A Highly Efficient and Chemoselective Synthetic Protocol for Tetrahydropyranylation/Depyranylation of Alcohols and Phenols

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Dedicated to the late Mr. Gadadhar Mondal[‡]

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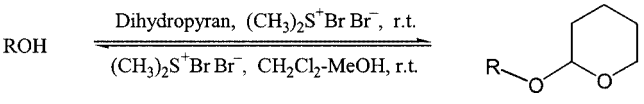
Various alcohols and phenols can be converted efficiently to the corresponding tetrahydropyranyl (THP) ethers in good yields using catalytic amounts of bromodimethylsulfonium bromide (0.005–0.02 equivalent) at room temperature. On the other hand, various THP ethers can also be deprotected to the parent alcoholic or phenolic compounds in CH_2Cl_2/MeOH (5:2) by employing 0.05 equivalent of the same catalyst. Some of the major advantages of this procedure are its mild conditions, that it is highly selective and efficient, high yielding, and cost-effective, that it needs no solvent and is compatible with the presence of other protecting groups. Furthermore, no brominations occur at a double or triple bond, at an allylic position or even at an aromatic ring.

Introduction

The protection−deprotection of hydroxyl compounds as tetrahydropyranyl (THP) ethers is one of the most frequently employed transformations in multi-step organic syntheses[1] because of their low cost, ease of preparation, stability towards basic media and ease of removal of protecting groups at a later stage. Over the years, numerous methods have been developed for the protection of hydroxyl groups as THP ethers[2] and their deprotection,[3] but there is still a need to find better alternatives that work under mild conditions. Some of the recently used reagents that can catalyze both tetrahydropyranylation and depyranylation are $ZrCl_4$,[4] I_2,[5] LiBr,[6] acetonylphenylphosphonium bromide,[7] TBATB,[8] aluminum chloride hexahydrate,[9] $In(OTf)_3$,[10] dialkylimidazolium tetrachloroaluminates,[11] and $InCl_3$ immobilized in ionic liquids.[12] However, some of the reported procedures have drawbacks, such as requiring higher reaction temperatures, much longer reaction times and the use of volatile organic solvents, being incompatible with other acid-sensitive functional groups, and involving expensive catalysts. In an endeavor to gradually change the current working practices to greener alternatives and to meet environmental demands,[13] there is a need for a solvent-free and catalytically efficient alternative for protection and deprotection of the hydroxy functionality as a THP ether, which works under mild and economically cheaper reaction conditions. As part of our research program to develop new synthetic methodologies,[14] we conceived that bromodimethylsulfonium bromide, which can generate HBr in the reaction medium on reaction with alcohol, might be a useful catalyst for tetrahydropyranylation and depyranylation of alcohols and phenols. The catalyst bromodimethylsulfonium bromide has been utilized so far for the transformation of alcohols to the corresponding bromides,[15] oxidation of sulfides to disulfides,[16] deprotection of dithioacetals,[17] and preparation of α-bromoenones.[18] In this communication, we report a simple and convenient synthetic protocol for tetrahydropyranylation of alcohols and phenols catalyzed by bromodimethylsulfonium bromide under solvent-free conditions, and their depyranylation to the corresponding parent compounds using the same catalyst in CH_2Cl_2/MeOH (Scheme 1).



R = alkyl / aryl / sugar residue / nucleoside residue

Scheme 1

Results and Discussion

As expected, a mixture of 1-decanol (5 mmol) and 3,4-dihydro-2*H*-pyran (6 mmol) in the presence of bromodime-

