



CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF₂₅₄). Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh).

The ¹H- and ¹³C-NMR spectra were performed in deuterated chloroform (CDCl₃) with tetramethylsilane (TMS) as an internal reference on the Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ¹H and 100.54 MHz for ¹³C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents used for synthesis were purchased from Fluka chemical company or otherwise stated and were used without further purification.

2.3 Preparation of Brominating Agents

Ethyl tribromoacetate [5, 36]

One mL of concentrated H₂SO₄ was cautiously added to the mixture of Br₃CCO₂H 1 eq (40 mmol, 11.87 g) and EtOH 4.5 mL. The mixture was refluxed for 3-6 h and then poured into 100 mL of water in a separatory funnel. The upper layer of crude ester was removed and washed with 50 mL of water, saturated aqueous NaHCO₃ and water, respectively, and dried over anhydrous Na₂SO₄.

Ethyl tribromoacetate: colorless oil (82%). $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.40 (t, 3H, $J = 7.2$ Hz, CH_2CH_3) and 4.43 (q, 2H, $J = 7.2$ Hz, CH_2CH_3). $^{13}\text{C-NMR}$ (CDCl_3) δ (ppm): 13.7, 29.5, 65.7 and 162.1.

Hexabromoacetone [37]

Anhydrous NaOAc 7 g was mixed with 20 mL of glacial CH_3COOH . The reaction mixture was stirred and heated to 60 °C, acetone 1.4 mL was added and followed by dropwise addition of Br_2 5 mL over a 10 min period with stirring. The mixture was then heated to 95 °C for 2 h. After which it was cooled to RT and mixed with 100 mL of water to precipitate the desired product as white solid. After air drying, the pure product was obtained upon recrystallization from hexane.

Hexabromoacetone: white solid (60%), $^{13}\text{C-NMR}$ (CDCl_3) δ (ppm): 24.6 and 173.4.

2.4 General Procedure

2.4.1 Preparation of Alcohols

1-Phenylethanol [5]

The mixture of acetophenone (5.10 mmol, 0.61 g) and 95% EtOH 10 mL was added NaBH_4 (1.45 mmol, 0.20 g) by portion at least 5 min. Then the mixture was stirred for additional 20 min. After the reaction has completed (monitoring by TLC, hexane:EtOAc 3:1), the reaction was quenched by cautiously adding water 15 mL in an ice bath. 6M HCl was slowly added into the reaction until the reaction mixture became acidic. Finally, the reaction mixture was extracted with ether and dried over anhydrous NaSO_4 .

1-Phenylethanol: yellow oil (60%). $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.50 (d, 3H, $J = 6.4$ Hz, CHCH_3), 1.91 (s, 1H, CHOH), 4.90 (m, 1H, CHOH) and 7.26-7.40 (m, 5H). $^{13}\text{C-NMR}$ (CDCl_3) δ (ppm): 25.2, 70.4, 125.4, 127.5, 128.5 and 145.8.

Ethyl mandelate [5, 36]

One mL of concentrated H₂SO₄ was cautiously added to the mixture of mandelic acid (PhCH(OH)CO₂H) 1 eq (40 mmol, 6.09 g) and EtOH 4.5 mL. The mixture was refluxed for 3-6 h and then poured into 100 mL of water in a separatory funnel. The upper layer of crude ester was removed and washed with 50 mL of water, saturated aqueous NaHCO₃ and water, respectively, and dried over anhydrous Na₂SO₄.

Ethyl mandelate: colorless oil (37%). ¹H-NMR (CDCl₃) δ (ppm): 1.22 (t, 3H, *J* = 6.0 Hz, CH₂CH₃), 3.8 (s, 1H, CHOH), 4.21 (q, 2H, *J* = 9.0 Hz), 5.15 (s, 1H, CHOH) and 7.33-7.43 (m, 5H). ¹³C-NMR (CDCl₃) δ (ppm): 14.0, 62.2, 72.9, 126.5, 128.6, 138.4 and 173.7.

2.4.2 Optimum Conditions Study for the Conversion of Benzylic and Allylic Alcohols to Their Corresponding Chlorides

A stirred solution of alcohol 1 eq (0.25 mmol) and selected chlorinating agent 1.5 eq (0.375 mmol) in dry CH₂Cl₂ (0.5 mL) was successively added PPh₃ 1.5 eq (0.375 mmol) at RT (30 °C) under N₂ atmosphere. After 30 min, the reaction was quenched by solvent evaporation, and then the corresponding product was determined by ¹H-NMR on the crude mixture with toluene as an internal standard or purified by silica gel column chromatography (eluent: hexane).

