CHAPTER II

EXPERIMENTAL

2.1 General

All chemicals were purchased from Aldrich Chemical Company and without any further purification. Melting points were determined using a Fisher-John melting point apparatus. NMR spectra were recorded on a Bruker FT-NMR (200 and 50.3 MHz for ^{1}H and ^{13}C respectively) with TMS or $CDCl_3$ as internal standards. Infrared spectra were recorded on a Perkin Elmer PE 1721 FT spectrophotometer. Ultraviolet absorption spectra were obtained using Hitachi U-2000 spectrophotometer and data collected using LabCalc™ software. Gas liquid chromatography (GLC) analyses were performed on PE-8500 FID instrument equipped with a 30m x 0.25mm i.d. fused silica column coated with 0.25μ Supelwax 10 bonded phase (GC1) or on a Perkin Elmer Autosystem (9000) equipped with 15m x 0.53mm 50% phenyl silicone phase capillary column (GC2). Mass spectra were recorded on Hewlett Packard HP 5890A GC coupled HP 5970B mass spectrometer on 30m x 0.25mm Suplexcowax™ 10 column. Photochemical reactions were carried out with 3 mL of 2.0 x 10^{-2} M pyrazole solutions in acetonitrile in a quartz tube 1cm x 11.5cm after removal of air with N_2 purging for a minimum of 10 min. A Hanovia high-pressure arc lamp was used for photolysis.

2.2 Preparation of starting materials and products.

2.2.1 Preparation of *N*-methylpyrazole [9]

A mixture of pyrazole (9.6 g, 0.14 mol), tri-n-butylamine (14 mL. 0.075 mol), and trimethylphosphate (8.5 mL, 0.070 mol) were heated and N-methylpyrazole was removed by distillation and collected as an oil. Fractional distillation of the oil provided pure *N*-methylpyrazole as a colorless liquid [bp 125-128°C (atm. pressure),

yield 5.4 g (0.07 mol, 47%)] ; IR (neat): 3450, 3110, 2940, 2820, 1520, 1490, 1440, 1400, 1281, 1210, 1090 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 3H), δ 6.22 (t, J = 2.5 Hz, 1H), δ 7.35 (d, J = 2.5 Hz, 1H), δ 7.49 (br. s, 1H).

2.2.2 Preparation of 3-amino-1-methylpyrazole

Methylhydrazine (2.76 g, 3.25 mL. 0.06 mol) was dissolved in a solution of potassium carbonate (25 g) in water (25 mL) at 0 °C. 2-Chloroacrylonitrile (5.25 g, 4.83 mL, 0.06 mol) was added dropwise to the stirred solution while maintaining the temperature at 0°C. The resulting solution was allowed to stir at room temperature for another 4 hours, then at 40-50 °C for 3 hours, and then at room temperature overnight. This solution was extracted continuosly with ethyl acetate for 48 hours. The ethyl acetate extract was separated, dried with sodium sulfate and the ethyl acetate was removed under reduced pressure. Vacuum distillation of the remaining oil provided 3-amino-1-methylpyrazole as a colorless liquid [bp 67-69 °C (0.70 torr), yield 4.12 g (0.04 mol, 67%)] ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.99 (d, J= 4Hz, 1H), 5.47 (d, J= 4Hz, 1H), 3.61 (s, 6H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 154.1, 130.6, 91.9, 37.6; MS m/z (%) 97(100), 82(4), 79(4), 69(14), 54(20), 52(23), 42(19).

2.2.3 Preparation of 3-bromo-1-methylpyrazole

3-Amino-1-methylpyrazole (8 g, 0.082 mol) was dissolved in 57 mL of 48% HBr at 0 °C with stirring. Sodium nitrite (5.97 g, 0.083 mol) in 5.7 mL of water was added dropwise to the stirred solution over a period of an hour while maintaining the temperature at 0-5 °C until the white precipitate had dissolved and a positive starch-iodide test was obtained. While maintaining the solution of diazonium ion at 0-5 °C, it was added slowly in small portions to a solution of freshly prepared Cu_2Br_2(in 72 mL of 48% HBr) also maintained at 0 °C. The resulting solution was stirred at 0-5 °C for 3 hours, warmed to room temperature and neutralized with sodium bicarbonate. The resulting solid was collected by suction filtration. The solid was extracted by ethyl acetate using soxhlet extraction for 24 hours. The ethyl acetate extract was separated, dried with sodium sulfate and then ethyl acetate was removed under reduced pressure.

