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ORIGINAL PAPER

A highly efficient and ecofriendly procedure for tetrahydropyranylation of alcohols and phenols in the presence of in-situ generated I_2 under heterogeneous and neutral conditions

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Abstract Molecular iodine generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI acts as a highly efficient catalyst for tetrahydropyranylation of various alcohols and phenols with 3,4-dihydro-2*H*-pyran in almost quantitative yields. The reaction occurs rapidly in dichloromethane at room temperature, and use of toxic molecular iodine is avoided.

Keywords Tetrahydropyranylation · Alcohols · Phenols · In-situ I_2 · $Fe(NO_3)_3{\cdot}9H_2O$/NaI

Introduction

Protection of hydroxyl groups by conversion into the corresponding tetrahydropyranyl ethers (THP ethers) is a common and extensively used transformation in organic synthesis [1]. Tetrahydropyranyl (THP) is a very attractive group for protection of hydroxyl groups, because of its low cost and stability under many reaction conditions and its compatibility with several reagents, for example metal hydrides, Grignard, and organolithium reagents [2]. Consequently, a variety of reagents have been introduced for THP protection of alcohols and phenols, for example *p*-toluenesulfonic acid (PTSA) [3, 4], pyridinium *p*-toluenesulfonate (PPTS) [5], iodotrimethylsilane [6], acidic clay [7], NH_4Cl [8], acetonyltriphenylphosphonium bromide [9], I_2 [10, 11], LiBr [12], $ZrCl_4$ [13], tetrabutylammonium tribromide [14], $Fe(ClO_4)_3$ [15], $K_5PW_{12}O_{40}{\cdot}3H_2O$ [16], $PdCl_2(CH_3CN)_2$ [17], trichloroisocyanuric acid [18], silica sulfuric acid [19], $Bi(NO_3)_3{\cdot}5H_2O$ [20], aqueous zinc tetrafluoroborate [21], $AlCl_3{\cdot}6H_2O$ [22], LiOTf [23], $VO(OAc)_2$ [24], $CaCl_2$ [25], $La(NO_3)_3{\cdot}6H_2O$ [26], bismuth triflate [27], H_2O [28], and copper(II) chloride–acetic acid [29].

However, several of the reported methods are associated with drawbacks, including long reaction times under reflux, expensive reagents, and incompatibility with other functionalities. Thus, there is still a need for a mild, neutral, catalytically efficient alternative, preferably using a heterogeneous catalyst, the protection of hydroxyl groups as THP ethers.

Although molecular iodine is a versatile reagent in organic synthesis [30], it is corrosive and toxic, making its use somewhat unattractive. To overcome these disadvantages with molecular iodine, Bailey et al. reported a convenient method for in situ generation of I_2 using $CuSO_4$/NaI [31].

Results and discussion

As a part of our ongoing research program to develop new synthetic methods for protection of hydroxyl functional groups [32–35], we wish to describe a new procedure for tetrahydropyranylation of a wide variety of alcohols and phenols using 3,4-dihydro-2*H*-pyran (DHP) in the presence of I_2 generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI under mild and heterogeneous conditions (Scheme 1).

It should be mentioned that molecular iodine is generated in situ by oxidation of NaI using $Fe(NO_3)_3{\cdot}9H_2O$. We

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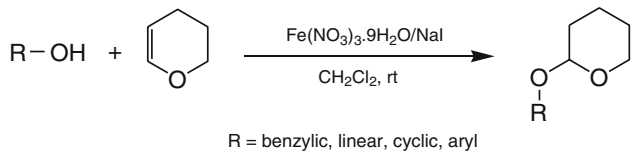


Scheme 1

measured the amount of I_2 generated in situ in CH_2Cl_2 by UV–visible spectrophotometry (NaI is the limiting reagent). It was found that 0.142 mmol I_2 is produced for every mmol NaI.

Our initial efforts focused on identifying the optimum conditions for the tetrahydropyranylation of benzyl alcohol as model substrate in the presence of various salts and solvents at room temperature. These results are summarized in Table 1. Among the salts and solvents used, the combination $Fe(NO_3)_3{\cdot}9H_2O$/NaI in dichloromethane delivered the best results (Table 1, Entry 1) and was then used for all other substrates.

Compounds that were tetrahydropyranylated in this way are primary, allylic, benzylic, propargylic, hindered and unhindered secondary, tertiary, acid-sensitive alcohols and phenols (Table 2).

