

CHAPTER 2

MATERIALS AND EXPERIMENTAL

DETAILS FOR SYNTHESIS

2. Experimental Details

2.1 Materials

All the reagents that been used in this study were reagent grade chemicals obtained from Aldrich, Fluka, Fischer Scientific, R & M Chemicals and Merck with the highest available purity, and used without further purification, unless otherwise stated. Stock solutions of varying concentration were prepared by dilution process. Concentration of HCl stock solution was determined by titration method with standardized NaOH, using phenolphthalein as indicator. The purities of some of the reagents used are show below:

- 4-nitrophenol (Sigma-Aldrich, 98%)
- 4-nitrophenylacetate (Fluka, > 99.0 %)
- Acetyl Chloride (Merck \geq 99 %)
- Acetone-D₆ (Merck \geq 99.8 %)
- Acetonitrile (Merck \geq 99 %; Fisher Scientific HPLC Grade)
- Benzophenone (Fluka, \geq 99.0 %)
- Benzylamine (Riedel-de-Haen)
- Benzylmethanamine (Fluka > 98 %)
- Borane-methyl Sulfide Complex (Aldrich)
- Chloroform (Merck)
- Chloroform-D₁ (Merck \geq 99.8 %)
- Diethyl Ether (Merck)
- Diethylamine (Merck, 99.0 %)
- Diethylamine hydrochloride (Fluka > 98 %)
- Dimethylamine hydrochloride (Fluka > 98 %)

- Ethyl Acetate (Mallinckrodt Chemicals, 99.5%)
- Ethylbenzylamine (Aldrich, 97 %)
- Hydrochloric Acid Fuming (R & M Chemicals, 37 %)
- Lithium Aluminum Hydride (Merck)
- Methyl Amine (Fluka > 98 %)
- Methylbenzylamine (Fluka > 98%)
- Phthalic Anhydride (Merck > 98 %)
- Sodium Bromide (Merck > 99.5 %)
- Sodium Hydroxide (Merck > 99.5 %)
- Sodium Rod (Merck, ≥ 99.0 %)
- Sodium sulphate anhydrous (Merck, proanalysis)
- Tetrahydrofuran (Fischer Scientific HPLC Grade)
- Triethylamine (Fischer Scientific, Analytical Reagent Grade)

2.2 General Procedures

The identification of isolated compounds was confirmed by means of melting points, IR and NMR spectra, GC-MS, UV-Vis and Elemental Analysis (C, H, and N). Reverse-Phase HPLC (RP-HPLC) was used for characterization of product from reaction of aminolysis and hydrolysis of **26**.

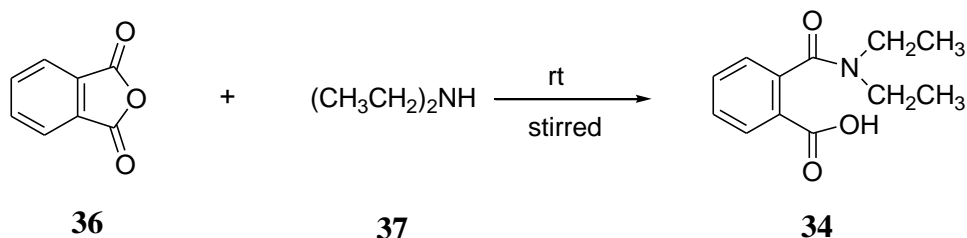
Melting points were determined using a Fargo melting Point Apparatus MP-1D. Infrared (IR) spectra were recorded using a Perkin-Elmer Spectrum RX 1 FTIR spectrometer. Infrared are measured in the range of $4000 - 600 \text{ cm}^{-1}$. All the NMR spectra were recorded on the JEOL JNM-LA 400 FT NMR spectrometer with

tetramethylsilane (TMS) as internal standard. CDCl_3 , Acetone- d_6 and DMSO were used depending on the solubility of the isolated compounds.

