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Synthesis and unusual photochemistry of a highly reactive pyrimidinedione

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Experimental.

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC+300 and Varian MercuryPlus 300 (300 MHz) spectrometers using DMSO-d_6 and $CDCl_3$ as solvents. The melting points are uncorrected. The progress of the reactions and the purity of the products were monitored by TLC on Merck 60 F254 plates. All the reactants and solvents were purchased from Aldrich Chemical Company, Inc. Tetrahydrofuran, 1,4-dioxane and diethyl ether were distilled over sodium benzophenone ketyl prior to use. Toluene, benzene, hexane, pentane, cyclohexane, dichloromethane and DMSO were distilled over calcium hydride. Ethanol, methanol, isopropanol, chloroform, DMF, ethyl acetate were used without further purification. Silica gel Merck 60 (0.040–0.063 mm) was used for column chromatography. Quartz columns were employed with uv phosphor added to the silica gel to permit monitoring of bands with a ultraviolet lamp.

2,2-Diphenyl-3-nitropropionitrle 4.

Step 1. Diphenylketimine. To a refluxing solution of phenylmagnesium bromide [prepared from bromobenzene (50.8 g, 0.32 mol) and magnesium (8.0 g, 0.33 mol) in diethyl ether (150 ml)] was added dropwise a solution of benzonitrile (24.5 g, 0.24 mol) in diethyl ether (100 ml). During the addition, a large amount of precipitate was formed. Additional ether (100 ml) was added to make stirring easier, and the reaction mixture was refluxed for 6 h and left overnight at room temperature. Methanol (65 ml) was added dropwise at a rate allowing keeping the vigorous reaction under control. The mixture was stirred for 2.5 h at room temperature, filtered, washed with ether (500 ml), and concentrated *in vacuo*. The residue was distilled on the oil pump. B.p. 100 °C/0.6 Torr. Yield: 37.4 g (87%). Colourless liquid. ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 7.41-

7.50 (m, 8H), 7.62-7.65 (m, 2H), 10.54 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, (δ) ppm) 127.4; 128.1; 128.2; 128.9; 129.1; 129.4; 129.6; 130.4; 131.0; 139.1; 140.2; 176.3.

Step 2. 1,1-Diphenyl-2-nitroethylene. **(Caution! Plastic shield should be used when working with nitromethane, since compound is explosive).** A solution of diphenylketimine (40.5 g, 0.22 mol) in nitromethane (65 ml) was refluxed for 24 h. Excess nitromethane was removed *in vacuo*, and the yellow solid residue was recrystallized from isopropanol (75 ml). Yield: 35.4 g (70%); mp. 87-89 °C. The mother liquor was concentrated *in vacuo* and the residue was recrystallized from isopropanol (5 ml) to afford the second crop (2.06 g, 4%) of the product; mp 88-89 °C. Total yield: 37.46 g (74%). ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 7.20-7.23 (m, 2H), 7.32-7.35 (m, 2H), 7.41-7.50 (m, 6H), 7.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 128.7; 129.0; 129.1; 129.2; 129.5; 131.1; 134.6; 135.7; 137.3; 150.6. HRMS (EI) Calcd for $C_{14}H_{11}NO_2^+$ ([M^+]) 225.0785. Found 225.0786.

Step 3. 2,2-Diphenyl-3-nitropropionitrle **4**. **(Caution! All the manipulations must be carried out in efficient fume hood! Use of thick neoprene gloves is recommended since a solution of KCN in DMSO may be quickly adsorbed through skin).** A solution of 1,1-diphenyl-2-nitroethylene (37.5 g, 0.17 mol) in DMSO (250 ml) was added all at once to a solution of potassium cyanide (23 g, 0.35 mol) in DMSO (400 ml). The mixture was stirred at room temperature for 3 h and then poured with vigorous stirring into mixture of water (1000 ml), of ice (200 g) and concentrated HCl (150 ml) **(caution, HCN evolves!)**. The mixture was left overnight. The precipitate was filtered, washed with water (2000 ml) and dissolved in ethyl acetate (500 ml). The organic solution was washed with brine (200 ml), dried with sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from isopropanol (65 ml). Yield: 39.6 g (94%); mp. 113-115 °C. The mother liquor was concentrated *in vacuo* and the residue was recrystallized from isopropanol (4 ml) to afford the second crop (1.42 g, 4%) of the title product; mp. 113-115 °C. Total yield: 41.02 g (98%). ^{1}H NMR (300 MHz, $CDCl_3$, (δ) ppm) 5.22 (s, 2H) 7.38-7.43 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 50.3; 79.6; 119.9; 127.0; 129.5; 129.7; 135.6. HRMS (EI) Calcd for $C_{15}H_{12}N_2O_2^+$ ([M^+]) 252.0894. Found 252.0901.

