IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 8, Issue 8 Ver. I (Aug. 2015), PP 20-25
www.iosrjournals.org

Green Synthesis of Tetrahydropyranyl Ethers of Phenols In The Presence Of Triethylamine in Water as Solvent

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***Abstract**: Green synthesis of tetrahydropyranylation of phenols has been developed in the presence of water and triethylamine as catalyst. The protocol allows different phenols into tetrahydropyranyl ethers in good to excellent yields. Phenols carrying electron-withdrawing groups respond well in this procedure.*

Keywords: *Tetrahydroyranylation, Phenols, Triethylamine, Protection, Organic catalyst*.

I. Introduction

The selection of protection deprotection strategy in synthetic organic chemistry is unavoidable owing to its chemoselcetive transformations in the presence of diverse functional groups[1]. In this line of strategy, protection of hydroxyl functional group plays a vital role in synthetic chemistry. Among the various hydroxyl protection groups, the tetrahydropyranyl ethers (THP ethers) are attractive because of low cost of 3,4-dihydro-2H-pyran (DHP) and stability of THP derivatives towards a variety of reaction conditions such as strong bases, Grignard reagents, hydrides, redox reagents, alkylating, acylating agents and catalytic hydrogenation and easy removal under mild acidic conditions.

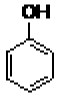
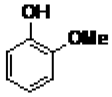
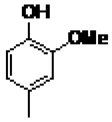
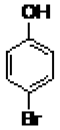
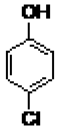
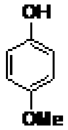
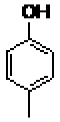
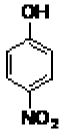
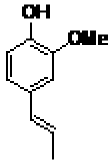
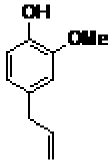
This transformation is generally achieved using both protonic as well as Lewis acid catalysts. Consequently a variety of reagents such as pTSA,[2] $BF_3.OEt_2$,[3] $ZnCl_2$ impregnated alumina,[4] TBATB,[5] PPTS,[6] acetonyltriphenylphosphonium bromide,[7] aluminium chloride hexahydrate,[8] $In(OTf)_3$,[9] $Bi(OTf)_3$,[10] LiOTf,[11] dialkylimidazolium tetrachloroaluminates,[12] $InCl_3$ immobilized in ionic liquids,[13] bromodimethylsulfonium bromide,[14] cupric sulphate pentahydrate,[15] CAN,[16] and bismuth(III) nitrate pentahydrate[17] and photosensitization[18] have been introduced for tetrahydropyranyl protection of alcohols and phenols. However, some of these procedures suffer due to the use of expensive and moisture sensitive catalysts, high temperature, longer reaction times and incompatibility with other functional groups, and some reagents also have to be freshly prepared prior to use.[6,8,11,15] Though metal triflates have been found to be effective catalysts for tetrahydropyranylation, these reagents have limited applicability since they are relatively expensive, difficult to handle, and not readily available. Furthermore, the procedures involving these reagents require harsh and inert reaction conditions.

II. Results And Discussion

With an objective of developing a viable and green procedure for tetrahydropyranylation, we focused on finding a cheap and efficient green protocol that would give high yields and easy handling procedure under aerobic conditions. In continuation of our work on novel organocatalysts for organic transformations, we became interested to use very cheap triethylamine as organocatalyst for the aforementioned reaction. To the best of our knowledge triethylamine has not been used as a catalyst for tetrahydropyranylation of phenols. In this paper, we describe the successful implementation of triethylamine as an organocatalyst for the tetrahydropyranylation of various phenols.

Initially, the tetrahydropyranylation of phenol (1 m mol) was performed with DHP (1 m mol) in water (5 ml) in the presence of 20 mol% triethylamine at room temperature under aerobic conditions (Table 1, Entry 1). As a result the transformation took place in 24 h to afford its tetrahydropyranyl ether **2g** in 88% yield. We have also performed the reaction with 10 mol% catalyst but the reaction was completed in 36 h with 85% yield of **2g**. Using the protocol, various phenols were transformed easily into the corresponding THP-ethers in good yields (Table 1). It is observed that phenols bearing electron withdrawing substituents gave protected THP-ethers in good yields (Table 1, Entry 8). Importantly, no isomerisation of double bond took place in case of eugenol (Table 1, Entry 10).

