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Photochemical ring contraction of 1-aryl-1,4-dihydropyrazine to 1-aryl-1*H*-imidazole

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ABSTRACT

The photochemical properties of 1-aryl-1,4-dihydropyrazines, including their UV–vis absorption, photostability and photoreaction, are investigated. The photostability of the 1-aryl-1,4-dihydropyrazines is studied in conventional solvents, and the results demonstrated that the 1-aryl-1,4-dihydropyrazines are unstable under irradiation with UV light. The 1-aryl-1,4-dihydropyrazines undergo photochemical ring contractions to 1-aryl-1*H*-imidazoles, as determined by ^{1}H NMR, ^{13}C NMR, HRMS, and single crystal X-ray diffraction analyses. The photochemical ring contraction is proposed to occur through a 6 π-electron cyclisation and a [1 + 2] cycloreversion.

1. Introduction

1,4-Dihydropyrazines are widely used as biological agents and medicine. The discovery that the 1,4-dihydropyrazine unit is a component of flavin coenzymes and several marine luciferins attracted interest and led to detailed investigations of its properties [1,2]. Although 1,4-dihydropyrazines have been synthesized for many years [3–7], their photochemical properties have not been the focus of many studies. In the vapor phase, pyrazine and methyl pyrazine were found to be unstable and to isomerize to pyrimidines upon exposure to UV light [8,9]. Additionally, upon UV irradiation, pyrazine ethoxycarbonylimides contract to pyrazoles, 2-azidopyrazines contract to 1-cyanoimidazoles and 1,4-diaryl-1,4-dihydropyrazine hydrochlorates contract to 1,2,5-triarylpyrroles [10–12]. Here, the photochemical properties, including the UV–vis absorption, photostability, and photoreactions, of 1-aryl-1,4-dihydropyrazines were investigated to continue our studies on the photochemical properties of heterocyclic compounds [13–16]. The 1-aryl-1,4-dihydropyrazines underwent a photochemical ring contraction to 1-aryl-1*H*-imidazoles during UV irradiation (Scheme 1). A mechanism is proposed for the photochemical ring contraction of the 1-aryl-1,4-dihydropyrazines to 1-aryl-1*H*-imidazoles.

2. Experimental

All chemicals were of commercial quality. Solvents were dried and purified using conventional methods. UV–vis absorption spectra were measured using a U-4100 UV-vis spectrophotometer (Hitachi). Melting points were determined on a XT-5A digital melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. HRMS spectra were recorded using an Agilent G3250AA LC/MSD TOF mass spectrometer. The ESR spin-trapping experiment was conducted using a Bruker A300 X-band spectrometer at 100 kHz magnetic field modulation.

2.1. Procedure for determining photochemical stability

A series of 2,6-diethoxycarbonyl-3,5-dimethyl-1-aryl-1,4-dihydropyrazines **1** were prepared via the cyclization of *N*,*N*-bisalkylated anilines with ammonium acetate using the procedure improved by our group [7]. Lights of different wavebands were obtained by filtering the light of an Osram HBO 450 W medium pressure mercury lamp. The filter that was composed of a solution of 0.44 g $CuSO_4 \cdot 5H_2O$ in 25 mL of 25% $NH_3 \cdot H_2O$ gave 320–440 nm UVA light, and the ZWB1 and ZWB3 spectral filters gave 280–320 nm UVB light and 200–280 nm UVC light, respectively. The samples were irradiated in quartz cuvettes.

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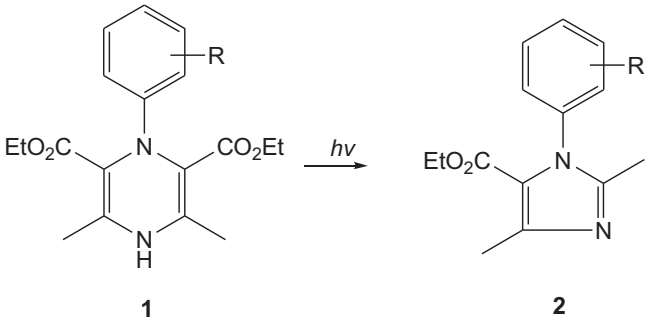

Scheme 1. Photochemical ring contraction of 1-aryl-1,4-dihydropyrazines **1** to 1-aryl-1*H*-imidazoles **2**.

