One-Step Transformation of Tetrahydropyranyl Ethers Using Indium(III) Triflate as the Catalyst

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Received June 26, 2009; accepted July 18, 2009; published online July 27, 2009

A convergent one-step transformation of tetrahydropyranyl (THP) ethers is described. According to our earlier experiments, indium(III) triflate has proven to be an efficient catalyst for the transformation of THP ethers into their corresponding acetates. In further intensive work, we have developed a useful transforming reaction of THP ethers using various anhydride moieties. Indium(III) triflate was confirmed as a suitable catalyst, furnishing good to excellent yields. The details of this one-step transformation are described.

Key words tetrahydropyranyl ether; indium(III) triflate; catalyst; one-step transformation

Tetrahydropyranyl (THP) group is a well-utilized moiety, mainly as a tool to protect alcohol units due to its feasibility of installation and low cost. Stirring the free alcohols with 3,4-dihydro-2*H*-pyran (DHP) under acidic conditions can easily produce THP-protected alcohols.[1—8] Also, THP-protected alcohols are generally stable under a wide range of reaction conditions and reagents, such as metal hydrides, alkyllithiums, Grignard reagents, and catalytic hydrogenation.[9—13] For the THP ethers, a number of deprotecting methods have been introduced.[14] Various acids, including AcOH,[15] pyridinium *para*-toluenesulfonate (PPTS),[1] boric acid,[16] and TsOH,[17] can cleave THP ethers to regenerate free alcohols with high efficacy. Although some of the metal reagents can be expensive and toxic, the cleavage of THP ethers using transition metal reagents, such as $PdCl_2(CH_3CN)_2$,[18] $CuCl_2 \cdot 2H_2O$,[19,20] and $CuSO_4 \cdot 5H_2O$,[21] has also been reported.

Previously, we have reported a couple of convenient reaction methods using indium or indium-related reagents.[22—25] The authors have recently developed a practical approach to tetrahydropyranylation and depyranylation of various alcohols using indium(III) triflate.[26] It is worth noting that with the same catalyst, the reactions proceed in directions of both protection and deprotection. In the presence of a catalytic amount of indium(III) triflate, protection of alcohols is carried out using CH_2Cl_2 as the solvent, whereas deprotection uses $MeOH/H_2O$ as the solvent. Kamal *et al.* also reported that tetrahydropyranylation can be controlled using catalytic aluminum(III) triflate.[27] Another report has shown the cleavage of THP ethers using titanium(III) triflate in good yields.[28] According to our earlier experiments, indium(III) triflate was revealed to be an efficient catalyst for the transformation of THP ethers into their corresponding acetates. In further intensive work, we have developed a useful transforming reaction of THP ethers using various anhydride moieties with indium(III) triflate as the catalyst. Herein, we report the details of this one-step transformation.

Results and Discussion

THP-protected benzyl alcohol and *N*-(2-hydroxyethyl)-phthalimide were used as the starting materials. First, the suitability of the catalysts was examined by reactions with acetic anhydride (Chart 1). In both cases, the reaction proceeded and produced excellent yields in a shorter time when indium(III) triflate was employed as the catalyst (Table 1, entries 1 and 3), as compared with indium(III) chloride (Table 1, entries 2 and 4). Giving the satisfactory results with indium(III) triflate, we then expanded our investigation to the other types of anhydrides. The reactions were carried out with THP-protected benzyl alcohol, *N*-(2-hydroxyethyl)phthalimide, and a wide range of anhydrides (Chart 2).

