Rapid Communication

Chemoselective tetrahydropyranylation of primary alcohols under freezing water pressure

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A highly efficient environmentally friendly method for selective tetrahydropyranylation of primary alcoholic groups under pressure exerted by freezing water has been described.

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The importance of selective introduction of protecting group in organic synthesis is well established. Tetrahydropyranyl ethers are one of the most frequently used hydroxy protecting groups because they are less expensive, easy to deprotect and stable towards strong bases, Grignard reagent, hydrides, redox reagents, alkylating and acylating reagents.

There are several reagents available for tetrahydropyranylation, which include the use of Bronsted and Lewis acid, ion exchange resins, ionic liquid, iodine-microwave irradiation, zeolites, montmorillonite K-10, tributylammonium bromide, heteropoly acids, cyclodextrin, aluminium chloride hexahydrate, etc. Although these methods have their own advantages, some of them suffer from the drawback of using expensive and toxic reagents, drastic conditions like high temperature or microwave irradiation, which cannot be recommended where other sensitive functional groups are present particularly in multistep synthesis. The use of volatile organic solvents and solid supports results in the generation of toxic wastes.

Importantly, most of these methods suffer from the drawback of lack of selectivity. Thus, development of a mild and environmentally friendly method for selective tetrahydropyranylation is still a need.

The choice of the solvent plays a vital role in a protection/deprotection sequence. The general protocol for tetrahydropyranylation is that protection is achieved with a mild acidic reagent in an aprotic solvent such as CH₂Cl₂, THF, acetone, etc., while deprotection takes place also with an acidic reagent but in a protic or polar solvent like water, methanol, ethanol, 2-propanol, acetonitrile, etc. p-Toluenesulfonic acid is the most commonly used acid catalyst for tetrahydropyranylation of alcohols and phenols, but under normal condition this catalyst does not show any selectivity.

During our recent studies on organic reactions in aqueous media we have found that in contrast to the general protocol, selective tetrahydropyranylation of primary alcohols takes place under high pressure exerted by freezing water in the presence of a catalytic amount of p-toluenesulfonic acid (Scheme I).

High pressure is one factor that can accelerate organic reactions, but its use is limited because of the need of special high pressure apparatus. Hayashi et al. has demonstrated that when water freezes to –20°C in a sealed autoclave, a high pressure (ca. 200 Mpa) is achieved. This high pressure has been used to carry out Michael reaction, Baylis’Hillman reaction, three-component List-Barbas-Mannich reaction and asymmetric aldol condensation reaction. In a modification of this we have applied pressure directly by freezing an aqueous mixture of alcohol, 3,4-dihydro-2H-pyran (DHP) and a catalytic amount of p-toluenesulfonic acid. When water freezes then the pressures of aqueous vapour over ice at 0°C and –20 °C are 101935.49 Pa and 101428.46 Pa respectively which are slightly higher than 1

Scheme I
### Table I — Selective tetrahydropyranylation of alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product a</th>
<th>Reaction Time (h)</th>
<th>Yield (%)b</th>
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</table>

a Products were characterized by IR, 1HNMR, and Mass spectra. b Yields of pure isolated products. Yields in the parentheses correspond to the ditetrahydropyranlated product.
atmospheric pressures. Again internal pressures of ice at 0°C and –20°C are –36.47 × 10^6 Pa and –260.28 × 10^6 Pa which are lower than water. But, surprisingly, the reaction takes place smoothly at 0°C or below it without any side product. On carrying out the reaction in a sealed autoclave (when high pressure is generated) products were obtained almost in the same yield.

**Results and Discussion**

Benzyl alcohol and its analogues (Table I, entry 1), straight chain primary alcohols (entries 2 and 3) and 2-nitroethanol (entry 4) were studied. When the same reaction was attempted with phenols no tetrahydropyranylated product was formed. This result encouraged us to study the selectivity between primary alcohol and phenol (entries 5 and 6). It was observed that an alcoholic group was selectively protected under these conditions. On performing the reaction with a secondary alcohol the tetrahydropyranylated product was produced only in very low yield (entries 7 and 8). No change in the yield was observed by increasing reaction time (up to 24 h), increasing the amount of catalyst or changing the temperature between 0 and –20°C. Also, no product was formed with tertiary alcohols. Some competitive experiments with an equimolar mixture of primary alcohol, secondary alcohol and phenol have been conducted as shown in Scheme II. The primary alcohol gave the protected product in 91% yield; the secondary alcohol yielded only 8% of the tetrahydropyranyl (THP) ether, while 98% of the unreacted phenol was recovered. In the case of p-hydroxyacetophenone (entry 9) the secondary alcoholic group was protected although the yield was poor.

