

## ***N*-Bromosuccinimide (NBS): a Mild and Efficient Catalyst for Tetrahydropyranylation of Alcohols and Phenols under Solvent-Free Conditions**

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Different types of alcohols and phenols are tetrahydropyranylated in the presence of NBS catalyst in good to excellent yields under mild, neutral and solvent-free conditions.

**Keywords:** *N*-Bromosuccinimide; Alcohols; Tetrahydropyranylation; Phenols; Solvent-free; DHP.

### INTRODUCTION

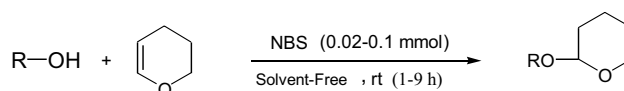
Protection of hydroxyl groups by their conversion to the corresponding tetrahydropyranyl ethers (THP ethers) is a common and extensively used transformation in organic synthesis.<sup>1</sup> This wide spread use is undoubtedly due to the stability of the THP group against a wide range of strong nucleophilic and basic reagents.<sup>2</sup> THP groups are also the protective groups of choice in peptide, nucleotide, carbohydrate, and steroid chemistry.<sup>3</sup> A variety of catalysts that have been reported for this conversion include the use of protic acids,<sup>4</sup> Lewis acids,<sup>5</sup> ionexchange resins,<sup>6</sup> alumina impregnated with ZnCl<sub>2</sub>,<sup>7a</sup> silica chloride,<sup>7b</sup> heteropoly acids,<sup>7c</sup> ionic liquids,<sup>7d,e</sup> K-10 clay,<sup>7f</sup> I<sub>2</sub>,<sup>7g</sup> trichloroisocyanuric acid,<sup>7h</sup> polystyrene supported aluminum chloride,<sup>7i</sup> PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub><sup>7j</sup> and tetrabutylammonium bromide.<sup>7k</sup> Although these methods are suitable for many synthetic conditions, most of them have drawbacks such as harsh and strong acidic conditions, expensive reagents, high temperature, special efforts required to prepare the catalyst, and also volatile organic solvents or large amounts of solid supports are usually used, which would eventually result in the generation of a large amount of toxic waste. Thus, it is interesting to devise a solventless, neutral, inexpensive, mild and catalytically efficient alternative for the protection of hydroxyl functionality as THP ether.

### RESULTS AND DISCUSSION

During the course of our systematic study on the ap-

plication of *N*-halo reagents in the transformation of organic functional groups,<sup>8</sup> we have found that NBS is an inexpensive, commercially available reagent. This reagent has recently been used as an effective catalyst for acetalization of carbonyl compounds,<sup>9a,b</sup> the conversion of aldehydes to 1,1-diacetates,<sup>9c</sup> and acylation of alcohols<sup>9d</sup> under mild and nearly neutral reaction conditions. In this article we wish to report a novel and efficient protocol for the tetrahydropyranylation of a variety of alcohols and phenols using dihydro-4H-pyran in the presence of a catalytic amount of NBS at room temperature under solvent-free conditions, as depicted in Scheme I.

**Scheme I**

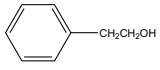
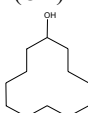
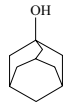


R=benzylic, linear, Cyclic, Aryl

We first examined the effect of different ratios of ROH/DHP/catalyst. Ratios of 1:1.5:0.02 for alcohols and 1:3:0.1 for phenols gave the best result and furnished the protected products in high yields (Table 1). Using this catalyst, different kinds of alcohols (primary, secondary, tertiary and benzylic) and phenols underwent tetrahydropyranylation in good to excellent yields (Table 1). Due to the nearly neutral nature of the reaction medium, no elimination by products were observed at all.

