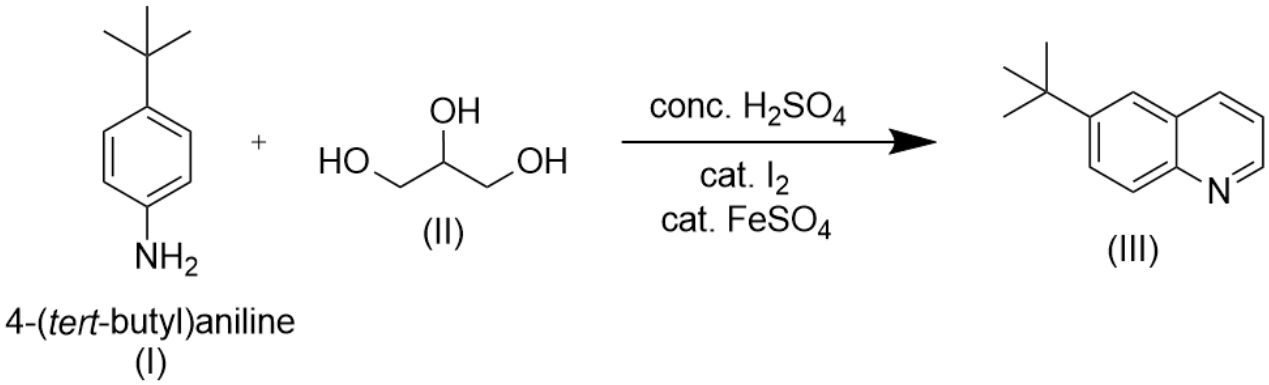
CHEM202 LABORATORY REPORT **Name:** Harry Stanley

Experiment 4 **Lab Day:** **Thursday** **Date:** **3/04/25**

Synthesis of a substituted quinoline

Abstract

In this experiment, a mono-substituted quinoline was synthesised via the Skraup synthesis by refluxing a substituted aniline with glycerol under strongly acidic and oxidizing conditions (conc. H_2SO_4, I_2, $FeSO_4$). Glycerol dehydrated to form acrolein, followed by coupling of the aniline with the acrolein to produce a quinoline ring system. After 90 minutes of reflux at 150^oC the reaction mixture was then neutralized and worked up by extraction, drying and removing solvent. The product was then analysed using ^1H NMR, including COSY and NOESY data which allowed for precise assignment of proton signal and confirmation of the unknown starting aniline.



4-(*tert*-butyl)aniline (I) (II) (III)

Experimental

The experiment was performed as detailed in the CHEM202 laboratory manual (p29), without modification. The accurate masses used of the reagents are detailed below.

Substance	Formula	M_r	mass (g)	amount (mmol)
4-(tert-butyl)aniline	$C_{10}H_{15}N$	149.23	0.863	5.78
Glycerol	$C_3H_8O_3$	92.09	3.09	33.55

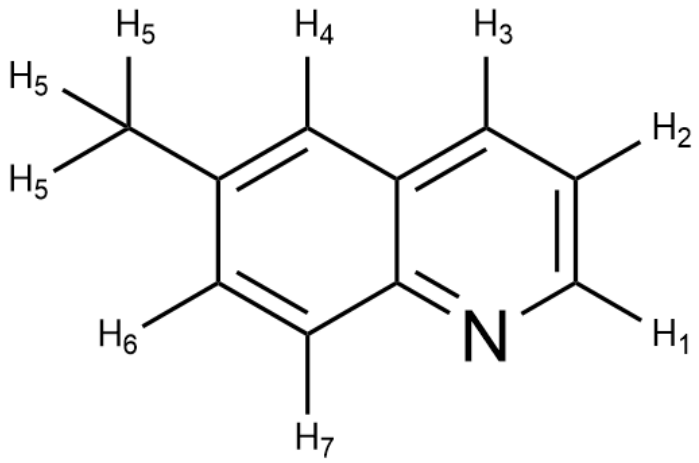
During the reaction acid vapours were minimised by maintaining a proper reflux under the fume hood. After the reaction was completed the acid solution containing the product was neutralised using 5M NaOH until it tested basic on litmus paper. The celite used to gravity filter the solution was disposed of in the celite waste container. After washing of the solution, the aqueous layer was disposed of down the fume hood sink with excess water, the organic extract was dried using anhydrous $MgSO_4$ which was filtered of and disposed of down the fume hood sink with excess water. Diethyl ether was distilled of from the product using the rotary evaporator.

Results and calculations

Percentage yield calculation

The limiting reagent in this reaction was (**4-(tert-butyl)aniline**).

