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TRIPHENYLPHOSPHINE HYDROBROMIDE : A MILD AND EFFICIENT CATALYST FOR TETRAHYDROPYRANYLATION OF TERTIARY ALCOHOLS

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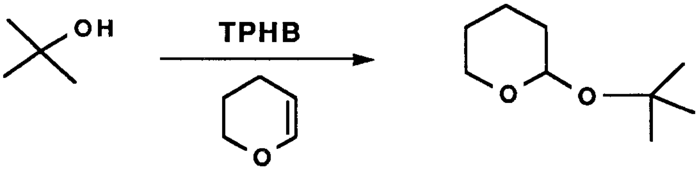
Summary : Triphenylphosphine hydrobromide is a convenient and highly effective catalyst for tetrahydropyranylation of tertiary alcohols with dihydropyran in dichloromethane at ambient temperature .

Protection of the hydroxy function is frequently required in the synthesis of polyfunctional organic compounds . However, of the numerous procedures currently available[1], few are applicable to tertiary alcohols which are generally highly hindered and quite susceptible to dehydration and/or rearrangement . Reagents that have been used for tertiary alcohol protection include silyl chlorides [2] and triflates[3] , p-methoxybenzyl chloromethyl ether[4] (PMBM-Cl) , β-(trimethylsilyl)ethoxymethyl chloride[5] (SEM-Cl) , β-methoxyethoxymethyl chloride[6] (MEM-Cl),and methylthiomethyl (MTM) ether generating systems such as DMSO/acetic anhydride[7] . In some instances these reagents are unsatisfactory for reasons of cost , instability , mutagenicity , or yield . Dihydropyran (DHP) , in contrast , is commercialy available , inexpensive , and easy to handle . The corresponding 2-tetrahydropyranyl (THP) ethers are stable, inter alia, to hydrides , redox reagents , organometallics , strong bases , alkylating/acylating agents , and catalytic reduction[1]. Herein, we report a mild and very effective tetrahydropyranylating catalyst , triphenylphosphine hydrobromide (TPHB) , and its application to the protection of a variety of sensitive tertiary alcohols [8] .



Crystalline TPHB is easily prepared [9] by addition of a slight excess of gaseous HBr to an ethereal solution of triphenylphosphine at 0°C . The resultant precipitate is filtered , washed with anhydrous ether , and dried to give TPHB in 92% yield as a white powder which can be recrystallised from CH_2Cl_2/Et_2O (m.p. 188-189.5°C) . The catalyst is soluble in dichloromethane , chloroform and slightly soluble in benzene or THF , but insoluble in ether . It is indefinitely stable when stored dry at room temperature .

THP ethers[10,11] were prepared by the following general procedure . A solution of tertiary alcohol (5 mmol) and DHP (7.5 mmol , 1.5 equiv) in 10 ml of anhydrous dichloromethane containing TPHB (0.25 mmol , 0.05 equiv) was stirred under an inert atmosphere at room temperature . After complete reaction (TLC monitoring) , the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 , concentrated and the residue purified by chromatography .

The results are summarised in the Table . All products were characterised by ^1H (200 MHz) and ^{13}C (50 MHz) NMR , IR , mass spectroscopy and had satisfactory microanalysis . It is noteworthy that THP ethers of allylic (entry 4) , propargylic (entries 5 and 6) , and benzylic (entry 7) alcohols can be obtained in good to excellent yields . Dehydration can be avoided even with the highly sensitive terpene precursor mevalonolactone (entry 3). The efficacy of TPHB was clearly evident when compared with other widely used catalysts . Under comparable conditions , yields of tertiary THP ethers were significantly better with TPHB than with pyridinium p-toluenesulfonate[10e,12] (PPTS) or Amberlyst H-15 resin[10c] . p-Toluenesulfonic, acid, phosphorus oxychloride , and other strongly acidic agents led to polymeric or dehydration products .

We anticipate, that because of its mild nature , TPHB will be a useful catalyst for the formation of other ketals and acetals[13] . Exploitation of the unique characteristics of TPHB for the preparation of carbohydrates will be reported elsewhere .

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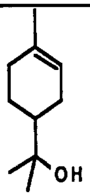
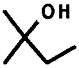
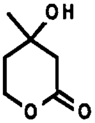
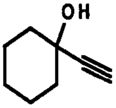
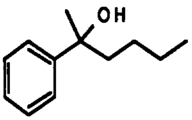
Table.Tetrahydropyranylation of tertiary alcohols catalysed by triphenylphosphine hydrobromide

Entry	Alcohol	Time[a] h	Isolated yield , %
1		24	88[b]
2		17	92
3		7	96[b]
4		21	87[b]
5		23	93
6		17	77.5[c]
7		6	80[b]

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[a] For convenience , most reactions were run overnight and , therefore , reaction times are not optimized . [b] Obtained as a mixture of diastereomers . [c] The volatility of the product may have resulted in a somewhat reduced yield .

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