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2,3-Dihydropyrrolo[1,2-b]benzisothiazole 5,5-Dioxide들의 비대칭성 광이성질화 반응

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A New Asymmetric Photoisomerization of 2,3-Dihydropyrrolo[1,2-b]benzisothiazole 5,5-Dioxides

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요약. 245 nm mercury lamp를 사용하여 2,3-dihydropyrrolo[1,2-b]benzisothiazole 5,5-dioxide를 광이성질화 반응시켜서 2,3-dihydro[1]benzothieno[3,2-b]pyrrole 4,4-dioxide를 가지고 있는 tricyclic ring system 화합물을 합성하는 방법을 개발하였다. 합성한 화합물들에 대한 구조는 IR, NMR, MS 및 single crystal X-ray crystallography를 이용하여 결정하였다.

주제어: 광이성질화반응, 입체선택성, Photodeconjugation, Stereogenic center

ABSTRACT. A tricyclic ring system bearing new stereogenic center namely 2,3-dihydro[1]benzothieno[3,2-b]pyrrole 4,4-dioxide was synthesized by asymmetric photoisomerization of 2,3-dihydropyrrolo[1,2-b]benzisothiazole 5,5-dioxide by irradiation with 245 nm emission of the low-pressure mercury lamp. The chemical structure and the purity of the photoproduct were delineated preliminarily by IR, NMR, and MS and finally confirmed by single crystal X-ray crystallography

Keywords: Photoisomerization, Stereoselectivity, Photodeconjugation, Stereogenic center

INTRODUCTION

Asymmetric photochemistry[1,2] has attracted enormous interest in recent years as an appealing alternative or substitute for their thermal and enzymatic counterparts in the asymmetric syntheses.[3-6] Chirality control in the electronically excited state is central to photochirogensis but in general is still a difficult task to achieve. This is mainly due to the lack of a well established methodology and in-depth knowledge of the mechanism and factors that govern the chirality transfer process in the excited state.[1]

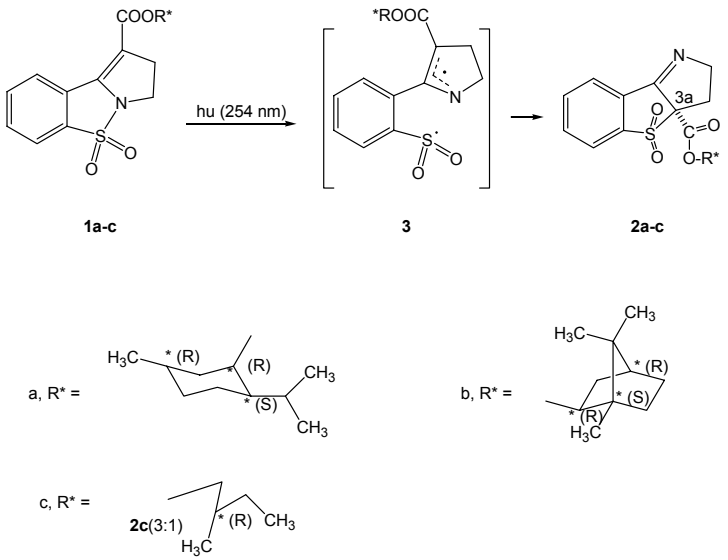
RESULTS AND DISCUSSION

In a recent work we reported a new interamolecular photoisomerization of 2,3-dihydropyrrolo[1,2-b]benzisothiazole 5,5-dioxide **(1)** (R = CN, CO_2Et, CO_2Me) into 2,3-dihydro [1]benzothieno[3,2-b]pyrrole 4,4-dioxide **(2)** (*Scheme* 1).[7] This transformation provides a new and efficient access to a tricyclic ring-system bearing a new stereogenic center. Here we report another application of this photoisomerization by introducing a chiral auxiliary at the ester group in substrate **1**, which is proposed to influence the stereoselectivity and the formation of the photoproduct **2**.

Thus, esters **1a-c** with chiral auxiliaries were synthesized from acid chloride which in turn refluxed in the presence of chiral alcohols [(-)-menthol, (-)-borneol and (-)-2-methyl-1-butanol] in dry benzene to afford the substrate esters **1a-c** respectively, in almost quantitative yield. Ester groups were used because they allow the easy removal of the chiral auxiliary. Now, when compounds **1a-c** were irradiated with 254 nm emission of the low-pressure mercury lamp in Argon-purged acetonitrile through a quartz jacket retaining the 185 nm emission, the photoproducts **2a-c** were obtained in excellent yield.