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thylsulfonium bromide (0.05 mmol) at room temperature was converted smoothly to the corresponding tetrahydropyranyl ether of 1-decanol within 5 min in 97% yield (run 1). Similarly, a mixture of cetyl alcohol (5 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (6 mmol) provided the corresponding THP ether within 15 min in 98% yield (run 2) under identical reaction conditions. Using the above typical procedure, various secondary alcohols (runs 3−8) were transformed easily to the corresponding THP ethers in good yields. Interestingly, mono protection of an alcoholic hydroxyl group is possible in the presence of a phenolic OH group (run 9) and other alcoholic OH group (run 10) if 10% of the starting material is left unchanged. The conversion (run 1) is more efficient in terms of yield and reaction time than another recently reported procedure.[8] Moreover, a wide variety of protected alcoholic compounds were transformed to the corresponding THP ethers under identical reaction conditions using the same catalyst (runs 11−15). It should be noted that various other protecting groups such as acetyl, benzoyl, trityl, ester and TBDPS groups remain unaffected during the reaction. In addition, various double bonded and triple bonded substrates also provided the corresponding THP ethers under identical reaction conditions (runs 16−20). Importantly, no brominations took place at the double or triple bonds. It is worth mentioning that geraniol was smoothly transformed to the corresponding THP ether at a much faster rate than it was by a recently reported procedure,[9] which also shows the efficiency of our protocol. Subsequently, various phenolic compounds were converted into the corresponding THP ethers (runs 21−24) using the same catalyst without solvent. It is noteworthy that no brominations take place in the aromatic ring even for an electron-rich aromatic substrate (run 24) and that there is no cleavage of the dithioacetal group (run 23). Remarkably, a highly acid-sensitive substrate can be protected to the corresponding THP ethers using the same catalyst (runs 25 and 26). Furthermore, various carbohydrate and nucleosidic compounds were transformed smoothly to the corresponding THP ethers (runs 27−32) by the same reaction procedure. The results are summarized in Table 1. The products were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and by elemental analyses. It is worth mentioning that benzyl, isopropylidene, and a thio group at the anomeric position were unaffected by the experimental conditions.

Next, we searched for suitable reaction conditions for deprotection of THP ethers to the parent hydroxyl compounds. The THP ether of cetyl alcohol was deprotected smoothly to the parent cetyl alcohol within 30 min on treatment with 0.05 equivalents of bromodimethylsulfonium bromide in dichloromethane/methanol at room temperature (run 1). Similarly, we successfully converted various THP ethers to the parent hydroxyl compounds under identical reaction conditions (runs 2−18). The results are summarized in Table 2 and the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analyses, as well as by comparison with the authentic compounds. We also observed that various protecting groups such as acetyl, benzoyl, benzyl, TBDPS, ester, thioketal, allyl, and isopropylidene were unaffected by the deprotection reaction conditions. Moreover, no brominations occurred at a double or triple bond or in the aromatic ring.

The formation of the product can be explained as follows. It has been shown that bromodimethylsulfonium bromide can generate HBr on reaction with alcohol.[14] We believe that in situ-generated HBr catalyzes the conversion of hydroxyl compounds into the corresponding tetrahydropyranyl ethers (Scheme 2**)**. We have observed that the pH of the solution was ca. 2−3 while the reaction was proceeding.

Similarly, the deprotection of THP ethers can be explained by the fact that bromodimethylsulfonium bromide generates HBr on reaction with methanol, which is utilized for cleavage of THP ethers to the corresponding hydroxyl compounds.

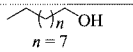
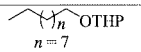
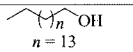
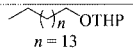
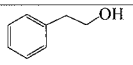
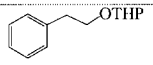
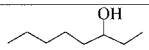
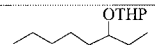
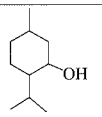
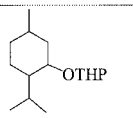
Conclusion

We have demonstrated a simple and convenient method for preparation of tetrahydropyranyl (THP) ethers from the corresponding alcohols and phenols under solvent-free conditions as well as deprotection to the parent hydroxyl compounds chemoselectively using the same catalyst by tuning the amount of reagent and the reaction conditions. In addition, this method is very simple and mild, easy to handle, and compatible with the presence of a large number of other protecting groups. It is noteworthy that no brominations take place at double or triple bonds, or even in aromatic rings. Because of its operational simplicity, generality, and efficacy, this method is expected to have wide applicability for the conversion of various hydroxyl compounds to the corresponding tetrahydropyranyl (THP) ethers and vice-versa.

