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Solvent Free Tetrahydropyranylation of Phenols and Alcohols over Zeolites HSZ as Reusable Catalysts

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Abstract: Phenols and alcohols are tetrahydropyranylated in the presence of zeolites HSZ in good to excellent yields and selectivities. Addition of methanol performs the complete deprotection.

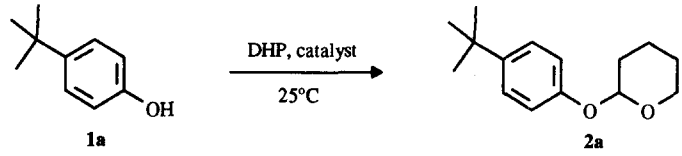
3,4-Dihydro-2H-pyran (DHP) has been widely utilized as a protective group of hydroxy compounds requiring protic or Lewis acids as typical promoters.[1] More recently the tetrahydropyranylation process (THP ethers synthesis) has been performed under environmentally friendly conditions with concomitant minimum purification requirements. These include use of heterogeneous catalysts such as K10 montmorillonite,[2] sulfonated charcoal,[3] HY-zeolite,[4] zinc chloride on alumina,[5] Envirocat-EPZG[6] and natural kaolinite clay.[7] Moreover, a bentonitic clay has been used to deprotect THP ethers.[8]

However none of the above mentioned catalysts is claimed to give protection as well as deprotection of hydroxy compounds and to be reusable.[9] Taking into account the increasing demanding of new and cleaner chemical processes,[10] we undertook a study directed toward discovering new catalytic applications of solid acids.[11]

In this letter we present the protection of hydroxy compounds as THP ethers and removal of the protective group over zeolites HSZ as reusable catalysts.

HSZ zeolites are produced on a large scale by Tosoh Corporation for the refinery and petrochemical industry and thus represent easily accessible solid acids employable without previous thermal or chemical treatment. Our initial efforts were focused on achieving the optimum conditions for tetrahydropyranylation of *para-tert*-butylphenol and (-)-menthol chosen as model hydroxy compounds in the presence of zeolites HSZ-330 [acid faujasitic-type zeolite with 5.9 SiO_2/Al_2O_3 molar ratio, pore size 8Å, surface area 460±10 m^2/g[12] and acidity 1.39 meq. H^+/g[13]] and HSZ-360 [acid faujasitic-type zeolite with 13.9 SiO_2/Al_2O_3 molar ratio, pore size 8Å, surface area 500±10 m^2/g and acidity 0.51 meq. H^+/g]. All reactions were carried out at room temperature, without solvent. Results are summarised in Tables 1 and 2.

Table 1. Reaction of *para-tert*-butylphenol (**1a**) with DHP under different conditions.*

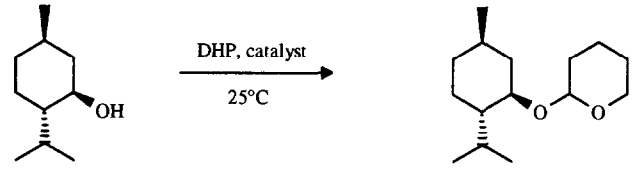


1a **2a**

Entry	DHP/**1a** molar ratio	Catalyst (g)	Time (h)	Yield (%)
a	1	HSZ-360 (0.5)	1.5	33
b	1	HSZ-330 (0.5)	1.5	40
c	1	"	5.0	40
d	2	"	1.5	68
e	2	HSZ-330 (1.0)	1.5	88
f	1	"	1.5	51

* All reactions were carried out by stirring a mixture of **1a** (10 mmol), DHP and zeolite without solvent at 25°C for the selected reaction time. Yields were estimated by g.l.c. analysis [SPB-1 Supelco column, 30 m, 60°C (1), 15°C/min, 280°C (5)].

Table 2. Reaction of (-)-menthol (**1g**) with DHP under different conditions.*



1g **2g**

Entry	DHP/**1g** molar ratio	Catalyst (g)	Time (h)	Yield (%)
a	1	HSZ-360 (0.5)	1.5	45
b	1	HSZ-330 (0.5)	1.5	10
c	1	HSZ-360 (0.5)	5.0	63
d	2	"	5.0	79
e	2	HSZ-360 (1.0)	5.0	54

* Experimental conditions: see Table 1.

Comparing the results obtained, we noted that the best yields were respectively achieved with zeolite HSZ-330 at 25°C for 1.5 hours for *para-tert*-butylphenol (**1a**) [88%] (Table 1, entry e) and with zeolite HSZ-360 at 25°C for 5 hours for (-)-menthol (**1g**) [79%] (Table 2, entry d).

Application of these procedures to the preparation of THP ethers from different phenols and alcohols was then investigated. Results reported in Table 3 show that the yields are comparable to those observed with different heterogeneous catalysts,[2-8] but the present reaction has the advantage of being performed at room temperature and avoiding the use of solvents.

Table 3. Tetrahydropyranylation of hydroxy compounds under zeolite catalysis.

