

Niobium(V) chloride: an active Lewis acid catalyst for tetrahydropyranylation of alcohols and phenols

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Dedicated to Dr. A.V. Rama Rao on the occasion of his 70th birthday

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Abstract

Diverse alcohols and phenols were effectively converted into their corresponding THP-ethers with DHP and catalytic amount of Niobium(V) chloride. The reactions were carried out in DCM at room temperature with short reaction time and excellent yields.

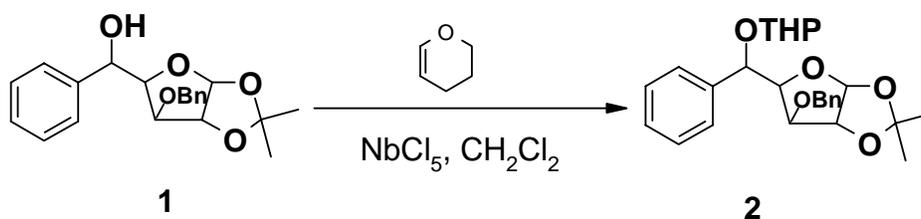
Keywords: Dihydropyran, alcohols, phenols, tetrahydropyranylation, niobium (V) chloride

Introduction

During endeavors of the total synthesis of biologically active natural products, which involves the protection and deprotection of a variety of functional groups. Among the various functional groups, hydroxy is very familiar and its protection as tetrahydropyranyl ether (THP) is a common and widely used transformation in organic synthesis.¹ The tetrahydropyran derivatives are attractive for the reason that they are less expensive, easily deprotected and stable under variety of reaction conditions such as strongly basic media, metal hydrides, metal triflates, Grignard reagents, acylating agents, oxidative reagents and alkylating agents.² THP groups are also the protective groups of choice in peptide, nucleotide, carbohydrate and steroid chemistry.³

A variety of Brønsted as well as Lewis acid catalysts are used for tetrahydropyranylation of hydroxy functions.⁴ These include *p*-TsOH,⁵ ion-exchange resins,^{5c} heteropoly acids,^{5d} Nafion-H,^{5e} Montmorillonite K-10,^{5f} Amberlyst H-15,^{5g} ceric ammonium nitrate,^{5h} sulfuric acid on silica gel,⁵ⁱ and ionic liquid.⁶ However, many of these methods have drawbacks such as harsh acidic conditions, long reaction times, expensive catalyst, the lack of generality, reflux conditions, formation of polymeric by-products of the dihydropyran and isomerization. In addition, stoichiometric amounts of reagents or even in excess are sometime required to effect complete

conversion of the substrate. Niobium (V) chloride is a well-known mild Lewis acid catalyst useful for effecting a variety of transformations.⁷



Scheme 1

Results and Discussion

As part of our continuing interest in the development of new synthetic methodologies,⁸ we wish to report the Lewis acid efficiency of niobium(V) chloride for the tetrahydropyranylation of various alcohols and phenols. Reactions were carried out in dichloromethane. In a typical experimental procedure, a variety of alcohols (primary, secondary, benzylic, allylic and phenolic) were treated with 3,4-dihydro-2*H*-pyran (DHP, 1.2 equiv.), and niobium(V) chloride (10 mol%) in DCM to obtain the corresponding THP-ethers. We investigated the substrate scope of diverse alcohols including those that contain sensitive functionalities like acetonide (entry **q**), esters (entries **d** and **g**), ether (entry **1**) and carbamates (entries **h** and **p**) presents (Table 1) our observation along with the optimized parameters for obtaining the best yields of tetrahydropyranyl derivatives. In all cases, the THP-protection took place efficiently and gave excellent yields without affecting the other protecting groups. The reactions are reasonably fast, 2-3 h, which holds well even with hindered alcohols like menthol (entry **l**) and borneol (entry **n**). The reaction conditions are mild enough not to induce any isomerization of double bonds or chiral centres during tetrahydropyranylation of allylic moieties (entries **d**, **h** and **s**). The acid sensitive alcohol like Baylis-Hillman adduct (entry **d**) also underwent protection without formation of any side products. Another important feature of this method is that absolute anhydrous conditions are not required.