2.2. Procedure for photoreaction

Compound **1** (10^{-3} mol) and 0.05 equiv. of benzophenone were dissolved in 200 mL of dry benzene and irradiated with UVA light at room temperature under nitrogen. The reaction progress was monitored by TLC. After completion, the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel using a mixed solvent of petroleum ether and ethyl acetate (10:1, v/v) to produce **2** and **4g**.

Ethyl 2,4-dimethyl-1-phenyl-1*H*-imidazole-5-carboxylate **2a**. 43% yield as yellow lamellae; mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (q, J = 7.2 Hz, 3H), 2.17 (s, 3H), 2.52 (s, 3H), 4.09 (q, J = 7.2 Hz, 2H), 7.18–7.20 (m, 2H), 7.46–7.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.2, 59.8, 120.6, 127.3, 128.7, 129.0, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 244.1212 for $C_{14}H_{16}N_2O_2$ [M]$^+$, found 244.1233.

Ethyl 2,4-dimethyl-1-(4-methylphenyl)-1*H*-imidazole-5-carboxylate **2b**. 35% yield as yellow lamellae; mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 2.28 (s, 3H), 2.53 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 12.5, 13.1, 15.5, 59.5, 120.8, 127.5, 129.7, 137.3, 146.7, 148.9, 161.4. HRMS (ESI$^+$) m/z calcd 258.1368 for $C_{15}H_{18}N_2O_2$ [M]$^+$, found 258.1372.

Ethyl 2,4-dimethyl-1-(3-methylphenyl)-1*H*-imidazole-5-carboxylate **2c**. 38% yield as yellow lamellae; mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (q, J = 7.2 Hz, 3H), 2.19 (s, 3H), 2.52 (s, 3H), 4.11 (t, J = 7.2 Hz, 2H), 6.72–7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 12.5, 13.3, 16.6, 60.3, 120.5, 127.2, 129.7, 136.5, 145.6, 148.3, 162.1. HRMS (ESI$^+$) m/z calcd 258.1368 for $C_{15}H_{18}N_2O_2$ [M]$^+$, found 258.1360.

Ethyl 2,4-dimethyl-1-(4-nitrophenyl)-1*H*-imidazole-5-carboxylate **2d**. 35% yield as yellow lamellae; mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.55 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 7.54–8.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.2, 59.8, 120.6, 127.3, 128.7, 129.6, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 289.1063 for $C_{14}H_{15}N_3O_4$ [M]$^+$, found 289.1042.

Ethyl 2,4-dimethyl-1-(3-nitrophenyl)-1*H*-imidazole-5-carboxylate **2e**. 36% yield as yellow lamellae; mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 2.54 (s, 3H), 4.14 (q, J = 7.2 Hz, 2H), 7.56–8.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 13.8, 15.5, 61.3, 120.8, 126.5, 128.7, 129.6, 137.5, 146.9, 147.4, 160.8. HRMS (ESI$^+$) m/z calcd 289.1063 for $C_{14}H_{15}N_3O_4$ [M]$^+$, found 289.1071.

Ethyl 2,4-dimethyl-1-(4-methoxyphenyl)-1*H*-imidazole-5-carboxylate **2f**. 35% yield as yellow lamellae; mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 2.55 (s, 3H), 3.82 (s, 3H), 4.11 (q, J = 7.2 Hz, 2H), 6.72–7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.2, 59.8, 62.3, 120.6, 127.3, 128.7, 129, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 274.1317 for $C_{15}H_{18}N_2O_3$ [M]$^+$, found 274.1332.