Characterization of the kinetic products determined using a SHIMADZU RP-HPLC with detection under UV-Vis detector at 254 nm. The mixture of Isopropanol HPLC Grade and double-distilled water in ratio (35 % : 65 % v/v and 20 % : 80 % v/v) were used as a mobile phase. The preparation of reaction mixture was carried out as same as preparation of reaction mixture for kinetic run. pH measurements were done with WITEG digital pH meter at room temperature. The solution of reaction mixtures were transferred using 50 μl syringes at different time. The experiments were carried out at different reaction time; depend on the class of buffer. The product fractions with different retention time were detected. The retention time of each product were compared with the retention time of the standards.

2.3 Experimental Details for Synthesis

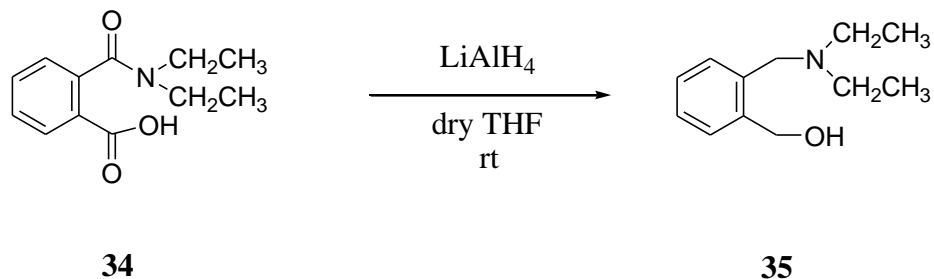
2.3.1 Synthesis of *N,N*-Diethylphthalamic Acid (**34**)^{1,2}



Scheme 2-1

Phthalic anhydride (**36**) (21.9 g, 0.1480 mol) was dissolved in 60 ml THF in 250 ml round bottom flask. *N,N*-Diethylamine (**37**) (15.2 ml, 0.1480 mol) was added to the solution of phthalic anhydride slowly. The reaction mixture was stirred vigorously at room temperature until white precipitates appeared. The reaction progress was checked by TLC (solvent CHCl_3 : EtOH 2:3). The resulting white precipitates were filtered through suction, washed with cold diethyl ether and dried under high vacuum pump to give white solid **34** (21.80 g, 66.6 %), mp. 162-163°C. δ_{H} (400 MHz, CDCl_3 , TMS) : 1.00 – 1.04 (t, $J = 8$, 3H, CH_2CH_3), 1.25 – 1.29 (t, $J = 8$, 3H, $-\text{CH}_2\text{CH}_3$), 3.08- 3.13 (q, $J = 4$, 2H, $-\text{CH}_2\text{CH}_3$), 3.58 (s, 2H, $-\text{CH}_2\text{CH}_3$), 6.71 (s, $-\text{COOH}$), 7.27 – 7.60 (m, 3H, ArH), 8.07 – 8.09 (d, $J = 8$, 1H, ArH), 6.71 (s, 1H, CO-OH) ; δ_{C} (100 MHz, CDCl_3 , TMS): 12.03, 13.44 (2CH_3), 38.85, 42.89 (2CH_2), 126.65, 128.53, 131.18, 132.63, 136.00, 139.00 (ArCH), 169.48, 171.09 ($2\text{C}=\text{O}$); (Nujol / cm^{-1}): 1701 (Carboxylic acid, $\nu_{\text{C}=\text{O}}$), 1560 (Amide, $\nu_{\text{C}=\text{O}}$), 1377 – 1458 (Aromatic, $\nu_{\text{C}=\text{C}}$), 748-769 (Ar, ortho substituted).