Benzyl chloride: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 7.35 (m, 5H), 4.58 (s, 2H).

1-Phenyethyl chloride: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 1.88 (d, 3H, *J* = 7.2 Hz), 5.12 (m, 1H), 7.36 (m, 5H).

Furfuryl chloride: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 4.49 (s, 2H, CH₂Cl), 6.20-6.30 (m, 2H), 7.35-7.45 (m, 1H).

Desyl chloride: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 6.32 (s, 1H) and 7.33-7.99 (m, 10H).

Trans-cinnamyl chloride: colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 4.24 (d, 2H, $J = 7.0$ Hz), 6.29 (dt, 1H, $J = 15.9, 7.0$ Hz), 6.65 (d, 1H, $J = 15.9$ Hz), 7.26-7.41 (m, 5H).

1-Chloro-2-hexene: colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 0.90 (t, 3H, $J = 7.1$ Hz), 1.37 (m, 4H), 4.05 (d, 2H, $J = 7.1$ Hz), 5.62 (m, 1H), 5.79 (m, 1H).

Geranyl chloride: colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.71 (s, 3H), 2.05 (m, 4H), 4.05 (d, 2H, $J = 7.1$ Hz, CHCH_2Cl), 5.20 (m, 1H), 5.43 (m, 1H).

2.4.2.1 Effects of Chlorinating Agents

The synthesis of benzyl chloride and *trans*-cinnamyl chloride as two model compounds for benzylic and allylic alcohols, respectively were carried out using the reaction conditions described in the general procedure. Eleven different chlorinating agents: CCl_4 , CHCl_3 , trichloroethane (Cl_3CCH_3), hexachloroethane (Cl_3CCCl_3), 2,2,2-trichloroethanol ($\text{Cl}_3\text{CCH}_2\text{OH}$), trichloroacetonitrile (Cl_3CCN), hexachloro-2-propanone ($\text{Cl}_3\text{CCOCCl}_3$), trichloroacetic acid ($\text{Cl}_3\text{CCO}_2\text{H}$), ethyl trichloroacetate ($\text{Cl}_3\text{CCO}_2\text{Et}$), 2,2,2-trichloroethyl acetate ($\text{Cl}_3\text{CCH}_2\text{O}_2\text{CCH}_3$) and trichloroacetamide ($\text{Cl}_3\text{CCONH}_2$) were utilized.

2.4.2.2 Effects of PPh_3 and Chlorinating Agent Ratio

Various ratios of PPh_3 and chlorinating agent for the synthesis of benzyl chloride and *trans*-cinnamyl chloride utilizing the general procedure were varied (based on the alcohols 1 eq). After 30 min, the yield of chlorides in the crude mixture was quantified by $^1\text{H-NMR}$ with the addition of toluene as an internal standard. The selected chlorinating agent was $\text{Cl}_3\text{CCONH}_2$.

2.4.2.3 Effects of Reaction Time

The ratios of PPh_3 and $\text{Cl}_3\text{CCONH}_2$ for the synthesis of the chlorides were varied (based on alcohols 1 eq) as follows: 1:1, 1:1.5, 1:2, 1.5:1.5, 1.5:2, 2:2, 2:3, 2:4 and 2.5:2.5, respectively. Determine the yield of the chlorides by $^1\text{H-NMR}$ in the crude mixture with toluene as an internal standard. Furthermore, employing the

above-mentioned reaction conditions, the reaction was operated by altering reaction time at RT (30 °C) under N₂ atmosphere.

2.4.3 Optimum Conditions Study for the Conversion of Benzylic and Allylic Alcohols to Their Corresponding Bromides

A stirred solution of alcohol 1 eq (0.25 mmol) and selected brominating agent 1.5 eq (0.375 mmol) in dry CH₂Cl₂ (0.5 mL) was successively added PPh₃ 1.5 eq (0.375 mmol) at RT under N₂ atmosphere. After 30 min, the reaction was quenched by solvent evaporation, and then the quantification of the corresponding product was performed by ¹H-NMR on the crude mixture with toluene as an internal standard or purified by silica gel column chromatography (eluent: hexane).

