Journal of the Korean Chemical Society
2022, *Vol. 66, No. 1*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2022.66.1.9

Intramolecular Oxa-Mannich Reaction of 1,3-Dihydro-2-benzofuran-1-ol for Efficient Synthesis of 1-Aminophthalan Derivatives

Heebum Kim and Sung-Gon Kim*
Department of Chemistry, Kyonggi University, 154-42 Gwanggyosan-ro, Yeongtong-gu, Suwon 16227, Korea.
**E-mail: sgkim123@kyonggi.ac.kr*
(Received October 25, 2021; Accepted November 17, 2021)

ABSTRACT. An efficient method for the synthesis of 1-aminophthalans has been developed. The intramolecular oxa-Mannich reaction of 1,3-dihydro-2-benzofuran-1-ols with *p*-toluenesulfonylamine in the presence of Cs_2CO_3 as a base, without using any catalyst, provided the desired 1-aminophthalans in moderate to good yields.

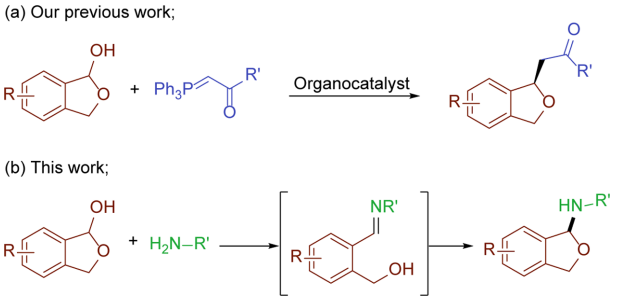
Key words: 1,3-Dihydroisobenzofuran, Phthalan, *p*-Toluenesulfonylamine, Mannich reaction

INTRODUCTION

N,*O*-Acetals, which are important intermediates for various valuable synthetic transformations in organic synthesis,[1,2] are found in natural products and bioactive compounds.[3] In particular, cyclic *N*,*O*-acetals are common privileged structural motifs in many natural products and synthetic pharmaceutical compounds that show important biological activities, including antifungal, antiviral, and anticancer properties.[4] Despite its prevalence and significance, the acyclic *N*,*O*-acetal has received little attention from organic chemists. Because of the inherent instability of *N*,*O*-acetals, the development of a suitable synthetic method is very difficult, and direct reactions of *N*,*O*-acetals are limited.[5] Therefore, the development of an efficient strategy for constructing the *N*,*O*-acetal skeleton remains an active area of research in organic chemistry.

Recently, we reported the enantioselective synthesis of 1-substituted phthalans via the asymmetric catalytic oxa-Michael reaction of 1,3-dihydro-2-benzofuran-1-ols with triphenylphosphoranes using an organocatalyst (*Scheme* 1a).[6] We were interested in further expanding the synthesis of 1-substituted phthalans from 1,3-dihydro-2-benzofuran-1-ols as starting materials. Thus, we focused our attention on the synthetic application of 1,3-dihydro-1-isobenzofuranamines (1-aminophthans) via the reaction of 1,3-dihydro-2-benzofuran-1-ols with amines (*Scheme* 1b).

Phthalans, which are referred to as 1,3-dihydrobenzofurans, are widespread in natural products and biologically active compounds. They exhibit a broad spectrum of pharmacological properties such as antibacterial, antidepressive, anti-inflammatory, and anti-influenza activities.[7]



***Scheme* 1.** Synthesis of 1-substituted phthalan derivatives.

Hence, much effort has been undertaken to develop synthetic routes to new phthalan-containing heterocyclic compounds.[8] However, there are very few reports on the synthesis methods of 1-aminophthans.[9] Herein we present a metal and catalyst free intramolecular oxa-Mannich reaction[10] of 1,3-dihydro-2-benzofuran-1-ol with *p*-toluenesulfonylamine for the efficient synthesis of 1-aminophthalans.

EXPERIMENTAL

General Procedures

Organic solvents were distilled prior to use. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms were visualized by fluorescence quenching and with anisaldehyde stain. ^{1}H and ^{13}C NMR spectra were recorded (400

MHz for ^{1}H and 100 MHz for ^{13}C), and were internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on an FT IR spectrometer and are reported in wave numbers. High-resolution mass spectroscopy (HRMS) was performed by electron impact (EI).