The substrates with multiple bonds (entries 10, 19, and 20) were tetrahydropyranylated without any addition product of iodine as side products.

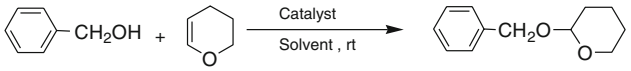
To illustrate the catalytic activity of this system, we compared our results for the tetrahydropyranylation of benzyl alcohol on the basis of reaction conditions, molar ratio of catalyst/DHP, time of reaction, and yield of product, with the best of well known data from the literature (Table 3). The notable features of this procedure are mild reaction conditions, cleaner reactions, improved yields, and enhanced reaction rates.

Experimental

Determination of amount of I_2 generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI

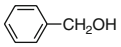
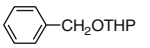
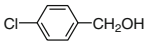
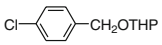
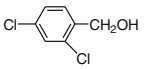
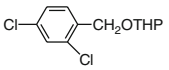
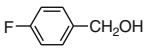
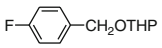
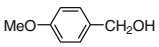
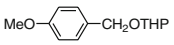
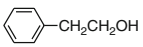
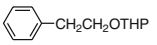
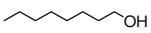
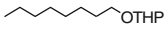
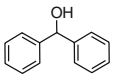
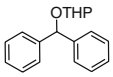
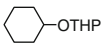
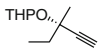
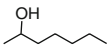
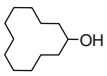
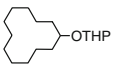
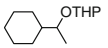
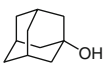
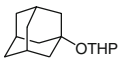
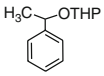
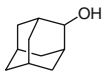
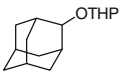
A series of standard solutions of I_2 (0.0, 0.01, 0.02, 0.03, and 0.04 mmol) in 25 cm^3 CH_2Cl_2 was prepared and a calibration plot (Beer's Law plot) was obtained. The unknown concentration of I_2 solution [$Fe(NO_3)_3{\cdot}9H_2O$ (0.1 mmol) and NaI (0.2 mmol)] was determined by measuring UV absorbance.

Table 1 Tetrahydropyranylation of benzyl alcohol with DHP in the presence of various salts and solvents at room temperature



Entry	Mineral salt	Solvent	Time (h)	Yields (conversion) (%)
1	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	CH_2Cl_2	0.13	100
2	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	H_2O	12	40
3	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	Ethyl acetate	12	0
4	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	Et_2O	12	50
5	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	*n*-Hexane	1	100
6	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	Acetone	12	40
7	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	Ethanol	12	0
8	$Fe(NO_3)_3{\cdot}9H_2O$/NaI	CH_3CN	12	90
9	$Fe_2(SO_4)_3{\cdot}5H_2O$/NaI	CH_2Cl_2	0.44	100
10	$FeCl_3{\cdot}6H_2O$/NaI	CH_2Cl_2	12	95
11	$CuCl_2{\cdot}2H_2O$/NaI	CH_2Cl_2	10	80
12	$Cu(CH_3COO)_2{\cdot}H_2O$/NaI	CH_2Cl_2	10	5
13	$CuSO_4{\cdot}5H_2O$/NaI	CH_2Cl_2	2	100
14	$Cu(NO_3)_2{\cdot}3H_2O$/NaI	CH_2Cl_2	0.4	100
15	$CuCO_3{\cdot}Cu(OH)_2$/NaI	CH_2Cl_2	10	0
16	$CrCl_3{\cdot}6H_2O$/NaI	CH_2Cl_2	0.5	100
17	$ZnNO_3{\cdot}6H_2O$/NaI	CH_2Cl_2	24	0
18	$Co(NO_3)_6$/NaI	CH_2Cl_2	14	100
19	$Zr(NO_3)_4$/NaI	CH_2Cl_2	1.5	100

Table 2 Tetrahydropyranylation of alcohols and phenols (5 mmol) using 0.59 g DHP (7 mmol) catalyzed with I_2 generated in situ from 28.3 mg $Fe(NO_3)_3{\cdot}9H_2O$ (0.07 mmol) and 19.5 mg NaI (0.13 mmol) in CH_2Cl_2 at room temperature