Vacuum distillation of the remaining oil provided 3-bromo-1-methylpyrazole as a colorless liquid [bp. 36-38 °C (0.45 torr), yield 5.22 g (0.03 mol, 36%)] ; IR(neat) 3144, 3118, 2943, 1507, 1359, 1333, 1284, 1168, 1070, 1034, 954, 752 cm^{-1} ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.23 (d, J= 2Hz, 1H), 6.22 (d, J= 2Hz, 1H), 3.85 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 131.9, 126.9, 106.4, 39.3 ; MS m/z (%) 169.1(98), 160.9(27), 159.9(100), 158.9(22), 81.1(23), 80.0(15), 78.9(13), 54.0(19), 53.0(7), 52.1 (17), 51.0(10).

2.2.4 Preparation of 3-(trimethylsilyl)-1-methylpyrazole

To a stirred solution of 0.96 g (6.0 mmole) of 3-bromo-1-methylpyrazole, dissolved in 30 mL of anhydrous ether at -76 °C under nitrogen was added dropwise 8.0 mL (13 mmole) of n-butyllithium over 15 minutes. After the addition was complete, the solution was stirred at -76 °C for 1 hour. The reaction was quenched by addition of chlorotrimethylsilane (3.26 g , 3.8 mL, 30 mmole) dropwise. The reaction mixture was allowed to warm to room temperature overnight with stirring. The solution was poured into 100 mL 1M $NaHCO_3$ solution with stirring. The aqueous layer was extracted with ether. The ether extract was separated, dried with sodium sulfate and then ether was removed under reduced pressure. Ditillation provided 3-(trimethylsilyl)-1-methylpyrazole as a colorless liquid [bp 65 - 70 °C (5 torr), yield 0.57 g (0.004 mol, 67 %)] ; ^{1}H-NMR (200MHz, $CDCl_3$) δ 7.36 (d, J= 2Hz, 1H), 6.35 (d, J= 2Hz, 1H), 3.94 (s, 3H), 0.26 (s, 9H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 155, 129.9, 111.9, 38.5, -1.03 ; MS m/e (%) 154(19), 139(100), 113(6), 98(8), 84(4), 73 (15), 59(16), 45(7), 43(13) ; UV λ_{max} (CH_3CN) 220 nm, ε 11,181 $M^{-1}cm^{-1}$.

2.2.5 Preparation of 5-(Trimethylsilyl)-1-methylpyrazole [7, 8]

1-Methylpyrazole (2.42 g, 0.0295 mol) and 4.50 mL (0.0295 mol) of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were dissolved in 20mL anhydrous ether (dried over benzophenone ketyl radical). The mixture was cooled to -76 °C (dry ice /ethanol-acetone bath) and nitrogen stream was then allowed to flow through the

system. n-Butyllithium 1.6 M (19.7 mL, 0.315 mol) in hexane was added dropwise with stirring at -76 °C over 15-30 minutes and stirred for 3 more hours at -76 °C. Chlorotrimethylsilane (4.05 mL, 0.0316 mol) in 10 mL anhydrous ether was added over a period of 15 minutes and the resulting mixture was allowed to warm to room temperature overnight. The resulting mixture was extracted, dried (Na_2SO_4) and concentrated. Distillation provided 5-(trimethylsilyl)-1-methylpyrazole as a colorless liquid [bp 78 -80 °C (12 torr), yield 3.10 g (0.02 mol, 68%)] ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.44 (d, J= 2Hz, 1H), 6.33 (d, J= 2Hz, 1H), 3.94 (s,3H), 0.30 (s, 9H) ; ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 146, 138.1, 114.4, 39.5, -1.10 ; MS m/z (%) 154(27), 139(100), 112(10), 96(4), 83(11), 69(7), 59(29), 55(9), 45(11), 43(24) ; UV λ_{max} ($CDCl_3$) 220 nm, ε 7,960 $M^{-1}cm^{-1}$.

2.2.6 Preparation of 2-(Trimethylsilyl)-1-methylimidazole [12]

A solution of 1-methylimidazole (0.985 g, 12 mmol) in 30 mL anhydrous ether was added dropwise to a stirred solution of n-butyllithium (7.5 mL, 12 mmol) in hexane and 15 mL anhydrous ether. The reaction mixture was heated under reflux for 1 hour. The mixture was cooled to room temperature and then chlorotrimethylsilane (1.3 g, 1.52 mL, 12.0 mmol) was added dropwise. The solution was stirred for 2 hours. The LiCl was filtered using double ended filter and the solvent was removed by distillation under reduced pressure to provide 2-(trimethylsilyl)-1-methylpyrazole as a yellow solid [yield 1.41 g (0.009 mol, 75 %)] ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.20 (d, J= 2Hz, 1H), 7.02 (d,J= 2 Hz, 1H), 3.77 (s, 3H), 0.41 (s,9H) ; MS m/z (%)154 (59), 139(100), 123(3), 113(68), 112(14), 98(9), 73(20), 59(22), 45(12), 43(17), 28(9).