∴ n (product) expected	=	0.00578	mol		
M (product)	=	185.270	g mol^{-1}		
Theoretical yield	=	N	x	M	
	=	0.00578	mol x	185.270	g mol^{-1}
	=	1.071	g		
Actual yield	=	0.192	g		
∴ Percentage yield	=	$\frac{0.192}{1.071} \times 100$			
	=	17.92	%		



[1]H NMR (500 MHz, $CDCl_3$)

δ/pm	Integration	multiplicity	J / Hz	COSY shows coupling to	Assignment
8.85	1H	dd	$J_{1,2}$ 7.7, $J_{1,3}$ 1.7	H_2	H_1
8.12	1H	d	$J_{3,2}$ 8.2	H_2	H_3
8.05	1H	d	$J_{7,6}$ 8.9	H_6	H_7
7.81	1H	dd	$J_{6,7}$ 8.9, $J_{6,4}$ 2.2	H_4, H_7	H_6
7.72	1H	d	$J_{4,6}$ 2.2	H_6	H_4
7.36	1H	dd	$J_{2,3}$ 8.2, $J_{2,1}$ 4.2	H_1, H_3	H_2
1.43	12H	s	~	~	H_5

ESI-MS

m/z	[Assignment]^{charge}
171.09	$[C_{13}H_{16}N - CH_3]^+$
186.12	$[C_{13}H_{16}N]^-$
187.13	$[C_{13}H_{16}N + H]^+$

Discussion

To assign the proton resonances of our substituted quinoline we began by assigning the chemical shift and coupling constants of the H-2, H-3 and H-4 pyridine protons and the four benzene protons in unsubstituted quinoline. We then compared these with the provided COSY/NOESY spectra of the product derived from our unknown aniline and matched theses to the ^{1}H NMR spectrum of our final product. The most downfield signal at 8.85 ppm (dd, J = 7.7, 1.7 Hz) was assigned to H_1 the proton adjacent to ring nitrogen as the electronegativity of nitrogen shift the signal downfield. The 7.36 ppm (dd, J = 8.2, 4.2 Hz) was assigned to H_2 as ortho-coupling (6-10 Hz) with H_1 was observed on the COSY and NOESY spectra, additionally this allowed us to identify the signal at 8.12 ppm (d, J = 8.2 Hz) as H_3 ortho-coupling with H_2 was observed.

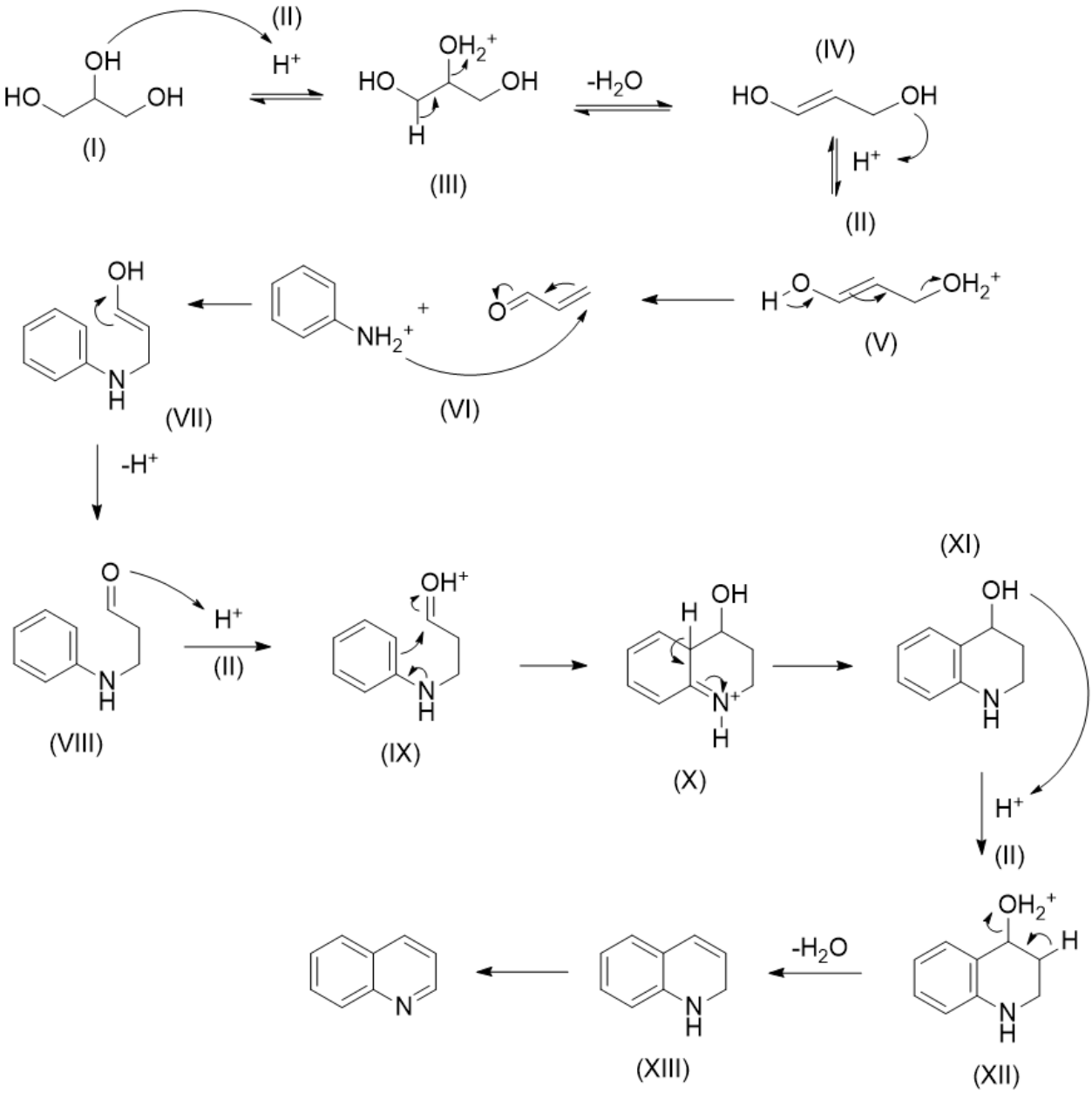
On the benzene ring the doublet of doublets at 7.81 ppm (J = 8.9, 2.2 Hz) was assigned to H_6 (ortho-coupled to H_7, meta coupled to H_4); the doublet at 8.05 ppm (J = 8.9 Hz) to H_7; and the doublet at 7.72 ppm (J = 2.2 Hz) to H4. The singlet at 1.43 ppm with an integration of 12 H was characteristic of a tert-butyl group (H_5), all of these assignments are confirmed by the COSY cross-peaks. Additionally, the NOESY spectrum shows cross-peaks between the tert-butyl protons (1.43 ppm) and the aromatic protons at 7.73 ppm (H_4) and 7.81 ppm (H_6) confirming the placing of the substituent between those two protons.

