

Zeolite H-beta: an Efficient and Recyclable Catalyst for the Tetrahydropyranylation of Alcohols and Phenols, and the Deprotection of Tetrahydropyranyl Ethers

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Use of protective groups is an important procedure in organic synthesis.¹ Protection of alcohols and phenols as their corresponding ethers or acetals/ketals is a well-known method for protection of hydroxyl groups. Tetrahydropyranyl (THP) ether is one of the useful protective groups due to its low cost and stability toward strongly basic reaction conditions, even though one additional stereocenter is generated during the THP ether formation. Tetrahydropyranylation has been performed with a variety of reagents or catalysts. Recent examples include stannous chloride dihydrate,² tetrafluoroborate,³ and heterogeneous catalysts such as sulfuric acid adsorbed on silica gel,⁴ ionic liquids⁵ and polyoxometalate.⁶ For the deprotection of THP ethers, reagents including sodium bromate,⁷ CBr₄,⁸ and montmorillonite clays^{9,10} have been employed. Also, reductive¹¹ and oxidative deprotections¹² were reported in the literature.

In recent years, organic reactions on solid supports such as zeolites¹³ or mesoporous molecular sieves^{14,15} have attracted much attention because of advantages these catalysts possess, such as acidic properties, shape-selectivities, environment-friendly nature of catalysts, the easy work-up, the high purity of the products, and the recycling of catalysts. Therefore, it is not surprising that zeolites such as H-Y zeolite,¹⁶ H-MCM-41,¹⁷ HSZ[®]-330/360¹⁸ and delaminated zeolites¹⁹ have been already used as catalysts for the THP ether formation.

Zeolite H-beta has been used as an acid catalyst in organic chemical conversion such as alkylation²⁰ and acylation.²¹ This catalyst is reported to have Brønsted acid sites in the micropores and on the external surface, and Lewis acid sites predominantly at the internal surface due to the local defects.²² Surprisingly, zeolite H-beta has not been yet widely used as a solid acid catalyst in organic transformation.^{20,21} In this letter, we like to report the tetrahydropyranylation of alcohols and phenols, and deprotection of THP ethers using zeolite H-beta as a reusable acid catalyst, as shown in Table 1.²³

Tetrahydropyranylation was performed by refluxing a mixture of alcohols (1 mmol) or phenols and dihydropyran (DHP, 1.15 equiv.) in hexanes (10 mL) in the presence of zeolite H-beta (10 mg or 20 mg). After the conversion was finished, the reaction mixture was filtered through filter paper. The filtrate was concentrated and the crude product was purified by vacuum distillation or column chromatography. As shown in Table 1, primary alcohols (entries 1-5) and less hindered secondary alcohols (entries 6-8) were protected as THP ethers within 15 min in high yields. Protection of hindered secondary alcohols such as (-)-menthol,

benzhydrol and cholesterol (entries 9-11), and tertiary alcohols (entries 12-14) was sluggish. Especially, cholesterol, a bulky alcohol was very reluctant to undergo the protection (entry 11). Generally, aromatic phenols were less reactive than aliphatic alcohols (entries 15-18) and bulky phenol (entry 19) was inert to the reaction condition. Compared with H-Y zeolite,¹⁶ the present method is faster (5 min vs. 10 h for benzyl alcohol) and requires less amount of catalyst (10 mg vs. 110 mg for benzyl alcohol). Also, compared with the solvent-free protection over HSZ[®]-330/360,¹⁸ the present method uses smaller amount of catalyst (10 mg of zeolite H-beta vs. 50-100 mg of HSZ[®]-330/360 per 1 mmol of alcohols) and DHP (1.15 equiv. vs. 2 equiv.), and gives the THP ether in a shorter reaction time (5 min vs. 5 h for benzyl alcohol). Then, we studied the zeolite H-beta-catalyzed deprotection of THP ethers, which was performed by refluxing a mixture of THP ether (1 mmol) and zeolite H-beta (10 mg) in methanol (10 mL). As shown in Table 1, most deprotection was completed within 5-20 min, except for entry 10. Remarkably, THP ether of (-)-menthol was deprotected without loss of optical activity with a similar rate as other alcohols (entry 9), even though the protection of menthol required much a longer reaction time than that of less hindered alcohols. Also, deprotection of THP ethers of tertiary alcohols was as fast as that of THP ethers of primary alcohols (entries 12-13 vs. entries 1-5), though the formation of THP ethers from tertiary alcohols was very sluggish. Similarly, deprotection of phenolic THP ethers was achieved within 5 min (entries 15-18) as in the case of normal alcohols, in contrast to the slower formation of THP ethers than ordinary alcohols. These observations suggest that the deprotection of THP ethers and the protection may take place in different sites of zeolite H-beta:²² in aprotic solvent such as hexanes, zeolite H-beta acts as Lewis acid at the internal micropore surface, thus showing the shape-selectivity, as evidenced in Table 1. In contrast, the large external surface of this catalyst may behave mainly as Brønsted acid in the presence of protic solvent such as methanol that was used in deprotection. Then, shape-selectivity will be decreased, as shown in Table 1.