2.2.7 Preparation of 5-(Trimethylsilyl)-1-methylimidazole [13]

To a stirred solution of 1-methylimidazole (1.97 g, 24 mmol) in anhydrous ether at -76 °C (dry ice/ethanol-acetone bath), was added dropwise a solution of n-butyllithium (24 mL, 48.0 mmol) in pentane. The mixture was allowed to slowly warm to room temperature and stirred for another 3 hours. Chlorotrimethylsilane

(5.21 g, 6.09 mL, 48.0 mmol) was then added dropwise. The resulting mixture was heated under reflux for 4 hours and allowed to cool. LiCl was removed by filtration and the solvent was removed under reduced pressure. The residue was crystallized from pentane to give colorless crystals of 2,5-bis(trimethylsilyl)-1-methylimidazole mp 119-121 °C. Water (0.11 g, 6.0 mmol) was added to a stirred solution of 2,5-bis (trimethylsilyl)-1-methylimidazole (1.36 g, 6.0 mmol) in 5.0 mL dichloromethane. It was stirred for 30 minutes and then the solvent was removed under reduced pressure. 5-(Trimethylsilyl)-1-methylimidazole was isolated by vacuum distillation to provide 5-(trimethylsilyl)-1-methylimidazole as a colorless liquid [yield 0.80 g (5 mmol, 83%)] ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.10 (s, 1H), 3.69 (s, 3H), 0.28 (s, 9H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ141.4, 136.5, 33.7, -1.2 ; MS m/z (%) 154 (32), 139(100), 112(14), 98(24), 84(5), 73(5), 59(6),43(10), 28(3).

2.2.8 Preparation of 3-(*N*-methylamino)propenenitrile (2-cis and 2-trans) [14]

3-Ethoxyacrylonitrile (51.9, 0.053 mL) and 40% methylamine (5.8 g, 0.053 mol) in water were stirred at room temperature overnight. The solution was extracted with dichloromethane (3x10 mL). The extract was combined, dried (Na_2SO_4), and concentrated. Half of the resulting oil (2.0 g) was distilled to provide 3-(*N*-methylamino)propenenitrile (78% trans, 22% cis) as a colorless liquid [bp 78-83 °C (0.6 torr), yield 1.5 g (0.018 mol, 37%)] ; IR(neat) 3364, 3075, 2937, 2817, 2194, 1630, 1520, 1425, 1308, 1153, 970, 728 cm^{-1} ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.85 (d, J_{trans} = 13.7 Hz, 1H), 3.66 (d, J_{cis} = 7.0 Hz, 1H), 2.68 (d, J_{trans} = 5.0 Hz, 3H), 2.96 (d, J_{cis} = 5.0 Hz, 3H), 7.05 (dd, J_{trans} = 13.7 Hz, 7.1 Hz, 1H), 6.55 (dd, J_{cis} = 7 Hz, 1H), 4.89 (m, 2H); UV λ_{max}(CH_3CN) 259 nm, ε 14,500 $M^{-1}cm^{-1}$; ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 152.1, 122.5, 59.9, 29.3 ; MS m/z (%) 82(100), 81(84), 55(72), 54(98), 52 (33), 51(30), 42(53), 41(28).

2.2.9 Preparation of 4-bromo-1-methylpyrazole [15]

A solution of 1-methylpyrazole (3.05 g, 0.037 mol) in chloroform was slowly added dropwise to a solution of bromine (23.0 g, 0.14 mol) in chloroform (10 mL) without cooling. Every drop produced a yellow precipitate which redissolved when the reaction mixture was stirred. After half of 1-methylpyrazole was added, a heavy brown oil formed, which then solidified. The reaction mixture was finally heated for 8 hours at reflux. After cooling, the reaction mixture was extracted with dilute NaOH until the extract was colorless . The chloroform phase was then washed with a small amount of dilute HCl. After drying and evaporation of the solvent, a yellow oil was obtained. Vacuum distillation of the remaining oil provided 4-bromo-1-methylpyrazole as a colorless liquid [bp. 72-74 °C (10 torr), yield 3.80 g (0.024 mol, 65%)]; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.36 (s, 1H), 3.87 (s, 3H); MS m/z (%) 161.7(95), 160.8(34), 159.8(100), 158.7(24), 133.8(7), 119.9(7), 105.8(9), 80.9(29), 51.9(29).

