Preparation of an Important Intermediate in the Synthesis of anti-tuberculosis natural agent Escobarines

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Background

Tuberculosis:

- Multi-drug resistant tuberculosis (MDR-TB) is a major public health issue on the rise (WHO, 2015)
- First-line drugs against TB: isoniazid, ethambutol, streptomycin, rifampicin and pyrazinamide
- Currently, MDR -TB makes up 5% of all TB cases

Escobarines:

- Escobarines A and B are organic molecules extracted from the *Calliandra californica* plant
- Escobarine A shows promising activity against certain MDR-TB strains
- Synthesis of Ring C is the focus of this project
- Chemical structure of escobarine A:

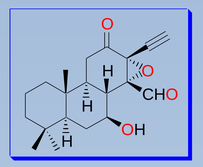


Figure 1. The three ring structure of Escobarine A, with the top right ring as ring C

Objective

Short Term:

- Prepare ring C of Escobarine A in six steps
- Build β-hydroxymethylcyclohexenone from cyclohexenone by inserting a hydroxymethyl group in one a one-pot procedure
- Previously, a six-step procedure was used to prepare β-hydroxymethylcyclohexenone

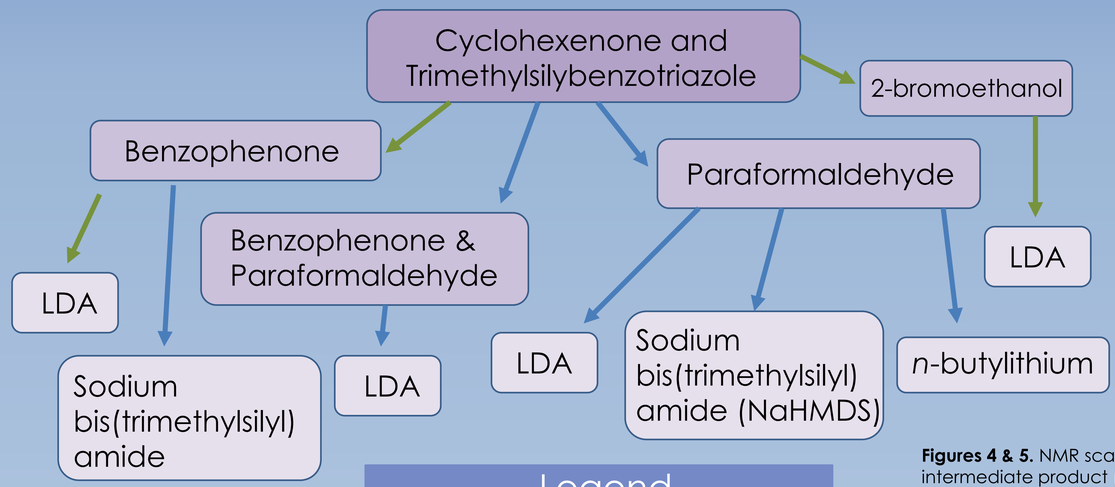
Long Term:

- Test the effectiveness of Ring C and Escobarine A compounds against strains of MDR- TB
- Develop an anti-MDR-TB drug based on this synthetic work

Method

- Control group procedure (and subsequent methods) comes from paper by Katritzky (1995)
- Firstly, mix cyclohexenone and $BtSiMe_3$ in a flask under argon atmosphere for 30 minutes
- Next, the addition of electrophile:
  Benzophenone (control)
  Paraformadehyde (**independent**)
  Bromoethanol (**independent**)
- Mixture is cooled to -78 °C with a mixture of dry ice and acetone
- Base (**independent** variable) added dropwise
  Lithium diisopropylamide (LDA)
  n-butylithium
  Sodium bis(trimethylsilyl)amide
- Mixture stirred for a minimum of 1 hour
- Signs of working reaction:
  -change in colour
  -precipitate
- Quenching reaction with aq. HCl
- Extraction with ethyl acetate
- Purification with silica powder

