Facile Transformation of Benzocyclobutenones into 2,3-Benzodiazepines via 4π – 8π Tandem Electrocyclic Reactions Involving Net Insertion of Diazomethylene Compounds

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Supporting Information

Experimental procedures

Compounds characterization data

^1H and ^{13}C NMR chart for the compounds **5a–d**, **6a–d**, and **11**

General Remarks. All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over CaH_2 , or purchased from commercial sources. ^1H and ^{13}C NMR spectra were obtained on a Varian UNITY plus 500 instrument, using chloroform peak as an internal reference. Mass spectra were measured on a JEOL D-200 or a JEOL AX 505 mass spectrometer, and the ionization method was electron impact (EI, 70 eV). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica Silica Gel 60N (spherical, neutral, 40-50 μm or 63-210 μm). Starting benzocyclobutenones **1a–d** were prepared according to the reported method or its modification.¹

CAUTION; Some of the diazo compounds may be explosive and should be handled with great care.

General Procedure for the Synthesis of 2,3-Benzodiazepines 5a–d. To a solution of TMSCHN_2 (0.36 mmol, 180 μL of 2.0M Et_2O solution) in dry THF (1 mL) was added 1.6M *n*-BuLi (hexane solution, 243 μL , 0.39 mmol) at -78°C , and the mixture was stirred at -78°C for 0.5 h. A solution of benzocyclobutenone **1** (0.1 mmol) in dry THF (1 mL) was added, and immediately the cooling bath was removed to allow the reaction to warm up to ambient temperature for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 , and dried over MgSO_4 . The solvent was evaporated in vacuo to leave a residue, which was chromatographed on silica gel with hexane– EtOAc (1 : 2) to afford the diazepine **5** as a colorless solid.

1,2-Dihydro-4-(trimethylsilyl)-2,3-benzodiazepin-5-one (5a). mp $103\text{--}105^\circ\text{C}$; ^1H NMR (500MHz, CDCl_3): δ 7.85–7.70 (1H, br), 7.68 (1H, d, $J=7.7$ Hz), 7.51 (1H, t, $J=7.7$ Hz), 7.36 (1H, t, $J=7.7$ Hz), 7.14 (1H, d, $J=7.7$ Hz), 4.48 (2H, s), 0.23 (9H, s); ^{13}C NMR (125MHz, CDCl_3): δ 192.8, 148.4, 141.4, 135.4, 133.3, 128.3, 128.2, 126.1, 54.6, –1.1; IR (KBr): 3247, 1589, 1563 cm^{-1} ; MS m/z 232 (M^+); HRMS Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{OSi}$: 232.1032 (M^+), found: 232.1020.

1,2-Dihydro-8-methoxy-4-(trimethylsilyl)-2,3-benzodiazepin-5-one (5b). mp $144\text{--}146^\circ\text{C}$; ^1H NMR (500MHz, CDCl_3): δ 7.80–7.55 (1H, br), 7.72 (1H, d, $J=8.5$ Hz), 6.87 (1H, dd, $J=8.5$, 2.6 Hz), 6.62 (1H, d, $J=2.6$ Hz), 4.42 (2H, s), 3.85 (3H, s), 0.22

(9H, s); ^{13}C NMR (125MHz, CDCl_3): δ 190.6, 163.9, 149.2, 137.7, 133.9, 130.9, 113.4, 111.4, 55.5, 54.9, -0.9 ; IR (KBr): 3378, 1617, 1591 cm^{-1} ; MS m/z 262 (M^+); HRMS Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2\text{Si}$: 262.1138 (M^+), found: 262.1131.

1,2-Dihydro-7-methoxy-4-(trimethylsilyl)-2,3-benzodiazepin-5-one (5c). mp 139–141°C; ^1H NMR (500MHz, CDCl_3): δ 7.90–7.60 (1H, br), 7.20 (1H, d, $J=2.6$ Hz), 7.07–7.03 (2H, m), 4.43 (2H, s), 3.83 (3H, s), 0.23 (9H, s); ^{13}C NMR (125MHz, CDCl_3): δ 192.2, 159.4, 147.9, 142.4, 128.1, 127.6, 120.5, 111.4, 55.5, 53.9, -1.0 ; IR (KBr): 3249, 1609, 1582 cm^{-1} ; MS m/z 262 (M^+); HRMS Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2\text{Si}$: 262.1138 (M^+), found: 262.1096.

1,2-Dihydro-7,8-dimethoxy-4-(trimethylsilyl)-2,3-benzodiazepin-5-one (5d). mp 166–168°C; ^1H NMR (500MHz, CDCl_3): δ 7.75–7.70 (1H, br), 7.28 (1H, s), 6.59 (1H, s), 4.40 (2H, s), 3.92 (3H, s), 3.90 (3H, s), 0.22 (9H, s); ^{13}C NMR (125MHz, CDCl_3): δ 190.0, 153.3, 149.1, 148.7, 133.5, 129.6, 110.7, 108.7, 56.11, 56.07, 54.6, -0.9 ; IR (KBr): 3233, 1592, 1577 cm^{-1} ; MS m/z 292 (M^+); HRMS Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3\text{Si}$: 292.1243 (M^+), found: 292.1194.

General Procedure for the Synthesis of 2,3-Benzodiazepines 6a–d. To a solution of LDA (0.35 mmol, prepared from diisopropylamine and *n*-BuLi) in dry THF (1 mL) was added ethyl diazoacetate (34 mg, 0.3 mmol) in dry THF (1 mL) at -78°C , and the mixture was stirred at -78°C for 0.5 h. A solution of benzocyclobutenone **1** (0.1 mmol) in dry THF (1 mL) was added, and after stirring for 15 min at same temperature the cooling bath was removed to allow the reaction to warm up to ambient temperature for 1 h. The reaction mixture was diluted with water, acidified with 10% HCl, and extracted with CH_2Cl_2 , and dried over MgSO_4 . The solvent was evaporated in vacuo to leave a residue, which was chromatographed on silica gel with hexane–EtOAc (1 : 10) to afford the diazepine **6** as a colorless solid.

