CHAPTER II

EXPERIMENTAL

2.1 General

All chemicals were purchased from Aldrich Chemical Company and were used without any further purification except ethanol, which was purified by refluxing over magnesium ethoxide followed by fractional distillation.[16] Melting points were determined using a Mel-Temp 1001 melting point apparatus. NMR spectra were recorded on a Bruker FT-NMR (400 and 100 MHz for ^{1}H and ^{13}C –NMR respectively) with $CDCl_3$ as internal standards. Infrared spectra were recorded on a Perkin Elmer FT spectrophotometer using bounce Di/ZnSe plate. Ultraviolet absorption spectra were obtained using a Hitachi U-2000 spectrophotometer and data collected using LabCalc™ software. Gas liquid chromatography (GLC) analyses were performed on GC1, a PE-8500 FID instrument equipped with a 30m x 0.25mm i.d. fused silica column coated with 0.25μ Supelwax 10 bonded phase, and/or on GC2, a Perkin Elmer Autosystem (9000) equipped with 15m x 0.53mm 50% phenyl silicone phase capillary column. Mass spectra were recorded on Hewlett Packard 5970B mass selective detector interfaced to a Hewlett Packard 588 capillary gas chromatograph. Photochemical reactions were carried out with 3.0 ml of 1.5 x 10^{-2} M solutions of the appropriate pyrazole in acetonitrile or methanol in a quartz tube 1 cm x 12 cm after removal of air with N_2 purging for a minimum of 10 min. A Hanovia medium-pressure Hg lamp was used for photolysis.

2.2 Preparation of starting materials and products for photoreaction studying.

2.2.1 Preparation of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one [38].[8]

Ethyl vinyl ether (10.5 ml, 7.92 g, 110 mmol) in absolute pyridine (8.5 ml, 7.9 g, 100 mmol) was added dropwise (6 drops/min) to trifluoroacetic anhydride (14.5

mL, 21.0 g, 100 mmol) while the temperature was maintained at –10 °C to 0 °C until precipitation of the pyridinium salt commenced. The resulting solution was stirred at rt for 16 hours. The precipitate was filtered, and washed with Et_2O (75 mL). The di ethylether was combined with the original diethyl ether filtrate and evaporated slowly (bath temperature max. 30 °C, 40 Torr), and the oily residue taken up in CH_2Cl_2 (30 mL). The solution was extracted with 0.1 N HCl (3x75 mL, until the aqueous phase remained colorless), then with H_2O (25 mL), and dried (Na_2SO_4). The solvent was evaporated at 15 Torr for 3-5 h (bath temperature max. 30 °C): yield 15.1 g (90 mmol, 90%) of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one [38]; IR; 1709, 1587, 1475, 1448, 1382, 1359, 1313, 1276, 1263, 1194, 1135, 1065, 1053, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7 Hz), 4.04 (q, 2H, J = 7 Hz), 5.79 (d, 1H, J = 12 Hz), 7.83 (d, 1H, J = 12 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 69.4, 98.3, 116.8 (J = 291 Hz), 168.5, 180.4 (J = 35 Hz).

2.2.2 Preparation of 1-methyl-3-(trifluoromethyl)pyrazole [39] and 4,5-dihydro-1-methyl-5-(trifluoromethyl)-1H-pyrazole [40][9, 10]

Methylhydrazine **[41]** (1.50 g, 33.0 mmol) was added dropwise to a stirred solution of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one **[38]** (4.12 g, 24.5 mmol) in absolute ethanol (16 mL) at room temperature. The resulting solution was stirred and refluxed for 2 hours and then diluted with dichloromethane (20 mL). The solution was extracted with water (5x5 mL). The aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3X15 mL). The combined organic phase was dried (sodium sulfate) and concentrated by distillation through a Vigreux column. The residue (3.2 g) was connected to a vacuum line and pumped down to 0.1-1.0 Torr [9]. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 3 hours the trap contained 1-methyl-3-(trifluoromethyl)pyrazole **[39]** as an oil (1.9 g, 12.7 mmol, 52%); IR: 1527, 1498, 1380, 1318, 1245, 1169, 1116, 1071, 1042, 1005 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 3.86 (s, 3H), 6.58(d, 1H, J = 2.0 Hz), 7.32 (br. s, 1H); ^{13}C-NMR ($CDCl_3$): δ 39.8, 104.9, 121.7 (q, J = 267 Hz), 131.8, 142.7 (q, J = 37.9 Hz); ms: m/z 150 (M^+); UV: λ_{max} 215 (ε = 3267 $M^{-1}cm^{-1}$). The non-volatile residue (1.07 g) was crystallized from dichloromethane to give 4,5-dihydro-1-methyl-5-

(trifluoromethyl)-1H-pyrazol-5-ol **[40]** as white crystals (739 mg, 4.4 mmol, 18%) m.p. 69-70 °C, lit [9], mp 75-76 °C; IR; br. 3100, 3082, 1600, 1454, 1419, 1377, 1330, 1291, 1218, 1189, 1148, 1087, 1037, 1005 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.95 (s, 3H), 2.89 (dt, 1H, J = 18.8, 1.3 Hz), 3.20 (dd, 1H, J = 0.8, 18.8 Hz), 6.67 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 34.5, 45.0, 92.0 (q, J = 31.4 Hz), 124.0 (q, J = 283 Hz), 139.1; ms (70 °C): m/z 168 (M^+); ms (100 °C): m/z 150 (M^+).

