Organic Synthesis of 2-*n*-Nonyl-4-hydroxyquinoline-*N*-oxide

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Introduction

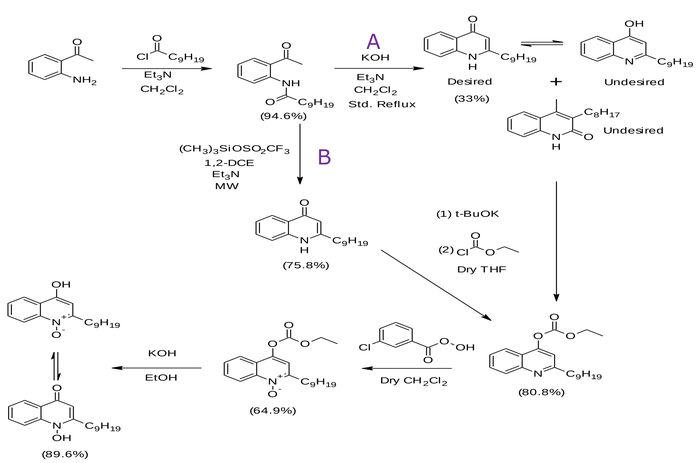
With the world becoming more dependent upon fossil fuels, alternative means of energy sources will be required to replace naturally occurring finite ones. A particular area of interest lies in what are referred to as bio-fuels. Production of sustainable bio-fuels requires a molecule known as isoprene. Characteristics of isoprene allow it to play dual roles in sustainability in its ability to be used to produce fuels as well as plastics.

In order to study the pathways leading to isoprene generation, a type of cyanobacteria known as *Synechococcus* PCC 7002 has been engineered to produce the precursor. Studies of this algae require use of an known inhibitor known as 2-*n*-nonyl-4-hydroxyquinoline-*N*-oxide (NQNO). Because NQNO is not commercially available, we set out to synthesizing NQNO in the laboratory.

Isoprene

Scheme 1 is the proposed approach to synthesize NQNO (E) from 4(1*H*)-Q (B) which was successfully synthesized in our lab from a 10 carbon acid chloride and 2-aminoacetophenone. However this process suffered from issues such as selectivity and poor yields. Pathway B is a revised approach, which was able to overcome both problems encountered by Pathway A, the original synthesis route. From this key intermediate, production of NQNO was completed with the addition of a protecting group, oxidation of the nitrogen, and removal of the protecting group via base-promoted hydrolysis. Reaction progress was monitored using thin-layer chromatography (TLC). Column chromatography was also utilized to obtain products in highly pure quantities, and nuclear magnetic resonance spectroscopy (NMR) utilized in ensuring that each reaction had been successfully performed.

Figure 1. The proposed synthesis of NQNO.

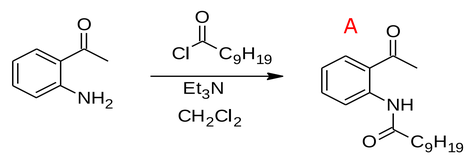


Methods and Results

Step 1- reaction of decanoyl chloride and 2'-aminoacetophenone

In scheme 2 decanoyl chloride was mixed with 2'-aminoacetophenone and Et_3N in CH_2Cl_2 at room temperature for 3 hours. Afterward the crude product was extracted/washed with deionized water (DI H_2O), 1M HCl, sat $NaHCO_3$, and sat NaCl. The solution was then dried with $MgSO_4$ and volatiles removed. The resulting crude was then submitted to column chromatography using 5%MeOH in CH_2Cl_2 and a golden yellow oil was produced. NMR (Figure 3) verified the product as the desired amide (A).

Scheme 2



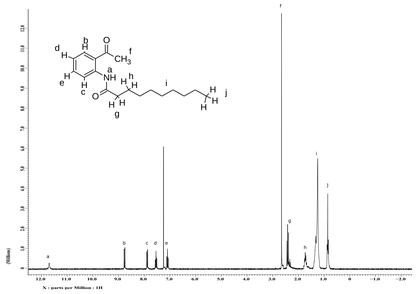
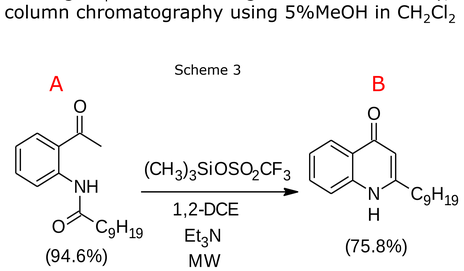


Figure 3-NMR results of amide using chloroform-d ($CDCl_3$)

Step 2-Cyclization of the amide

Product (A) from step 1 was combined with TMSOTf, Et_3N in CH_2Cl_2, and refluxed using microwave radiation for 1 hour under an argon atmosphere (Scheme 3). The crude product was quenched with MeOH, volatiles removed, and washed/extracted using 3M NaOH and EtOAc. Crude was then dried with $MgSO_4$ and volatiles again removed. Finally, the desired product, 4(1H)Q (B), was purified by column chromatography using 5%MeOH in CH_2Cl_2 and confirmed by NMR (Figure 4).