2.3.2 Synthesis of *N,N*-(Diethylmethylamino)benzyl Alcohol (35**) using LiAlH_4 ³⁻⁵**

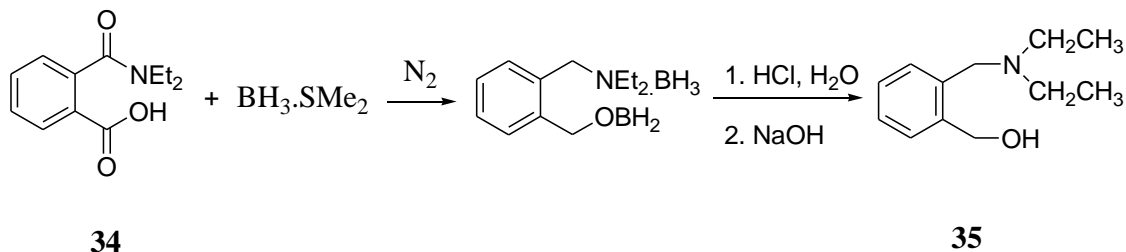


Scheme 2-2

N,N-Diethylphthalamic acid (**34**) (13.16 g, 0.0595 mol) was dissolved in 90 ml dry THF in a 500 ml 3 neck round bottom flask attach with a condenser. Lithium aluminum hydride (7.15 g, 0.1885 mol, 3.2 eq.) in 130 ml dry THF was then added drop wise to the solution through dropping funnel at room temperature under inert atmosphere. The mixtures were stirred at room temperature for 3 days. To make sure that the reactions were complete, the reaction mixtures were further reflux and the completion of the reaction was monitored by TLC (solvent CHCl_3 : EtOH 2:3). The reaction mixtures were cooled at room temperature. Excess reducing agent was decomposed with water (200 ml) and 15 % sodium hydroxide, until there is no gas released. The white precipitate was filtered off, wash with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate anhydrous and evaporated under reduce pressure to give oily product. The product was further purified by column chromatography with diethyl ether as a solvent. The residue was vacuum distilled to give colorless liquid, **35**, (9.79 g, 85.1 %), bp. 234 - 236 °C. δ_{H} (400 MHz, CDCl_3 , TMS): 1.06 – 1.10 (t, J = 8, 6H, NCH_2CH_3), 2.52 – 2.57 (q, J = 8, 4H, $-\text{NCH}_2\text{CH}_3$), 3.66 (s, 2H, ArCH_2N), 4.59 (s, 2H, ArCH_2O), 7.23 – 7.35 (m, 4H,

ArH). δ_C (100 MHz, $CDCl_3$, TMS): 10.80 ($-CH_3$, C_{12} , C_{14}), 45.91 ($-CH_2-$, C_{11} , C_{13}), 57.26 ($ArCH_2N-$, C_7), 64.77 ($ArCH_2O-$, C_8), 127.60, 128.82, 129.99, 131.13, 137.41, 141.89 ($ArCH-$, C_3 , C_1 , C_2 , C_6 , C_5 , C_4). (IR / cm^{-1}): 3188 – 3381 (ν_{OH}), 1300 (ν_{C-N}) 1023-1054 (ν_{CO}), 742-777 (Ar , ortho substituted), 1387 - 1459 (Aromatic, $\nu_{C=C}$). Anal. calcd for $C_{12}H_{19}NO$: C, 74.5; H, 9.93; N, 7.25; found: C, 74.4; H, 10.77; N, 7.22.

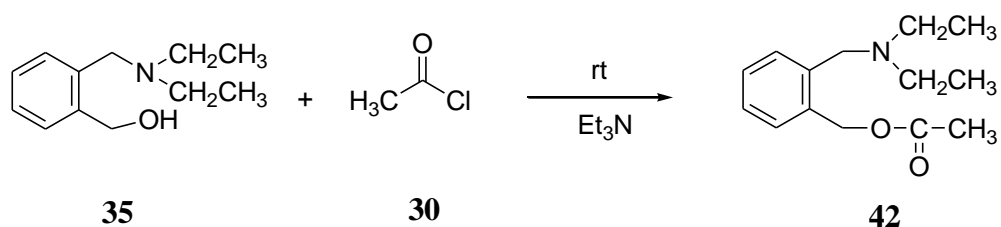
2.3.3 Synthesis of *N,N*-(Diethylmethylenamino)benzyl Alcohol (**35**) using $\text{BH}_3 \cdot \text{SMe}_2$ ⁶⁻⁸



