Synthesis of a substituted quinoline

Abstract

A Grignard reagent was prepared by refluxing benzyl chloride(I) with magnesium turning in dry ethyl ether under anhydrous conditions. After initiation with iodine, benzylmagnesium chloride (II) was formed and reacted pentan-3-one (III) to give a tertiary alcohol 3 benzylpentan-3-ol (IV). The crude alcohol was purified by vacuum distillation (b.p. 110 ºC, 40 mbdr) to yield 4.683 g of (IV) (39.7 % yield). IR spectroscopy showed complete disappearance of the carbonyl band (1712 cm^{-1}) and the appearance of a broad O-H stretch showed at 3425 cm^{-1}. Full ^{1}H and ^{13}C NMR characterisation (including COSY, HECTOR, DEPT) allowed unambiguous assignment of all resonance, confirming the structure of (IV)

Dehydration of (IV) was completed by reacting our tertiary alcohol with orthophosphoric acid in a microwave reactor for 15 minutes to furnish a mixture of three alkenes in a combined yield of 50 % (0.7 g). Analysis of the ^{1}H NMR spectrum (integrals of olefinic vs benzylic signals) have a product ration of 1:1.10:1.03. NOESY experiment revealed key through-space cross-peaks that enabled assignment of E/Z geometry of the olefinic protons in each isomer. The observed chemical shift agreed with predicted values.
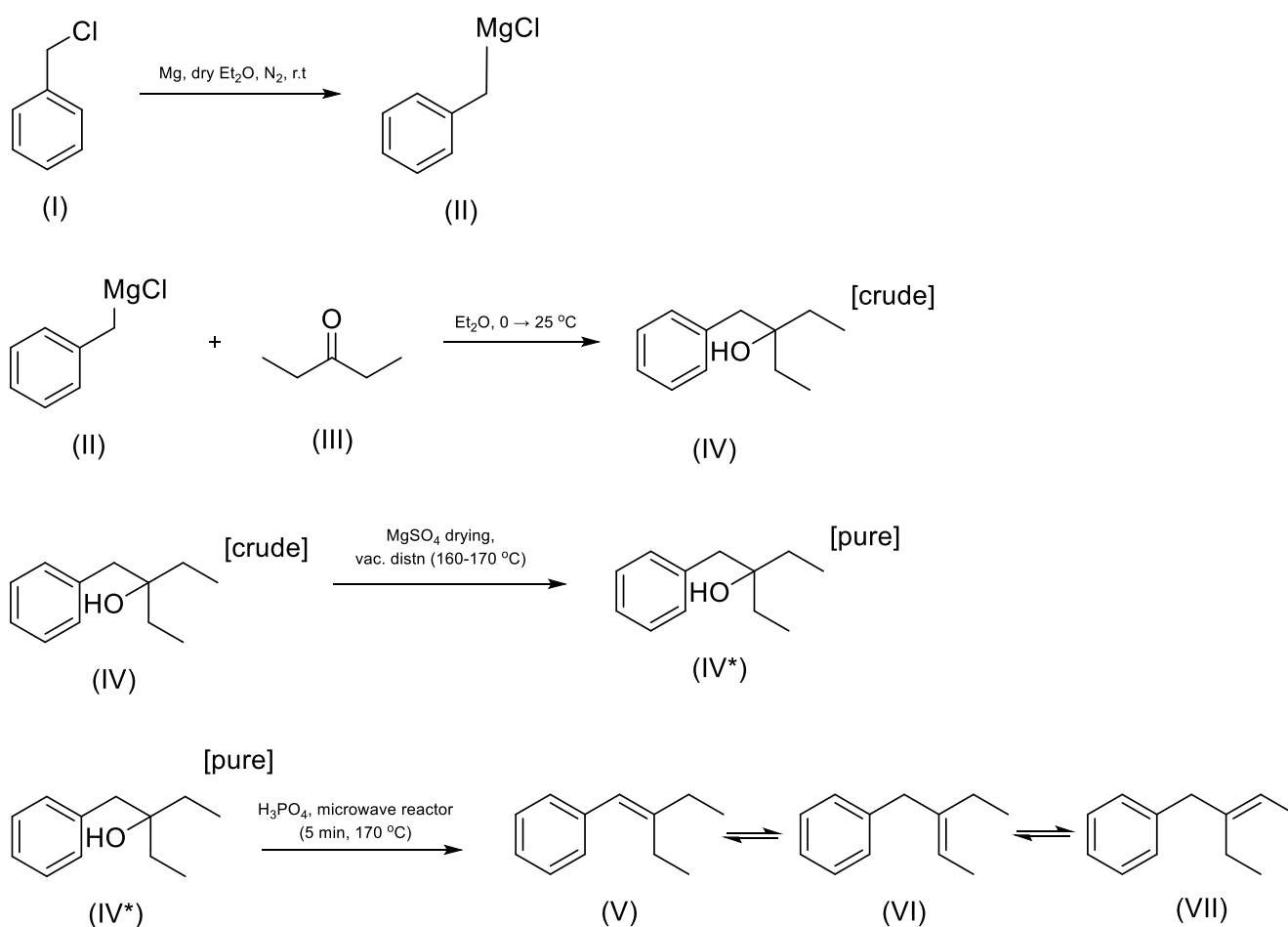
Experimental