4-Ethoxycarbonyl-1,2-dihydro-2,3-benzodiazepin-5-one (6a). mp 116–118°C; ^1H NMR (500MHz, CDCl_3): δ 8.99 (1H, brs), 7.73 (1H, d, $J=7.7$ Hz), 7.53 (1H, t, $J=7.7$ Hz), 7.39 (1H, t, $J=7.7$ Hz), 7.19 (1H, d, $J=7.7$ Hz), 4.60 (2H, d, $J=3.0$ Hz), 4.35 (2H, q, $J=7.1$ Hz), 1.37 (3H, t, $J=7.1$ Hz); ^{13}C NMR (125MHz, CDCl_3): δ 186.2, 165.1, 140.9, 133.6, 133.2, 131.2, 128.6, 128.3, 126.7, 61.6, 54.4, 14.3; IR (KBr): 3210, 1687, 1619, 1600 cm^{-1} ; MS m/z 232 (M^+); HRMS Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$: 232.0848 (M^+), found:

232.0850.

4-Ethoxycarbonyl-1,2-dihydro-8-methoxy-2,3-benzodiazepin-5-one (6b). mp 163–165°C; ¹H NMR (500MHz, DMSO-*d*₆): δ 10.22 (1H, brs), 7.63 (1H, d, *J*=9.3 Hz), 7.05–6.95 (2H, m), 4.53 (2H, d, *J*=2.5 Hz), 4.18 (2H, q, *J*=7.1 Hz), 3.84 (3H, s), 1.24 (3H, t, *J*=7.1 Hz); ¹³C NMR (125MHz, DMSO-*d*₆): δ 181.7, 165.2, 163.9, 136.6, 132.7, 132.0, 130.0, 114.1, 112.0, 60.4, 55.7, 53.5, 14.1; IR (KBr): 3216, 1692, 1611, 1597 cm⁻¹; MS *m/z* 262 (M⁺); HRMS Calcd for C₁₃H₁₄N₂O₄: 262.0954 (M⁺), found: 262.0955.

4-Ethoxycarbonyl-1,2-dihydro-7-methoxy-2,3-benzodiazepin-5-one (6c). mp 91–93°C; ¹H NMR (500MHz, CDCl₃): δ 8.63 (1H, brs), 7.26 (1H, d, *J*=1.7 Hz), 7.12–7.05 (2H, m), 4.54 (2H, d, *J*=2.6 Hz), 4.36 (2H, q, *J*=7.3 Hz), 3.82 (3H, s), 1.38 (3H, t, *J*=7.3 Hz); ¹³C NMR (125MHz, CDCl₃): δ 185.8, 165.2, 159.5, 141.9, 130.9, 128.1, 125.6, 120.7, 111.6, 61.6, 55.6, 53.8, 14.3; IR (KBr): 3217, 1692, 1599, 1584 cm⁻¹; MS *m/z* 262 (M⁺); HRMS Calcd for C₁₃H₁₄N₂O₄: 262.0954 (M⁺), found: 262.0948.

4-Ethoxycarbonyl-1,2-dihydro-7,8-dimethoxy-2,3-benzodiazepin-5-one (6d). mp 169–170°C; ¹H NMR (500MHz, CDCl₃): δ 7.95 (1H, brs), 7.39 (1H, s), 6.63 (1H, s), 4.53 (2H, d, *J*=3.0 Hz), 4.37 (2H, q, *J*=7.3 Hz), 3.94 (3H, s), 3.91 (3H, s), 1.38 (3H, t, *J*=7.3 Hz); ¹³C NMR (125MHz, CDCl₃): δ 183.0, 165.7, 153.6, 148.8, 133.0, 132.5, 127.6, 110.8, 109.2, 61.6, 56.2, 56.0, 54.5, 14.3; IR (KBr): 3269, 1712, 1595, 1570 cm⁻¹; MS *m/z* 292 (M⁺); HRMS Calcd for C₁₄H₁₆N₂O₅: 292.1059 (M⁺), found: 292.1069.

Isolation of the intermediary adduct 11. According to the general procedure for the synthesis of **6**, the reaction was performed using **1b** (15 mg, 0.1 mmol) as a substrate and quenched with water at –78°C. The aqueous mixture was extracted with CH₂Cl₂, dried over MgSO₄, and evaporated. The residue obtained was chromatographed on silica gel with hexane–EtOAc (2 : 1) to afford the adduct **11** (25 mg, 95%) as a pale yellow oil. ¹H NMR (500MHz, acetone-*d*₆): δ 7.17 (1H, d, *J*=8.5 Hz), 6.81 (1H, s), 6.79 (1H, d, *J*=8.5 Hz), 4.28–4.18 (2H, m), 3.78 (3H, s), 3.66 (1H, d, *J*=14 Hz), 3.37 (1H, d, *J*=14 Hz), 1.24 (3H, t, *J*=7.3 Hz); ¹³C NMR (125MHz, acetone-*d*₆): δ 162.4, 143.2, 139.7, 123.6, 114.8, 109.8, 75.4, 61.1, 55.7, 55.6, 47.4, 14.7; IR (neat): 3419, 2093, 1695, 1604, 1590 cm⁻¹; MS *m/z* 262 (M⁺); HRMS Calcd for C₁₃H₁₄N₂O₄: 262.0954 (M⁺), found: 262.0994.

References

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5a

5c

TMS

5d

6d