Scheme 2-3

N,N-Diethylphthalamic acid (**34**) (6.23 g, 0.0282 mol) was dissolved in 130 ml dry THF in 500 ml 3 neck round bottom flask attach with a condenser. $\text{BH}_3 \cdot \text{DMS}$ (13.3 ml, 0.1402 mol) was added drop wise into reaction mixture using dropping funnel at room temperature under inert atmosphere. The reaction mixture was heated to reflux in oil bath. Progress of reaction was monitored by TLC (solvent CHCl_3 : EtOH 2:3). The excess of dimethyl sulfide and THF was distilled out. The reaction mixture was cooled to room temperature and quenching with water until major bubbling ceased. HCl was added and the solution was reflux for 45-min to 1 hour to break up any borane complex formed. The solution was cooled to room temperature. The combined aqueous layer was extracted with diethyl ether (8 x 30ml). Organic layer were combined and dried over Na_2SO_4 and concentrated using rotary evaporator to give oily product. The product was further purified with column chromatography using diethyl ether as a solvent. The residue was vacuum distilled to give colorless liquid, (**35**) (4.0643 g, 74.7 %), bp. 234 -236 °C. All the spectroscopic data are identical with 2.3.2.

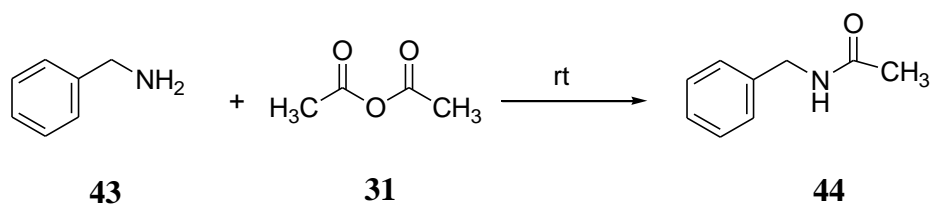
2.3.4 Synthesis of 2-((Diethylamino)methyl)benzyl Acetate (**42**)^{9,10}



Scheme 2-4

2-((diethylamino)methyl)phenylmethanol (**35**) (2.06 g, 0.0103 mol) was dissolved in 20 ml of dry ether in 50 ml round bottom flask. Triethylamine (2.0 ml, 14.4 mmol) was added to the reaction mixture and stirred vigorously at room temperature. Acetyl chloride (**30**) (1.76 ml, 0.0247 mmol) was then added dropwise into reaction mixture. Progress of the reaction was monitored by TLC (solvent 100% ethyl acetate). Yellowish precipitate was filtered off and washed with cold diethyl ether. The filtrate was dried under reduced pressure. Further purification was carried out with column chromatography using various percentage of hexane: ethyl acetate. The combined fraction was dried under reduced pressure to give colorless liquid product, (**42**) (1.81 g, 74.2 %), bp. 158 – 160 °C. δ_{H} (400 MHz, CDCl_3 , TMS): 0.97 – 1.00 (t, $J = 7$, 6H, NCH_2CH_3), 2.08 (s, 3H, COCH_3), 2.43 – 2.48 (q, $J = 7$, 4H, NCH_2CH_3), 3.57 (s, 2H, ArCH_2N), 5.28 (s, 2H, ArCH_2O), 7.21 – 7.35 (m, 4H, ArH). δ_{C} (100 MHz, CDCl_3 , TMS): 11.64 ($-\text{CH}_3$, C_{10} , C_{12}), 21.04 ($-\text{CO}-\text{CH}_3$, C_{14}), 46.7 ($-\text{CH}_2-$, C_{91} , C_{11}), 55.67 (ArCH_2N , C_7), 64.13 (ArCH_2O , C_8), 126.98, 127.94, 129.05, 130.14, 134.92, 138.61, 138.72 (ArCH , C_3 , C_1 , C_2 , C_6 , C_5 , C_4), 170.90 ($-\text{C}=\text{O}$, C_{13}). (IR / cm^{-1}): 1231 (Acetate, ν_{CO}), 1736 (Ester, $\nu_{\text{C}=\text{O}}$), 1301 ($\nu_{\text{C-N}}$), 1026 (ν_{CO}), 751-776 (Ar, ortho substituted), 1377 - 1458 (Aromatic, $\nu_{\text{C}=\text{C}}$). Analytical Calculated for $\text{C}_{14}\text{H}_{21}\text{NO}$: C, 71.44; H, 9.01; N, 5.95; found: C, 70.28; H, 9.59; N, 5.82.