Table 1. Tetrahydropyranylation of alcohols and phenols catalyzed by triethylamine.[a]

Entry	**Substrate (ROH)**	**Time (h)**	**Product (ROTHP)**	**Yield[b] (%)**
1		24	**2a**	88
2		24	**2b**	80
3		24	**2c**	86
4		24	**2d**	91
5		24	**2e**	82
6		24	**2f**	91
7		24	**2g**	85
8		24	**2h**	84
9		24	**2i**	80
10		24	**2j**	81

[a] Yields are pure and isolated

III. Conclusion

In conclusion, we have developed a simple and convenient method for tetrahydropyranylation of phenols in the presence of triethylamine. triethylamine is an effective, very cheap and viable catalyst in above synthetic transformations with various phenols. We believe that this methodology is valuable addition to modern synthetic methodologies.

Experimental Section

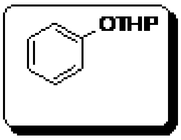
General. All starting materials and other reagents were purchased from commercial suppliers and were used without further purification. Nuclear Magnetic Resonance (NMR) spectra were recorded on bruker instrument operating at 500 MHz and ^{1}H NMR spectra are obtained with TMS as internal standard in CDCl3 solvent. ^{13}C

NMR spectra are also obtained in CDCl3 instrument operating at 125 MHz. IR and Mass spectra were recorded. The reactions were assayed by thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. When peak multiplicities are reported, the following abbreviations are used s$_=$singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublet, dt=doublet of triplet. Coupling constants are reported in Hertz.

General procedure for the synthesis of tetrahydropyranyl ethers

A solution of phenol (1 m mol), dihydro-2H-pyran (DHP, 1 m mol), and triethylamine (0.2 m mol, 20 mol%), in H_2O (2 ml) were stirred at ambient temperature for an appropriate time (monitored by TLC or GC). After completion of the reaction (24 h), the compounds were extracted with CH_2Cl_2 and dried (anhydrous. Na_2SO_4), and concentrated under reduced pressure to yield almost pure product. The product was purified further by column chromatography on silica gel using ethyl acetate/hexanes as the eluent (1:9).

Phenyl tetrahydro-2H-pyran-2-yl ether (2a):



Reaction time: 24 h.

Yield: 0.170 g (88%) as colourless oily liquid.

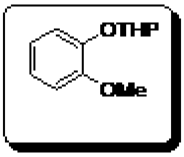
IR (neat) ν_{max}: 3059, 2943, 1598, 1589, 964, 920, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): 7.32-7.28 (m, 2H), 7.09-7.06 (m, 2H), 7.02-6.99 (m, 1H), 5.44 (t, J = 3.5 Hz, 1H), 3.97-3.92 (m, 1H), 3.64-3.60 (m, 1H), 2.07-2.00 (m, 1H), 1.90-1.87 (m, 2H), 1.75-1.59 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): 157.0, 129.3, 121.5, 116.4, 96.2, 61.9, 30.3, 25.1, 18.7 ppm.

MS: m/z = 179 [M + H]$^+$.

2-Methoxyphenyl tetrahydro-2H-pyran-2-yl ether (2b):



Reaction time: 24 h.

Yield: 0.191 g (80%) as colourless oily liquid.

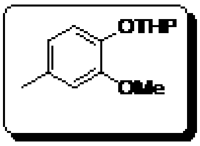
IR (neat) ν_{max}: 3055, 2943, 1592, 1502, 1455, 872, 770 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): 7.02-6.99 (m, 2H), 6.84-6.82 (m, 2H), 5.29 (t, J = 3.5 Hz, 1H), 3.97-3.92 (m, 1H), 3.76 (s, 3H), 3.61-3.58 (m, 1H), 2.02-1.98 (m, 1H), 1.87-1.83 (m, 2H), 1.69-1.60 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): 154.9, 151.5, 118.2, 114.9, 97.7, 62.4, 56.0, 30.9, 25.7, 19.3 ppm.

MS: m/z = 209 [M + H]$^+$.

2-Methoxy-4-methylphenyl tetrahydro-2H-pyran-2-yl ether (2c):



Reaction time: 24 h.

Yield: 0.202 g (86%) as colourless oily liquid.