Benzyl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 4.52 (s, 2H), 7.19–7.36 (m, 5H).

1-Phenyethyl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 2.06 (d, 3H, *J* = 7.0 Hz), 5.24 (q, 1H, *J* = 7.0 Hz), 7.31–7.49 (m, 5H).

Furfuryl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 4.41 (s, 2H), 5.88 (m, 1H), 6.88 (m, 1H) and 7.21 (d, 1H, *J* = 10.0 Hz).

Desyl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 6.45 (s, 1H), 7.30–8.15 (m, 10H)

Trans-cinnamyl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 3.80 (d, 2H, *J* = 7.1 Hz), 6.50 (t, 1H, *J* = 7.0 Hz), 7.10 (d, 2H, *J* = 7.0 Hz), 7.90 (d, 3H, *J* = 7.1 Hz), 8.01 (d, 1H, *J* = 7.0 Hz).

Geranyl bromide: colorless oil. ¹H-NMR (CDCl₃) δ (ppm): 1.60 (s, 3H, CHCH₃), 1.68 (s, 3H), 1.72 (s, 3H), 2.07 (m, 2H), 4.02 (d, 2H, *J* = 7.0 Hz, CH₂Cl), 5.07 (m, 1H), 5.53 (m, 1H).

2.4.3.1 Effects of Brominating Agents

The synthesis of benzyl bromide and *trans*-cinnamyl bromide were carried out using the reaction conditions described in the general procedure. Eight different brominating agents: CBr_4 , CHBr_3 , $\text{Br}_3\text{CCOCBr}_3$, $\text{Br}_3\text{CCO}_2\text{H}$, $\text{Br}_3\text{CCO}_2\text{Et}$, trichlorobromomethane (BrCCl_3), dibromoacetic acid (Br_2HCCOOH) and bromoethane (BrCH_2CH_3) were utilized.

2.4.3.2 Effects of PPh_3 and Brominating Agent Ratio

The ratios of PPh_3 and brominating agent for the synthesis of benzyl bromide and *trans*-cinnamyl bromide utilizing the general procedure were varied (based on the alcohols 1 eq). After 30 min, the yield of bromides in the crude mixture was determined by $^1\text{H-NMR}$ with the addition of toluene as an internal standard. Selected brominating agents were $\text{Br}_3\text{CCO}_2\text{Et}$ and $\text{Br}_3\text{CCOCBr}_3$.

2.4.3.3 Effects of Reaction Time

According to the general procedure, the reaction time for each brominating agent can procure using suitable ratios of PPh_3 and brominating agent as follows: 1.5:1 and 1.5:0.3 eq in the case of utilizing $\text{Br}_3\text{CCO}_2\text{Et}$ and $\text{Br}_3\text{CCOCBr}_3$, respectively. The time variations are as follows: 5, 15 and 30 min at RT under N_2 atmosphere. The bromide product in the crude mixture was quantified by $^1\text{H-NMR}$ with the addition of toluene as an internal standard.

2.5 Comparative Reactivity Study of Halogenation between Benzylic and Allylic Alcohols

The relative reactivity of $\text{PPh}_3/\text{Cl}_3\text{CCONH}_2$, $\text{PPh}_3/\text{Br}_3\text{CCO}_2\text{Et}$ and $\text{PPh}_3/\text{Br}_3\text{CCOCBr}_3$ with two alcohols was further studied by competing two selected alcohols in the same reaction vessel.

In case of $\text{PPh}_3/\text{Cl}_3\text{CCONH}_2$, a stirred solution of two selected alcohols (1 eq each) in dry CH_2Cl_2 (0.5 mL) were successively added PPh_3 (2 eq) and $\text{Cl}_3\text{CCONH}_2$ (2 eq).

In case of $\text{PPh}_3/\text{Br}_3\text{CCO}_2\text{Et}$ and $\text{PPh}_3/\text{Br}_3\text{CCOCBr}_3$, a stirred solution of two chosen alcohols (1 eq) in dry CH_2Cl_2 (0.5 mL) were added PPh_3 (1.5 eq) and $\text{Br}_3\text{CCO}_2\text{Et}$ (1.0 eq) or $\text{Br}_3\text{CCOCBr}_3$ (0.3 eq) under the same condition as the chlorination.