General procedure for the reaction of 1,3-dihydro-2-benzofuran-1-ols with amines

To a solution of 1,3-dihydro-2-benzofuran-1-ol **1** (0.2 mmol), Cs_2CO_3 (0.24 mmol) and molecular sieves 4Å (20 mg) in CH_2Cl_2 (2 mL) was added amine **2** (0.2 mmol) at room temperature. The reaction mixture was stirred at the same temperature until 1,3-dihydro-2-benzofuran-1-ol **1** was complete consumed, as determined by TLC. Then, the resulting mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography with EtOAc/hexanes as eluent to afford desired product **3**.

Benzyl (1,3-dihydroisobenzofuran-1-yl)carbamate (3ab). White solid; m.p. 112–115°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.49 (m, 1H), 7.36 (dd, *J* = 9.7, 6.2 Hz, 7H), 7.25 (s, 1H), 6.91–6.72 (m, 1H), 5.41 (s, 1H), 5.26–5.12 (m, 3H), 5.04 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 140.0, 136.2, 134.1, 129.4, 128.7, 128.4, 128.1, 126.0, 122.8, 121.4, 71.9, 69.8, 67.3; IR (film) 3033, 3032, 2923, 2853, 1746, 1698, 1669, 1527, 1461, 1353, 1263, 1246, 1051, 1011 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{15}NO_3$: 269.1052 Found: 269.1050.

***N*-(1,3-Dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3ac).** White solid; m.p. 169–171°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.40–7.29 (m, 5H), 7.21 (d, *J* = 6.8 Hz, 1H), 6.56 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 5.00 (dd, *J* = 12.6, 2.3 Hz, 1H), 4.92 (d, *J* = 12.7 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 139.4, 138.8, 136.7, 129.8, 129.6, 128.3, 127.4, 123.2, 121.3, 89.1, 72.1, 21.7; IR (film) 3354, 3259, 3063, 3032, 2921, 1597, 1525, 1501, 1450, 1386, 1299, 1153, 1096, 1005 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{15}NO_3S$: 289.0773 Found: 289.0794.

4-Methyl-*N*-(5-methyl-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3bc). White solid; m.p. 159–161°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.01 (s, 1H), 6.51 (d, *J* = 10.1 Hz, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 4.95 (dd, *J* = 12.6, 2.5 Hz, 1H), 4.87 (d, *J* = 12.5 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.8, 139.7, 138.8, 134.0, 129.7, 129.2, 127.3, 122.9, 121.7, 89.0, 72.0, 21.7, 21.5; IR (film) 3253, 2952, 2931, 2855, 1705, 1444, 1342, 1159, 1017 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_3S$: 303.0929 Found: 303.0941.

4-Methyl-*N*-(6-methyl-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3cc). White solid; m.p. 140–142°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.19–7.12 (m, 2H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.50 (s, 1H), 5.14 (s, 1H), 4.96 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.87 (d, *J* = 12.3 Hz, 1H), 2.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 138.8, 138.3, 137.0, 136.5, 130.6, 129.7, 127.4, 123.6, 121.0, 89.0, 72.1, 21.7, 21.3; IR (film) 3267, 2922, 2854, 1756, 1567, 1495, 1443, 1340, 1297, 1156, 1066, 1013 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_3S$: 303.0929 Found: 303.0922.

4-Methyl-*N*-(7-methyl-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3dc). White solid; m.p. 161–163°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 6.4 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.58 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.99 (d, *J* = 12.5 Hz, 2H), 4.88 (d, *J* = 12.8 Hz, 1H), 2.45 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 139.4, 138.9, 134.8, 134.2, 129.9, 129.7, 129.5, 127.3, 118.5, 88.6, 72.2, 22.8, 21.7; IR (film) 3273, 2931, 2920, 2853, 1609, 1597, 1443, 1339, 1304, 1156, 1066, 1002 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_3S$: 303.0929 Found: 303.0933.

4-Methyl-*N*-(4-methyl-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3ec). White solid; m.p. 155–157°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 6.7 Hz, 2H), 6.55 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 10.3 Hz, 1H), 4.95 (dd, *J* = 12.7, 2.2 Hz, 1H), 4.87 (d, *J* = 12.6 Hz, 1H), 2.45 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 138.8, 138.4, 136.4, 131.7, 130.3, 129.7, 128.6, 127.3, 120.4, 89.5, 71.7, 21.7, 18.5; IR (film) 3263, 2940, 2918, 2850, 1722, 1605, 1486, 1443, 1339, 1314, 1264, 1157, 1064, 1010 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_3S$: 303.0929 Found: 303.0899.