Experimental Section

General Procedure for Tetrahydropyranylation: Bromodimethylsulfonium bromide (0.011 g, 0.05 mmol) was added to a mixture of 1-decanol (0.790 g, 5 mmol, run 1) and 3,4-dihydro-2*H*-pyran (0.550 mL, 6 mmol) and the resulting mixture was stirred at room temperature. The reaction was complete within 5 min as monitored by TLC and it was neutralized by addition of saturated $NaHCO_3$ solution (2−3 drops). The mixture was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed with water (10 mL), brine (10 mL), and dried with Na_2SO_4. The organic layer was concentrated in vacuo and the crude residue was purified through a short alumina column. The pure product was obtained (1.170 g) in 97% yield as a colorless liquid. Spectroscopic data of THP ether of *p*-allyloxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46−1.86 (m, 6 H, CH_2), 3.46−3.50 (m, 1 H, OCH_2), 3.82−3.92 (m, 1 H, OCH_2), 4.49 (s, 2 H, OCH_2), 4.65−4.70 (m, 3 H, OCH_2, OCHO-), 5.24 (dd, *J* = 1.4, *J* = 10.5 Hz, 1 H, CH=CH_2), 5.37 (dd, *J* = 1.7, *J* = 17.3 Hz, 1 H, CH=CH_2), 5.97−6.06 (m, 1 H, CH=CH_2), 6.86 (d, *J* = 8.5 Hz, 2 H, ArH), 7.24 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.35, 25.39, 30.53, 62.08, 68.44, 68.76, 97.44, 114.54 (2 C), 117.58, 129.41

Table 1. Protection of various hydroxyl compounds to the corresponding tetrahydropyranyl ethers using catalytic amount of bromodimethylsulfonium bromide

Run	Substrate	Catalyst used	Time min/[h]	Product[a]	Yield[b] /%
1		0.01	5		97
2		0.01	15		98
3		0.01	5		85
4		0.01	5		87
5		0.01	10		88
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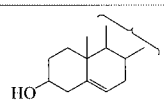
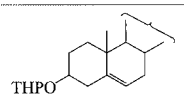
7		0.01	20		90
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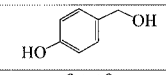
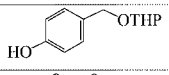
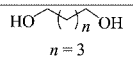
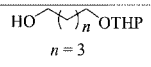
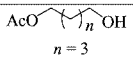
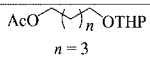
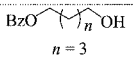
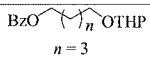
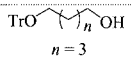
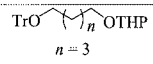
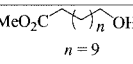
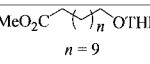
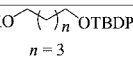
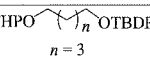
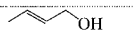
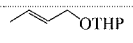
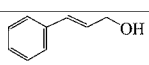
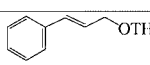
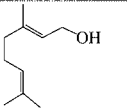
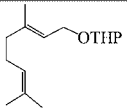
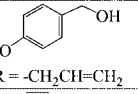
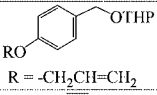
9		0.01	7		85[c]
10		0.01	40		88[c]
11		0.01	15		81
12		0.01	15		87
13		0.01	5		85
14		0.01	15		87
15		0.01	20		89
16		0.01	15		83
17		0.01	15		92
18		0.01	12		78
19		0.01	10		95
20		0.01	25		95

Run	Substrate	Catalyst used	Time min/[h]	Product[a]	Yield[b] /%
21		0.01	[4]		90
22		0.01	[6]		92
23		0.01	35		94
24		0.01	20		83
25		0.005	5		93
26		0.005	7		81
27		0.01	20		84
28		0.01	15		93
29		0.02	[1]		95
30		0.02	[1]		96
31		0.02	[3.5]		83
32		0.01	30		95

[a] All final products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis. [b] Isolated yield. [c] Reaction was carried out by keeping 10% starting material unchanged.