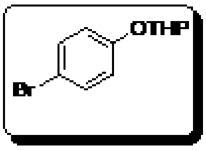
IR (neat) ν_{max}: 3035, 2941, 1590, 1511, 912, 871, 812 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): 7.01 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 1.5 Hz, 1H), 6.69 (dt, J = 8.0, 1.0 Hz, 1H), 5.33 (t, J = 3.0 Hz, 1H), 4.05-4.00 (m, 1H), 3.84 (s, 3H), 3.60-3.57 (m, 1H), 2.30 (s, 3H), 2.03-2.01 (m, 1H), 1.94-1.93 (m, 1H), 1.90-1.87 (m, 1H), 1.69-1.60 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): 150.1, 143.9, 132.3, 121.0, 118.2, 113.3, 97.8, 62.1, 55.9, 30.3, 25.2, 21.0, 18.8 ppm.

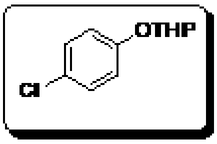
MS: m/z = 222 [M]$^+$.

4-Bromophenyl tetrahydro-2H-pyran-2-yl ether (2d):



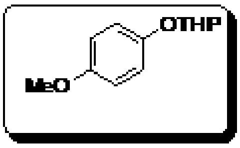
Reaction time: 24 h.
Yield: 0.241 g (91%) as colourless oily liquid.
IR (neat) ν_{max}: 3064, 2943, 1589, 1578, 919, 823, 645 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 7.38-7.35 (m, 2H), 6.95-6.92 (m, 2H), 5.37 (t, J = 3.0 Hz, 1H), 3.89-3.84 (m, 1H), 3.61-3.57 (m, 1H), 1.86-1.83 (m, 2H), 1.72-1.63 (m, 2H), 1.62-1.57 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 156.1, 132.1, 118.2, 113.7, 96.4, 61.9, 30.1, 25.0, 18.5 ppm.
MS: m/z = 258 $[M + 2]^+$.

4-Chlorophenyl tetrahydro-2H-pyran-2-yl ether (2e):



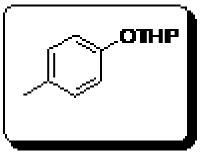
Reaction time: 24 h.
Yield: 0.191 g (82%) as colourless oily liquid.
IR (neat) ν_{max}: 3076, 2944, 1596, 1583, 1489, 1021, 965, 919 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 7.22-7.19 (m, 2H), 6.99-6.96 (m, 2H), 5.34 (t, J = 3.0 Hz, 1H), 3.88-3.83 (m, 1H), 3.60-3.56 (m, 1H), 2.00-1.95 (m, 1H), 1.86-1.82 (m, 2H), 1.68-1.56 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 156.1, 129.7, 126.9, 118.3, 97.1, 62.4, 30.7, 25.6, 19.1 ppm.
MS: m/z = 214 $[M + 2]^+$.

4-Methoxyphenyl tetrahydro-2H-pyran-2-yl ether (2f):



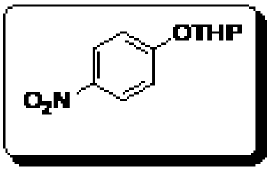
Reaction time: 24 h.
Yield: 0.199 g (91%) as colourless oily liquid.
IR (neat) ν_{max}: 3039, 2943, 2872, 1506, 969, 920, 827 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 7.19 (dd, J = 8.0, 1.5 Hz, 1H), 6.98-6.95 (m, 1H), 6.91-6.88 (m, 2H), 5.38 (t, J = 3.5 Hz, 1H), 4.04-3.99 (m, 1H), 3.85 (s, 3H), 3.61-3.58 (m, 1H), 2.07-2.04 (m, 1H), 1.95-1.94 (m, 1H), 1.90-1.88 (m, 1H), 1.69-1.59 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 154.4, 151.0, 117.7, 114.4, 97.2, 61.9, 55.5, 30.4, 25.2, 18.8 ppm.
MS: m/z = 193 $[M + H]^+$.