As expected, the reactions with another aliphatic anhydride of isobutyric anhydride generated similar satisfactory results (Table 2, entries 1 and 7). In the case of benzoic anhydride, the reaction required an extended period of time, although acceptable results were obtained (Table 2, entries 2 and 8). With the exception of entry 5, these conditions were then applied to the cyclic anhydrides, and the reactions produced entirely poor yields. These results were presumably due to the low reaction temperature. When reactions were resumed at reflux using THF as the solvent, good to excellent outcomes were yielded. Meanwhile, the reaction was completed in the case of *cis*-1,2-cyclohexanedicarboxylic anhydride (Table 2, entry 5) without stirring at reflux, which was

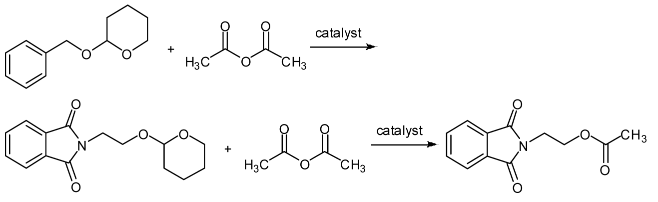

Chart 1

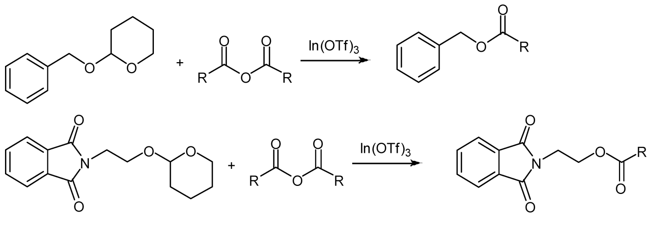

Chart 2

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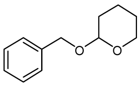
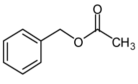
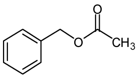
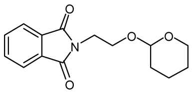
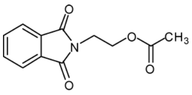
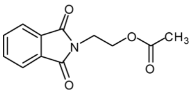
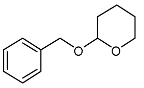
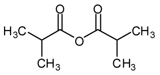
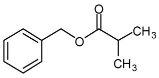
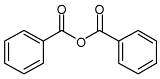
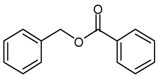
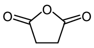
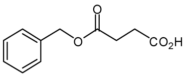
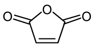
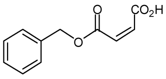
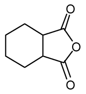
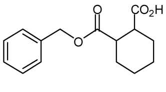
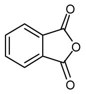
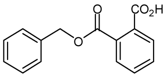
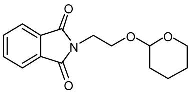
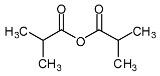
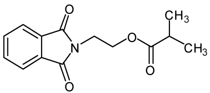
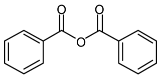
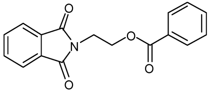
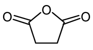
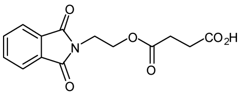
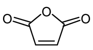
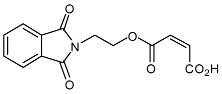
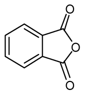
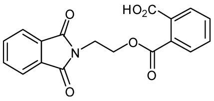
Table 1. Reactions to Compare the Catalysts

Entry	Starting Material	Product	Catalyst[a]	Solvent	Temp. (°C)	Time	Yield[b] (%)
1			In(OTf)$_3$	CH_2Cl_2	r.t.	1 h	93
2			$InCl_3$	CH_2Cl_2	r.t.	24 h	61
3			In(OTf)$_3$	CH_2Cl_2	r.t.	40 min	96
4			$InCl_3$	CH_2Cl_2	r.t.	24 h	67

a) The reactions were performed using 0.05 eq of the catalysts. *b*) Isolated yields.