***N*-(5-Methoxy-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3fc).** White solid; m.p. 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.40–7.28 (m, 3H), 7.25–7.23 (m, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.14 (d, *J* = 10.1 Hz, 1H),

4.90 (dd, J = 13.4, 2.3 Hz, 1H), 4.83 (d, J = 13.4 Hz, 1H), 3.92 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 143.8, 142.1, 138.6, 134.2, 130.1, 129.8, 127.4, 122.8, 112.0, 89.8, 73.1, 56.9, 22.8; IR (film) 3239, 2955, 2921, 2852, 1612, 1463, 1439, 1377, 1288, 1262, 1158, 1135, 1067, 1020 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_4S$: 319.0878 Found: 319.0907.

***N*-(4-Methoxy-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3gc).** White solid; m.p. 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.54 (dd, J = 10.2, 2.7 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 4.97 (dd, J = 12.9, 2.8 Hz, 1H), 4.89 (d, J = 12.9 Hz, 1H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 143.6, 138.8, 138.6, 130.2, 129.7, 127.5, 127.3, 115.0, 110.7, 89.5, 70.7, 55.5, 21.7; IR (film) 3263, 2937, 2915, 2865, 1605, 1486, 1443, 1339, 1314, 1264, 1157, 1064, 1010 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{17}NO_4S$: 319.0878 Found: 319.0880.

***N*-(5-Bromo-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3hc).** White solid; m.p. 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.81 (m, 2H), 7.50–7.43 (m, 1H), 7.36 (d, J = 0.7 Hz, 1H), 7.33 (dd, J = 8.5, 0.6 Hz, 2H), 7.22 (d, J = 8.1 Hz, 1H), 6.57–6.45 (m, 1H), 5.17 (d, J = 10.3 Hz, 1H), 4.96 (dd, J = 13.0, 2.3 Hz, 1H), 4.88 (d, J = 12.9 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 141.7, 138.5, 135.8, 131.5, 129.8, 127.3, 124.7, 124.7, 123.8, 88.8, 71.5, 21.7; IR (film) 3245, 2925, 2921, 2867, 1441, 1342, 1323, 1159, 1056, 1013 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}BrNO_3S$: 366.9878 Found: 366.9887.

***N*-(6-Bromo-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3ic).** White solid; m.p. 162–163°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.48 (s, 1H), 7.43 (s, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 10.2 Hz, 1H), 5.20 (d, J = 10.1 Hz, 1H), 5.01–4.92 (m, 1H), 4.86 (d, J = 12.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 139.0, 138.5, 138.4, 132.8, 129.8, 127.3, 126.5, 122.8, 121.9, 88.6, 71.9, 21.8; IR (film) 3255, 2931, 2928, 2877, 1554, 1507, 1443, 1340, 1009 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}BrNO_3S$: 366.9878 Found: 366.9859.

***N*-(4-Bromo-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3jc).** White solid; m.p. 171–173°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.81 (m, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 16.9 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 6.62 (dd, J = 10.5, 2.3 Hz, 1H), 5.17 (d, J = 10.3 Hz, 1H), 4.93 (dd, J = 13.4, 2.6 Hz, 1H), 4.86 (d, J = 13.3 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.1, 138.7, 138.5, 132.6, 130.3, 129.8, 127.4, 122.1, 116.0, 90.0, 73.1, 21.8; IR (film) 3263, 2929, 2915, 2850, 1450, 1341, 1315, 1159, 1077, 1014 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}BrNO_3S$: 366.9859 Found: 366.9887.

***N*-(6-Chloro-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3kc).** White solid; m.p. 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.37–7.28 (m, 4H), 7.14 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 8.6 Hz, 1H), 5.18 (d, J = 10.2 Hz, 1H), 4.98 (dd, J = 12.8, 2.4 Hz, 1H), 4.88 (d, J = 12.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.7, 138.5, 137.8, 134.2, 123.0, 129.8, 127.3, 123.5, 122.5, 88.7, 71.8, 21.7; IR (film) 3244, 2915, 2925, 2845, 1442, 1342, 1324, 1160, 1061, 1013 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}ClNO_3S$: 323.0383 Found: 323.0380.

