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Synthesis and biological evaluation of diverse tetrahydrobenzofuran-4-ones as potent antibacterial agents

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ABSTRACT

Diverse 3,5,6,7-tetrahydrobenzofuran-4-one derivatives (**3a**–**3n**) were synthesized in high yields by ruthenium complex or rhodium complex catalyzed [3 + 2] cycloaddition. The antibacterial activities of these 3,5,6,7-tetrahydrobenzofuran-4-ones were evaluated against Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter aerogenes*) and Gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*). In particular, compound **3b** showed the highest antibacterial activity against *P. aeruginosa* and *S. aureus* (both MICs: 2 μg/mL). Compound **3l**, which has the 2*H*-pyrano[2,3-*b*]benzofuran skeleton, exhibited excellent inhibitory activity against *B. cereus* (MIC: 0.5 μg/mL) as compared with ciprofloxacin (MIC: 2 μg/mL) and ampicillin (MIC: 1 μg/mL).

Introduction

The incidence of bacterial infection has increased alarmingly during the last two decades. Nowadays, infectious diseases caused by microorganisms are a major concern and account for almost 50,000 deaths worldwide daily [1]. Meanwhile, the overuse and abuse of antibiotics have led to the evolution of antibacterial resistance in bacterial strains against currently available antibacterial agents. For instance, Gram-positive bacterial pathogens, such as, *Staphylococus aureus* are resistant to methicillin, *Streptococcus pneumoniae* and *Enterococci* are resistant to penicillin and vancomycin, respectively [2], while Gram-negative bacteria are resistant to β-lactams, quinolones, and macrolides [3]. Accordingly, to overcome the threats posed by multi-drug resistant Gram-positive and Gram-negative bacterial strains, there is an ongoing demand for new antibacterial agents.

Natural products containing furans and dihydrofurans are attractive developmental leads due to their broad spectrum biological activities. Benzofurans bearing various amide, ester, ether, and thioether functional groups exhibit antifungal activities [4], whereas 3-substituted benzofuran-2-amide derivatives have been reported to be cysteine protease inhibitors [5] and anti-proliferative agents against lung cancer cell lines [6]. Benzofuran and benzothiophene derivatives substituted with amide effectively inhibit ischemic cell death and can be useful for the treatment of many diseases [7], and various 2-substituted amide derivatives of benzofuran have been reported to be potent orexin receptor antagonists [8] and anti hyperlipidemic agents [9]. Various 2-substituted benzofuran amide derivatives and 2,3-substituted benzofuran derivatives have good antimicrobial activity [10]. Ethyl ester derivatives of 4-hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid have been reported to act as antitumor agents [11]. Several 2-substituted vinyl ester derivatives of benzofurans have also been reported to be inhibitors of angiogenesis [12]. Furthermore, benzofuran-2-biphenyl sulfonamide derivatives are useful for the treatment of osteoarthritis [13], and substituted benzofuran-1,3-diazepin derivatives have been reported to act as CNS depressants [14].

A literature survey showed that some benzofuran derivatives have antimicrobial activity, but a little work has been conducted on 3,5,6,7-tetrahydrobenzofuran-4-one derivatives [15]. During our studies on the synthesis of bio-active heterocycles [16] and search for novel antibacterial agents [17], we synthesized a series of 3,5,6,7-tetrahydrobenzofuran-4-one derivatives and evaluated

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their *in vitro* antibacterial activities against Gram-negative bacteria [*Escherichia coli* (*E. coli*, KCTC-1924), *Pseudomonas aeruginosa* (*P. aeruginosa*, KCTC-2004), *Enterobacter aerogenes* (*E. aerogenes*, KCTC-2190)] and Gram-positive bacteria [*Staphylococcus aureus* (*S. aureus*, KCTC-1916) and *Bacillus cereus* (*B. cereus*, KCTC-1012)] with the aim of developing novel potent antibacterial agents.

Experimental

Materials and apparatus

Chemicals were purchased from Sigma-Aldrich, Fluka, or Tokyo Chemical Industry (TCI), and used without further purification. All solvents were dried and distilled prior to use. Experiments were conducted in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) containing a fluorescent indicator were used for analytical TLC, and flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Model DPX-300 or Varian VNS-300 spectrometers (at 300 and 75 MHz, respectively). IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-600 mass spectrometer at the Korean Basic Science Institute.

General procedure for the synthesis of 3,5,6,7-tetrahydrobenzofuran-4-ones ***3***.