Ethyl 2,4-dimethyl-1-(4-chlorophenyl)-1*H*-imidazole-5-carboxylate **2g** and ethyl 3-methyl-1-(4-chlorophenyl)-1*H*-imidazole-2,5-dicarboxylate **4g**. **2g**: 40% yield as yellow lamellae; mp 112–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 2.53 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.5, 59.8, 120.6, 127.3, 128.7, 129.4, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 278.0822 for $C_{14}H_{15}ClN_2O_2$ [M]$^+$, found 278.0813. **4g** 8% yield as a white powder; mp 147–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (q, J = 7.2 Hz, 6H), 2.16 (s, 3H), 4.24 (t, J = 7.2 Hz, 4H), 7.18 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.0, 15.5, 60.9, 62.1, 128.4, 128.8, 135.1, 136.3, 147.5, 157.8, 159.6, 206.8, 206.9. HRMS (ESI$^+$) m/z calcd 336.0877 for $C_{16}H_{17}ClN_2O_4$ [M + H]$^+$, found 336.0891.

Ethyl 2,4-dimethyl-1-(3-chlorophenyl)-1*H*-imidazole-5-carboxylate **2h**. 37% yield as yellow lamellae; mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 7.09–7.48 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 13.9, 15.5, 59.8, 121.6, 127.5, 128.7, 129.3, 137.8, 146.1, 148.8, 160.5. HRMS (ESI$^+$) m/z calcd 278.0822 for $C_{14}H_{15}ClN_2O_2$ [M]$^+$, found 278.0807.

Ethyl 2,4-dimethyl-1-(4-ethoxycarbonylphenyl)-1*H*-imidazole-5-carboxylate **2i**. 35% yield as yellow lamellae; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.4 Hz, 3H), 2.20 (s, 3H), 2.54 (s, 3H), 4.11 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.2, 15.6, 59.8, 60.6, 120.6, 127.3, 128.7, 129.6, 137.8, 146.9, 148.6, 160.5, 160.8. HRMS (ESI$^+$) m/z calcd 316.1423 for $C_{17}H_{20}N_2O_4$ [M]$^+$, found 316.1444.

Ethyl 2,4-dimethyl-1-(2,5-difluorophenyl)-1*H*-imidazole-5-carboxylate **2j**. 34% yield as yellow lamellae; mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 2.17 (s, 3H), 2.53 (s, 3H), 4.09 (q, J = 7.2 Hz, 2H), 7.18–7.20 (m, 2H), 7.46–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 15.2, 59.8, 120.6, 127.3, 128.7, 129, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 280.1023 for $C_{14}H_{14}F_2N_2O_2$ [M]$^+$, found 280.1042.

Ethyl 2,4-dimethyl-1-(3,5-di(trifluoromethyl)phenyl)-1*H*-imidazole-5-carboxylate **2k**. 36% yield as yellow lamellae; mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.2 Hz, 3H), 2.25 (s, 3H), 2.55 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 7.70 (s, 2H), 8.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.9, 16.4, 59.9, 121.6, 127.3, 128.7, 129.6, 133.5, 133.7, 137.8, 146.9, 148.6, 160.3. HRMS (ESI$^+$) m/z calcd 380.0959 for $C_{16}H_{14}F_6N_2O_2$ [M]$^+$, found 380.0947.

2.3. X-ray crystallography

Crystals of **2g** suitable for X-ray diffraction analysis were obtained by the slow evaporation of an ethyl acetate solution of **2g** at room temperature. The single crystal X-ray diffraction measurement was conducted on a Rigaku RAXIS RAPID IP CCD area-detector diffractometer at 293(2) K using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) in the ω scanning mode. An empirical absorption correction was applied using the ABSCOR program [17]. All structures were solved by direct methods using the SHELXS-97 program [18] and refined by full matrix least squares on F^2 using the SHELXL-97 program [19]. All of the hydrogen atoms were geometrically fixed using the riding model. Details, including the crystal data, data collection, and structure refinements, are summarized in Table 1. CCDC-936194 contains the supplementary crystallographic data for this paper. These data can be obtained, free of charge, from www.ccdc.cam.ac.uk/conts/retrieving.html.