The experiment was performed as detailed in the CHEM202 laboratory manual (p33), without modification. The accurate masses used of the reagents are detailed below.

Substance	Formula	M_r	mass (g)	amount (mmol)
Magnesium turnings	Mg	24.305	2.521	103.72
Benzyl chloride	$PhCH_2Cl$	126.58	12.65	99.94
Pentan-3-one	$C_5H_{10}O$	86.1	5.70	66.20
Orthophosphoric acid	H_3PO_4	97.994	3.79	43.17
3-benzylpentan-ol	$C_{12}H_{18}O$	174.14	1.512`	8.68

All reactions were carried out in a fume-hood to contain ether and acid vapours. After the Grignard reaction the mixture was quenched by slow addition of ice-cold saturated NH_4Cl, the aqueous layer was separated and washed down the fume-hood sink with excess water. The organic layer was dried over anhydrous $MgSO_4$, the drying agent was filtered off and washed into the sink with water; diethyl ether was removed on the rotary evaporator. The final extracts were dried, filtered and stripped of solvent by rotavap. Contaminated waste when in the contaminated waste bin.

Results and calculations

Reaction 1 percentage yield calculation:

The limiting reagent in this reaction was (Pentan-3-one)

$\therefore$ n (product) expected $=$ 0.0662 mol

M (product) $=$ 178.14 g mol^{-1}

Theoretical yield $=$ N x M

$=$ 0.0662 mol x 178.14 g mol^{-1}

$=$ 11.792 g

Actual yield $=$ 4.683 g

$\therefore$ Percentage yield $= \dfrac{4.683}{11.792} \times 100$

$=$ 39.7 %

Reaction 2 percentage yield calculation:

The limiting reagent in this reaction was (3-benzylpentan-ol)

∴ n (product) expected   =   0.00868 mol

M (product)   =   160.13 g mol^{-1}

Theoretical yield   =   N   x   M

    =   0.00868 mol x   160.13   g mol^{-1}

    =   1.39 g

Actual yield   =   g

∴ Percentage yield   = $\dfrac{0.7}{1.39} \times 100$

    =   50.3 %

IR spectrum of ketone($C_5H_{10}O$*)*

ν / cm^{-1}	intensity	appearance	assignment	inference
2997	m	sh	C-H stretch	alkyl C-H
2940	m	sh	C-H stretch	alkyl C-H
1712	s	sh	C=O stretch	non-conjugated ketone
1376	m	sh	C-H bend	methyl C-H
1357	m	sh	C-H bend	methyl C-H

