Efficient Trimethylsilylation and Tetrahydropyranylation of Alcohols in the Presence of 1,3-Dibromo-5,5-dimethylhydantoin

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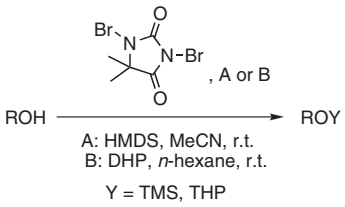
Abstract: Chemoselective trimethylsilylation and tetrahydropyranylation of benzylic and primary and secondary aliphatic alcohols proceed efficiently in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBH) under mild and completely heterogeneous reaction conditions in excellent yields.

Key words: alcohols, 1,3-dibromo-5,5-dimethylhydantoin, trimethylsilylation, tetrahydropyranylation, heterogeneous reaction conditions

Trimethylsilylation and tetrahydropyranylation are popular methods widely used for the protection of the hydroxyl group of alcohols. Among the many silylating agents which have been used for the silylation of alcohols,[1] hexamethyldisilazane (HMDS), a cheap, stable and commercially available reagent,[2] is selected as one of the best candidates for this purpose. Its handling does not need special precaution, and the work-up is not time-consuming, as the by-product of the reaction is ammonia, which is simple to remove from the reaction medium. However, its poor silylating power is the main drawback of its application.[3] A variety of catalysts have been used for the activation of HMDS;[4] however, low selectivity, forcing conditions, tedious work-ups and long reaction times have been described in many of these reports. Consequently, a new procedure that addresses these drawbacks is desirable.

Due to the remarkable stability of tetrahydropyranyl ethers towards a variety of reaction conditions such as strongly basic media, reactions involving Grignard reagents and lithium alkyls, reduction with hydride, oxidation, oxidative alkylation and acylation reactions, and due to its low cost and ease with which it can be removed, 3,4-dihydro-2*H*-pyran is the reagent of choice for hydroxyl group protection in multi-step organic synthesis. There are several reagents available for the tetrahydropyranylation of alcohols, which include the use of protic[5] and Lewis acids,[6] silica-chloride,[7] $ZrCl_4$,[8] solid silica-based sulfonic acid,[9] LiOTf,[10] ionic liquid,[11] silica-sulfuric acid,[12] trichloroisocyanuric acid,[13] $K_5CoW_{12}O_{40}\cdot 3H_2O$[14] and H-Y zeolite.[15] Although these methods are suitable for many synthetic conditions, many of these are associated with several drawbacks, which include use of strongly acidic media, expensive reagents, tedious and time-consuming work-up procedures, refluxing conditions, long reaction times, poor selectivity, formation of polymeric by-products of the dihydropyran and isomerization. Thus there is still a need for mild and selective methods, especially using heterogeneous catalysts for this purpose.

During the course of our studies on the application of *N*-haloamides in organic synthesis,[16] we have found that 1,3-dibromo-5,5-dimethylhydantoin (DBH) is a cheap, stable and commercially available reagent. 1,3-Dibromo-5,5-dimethylhydantoin recently have been used as an efficient reagent for the selective mononitration of phenols,[17] oxidation of 1,3,5-trisubstituted pyrazolines,[18] thiols,[19] and urazoles[20] and acylation of alcohols.[21] Herein we wish to report the use of DBH in the efficient and chemoselective trimethylsilylation and tetrahydropyranylation of benzylic and primary and secondary aliphatic alcohols under mild and completely heterogeneous reaction conditions (Scheme 1).



Scheme 1

Different types of alcohols, were subjected to trimethylsilylation using this method at room temperature in MeCN (Table 1, entries 1–19). Trimethylsilylation of benzylic alcohols including acid sensitive, electron-donating or electron-withdrawing groups proceed efficiently with relatively high isolated yields (Table 1, entries 1–13). Primary and secondary aliphatic alcohols were also successfully converted to their corresponding trimethylsilyl ethers in almost quantitative yields under the same reaction conditions (Table 1, entries 14–18). This method was also found to be useful for the protection of allylic alcohols (Table 1, entry 19). Tertiary alcohols were resistant to this reagent system and remained intact during the course of the reaction (Table 1, entries 20 and 21).