2.2.3 Preparation of 1-methyl-5-(trifluoromethyl)pyrazole [42].[11]

Concentrated hydrochloric acid (6 drops) was added to a stirred solution of 4,5-dihydro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-5-ol **[40]** (1.03 g, 6.1 mmol) in dichloromethane (30 mL) at room temperature. After stirring for 30 minutes saturated aqueous sodium bicarbonate (25 mL) was added. The organic layer was separated, dried (sodium sulfate) and concentrated by distillation. The residue (823 mg) was connected to a vacuum line and pumped down to 0.1-1.0 Torr. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 30 minutes the trap contained 1-methyl-5-(trifluoromethyl)pyrazole **[42]** as an oil (732 mg, 4.9 mmol, 80%): IR; 1552, 1488, 1412, 1393, 1346, 1295, 1199, 1259, 1156, 1117, 1087 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.52 (d, 1H, J = 1.2 Hz), 7.39 (br. s, 1H); ^{13}C-NMR ($CDCl_3$) δ 38.8, 107.9, 120.6 (q, J = 268 Hz), 132.2 (q, J = 39 Hz), 138.5; ms: m/z 150 (M^+); UV: λ_{max} 220 (ε = 5300 $M^{-1}cm^{-1}$).

2.2.4 Preparation of 1-methyl-4-(trifluoromethyl)pyrazole [43].[12]

Methylhydrazine **[41]** (65 mg, 1.4 mmol) was added dropwise to a stirred solution of 1,1,5,5-tetramethyl-1,5-diaza-3-(trifluoromethyl)-1,3-pentadienium hexafluorophosphate **[44]** (340 mg, 1.0 mmol) in acetronitrile (2 mL) at room temperature. The resulting solution was stirred at room temperature under argon atmosphere for 1 hour and then glacial acetic acid (180 mg, 3.0 mmol) was added. The solution was stirred at 70 °C for 1 hour, and then diluted with dichloromethane (20 mL). The solution was extracted with water (20 mL). The aqueous phase was extracted with dichloromethane (2X20 mL), and the combined dichloromethane

extracts were washed with aqueous sodium bicarbonate (10 mL) and saturated sodium chloride (10 mL). The combined organic phase was dried (sodium sulfate) and concentrated by distillation through a vigreux column. The residue (3.2 g) was connected to a vacuum line and pumped down to 0.1-1.0 Torr [9]. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 30 minutes the trap contained 1-methyl-4-(trifluoromethyl)pyrazole as an oil (42 mg, 0.3 mmol, 30%) IR; 1576, 1397, 1232, 1200, 1116 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.87 (s, 3H), 7.58 (s, 1H), 7.61 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 37.5, 111.8 (q, J = 38 Hz), 120.7 (q, J = 266 Hz), 127.4, 135.1; ms: m/z 150 (M^+); UV: λ_{max} 210 (ε = 2605 $M^{-1}cm^{-1}$).

2.2.5 4-Deuterio-1-methyl-3-(trifluoromethyl)pyrazole [39-4d$_1$] synthesis.[3]

1-methyl-3-(trifluoromethyl)pyrazole **[39]** (0.42 g, 0.8 mmol) was dissolved in D_2SO_4 (4.6 ml, 70 %), protected from atmospheric moisture, and maintained at 70 °C for 12 days. The solution was neutralized (sodium bicarbonate) and extracted with dichloromethane. The resulting solution was dried (sodium sulfate) and concentrated by distillation through a vigreux column. The flask contained 4-Deuterio-1-methyl-3-(trifluoromethyl)pyrazole **[39-4d$_1$]** (68 mg, 0.5 mmol, 16%); ^{1}H-NMR ($CDCl_3$): δ 3.89 (s, 3H), 7.34 (s, 1H); ms: m/z 151 (M^+).

2.2.6 Preparation of trifluoromethyl substituted-1-methylimidazoles [45-47].[13]

Trifluoromethyl iodide was bubbled into a solution of 1-methylimidazole **[2]** (3.6 mL, 3.7 g, 45 mmol) in methanol (9 mL), contained in a quartz tube sealed with a rubber septum until the weight of tube had increased by 1.7 g (9 mmol of CF_3I). The resulting solution was irradiated at 254 nm using two 8 watt low pressure Hg lamps for 47 hours and then saturated aqueous sodium bicarbonate (10 mL) was added. The organic layer was separated, dried (sodium sulfate) and concentrated by distillation through a vigreux column. The precipitate (844 mg) was filtered, and washed with CH_2Cl_2 (10 mL). The solution was concentrated by distillation through

