Tetrahedron Letters 50 (2009) 6236–6240

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Allyl tetrahydropyranyl ether: a versatile alcohol/thiol protecting reagent

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ARTICLE INFO

Article history:
Received 17 June 2009
Revised 3 September 2009
Accepted 4 September 2009
Available online 9 September 2009

Keywords:
Allyl tetrahydropyranyl ether
NBS
I_2
Alcohol
Thiol
Lewis acid

ABSTRACT

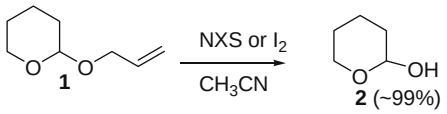
Allyl tetrahydropyranyl ether (ATHPE) can be used as a versatile protecting reagent. In combination with NBS/I_2, *O*-allyl group can easily be replaced by hydroxyls (including tertiary-OH) or thiols, in the molecules comprising other reactive functional groups such as halogen, nitro, acetonide and alkene under mild reaction conditions (near neutral pH and ambient temperature).

Protection–deprotection strategies are the most frequently encountered functional-group manipulations in organic synthesis.[1,2] In particular, the protection of hydroxyl groups is extremely important because of its enormous demand for the synthesis of a number of compounds of biological and synthetic interest, such as nucleotides, carbohydrates, steroids, macrolides, polyethers and the side chains of some amino acids.[3]

Protection of hydroxyl groups by 3,4-dihydro-2*H*-pyran is one of the frequently used methods due to stability of the resulting 2-tetrahydropyranyl ethers in the presence of strong bases or nucleophiles such as Grignard reagents, organolithium compounds, metal hydrides, alkylating and acylating agents. Tetrahydropyranylation is frequently used to protect hydroxyl groups in multistep syntheses.[4] Moreover, THP-ethers can be converted directly to the corresponding bromides,[5] iodides,[6] sulfides,[7] acetates,[8] esters[9], cyanides and carbonyl compounds[10] using a variety of methods.

A number of methods have been reported for the preparation of tetrahydropyranylated alcohols, such as catalyzed by acidic reagents,[11] neutral regents,[12] or solid supported reactions.[13] Most of these protection strategies focus on the utilization of 2,3-dihydropyran as the specific reagent in the presence of the aforementioned catalysts. However, some of the above reported methods suffer from one or the other disadvantages, for example, (a) high cost of preparation, (b) hygroscopicity of the reagents (DDQ, triflates and iron perchlorate), (c) high acidity of the medium, (d) instability of the reagents (inorganic complexes and PPTC) (e) photosensitivity (DDQ), (f) requirement of complex experimental conditions and (g) tedious work-up.

As part of our ongoing interest in developing new protection strategies,[14] we now introduce allyl tetrahydropyranyl ether **1** (ATHPE) as a THP-protecting agent of alcohols and thiols, in the presence of promoters such as NXS and iodine. The ATHPE has earlier been used as a reaction intermediate in the preparation of a phytotoxin.[15] It may be useful as a reagent of choice due to its stability at room temperature (a high boiling liquid with bp 165–167 °C),[16] and usability under mild and neutral conditions. The procedure for the preparation of tetrahydropyranyl allyl ether is available in the literature.[17] Initially our studies were intended towards the determination of suitable experimental conditions for the replacement of *O*-allyl group with hydroxyl. Using various permutations of the mild reagents/catalysts we observed that halogenating reagents such as NXS and I_2 in aqueous acetonitrile smoothly facilitated the formation of 2-hydroxytetrahydropyran in almost quantitative yield (Scheme 1). This led us to believe that the replacement of water with suitable nucleophiles, such as alcohol/thiol, may facilitate the transfer of THP from THP-allyl ether to alcohol/thiol under mild reaction conditions in the presence of suitable activators. To verify the feasibility of the envisaged con-



Scheme 1. Formation of 2-hydroxytetrahydropyran from ATHPE.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.026

version, ATHPE was stirred with bromopropanol in the presence of various catalysts (Table 1) under different reaction conditions.

