

Iodine-Catalyzed Mild and Efficient Tetrahydropyranylation / Depyranylation of Alcohols

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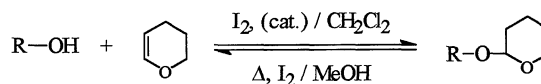
Alcohols and phenols are tetrahydropyranylated rapidly in high yields in the presence of catalytic amount of iodine at room temperature. Depyranylation is effected readily by refluxing with iodine in methanol for few hours.

Importance of protection and deprotection of functional groups in organic synthesis is well established. Among various procedures available for the protection of hydroxyl groups, tetrahydropyranylation is one of the methods of choice due to its easy installation, remarkable stability to non-acidic conditions (such as hydrides, strong bases, organometallics and also catalytic reductions) and ease with which it can be removed. Thus 3,4-dihydro-2H-pyran (DHP) has been widely used as a protecting group to hydroxyl compounds in multistep organic synthesis¹ requiring protic² or Lewis acids³ as typical promoters. Numerous other methods reported⁴ for the preparation of tetrahydropyranyl ethers using catalysts like Aluminium sulphate on SiO₂, pyridinium-p-toluene sulfonate, bis-(trimethyl silyl sulfate), DDQ, charcoal, tetra-n-butylammonium peroxydisulfate and ion-exchange resins⁵ such as Nafion-H and Amberlyst-15 and high surface area solids⁶ like clays and zeolites. Simultaneously various methods⁷ have been evolved for the deprotection of THP ethers which involve reagents such as MgBr₂, Me₂AlCl, (NCS Bu₂Sn)₂O, NaBH₃CN / BF₃·OEt₂, Ph₃PBr, MeOH/HCl, boric acid, LiCl / DMSO etc.

Taking into account the variety of reagents employed and the complexity of procedures followed, we felt that a highly economical and convenient strategy for the pyranlation / depyranylation would be through the use of a common catalyst which catalyses both these transformations effectively by a mere variation in the experimental protocol (a recent report on the application of NH₄Cl⁸ employs such a strategy).

The use of iodine as catalyst in various organic transformations⁹ such as acetylation of aldehydes, alcohols and cleavage of *p*-methoxybenzyl ethers, cleavage of alkylsilyl ethers etc., is well established. Herein we describe an efficient and quick tetrahydropyranylation procedure, which require stirring stoichiometric quantities of alcohol and dihydropyran (DHP) in presence of catalytic amount of resublimed iodine in dichloromethane (CH₂Cl₂) at room temperature. Deprotection of these THP ethers could be readily achieved using the same catalyst merely by heating under reflux in methanol.


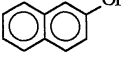
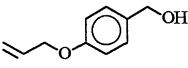
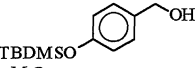
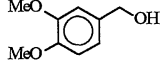
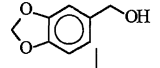
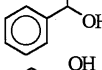
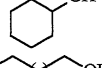
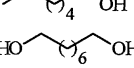
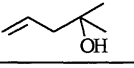
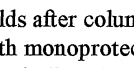
Several examples illustrating this novel and rapid procedure for tetrahydropyranylation of alcohols and their successive deprotection are presented in table. General feasibility of this reaction is evident as a variety of hydroxyl compounds like 1°, 2°, 3°, benzylic alcohols and phenols are protected / deprotected as THP ethers in high yields with iodine catalyst. The condition offers good selectivity for monoprotection of symmetric diols



R = alkyl, aryl, benzyl, benzoyl, and allyl.

Scheme.

Table. Iodine catalysed tetrahydropyranylation / depyranylation of alcohols and phenols

entry	Alcohol	Protection		Deprotection	
		Time / h	Yield / % ^a	Time / h	Yield / % ^a
1	PhCH ₂ OH	0.5	90	3	83
2	PhCH ₂ CH ₂ CH ₂ OH	1.0	87	5	80
3	PhCH=CHCH ₂ OH	0.5	92	4	85
4	CH ₃ CH=CH-CH ₂ OH	0.5	88	4	85
5	BnO-CH ₂ -CH ₂ -CH ₂ -OH	3.5	86	5	82
6	BzO-CH ₂ -CH ₂ -CH ₂ -OH	3.0	84	5	80
7		2.5	82	6	75
8		3	80	6	73
9		0.5	88	3	82
10		0.5	85	2	75 ^c
11		1.0	83	3	77
12		0.5	86	2	78
13		0.5	95	4	84
14		2	85	4	77
15		3	88	5	80
16		3.5	85 ^b	5	78
17		2.5	87	4	76

^a Isolated yields after column chromatography.

^b Product with monoprotection was isolated.

^c Both THP and TBDMS groups were deprotected

whenever stoichiometric quantity of reactants are employed. The tolerance of various protecting groups under the reaction conditions has been examined by reacting substrates bearing OBn,

OBz, O-allyl, O-TBDMS groups and the reaction conditions were compatible in most of the cases, both in protection and deprotection stages. Further to confirm the actual catalysis by elemental iodine, all the reactions were conducted using the resublimed iodine free from acidic impurities, carefully excluding moisture by carrying out pyranilation experiments under nitrogen atmosphere using dry DCM (distilled over calcium hydride). This clearly rules out any possibility of catalysis by acidic impurities. These reactions did not occur when the blank runs were carried out in the absence of iodine. Despite the use of an aprotic solvent during pyranilation stage (avoiding external proton source which may generate HI with I_2), the occurrence of this reaction may be attributed to the in situ formation of HI itself by the interaction of alcohols and I_2 as explained by Ryu et al.,¹⁰ during the cyclisation of alkenols using dichloromethane/catalytic quantity of I_2 .

In conclusion, iodine catalyzed tetrahydropyranilation presented in this paper is a convenient, quick and clean, general method for the protection of hydroxyl functionalities. The possibility of deprotection using the same catalyst with slight change in experimental protocol makes this method an attractive strategy, offering advantages over methods which use different catalysts for protection and deprotection of hydroxyl groups.

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- 11 a) General Procedure for the tetrahydropyranilation of alcohols : To the alcohol (10 mmol) and DHP (10 mmol) in dry dichloromethane (10 ml), resublimed iodine (0.1 mmol) was added and stirred for 0.5-3.5 h. After DCM was removed, the residue was diluted with water (20 ml) and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with 10% sodium thiosulphate solution, brine and dried over anhydrous Na_2SO_4 . Evaporation of the solvent followed by column chromatography (EtOAc - Hexane, 2 : 8) afforded THP ethers (time and yields see table).
b) Detetrahydropyranilation of alcohols : To the THP ether (10 mmol) in methanol (20 ml), resublimed iodine (0.1 mmol) was added and heated under reflux for 3-6 h. After Methanol was removed, the residue was diluted with 20 ml of water and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with 10% sodium thiosulphate solution, brine and dried over Na_2SO_4 . Evaporation of solvent followed by column chromatography (EtOAc - Hexane, 3 : 7) afforded alcohols (time and yields see table).

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