The transformation proceeds via homolytic cleavage at S-N bond to produce relatively stable biradical **3** which in turn recylcizes to the final product **2** (*Scheme* 1).

The spectroscopic data of the photoproducts **2a-c** revealed two main events namely photodecojugation of α,β-unsaturated ester and the stereoselectivity in the photoisomerization process. Firstly, in the ultra violet spectra the values of the longest wave length of **1a-c** (being α,β-unsaturated esters and the carbonyl group extends the pi-electron system) is λ_{max} = 325 nm (log ε = 4.10, 3.24, and 4.10 respectively), this value is dramatically shifted to 245 (4.01), 275 (3.26)



***Scheme* 1**

***Table* 1.** Specific rotation and Uv for **1a-c** and **2a-c**

Entry	$[\alpha]^{20}$/Ethanol	Uv (acetonitrile) λ_{max} (log ε)
1a	57.0 (C = 1.0)	325 (4.10), 242 (3.97), 208 (4.54)
1b	-28.0 (C = 0.5)	325 (3.24), 274 (3.06)
1c	-19.0 (C = 0.5)	325 (4.10), 252 (395), 208 (4.54)
2a	-36.0 (C = 0.5)	245 (4.01), 209 (4.42)
2b	-54.0 (C = 0.5)	275 (3.26), 244 (3.92), 208 (4.36)
2c	-11.0 (C = 0.5)	273 (3.30), 209 (4.10)

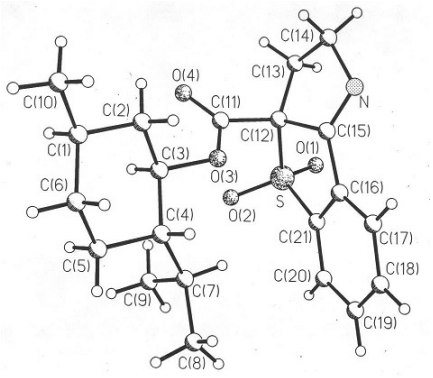
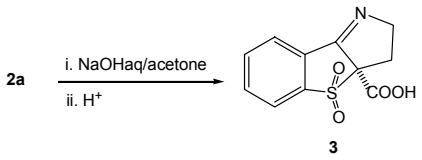


***Fig*. 1.** ORTEP-plot of molecular structure **2a** in the crystal. The crystallographic numbering does not reflect the systematic number.

and 275 (3.30) in photoproducts **2a-c** respectively. Also, in the infrared spectra, the carbonyl absorption bands in **1a-c** appeared at 1689, 1696 and 1688 cm^{-1} are shifted towards higher wavenumber and appeared at 1733, 1721, and 1734 cm^{-1} in **2a-c** respectively.

Secondly, The photoisomerization of **1a**,**b** to **2a**,**b** proceed



***Scheme* 2**

with the retention of the stereoselectivity however in the case of **1c** to **2c** the diastereomeric purity is lost: By ^{1}H NMR of the photoproducts **2a**,**b** revealed only one set of signals even when a chiral shift agent[8] was used with different concentration and the absolute configuration of the photoproduct **2a** at the new stereogenic center at Carbon-3a is assigned by the single crystal X-ray structure analysis as *R* configuration (*Figure* 1).

While **2c** revealed a broad set of signals but after adding the chiral shift agent, the ^{1}H NMR signals split into two sets with integration ratio of the two stereoisomers formed upon photolysis of **1c** is 3:1 (no further attempts were made to separate use any other techniques). It was reported that, the bulk of the substituents at the chiral center improves the stereoselectivity of the photoisomerization therefore, difference in the stereoselectivity in the photoconversion **1a**,**b** to **2a**,**b** and **1c** to **2c** can be attributed to the size of the introduced chiral auxiliaries.[1,2] Furthermore, the specific rotations of the photoproducts **2a-c** were measured and compared with those of the starting materials (*Table* 1). Therefore, the value of the specific rotation $[\alpha]^{20}$ shifted from -57.0 to -36.0 for **1a** and **2a** respectively. Furthermore, the basic hydrolysis of **2a** afforded the enantiomeric pure free

acid **3** with specific rotation $[\alpha]^{20}$ + 14.0 (C = 1 ethanol) (*Scheme* 2). Also, the ^{1}H NMR of the free acid **3** revealed one set of signals even after adding the chiral shift agent.[8]