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Table 1 Trimethylsilylation and Tetrahydropyranylation of Alcohols[a]

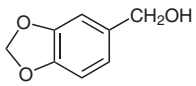
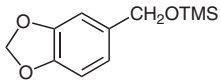
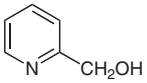
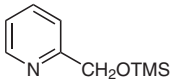
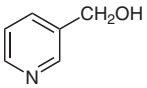
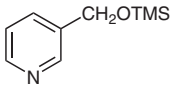
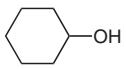
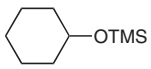
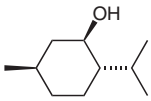
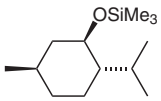
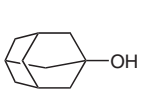
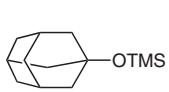
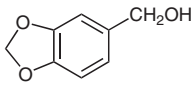
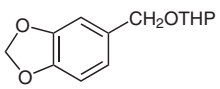
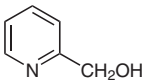
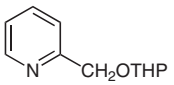
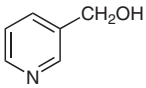
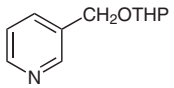
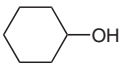
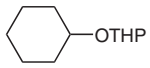
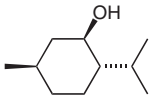
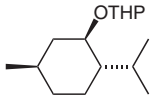
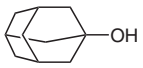
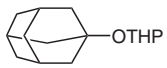
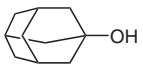
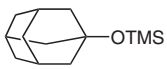
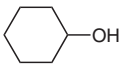
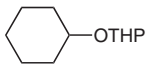
Entry	Substrate	Product	Time (min)	Yield (%)[b]
1	2-$BrC_6H_4CH_2OH$	2-$BrC_6H_4CH_2OTMS$	<1[c]	95
2	2-$ClC_6H_4CH_2OH$	2-$ClC_6H_4CH_2OTMS$	<1[c]	97
3	4-$ClC_6H_4CH_2OH$	4-$ClC_6H_4CH_2OTMS$	<1[c]	95
4	2-$NO_2C_6H_4CH_2OH$	2-$NO_2C_6H_4CH_2OTMS$	5	85
5	4-$NO_2C_6H_4CH_2OH$	4-$NO_2C_6H_4CH_2OTMS$	9	90
6	2-$MeC_6H_4CH_2OH$	2-$MeC_6H_4CH_2OTMS$	<1[c]	95
7	4-(*t*-Bu)$C_6H_4CH_2OH$	4-(*t*-Bu)$C_6H_4CH_2OTMS$	<1[c]	85
8			5	95
9	PhCH(OH)Me	PhCH(OTMS)Me	<1[c]	95
10	Ph_2CHOH	$Ph_2CHOTMS$	<1[c]	90
11			25	80
12			15	90
13	PhCH(OH)COPh	PhCH(OTMS)COPh	<1[c]	92
14	PhCH(Me)CH_2OH	PhCH(Me)CH_2OTMS	<1[c]	95
15	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OTMS$	<1[c]	96
16	$PhCH_2CH(OH)CH_3$	$PhCH_2CH(OTMS)CH_3$	<1[c]	92
17			<1[c]	85
18			<1[c]	90
19	PhCH=$CHCH_2OH$	PhCH=$CHCH_2OTMS$	<1[c]	80
20			30	0[d]
21	Me_3COH	Me_3COTMS	40	0[d]
22	$PhCH_2OH$	$PhCH_2OTHP$	55	85
23	2-$BrC_6H_4CH_2OH$	2-$BrC_6H_4CH_2OTHP$	20	90
24	2-$ClC_6H_4CH_2OH$	2-$ClC_6H_4CH_2OTHP$	30	85
25	4-$ClC_6H_4CH_2OH$	4-$ClC_6H_4CH_2OTHP$	25	92
26	2-$NO_2C_6H_4CH_2OH$	2-$NO_2C_6H_4CH_2OTHP$	7	90
27	3-$NO_2C_6H_4CH_2OH$	3-$NO_2C_6H_4CH_2OTHP$	22	85
28	4-$NO_2C_6H_4CH_2OH$	4-$NO_2C_6H_4CH_2OTHP$	5	90
29	2-$MeC_6H_4CH_2OH$	2-$MeC_6H_4CH_2OTHP$	25	85
30	4-(*t*-Bu)$C_6H_4CH_2OH$	4-(*t*-Bu)$C_6H_4CH_2OTHP$	35	80