Table 2. Deprotection of various tetrahydropyranyl ethers to the corresponding hydroxyl compounds using catalytic amount of bromodimethylsulfonium bromide in dry dichloromethane/methanol

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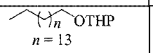
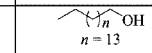
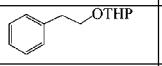
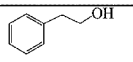
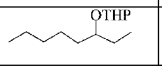
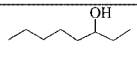
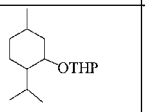
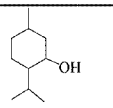
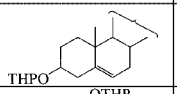
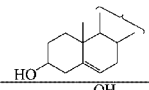
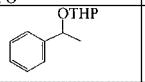
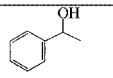
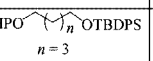
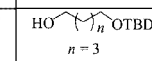
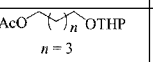
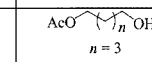
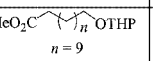
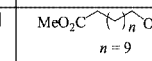
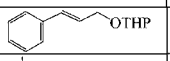
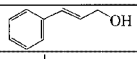
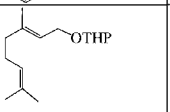
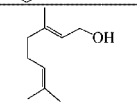
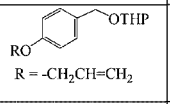
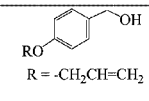
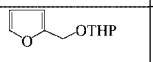
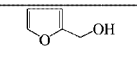
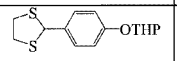
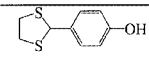
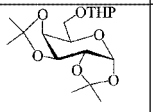
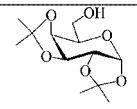
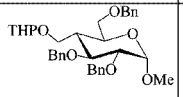
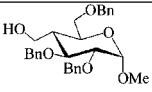
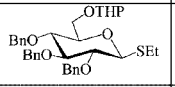
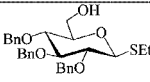
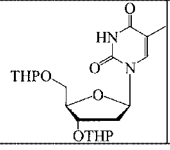
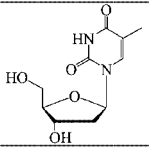
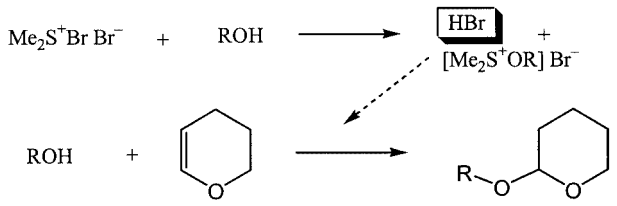
1		0.05	30		90
2		0.05	25		97
3		0.05	25		92
4		0.05	15		95
5		0.05	40		70
6		0.05	25		70
7		0.05	30		90
8		0.05	15		90
9		0.05	[1]		72
10		0.05	[1]		90
11		0.05	[2]		98
12		0.05	50		93
13		0.05	35		80
14		0.05	40		82
15		0.05	30		76
16		0.05	[2]		85
17		0.05	[1]		73
18		0.05	[1.5]		80

[a] All final products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis. [b] Isolated yield.



Scheme 2. Proposed mechanism of protection

(2 C), 130.42, 133.23, 158.07 ppm. $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12; found: C 72.38, H 8.01%.

General Procedure for Depyranylation: Bromodimethylsulfonium bromide (0.056 g, 0.25 mmol) was added to a well-stirred solution of the THP ether of 2-phenylethanol (1.060 g, 5 mmol, run 2) in CH_2Cl_2/MeOH (5:2; 10 mL) at room temperature. The reaction was complete within 25 min as monitored by TLC. The mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), and dried with Na_2SO_4. The organic layer was concentrated in vacuo and finally purified by silica-gel column chromatography. The pure product was obtained in 97% yield. Spectroscopic data of *p*-allyloxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (br. s, 1 H, OH, D_2O exchangeable), 4.38−4.40 (m, 2 H, OCH_2), 4.45 (s, 2 H, OCH_2), 5.15 (dd, J = 1.4, J = 10.5 Hz, 1 H, CH=CH_2), 5.28 (dd, J = 1.5, J = 17.8 Hz, 1 H, CH=CH_2), 5.86−5.96 (m, 1 H, CH=CH_2), 6.76 (d, J = 8.0 Hz, 2 H, ArH), 7.12 (d, J = 8.3 Hz, 2 H, ArH) ppm. $C_{10}H_{12}O_2$ (164.20): calcd. C 73.15, H 7.37; found: C 72.87, H 7.28%.

Acknowledgments

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