A New, Mild Heterogeneous Catalyst for the Tetrahydropyranylation of Alcohols and Phenols

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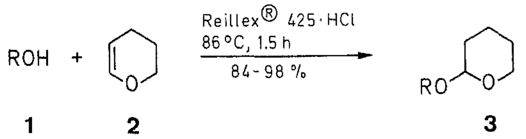
The hydrochloride salt of a cross-linked macroreticular poly(4-vinylpyridine) resin in bead form is an effective, yet mild acid catalyst for the tetrahydropyranylation of alcohols (primary, secondary, and tertiary) and phenols. The reaction is carried out in the presence of excess dihydropyran without the formation of troublesome oligomeric pyrans. High yields of the desired ethers are obtained even in reactions with alcohols having steric restrictions or acid sensitive amine functionalities.

The tetrahydropyranyl group has been recognized as a useful hydroxyl protecting group for a great number of alcohols and phenols. It is stable under a variety of reaction conditions such as strongly basic media, reduction with hydrides, and contact with Grignard, oxidative, alkylating, and acylating reagents.[1] Not surprisingly, the outstanding stability of tetrahydropyranyl ethers often makes dihydropyran the reagent of choice for hydroxyl group protection in peptide, nucleotide, carbohydrate, and steroid chemistry.[2]

Generally alcohols are converted to their tetrahydropyranyl derivatives under acid catalyzed conditions.[3-10] We report here that the mildly acidic hydrochloride salt of commercially available Reillex® 425, a macroreticular 4-vinylpyridine-divinylbenzene copolymer in bead form, is an efficient catalyst for the tetrahydropyranylation of alcohols (primary, secondary, and tertiary) and phenols. As with other heterogeneous acid catalysts, the work-up is reduced to a simple filtration with no need for acid removal or troublesome neutralization. The Reillex® 425 hydrochloride catalyst is recovered unchanged with no loss of catalytic activity and may be reused in numerous subsequent reactions.



1 2 3

Table 1. Tetrahydropyranylation of Alcohols and Phenols Using Reillex® 425 Hydrochloride

Alcohol 1	Reaction Time (h)	Yield[a] of 3 (%)	bp (°C)/mbar or mp (°C)	Molecular Formula or Lit. bp (°C)/mbar or mp (°C)
2-Pyridine-propanol	1.5	94	133/1[b]	$C_{13}H_{19}NO_2$[c] (221.3)
3-Pyridine-methanol	1.5	93	–[d]	$C_{11}H_{15}NO_2$[d] (193.3)
Cyclohexanol	1.5	98	79–80/3	79–80/3[8]
Benzyl alcohol	1.5	97	105/5	105/5[9]
Phenol	2.5	91	79–80/3	90–92/5[9]
Menthol	18	96	88/3	88/3[8]
4-Methoxyphenol	1.5	90	133/1	131/3[8]
Cholesterol	2.5	94[e]	148–149	149–150[8]
2-Phenyl-2-propanol	4.0	84	102/13	–[f]

[a] Yield of isolated product purified by vacuum distillation, except as noted; the purity of isolated products was 97% or higher as analyzed by GC (12 m DB-1, 80–250 °C at 16 °C/min), except as noted.

[b] ^{1}H-NMR (CDCl$_3$/TMS): $\delta = 1.43$–2.28 (m, 8H); 2.91 (t, 2H, $J = 7$ Hz); 3.23–4.02 (m, 4H); 4.60 (br s, 1H); 6.98–7.22 (m, 2H); 7.59 (dt, 1H, $J = 7, 2$ Hz); 8.50 (dd, 1H, $J = 7, 2$ Hz).

[c] $C_{13}H_{19}NO_2$ calc. C 70.59 H 8.60 N 6.33
(221.3) found 70.43 8.54 6.19

[d] Analytical purity could not be obtained by vacuum distillation as decomposition to a mixture of **1**, **2**, and **3** resulted (112 °C/1 mbar). GC of crude reaction product: **3** (92%), rest oligomers of **2**, and no detectable **1**. ^{1}H-NMR (CDCl$_3$/TMS): $\delta = 1.46$–2.04 (m, 6H); 3.40–4.07 (m, 2H); 4.38–4.92 (m, 3H); 7.26 (dd, 1H, $J = 8, 5.2$ Hz); 7.80 (dt, 1H, $J = 8, 2$ Hz); 8.43–8.60 (m, 2H).

