Michael Onoufriou - Mar 23, 2022, 2:42 AM EET

Title: Synthesis of 4-ethylphenyl (1r,4r)-4-methylcyclohexane-1-carboxylate via esterification

Date: 15th of March 2022

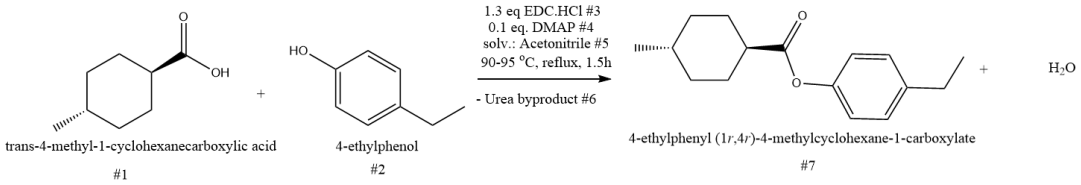
Abstract:

A simple esterification reaction was conducted by reacting trans-4-methyl-1-cyclohexanecarboxylic acid with excess 4-ethylphenol. This was done by heating the reactants under reflux in the presence of DMAP catalyst (4-(dimethylamino)pyridine (0.5 mmol)), EDC.HCl (1-ethyl-3-(3 dimethylaminopropyl) carbodiimide hydrochloride 6.5 mmol) and acetonitrile solvent. Monitoring of the reaction was done at regular intervals and then the mixture was processed via liquid-liquid extraction, addition of drying agent and then gravity filtration to isolate the organic solution. The solvent was removed with a rotary evaporator and a pure sample of the ester product was used for IR and 1H-NMR analysis. This process provided a straightforward synthesis route for obtaining 4-ethylphenyl (1r,4r)-4-methylcyclohexane-1-carboxylate.

Objectives:

The main objectives of the process were to apply basic laboratory technical skills such as thin layer chromatography, heating under reflux, aqueous/organic work-up and gravity filtration in order to isolate a pure product and demonstrate the importance of these processes. Additionally, product analysis via IR spectroscopy and 1H-NMR was provided as an opportunity to apply chemistry and spectroscopy knowledge in a real laboratory environment.

Reaction Scheme:



Urea byproduct = 1-(3-(diethylamino)propyl)3-ethylurea

Detailed Experimental Procedure:

Assembly of reflux reaction and monitoring:

- A 100 mL round-bottomed flask was set up with a magnetic stirrer
- 25 mL of Acetonitrile solvent was added
- ~0.06 g (0.5 mmol) of DMAP was added
- 1.25 g (6.5 mmol) of EDC.HCl was added
- ~0.78 g (5.5 mmol) of trans-4-methyl-1-cyclohexanecarboxylic acid was transferred with 2 mL of acetonitrile for washings
- ~0.61 g (5.0 mmol) of 4-ethylphenol was transferred with 2 mL of acetonitrile for washings
- Reflux apparatus was set up with the heating mantle initially at 90 **°C** with gradual increase of the temperature to 95 **°C** in the 1.5 h period of the process.
- TLC 20 ethyl acetate:80 hexane was carried out every 20 min to monitor the reaction
- TLC was 4 cm, phenol travelled 2.5 cm and rm 3.5 cm with c. Acid at the start

Product isolation:

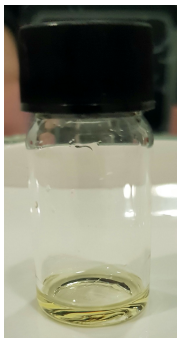
- Isolation of the product was carried out by liquid-liquid extraction
- After the reflux, the reaction mixture was allowed to cool to room temperature