The effect of the solvents, halogentaing agents and Lewis acid catalysts on the reaction time and the yields were studied. The transfer of THP took place efficiently in acetonitrile or CH_2Cl_2 in 10 h with 81% and 72% yields, respectively (Table 1, entries 1 and 2). However, switching the solvent to *N*,*N*-dimethylformamide led to the decomposition of the product (Table 1, entry 5). Addition of catalytic amount of Lewis acid dramatically reduced the reaction time. Thus, the reaction was completed in just 2 h at room temperature with the addition of 1 mol % $BF_3{\cdot}OEt_2$ in acetonitrile or CH_2Cl_2 (Table 1, entries 7 and 12), affording the product in a practicable yield.

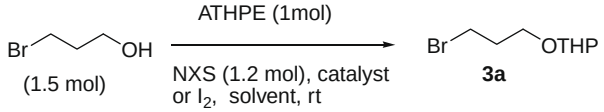
The use of $SnCl_4$ and $TiCl_4$ as catalysts resulted in comparatively lower yields of the products (Table 1, entries 10, 11 and 15). With a higher amount of the Lewis acid (1.0 equiv), no improvements in the yield or selectivity observed, even when the reaction was performed at room temperature for 6 h (see Supplementary data). Iodine alone could bring about the transformation in moderate yield (Table 1, entry 21). Table 2 depicts the results THP protection with less sensitive substrates while in Table 3, THP protection of comparatively more acid sensitive substrates under optimized conditions are shown. In the present protection methodology we successfully used halogenating agents such as NBS, considering the fact that it also finds application in regeneration of alcohols from their allylic ethers under mild condition.[18] In general NBS was superior to I_2 with regard to reaction time except with the substrates comprising double bond such as cholesterol and citronellol (Table 3, entries 7 and 8), where NBS was unsuitable due to the formation of side products. A variety of alcohols and couple of thiols produced corresponding tetrahydropyranyl ethers in high yields (60–91%) when treated with ATHPE at room temperature in the presence of NBS[19] or I_2.[20] Primary, secondary, tertiary, benzylic alcohols and thiols were conveniently protected as tetrahydropyranyl ethers at room temperature and neutral pH.

The tolerance of various functional groups under the optimized reaction conditions was studied in the substrates bearing substituents such as nitro, halo and alkenes. The reagent is also mild enough to be used in systems containing acid sensitive multifunctional groups. Thus, we have encountered no serious difficulty for the tetrahydropyranylation of alcohols such as tertiary butanol, cholesterol, citronellol, 1-phenyl ethanol and furfuryl alcohol, respectively (Table 3) possessing acid sensitive functional groups, effecting smooth transformations at room temperature without the formation of side products.

A tertiary alcohol as anticipated, takes longer time than a secondary alcohol that in turn takes more time than a primary alcohol, presumably due to their reactivity and steric factors. One of the other important applications of the present protection methodology has been the THP protection of sugar alcohols bearing acid-sensitive acetonide protections (Table 3, entries 3 and 4). The preparation of THP protected sugar derivatives in good yields (70–75%) may find useful applications in carbohydrate chemistry.

As THP is only a protecting group, therefore, it has minimal implications on the formation of diastereoisomers and stereochemical outcome of the products. Thus in the substrates having chiral centre/s the formation of more than one diastereoisomers cannot be ruled out. For example both 1-phenyl ethanol and cholesterol (Table 2, entry 11 and Table 3, entry 8) gave a mixture of two diastereoisomers in unequal proportions (3:1 and 2:1, respec-