Table 2. Reactions with Indium(III) Triflate[a]

Entry	Starting material	Reactant	Product	Solvent	Temp. (°C)	Time	Yield[b] (%)
1				CH_2Cl_2	r.t.	50 min	82
2				CH_2Cl_2	r.t.	22 h	69
3				THF	Reflux	50 min	86
4				THF	Reflux	22 h	94
5				CH_2Cl_2	r.t.	18 h	90
6				THF	Reflux	21 h	60
7				CH_2Cl_2	r.t.	50 min	96
8				CH_2Cl_2	r.t.	20 h	76
9				THF	Reflux	17 h	54
10				THF	Reflux	22 h	61
11				THF	Reflux	26 h	73

a) The reactions were performed using 0.05 eq of indium(III) triflate. *b*) Isolated yields.

driven presumably by the release of a steric strain of the 5-member ring of 1,2-cyclohexanedicarboxylic anhydride. However, the reaction of THP-protected *N*-(2-hydroxyethyl) phthalimide with 1,2-cyclohexanedicarboxylic anhydride did not produce satisfactory results regardless of the solvent. It is worth noting that no major structural isomerization was observed in the cases of maleic anhydride (Table 2, entries 4 and 10) or *cis*-1,2-cyclohexanedicarboxylic anhydride (Table

2, entry 5).

Conclusion

In summary, we have developed a valid method for a one-pot transformation of THP ethers. The reaction is not structurally restricted, and it is widely applicable to transformations with the various types of anhydrides. Compared with indium(III) chloride, another possible catalyst, indium(III) triflate suitably catalyzed the transformation and furnished high yields. Further utility for these methods is being studied.

Experimental

General Information ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-ECA-500. The Chemical shifts (δ) are reported in parts per million (ppm) and J values in Hz. High resolution mass spectra were measured on a JEOL JMS-BU20 (EI), JEOL JMS-700 MStation (FAB), and Shimadzu LCMS-IT-TOF (ESI). Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrometer. Melting points were measured on a Yanaco MP-S3 melting points apparatus and were uncorrected. All commercially available chemicals were used without purification.

Representative Experimental Procedure *N*-(2-Hydroxyethyl)phthalimide THP ether (143 mg, 0.52 mmol, entry 3, Table 1) was taken in dry CH_2Cl_2 (5 ml) under argon atmosphere at 0 °C, to which Ac_2O (63 mg, 0.62 mmol) and In(OTf)$_3$ (15 mg, 0.026 mmol) were added and stirred at the same temperature for 10 min and then at room temperature for 40 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated by rotary evaporation. Purification by flash chromatography using hexane/ethyl acetate (8 : 2) furnished acetyl-protected *N*-(2-hydroxyethyl)phthalimide as a white solid (116 mg, 96% yield).

Benzyl Acetate: Colorless oil; yield 93%; IR (neat) ν: 3067, 3034, 2955, 1740, 1381, 1364, 1229, 1026, 750, 698 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.38—7.31 (m, 5H), 5.12 (s, 2H), 2.09 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.3, 135.7, 128.2, 127.92, 127.87, 65.9, 20.5; MS (EI): [M]$^+$ Calcd for $C_9H_{10}O_2$ *m/z*: 150.0681, Found 150.0666.

2-Phthalimidoethyl Acetate: White solid; yield 96%; mp 88.5—89.1 °C; IR (KBr) ν: 1775, 1740, 1709, 1429, 1397, 1371, 1358, 1244, 1036, 721 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.84 (dd, 2H, J=5.7, 2.9 Hz), 7.72 (dd, 2H, J=5.8, 2.9 Hz), 4.30 (t, 2H, J=5.2 Hz), 3.94 (t, 2H, J=5.2 Hz), 2.00 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.8, 168.1, 134.0, 131.9, 123.3, 61.5, 37.0, 20.7; MS (FAB): [M+H]$^+$ Calcd for $C_{12}H_{12}NO_4$ *m/z*: 234.0761, Found 234.0767.