Selectivity of a method is important in the multi-step preparation of organic compounds and provides a broad spectrum for its use in functional group transformation re-

Table 1. Tetrahydropyranylation of alcohols and phenols using DHP catalyzed with NBS at room temperature under solvent-free conditions

Entry	ROH	Subst/DHP/NBS	Time (h)	Yield (%) <sup>a,b</sup>
1	PhCH <sub>2</sub> OH	1:1.5:0.02	2.5	95
2	4-(OMe)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	1:1.5:0.02	3.5	78
3	4-(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	1:1.5:0.02	2.5	90
4	4-(Br)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	1:1.5:0.02	1	95
5	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> OH	1:1.5:0.05	3.5	85
6		1:1.5:0.02	5.5	95
7	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub> OH	1:1.5:0.02	6.5	83
8	PhCH(OH)CH <sub>3</sub>	1:1.5:0.02	4	95
9	PhCH(OH)Ph	1:1.5:0.02	9	90
10		1:1.5:0.02	8	90
11		1:5:0.3	4.5	86
12	4-(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> OH	1:3:0.1	3.5	95
13	C <sub>6</sub> H <sub>5</sub> OH	1:3:0.1	4	90
14	4-(Cl)C <sub>6</sub> H <sub>4</sub> OH	1:3:0.1	4	92
15	4-(MeO)C <sub>6</sub> H <sub>4</sub> OH	1:3:0.1	4	90
16	1-Naphthol	1:3:0.1	6	92
17	5-Indanol	1:3:0.1	4.5	81
18	2-Naphthol	1:3:0.1	2.5	87
19	Resorcin	1:6:0.2	5	70

<sup>a</sup> All products were characterized by comparison of their spectral data (<sup>1</sup>H-NMR, IR spectroscopies) and physical properties with those of authentic compounds.

<sup>b</sup> Isolated yields.

actions. Therefore, we tried several competitive reactions under similar conditions in order to show the scope and limitation of this catalytic system. By this system, a primary benzylic hydroxyl group can be protected in the presence of a secondary benzylic alcohol with the ratio of 90:10 (Table 2, entry 1). A primary aliphatic alcohol was protected in the presence of tertiary alcohols with the ratio of 100:0 (Table 2, entry 2). An unhindered phenolic group can be very selectively protected in the presence of a hindered phenolic functional group (Table 2, entry 3).

In order to illustrate the catalytic activity of NBS, we compared our obtained results for the tetrahydropyranylation of benzyl alcohol (as a model of alcohols) and phenol (as a model of phenols) with the best of the well-known data from the literature (Table 3).

On the basis of a previously reported mechanism,<sup>7g</sup> and our observation during the course of reaction for the

tetrahydropyranylation of alcohols and phenols using DHP, we propose a mechanism in which the role of NBS for the protection of hydroxyl groups as DHP ethers is by the *in situ* generation of catalytic amounts of HBr (Scheme II).

## CONCLUSIONS

In conclusion, we have introduced a new, selective and efficient catalytic system for the tetrahydropyranylation reactions under mild and solvent-free conditions. NBS is a safe, commercially available, inexpensive industrial chemical. Due to the catalytic nature of the reaction, absence of volatile solvent, its mildness, non-toxic nature, neutrality of conditions, availability and the low cost of the reagent, we predict that this method will find useful appli-

Table 2. Competitive tetrahydropyranylation reactions of alcohols using DHP in the presence of NBS under solvent-free conditions

1		(90%)	(10%)
	2		(100%)
3		(100%)	(0%)

The percentage of the product in the reaction mixture was determined by GC analysis.

Table 3. Comparison of the activity of various catalysts in the tetrahydropyranylation of benzyl alcohol and phenol