4-Methylphenyl tetrahydro-2H-pyran-2-yl ether (2g):



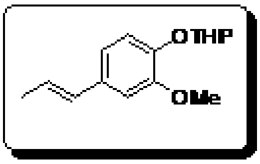
Reaction time: 24 h.
Yield: 0.180 g (85%) as colourless oily liquid.
IR (neat) ν_{max}: 3027, 2942, 1609, 1585, 969, 920, 817 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 7.07-7.05 (m, 2H), 6.95-6.92 (m, 2H), 5.35 (t, J = 3.5 Hz, 1H), 3.93-3.88 (m, 1H), 3.59-3.55 (m, 1H), 2.27 (s, 3H), 2.01-1.96 (m, 1H), 1.85-1.81 (m, 2H), 1.67-1.55 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 154.9, 130.8, 129.7, 116.4, 96.5, 61.9, 30.4, 25.2, 20.4, 18.8 ppm.
MS: m/z = 193 $[M + H]^+$.

4-(Tetrahydro-2H-pyran-2-yloxy)benzaldehyde (2h):



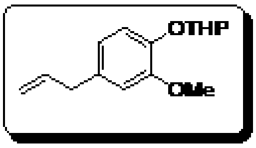
Reaction time: 24 h.
Yield: 0.187 g (84%) as colourless oily liquid.
IR (neat) ν_{max}: 3050, 2947, 2756, 1669, 1602, 966, 834, 787 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 9.90 (s, 1H), 7.85-7.83 (m, 2H), 7.18-7.16 (m, 2H), 5.56 (t, J = 3 Hz, 1H), 3.86 (td, J = 22.0, 11.0, 3.5 Hz, 1H), 3.66-3.63 (m, 1H), 2.04-1.98 (m, 1H), 1.92-1.89 (m, 2H), 1.77-1.69 (m, 2H), 1.65-1.61 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 190.9, 162.1, 131.7, 130.4, 116.4, 96.0, 62.0, 30.0, 24.9, 18.3 ppm.
MS: m/z = 206 [M]$^+$.

2-Methoxy-4-(1-propenyl)phenyl tetrahydro-2H-pyran-2-yl ether (2i):



Reaction time: 24 h.
Yield: 0.225 g (80%) as colourless oily liquid.
IR (neat) ν_{max}: 3045, 2950, 1600, 1591, 965, 927, 882 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 6.95 (d, J = 8.5 Hz, 1H), 6.79 (bs, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.23 (d, J = 15.5 Hz, 1H), 6.05-5.98 (m, 1H), 5.27 (t, J = 3.0 Hz, 1H), 3.92-3.87 (m, 1H), 3.75 (d, J = 1.5 Hz, 3H), 3.50-3.47 (m, 1H), 1.98-1.91 (m, 1H), 1.85-1.83 (m, 1H), 1.76 (d, J = 6.5 Hz, 3H), 1.58-1.50 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 150.3, 145.4, 132.8, 130.7, 124.1, 118.7, 118.0, 109.8, 97.7, 62.1, 56.0, 30.3, 25.3, 18.8, 18.3 ppm.
HRMS (ESI) m/z Calcd for $C_{15}H_{21}O_3$ (M+H)$^+$, 249.1491; Found, 249.1495.

2-Methoxy-4-(2-propenyl)phenyl tetrahydro-2H-pyran-2-yl ether (2j):



Reaction time: 24 h.
Yield: 0.233 g (81%) as colourless oily liquid.
IR (neat) ν_{max}: 3019, 2941, 1600, 1581, 962, 917, 871 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): 7.05 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 8.0, 1.5 Hz, 1H), 6.00-5.92 (m, 1H), 5.35 (t, J = 3.0 Hz, 1H), 5.11-5.05 (m, 2H), 4.04-3.99 (m, 1H), 3.83 (s, 3H), 3.60-3.57 (m, 1H), 3.33 (d, J = 6.5 Hz, 2H), 2.03-1.86 (m, 3H), 1.66-1.61 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): 150.6, 144.9, 137.9, 134.8, 121.0, 118.5, 115.9, 113.2, 98.1, 62.4, 56.3, 40.2, 30.7, 25.6, 19.2 ppm.
MS: m/z = 248 [M]$^+$.

Associated Contents

Supporting Information

^{1}H NMR, ^{13}C NMR, IR and Mass spectra for compounds 2a-2j. This material is available free of charge via internet at http://pubs.acs.org.

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Author Contribution

These authors contributed equally to the work described in this paper.

Acknowledgment

I am thankful to Department of Chemistry, Acharya Nagarjuna University, Guntur, Andhra Pradesh for providing the facilities to carry out research work and I am gratefully acknowledge financial support from University Grant Commission (UGC) New Delhi, India.

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