The results of selective tetrahydropyranylation of a variety of alcohols are summarized in Table I.

Based on these observations, the selectivity between primary and secondary alcohols (entries 10 to 15) was investigated and it was found that primary alcoholic groups were protected selectively in preference to the secondary alcoholic groups.

Interestingly, for the symmetrical diol, ethylene glycol (entry 16) the monotetrahydropyranylated product was formed as the major product. This selectivity was much superior than the previous reports.

In conclusion, our protocol provides a practically efficient method for chemo selective tetrahydropyranylation of primary alcohols using the most commonly used inexpensive reagent under mild and environment-friendly conditions. The advantages of this methodology are mild conditions, excellent yields, absence of volatile solvents and good selectivity.

**Experimental Section**

Infrared (IR) spectra were recorded on a Perkin Elmer 1640 FT-IR spectrometer on chloroform. 1H-NMR spectra were recorded in a Bruker DPX-300 NMR machine in deuterio-chloroform. Mass spectra were recorded on Brucker Daltonic Data Analysis 2.0 Spectrometer. All reagents were of commercial quality from freshly opened containers and were purchased from Aldrich Chemical Company and used without further purification. Distilled water was used for all-purpose.

**General procedure for preparation of THP ethers**

1 mmol of the alcohol was mixed with 1.5 mmol of 3,4-dihydro-2H-pyran (DHP) in 2 mL water in a round-bottomed flask, to this was added 0.1 mmol p-toluenesulfonic acid. The flask was fitted with a stopper and the reaction mixture was cooled in a domestic refrigerator to –20°C and kept in that state for the specified time. The reaction mixture was allowed to come to room temperature, extracted with chloroform, the extract washed first with sodium bicarbonate (NaHCO₃) and then with water, dried.

![Scheme II](image-url)
over anhydrous sodium sulphate (Na₂SO₄) and the solvent was distilled under reduced pressure and the residue was purified by chromatography to obtain the product. For comparison of the effect of temperature the reaction was performed at –5°C and –20°C but the yields were nearly equal at both the temperatures.

Selected spectral data of some of the compounds

6a: IR (CHCl₃): 3387, 2944, 1457, 1352, 1273, 1240, 1122, 1074, 1024, 903, 770 & 755 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.57 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.71-4.82 (m, 1H), 4.66 (d, J = 12 Hz, 2H), 3.58-3.70 (m, 2H), 1.51-1.98 (m, 6H). MS (m/z): 231.1 (M+ +Na). Anal. Calc. for C₁₂H₁₆O₃: C, 69.23; H, 7.69. Found: C, 69.02; H, 7.98%.

10a: IR (CHCl₃): 3388, 2944, 1455, 1442, 1355, 1200, 1138, 1118, 1075, 1028, 977, 901, 770 & 753 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 4.75-4.89 (m, 1H), 3.98-4.02 (m, 2H), 3.55-3.70 (m, 2H), 3.30 (m, 1H), 2.10 (br, s, 1H), 1.51-1.98 (m, 6H), 0.99 (s, 3H). MS (m/z): 183.1 (M+ +Na). Anal. Calc. for C₈H₁₆O₃: C, 60.00; H, 10.00. Found: C, 59.81; H, 10.33%.

15a: IR (CHCl₃): 3388, 2935, 2871, 1466, 1454, 1365, 1352, 1200, 1126, 1079, 1033, 986, 905, 869, 815, 757 & 726 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.31 (s, 5H), 4.92 (m, 1H), 4.55 (m, 1H), 3.98-4.00 (m, 2H), 3.55-3.70 (m, 2H), 2.05 (br, s, 1H), 1.50-2.00 (m, 6H). MS (m/z): 222.0 (M⁺). Anal. Calc. for C₁₃H₁₆O₃: C, 70.27; H, 8.10. Found: C, 70.89; H, 7.95%.

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References