Table1. Niobium(V)chloride promoted tetrahydropyranylation of alcohols

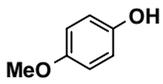
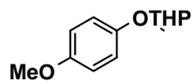
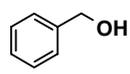
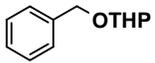
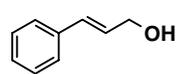
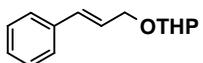
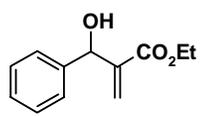
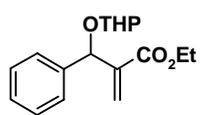
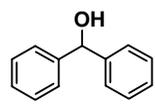
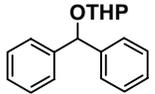
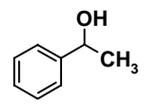
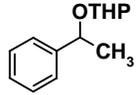
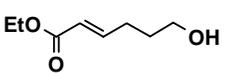
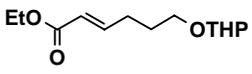
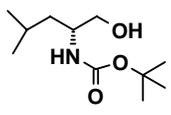
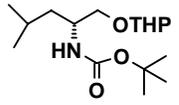
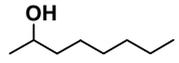
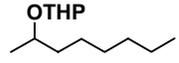
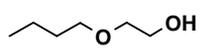
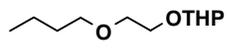
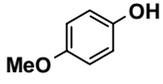
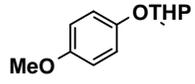
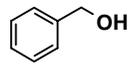
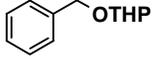
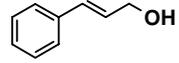
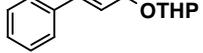
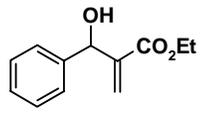
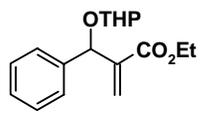
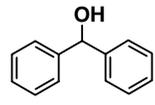
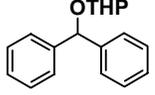
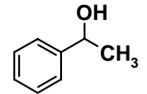
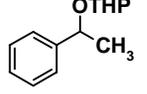
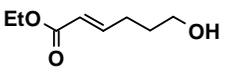
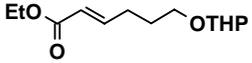
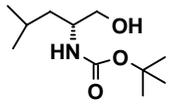
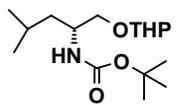
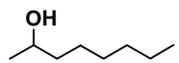
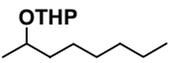
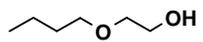
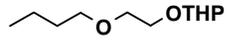
Entry	Substrate	Reaction time (h)	Producta	Yield ^b	Ref
a		2.0		92	5f
b		2.5		90	5f
c		2.5		86	2b
d		2.0		90	
e		2.0		94	2c
f		2.0		95	2b
g		2.5		88	
h		3.0		86	
i		3.0		91	
j		3.0		87	

Table1. Continued

Entry	Substrate	Reaction time (h)	Product ^a	Yield ^b	Ref
a		2.0		92	5f
b		2.5		90	5f
c		2.5		86	2b
d		2.0		90	
e		2.0		94	2c
f		2.0		95	2b
g		2.5		88	
h		3.0		86	
i		3.0		91	
j		3.0		87	

^a All products were characterised by ¹H NMR, IR and mass spectrometry.

^b Yield refers to pure products after column chromatography.

In conclusion, the present method describes an efficient and practical method for the protection of a wide range of structurally varied alcohols and phenols as tetrahydropyranyl ethers using niobium(V) chloride as catalyst. The significant advantages of this methodology over previously reported methods are milder reaction temperatures (room temperature), shorter reaction times, higher substrate to catalyst ratios, better yields, easier work-up conditions and a greater tolerance of functional groups present on substrates. We envisage that this method will find practical application for the protection of alcohols in multistep organic synthesis.

Experimental Section

General Procedures. All commercial reagents were used without purification. The reaction mixtures were stirred magnetically and monitored by TLC using 0.25 mm E-Merck silica gel 60 F₂₅₄ precoated glass plates, which were visualized with UV light. IR spectra were recorded on a Perkin Elmer FT-IR-240 C spectrophotometer. ¹H NMR spectra were recorded on Bruker Avance 300 MHz spectrometer and Unity 400 MHz spectrometer. Chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. Mass spectra were recorded on a Finnigan Mat 1020 mass spectrometer operating at 70 eV. Niobium(V) chloride was purchased from Aldrich (99%) and used as such.

General procedure for the tetrahydropyranylation of alcohols

To a solution of alcohol (5 mmol), and dihydropyran (6 mmol) in dichloromethane (10 ml) was added niobium(V) chloride (0.5 mmol) and the mixture stirred at room temperature. The reaction progress was monitored by thin layer chromatography (Table 1). After the complete conversion of the starting material, the reaction mixture was diluted by adding dichloromethane (20 ml) and washed with water (2 x 20 ml) followed by brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography by eluting with a mixture of ethyl acetate and *n*-hexane.

