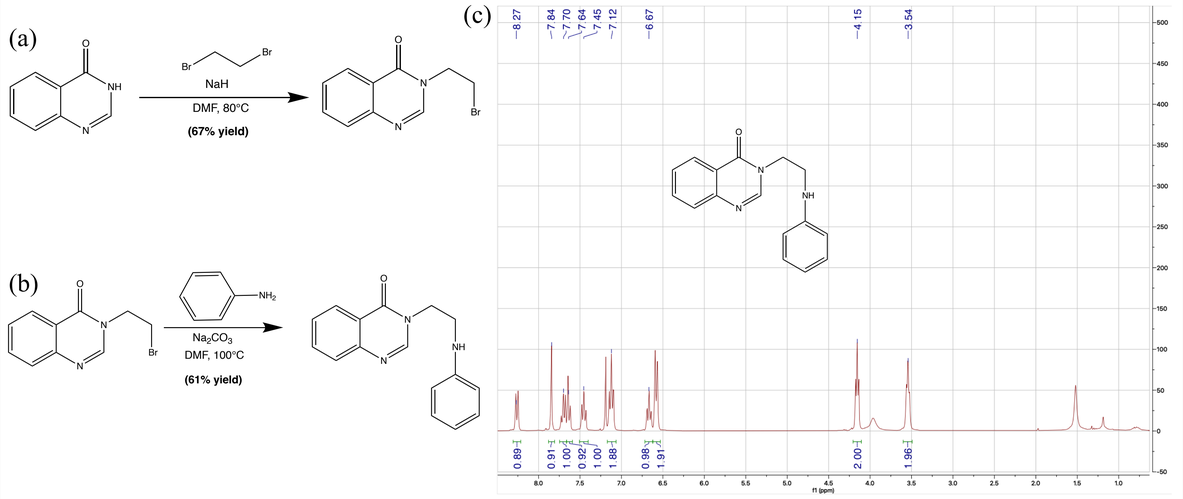

Figure 5: (a) Alkylation to form *N*3-ethylbromo-substituted quinazolinone. (b) Amination of product from part a with $PhNH_2$. (c) H-NMR (in $CDCl_3$, 400 MHz) of the product from part b.

CONCLUSION

PART I:

- Optimal *N*3-alkylation requires a strong base for substrates without electron-withdrawing substituents.
- Less bulky groups at the C2 position give a better yield of the product.
- Only *N*-alkylation occurs.

PART II:

- Subsequent amination of the *N*3-alkylated quinazolinones is promoted by increased reaction times.
- Side reactivity of quinazolinones was frequently noted that resulted in an elimination reaction product, alkene at the *N*3 position.
- Shape and bulkiness of 1° amine influence yield and product identity.

FUTURE DIRECTIONS

- Explore increased reaction times for Part I reactions.
- Synthesize more C2-substituted starting materials for Part I.
- Experiment with other 1° amines in Part II to confirm the effect of shape and bulkiness on the reaction
- Study further reactivity of *N*3-alkylamino quinazolinone products.

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REFERENCES

- Chen, G. S.; Kalchar, S.; Kuo, C.-W.; Chang, C.-S.; Usifoh, C. O.; Chern, J. Org. Chem. 2003, 68, 2502-2505.
- Hori, M.; Ohtaka, H. Chem. Pharm. Bul. 1993, 41, 1114-1117.
- Wang Chen J Chem Res 2011 4