Entry	Substrate	Reagent	Condition	Cat/DHP	Time (hrs)	Yield (%)	Ref
1	Benzyl alcohol	a) NBS	Solvent free, rt	0.02:1.5	2.5	95	This work
		b) $K_5CoW_{12}O_{40} \cdot 3H_2O$	Acetone, $H_2O$ , Reflux	0.01:2	5 min	97	7c
		c) $PdCl_2(CH_3CN)_2$	THF, rt	0.1:1.1	1	72	7j
		d) LiOTf	$ClCH_2CH_2Cl$ , reflux	0.6:1.6	2.5	96	5c
		e) $Fe(ClO_4)_3$	$Et_2O$ , rt	0.03:1	1.5	98	5h
		f) TCCA	Solvent-free 60-70 °C	0.1:1.4	5	92	7g
		g) Silica sulfuric acid	$CH_2Cl_2$ , rt	0.039:1.1	30 min	91	4e
2	Phenol	a) NBS	Solvent free, rt	0.1:3	4	90	This work
		b) $K_5CoW_{12}O_{40} \cdot 3H_2O^a$	Acetone, $H_2O$ , Reflux	0.01:2	NR	-	7c
		c) $PdCl_2(CH_3CN)_2^a$	THF, rt	0.1:1.1	NR	-	7j
		d) LiOTf	$ClCH_2CH_2Cl$ , reflux	0.6:1.7	5.5	94	5c
		e) $Fe(ClO_4)_3$	$Et_2O$ , rt	0.03:1	N.R	-	5h
		f) TCCA	Solvent-free, 60-70 °C	0.1:1.4	36	85	7g
		g) Silica sulfuric acid	$CH_2Cl_2$ , rt	0.039:1.1	NR	-	4e

<sup>a</sup> The reaction with substituted phenols gave traces of the corresponding products.

cation for the protection of the alcohols and phenols in modern synthetic chemistry.

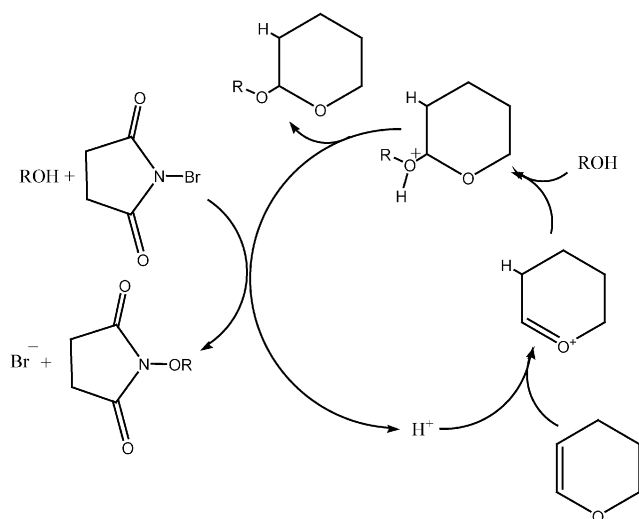
## EXPERIMENTAL

### General procedure for tetrahydropyranylation of alcohols and phenols catalyzed by NBS

The alcohol or phenol (1 mmol) was added to a mix-

ture of DHP (0.1262-0.2524 g, 1.5-3 mmols) and NBS (0.00356-0.01780 g, 0.02-0.1 mmols). The mixture was stirred at room temperature for the appropriate reaction time (Table 1). After completion of the reaction (TLC), the resulting mixture was passed through a short column of silica gel using a mixture of *n*-hexane/acetone (10:1) as eluent. Evaporation of the solvent under reduced pressure gave the desired compound in high purity.