Table 1 Trimethylsilylation and Tetrahydropyranylation of Alcohols[a] (continued)

Entry	Substrate	Product	Time (min)	Yield (%)[b]
31			35	85
32	PhCH(OH)Me	PhCH(OTHP)Me	7	90
33			27	70
34			10	80
35	PhCH(Me)CH_2OH	PhCH(Me)CH_2OTHP	45	80
36	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OTHP$	98	90
37	$PhCH_2CH(OH)CH_3$	$PhCH_2CH(OTHP)CH_3$	60	80
38			30	85
39			35	85
40	PhCH=$CHCH_2OH$	PhCH=$CHCH_2OTHP$	25	85
41	*t*-BuOH	*t*-BuOTHP	50	0[d]
42			60	0[d]
	2-$BrC_6H_4CH_2OH$ +	2-$BrC_6H_4CH_2OTMS$ +		
43			<1[c]	100[d] + 0[d]
44	 + *t*-BuOH	 + *t*-BuOTHP	30	95[d] + 0[d]

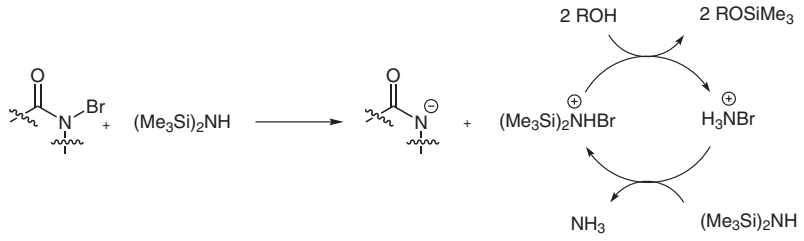
[a] Products were identified spectroscopically and also by the conversion of the products to their corresponding alcohols.
[b] Isolated yields.
[c] Reaction was instantaneous.
[d] GC yields.

Although the actual role of DBH is not clear, on the basis of the previously reported mechanism for the silylation of alcohols with HMDS in the presence of I_2,[4d] the mechanism that is shown in Scheme 2 is selected as a most probable one.

1,3-Dibromo-5,5-dimethylhydantoin can also be used as an efficient reagent for the promotion of tetrahydropyranylation of benzylic, allylic and primary and secondary aliphatic alcohols with 3,4-dihydro-2*H*-pyran. Reactions were carried out in *n*-hexane at room temperature and under completely heterogeneous reaction conditions to give the products in good to high yields (Table 1, entries 22–40). Tertiary alcohols did not react under the same reaction conditions (Table 1, entries 41, 42).

The resistance of tertiary alcohols against trimethylsilylation and tetrahydropyranylation reactions in the presence of DBH, led us to investigate the possibility of the selective protection of the different types of alcohols in the presence of tertiary ones. This is exemplified by the competitive reactions between 2-bromobenzyl alcohol and 1-adamantanol and between cyclohexanol and *tert*-BuOH (Table 1, entries 43,44).