Method A: To a solution of a cyclic diazodicarbonyl **2** (1.0 mmol) and the corresponding olefin (5.0 mmol) in toluene (2.0 mL) was added tris(triphenylphosphine)ruthenium(II) dichloride [$Ru(PPh_3)_3Cl_2$] (2.0 mol%) at room temperature. The reaction mixture was stirred at 70 °C for the required time and then cooled to room temperature. Water (15 mL) was added and the solution was extracted with ethyl acetate (15 mL × 3). Evaporation of solvent and purification by column chromatography on silica gel using hexane-ethyl acetate (4:1) gave the required products.

Method B: To a solution of a cyclic diazodicarbonyl **2** (1.0 mmol) and the corresponding olefin (5.0 mmol) in fluorobenzene (2.0 mL) at room temperature was added rhodium(II) acetate dimer [$Rh_2(OAc)_4$] (1.0 mol%). The reaction mixture was stirred for the required time and then water (15 mL) was added. The solution was extracted with ethyl acetate (15 mL × 3), and evaporation of the solvent and purification by column chromatography on silica gel using hexane-ethyl acetate (4:1) gave the required products.

*2-Ethoxy-6,6-dimethyl-2,3,6,7-tetrahydrobenzofur-an-4(5*H*)-one (**3a**)*

Yellow oil (Method A, yield: 90%; Method B, yield: 95%). (Refs. [16i,18]). IR (neat): 2960, 2724, 1726, 1636, 1405, 1255, 1195, 1111, 1047, 880, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66–5.62 (m, 1*H*), 3.82–3.71 (m, 1*H*), 3.56–3.46 (m, 1*H*), 2.82 (ddd, *J* = 13.5, 7.2, 1.8 Hz, 1*H*), 2.54 (d, *J* = 15.9 Hz, 1*H*), 2.28–2.04 (m, 4*H*), 1.12 (t, *J* = 7.2 Hz, 3*H*), 1.00 (s, 3*H*), 0.96 (s, 3*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 174.4, 110.6, 108.6, 64.8, 50.6, 37.5, 33.8, 32.4, 28.9, 28.1, 14.8. HR-MS (EI): calcd. for $C_{12}H_{18}O_3$ [M$^+$]: 210.1256, found: 210.1258.

*2-Methoxy-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzo-furan-4(5*H*)-one (**3b**)*

Yellow oil (Method A, yield: 98%; Method B, yield: 92%). (Refs. [16i,19]). IR (neat): 2960, 1720, 1641, 1569, 1385, 1248, 1156, 1064, 934, 838, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 3*H*), 2.77 (d, *J* = 15.9 Hz, 1*H*), 2.56 (d, *J* = 15.9 Hz, 1*H*), 2.21 (s, 2*H*), 2.11 (s, 2*H*), 1.50 (s, 3*H*), 1.00 (s, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 174.1, 115.1, 110.9, 50.5, 50.0, 37.3, 34.9, 33.8, 28.6, 28.4, 25.1. HR-MS (EI): calcd. for $C_{12}H_{18}O_3$ [M$^+$]: 210.1256, found: 210.1257.

*6,6-Dimethyl-3,3a,5,6,7,8a-hexahydrofuro[2,3-*b*]benzofuran-4(2*H*)-one (**3c**)*

Yellow oil (Method A, yield: 97%; Method B, yield: 90%). (Refs. [16i,20]). IR (neat): 2955, 2873, 1723, 1637, 1405, 1253, 1076, 946, 886, 817, 661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, *J* = 5.7 Hz, 1*H*), 4.07 (dd, *J* = 7.5, 7.2 Hz, 1*H*), 3.69 (uneven t, *J* = 7.2, 6.3 Hz, 1*H*), 3.62–3.54 (m, 1*H*), 2.31 (s, 2*H*), 2.19 (d, *J* = 4.2 Hz, 2*H*), 2.08–2.01 (m, 2*H*), 1.01 (s, 3*H*), 1.04 (s, 3*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 176.3, 113.0, 112.1, 67.8, 51.0, 43.6, 37.5, 33.9, 30.3, 28.8, 28.2. HR-MS (EI): calcd. for $C_{12}H_{16}O_3$ [M$^+$]: 208.1099, found: 208.1101.