Scheme 3



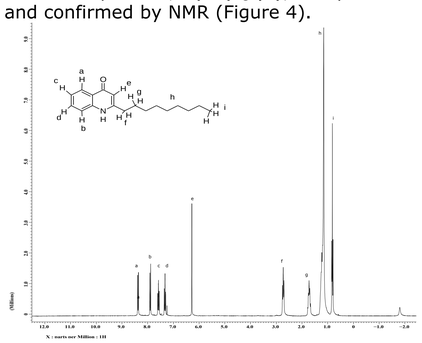
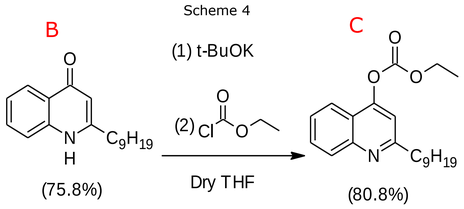


Figure 4-NMR of 4(1H)Q using $CDCl_3$

Step 3-Addition of a protecting group to 4(1H)Q

In scheme 4, purified 4(1*H*)Q(B) was reacted with potassium t-butoxide (t-BuOK) in dry tetrahydrofuran (THF) for 1 hour with stirring under an argon atmosphere. This produced a nitrogen anion which delocalized its negative charge to the oxygen atom. Ethyl chloroformate was then added and the mixture stirred for another 30 minutes to place the protecting group on the oxygen (C). Next, the product was quenched with DI H_2O, extracted with EtOAc and rinsed with an additional quantity of DI H_2O. Volatiles were then removed and resulting yellow oil was confirmed as the desired product via NMR (Figure 5).

Scheme 4



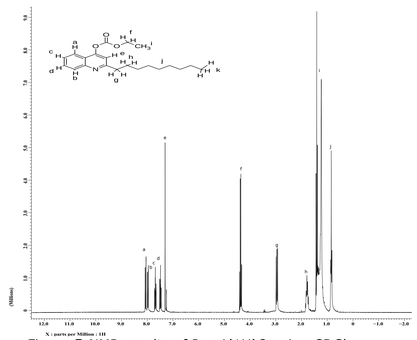
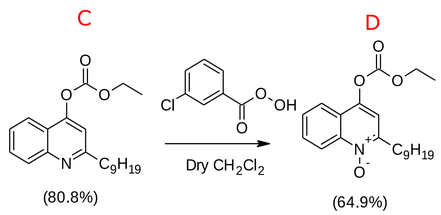


Figure 5-NMR results of Pro 4(1H)Q using $CDCl_3$

Step 4-Oxidation of protected 4(1HQ)

The product (D), oxidized 4(1H)Q (Ox 4(1H)Q) of this step was derived by mixing (C) with purified *meta*-chloroperoxybenzoic acid (m-CPBA) at room temperature in anhydrous CH_2Cl_2 for 3 hours.(Scheme 5) Once all starting material had been fully consumed, the crude product was submitted to a column using 1:1 EtOAc:hexane as the eluting solvent. (D) was then obtained by removing the solvents under pressure, and found to be in high purity by NMR. (Figure 6)

Scheme 5



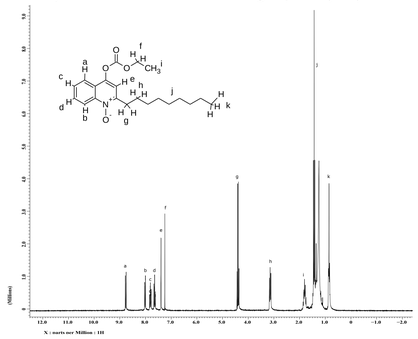
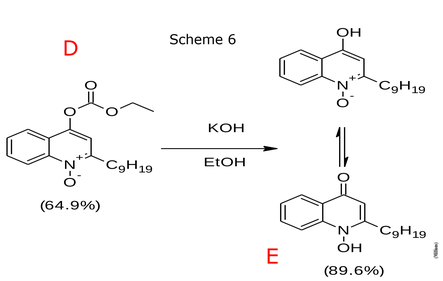


Figure 6-NMR of protected 4(1H)Q using $CDCl_3$

Step 5-Deblocking Ox 4(1H)Q

The final product, NQNO (E) was formed by removing the protecting group from (D)(Scheme 6). This was done by mixing Ox 4(1H)Q with 5 M KOH at room temperature for an hour. Once the reaction was finished, it was quenched with DI H_2O. Next, concentrated HCl was added in a drop-wise fashion until the solution had turned milky white. The milky white product was collect via filtration and analyzed by NMR (Figure 7). NQNO was collected as a cream-colored, iridescent solid.

Scheme 6



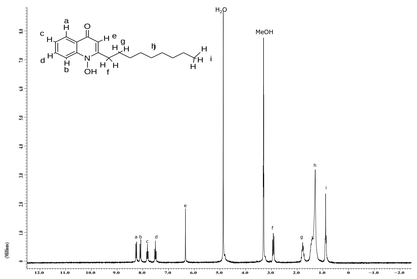


Figure 7- NMR data of NQNO using MeOH

Conclusion

Synthesis of NQNO was successfully achieved as descirbed. The revised approach to synthesizing NQNO using TMSOTf has proven itself a better reagent in achieving a higher yield while avoiding issues such as selectivity previously encountered. Each step of the overall process may be further explored upon to increase their percent yields. Currently the literature does not reflect using TMSOTf within a microwave reaction, which is an area of significant interest of this lab in further exploring for similar cyclization reactions.

Acknowledgment

Ronald McNair Post-Baccalaureate Achievement Program
University of Wisconsin Oshkosh Chemistry Department
Special thanks to Dr. Kedrowski, Dr. Xie, Mary Seaman and Christine Webb

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The UW Oshkosh McNair Scholars Program is 100% funded through a TRIO grant from the United States Department of Education PR/Award Number P217A070188. For 2012/2013, the UW Oshkosh McNair Scholars Program will receive $213,000 each year in federal funds.