***N*-(6-Fluoro-1,3-dihydroisobenzofuran-1-yl)-4-methylbenzenesulfonamide (3lc).** White solid; m.p. 145–147°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.20–6.96 (m, 3H), 6.51 (s, 1H), 5.19 (s, 1H), 4.97 (d, J = 12.3 Hz, 1H), 4.88 (d, J = 12.4 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J^1 = 246.6 Hz), 143.8, 138.9 (d, J^3 = 8.6 Hz), 138.5, 134.7 (d, J^4 = 2.3 Hz), 129.8, 127.3, 122.6 (d, J^3 = 8.7 Hz), 117.2 (d, J^2 = 23.3 Hz), 110.3 (d, J^2 = 23.9 Hz), 88.8 (d, J^4 = 2.8 Hz), 71.8, 21.7; IR (film) 3245, 2945, 2928, 2844, 1605, 1491, 1437, 1342, 1323, 1245, 1159, 1062, 1011 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}FNO_3S$: 307.0678 Found: 307.0689.

4-Methyl-*N*-(6-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3mc). White solid; m.p. 159–161°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.34 (d, J = 8.1 Hz, 3H), 6.58 (d, J = 10.5 Hz, 1H), 5.21 (d, J = 10.3 Hz, 1H), 5.07 (d, J = 13.5 Hz, 1H), 4.97 (d, J = 13.3 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.4, 142.0, 138.4, 137.6, 131.0, 129.9, 127.3, 126.9, 122.0, 120.6, 88.8, 71.9, 21.7; IR (film) 3248, 2930, 2935, 2848, 1452, 1435, 1328, 1283, 1215, 1158, 1122, 1086, 1057 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{16}H_{14}F_3NO_3S$: 357.0646 Found: 357.0623.

4-Methyl-*N*-(6-nitro-1,3-dihydroisobenzofuran-1-yl)benzenesulfonamide (3nc). White solid; m.p. 190–192°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.9 Hz, 1H), 8.10 (s, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.36 (dd, J = 20.1, 8.1 Hz, 3H), 6.59 (d, J = 8.7 Hz, 1H), 5.30 (s, 1H), 5.11 (d, J = 14.2 Hz, 1H), 5.01 (d, J = 14.1 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.2, 138.6, 138.3, 129.9, 127.3,

126.6, 125.3, 122.3, 119.1, 88.6, 71.8, 21.8; IR (film) 3304, 2952, 2915, 2865, 1555, 1524, 1337, 1321, 1158, 1016 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{15}H_{14}N_2O_5S$: 334.0623 Found: 334.0618.

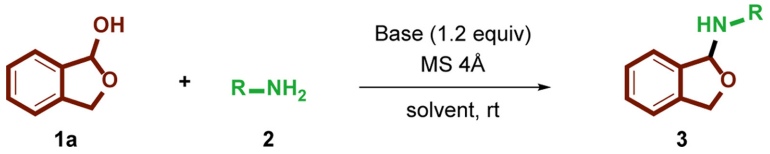
RESULTS AND DISCUSSION

Based on our previous intramolecular oxa-Michael reaction of 1,3-dihydro-2-benzofuran-1-ols with triphenylphosphoranes,[6] we first evaluated the suitability of a protected amine for the oxa-Mannich reaction of 1,3-dihydro-2-benzofuran-1-ol to afford 1-aminophthan. Initially, we carried out the reaction of 1,3-dihydro-2-benzofuran-1-ol **1a** with $BocNH_2$ **2a** in the presence of $CsCO_3$ as the base and 4 Å molecular sieves as the water scavenger (*Table* 1). When the reaction was conducted for 72 h in CH_2Cl_2 at room temperature, 1-aminophthan **3aa** was obtained in only 11% yield (*Table* 1, entry 1). However, when using $CbzNH_2$ **2b**, the yield increased to 41% (*Table* 1, entry 2). Moreover, when using $TsNH_2$ **2c**, the reaction proceeded to completion in 24 h to afford 1-aminophthan **3ac** in 45% yield (*Table* 1, entry 3). Next, Ph_2PONH_2 **2d** was also examined for this oxa-Mannich reaction, and a trace amount of 1-aminophthan **3ad** was obtained (*Table* 1, entry 4). Ts-NH_2 **2c** was identified as the best protected amine for this oxa-Mannich reaction. Next, bases and organic solvents were screened to further optimize the reaction conditions. The use of inorganic bases such as K_2CO_3 and Na_2CO_3 did not improve the results (*Table* 1, entries 5 and 6). Among the various solvents employed, CH_2Cl_2 was the ideal choice for this asymmetric reaction in terms of the reaction outcome (*Table* 1, entries 7−11).