*7,7-Dimethyl-4,4a,6,7,8,9a-hexahydro-2*H*-pyrano[2,3-*b*]benzofuran-5(3*H*)-one (**3d**)*

Yellow oil (Method A, yield: 82%; Method B, yield: 80%). (Refs. [16i,20b–d]). IR (neat): 2957, 1725, 1638, 1402, 1225, 1139, 1080, 918, 844 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, *J* = 7.8 Hz, 1*H*), 3.74–3.57 (m, 2*H*), 3.05–2.99 (m, 1*H*), 2.24 (s, 2*H*), 2.11 (d, *J* = 4.5 Hz, 2*H*), 1.84–1.68 (m, 2*H*), 1.62–1.53 (m, 1*H*), 1.48–1.38 (m, 1*H*), 1.01 (s, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 175.1, 114.2, 106.6, 60.0, 50.8, 37.3, 35.0, 33.6, 28.9, 27.9, 19.7, 19.0. HR-MS (EI): calcd. for $C_{13}H_{18}O_3$ [M$^+$]: 222.1256, found: 222.1254.

*6,6-Dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl acetate (**3e**)*

Yellow oil (Method A, yield: 75%; Method B, yield: 71%). (Refs. [16i,20b]). IR (neat): 2960, 2879, 1760, 1649, 1407, 1212, 1165, 1052, 946, 849, 780, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 7.5, 2.4 Hz, 1*H*), 3.02 (dd, *J* = 16.2, 7.5 Hz, 1*H*), 2.74 (dd, *J* = 16.2, 2.4 Hz, 1*H*), 2.30 (d, *J* = 8.1 Hz, 2*H*), 2.20 (d, *J* = 5.4 Hz, 2*H*), 2.06 (s, 3*H*), 1.08 (s, 3*H*), 1.03 (s, 3*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 174.2, 169.4, 110.8, 98.8, 50.8, 37.2, 34.2, 31.7, 28.9, 28.2, 20.9. HR-MS (EI): calcd. for $C_{12}H_{16}O_4$ [M$^+$]: 224.1049, found: 224.1051.

*2,6,6-Trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofur-an-2-yl acetate (**3f**)*

Yellow oil (Method A, yield: 80%; Method B, yield: 64%). (Refs. [16i,19a]). IR (neat): 2961, 1767, 1671, 1424, 1362, 1193, 1059, 865, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (s, 2*H*), 2.46 (s, 2*H*), 2.28 (s, 2*H*), 2.13 (s, 3*H*), 2.07 (s, 3*H*), 1.05 (s, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 198.0, 167.3, 165.0, 121.7, 50.4, 42.4, 37.6, 32.8, 29.3, 28.0, 20.7. HR-MS (EI): calcd. for $C_{13}H_{18}O_4$ [M$^+$]: 238.1205, found: 238.1202.

*2,6,6-trimethyl-2-(prop-1-en-2-yl)-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (**3g**)*

Yellow oil (Method A, yield: 87%; Method B, yield: 39%). (Refs. [16i,21]). IR (neat): 2957, 2873, 1637, 1402, 1244, 1165, 1144, 1026, 907, 758, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90, (s, 1*H*), 4.76 (s, 1*H*), 2.76 (d, *J* = 14.7 Hz, 1*H*), 2.55 (d, *J* = 14.4 Hz, 1*H*), 2.23 (s, 2*H*), 2.15 (s, 2*H*), 1.69 (s, 3*H*), 1.43 (s, 3*H*), 1.04 (s, 3*H*), 1.02 (s, 3*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 175.0, 146.4, 110.9, 110.0, 93.5, 50.7, 37.8, 37.2, 34.0, 28.7, 28.3, 26.0, 18.2. HR-MS (EI): calcd. for $C_{14}H_{20}O_2$ [M$^+$] 220.1463; found: 220.1464. HR-MS (EI): calcd. for $C_{14}H_{20}O_2$ [M$^+$]: 220.1463, found: 220.1464.

*Methyl 2,6,6-trimethyl-4-oxo-2,3,4,5,6,7-hexahydro-benzofuran-2-carboxylate (**3h**)*

Yellow oil (Method A, yield: 73%; Method B, yield: 62%). (Refs. [16i,22]). IR (neat): 2956, 1741, 1644, 1450, 1402, 1237, 1172, 1030, 918, 813, 629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3*H*), 3.14 (d, *J* = 14.7 Hz, 1*H*), 2.72 (d, *J* = 14.7 Hz, 1*H*), 2.31 (d, *J* = 10.1 Hz, 2*H*), 2.20 (s, 2*H*), 1.62 (s, 3*H*), 1.07 (s, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 175.0, 172.3, 110.8, 89.3, 52.9, 50.9, 37.6, 37.1, 34.2, 28.7, 28.5, 24.6. HR-MS (EI): calcd. for $C_{13}H_{18}O_4$ [M$^+$]: 238.1205, found: 238.1203.