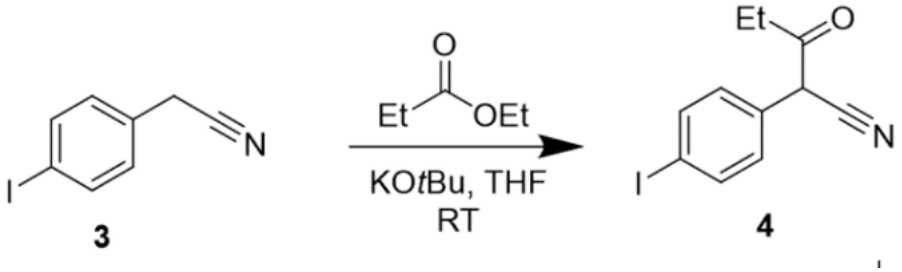
Title: Synthesis of a *2-(4-iodophenyl)-3-oxopentanenitrile*

- BBG-2020-7

Date: 04/12/2020
Experimentalist(s): Dr Terrett, Maxine Wu
Purpose: In this experiment, we tried to synthesis the first part of the three step synthesis of the 4-iodo pyrimethamine. The hypothesis is that the *2-(4-iodophenyl)-3-oxopentanenitrile* can be synthesised. The rationale behind conducting this experiment is to optimise yield and conduct biological testing on 4-iodo pyrimethamine, building on Kai Wong's synthesis from last year.

Reaction Scheme:



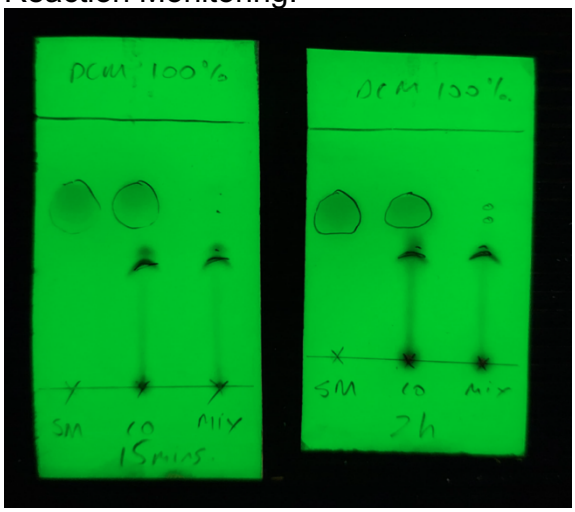
Reagent Table:

Chemical	4-iodophenylacetonitrile	Ethyl propionate	Potassium tert-butoxide
Hazards	Irritant	Irritant, toxic if ingested	Flammable solid, keep away from water, corrosive and irritant in contact with skin
Equivalents	1	1.05	2
Molecular weight	243.04 g/mol	102.13 g/mol	112.21 g/mol
Mass	10.00 g	5.00 g	10.46 g
Density	-	0.89 g/mL	-
Volume	-	5.63 mL	-
Number of moles	0.0466 mol	0.0490 mol	0.0933 mol

Procedure and observations:
4-iodophenylacetonitrile (10.00 g, 0.046 mol, 1 equiv.), ethyl propionate (5.00 g, 0.049 mol, 1.05 equiv.) and potassium tert-butoxide (10.47 g, 0.093 mol, 2 equiv.) were combined in THF (100 mL) at room temperature, with stirring in a round bottom flask. The reaction mixture turned to a dark red and heated up rapidly. The reaction was sealed and stirred for 2 hours in a fume hood.
The reaction mixture was worked up by the addition of 1.0 M HCl (100 mL) to the reaction vessel. The acidified reaction mixture was transferred to a separating funnel and the aqueous layer was extracted with DCM (3 x 65 mL). The combined organic layer was washed with brine (100mL), dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(4-iodophenyl)-3-oxopentanenitrile (**4**) (12.699 g, 0.042 mol, 91%) as a reddish oil. TLC was conducted with 50:50 DCM : hexane

as the eluent. The crude 2-(4-iodophenyl)-3-oxopentanenitrile was used without purification in the second step of the synthesis.

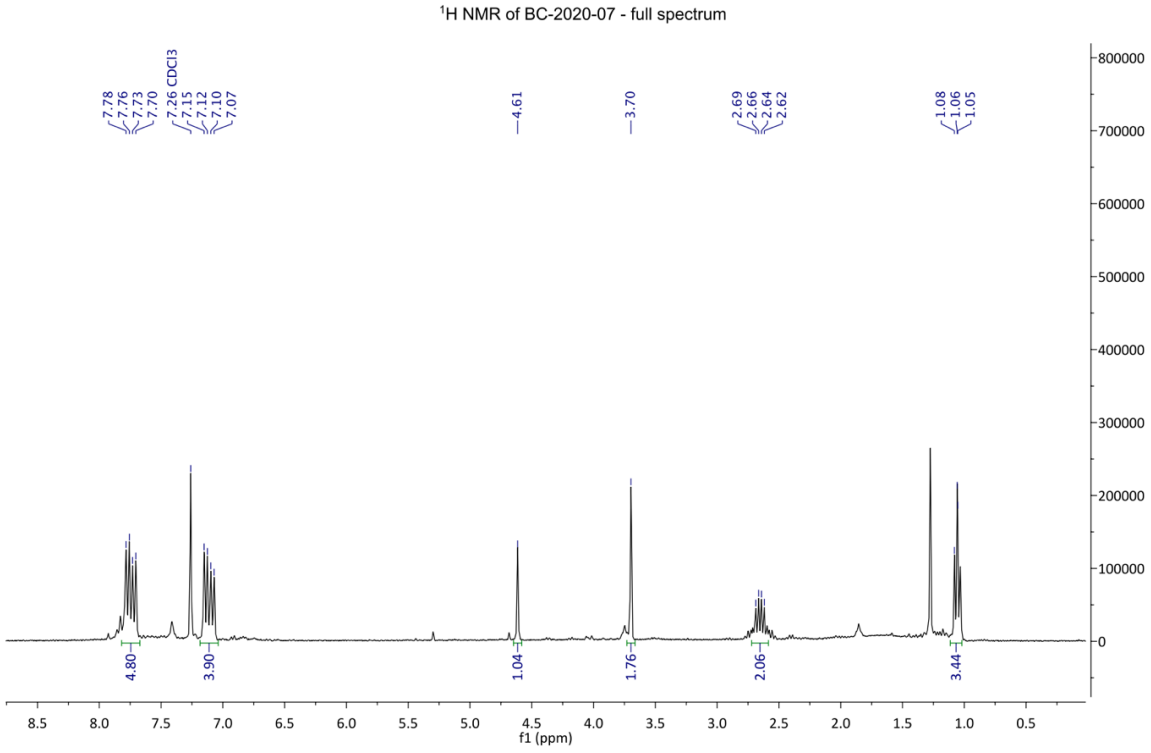
Reaction Monitoring:



Product table:

Description of product	Theoretical yield	Experimental yield	Percentage yield
Reddish oil, liquid	0.0467 x 299.10 g/mol= 13.948	12.699g	12.699g / 13.948 x 100 = 91 %

Analytical data:



Reference:

Open Source Malaria 2018, *Daraprim Synthesis*, viewed 20 February 2021, <https://malaria.ourexperiment.org/daraprim_synthesis>.