**Scheme II** Proposed mechanism for the NBS-catalyzed tetrahydropyranylation of alcohols and phenols



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## REFERENCES

- (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd Ed.; Wiley: New York, 1991. (b) Kocienski, I. *Protecting Groups*; Enders, Eds.; Thieme: Stuttgart, 1994.
- Katritzky, A. R. C. W.; Rees, O. Meth-Cohn, *Comprehensive Organic Functional Group Transformations*; Pergamon Press: Oxford, Vol. 4, 1995.
- Hoyer, S.; Laszlo, P. *Synthesis* **1986**, 655.
- (a) Van Boom, J. H.; Herschied, J. D. M.; Reese, C. B. *Synthesis* **1973**, 169. (b) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (c) Nouquier, R. *Tetrahedron Lett.* **1982**, *23*, 2951. (d) Wang, B.; Yang, L. M.; Suo, J-S. *Synth. Commun.* **2003**, *33*, 3929. (e) Pore, D. M.; Desai, U. V.; Mane, R. B.; Wadgaonkar, P. P. *Synth. Commun.* **2004**, *34*, 2135.
- (a) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, *39*, 9287. (b) Karimi, B.; Maleki, J. *Tetrahedron Lett.* **2002**, *43*, 5353. (c) Namboodiri, V. V.; Varma, R. S. *Tetrahedron Lett.* **2002**, *43*, 1143. (d) Watahiki, T.; Kikumoto, H.; Matsuzaki, M.; Suzuki, T.; Oriyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 367. (e) Mineno, T. *Tetrahedron Lett.* **2002**, *43*, 7975. (f) Stephens, J. R.; Butler, P. L.; Clow, C. H.; Oswald, M. C.; Smith, R. C.; Mohan, R. S. *Eur. J. Org. Chem.* **2003**, 3827. (g) Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Hekmat, S. R. *Tetrahedron Lett.* **2005**, *46*, 543.
- (a) Menger, F. M.; Chu, H. *J. Org. Chem.* **1981**, *46*, 5044. (b) Olah, G. A.; Husain, A.; Singh, B. P. *Synthesis* **1983**, 892. (c) Johnston, R. D.; Marston, C. R.; Krieger, P. E.; Goe, G. L. *Synthesis* **1988**, 393.
- (a) Ranu, B. C.; Saha, M. *J. Org. Chem.* **1994**, *59*, 8269. (b) Ravindranath, N.; Ramesh, C.; Biswanath, D. *Synlett* **2001**, *III*, 777. (c) Habibi, H. M.; Tangestaninejad, S.; Mahammadpoor-Baltork, I.; Mirkhani, V.; Yadollahi, D. *Tetrahedron Lett.* **2001**, *42*, 2851. (d) Namboodiri, V. V.; Varma, R. S. *Chem. Commun.* **2002**, 342. (e) Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 467. (f) Deka, N.; Samara, J. C. *J. Org. Chem.* **2001**, *66*, 1947. (g) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Synth. Commun.* **2004**, *34*, 3623. (h) Tamami, B.; Parvanak Borujeny, K. *Tetrahedron Lett.* **2004**, *45*, 715. (i) Wang, Y.-G.; Wu, X.-X.; Jiang, Z.-Y. *Tetrahedron Lett.* **2004**, *45*, 2973. (j) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679.
- (a) Khazaei, A.; Rostami, A.; Manesh, A. A. *J. Chin. Chem. Soc.* **2006**, *53*, 43. (b) Khazaei, A.; Zolfigol, M. A.; Manesh, A. A. *J. Chin. Chem. Soc.* **2005**, *52*, 515. (c) Khazaei, A.; Aminimanesh, A.; Rostami, A. *J. Chem. Res.* **2005**, 391. (d) Khazaei, A.; Manesh, A. A. *J. Chin. Chem. Soc.* **2005**, *52*, 1017. (e) Khazaei, A.; Manesh, A. A.; Safi, V. R. *J. Chin. Chem. Soc.* **2005**, *52*, 559. (f) Khazaei, A.; Zolfigol, M. A.; Rostami, A. *Synthesis* **2004**, 2959. (g) Khazaei, A.; Rostami, A.; Tanbakochian, Z.; Zinati, Z. *J. Braz. Chem. Soc.* **2006**, *17*, 206. (h) Khazaei, A.; Rostami, A.; Tanbakochian, Z.; Zinati, Z. *Cat. Commun.* **2006**, *7*, 214.
- (a) Karimi, B.; Ebrahimian, G. R.; Seradj, H. *Org. Lett.* **1999**, *1*, 1737. (b) Karimi, B.; Seradj, H.; Ebrahimian, G. R. *Synlett* **1999**, 456. (c) Karimi, B.; Seradj, H.; Ebrahimian, G. R. *Synlett* **2000**, 623. (d) Karimi, B.; Seradj, H. *Synlett* **2001**, 519.