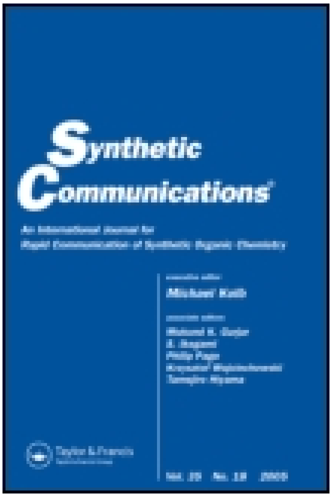


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Mild and Efficient Tetrahydropyranylation of Alcohols

Kyung Hoi Cha [a] , Tae Won Kang [a] , Hong-Woo Lee [a] , Eung-Nam Kim [a] , Nam-Hee Choi [a] , Jung-Woo Kim [a] & Chung Il Hong [a]

[a] Chong Kun Dang Research Institute , 410, Shindorim-Dong, Guro-Gu, Seoul, 152-600, Korea

To cite this article: Kyung Hoi Cha , Tae Won Kang , Hong-Woo Lee , Eung-Nam Kim , Nam-Hee Choi , Jung-Woo Kim & Chung Il Hong (1998) A Mild and Efficient Tetrahydropyranylation of Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:12, 2131-2136, DOI: 10.1080/00397919808007027

To link to this article: http://dx.doi.org/10.1080/00397919808007027

SYNTHETIC COMMUNICATIONS, 28(12), 2131-2136 (1998)

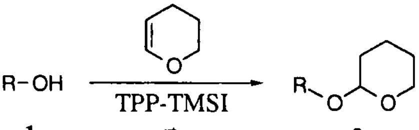
A MILD AND EFFICIENT TETRAHYDROPYRANYLATION OF ALCOHOLS

Kyung Hoi Cha*, Tae Won Kang*, Hong-Woo Lee, Eung-Nam Kim,
Nam-Hee Choi, Jung-Woo Kim, and Chung Il Hong

Chong Kun Dang Research Institute,
410, Shindorim-Dong, Guro-Gu, Seoul 152-600, Korea

Abstract : Triphenylphosphine (TPP)-iodotrimethylsilane (TMSI) was found to be a convenient and highly effective catalyst for the tetrahydropyranylation of aliphatic and aromatic alcohols with dihydropyran in dichloromethane at ambient temperature.

Tetrahydropyranyl (THP) ether is one of the most widely used protective groups for alcohols and phenols in organic synthesis because of its low cost, its general stability to most nonacidic reagents such as hydrides, organometallics, strong bases and catalytic reduction, and the ease with which it can be removed.[1)]



1 2

So far, a number of methods have been reported for the preparation of tetrahydropyranyl ether using TsOH,[2)] PPTS,[3)] K-10 clay,[4)] TMSI,[5)] and

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*To whom the correspondence should be addressed.

$Ph_3P.HBr$⁶⁾ and so on as a catalyst. However a few methods were published in literature for the tetrahydropyranylation of tertiary alcohols.⁷⁾

Now we wish to report a mild and efficient tetrahydropyranylation of aliphatic alcohols (primary, secondary and tertiary) and aromatic alcohols with triphenylphosphine (TPP)-iodotrimethylsilane (TMSI).

All alcohols employed in this reaction except for tertiary alcohols were converted to the corresponding THP ethers within 2 hours without side reaction (entry **a-i**). Although longer reaction time was required in case of tertiary alcohols (entry **j-l**), their THP ethers were obtained in good yields. Moreover, the present method can be effectively applied to the substrates containing a variety of functional group including acid sensitive group (entry **d-f**).

It is well known that TMSI catalyzes the tetrahydropyranylation of alcohols. But, according to the literature,⁵⁾ the reaction of tertiary alcohol with TMSI failed to give the THP ether. On the contrary, not only our present method can be utilized for tertiary alcohol, but also provide useful alternative to the tetrahydropyranylation.

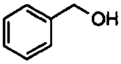
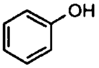
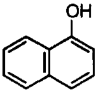
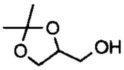
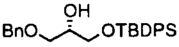
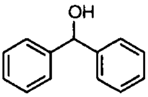
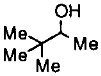
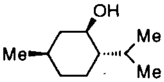
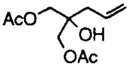
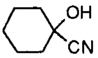
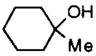
It seems that TPP plays a key role in this reaction by scavenging hydrogen iodide (HI) generated from the reaction of alcohol and TMSI, followed by TPP.HI-catalyzed tetrahydropyranylation.

The desired THP ethers were simply purified by column chromatography and the results are summarized in table 1.

Experimental Section

All reactions were conducted under anhydrous conditions in solvents dried over molecular sieves type 4 A under nitrogen atmosphere. ^1H-NMR spectra were recorded on a Bruker DPX400 MHz spectrometer using TMS as an internal

Table 1 Tetrahydropyranylation of alcohols with Ph_3P-TMSI

Entry	Alcohol[a]	DHP[b] (eq.)/Catalyst (mol %)	Time (h)	Yield[c] (%)
a		1.2/1	0.5	97
b		1.2/1	1	90
c		1.2/2	1	93
d		1.2/1	0.5	92
e		1.2/1	0.5	95
f		1.5/1	2	90
g		1.2/1	0.5	96
h		1.2/1	1	92[d]
i		1.5/3	2	95
j		2/3	40	80
k		2/3	12	92
l		2/3	6	92[d]

[a] MEM=2-methoxyethoxymethyl; Bn=benzyl; TBDPS=*t*-butyldiphenylsilyl [b] DHP= dihydropyran [c] Yield refers to the pure isolated product but not optimized. [d] volatile

standard. The coupling constants (*J*) are reported in Hz. Merck silica gel 60 (70-230 mesh) was used for thin layer chromatography (TLC) analysis. The yields reported refer to the pure isolated products.

