Synthesis and Characterization of Ethyl Nalidixate Followed by Optimization of Literature Procedure

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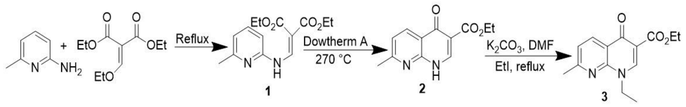
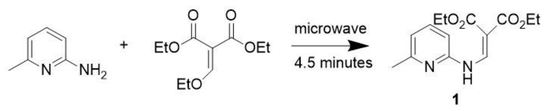
Introduction

Ethyl nalidixate is a parent compound in a range of quinolone antibiotics, an important drug in curing various illnesses.[1] The published procedure of the three-week synthesis of ethyl nalidixate involves a Michael addition/elimination, a Gould-Jacobs cyclisation, and an alkylation.[2] The goal of the experiment was too replicate the literature procedure, obtaining the correct products and similar percent yields. Three optimizations were then performed in an attempt to improve the original synthesis.

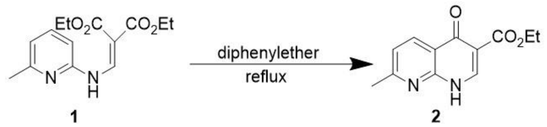


Scheme 1: Synthesis of ethyl nalidixate **(3)** following literature procedure.

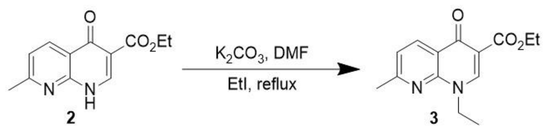
Experimental Design[2]



Scheme 2: Optimization synthesis of diethyl (6-methyl-2-pyridyl) amino ethylene malonate **(1)**[3].



Scheme 3: Optimization synthesis of ethyl-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate **(2)**[4].



Scheme 4: Optimization synthesis of ethyl nalidixate **(3)**[5].

The first optimization substitutes microwave irradiation for conventional heating methods to simplify the work up procedure and make the reaction more time efficient. The second optimization substitutes diphenyl ether for Dowtherm A to lower the reflux temperature and simplify the work up procedure. The third optimization substitues an oil bath for a sand bath to obtain more uniform heating.

Structural characterization via nuclear magnetic resonance spectroscopy (NMR) for products produced by literature procedure. Structural characterization vis Infrared spectroscopy (IR) and melting point for all products.

Results

Resulting NMR spectra support that the literature procedure was succesfully reproduced to yield ethyl nalidixate **(3)** as a final product.

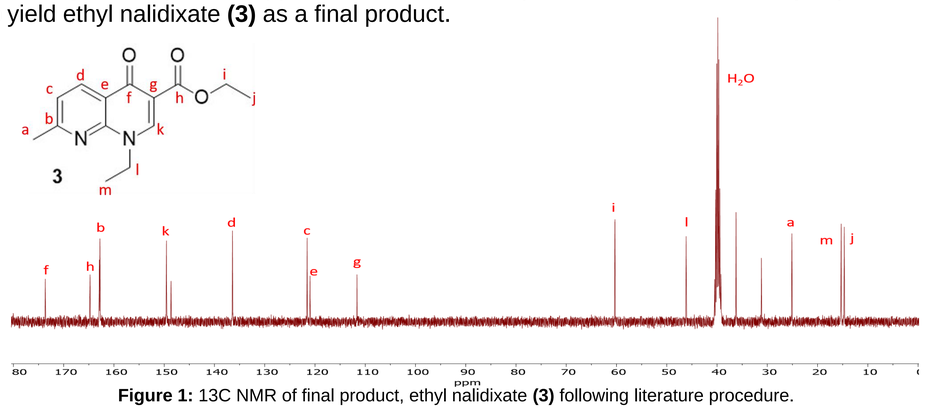


Figure 1: 13C NMR of final product, ethyl nalidixate **(3)** following literature procedure.

Product	Literature Procedure*	Optimization*
(1)	3267, 3083, 2980, 2930, 2905 cm^{-1}	3267, 3083, 2980, 2930, 2905 cm^{-1}
(2)	2981, 2906 cm^{-1}	2981, 2911 cm^{-1}
(3)	-	3304 cm^{-1}

Figure 2: IR spectroscopy data obtained from the literature procedure vs. optimization procedure.

IR spectroscopy data, seen in Figure 2, supports the prodcution of all three products following the optimization procedure. **(1)** and **(2)** are confirmed via NMR data of literature products. The IR spectrum produced by **(3)** is compared to lliterature IR spectral data to confirm its successful production.

The melting point data, seen in Figure 3, supports the synthesis of **(1)** and **(2)** following optimization procedure. The data shows that the optimization of **(1)** produces a less pure product. This, in part, is due to starting materials present in the product sample.

Product	Literature Value	Literature Procedure	Optimization
(1)	104-106°C	106-107.8°C	90-100.4°C
(2)	272-274°C	>260°C	>260°C
(3)	120.8-121.6°C	-	-

Figure 3: Melting point data of products obtained from the literature and optimization procedures.

Product	Literature Procedure sand bath	Optimization oil bath
(3)	70-120°C	65-90°C

Figure 4: Observed temperature ranges of a sand bath vs. an oil bath. Goal temperature of 80˚ C.

The observed temperature range of the sand bath vs. the oil bath, seen in Figure 4, of the third optimization supports that uniform heating maintains a temperature closer to the goal temperature.

Percent yield data, seen in Figure 5, for **(1)** does not support the optimization procedure producing a higher yield than the literature procedure as the mass of **(1)** included starting materials and other impurities. The calculated percent yield for **(2)** and **(3)** indicate that the optimization procedure produced a higher yield of product than the literature procedure.

Product	Literature Procedure	Optimization
(1)	90%	120%
(2)	39%	79%
(3)	18%	40%

Figure 5: Calculated percent yield of products obtained from the literature procedure vs. optimization procedure.

Cost analysis gives that 1 gram of ethyl nalidixate costs $526.79 to synthesize.

Discussion

The first step optimization, utilizing microwave chemistry, was unsuccessful. The second and third step optimizations were successful with a percent yield increase of 40% and 22% respectively. The results of the optimizations of **(2)** and **(3)** support that diphenylether is a better heating solution for the synthesis of **(2)** and that uniform heating results in a higher percent yield.

Microwave chemistry proved challenging to conduct. The mixed initial reagents solidify in air over a short time making microwave chemistry impossible to conduct or more dangerous due to pressure spikes. The third step, in both the literature and optimization procedures proved challenging due to low product volume and the multiple extraction steps.

Errors within this lab were due to overheating in step 1 of the literature procedure, turning the product brown and decreasing yield. In step 3, solvent grade ether had to be utilized to obtain any product via extraction. In the first optimization no work up step after microwave irradiation left starting materials and other impurities in the product sample. In the third optimization the product sample contained a small amount of water after extraction.

Summary and Conclusions

- Successful synthesis of ethyl nalidixate **(3)**
- Optimization of step 2, synthesis of ethyl-4-hydroxy-7-methyl-1,8-naphyridine **(2)**
- Optimization of step 3, synthesis of ethyl nalidixate **(3)**

Acknowledgements

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