2,2-Diphenyl-3-aminopropropanamide (5). (To get a reasonable yield of the product, it is important to apply external cooling of the reaction flask with tap water at all the times). To a solution of 2,2-diphenyl-3-nitropropionitrle **4** (19.6 g, 77.7 mmol) in a

mixture of THF (200 ml) and ethanol (1000 ml) was added 10% palladium on charcoal (1.0 g). Sodium borohydride (29.5 g, 0.78 mol) was then added over a period of 50 min. The mixture was stirred for 35 min, poured into water (4500 ml), and extracted with dichloromethane (8x300 ml) and chloroform (2x300ml). The combined organic phase was washed with water (2x1000 ml), dried with sodium sulfate, and filtered through a short pad of silica (which was then washed with 200 m of ethanol-dichloromethane 1:1 mixture and the washing was combined with the filtrate). The combined organic phases were concentrated *in vacuo*, and the residue was recrystallized from isopropanol (30 ml). Yield: 9.7 g (52%); mp. 152-153 °C. ^{1}H NMR (300 MHz, $CDCl_3$, (δ) ppm) 1.43 (br s, 2H) 3.66 (s, 2H), 5.89 (br s, 1H) 7.20-7.37 (m, 10H), 7.84 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 49.6; 61.4; 127.4; 128.7; 128.8; 142.0; 177.3. HRMS (MALDI) Calcd for $C_{15}H_{17}N_2O^+$ ([M+H]) 241.1336. Found 241.1335.

2,2-Diphenyl-3-(*N*-ethoxycarbonylamino)propropanamide 6. To a vigorously stirred solution of 2,2-diphenyl-3-aminopropropanamide **5** (13.8 g, 57.4 mmol) in a mixture of ethanol (480 ml) and dioxane (350 ml), were added dropwise simultaneously over period of 1 h a solution of ethyl chloroformate (6.39 g, 59 mmol) in dioxane (140 ml) and a solution of sodium carbonate (6.09 g, 57 mmol) of in water (140 ml). During the addition, the temperature was kept at -5 °C. After the addition was completed, the mixture was stirred for 45 min at 0 °C. The mixture was poured into water (3000 ml) and extracted with dichloromethane (6x200 ml). The combined organic phases were washed with water (3x400 ml), dried with sodium sulfate, and concentrated *in vacuo*. The residue was recrystallized from toluene (100 ml) yielding 15.65 g (88%) of 2,2-diphenyl-3-(*N*-ethoxycarbonylamino)propropanamide **6**; mp. 152-154 °C. The mother liquor was evaporated *in vacuo*, and the residue was recrystallized from toluene (5 ml) affording more (0.87 g, 5%) product; mp. 153-155 °C. The total yield was 16.52 g (93%). ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 0.98 (t, 3H, J = 6.9 Hz), 3.79 (q, 2H, J = 6.9 Hz), 3.95 (d, 2H, J = 6.3 Hz), 6.14 (br s, 1H), 6.75 (s, 1H), 7.21-7.35 (m, 10H), 7.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 14.7; 48.1; 60.8; 61.1; 127.8; 128.8; 128.9; 141.1; 156.8; 177.9. HRMS (EI) Calcd for $C_{18}H_{20}N_2O_3^+$ ([M^+]) 312.1469. Found 312.1472.

5,5-Diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione 7. To a solution of sodium ethoxide [prepared by dissolving sodium (12 g, 0.52 mol) in ethanol (1000 ml)] was added a solution of 2,2-diphenyl-3-(*N*-ethoxycarbonylamino)propropanamide **6** (16.52 g, 52.8 mmol) in dioxane (300 ml) and ethanol (100 ml). The mixture was stirred at room

temperature for 20 h. A voluminous precipitate formed. Everything was poured with stirring into mixture of water (1500 ml), conc HCl (150 ml), ice (1 kg), and NaCl (100 g). After stirring for 1 h, the precipitate was filtered, washed with water (4x1000 ml), and air dried. Yield: 13.4 g (95%); mp. 317-320 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 3.88 (d, 2H, J = 3 Hz), 7.14-7.17 (m, 4H), 7.30-7.38 (m, 6H), 7.83 (br s, 1H), 10.35 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, (δ) ppm) 46.5; 55.8; 128.0; 128.9; 129.0; 140.3; 153.7; 173.5. HRMS (EI) Calcd for $C_{16}H_{14}N_2O_2^+$ ([M^+]) 266.1050. Found 266.1049.