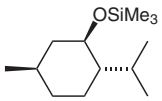
According to the selected mechanism for the tetrahydropyranylation of alcohols in the presence of trichloroisocy-



Scheme 2

anuric acid,[13] the mechanism that is shown in Scheme 3 is proposed for the clarification of the role of DBH in the protection of alcohols as their corresponding THP ethers. In order to show the efficiency of the proposed method, Table 2 compares some of the results with some of those reported in the literature.[4e,g,13]

Table 2 Comparison of Trimethylsilylation and Tetrahydropyranylation of Alcohols in the Presence of DBH (I) with Trichloroisocyanuric Acid (II) and $Al(HSO_4)_3$ (III)

Entry	Product	Time (min); yield (%)		
		I	II[4e,13]	III[4g]
1	PhCH(OTMS)COPh	<1[a]; 92	600; 96	–
2		<1[a]; 90	180; 95	60; 95
3	4-$ClC_6H_4CH_2OTHP$	25; 92	300; 92	20; 90
4	$PhCH_2CH_2CH_2OTHP$	98; 90	330; 94	30; 85

[a] Reaction was instantaneous.

In conclusion, in this study, we have developed an efficient, simple and chemoselective method for trimethylsilylation and tetahydropyranylation of benzylic and primary and secondary aliphatic alcohols in the presence of 1,3-dibromo-5,5-dimethylhydantoin. Due to the short reaction times, availability and low cost of the reagent, heterogeneous reaction conditions, selectivity, easy and clean work-up and good to high yields of the products, we believe it would be a useful addition to the available methodologies.

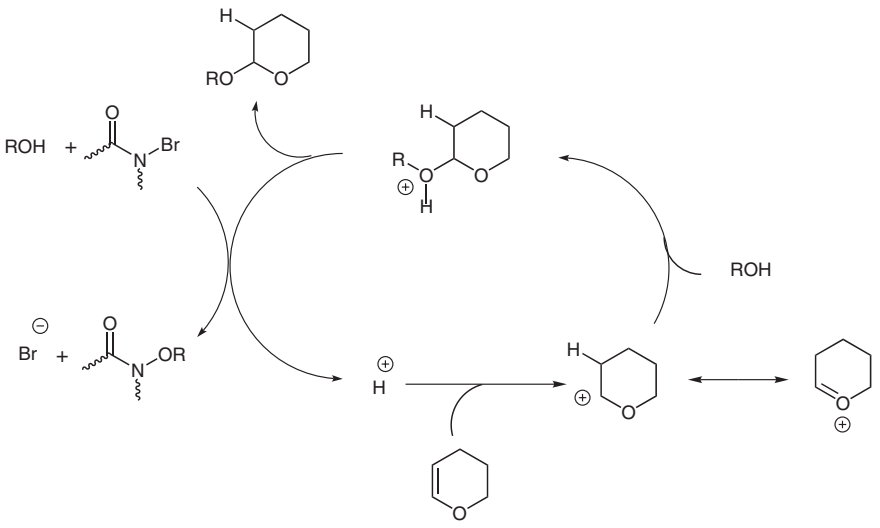
Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. All of the trimethylsilyl and tetrahydropyranyl ethers are known compounds, and were characterized by spectral analyses, comparisons with authentic samples (IR and NMR), and also by regeneration of the corresponding alcohols. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by TLC on silica gel polygram SILG/UV 254 plates.

Trimethylsilylation of Alcohols; General Procedure

To a mixture of the substrate (1 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (0.15 mmol, 0.04 g) in MeCN (30 mL), was added dropwise HMDS (7 mmol, 1.1 g) within 5 min under stirring at r.t. After completion of the reaction (TLC or GC), the mixture was filtered through a silica gel pad and the filter cake was washed with MeCN (2 × 10 mL). Evaporation of the solvent gave almost pure product(s). Further purification proceeded by bulb-to-bulb distillation under reduced pressure or recrystallization to afford pure silyl ether.

Tetrahydropyranylation of Alcohols; General Procedure

A mixture of alcohol (1 mmol), 3,4-dihydro-2*H*-pyran (1.4 mmol, 0.12 g) and 1,3-dibromo-5,5-dimethylhydantoin (0.5 mmol, 0.143



Scheme 3

g) in *n*-hexane (3 mL) was stirred at r.t. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered through a silica gel pad, and the solid residue was washed with *n*-hexane (2 × 5 mL). Evaporation of the solvent gave the desired products in high purity.

Acknowledgment

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