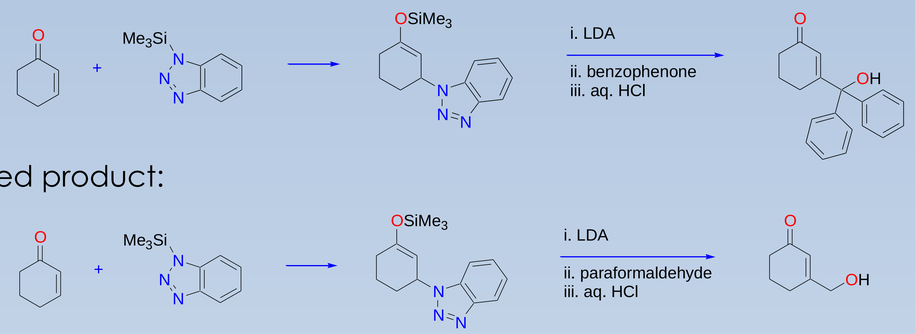
Overview of Experiments



Legend

- Substrate and reagent --
- Base --
- Electrophile --

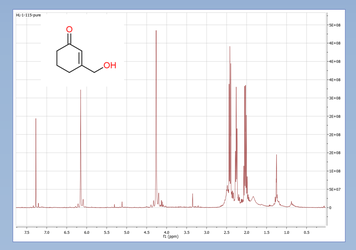
Control group:

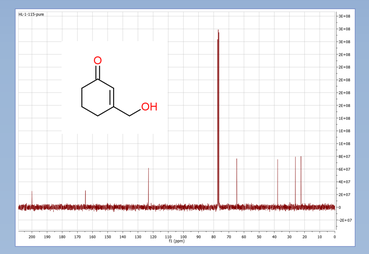


Desired product:

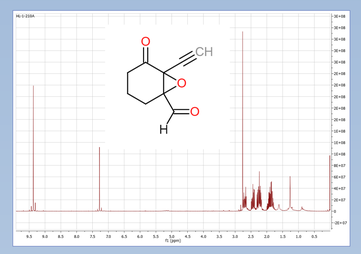
Results

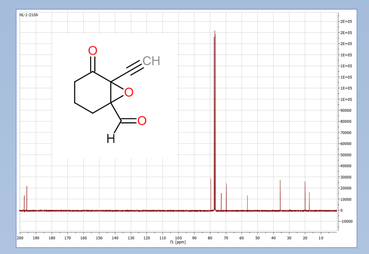
β-hydroxymethylcyclohexenone:





Ring C of Escobarine A:





Figures 4 & 5. NMR scan of intermediate product (4) and final ring product (5). Left are the ^{13}C scans and right are the ^{1}H scans.

Results

TLC of product:

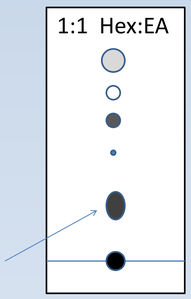
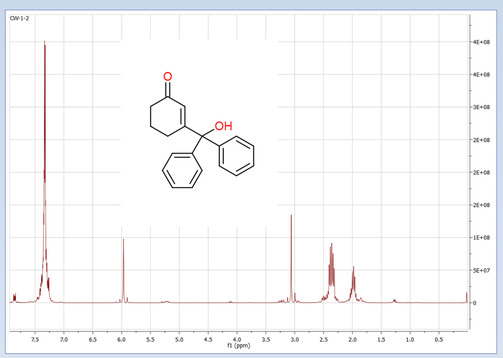


Figure 2. Thin-layer chromatography done to reveal polarity of product.

^{1}H and ^{13}C NMR studies (control):



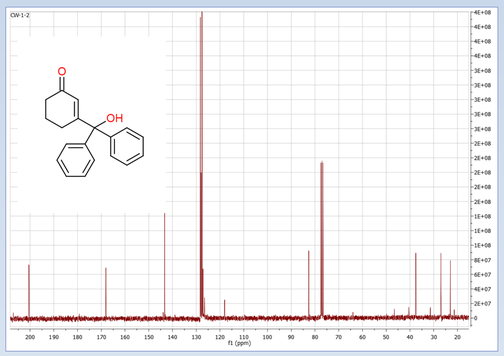


Figure 3a. and 3b. NMR studies of product after benzophenone and LDA mixture. Left is ^{1}H and right is ^{13}C scan.

Conclusion

Discussion:

- The preparation of ring C of escobarine B took 11 steps to make. A key intermediate in the synthesis required six steps.
- A one-pot procedure developed by Katritzky was tested. The control group experiment was successful (using benzophenone).
- If the one-pot procedure is successful, only one step will be required to prepare the key intermediate.
- Replacement of benzophenone for paraformaldehyde proved successful in the one-pot procedure.

Future pursuits:

- Complete the synthesis of Escobarines A and B
- Test activity against MDR tuberculosis strains

Acknowledgements

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