With the optimized conditions in hand, we then explored the substrate scope of 1,3-dihydro-2-benzofuran-1-ols for this intramolecular oxa-Mannich reaction (*Table* 2). The electronic nature and position of the substituents influenced the reaction yield. The reactions proceeded well with both electron-donating substituents such as Me (**3cc**) and electron-withdrawing substituents such as Br (**3ic**), Cl (**3kc**), F (**3lc**), CF_3 (**3mc**), and NO_2 (**3nc**) at the 6-position of the aromatic ring. While the reaction of 5-methyl-substituted benzofuranol **1b** provided the desired product **3bc** in a moderate yield (45%), 5-bromo substituted benzofuranol **1h** gave low yield (24%). In the case of 4-substituted benzofuranols, the electron-donating methyl and methoxy groups gave different results; 4-methoxy-substituted benzofuranol **1g** furnished 1-aminophthalan **3gc** in a high yield (68%), but 4-methyl-substituted benzofuranol **1e** gave a low product yield (20%). Most of the reactions did not proceed completely and the starting material remained, resulting in a moderate yield.

Next, the asymmetric intramolecular oxa-Mannich reaction of 1,3-dihydro-2-benzofuran-1-ol with $TsNH_2$ was attempted. (*Scheme* 2). Unfortunately, the asymmetric oxa-Mannich reaction of benzofuranol **1a**[11] with $TsNH_2$ **2c**, in the presence of squaramide-based catalyst **I** in toluene, furnished

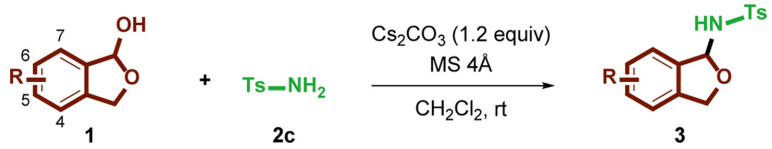
***Table* 1.** Optimization of reaction of **1a** with **2**.[a]