Entry	Substrate	Time/min	Product[a]	Isolated yields/%	References for spectroscopic data of products
1		5		96	[7, 27]
2		30		92	[6, 7]
3		70		90	[28]
4		30		94	[33]
5		7		91	[7, 28]
6		15		87	[20]
7		7		91	[7]
8		70		89	[29]
9		10		83	[7]
10		120		78	[6, 7]
11		5		80	[33]
12		40		87	[6, 7]
13		10		84	[33]
14		180		85	[20]
15		60		80	[7, 28]
16		30		89	[33]
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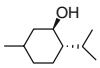
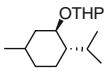
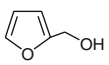
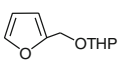
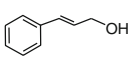
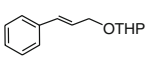
18		8		78	[28]
19		15		92	[7]
20		90		88	[27, 28]

Table 2 continued

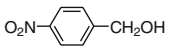
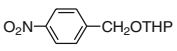
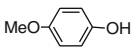
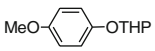
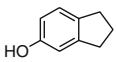
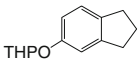
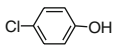
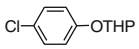
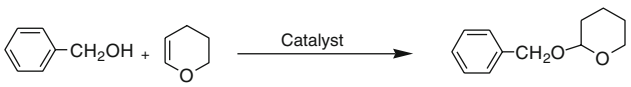
Entry	Substrate	Time/min	Product[a]	Isolated yields/%	References for spectroscopic data of products
21		150		89	[20, 27]
22		20		80	[7]
23		50		83	[33]
24		70		90	[6, 7]

Table 3 Comparison of the activity of various catalysts in the tetrahydropyranylation of benzyl alcohol



Entry	Reagent	Conditions	Cat:DHP (mmol:mmol)	Time (h)	Yield (%)	Refs.
1	$Fe(NO_3)_3{\cdot}9H_2O/NaI$	CH_2Cl_2, rt	0.014/0.026:1.4	0.08	96	This work
2	I_2	CH_2Cl_2, rt	0.01:1	0.5	90	Kumar et al. [11]
3	NBS	Solvent-free, rt	0.02:1.5	2.5	95	Khazaei et al. [32]
4	$K_5PW_{12}O_{40}{\cdot}3H_2O$	Acetone, H_2O, reflux	0.01:2	0.08	97	Habibi et al. [16]
5	LiOTf	$ClCH_2CH_2Cl$, reflux	0.6:1.6	2.5	96	Karimi and Maleki [23]
6	$Fe(ClO_4)_3$	Et_2O, rt	0.03:1	1.5	98	Heravi et al. [15]
7	TCCA	Solvent-free, 60–70 °C	0.1:1.4	5	92	Firouzabadi et al. [18]
8	Silica sulfuric acid	CH_2Cl_2, rt	0.39:1.1	0.5	91	Pore et al. [19]
9	$VO(OAc)_2$	$CHCl_3$, rt	0.27:1.2	1	95	Choudary et al. [24]
10	$CaCl_2$	CH_2Cl_2, rt	1:7	1.5	89	Bandgar et al. [25]
11	$La(NO_3)_3.6H_2O$	Solvent-free, rt	0.1:1	2.5	93	Reddy et al. [26]
12	$PdCl_2(CH_3CN)_2$	THF, rt	0.1:1.1	1	72	Wang et al. [17]
13	BNBBS	CH_2Cl_2, rt	0.01:1.2	1.83	89	Khazaei et al. [33]

General procedure for the tetrahydropyranylation of alcohols and phenols using DHP catalyzed with I_2 generated in situ from $Fe(NO_3)_3{\cdot}9H_2O/NaI$ in CH_2Cl_2

In a typical experiment, the alcohol or phenol (5 mmol) and 0.59 g DHP (7 mmol) were added to a mixture of 28.3 mg $Fe(NO_3)_3{\cdot}9H_2O$ (0.07 mmol) and 19.5 mg NaI (0.13 mmol) in 5 cm^3 CH_2Cl_2. The mixture was stirred at room temperature for the specified time (Table 2). After completion of the reaction (TLC), the mixture was filtered and the solids were washed with 5 cm^3 CH_2Cl_2. Powdered $Na_2S_2O_3$ ($\sim$2 g) was added in portions to the combined filtrate, the mixture was stirred for additional 5 min, and the resulting mixture was filtered. The organic layer was washed with 25 cm^3 water and 25 cm^3 brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was passed through a short column of silica gel using *n*-hexane as eluent. After evaporation to dryness the pure THP ethers were afforded. All products were characterized by comparison of their spectral data (^{1}H NMR, IR) with those of authentic samples [6, 7, 20, 27–29, 33].

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