- 20 mL of hexane was added to the reaction mixture
- The mixture was then transferred to a 100 mL separatory funnel
- The organic layer was washed 2x with 20 mL 1M HCl solution
- The aqueous layer was collected in a 500 mL conical flask labelled appropriately
- The organic layer was then washed 2x with 20 mL of 10 wt% $NaHCO_3$ solution (2x 20 mL) releasing any CO_2 gas evolved to relieve pressure
- The organic layer was then washed with 20 mL of water and then 2x with 20 mL of saturated aqueous sodium chloride (2x 20 mL)
- The organic layer was then transferred to a 100 mL conical flask along with anhydrous $MgSO_4$ drying agent
- Additional $MgSO_4$ was added to ensure the mixture is dry
- Gravity filtration was then carried out with a pre-weighed (20,92g difference) 100 mL round-bottomed flask
- 2x 10 mL of hexane were used to rinse the $MgSO_4$ solids left on the paper filter
- The flask containing the solution was then transferred to a rotary evaporator to remove the solvent
- The pre-weighed flask was re-weighed to find ~0.73 g of our product was isolated
- The product is a Yellow liquid 0.73 g ⇒ 59.3% yield
- Finally, the pure product was then transferred to a pre-weighed vial

Product Analysis:

- The product was analysed with IR spectroscopy and 1H-NMR.

Product Picture:

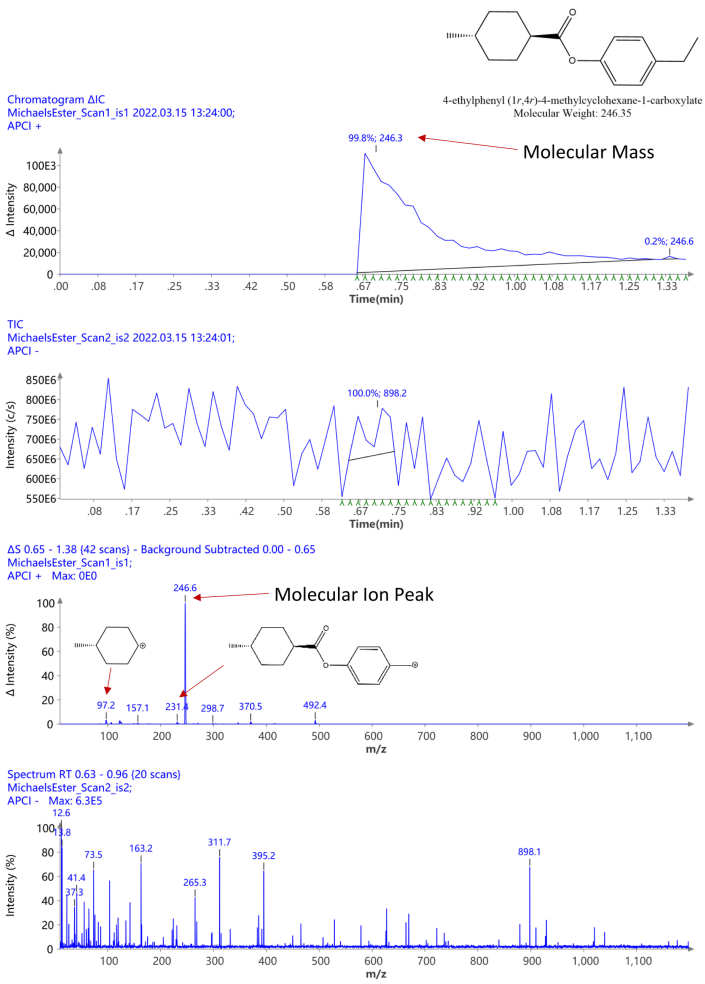


Data Recorded:

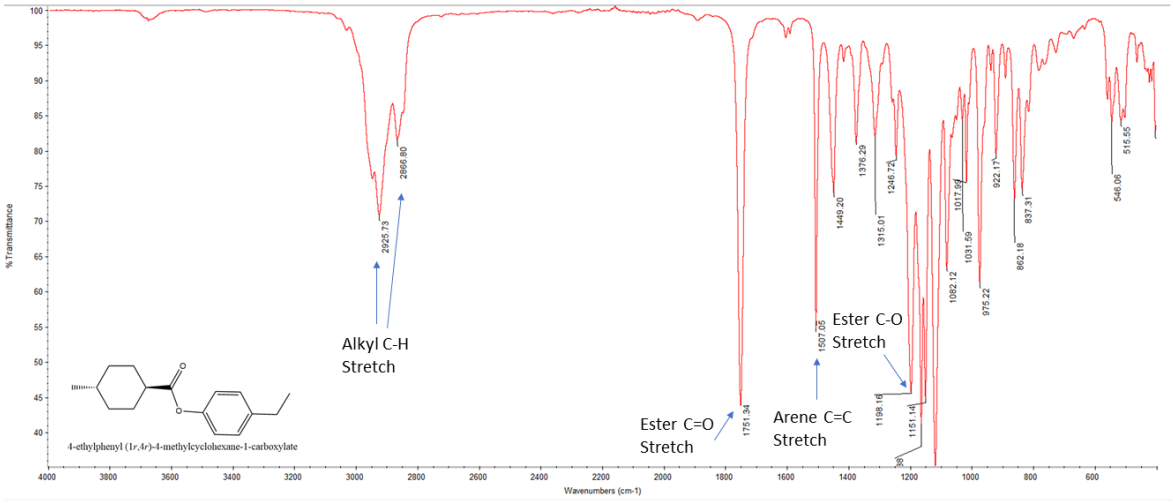
- Volume of acetonitrile solvent for reflux: 25 mL
- Mass of DMAP: 0.06 g (0.5 mmol)
- Mass of EDC.HCl: 1.25 g (6.5 mmol)
- Mass of trans-4-methyl-1-cyclohexanecarboxylic acid: 0.78 g (5.5 mmol) ~2 mL of acetonitrile for washings
- Mass of 4-ethylphenol: 0.61 g (5.0 mmol) with ~2 mL of acetonitrile for washings
- Reflux initial temperature: 90 **°C**
- Reflux final temperature: 95 **°C**
- Reflux period: 90 min
- TLC intervals: every 20 min
- TLC Eluent used: 20:80 (Ethyl Acetate:Hexane)
- Volume of Hexane for Extraction: 20 mL
- Volume of 1M HCl solution: 2x of 20 mL
- Volume of 10 wt% $NaHCO_3$ solution: 2x of 20 mL
- Volume of water washing: 20 mL of water
- Volume of sat. aq. NaCl: 2x of 20 mL
- Volume of Hexane for gravity filt. rinsings: 20 mL
- Mass of product: 0.73 g
- Yield: 59.3% (2.96 mmol)
- Description of isolated product: (colour, physical condition of product): Oily yellow liquid

Product Analysis:

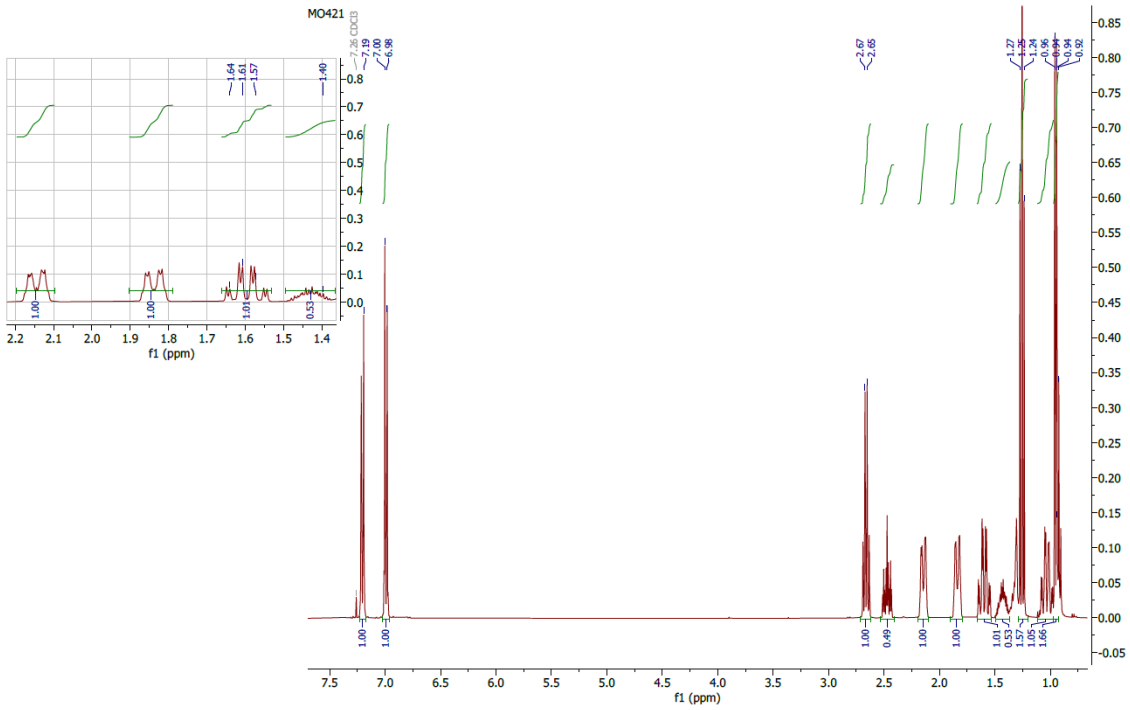
Mass Spectrum:



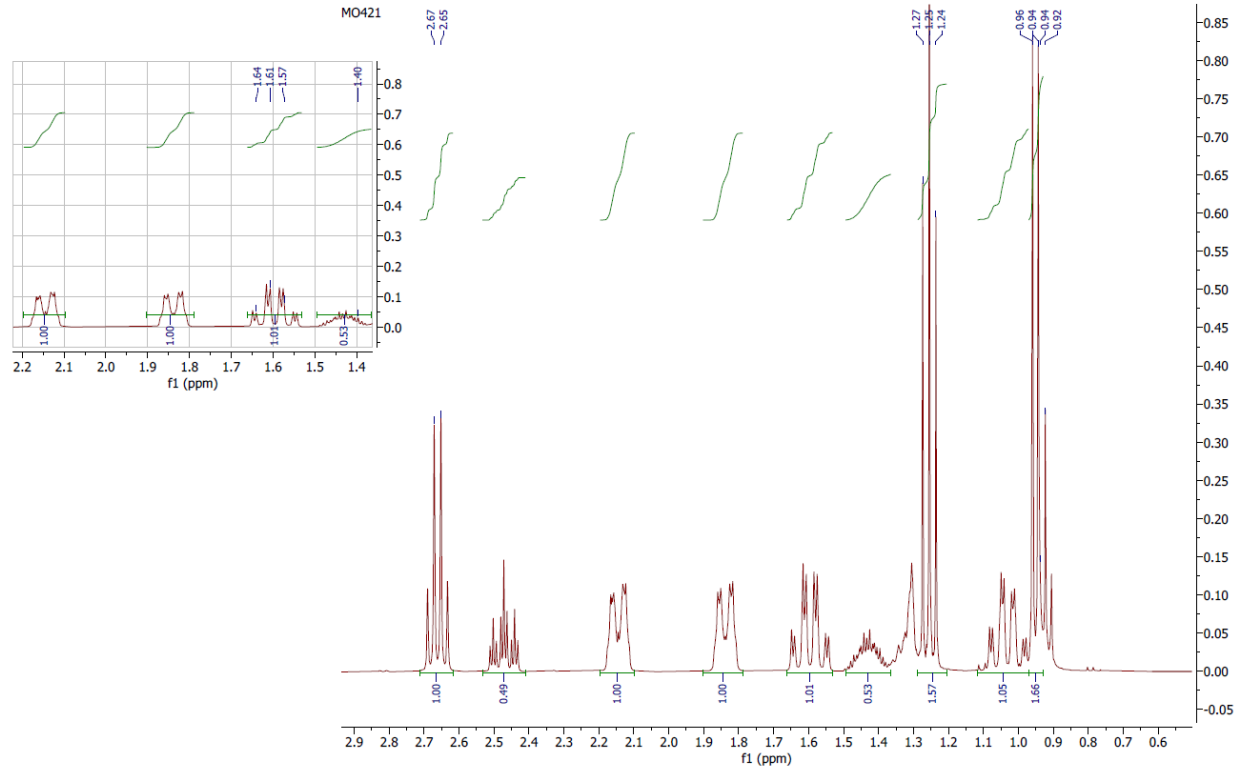
IR Spectrum:

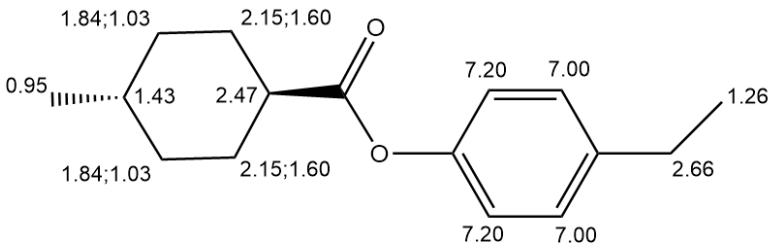


1H-NMR Spectrum:



Zoomed in on the Aliphatic Region:





δ/ppm	Integration	Multiplicity
0.95	1.5 ⇒ 3 H atoms	Doublet
1.03	1 ⇒ 2 H atoms	Quartet of Doublets
1.26	1.5 ⇒ 3 H atoms	Doublet
1.43	0.5 ⇒ 1 H atom	Multiplet
1.60	1 ⇒ 2 H atoms	Quartet of Doublets
1.84	1 ⇒ 2 H atoms	Doublet of Doublets
2.15	1 ⇒ 2 H atoms	Doublet of Doublets
2.47	0.5 ⇒ 1 H atom	Triplet of triplets
2.66	1 ⇒ 2 H atoms	Quartet
7.00	1 ⇒ 2 H atoms	Doublet
7.20	1 ⇒ 2 H atoms	Doublet

Experimental (synopsis) :

Trans-4-methyl-1-cyclohexanecarboxylic acid (0.78 g, 5.5 mmol) and 4-ethylphenol (0.61 g, 5.0 mmol) were dissolved in 29 mL acetonitrile along with DMAP catalyst (0.06 g, 0.5 mmol) and EDC.HCl (1.25 g, 6.5 mmol) and then refluxed for 90 min at 90-95 **°C**. TLC was carried out every 20 min with 80:20 Hexane:Ethyl Acetate eluent mixture. Hexane (20 mL) was then added to the reaction mixture which was then extraced after washing with 1M HCl (2x 20 mL), 10%wt NaHCO3 (2x 20 mL), water (1x 20 mL) and saturated NaCl solution (2x 20 mL). The organic layer was then dried with anhydrous MgSO4 (15.0 g) and was then filtered. The hexane was then evaporated off by using a rotary evaporator and the product was isolated which was an oily yellow liquid. Yield = 0.73 g, 3.0 mmol, 59.3%, Mass Spectrum: M^+ peak: 246.3 m/z, IR (ATR, neat) vmax/cm-1 1198 (s, CO), 1751 (s, CO), 1H NMR (400 MHz, CHLOROFORM-*D*) δ 7.20 (d, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.53-2.41 (tt, 1H), 2.19-2.09 (dd, 2H), 1.90-1.78 (dd, *J* = 3.6 Hz, 1H), 1.49-1.37 (m, 1H), 1.26 (d, *J* = 7.6 Hz, 3H), 1.09-0.97 (qd, 2H), 0.95 (d, 3H).

Conclusion:

The experiment was successful. The intended learning outcomes (learning about thin-layer chromatography, heating under reflux, and other basic chemistry laboratory techniques) were achieved.

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