General procedure for the tetrahydropyranylation of alcohols 1 and the spectral data of 2. To a solution of alcohol (**1**, 1 mmol) and dihydropyran (1.2-2 mmol) in 2-5 mL of anhydrous dichloromethane was added 0.1 M TPP-TMSI (1-3 mol %)[8] in dichloromethane. The above mixture was stirred under nitrogen atmosphere at room temperature. The progress of reaction was mornitored by thin layer chromatography. After the disappearance of starting material on TLC, the reaction mixture was diluted with dichloromethane (30 mL), then washed with 5% $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL) successively. The organic layer was dried over $MgSO_4$ and evaporated to give the crude THP ether, which was purified by column chromatography to afford the pure THP ether **2** as a colorless oil.

The spectral data for **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ **2a**: 1.54-1.91 (m, 6H), 3.54-3.60 (m, 1H), 3.91-3.97 (m, 1H), 4.65 (ABq, *J*=12 Hz, 2H), 4.72-4.74 (m, 1H), 7.26-7.40 (m, 5H); **2b**: 1.63-2.04 (m, 6H), 3.60-3.64 (m, 1H), 3.91-3.97 (m, 1H), 5.43-5.45 (m, 1H), 6.98-7.32 (m, 5H); **2c**: 1.60-2.30 (m, 6H), 3.60-3.70 (m, 1H), 3.95-4.01 (m, 1H), 5.69 (like t, *J*=3.0 Hz, 1H), 7.17 (d, *J*=7.0 Hz, 1H), 7.41 (t, *J*=7.7 Hz, 1H), 7.49-7.53 (m, 3H), 7.82-7.85 (m, 1H), 8.32-8.36 (m, 1H); **2d**: 1.40-1.80 (m, 6H), 3.34 (s, 3H), 3.40-3.60 (m, 4H), 3.60-3.71 (m, 4H), 3.80-3.90 (m, 2H), 4.50-4.60 (m, 1H), 4.71 (s, 2H); **2e**: 1.34 (s, 3H), 1.40, 1.48 (s, 3H), 1.47-1.80 (m, 6H), 3.45-3.50 (m, 2H), 3.69-3.73 (m, 1H), 3.75-3.82 (m, 2H), 4.03-4.06 (m, 1H), 4.27-4.30 (m, 1H), 4.60-4.62 (m, 1H); **2f**: 1.07, 1.09 (s, 9H), 1.40-1.90 (m, 6H), 3.30-4.04 (m, 7H), 4.58 (s, 2H), 4.83, 4.88 (like t, 1H), 7.30-

7.50 (m, 10H), 7.70-7.73 (m, 5H); **2g**: 1.54-1.98 (m, 6H), 3.51-3.55 (m, 1H), 3.89-3.95 (m, 1H), 4.70-4.72 (m, 1H), 5.85 (s, 1H), 7.23-7.42 (m, 10H); **2h**: 0.86, 0.91 (s, 9H), 1.05, 1.16 (d x 2, *J*=6.4, 6.2Hz, 3H), 1.40-1.90 (m, 6H), 3.26 (q, *J*= 6.4 Hz, 0.5H), 3.40-3.49 (m, 1.5H), 3.90-3.95 (m, 1H), 4.53-4.72 (m, 1H); **2i**: 0.75, 0.79 (d, *J*=7.0 Hz, 6H), 0.80-2.35 (m, 18H), 3.20-3.50 (m, 2H), 3.80-4.00 (m, 1H), 4.57-4.79 (m, 1H); **2j**: 1.40-1.80 (m, 6H), 2.04 (s, 6H), 2.30-2.50 (m, 2H), 3.40-3.45 (m, 1H), 3.88-3.91 (m, 1H), 4.15 (ABq x 2, *J*=11.6, 11.8 Hz, 4H), 4.90-4.95 (m, 1H), 5.06-5.11(m, 2H), 5.70-5.83 (m, 1H); **2k**: 1.20-2.30 (m, 16H), 3.53-3.58 (m, 1H), 3.91-3.97 (m, 1H), 5.04-5.06 (m, 1H); **2l**: 1.18 (s, 3H), 1.33-1.90 (m, 16H), 3.40-3.46 (m, 1H), 3.93-3.98 (m, 1H), 4.70-4.73 (m, 1H).

Acknowledgment : We would like to thank Mr. W. K. Choi for the support of ^{1}H NMR data.

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8. 0.1 M TPP-TMSI solution was prepared by adding iodotrimethylsilane (0.01 mole) freshly made by the reaction of hexamethyldisilane and iodine[9] to a solution of triphenylphosphine (0.01 mole) in dichloromethane (100 mL).

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(Received in UK 3 November 1997)