IR spectrum of intermediate product($C_{12}H_{18}O$*)*

ν / cm^{-1}	intensity	appearance	assignment	inference
3425	w	br	O-H stretch	alcohol
3028	w	sh	C-H stretch	aromatic C-H
2966	w	sh	C-H stretch	alkyl C-H
2938	w	slightly br	C-H stretch	alkyl C-H
1602	w	sh	C=C stretch	aromatic skeletal stretch
1495	w	sh	C=C stretch	aromatic skeletal stretch
1453	w	sh	C-H bend	sp^3 hybridised carbon
1380	w	slightly br	C-H bend	methyl C-H
756	w	sh	C-H deformation	monosubstituted benzene derivative
696	s	sh	C-H deformation	monosubstituted benzene derivative

IR spectrum of final product($C_{12}H_{16}$)

ν / cm⁻¹	intensity	appearance	assignment	inference
3061	w	sh	C-H stretch	alkene or benzene derivative
3026	w	sh	C-H stretch	alkene or benzene derivative
2963	w	sh	C-H stretch	alkyl C-H
2931	w	slightly br	C-H stretch	alkyl C-H
1648	w	sh	C=C stretch	C=C conjugated with aromatic ring
1601	w	sh	C=C stretch	Aroma tic skeletal stretch
1493	w	sh	C=C stretch	aromatic skeletal stretch
1452	w	sh	C-H bend	sp^3 hybridised carbon
839	w	sh	C-H deformation	trisubstituted alkene
722	s	sh	C-H deformation	monosubstituted benzene derivative
695	s	sh	C-H deformation	monosubstituted benzene derivative
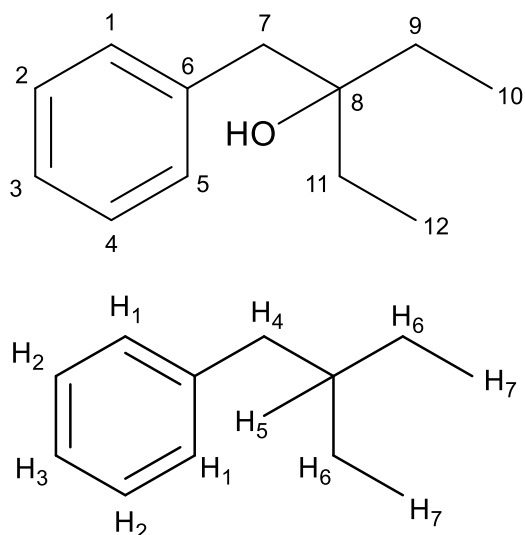
13C NMR Intermediate product (125 MHz, CDCl3)

d/ppm	HETCOR shows coupling to	Assignment
130.6		C-1, C-5
128.2	H1	C-2, C-4
126.4	H3	C-3
74.6	~	C-8
44.8	H4	C-7
30.5	H6	C-9, C-11
8.0	H7	C-10, C-12

1H NMR Intermediate product (500 MHz, CDCl3)

d/ppm	Integration	multiplicity	J/Hz	Assignment
7.28	2	m	~	H2, H3
7.23	3	m	~	H1
2.75	2	s	~	H4
1.46	4	qd	H7	H6
0.93	6	t	H6	H7
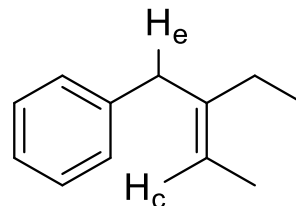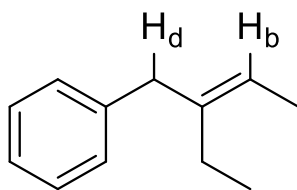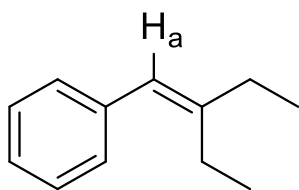
^{1}H NMR Final product (500 MHz, CDCl$_3$)

d/ppm	Integration	multiplicity	J/Hz	NOESY shows coupling to	Assignment
6.28	1.00	s	~	~	H$_a$
5.45	1.10	q	6.7	~	H$_b$
5.27	1.03	q	6.7	H$_d$	H$_c$
3.45	2.25	s	~	H$_c$	H$_d$
3.34	2.15	s	~	~	H$_e$