3-Methyl-5,5-diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione 8. To a solution of 5,5-diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione **7** (12.46 g, 46.8 mmol) in DMF (100 ml) was added potassium *tert*-butoxide (6.62 g, 59 mmol). The mixture was stirred for 1 h at room temperature (white precipitate formed). A solution of iodomethane (10.0 g, 70.4 mmol) in DMF (200 ml) was added dropwise, and the mixture was stirred for 1 h at room temperature (the precipitate dissolved). The mixture was poured into solution of conc HCl (60 ml) in water (3000 ml) and extracted with ethyl acetate (5x200 ml). The combined organic phase was washed with water (5x200 ml), dried with sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in chloroform (250 ml), filtered from unreacted **7**, and concentrated *in vacuo*. The residue was recrystallized from isopropanol (130 ml). Yield: 7.34 g (56%); mp. 193-195 °C. The mother liquor was concentrated *in vacuo* and the residue was recrystallized from isopropanol (15 ml) yielding the second crop (3.01 g, 23%) of the product; mp. 192-195 °C. Total yield: 10.35 g (79%). ^{1}H NMR (300 MHz, $CDCl_3$, (δ) ppm) 3.25 (s, 3H) 3.89 (d, 2H, J = 3.3 Hz), 6.53 (br s, 1H), 7.11-7.16 (m, 4H), 7.25-7.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 28.4; 46.3; 56.2; 128.1; 128.5; 128.8; 139.3; 154.7; 172.6. HRMS (EI) Calcd for $C_{17}H_{16}N_2O_2^+$ ([M^+]) 280.1207. Found 280.1209.

6-Hydroxy-3-methyl-5,5-diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione 9. To sodium hydride (0.17 g, 4.25 mmol of a 60% dispersion in mineral oil) in THF (25 ml) was added a solution of 3-methyl-5,5 -diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione **8** (1.0 g, 3.57 mmol) in THF (20 ml). The mixture was stirred for 1 h at room temperature and cooled to -78 °C. A solution of 90% *N-tert*-butylbenzenesulfinimidoyl chloride (1.0 g, 4.25 mmol) in anhydrous THF (15 ml) was rapidly added. Addition caused an immediate discoloration of the sulfinimidoyl chloride, and the reaction mixture turned pale-yellow. The mixture was stirred for 30 min at –78 °C, warmed to 0 °C, poured into 10% $NaHCO_3$ (aq., 500 ml) and stirred for 30 min. The aqueous phase was extracted with

ethyl acetate (4x150 ml) and the combined organic phases were washed with water (3x100 ml), dried with sodium sulfate, and concentrated *in vacuo*. The residue was triturated with diethyl ether (20 ml). The crystalline product was filtered, washed several times with diethyl ether, and air dried. Yield: 0.818 g (77%); mp. 200 °C. ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 3.07 (s, 3H) 5.34 (t, 1H, J = 4.8 Hz), 6.57 (d, 1H, J = 4.8 Hz), 7.14-7.38 (m, 10H), 8.79 (d, 1H, J = 4.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, (δ) ppm) 27.9; 61.2; 76.3; 126.9; 127.4; 128.0; 128.3; 129.2; 131.2; 140.7; 140.9; 152.6; 171.8. HRMS (EI) Calcd for $C_{17}H_{16}N_2O_3^+$ ([M^+]) 296.1156. Found 296.1165.

3-Methyl-5,5-diphenyl-6-(phenylsulfonyl)dihydropyrimidine-2,4-(1*H*,3*H*)-dione 10. To a cooled (–30 °C) suspension of 6-hydroxy-3-methyl-5,5-diphenyldihydropyrimidine-2,4(1*H*,3*H*)-dione **9** (4.0 g, 13.5 mmol) in dichloromethane (150 ml) was added freshly prepared benzenesulfinic acid (2.9 g, 20.3 mmol) and sodium sulfate (*ca* 15 g). The mixture was stirred for 3 h at –30 °C and then left overnight at room temperature. The partially solidified mixture was filtered under inert atmosphere and washed with THF until only sodium sulfate remained on the filter. The filtrate was concentrated using a rotary evaporator connected to a water aspirator via a tube filled with Drierite. The residue was triturated with diethyl ether and the solvent was pipetted out from crystalline solid. Washing with ether was repeated (3x20 ml). The crystalline solid was then dried under a stream of dry nitrogen. Yield: 4.05 g (72%); mp. 165-170 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6, (δ) ppm) 3.03 (s, 3H) 6.01 (d, 1H, J = 5.7 Hz), 7.06-7.12 (m, 3H), 7.27-7.36 (m, 3H), 7.39-7.44 (m, 4H), 7.48-7.57 (m, 4H), 7.62-7.64 (m, 1H), 9.07 (d, 1H, J = 5.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, (δ) ppm) 28.1; 55.0; 74.8; 127.8; 127.9; 128.6; 128.8; 129.3; 129.6; 131.3; 134.2; 138.0; 138.9; 140.7; 151.5; 169.4. HRMS (ESI) Calcd for $C_{23}H_{20}N_2O_4SNa^+$ ([M+Na]$^+$) 443.1036. Found 443.1027.