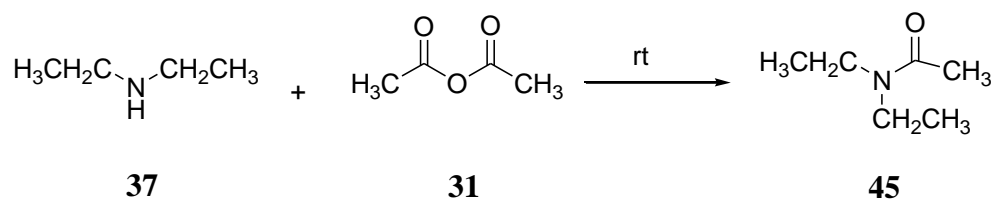
2.3.5 Synthesis of *N*-benzylacetamide (**44**)^{9,10}



Scheme 2-5

N-Benzylamine (**43**) (1.10 g, 10.27 mmol) was added into round bottom flask. Acetic anhydride (0.81 ml, 8.54 mmol) was then added dropwise into reaction mixture. The reaction mixtures were stirred at room temperature. Progress of the reaction was monitored by TLC solvent 100% ethyl acetate). The solution was dried under reduced pressure. Further purification was carried out with column chromatography using various percentage of hexane: ethyl acetate. The combined fraction was dried under reduced pressure to give colorless solution (**44**) (0.21g, 51.7 %). δ_{H} (400 MHz, CDCl_3 , TMS): 2.04 (s, 3H, COCH_3), 4.38 (s, 2H, $\text{Ar-CH}_2\text{-N}$), 6.77 (s, 1H, -NH-CO), 7.21 – 7.27 (m, 5H, Ar-H). δ_{C} (100 MHz, CDCl_3 , TMS): 23.01 ($\text{-CO-CH}_3\text{-}$, C_{10}), 44.12 ($\text{ArCH}_2\text{N-}$, C_7), 127.65 (ArCH- , C_6 , C_4), 127.96 (ArCH- , C_2), 128.73 (ArCH- , C_1 , C_3), 137.59 (ArCH- , C_5), 171.12 (-C=O , C_9). (Nujol / cm^{-1}): 3272 (Amides, $\nu_{\text{N-H}}$), 1646 (Acetate, $\nu_{\text{C=O}}$), 1375 (Metyl, $\nu_{\text{-CH}_3}$), 1376 - 1455 (Aromatic, $\nu_{\text{C=C}}$).

2.3.6 Synthesis of *N,N*-Diethylacetamide (**45**)^{9,10}



Scheme 2-6

N,N-Diethylamine (**37**) (0.8 ml, 7.76 mmol) was added into round bottom flask. Acetic anhydride (0.81 ml, 8.54 mmol) was then added dropwise into reaction mixture. The reaction mixtures were stirred at room temperature. Progress of the reaction was monitored by TLC solvent 100% ethyl acetate). Yellowish solution was dilute in chloroform and washed with distilled water (2 x 10 ml). The organic layer was dried reduced pressure to give yellowish liquid **45** (0.18 g, 19.9 %). δ_{H} (400 MHz, CDCl_3 , TMS): 1.10 – 1.20 (m, 6H, NCH_2CH_3), 2.09 (s, 3H, COCH_3), 3.28 – 3.41 (m, 4H, $-\text{NCH}_2\text{CH}_3$). δ_{C} (100 MHz, CDCl_3 , TMS): 13.08 ($-\text{CH}_3$, C_3) 14.25 ($-\text{CH}_3$, C_3) 21.34 ($\text{CO}-\text{CH}_3$), 40.06 ($-\text{CH}_2-$, C_4), 42.90 ($-\text{CH}_2-$, C_4), 169.93 ($-\text{CO}-$, C_2).

2.4 References

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