The olefinic region (6.3-5.0 ppm) of the ^{1}H-NMr spectrum contained three well-seperated signals that each integrated for a single proton. The most down-field resonance, a singlet at 6.28 ppm was assigned to H$_a$, the vinylic proton of the conjugated product, because conjugation with the aromatic ring is expected to deshield the proton by 0.7 ppm relative to a simple internal alkene. Two further quartets, at 5.45 and 5.27 ppm (J = 6.7 Hz) were attributed to the vinylic protons of the two possible internal alkenes. The quartet at 5.45 ppm showed no through-space correlation to any benzylic signal in the NOESY spectrum and was therefore assign to H$_c$, the E-isomer. The quartet at 5.27 ppm displayed a clear through-space correlation to a benzylic proton at 3.45 ppm, placing the olefinic and benzylic protons on the same side of the double bond and confirming it as H$_b$ of the Z-isomer.

Only the two internal alkene retain the benzylic CH$_2$ group, and two singlets at 3.45 ppm (H$_d$) and 3.34 ppm (H$_e$) together integrated for 4.40 H. the NOESY cross-peak between the 3.45 ppm and 5.27 ppm quartet linked these signal to the Z-alkene, leaving the singlet at 3.45 ppm as the benzylic CH$_2$ of the E-isomer.

Discussion

In this experiment we first converted pentant-3-one into a tertiary alcohol with benzylmagnesium chloride, then dehydrated that alcohol to a mixture of three alkenes. The IR spectra recorded at each step showed the expected changes in functional groups. The starting ketone exhibits a strong, sharp C=O stretch at 1712 cm^{-1} with no O-H absorption. After the Grignard addition and aqueous NH$_4$Cl work-up, this carbonyl band has disappeared and is replaced by a broad O-H stretch around 3400 cm^{-1}, confirming formation of the tertiary alcohol. In the final product the O-H band is gone, while a medium C=C stretch at 1648 cm^{-1} appears, clearly indicating that dehydration to alkenes has occurred. Throughout the aromatic C=C bands at 1600/1500 cm^{-1} and the C-H deformations in the fingerprint region remain unchanged, showing that the benzene ring was unaffected

Mechanistically, the first step required the generation benzylmagnesium chloride by insertion of magnesium into the C-Cl bond of benzyl chloride in dry diethyl ether (I). This organomagnesium reagent then attacks the electrophile carbonyl of pentan-3-one (II), forming a magnesium alkoxide intermediate. On addition of saturated NH$_4$Cl this alkoxide is protonated to give the tertiary alcohol (III). No rearrangements occur because the benzyl carbanion is resonance stabilized and adds cleanly to the ketone.

The second step is an acid-catalyzed dehydration of the isolated tertiary alcohol. Protonation of the hydroxyl group (IV) by orthophosphoric acid converts -OH into a good leaving group, and loss of water yields a tertiary benzylic carbocation. From this carbocation, β-elimination (V) of a proton can occur either at the benzylic potion, producing the conjugated double bond, or at one the adjacent methyl groups producing the non-conjugated internal alkene. Since elimination at the methyl can take place from either face of the planer carbocation, both E and Z stereoisomers of the internal alkene are formed. Although formation of the Conjugated alkene is thermodynamically favored, steric accessibility of the methyl protons makes internal elimination competitive, resulting in all three alkene in roughly equal proportions

(I)

(II) + (ketone) → (III) → work-up, sat. NH$_4$Cl →

(IV) + H—H$_2$SO$_4$ → (V) H$_2$PO$_4^-$ → + +

+ H$_2$PO$_4^-$

+ H$_2$PO$_4^-$