Spectral data for selected compounds

2-[Phenyl,tetrahydropyran-2-yloxy]methyl-2-propen-1-oate (2d). Colourless oil; I.R (neat): ν 3057, 2973, 2849, 1720, 1605, 1538, 1423, 1379, 1256, 1169, 1123, 1072, 983, 857, 741 cm⁻¹; ¹H NMR (CDCl₃): δ 1.23 (t, 3H, *J* = 6.0 Hz), 1.55-1.65 (m, 4H), 1.70-1.90 (m, 2H), 3.40-3.90 (m, 2H), 4.15 (q, 2H, *J* = 6.0 Hz), 4.50 (s, 1H), 5.58 (s, 1H), 6.08 (s, 1H), 6.32 (s, 1H), 7.30-7.40 (m, 5H); EIMS *m/z* (%): 290 (M⁺, 12), 244 (15), 206 (23), 189 (56), 143 (10), 115 (82), 105 (18), 85 (100), 67 (10), 57 (28), 41 (37); Anal. Calcd for C₁₇H₂₂O₄ C, 70.32; H, 7.64 Found: C, 70.29; H, 7.68.

Ethyl 6-(tetrahydropyran-2-yloxy)hex-2-en-1-oate (2g). Colourless oil; I.R (neat): ν 1728, 1598, 1522, 1447, 1368, 1207, 1126, 1064, 1012, 934, 821, 732 cm⁻¹; ¹H NMR (CDCl₃): δ 1.20 (t, 3H, *J* = 6.5 Hz), 1.50-1.65 (m, 6H), 1.80-1.95 (m, 2H), 2.15-2.24 (m, 2H), 3.40-3.70 (m, 4H),

4.15 (q, 2H, $J = 6.5$ Hz), 4.52 (s, 1H), 5.70 (d, 1H, $J = 14.0$ Hz), 6.78-6.96 (m, 1H). EIMS m/z (%): 242 (M^+ , 18), 213 (12), 169 (10), 157 (100), 128 (31), 85 (62), 59 (23), 41 (11); Anal.Calcd for $C_{13}H_{22}O_4$ C, 64.44; H, 9.15 Found: C, 64.42; H, 9.10.

[*N*-tert-Butyloxycarbonyl]-4-methyl-1-(tetrahydropyran-2-yloxy)pentan-2-amine (2h). Light yellow oil; I.R (neat): ν 3321, 1724, 1615, 1581, 1459, 1327, 1261, 1109, 1028, 972, 861, 741 cm^{-1} ; 1H NMR ($CDCl_3$): δ 0.96 (2s, 6H), 1.20-1.30 (m, 2H), 1.38 (s, 9H), 1.50-1.65 (m, 5H), 1.72-1.85 (m, 2H), 3.40-3.60 (m, 5H), 4.40 (s, 1H), 4.65 (br s, 1H). EIMS m/z (%): 301 (M^+ , 21), 244 (15), 216 (12), 200 (10), 159 (42), 115 (100), 97 (11), 85 (36), 56 (21), 42 (18); Anal.Calcd for $C_{16}H_{31}NO_4$ C, 63.75; H, 10.37; N, 4.65 Found: C, 63.70; H, 10.39; N, 4.71.

2-[Tetrahydropyran-2-yloxy]octane (2i). Colourless oil; I.R (neat): ν 1605, 1535, 1473, 1412, 1361, 1271, 1208, 1142, 1069, 1013, 918, 826, 732 cm^{-1} ; 1H NMR ($CDCl_3$): δ 0.90 (t, 3H, $J = 6.5$ Hz), 1.08-1.12 (m, 2H), 1.20-1.26 (m, 2H), 1.30-1.40 (m, 7H), 1.50-1.60 (m, 6H), 1.65-1.80 (m, 2H), 3.40-3.50 (m, 1H), 3.60-3.70 (m, 1H), 3.82-3.90 (m, 1H), 4.60 (s, 1H). EIMS m/z (%): 214 (M^+ , 12), 131 (25), 119 (10), 100 (12), 85 (18), 69 (100); Anal.Calcd for $C_{13}H_{26}O_2$ C, 72.84; H, 12.23 Found: C, 72.89; H, 12.19.