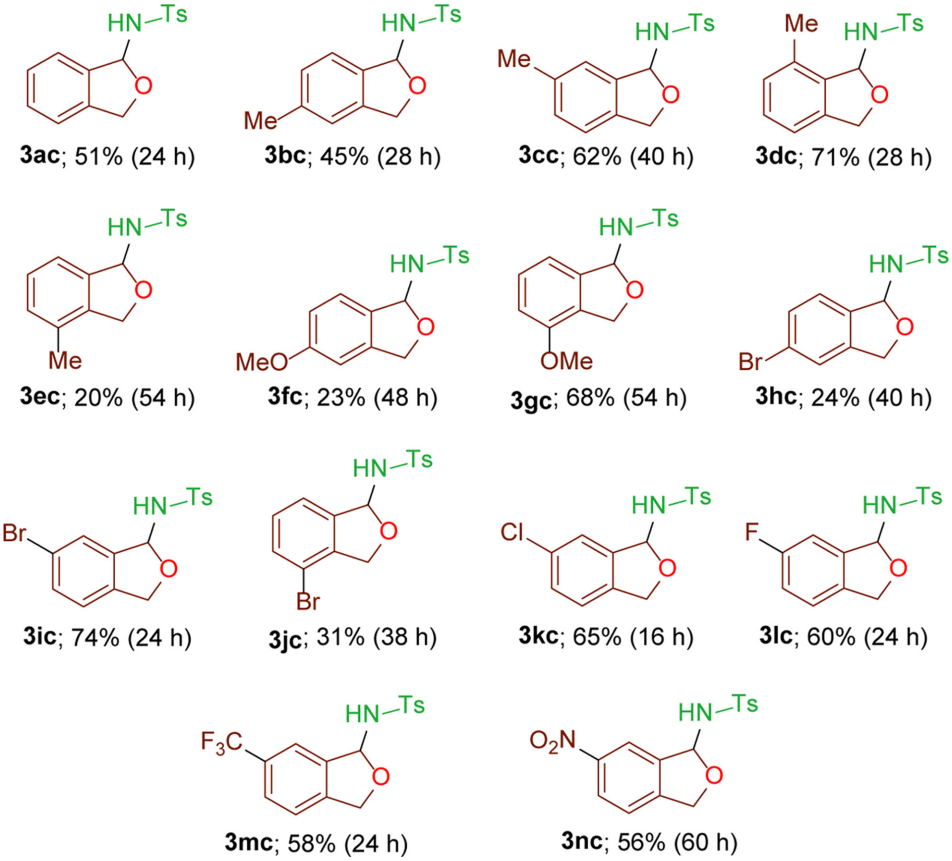


Entry	R	Base	Solvent	Time [h]	Yield[b]
1	Boc (**2a**)	Cs_2CO_3	toluene	72	11
2	Cbz (**2b**)	Cs_2CO_3	toluene	60	41
3	Ts (**2c**)	Cs_2CO_3	toluene	24	45
4	$POPh_2$ (**2d**)	Cs_2CO_3	toluene	72	4
5	Ts (**2c**)	K_2CO_3	toluene	48	43
6	Ts (**2c**)	Na_2CO_3	toluene	52	10
7	Ts (**2c**)	Cs_2CO_3	CH_3CN	72	-
8	Ts (**2c**)	Cs_2CO_3	THF	24	39
9	Ts (**2c**)	Cs_2CO_3	CH_2Cl_2	24	51
10	Ts (**2c**)	Cs_2CO_3	$CHCl_3$	24	37
11	Ts (**2c**)	Cs_2CO_3	MeOH	24	40

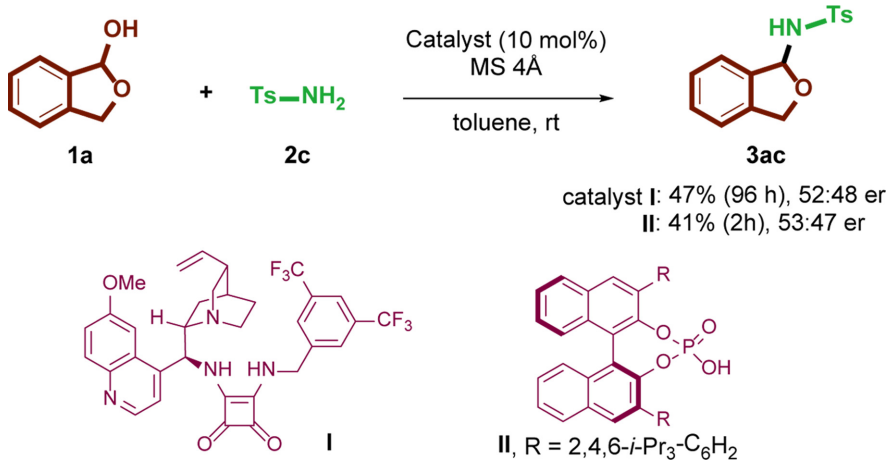
[a]All reactions were carried out in solvent (0.2 M) with **1a** (0.1 mmol), **2** (0.1 mmol), base (1.2 equiv) and molecular sieves 4Å (20 mg). [b]Isolated yield after chromatographic purification.

***Table* 2.** Substrate scope of 1,3-dihydro-2-benzofuran-1-ol.[a,b]





[a]All reactions were carried out in CH_2Cl_2 (0.2 M) with **1** (0.2 mmol), **2c** (0.2 mmol), Cs_2CO_3 (1.2 equiv) and molecular sieves 4Å (20 mg). [b]Isolated yield after chromatographic purification



***Scheme* 2.** Organocatalytic asymmetric reaction of **1a** with **2a**.

3ac in moderate yield but almost as a racemate. Similar results were obtained when using chiral phosphoric acid **II** as an organocatalyst.[12]

CONCLUSION

In summary, we developed a metal-free intramolecular oxa-Mannich reaction of 1,3-dihydro-2-benzofuran-1-ol with *p*-toluenesulfonylamine and obtained the desired 1-aminophthalan derivatives in moderate to good yields. Research on the asymmetric version of this intramolecular oxa-Mannich reaction is ongoing, and the results will be reported in due course.

Acknowledgments. This research was supported by Kyonggi University Research Grant 2020.