2.2.10 Preparation of 4-(trimethylsilyl)-1-methylpyrazole [16]

Magnesium chips (0.30 g, 0.0125 mol) and a tiny crystal of iodine were heated at 50 °C for 1 hour. After cooling to room temperature, a solution of chlorotrimethylsilane (1.36 g, 0.01 mol) was added. A few drops of a solution of 4-bromo-1-methylpyrazole (1.61 g, 0.01 mol) in anhydrous THF was added. Then 7 drops of 1,2-dibromoethene were also added and it was stirred. After bubbles were produced, the remained 4-bromo-1-methylpyrazole was added and it was heated at reflux for 40 hours. The solution was poured into 50 mL of ice-cold aqueous $NaHCO_3$ solution (0.25 g in 50 mL water) with stirring. Solid was removed by suction filtration. The filtrate was extracted with ether. After drying and evaporating the solvent, a yellow liquid was obtained. Flash column chromatography and vacuum distillation of the remaining oil provided 4-(trimethylsilyl)-1-methylpyrazole as a colorless liquid [bp. 80-83 °C (18 torr), yield 0.37 g (2.4 mmol, 24%)]; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.45 (s,1H), 7.27 (s, 1H), 3.89 (s, 3H), 0.17 (s, 9H).

2.2.11 Preparation of 1-methyl-2,4,5-tribromoimidazole [13,19]

A solution of bromine (35.04 g, 0.219 mol) in 15 mL glacial acetic acid was added dropwise to a mixture of 1-methylimidazole (6.0 g, 0.073 mol) and sodium acetate (24.82 g, 0.092 mol) in 125 mL glacial acetic acid with vigorous stirring and cooling to maintain the temperature below 60 °C. After the final addition, the red solution was stirred at ambient temperature for 2 hours. The solution was poured onto 250 mL ice. Then the solution was stirred and filtered to yield a yellow solid. The solid was then recrystallized from acetic acid/water (85:15) to afford 1-methyl-2,4,5-tribromoimidazole as a white solid [mp. 92-93 °C, yield 7.31 g (0.023 mol, 32%)]; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.62 (s).

2.2.12 Preparation of 4-bromo-1-methylimidazole

n-Butyllithium (6.0 mL, 12 mmol) in pentane was added dropwise to a stirred solution of 1-methyl-2,4,5-tribromoimidazole (1.595 g, 5 mmol) in 18 mL anhydrous ether at -76 °C (dry ice/ ethanol-acetone bath) under nitrogen and the resulting mixture was stirred for a further 1 hour at this temperature. Water 10 mL was added and the solution mixture was extracted with ether to provide a yellow liquid. Kugelohr distillation provided 4-bromo-1-methylimidazole as a colorless liquid [bp. 76-78 °C (1.5 torr), yield 0.50 g (3 mmol, 62%)]; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.84 (s, 1H), 3.65 (s, 3H).

2.3 Irradiation and Analysis Procedures

To monitor the photolysis of 5-(trimethylsilyl)-1-methylpyrazole or 3-(trimethylsilyl)-1-methylpyrazole on an analytical scale, a solution of the appropriate 5-(trimethylsilyl)-1-methylpyrazole or 3-(trimethylsilyl)-1-methylpyrazole (3.0 mL, 2.0 x 10^{-2} M) in acetonitrile was placed in a quartz tube (7 mm. x 13 cm. long), sealed with a rubber septum, and purged with nitrogen for 10 min prior to irradiation. The tubes were suspended in an ambient temperature water bath adjacent to a water-cooled quartz immersion well containing a 450 W high-

pressure Hg lamp. During irradiations, 1 μL of the solution was drawn off periodically to follow the reaction using GC1 at 145 °C oven temperature. After around 70% conversion, the reaction was stopped. The reaction mixture of each irradiation times was then rechecked by UV(after 1:200 dilution) and GC2 at 180 °C oven temperature. The retention time of photoproducts were compared with the retention time of authentic compounds. GC co-injection was also used to confirm the photoproducts formed. The identity of the photoproducts were further confirmed by injecting 1 μL of the photolysate in the GC-MS instrument and comparing the mass spectra of the photoproducts from the photolysate to the mass spectra of the authentic photoproducts synthesized. In addition, the photoproducts were further confirmed by IR and ^{1}H-NMR instruments after evaporating the solvent. The chemical shifts of photoproducts mixture were compared to the corresponding authentic compounds.