The ESI-MS of the product shows a protonated molecular ion at m/z 187.13 ($[C_{13}H_{16}N + H]^+$) and a fragment at 171.09 ($[M\text{-}CH_3]^+$) consistent with the lost of a methyl from the tert-butyl group. These peaks help confirm the molecular weight and presence of tert-butyl group, mass spectroscopy can't confirm the positional isomers of the molecule. Regioselective assignment relied on 2D NMR correlations.

This reaction starts with the acid-catalysed dehydration of glycerol to form acrolein. Under concentrated sulfuric acid glycerol undergoes protonation at the secondary hydroxyl group (II). The resulting oxonium ion readily loses a water molecule, generating a secondary carbocation at C-2 (III). This carbocation is stabilized through β-elimination, abstracting a proton from an adjacent carbon forming a double bond and forming a protonated enol (IV). Tautomerisation via proton transfer furnishes the neutral acrolein (V), which then acts the electrophile in the subsequent condensation.

In the next step, acrolein engages in a nucleophilic addition with aniline. Protonation of acrolein's double bond generates a resonance stabilised β-carbocation, creating a electrophilic centre that can be attacked by the nucleophilic nitrogen of aniline (VI). This step forms an aldehyde intermediate. Deprotonation return the reaction medium to neutrality allowing for cyclisation (VII). The imine that was formed undergoes further activation; the aldehyde is functionally protonated (VIII) increasing it electrophilic nature and allowing for intramolecular cyclisation. The ortho position of the aniline ring attacks the activated carbonyl carbon (IX) closing the quinoline ring and producing an arenium intermediate. Deprotonation restores aromaticity (X), yielding a protonated dihydroquinoline alcohol. Dehydration (XII) occurs generating the 1,2-dihydroquinoline system

Finally the 1,2-dihydroquinoline is oxidized to achieve complete aromatisation, delivering the substituted quinoline product. Although the full mechanisms for this oxidisation are not detailed, it constitutes the finally conversion necessary for creation of the aromatic quinoline ring system.


(II)
OH
HO
OH
H+
(I)
OH2+
HO
OH
H
(III)
-H2O
(IV)
HO
OH
H+
(II)
OH
N
H
(VII)
NH2+
+
O
(VI)
H
O
OH2+
(V)
-H+
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(II)
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(IX)
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(XI)
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(XIII)
N