REFERENCES

1. For a review, see: Warriner, S. *Category 4: Compounds with Two Carbon-Heteroatom Bonds in Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttguart, 2007; Vol 30, p 7.
2. For recent selected examples, see: (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510. (b) Liu, R.-C.; Huang, W.; Ma, J.-Y.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron Lett.* **2009**, *50*, 4046. (c) Liu, Y.-W.; Ma, R.-J.; Yan, J.-H.; Zhou, Z.; Wei, B.-G. *Org. Biomol. Chem.* **2018**, *16*, 771. (d) Mao, Z.-Y.; Liu, Y.-W.; Han, P.; Dong, H.-Q.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. *Org. Lett.* **2018**, *20*, 1090. (e) Han, P.; Mao, Z.-Y.; Si, C.-M.; Zhou, Z.; Wei, B.-G.; Lin, G.-Q. *J. Org. Chem.* **2009**, *50*, 4046.
3. (a) Tanaka, J.-I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535. (b) Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149. (c) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951.
4. (a) Corey, E. J.; Czakó, B.; Kürti, L. *Molecules and Medicine*; Wiley: Hoboken, 2007. (b) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. *Comprehensive Heterocyclic Chemistry III*; Elsevier: 2008; Vol. 4 and 8.
5. For selected recent examples on synthesis of *N*,*O*-acetals, see: (a) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519. (b) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011. (c) Nguyen, N. H.; Nguyen, Q. H.; Biswas, S.; Patil, D. V.; Shin, S. *Org. Lett.* **2019**, *21*, 9009.
6. (a) Son, E. C.; Kim, S. Y.; Kim, S.-G. *J. Org. Chem.* **2021**, *86*, 6826. (b) Son, E. C.; No, J.; Kim, S.-G. *Bull. Korean Chem. Soc.* **2021**, doi.org/10.1002/bkcs.12402.
7. (a) Waugh, J.; Goa, K. L. *CNS Drugs* **2003**, *17*, 343. (b) Kwon, Y.-J.; Sohn, M.-J.; Kim, C.-J.; Koshino, H.; Kim, W.-G. *J. Nat. Prod.* **2012**, *75*, 271. (c) Suzuki, M.; Honda, K.; Fukazawa, M.; Ozawa, K.; Hagita, H.; Kawai, T.; Takeda, M.; Yata, T.; Kawai, M.; Fukuzawa, T.; Kobayashi, T.; Sato, T.; Kawabe, Y.; Ikeda, S. *J. Pharmacol. Exp. Ther.* **2012**, *341*, 692. (d) Ariefta, N. R.; Azim, M.; Aboshi, T.; Koseki, T.; Taniguchi, Y.; Fujita, M.; Shiono, Y. *Org. Lett.* **2020**, *22*, 3161.
8. For reviews of phthalans, see: (a) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213. (b) Albano, G.; Aronica, L. A. *Synthesis* **2018**, *50*, 1209. (c) Ilya, E.; Kulikova, L.; Van der Eycken, E. V.; Voskressensky, L. *Chemistry Open* **2018**, *7*, 914.
9. (a) Takedam Y.; Hayakawa, J.; Yano, K.; Minakata, S. *Chem. Lett.* **2012**, *41*, 1672. (b) Prier, C. K.; Zhang, R. K.; Buller, A. R.; Brinkmann-Chen, S.; Arnold, F. H. *Nat. Chem.* **2017**, *9*, 629. (c) Wang, L.; Agnew, D. W.; Yu, X.; Figueroa, J. S.; Cohen, S. M. *Angew. Chem., Int. Ed.* **2018**, *57*, 511.
10. For selected recent examples on oxa-Mannich reaction, see: (a) Liu, Y.; Ao, J.; Paladhi, S.; Song, C. E.; Yan, H. *J. Am. Chem. Soc.* **2016**, *138*, 16486. (b) Li, T.-R.; Lu, L.-Q.; Wang, Y.-N.; Wang, B.-C.; Xiao, W.-J. *Org. Lett.* **2017**, *19*, 4098. (c) Wang, Z.-H.; Zhang, Z.-Y.; You, Y.; Zhao, J.-Q.; Zhou, M.-Q.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *Tetrahedron* **2019**, *75*, 3456.
11. For reviews on squaramide catalysis, see: a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253. (b) Rouf. A.; Tanyeli, C. *Curr. Org. Chem.* **2016**, *20*, 2996. (c) Zhao, B.-L.; Li, J.-H.; Du, A.-M. *Chem. Rec.* **2017**, *17*, 994.
12. For selected reviews on chiral phosphoric acid catalysis, see: (a) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (c) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G. *Chem.-Eur. J.* **2018**, *24*, 3925.