CONCLUSION

In conclusion, the influence of introducing chiral auxiliaries in substrate **1** on the stereoselectivity and the formation of the photoproduct **2** was studied**.** It was noticed that, the photoisomerization of **1a**,**b** with bulk chiral auxiliaries to **2a**,**b** proceeds with the retention of the stereoselectivity however in the case of **1c** to **2c** the diastereomeric purity is lost.

EXPERIMENTAL

General

All commercially available solvents and reagents were purchased from commercial sources and used without further purification unless otherwise noted. NMR spectra were recorded on Bruker WM 300 and DRX 500 spectrometers (300 MHz and 500 MHz, respectively for ^{1}H-NMR, 75 and 125 MHz, respectively, for ^{13}C-NMR) using TMS as internal standard and the deuterated solvent as lock. IR spectra were obtained by using a Perkin-Elmer 983 spectrophotometer. Electron impact ionisation mass spectrometry (EIMS) was performed on a Varian AMD 604 instrument using 70 eV ionization energy. The specific rotation was measured on a Polarimater. Melting points are uncorrected. All the chromatographic separations were performed on 48 × 20 cm glass plates covered with an air-dry layer (1 cm thick) of silica gel (Merck Kiesegel PF254).

General Procedure for Synthesis of Esters with Chiral Auxiliaries 1a-c

A mixture of 2,3-Dihydropyrrolo[1,2-b][1,2]benzisothiazole-5,5-dioxo-1-carboxylic acid [7] (1.10 g, 4.4 mmol) and excess thionyl chloride (5 mL) was refluxed for 4 h at 85 - 90 ^{o}C. Then the unreacted thionyl chloride was evaporated in vacuo to give the crude acid chloride as a pale yellow solid which was used directly in the next step.

A mixture of the acid chloride (0.86 g, 3.2 mmol) and the chiral alcohol (3.2 mmol) was refluxed overnight in dry benzene (50 mL). The solvent was evaporated completely in vacuo and the residue was washed several times with 10% $NaHCO_3$ solution and then with water, and air dried.

(-)-Menthyl 2,3-Dihydropyrrolo[1,2-b][1,2]benzisothiazole-1-carboxylate 5,5-dioxide (1a): Colourless crystals (from acetone, 98%), mp: 160 - 161 ^{o}C, Uv (acetonitrile): λ_{max} (log ε) = 325 (4.10), 242 (3.97), 208 (4.54). IR (KBr): ν = 1689s (CO), 1634s (C=C), 1367s ,1168s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.79 (m, 3H), 0.98 (m, 7H), 1.21 (m, 2H), 1.51 (m, 2H), 1.82 (m, 2H), 1.89 (m, 1H), 2.15 (m, 1H), 3.35 (m, 2H), 3.84 (m, 2H), 4.85 (m, 1H), 7.83 (m, 3H, Ar- H), 8.91 (m, 1H, Ar-H), ^{13}C NMR ($CDCl_3$): δ = 16.5, 20.8, 22.1, 23.8, 27.5, 31.3, 33.8, 34.1, 41.2, 41.8, 46.5, 74.5, 108.3, 121.4, 125.1, 129.1, 132.3, 133.2, 139.5, 157.4, 164.3.

MS: *m*/*z* (%) = 390 (M^++1, 0.4), 389 (M^+, 0.5), 252 (32.6), 234 (100), 187 (83.3), 138 (82.8); *Anal.*Calcd. for $C_{21}H_{27}N O_4S$ (389.27): C, 64.79; H, 6.99; N, 3.59; S, 8.24. Found: C, 64.81; H, 7.01; N, 3.61; S, 8.11.