a vigreux column. The residue (3.36 g) was purified by flash chromatography on siliga gel (30 g, 30 cm, 1.2 cm). The column was eluted with 10% ethylacetate in hexane and collecting with 15 mL fractions were collected. TLC analysis showed that tubes (17-25) have only one spot appearing at the same rf on the TLC plate, and tubes (33-42) have another spot with the same of each other. Fraction 1 (17-25) was concentrated by distillation through a vigreux column (7 c.m.), giving 1-methyl-2-(trifluoromethyl)imidazole **[45]** (129 mg, 0.9 mmol, 10%) ; ^{1}H-NMR ($CDCl_3$): δ 3.72 (s, 3H), 6.91(s, 1H), 6.99 (s, 1H); IR; 1560, 1500, 1454, 1421, 1289, 1270, 1185, 1121, 1094, 1042 cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ 32.7, 118.1 (q, J = 269 Hz), 123.8, 127.3, 134.7 (q, J = 39 Hz); ms: m/z 150 (M^+); UV: λ_{max} 221 (ε = 4200 $M^{-1}cm^{-1}$), and fraction 2 was connected to a vacuum line and pumped down to 0.1-1.0 Torr. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 1 hour the trap contained 1-methyl-5-(trifluoromethyl)imidazole **[46]** (major) as a white solid and 1-methyl-4-(trifluoromethyl)imidazole **[47]** (minor). The mixture was kept in freezer until precipitation occurred. The precipitate was then collected by filtration and washed with very cold hexanes (1 mL), giving 1-methyl-5-(trifluoromethyl)imidazole **[46]** (164 mg, 1.1 mmol, 12%) as white solid; IR; 1569, 1504, 1483, 1411, 1404, 1365, 1312, 1254, 1232, 1158, 1107, 1085, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.70 (s, 3H), 7.36 (s, 1H), 7.46 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 32.6, 121.2 (q, J = 266 Hz), 122.1 (q, J = 40 Hz), 131.7, 141.6; ms: m/z 150 (M^+); UV: λ_{max} 200 (ε = 5120 $M^{-1}cm^{-1}$). The non-volatile fraction was 1-methyl-4-(trifluoromethyl)imidazole **[47]** (19 mg, 0.1 mmol, 2%) as an oil; IR; 1575, 1505, 1477, 1426, 1401, 1364, 1339, 1314, 1218, 1151, 1111, 1096, 1062, 1049 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.67 (s, 3H), 7.16 (s, 1H), 7.40 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 34.1, 120.4, 121.9 (q, J = 267 Hz), 123.1 (q, J = 39 Hz), 139.6; ms: m/z 150 (M^+); UV: λ_{max} 203 (ε = 6080 $M^{-1}cm^{-1}$).

2.3 Irradiation and analysis procedures

To monitor the photolysis of 1-methyl-3-(trifluoromethyl)pyrazole **[39]**, 1-methyl-4-(trifluoromethyl)pyrazole **[43]**, 1-methyl-5-(trifluoromethyl)pyrazole **[42]**, or 4-deuterio-1-methyl-3-(trifluoromethyl)pyrazole **[39-4d$_1$]**, a solution of the

appropriate 1-methyl-3-(trifluoromethyl)pyrazole **[39]**, 1-methyl-4-(trifluoromethyl) pyrazole **[43]**, 1-methyl-5-(trifluoromethyl)pyrazole **[42]**, or 4-deuterio-1-methyl-3-(trifluoromethyl)pyrazole **[39-4d$_1$]** (3.0 mL, 1.5 x 10^{-2} M) in acetonitrile or methanol were placed in a quartz tube (diameter = 7 mm and length = 12 cm), sealed with a rubber septum, and purged with nitrogen for 5 minutes prior to irradiation. The quart tubes were suspended in an ambient temperature water bath adjacent to a water-cooled quartz immersion well containing a 450 W medium-pressure Hg lamp. During irradiations, 1 μL and/or 0.2 μL of the solution was drawn off periodically to follow the reaction using GC1(Perkin Elmer Autosystem (9000) equipped with 15m x 0.53mm 50% phenyl silicone phase capillary column using temperature program (40 °C for 25 minutes, 100 °C for 10 minutes, and 140 °C for 5 minutes with temperature changing rate of 20 °C per minute)) and/or GC2 (PE-8500 FID instrument equipped with a 30m x 0.25mm i.d. fused silica column coated with 0.25μ Supelwax 10 bonded phase using temperature program (35 °C for 5 minutes, 40 °C for 7 minutes, 60 °C for 15 minutes, 100 °C for 10 minutes, and 140 °C for 13 minutes with temperature changing rate of 20 °C per minute)), respectively. The reaction mixture after each irradiation time was also analysed by UV absorption spectroscopy (after 1:30 dilution for 1-methyl-3-(trifluoromethyl)pyrazole and 1-methyl-4-(trifluoromethyl)pyrazole or 1:75 for 1-methyl-5-(trifluoromethyl)pyrazole. The retention time of photoproducts were compared with the retention time of authentic compounds. GC co-injection was also used to confirm the identity of the photoproducts. The identity of the photoproducts were further confirmed by injecting 0.25 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 synthesized photoproducts. In addition, the photoproducts were further confirmed by IR and ^{1}H-NMR analysis after solvent evaporation. The chemical shifts of photoproducts were compared to the chemical shifts of authentic compounds.