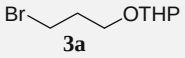
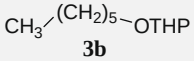
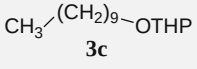
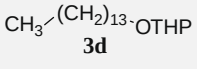
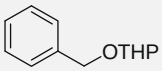
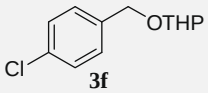
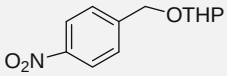
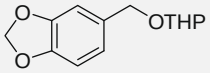
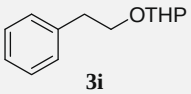
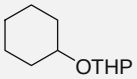
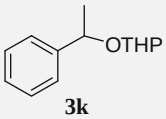
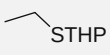
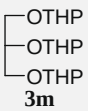
Table 1
Optimization of reaction condition for THP protection of 3-bromopropan-1-ol with ATHPE



Entry	Halogenating agent[a]	Solvent	Catalyst[b]	Time (h)	Yields[c] (%)
1	NBS	Acetonitrile	—	10.0	81
2	NBS	DCM	—	10.0	72
3	NBS	DCE	—	10.0	71
4	NBS	Diethylether	—	10.0	61
5	NBS	DMF	—	10.0	Traces
6	NBS	THF	—	10.0	52
7	NBS	Acetonitrile	$BF_3(OEt)_2$	2.0	85
8	NBS	Acetonitrile	$InCl_3$	2.0	71
9	NBS	Acetonitrile	$In(OTf)_3$	2.0	74
10	NBS	Acetonitrile	$TiCl_4$	2.0	51
11	NBS	Acetonitrile	$SnCl_4$	2.0	51
12	NBS	DCM	$BF_3(OEt)_2$	2.0	81
13	NBS	DCM	$InCl_3$	2.0	75
14	NBS	DCM	$In(OTf)_3$	2.0	72
15	NBS	DCM	$TiCl_4$	2.0	71
16	NBS	Diethylether	$BF_3(OEt)_2$	2.0	60
17	NBS	THF	$BF_3(OEt)_2$	2.0	62
18	NBS	Ionic liquid	$BF_3(OEt)_2$	2.0	70
19	NIS	Acetonitrile	$BF_3(OEt)_2$	2.0	81
20	NCS	Acetonitrile	$BF_3(OEt)_2$	2.0	75
21	I_2[d]	Acetonitrile	—	10.0	75
22	I_2[d]	DCM	—	10.0	65
23	I_2[d]	Diethylether	—	10.0	50
24	I_2[d]	THF	—	10.0	45
25	I_2[d]	Ionic liquid	—	10.0	55

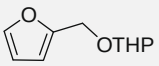
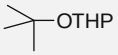
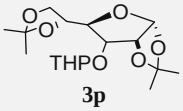
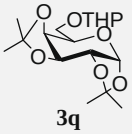
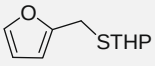
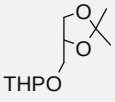
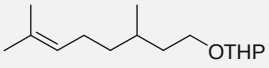
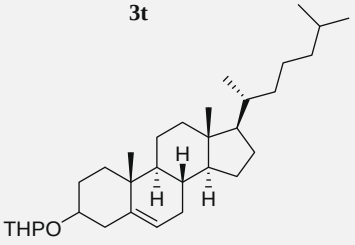
[a] 1.2 equiv of halogenating agents was used.
[b] 1 mol % of catalyst was used.
[c] Monitored by GLC.
[d] 1.0 mol % I_2 was used.

Table 2
Tetrahydropyranylation[a] of different alcohols and thiols with ATHPE

Entry	NuH	Product	Time (h)	Yield[b] (%)
1	3-Bromopropan-1-ol	 **3a**	20	85
2	Hexan-1-ol	 **3b**	20	82
3	Decan-1-ol	 **3c**	20	79
4	Tetradecan-1-ol	 **3d**	20	77
5	Benzyl alcohol	 **3e**	25	85
6	4-Chlorobenzyl alcohol	 **3f**	30	81
7	4-Nitrobenzyl alcohol	 **3g**	30	80
8	5-Hydroxymethyl benzo[*d*][1,3]dioxole	 **3h**	30	82
9	2-Phenylethanol	 **3i**	20	89
10	Cyclohexanol	 **3j**	40	86
11	1-Phenylethanol (racemic)	 **3k**	60	81
12	Ethanethiol	 **3l**	15	91
13	Glycerol	 **3m**	80	83
14	2-Aminobutanol	No reaction	—	—

[a] Reaction conditions: 1.5 equiv NuH, 1.0 equiv tetrahydropyranyl allyl ether, 1.2 equiv NBS, 1 mol % $BF_3(OEt)_2$ in acetonitrile.
[b] Isolated yield.