(-)-Bornyl 2,3-Dihydropyrrolo[1,2-b][1,2]benzisothiazole-1-carboxylate 5,5-dioxide (1b): Colourless crystals (from ethanol, 95%), mp: 175 - 176 ^{o}C. Uv (acetonitrile): λ_{max} (log ε) = 325 (3.24), 274 (3.06). IR (KBr): ν = 1696s (CO), 1636s (C=C), 1374s ,1137s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.81 (m, 6H), 0.95 (s, 3H), 1.21 (m,1H), 1.35 (m, 2H), 1.84 (m, 3H), 1.45 (m, 1H), 3.39 (m, 2H), 3.75 (m, 2H), 5.11 (m, 1H), 7.85 (m, 3H, Ar-H), m, 1H, Ar-H).^{13}C NMR ($CDCl_3$): δ = 13.6, 19.1, 20.1, 26.9, 27.3, 33.5, 37.3, 42.5, 45.1, 48.2, 49.3, 80.9, 107.8, 121.5, 124.9, 128.3, 132.1, 133.5, 139.5, 147.3, 164.1. MS: *m*/*z* (%) = 388 (M^+ +1, 0.3), 387 (M^+, 12.6), 251 (40.5), 234 (100), 207 (30.5), 186 (9.3), 164 (5.1). *Anal.*Calcd. for $C_{21}H_{25}N O_4S$ (387.49): C, 65.09; H, 6.50; N, 3.61; S, 8.27. Found: C, 64.91; H, 6.31; N, 3.52; S, 8.21.

S (-)-2-(methyl)butyl2,3-Dihydropyrrolo[1,2-b][1,2]benzisothiazole-1-carboxylate 5,5-dioxide (1c): Colourless crystals (from aqueous ethanol, quantitative), mp: 75 - 76 ^{o}C. Uv (acetonitrile): λ_{max} (log ε) = 325 (4.10), 252 (3.95), 208 (4.54). IR (KBr): ν = 1688s (CO), 1640s (C=C), 1322s, 1179s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.95 (m, 6H), 1.25 (m,1H), 1.49 (m, 1H), 1.85 (m, 1H), 3.36 (t, 2H, *J* = 9), 3.85 (t, 2H, *J* = 9), 4.13 (m, 1H), 4.24 (m, 1H), 7.75 (m, 3H, Ar-H), 8.94 (m, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 11.2, 16.5, 26.1, 33.8, 34.3, 41.9, 69.4, 107.5, 121.8, 125.2, 128.7, 132.1, 133.4, 139.8, 147.3, 164.4. MS: *m*/*z* (%) = 322 (M^+ +1, 8.0), 321 (M^+, 41.1), 251 (70.0), 234 (48.3), 207 (100), 186 (30.9), 143 (30.0). *Anal.*Calcd. for $C_{16}H_{19}N O_4S$ (321.39): C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found: C, 59.64; H, 6.01; N, 4.25; S, 10.01.

General Photolysis Procedure

Samples of **1a-c** (0.5 mmol) in acetonitrile (100 mL) were

irradiated for the period given below using a quartz immersion well in connection with a Hanau TNN 15 low-pressure mercury lamp (15 W input) with continuous argon purging. After concentration the residue was subjected to chromatography on two silica gel plates each with EtOAc/n-hexane (1:1). The R_f values of the appropriate zones are given below.

R-(-)-Menthyl-2,3-dihydro-[1]benzothieno[3,2-b]pyrrole-3a-carboxylate 4,4-dioxide (2a): It was obtained in 91% conversion after 5 h of irradiation, as colourless crystals (from acetone), R_f = 0.63, mp: 202 °C. Uv (acetonitrile): λ_{max} (log ε) = 245 (4.01), 209 (4.42). IR (KBr): ν = 1733s (CO), 1647s (C=N), 1321s, 1152s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.67 (m, 6H), 0.77 (m, 5H), 0.98 (m, 1H), 1.08 (m, 1H), 1.35 (m, 2H), 1.55 (m, 2H), 2.02 (m, 1H), 2.78 (m, 1H), 2.92 (m, 1H), 4.22 (m, 1H), 4.62 (m, 2H), 7.82 (m, 4H, Ar- H). ^{13}C NMR ($CDCl_3$): δ = 15.5, 20.8, 21.9, 22.7, 25.4, 30.1, 31.4, 33.9, 40.1, 46.8, 66.5, 77.0, 82.2, 122.4, 123.9, 131.9, 132.7, 133.9, 147.9, 163.2, 168.0. MS: *m*/*z* (%) = 390 (M^+ +1, 3.2), 389 (M^+, 12.0), 252 (18.4), 251 (100), 206 (21.0), 186 (25.0). *Anal.*Calcd. for $C_{21}H_{27}N\,O_4S$ (389.27): C, 64.79; H, 6.99; N, 3.59; S, 8.24. Found: C, 64.71; H, 6.91; N, 3.60; S, 8.30.

