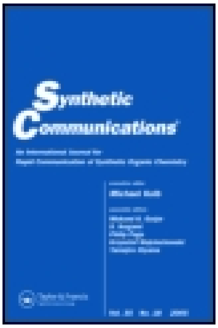

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MICROWAVE ASSISTED CATALYTIC PROTECTION AND DEPROTECTION OF ALCOHOLS WITH 3,4-DIHYDRO-2H-PYRAN

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Abstract: Protection of alcohols as their 2-tetrahydropyranyl ethers and their subsequent hydrolysis can be easily achieved through a microwave irradiated reaction catalysed by iodine.

During the course of a synthetic sequence, most of the time it becomes necessary to protect a free hydroxyl group present in the substrate or the intermediate. The protection of hydroxyl groups by etherification is quite common in the schemes of an organic synthetic strategy.[1] Tetrahydropyranylation of hydroxyl groups using 3,4-dihydro-2H-pyran (DHP) has been recognized as the useful and representative method for the protection of alcohols,[2] because of its ease of introduction and removal. It has been observed that 2-tetrahydropyranyl (THP) ethers are stable to various reaction conditions and reagents like strong bases, Grignard reagents, inorganic hydrides, redox reagents, alkylating and acylating agents and catalytic

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hydrogenation.[2,3] The tetrahydropyranyl group is often the protective group of choice in peptides,[4] nucleotides,[5] carbohydrates[6] and steroid[7] chemistry. In addition, the 2-tetrahydropyranyl ethers are important precursors for the synthesis of primary[8] as well as allylic alcohols[9] and alkyl halides.[10] Literature innumerates various examples of organic syntheses that utilize the hydroxyl group protection technique by making THP ethers.[11]

Preparation of tetrahydropyranyl ethers of alcohols is generally done by using an acidic catalyst - most common one being p-toluenesulfonic acid.[2] Several other catalysts reported for this reaction are pyridinium p-toluenesulfonate,[12] triphenylphosphine hydrobromide,[13] BF_3-etherate,[14] and iodotrimethylsilane.[15] Few supported reagents of acidic nature such as Amberlyst-15 resin,[3] Montmorillonite clay,[16] H_2SO_4-silica gel,[17] Nafion-H,[18] Reilex 425-HCl,[19] alumina impregnated with $ZnCl_2$,[20] Envirocat EPZG[21] etc. have been reported as catalyst recently. Very recently Balasubramanium *et al*[22] had reported lithium perchlorate as a new catalyst for this conversion while Moinar *et al*[23] utilized heteropolyacids of the type $H_3[PMo_{12}O_{40}]$ as a catalyst. But most of the reported catalysts are either expensive or commercially not available.

(1) (2) (3)

We would like to report here an efficient, inexpensive and less hazardous catalyst with a convenient procedure for tetrahydropyranylation of alcohols. When an alcohol (**1**) is treated with 3,4-dihydro-2H-pyran (**2**) (1.3 equiv.) in presence of catalytic amount (0.25 equiv.) of iodine (with 2 ml of THF to solubilise if needed) and gently irradiated by means of a conventional microwave oven (kitchen type, 2450 MHz, 980 W with power setting in 7 point scale) for 5 to 10 min. at power level 2 or 3, the corresponding 2-tetrahydropyranylated derivative **3** is obtained in excellent yield. In our earlier studies[24] we had demonstrated the catalytic property of iodine in various reactions. As the yields of the products are found to be less (65-70%) on treatment of equal mmol of DHP even at high power level and long irradiation time, so the use of DHP is optimised to 1.3 equivalent to get better yield (>80%).

The Table-1 above presents a list of alcohols that were protected as THP ethers following the present procedure.

From Table-1 it becomes clear that the reaction is very fast and completes within 8 minutes giving more than 90% yield in most of the cases. Review of the existing catalysts and procedures reveals that in few cases either the reaction takes long time (7-24 hr in case of triphenylphosphine hydrobromide[13] and 8-17 hr in case of lithium perchlorate[22]) or it needs dry reaction conditions.[12,16] In the present method using iodine as catalyst, the reaction conditions are very mild and suitable to acid and base sensitive compounds. All types of alcohols such as primary, secondary, tertiary and allylic alcohols are easily transformed into THP ethers with excellent yield.

Removal of the THP group through hydrolysis of the ether is also a convenient and high yielding reaction. Almost all the catalysts used for the preparation of THP ethers are also acidic enough to hydrolyse the same in alcoholic solvents. Interestingly these deprotecting reagents are mild enough to allow retention of other protecting groups such as MOM, MEM, MTM etc.. The most commonly used catalysts for deprotection of THP ethers are PTSA, CSA,

Table - 1[a] (Tetrahydropyranylation of alcohols)

Alcohol (1mmol)	Time (min.)	Power	DHP (mmol)	Yield (%)	Ref.
1. benzyl alcohol	7	3	1.3 equiv.	91	3
2. 1-octanol	7	3	1.3 "	93	3
3. 1- octadecanol	8	3	1.3 "	94	
4. 1-hexadecanol	8	3	1.3 "	94	
5. cyclohexanol	7	3	1.3 "	92	17
6. 1-docosanol	8	3	1.3 "	95	
7. cholesterol	7	3	1.3 "	94	17
8. geraniol	10	2	1.4 "	84	17
9. diethyl malate	8	3	1.3 "	80	
10. allyl alcohol	5	1	1.3 "	81	17
11. borneol	6	2	1.3 "	78[b]	
12. (-) menthol	6	3	1.3 "	83[b]	3
13. α-terpineol	5	3	1.3 "	76[b]	14

[a] All the compounds give satisfactory spectral analysis. These are also compared with authentic samples prepared by known methods (PTSA). [b] Combined yield of diastereomers.

PPTS, TMSI etc.. The present catalyst iodine has also been found to deprotect the THP ether giving excellent yield of the parent alcohol. The Table-2 below depicts a list of THP ethers cleaved by iodine.

Experimental

General Procedure for protection of alcohol : Benzyl alcohol (1 mmol) was mixed with 1.3 mmol of 3,4-dihydro-2H-pyran (DHP) and 0.2 mmol of iodine in a

Table-2[a] (Deprotection of THP ether)

Sl. No.	THP ether of	Time (min)	Power	Yield
1.	benzyl alcohol	10	5	84
2.	1-octanol	12	5	82
3.	1-octadecanol	12	5	80
4.	1-hexadecanol	10	5	81
5.	cyclohexanol	10	5	85
6.	1-docosanol	10	5	80
7.	cholesterol	10	5	80
8.	geraniol	10	4	78
9.	diethyl malate	10	4	80
10.	allyl alcohol	6	4	78

[a]All the products were compared with the authentic alcohols.

50 ml conical flask. (To maitain homogenity 2 ml of THF may be added). A small funnel was placed upside down on the mouth of the conical flask and the mixture was irradiated in a kitchen type microwave oven (2450 MHz, 980 W) for 7 minutes at power setting 3. The mixture was diluted with chloroform and washed with a dilute solution of sodium thiosulfate followed by water. The organic layer was dried over anhydrous sodium sulfate and evaporated at reduced pressure to get sufficiently pure benzyl THP ether (91% yield).

General Procedure for deprotection : A solution of the Benzyl THP ether (191 mg, 1 mmol) in 3 ml of methanol was treated with catalytic amount (~ 20%) of iodine and irradiated in the same manner in a microwave oven for 10 minutes at power 5. Usual workup of the reaction mixture yields the analytical pure benzyl alcohol (90 mg, 84%).

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