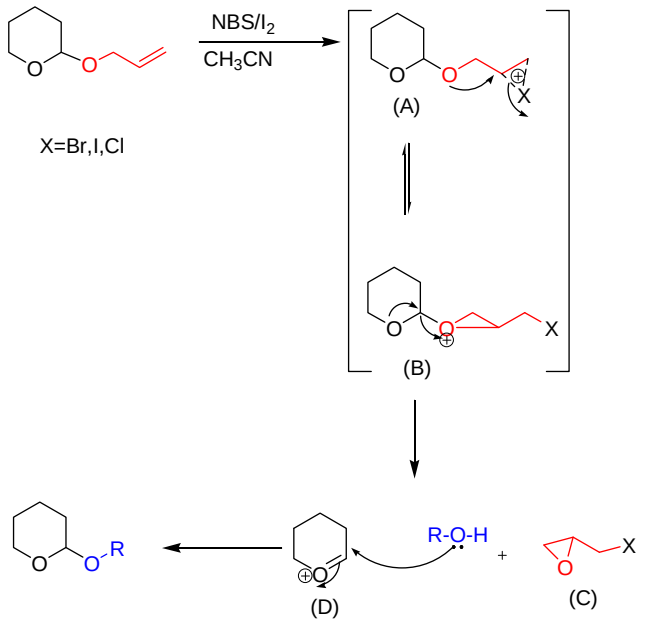
Table 3
Tetrahydropyranylation[a] of acid-sensitive alcohols and thiol with ATHPE

Entry	NuH	Product	Time (h)	Yield[c] (%)
1	Furfuryl alcohol	 **3n**	15	80
2	*tert*-Butanol	 **3o**	80	80
3	Glucose diacetonide	 **3p**	60	70
4	Galactose diacetonide	 **3q**	60	75
5	Furan methane thiol	 **3r**	15	85
6	Glycerol acetonide	 **3s**	60	70
7	Citronellol	 **3t**	80[b]	80
8	Cholesterol	 **3u**	80[b]	60

[a] Reaction conditions: 1.5 equiv NuH, 1.0 equiv allyl tetrahydropyranyl ether, 1.2 equiv NBS, in acetonitrile.
[b] 1.5 equiv NuH, 1.0 equiv allyl tetrahydropyranyl ether, 1 mol % I_2.
[c] Isolated yield.

tively) as calculated from NMR spectra (see Supplementary data); whereas, other molecules (Table 3, entries 4, 6 and 7) gave two diastereoisomers in approximately equal ratios. As expected, glycerol (Table 2 entry 13) gave a mixture of three diastereoisomers in almost equal amounts. Here, the role of steric factors could be important in deciding about the stereochemistry and the number of diastereoisomers.

Based on our own experiments, and a recent study on glycosylation by propargyl glycosyl donor,[21a] which is analogous to the mechanism earlier proposed for the glycosylation of 4-penten-1-ol donor,[21b] we suggest the following possible mechanism for tetrahydropyranylation using ATHPE in the presence of halogenating agents. The proximity of NBS and allyl tetrahydropyranyl ether facilitates the attack of a bromonium ion and the formation of the intermediate A, which equilibrates with the unstable intermediate B. The elimination of C (epihalohydrin) from B generates reactive oxocarbenium D which can easily capture the attacking nucleophiles (i.e., ROH and RSH) giving the desired product. The development of yellowish color (with NBS) which slowly disappears after the addition of alcohols and thiols support the forma-



Scheme 2. Plausible mechanism of replacement of *O*-allyl group by alcohol and thiol nucleophiles.

tion of halonium ion intermediate. Moreover, while working with NCS in a controlled experiment, we observed the formation of C (X = Cl) in the NMR-spectra of the reaction mixture. When the same reaction was performed on a molecule comprising a basic nitrogen, for example, 2-aminobutanol, the reaction did not proceed because the NH_2 group prevented the formation of the halonium ion intermediate A (Table 2, entry 14). This observation also supports the proposed mechanistic pathway.