R-(-)-Bornyl-2,3-dihydro-[1]benzothieno[3,2-b]pyrrole-3a-carboxylate 4,4-dioxide (2b): It was obtained in 90% conversion after 6 h of irradiation, as colourless crystals (from n-hexane), R_f = 0.41, mp: 117 - 118 °C. Uv (acetonitrile): λ_{max} (log ε) = 275 (3.26), 244 (3.92), 208 (4.36). IR (KBr): ν = 721s (CO), 1652s (C=N), 1321s ,1152s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.75 (m, 12H), 1.61 (m, 3H), 2.31 (m,1H), 2.74 (m, 1H), 3.10 (m, 1H), 4.32 (m, 1H), 4.65 (m, 1H), 4.82 (m, 1H), 7.65 (m, 2H, Ar-H), 7.91 (m, 2H, Ar-H). MS: *m*/*z* (%) = 388 (M^+ +1, 1.2), 387 (M^+, 8.3), 278 (18.6), 252 (8.1), 234 (8.5), 208 (14), 136 (100). *Anal.*Calcd. for $C_{21}H_{25}N\,O_4S$ (387.49): C, 65.09; H, 6.50; N, 3.61; S, 8.27. Found: C, 64.96; H, 6.45; N, 3.59; S, 8.30.

S (-)-2-(methyl)butyl -2,3-dihydro-[1]benzothieno[3,2-b]pyrrole-3a-carboxylate 4,4-dioxide (2c): It was obtained as colourless crystals (from n-hexane/benzene, 1:1), R_f = 0.45, mp: 188 - 189 °C. Uv (acetonitrile): λ_{max} (log ε) = 273 (3.30), 209 (4.10). IR (KBr): ν = 1734s (CO), 1664s (C=N), 1331s, 1152s (SO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 0.85 (m, 6H), 1.25 (m,1H), 1.51 (m, 1H), 1.61 (m, 1H), 2.25 (m, 1H), 2.75 (m,1H), 3.45 (m, 1H),3.61 (m, 1H), 3.85 (m, 1H), 4.15 (m, 1H), 7.75 (m, 2H, Ar-H), 8.12 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 11.2, 16.3, 25.8, 30.2, 36.9, 39.7, 66.3, 70.4, 71.5, 130.1, 135.0, 135.9, 138.3, 164.8, 166.3, 170.5. MS: *m*/*z* (%) = 322 (M^+ +1, 0.8), 321 (M^+, 0.9), 252 (19.5), 209 (32.0), 183 (44.0), 133 (100). *Anal*. Calcd. for $C_{16}H_{19}N\,O_4S$ (321.39): C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found: C, 59.72; H, 5.89; N, 4.41; S, 9.88.

2,3-Dihydro-[1]benzothieno[3,2-b]pyrrole- 4,4-dioxide R-3a-carboxylic acid (3): 10% aqueous NaOH solution (0.5 mL) was added to a solution of 1.00 g (2.57 mmol) of the ester **2a** in acetone (5 mL) at 0 °C. Then the mixture was stirred at room temperature for 4 h (TLC-monitoring) then 50 mL water was added. The resulting clear solution was neutralized with dil. HCl and the precipitate was collected by filtration and washed with water. It was obtained as colourless crystals (from acetone, 0.85 g, 87%), mp > 320 °C. IR (KBr): ν = 3150-2800 (br, OH), 1676_S (CO), 1620 (C=N), 1318, 1180 (SO_2) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.80 (m, 1H), 2.97 (m, 1H), 4.28 (m, 1H), 4.68 (m, 1H), 7.92 (m, 2H, Ar-H), 8.21 (m, 1H, Ar-H), 8.82 (m, 1H, Ar-H), 12.99 (s, 1H, COOH). MS: *m*/*z* (%) = 251 (M^+, 100), 234 (40.5), 208 (20.0), 136 (80.5). *Anal.* Calcd. for $C_{11}H_9O_4NS$ (251.12): C, 52.59; H, 3.59; N, 5.58; S, 12.75. Found: C, 52.56; H, 3.63; N, 5.64; S, 12.65.

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