Finally, we studied the recycling of zeolite H-beta. Thus, zeolite H-beta catalyst used for protection in entry 8 was recovered by filtration through filter paper. This recovered catalyst was washed with hexanes, dried in air and reused without calcination for the next protection run, which was finished in 9 min, giving 95% yield. The third run using the recovered catalyst from the second run gave 97% yield in 10

Table 1. Zeolite H-beta-catalyzed tetrahydropyranlation of alcohols and phenols, and deprotection of THP ethers

$\text{ROH} \xrightleftharpoons[\text{zeolite H-beta, methanol, reflux}]{\text{zeolite H-beta, dihydropyran, hexanes, reflux}} \text{RO-THP}$

Entry	Alcohols and Phenols	Protection Conditions ^a	Deprotection Conditions ^b
1	CH ₃ (CH ₂) ₆ CH ₂ OH	10 mg, 10 min (98)	10 mg, 10 min (98)
2	CH ₃ (CH ₂) ₃ CH(CH ₂ C H ₃)CH ₂ OH	10 mg, 10 min (95)	10 mg, 10 min (92)
3	PhCH ₂ OH	10 mg, 5 min (99)	10 mg, 5 min (93)
4	PhCH=CHCH ₂ OH	10 mg, 15 min (97)	10 mg, 10 min (99)
5	(CH ₃) ₂ C=CHCH ₂ OH	10 mg, 10 min (96)	10 mg, 10 min (94)
6	CH ₃ CH(OH)C ₆ H ₁₃	10 mg, 10 min (95)	10 mg, 5 min (92)
7	(ClCH ₂) ₂ CH(OH)	10 mg, 10 min (93)	10 mg, 5 min (96)
8	cyclohexanol	10 mg, 10 min (95)	10 mg, 5 min (96)
9	(-)-menthol	10 mg, 4 h (84) ^c	10 mg, 20 min (99)
10	Ph ₂ CH(OH)	10 mg, 30 min (98)	10 mg, 1 h (98)
11	cholesterol	10 mg, 24 h (20) ^c	
12	(CH ₃) ₂ CC ₆ H ₁₃ (OH)	20 mg, 40 min (98)	10 mg, 5 min (92)
13	(CH ₃) ₂ CPh(OH)	20 mg, 45 min (60) ^f	10 mg, 5 min (93)
14	1-phenylcyclohexanol	20 mg, 45 min (60) ^f	
15	C ₆ H ₅ OH	10 mg, 2 h (95)	10 mg, 5 min (95)
16	4-ClC ₆ H ₄ OH	10 mg, 2 h (95)	10 mg, 5 min (97)
17	2-naphthol	10 mg, 2 h (96)	10 mg, 5 min (96)
18	4-NO ₂ C ₆ H ₄ OH	10 mg, 6 h (65) ^c	10 mg, 5 min (93)
19	2- <i>tert</i> -BuC ₆ H ₄ OH	10 mg, 6 h (0)	

^aTHP ethers were prepared by heating a mixture of alcohol or phenol (1 mmol) and dihydropyran (1.15 mmol) in dry hexanes (10 mL) in the presence of specified amount of zeolite H-beta. Isolated yield is in the parenthesis. ^bDeprotection was performed by heating a mixture of THP ether (1 mmol) and catalyst in methanol (10 mL). ^cThe rest is the starting material.

min. Similarly, zeolite H-beta catalyst used for deprotection in entry 8 was recovered, as before and was reused for the second deprotection, which was finished in 6 min, giving 95% yield. The third run using the recovered catalyst from the second run gave 95% yield in 5 min. These results show that zeolite H-beta can be recycled for many times without loss of the activity.

In conclusion, the present method of using zeolite H-beta as an acid catalyst for protection of alcohols as THP ethers and deprotection of THP ethers provides a useful alternative to the known methods. The notable advantages of this method include the capability of both protection and deprotection catalyzed by the same catalyst, mild conditions (reflux in hexanes or methanol), short reaction time (5-15 min for normal alcohols), high yields (>90%), easy recyclability of used catalyst, and the use of less amount of catalyst compared to other catalysts such as H-Y zeolite or HSZ[®]-330/360.

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- Zeolite H-beta used in this study was purchased in a form of HSZ[®]-930 from Tosoh Corporation, Japan and was calcined at 450 °C for 3 h in the presence of air before use. This calcined catalyst showed the following physico-chemical properties: SiO₂/Al₂O₃ = 15.9; BET surface area = 685 m²/g; pore volume = 0.57 cm³/g; average pore diameter = 33.4 Å. We thank Mr. Jae-Heon, Kim (Department of Applied Chemistry) for providing us with these data.