In summary, we have demonstrated the usefulness of allyl tetrahydropyranyl ether (ATHPE) as a new tetrahydropyran protecting agent for alcohols and thiols under neutral conditions. The tolerance of various sensitive functional groups and mild and neutral conditions are the added advantages over classical THP protection using dihydropyran. The reagent system may also prove useful in the protection protocols in polyfunctional molecules (Scheme 2). Applications of the present protection strategy in carbohydrates are under progress.

Acknowledgement

The authors (B.K. and M.A.A.) thank UGC/CSIR, New Delhi for the award of junior research fellowships.

Supplementary data

Supplementary data (experimental procedures, characterization data, ^1H and ^{13}C spectra of the synthesized compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.026.

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19. A typical procedure for THP protection with ATHPE using NBS in acetonitrile: To a solution of ATHPE 100 mg (0.71 mol) and 3-bromopropanol 147 mg (1.05 mol) in acetonitrile (3 mL/mmol substrate), NBS (1.2 equiv) and $BF_3(OEt)_2$,(1 mol %) were successively added. The reaction mixture was allowed to stir for 2 h at room temperature, concentrated, extracted in diethyl ether (10 mL) and washed with saturated sodium bicarbonate solution (10 mL). The organic layer was separated, dried over Na_2SO_4, evaporated, and finally the product was purified by column chromatography on alumina to afford compound **1** as an oily liquid 132.8 mg (85%).2-(3-Bromopropoxy)-tetrahydro-2*H*-pyran: ^1H NMR (200 MHz, $CDCl_3$): δ 4.60 (t, 1H, J = 3.92 Hz), 4.41 (m, 2H), 3.50 (m, 4H), 2.13 (m, 2H), 1.51–1.79 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 99.2, 65.2, 62.6, 33.3, 31.1, 31.0, 25.8, 19.8; ESI-MS (M+Na) = 245; Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.07; H, 6.78. Found; C, 43.17; H, 6.71.
20. A typical procedure for THP protection with ATHPE using I_2 in acetonitrile: To a solution of ATHPE (100 mg 0.71 mol) and citronellol (147 mg, 1.05 mol) in acetonitrile (3 mL/mmol substrate), molecular I_2 (1.0 mol %) was added. The reaction mixture was allowed to stir for 8 h at room temperature, concentrated, extracted in diethyl ether (10 mL) and washed successively with 10% sodium thiosulfate (10 mL), saturated sodium bicarbonate solution (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4, evaporated, and finally the product was purified by column chromatography on alumina to afford compound **7** as colourless oily liquid 135.1 mg (80%).2-(3,7-Dimethyloct-6-enyloxy)-tetrahydro-2*H*-pyran. ^1H NMR (200 MHz, $CDCl_3$): δ 5.09 (t, 1H, J = 7.01 Hz), 4.58 (t, 1H, J = 3.30 Hz), 3.74–3.91 (m, 2H), 3.36–3.53 (m, 2H), 1.97 (m, 2H), 1.54–1.70 (m, 14H), 0.84–0.92 (m, 6H), ^{13}C NMR (125 MHz, $CDCl_3$): 130.3, 124.8, 98.8, 65.8, 62.1, 39.2, 37.2, 37.0, 30.7, 29.6, 25.5, 25.4, 24.8, 19.6, 17.5, ESI-MS (M+Na) = 264; Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found; C, 74.84; H, 11.78.
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