Entry	Hydroxy compound	Catalyst	Conditions*	THP ether **2** yield (%)
a	4-Bu^t-phenol	HSZ-330	A	**2a** 88
b	4-OMe-phenol	"	A	**2b** 77
c	4-Cl-phenol	"	A	**2c** 66
d	3-Cl-phenol[14]	"	A	**2d** 60
e	2-Cl-phenol	"	A	**2e** 44
f	Benzyl alcohol	HSZ-360	B	**2f** 100
g	(-)-Menthol	"	B	**2g** 79
h	Cynnamic alcohol	"	B	**2h** 70
i	2-Methyl-2-propenol	"	B	**2i** 95
j	2-Nitroethanol	"	B	**2j** 97
k	6-Chloroesanol	"	B	**2k** 98
l	Androsterone	"	B	**2l** 70
m	Salicylic alcohol[#15]	"	C	**2m** 95
n	1,6-Hexandiol[§]	"	C	**2n** 70

* A: 10 mmol phenol; 20 mmol DHP; 1.0 g catalyst; 25°C; 1.5 h. B: 10 mmol alcohol; 20 mmol DHP; 0.5 g catalyst; 25°C; 5 h. C: 10 mmol alcohol; 10 mmol DHP; 0.5 g catalyst; 0°C; 2 h.

Selective reaction at the alcoholic hydroxy group.

§ DiOTHP = 9% yield.

The process is of general applicability and tolerates different functional groups (e.g. C,C double bond, nitro, chlorine, carbonyl) [Table 3, entries h-l]. Of particular interest is the selective protection of the alcoholic OH group in the presence of the phenolic one (Table 3, entry m) and the good selectivity in the monoprotection of symmetric diols (Table 3, entry n).

We next investigated the ability of the catalysts to remove the protective group from THP ethers. To this end a slurry of compound **2a** (10 mmol) and zeolite HSZ-330 (0.5 g) in MeOH (20 ml) was stirred at room temperature for 2 hours affording **1a** in quantitative yield. Using the same methodology all THP ethers **2** were completely converted into the corresponding hydroxy compounds **1**. Similar results could be obtained with zeolite HSZ-360. Moreover optically active alcohol (-)-menthol was recovered without any racemization.

Finally we turned our attention towards the possible recycling of the catalyst in the reaction with the model substrate **1b**. The catalyst was filtered on buckner funnel, washed with acetone, dried in air and immediately reused. Unexpectedly, after allowing the reaction mixture to stir for 1.5 hours at 25°C, **2a** was obtained in a quantitative yield. Moreover, we recycled the zeolite for a further five experiments recovering the product **2a** with similar high yields.The recycling process with (-)-menthol gave less satisfactory results (average yield: 70%).

This result indicates that zeolites HSZ-330 and HSZ-360 are activated after the first cycle and can be, therefore, reused several times without losing activity.

In conclusion the present letter provides a novel, solvent free and general method for protecting hydroxy compounds as THP ethers and removing the protective group in the presence of zeolites HSZ as reusable catalysts.

Further studies to identify the mechanism of catalyst activation are currently under investigation.

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14. Pyran-2-(3-chlorophenyl)tetrahydro (**2d**). Colourless oil, b.p. 71-73°C/0.04 mm Hg (Found: C, 62.3; H, 6.5; Cl, 16.2. $C_{11}H_{13}ClO_2$ requires C, 62.1; H, 6.2; Cl, 16.7%); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm) 1.5-2.1 (m, 6 H, $\underline{CH_2CH_2CH_2}CH_2O$), 3.5-3.7 (m, 1 H, ½ $O\underline{CH_2}CH_2$), 3.8-4.0 (m, 1 H, ½ $O\underline{CH_2}CH_2$), 5.39 (t, 1 H, CH, J=3.1 Hz), 6.9-7.0 (m, 2 H, H-4 and H-6), 7.07 (t, 1H, H-2, J=2.1 Hz), 7.18 (t, 1 H, H-5, J=8.1 Hz); MS (EI) m/e 212 (M^+, 2%), 131 (34), 129 (100), 122 (23).
15. 2H-Pyran-tetrahydro-2-(2-hydroxybenzyl)oxy (**2m**). Pale yellow oil, b.p. 108-110°C/0.03 mm Hg (Found: C, 69.0; H, 8.0. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm) 1.5-1.9 (m, 6 H, $\underline{CH_2CH_2CH_2}CH_2O$), 3.5-3.7 (m, 1 H, ½ $O\underline{CH_2}CH_2$), 3.9-4.1 (m, 1 H, ½ $O\underline{CH_2}CH_2$), 4.66 (d, 1 H, ½ OCH_2Ar, J=12.2 Hz), 4.7-4.8 (m, 1 H, CH), 4.92 (d, 1 H, ½ OCH_2Ar, J=12.2 Hz), 6.85 (td, 1 H, H-5 or H-4, J=7.4 and 1.0 Hz), 6.90 (dd, 1H, H-3 or H-6, J=8.1 and 1.0 Hz), 7.09 (dd, 1H, H-6 or H-3, J=7.4 and 1.7 Hz), 7.22 (td, 1 H, H-4 or H-5, J=8.1 and 1.7 Hz); MS (EI) m/e 208 (M^+, 3%), 124 (32), 107 (43), 85 (100).

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