Benzyl Isobutyrate: Colorless oil; yield 82%; IR (neat) ν: 2974, 2938, 1736, 1470, 1456, 1190, 1152, 750, 698 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.38—7.31 (m, 5H), 5.14 (s, 2H), 2.63 (hep, 1H, J=7.5 Hz), 1.22 (d, 6H, J=7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 176.6, 136.1, 128.3, 127.9, 127.8, 65.8, 33.8, 18.8; MS (EI): [M]$^+$ Calcd for $C_{11}H_{14}O_2$ *m/z*: 178.0994, Found 178.0974.

Benzyl Benzoate: Colorless oil; yield 69%; IR (neat) ν: 3065, 3034, 1713, 1452, 1314, 1271, 1109, 1071, 1026, 712 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.16—8.14 (m, 2H), 7.58 (t, 1H, J=7.5 Hz), 7.52—7.37 (m, 7H), 5.42 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 166.2, 135.9, 132.9, 130.0, 129.5, 128.4, 128.2, 128.1, 128.0, 66.5; MS (FAB): [M+Na]$^+$ Calcd for $C_{14}H_{12}O_2Na$ *m/z*: 235.0730, Found 235.0747.

Benzyl Succinate: White solid; yield 86%; mp 54.0—54.8 °C; IR (KBr) ν: 3449, 3024, 2932, 1728, 1690, 1427, 1358, 1258, 1180 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.39—7.31 (m, 5H), 5.16 (s, 2H), 2.73—2.67 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 178.2, 172.0, 135.6, 128.5, 128.2, 128.1, 66.6, 28.84, 28.79; MS (FAB): [M+Na]$^+$ Calcd for $C_{11}H_{12}O_4Na$ *m/z*: 231.0628, Found 231.0653.

Benzyl Maleate: Colorless oil; yield 94%; IR (neat) ν: 3059, 2947, 2874, 1728, 1636, 1454, 1412, 1258, 1215, 1169 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ: 7.43—7.31 (m, 5H), 6.42 (d, 2H, J=2.3 Hz), 5.20 (s, 2H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 166.5, 166.1, 136.8, 131.6, 130.3, 129.3, 129.1, 129.0, 67.3; MS (FAB): [M+Na]$^+$ Calcd for $C_{11}H_{10}O_4Na$ *m/z*: 229.0471, Found 229.0485.

Benzyl 1,2-Cyclohexanedicarboxylate: Colorless oil; yield 90%; IR (neat) ν: 2942, 2859, 1728, 1701, 1454, 1246, 1217, 1175, 1128, 1028, 698 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.38—7.28 (m, 5H), 5.16 (d, 1H, J=12.1 Hz), 5.10 (d, 1H, J=12.6 Hz), 2.92—2.85 (m, 2H), 2.09—2.01 (m, 2H), 1.86—1.75 (m, 2H), 1.59—1.37 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 180.0, 173.3, 135.9, 128.4, 128.0, 127.9, 66.2, 42.4, 42.3, 26.1, 25.9, 23.6, 23.5; MS (ESI): [M−H]$^-$ Calcd for $C_{15}H_{17}O_4$ *m/z*: 261.1132, Found 261.1153.

Benzyl Phthalate: Colorless oil; yield 60%; IR (neat) ν: 3036, 2940, 2866, 1724, 1701, 1288, 1126, 1072, 741 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, 1H, J=7.5 Hz), 7.72 (d, 1H, J=7.5 Hz), 7.61—7.54 (m, 2H), 7.44—7.28 (m, 5H), 5.37 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.0, 167.9, 135.2, 133.1, 132.0, 130.8, 130.0, 129.7, 128.7, 128.5, 128.4, 128.3, 67.7; MS (FAB): [M+H]$^+$ Calcd for $C_{15}H_{13}O_4$ *m/z*: 257.0808, Found 257.0826.