[e] Purified by column chromatography (silica gel, EtOAc/cyclohexane, 1 : 3) and recrystallized from i-Pr$_2$O.

[f] Not reported in Ref. 11.

The cross-linked polymer and its salts are intrinsically insoluble in all solvents. In previous work, the *p*-toluenesulfonic acid salts of non-cross-linked homopolymers of vinylpyridines are found to be effective tetrahydropyranylation catalysts, but had to be absorbed on a large excess of filter aid to be heterogeneous.[11]

One advantage that Reillex® 425 hydrochloride possesses over other more strongly acidic resin catalysts is that the reaction may be carried out in the absence of a solvent other than excess dihydropyran. It has been reported that excess dihydropyran in the presence of the strongly acidic resin catalyst, Nafion-H, will produce polymeric by-products of dihydropyran while the yield of the tetrahydropyranyl ether is very low.[10] We have also found this to be true when using the strongly acidic resin, Amberlyst A-15.[8] Unlike these resins, Reillex® 425 hydrochloride is a milder catalyst which does not produce the excessive polymerization of dihydropyran.

The weak acidity of the catalyst allows for the tetrahydropyranylation of weakly basic alcohols such as 2-pyridinepropanol and 3-pyridinemethanol. The tetrahydropyranylation of these compounds appears not to have been reported. Reillex® 425 hydrochloride catalyzed these reactions to greater than 90% yields (Table 1). The strongly acidic Amberlyst A-15 resin gave a yield of only 47% in the tetrahydropyranylation of 3-pyridinemethanol and a yield of only 34% when the catalyst was recycled.

Reillex® 425 hydrochloride may be used several times whithout a loss of catalytic activity and there is no need for regeneration by reacidification. A series of reactions was carried out with Reillex® 425 hydrochloride in the catalytic tetrahydropyranylation of 4-methoxyphenol. Table 2 lists the results, illustrating that no loss of catalytic activity is seen after six successive uses.

Table 2. Recyclability of Reillex® 425 Hydrochloride in the Tetrahydropyranylation of 4-Methoxyphenol

Run	Yield of **3** (%)
Initial Run (Fresh Catalyst)	90
1st Recycle	96
2nd Recycle	92
3rd Recycle	89
4th Recycle	89
5th Recycle	91
Blank (No catalyst)	14

Reillex® 425 brand of cross-linked poly(4-vinylpyridine), 3-pyridinemethanol, and 2-pyridinepropanol were commercial materials from Reilly Tar & Chemical Corporation; samples or large quantities are available therefrom. 3,4-Dihydro-2*H*-pyran from Quaker Oats Company was redistilled before use. Other organic chemicals were purchased from Aldrich Chemical Co.

Preparation of Reillex® 425·HCl:
Reillex® 425 (110 g of polymer as received, 60% H_2O) is mixed with 1.0 L of 5% HCl and allowed to stand for several hours. The solid is filtered, then dried at 80 °C for 8–10 h.

Tetrahydropyranylation of Alcohols and Phenols; General Procedure:
A mixture of alcohol or phenol **1** (50 mmol) and Reillex® 425·HCl (1 g, ~ 5 meq) in 3,4-dihydro-2*H*-pyran (**2**; 20 mL, 220 mmol) is stirred magnetically and heated under reflux (86 °C) for 1.5 h. After completion of the reaction, the Reillex® 425·HCl is removed by filtration and washed with dihydropyran (5 mL). The excess dihydropyran is removed under reduced pressure with the aid of a rotary evaporator yielding the tetrahydropyranyl ether **3**. Further purification is carried out by vacuum distillation when necessary, except as noted in Table 1.

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