2-(2-*n*-Butoxyethoxy)tetrahydropyran (2j). Colourless oil; I.R (neat): ν 1518, 1453, 1361, 1208, 1172, 1064, 1026, 991, 817, 741 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 7.0$ Hz), 1.30-1.45 (m, 2H), 1.50-1.70 (m, 7H), 1.80-1.90 (m, 1H), 3.40-3.60 (m, 6H), 3.75-3.88 (m, 2H), 4.60 (s, 1H); EIMS m/z (%): 202 (M^+ , 11), 101 (15), 85 (100), 67 (13), 57 (63), 41 (38); Anal.Calcd for $C_{11}H_{22}O_3$ C, 65.31; H, 10.96 Found: C, 65.28; H, 10.99.

2-[(1,7,7-Trimethyl)bicyclo[2,2,1]hept-2-yloxy]tetrahydropyran (2n). Colourless oil. I.R (neat): ν 1459, 13570, 1309, 1205, 1179, 1131, 1109 1068, 1034, 1016, 993, 831, 753 cm^{-1} ; 1H NMR ($CDCl_3$): δ 0.85 (s, 6H), 0.91 (s, 3H), 1.20-40 (m, 4H), 1.50-1.65 (m, 6H), 1.80-1.90 (m, 1H), 2.00-2.10 (m, 2H), 3.40-3.50 (m, 1H), 3.70-3.90 (m, 2H), 4.55 (br s, 1H). EIMS m/z (%): 238 (M^+ , 12), 108 (10), 85 (100), 57 (20), 41 (30); Anal.Calcd for $C_{15}H_{26}O_2$ C, 75.58; H, 10.99 Found: C, 75.52; H, 10.96.

***N*-[tert-Butyloxycarbonyl]-3-(tetrahydropyran-2-yloxy)piperidine (2p).** Light yellowish oil; I.R (neat): ν 3349, 1726, 1610, 1596, 1528, 1439, 1382, 1256, 1192, 1121, 1063, 1008, 941, 829, 742 cm^{-1} ; 1H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.56-1.66 (m, 6H), 1.72-1.93 (m, 4H), 2.60-2.80 (m, 2H), 3.40-3.50 (m, 1H), 3.75-3.95 (m, 4H), 4.60 (s, 1H). EIMS m/z (%): 285 (M^+ , 20), 228 (12), 200 (31), 143 (22), 99 (100), 81 (51), 43 (33); Anal.Calcd for $C_{15}H_{27}NO_4$ C, 63.13; H, 9.54; N, 4.91 Found: C, 63.10; H, 9.59; N, 4.95.

2,2-Dimethyl-5-[phenyl(tetrahydropyran-2-yloxy)methyl]tetrahydrofuro[2,3-*d*][1,3]di-oxole (2q). Colourless oil; I.R (neat): ν 3072, 2964, 2832, 1597, 1536, 1471, 1347, 1290, 1223, 1169, 1043, 982, 837, 751 cm^{-1} ; 1H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.31 (s, 3H), 1.50-1.60 (m, 4H), 1.75-1.95 (m, 2H), 3.33 (br s, 1H), 3.60-3.95 (m, 2H), 4.05-4.18 (m, 1H), 4.40-4.50 (m, 1H), 4.58 (s, 1H), 4.65 (s, 2H), 4.90-4.98 (m, 1H), 5.98 (d, 1H, $J = 4.5$ Hz), 7.20-7.40 (m, 10H). EIMS m/z (%): 440 (M^+ , 12), 355 (21), 313 (15), 255 (27), 164 (52), 106 (100), 85 (61), 51 (35); HRMS (FAB) Calcd for $C_{26}H_{34}O_6$ (M^+) 442.2354 Found: 442.2348.

2-Phenyl-3-(tetrahydropyran-2-yloxy)-5-hexene (2s). Colourless oil; I.R (neat): ν 3057, 2982, 2834, 1592, 1523, 1461, 1312, 1247, 1168, 1042, 1013, 949, 861, 742 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 1.50 (s, 3H), 1.65-1.85 (m, 4H), 2.25-2.40 (m, 2H), 2.50-2.60 (m, 2H), 2.65-2.75 (m, 1H), 3.40-3.50 (m, 1H), 3.60-3.78 (m, 1H), 3.85-3.95 (m, 1H), 4.65 (d, 1H, $J = 5.0$ Hz), 5.00-5.10 (m, 2H), 5.70-5.90 (m, 1H), 7.10-7.25 (m, 5H). EIMS m/z (%): 260 (M^+ , 10), 219 (15), 159 (12), 143 (10), 106 (16), 117 (25), 91 (65), 85 (100), 67 (14), 57 (20), 41 (26); Anal.Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2$ C, 78.42; H, 9.29 Found: C, 78.47; H, 9.23.

Acknowledgements

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References and Notes

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