2-Phthalimidoethyl Isobutyrate: Colorless oil; yield 96%; IR (neat) ν: 2974, 2943, 1775, 1717, 1470, 1427, 1393, 1366, 1192, 1153, 999, 721 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (dd, 2H, J=5.8, 2.9 Hz), 7.64 (dd, 2H, J=5.8, 2.9 Hz), 4.24 (t, 2H, J=5.2 Hz), 3.87 (t, 2H, J=5.2 Hz), 2.40 (hep, 1H, J=6.9 Hz), 1.01 (d, 6H, J=6.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 176.5, 167.8, 133.8, 131.7, 123.1, 61.1, 36.9, 33.6, 18.6; MS (FAB): [M+H]$^+$ Calcd for $C_{14}H_{16}NO_4$ *m/z*: 262.1074, Found 262.1072.

2-Phthalimidoethyl Benzoate: White solid; yield 76%; mp 103.0—104.8 °C; IR (KBr) ν: 3055, 1775, 1767, 1709, 1424, 1393, 1277, 1119, 999, 714 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J=8.6, 1.2 Hz), 7.83 (dd, 2H, J=5.8, 2.9 Hz), 7.69 (dd, 2H, J=5.8, 2.9 Hz), 7.50 (t, 1H, J=7.5 Hz), 7.38 (t, 2H, J=7.5 Hz), 4.52 (t, 2H, J=5.2 Hz), 4.10 (t, 2H, J=5.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 167.9, 166.2, 134.0, 132.9, 131.8, 129.6, 129.5, 128.3, 123.3, 62.2, 36.9; MS (FAB): [M+H]$^+$ Calcd for $C_{17}H_{14}NO_4$ *m/z*: 296.0917, Found 296.0935.

2-Phthalimidoethyl Succinate: White solid; yield 54%; mp 106.9—107.3 °C; IR (KBr) ν: 3040, 2951, 2932, 1736, 1709, 1694, 1424, 1397, 1204, 1161, 725 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.86 (dd, 2H, J=5.2, 2.9 Hz), 7.73 (dd, 2H, J=5.2, 2.9 Hz), 4.34 (t, 2H, J=5.2 Hz), 3.96 (t, 2H, J=5.2 Hz), 2.66—2.58 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 177.5, 171.9, 168.1, 134.1, 131.9, 123.4, 62.0, 36.9, 28.70, 28.65; MS (FAB): [M+H]$^+$ Calcd for $C_{14}H_{14}NO_6$ *m/z*: 292.0816, Found 292.0828.

2-Phthalimidoethyl Maleate: Colorless oil; yield 61%; IR (neat) ν: 3366, 1773, 1713, 1586, 1427, 1397, 1223, 1177, 721 cm^{-1}; ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.84 (dd, 2H, J=5.8, 2.9 Hz), 7.79 (dd, 2H, J=5.8, 2.9 Hz), 6.52 (d, 1H, J=12.0 Hz), 5.71 (d, 1H, J=12.1 Hz), 4.35 (t, 2H, J=5.7 Hz), 3.96 (t, 2H, J=5.7 Hz); ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 174.3, 169.5, 167.2, 143.6, 135.4, 133.2, 124.2, 118.9, 62.4, 37.8; MS (FAB): [M+Na]$^+$ Calcd for $C_{14}H_{11}NO_6Na$ *m/z*: 312.0479, Found 312.0489.

2-Phthalimidoethyl Phthalate: White solid; yield 73%; mp 159.0—159.5 °C; IR (KBr) ν: 2953, 1742, 1702, 1697, 1427, 1399, 1292, 991, 721 cm^{-1}; ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 7.84 (dd, 2H, J=5.2, 2.9 Hz), 7.80—7.74 (m, 3H), 7.62—7.54 (m, 3H), 4.52 (t, 2H, J=5.2 Hz), 4.04 (t, 2H, J=5.2 Hz); ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 170.1, 169.7, 169.6, 135.4, 133.9, 133.3, 133.0, 132.4, 132.0, 130.2, 129.6, 124.2, 63.9, 37.9; MS (FAB): [M+H]$^+$ Calcd for $C_{18}H_{14}NO_6$ *m/z*: 340.0816, Found 340.0832.

Acknowledgments The authors are grateful to Professor T. Kunieda (Sojo University) for his kind suggestions.

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