3-Methyl-5,5-diphenylpyrimidine-2,4(3*H*,5*H*)-dione 3. (Due to the extreme sensitivity of compound 3 to water all manipulations should be carried out in an atmosphere of dry nitrogen, using rigorously dried glassware and anhydrous solvents). Sodium hydride (1.0 g, 25 mmol, 60% dispersion in mineral oil) was washed with anhydrous pentane (2x25 ml). Then anhydrous dichloromethane (60 ml) was added. The slurry was cooled to -5 °C, and powdered sulfone **10** (1.66 g, 3.9 mmol) was added as a slurry anhydrous dichloromethane (20 ml). The mixture was stirred for 2 h at -5 °C and then overnight at room temperature. The mixture was filtered under nitrogen through the pad of anhydrous $MgSO_4$ followed by washing with dichloromethane (2x100 ml).

The filtrate was concentrated using a rotary evaporator (connected to water aspirator via a tube filled with solid KOH pellets). The residue was refluxed for 5 min with anhydrous cyclohexane (250 ml), cooled to room temperature, kept for 1 h, and filtered under nitrogen through a thin pad of anhydrous $MgSO_4$. The filtrate was concentrated to dryness on a rotary evaporator (connected to water aspirator via tube filled with solid KOH pellets), triturated with pentane, and dried under stream of dry nitrogen. Yield: 0.79 g (72%); mp. 126-128 °C. ^{1}H NMR (300 MHz, $CDCl_3$, (δ) ppm) 3.40 (s, 3H), 7.19-7.22 (m, 4H), 7.40-7.43 (m, 6H), 8.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 28.0; 61.0; 128.6; 129.0; 129.4; 137.0; 155.8; 170.3; 178.3. HRMS (ESI) Calcd for $C_{17}H_{15}N_2O_2^+$ ($[M+H]^+$) 279.1129. Found 279.1126.

6-Methyl-3,3,8,8-tetraphenyl-8,8a-dihydroimidazo[1,5-*c*]pyrimidine-5,7(3*H*,6*H*)-dione 11. Photolysis of 3-methyl-5,5-diphenylpyrimidine-2,4(3*H*,5*H*)-dione 3. (Due to extremely water sensitive nature of compound 7 all manipulations should be carried out in atmosphere of dry nitrogen, using rigorously dried glassware and dry solvents). A solution of 3-methyl-5,5-diphenylpyrimidine-2,4(3*H*,5*H*)-dione **3** (0.2 g, 0.7 mmol) in dry benzene (300 ml) was purged with oxygen-free nitrogen for 1 h. Then the solution was irradiated with a 400 W medium pressure mercury lamp with circulating copper(II) sulfate solution as an UV-filter. After 4 h, ^{1}H NMR showed complete consumption of the starting compound **3**. The mixture was evaporated to dryness *in vacuo* and the residue was purified by column chromatography (17 x 2 cm) using hexane/ethyl acetate (5:1) as an eluent. Compound **11** was obtained as a colourless solid. The remaining material (128 mg) was eluted with methanol/ethyl acetate (1:1) whicj appeared to be a tarry polymeric material with uninterpretable NMR and mass spectra. Yield of **11**: 35 mg (21%); mp. 218-220 °C (from ether/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, (δ) ppm) 3.30 (s, 3H), 5.80 (s, 1H), 6.30 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 6.95 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.24-7.38 (m, 13H), 7.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, (δ) ppm) 28.9; 59.4; 69.1; 99.5; 127.3; 127.5; 128.1; 128.5; 128.6; 128.8; 129.3; 129.5; 129.7; 138.3; 138.9; 139.2; 139.6; 149.2; 157.8; 171.0. HRMS (ESI) Calcd for $C_{31}H_{26}N_3O_2^+$ ($[M+H]^+$) 472.2020. Found 472.2002.