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Simple Protocol for Synthesis and Cleavage of Tetrahydropyranyl Ethers Using $FeSO_4$ as an Inexpensive Catalyst

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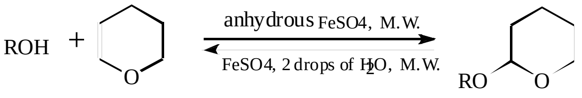
Protection and deprotection of alcohols and phenols as tetrahydropyranyl ethers (THP ethers) using anhydrous $FeSO_4$ under microwave irradiation without solvent is carried out.

INTRODUCTION

Hydroxyl groups are present in a number of compounds of biological and synthetic interest including nucleosides, carbohydrates, steroids and the side chain of some amino acids. During oxidation, acylation, halogenation and dehydration reactions of these compounds a hydroxyl group must be protected.[1] THP ethers are one of the most widely used protecting groups employed in chemical synthesis because of its low cost, the ease of installation, general stability to most non- acidic reagents and ease with which it can be removed.[1] Protic and Lewis acids,[1] other reagents such as iodotrimethylsilane,[2] triphenylphosphinehydrobromide,[3] montmorillonite clay,[4] envirocat EPZG,[5] lithium perchlorate-diethyl ether,[6] ion exchange resin,[7] zirconium sulfophenyl phosphonate[8] and alumina impregnated on zinc chloride[9] have been used to effect the tetrahydropyranylation of alcohols. In spite of several efforts, the methods available for selective protection and deprotection of THP ether without touching epoxy functionality present elsewhere in the molecule are limited.[10]

We report here use of $FeSO_4$ as an inexpensive catalyst for protection and deprotection of alcohols and phenols as THP ethers under microwave irradiation without solvent (Scheme I).

Scheme I



1 **2**

RESULTS AND DISCUSSION

We first examined tetrahydropyranylation of a series of primary, secondary, benzylic, allylic alcohols and phenols. A mixture of alcohol or phenol, 3,4-dihydro-2H-pyran and a catalytic amount of anhydrous $FeSO_4$ was irradiated with micro waves. The reaction was completed in a few minutes to give the corresponding THP ethers in good yields. The results are presented in the Table 1. Attempts to carry out tetrahydropyranylation of hydroxyl groups using anhydrous $FeSO_4$ in dichloromethane under mild conditions (25 °C) failed. Tetrahydropyranylation of primary as well as secondary alcoholic groups of 1,2-octanediol took place simultaneously under these reaction conditions. This indicates that the present method is not selective for tetrahydropyranylation of primary alcohols in the presence of secondary alcohols.

We next examined deprotection of THP ethers using $FeSO_4$ and micro waves with a few drops of water. Various THP ethers of primary, secondary, benzylic and allylic alcohols and phenols underwent smooth clevage under these reaction conditions. The results are summerized in the Table 1. It is important to note that other functional groups such as C=C, C≡C, methoxy, methylenedioxy and epoxide remain unaltered during protection and deprotection of THP ethers under these reaction conditions which depicts the applicability of this protocol.

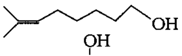
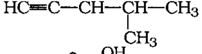
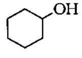
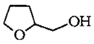
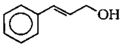
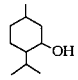
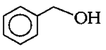
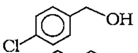
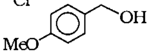
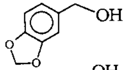
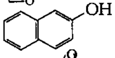
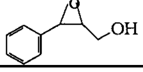
In conclusion the present results demonstrate the novelty of $FeSO_4$ which shows some selectivity and constitutes a useful alternative to the commonly accepted procedures of protection and deprotection of THP ethers.

EXPERIMENTAL

General Procedure for Tetrahydropyranylation

A mixture of alcohol or phenol (5 mmol), 3,4- dihydro-2H-pyran (5 mmol) and anhydrous $FeSO_4$ (1 mmol) was thoroughly mixed in a 25 mL glass beaker and irradiated by micro waves (Kelvinator, India make, model T-37 at 2450 MHz

Table 1. Protection and Deprotection of THP Ethers Using $FeSO_4$ and Microwave

Sr. No.	Alcohols/Phenols	Product	Protection		Deprotection	
			Time (min)	Yield[a,b] (%)	Time (min)	Yield[a,b] (%)
1a	$CH_3(CH_2)_5OH$	**2a**	1.0	84	1.5	80
1b		**2b**	1.0	88	1.0	83
1c	 $HC{\equiv}C{-}CH(OH){-}CH(CH_3){-}CH_3$	**2c**	3.0	79	1.2	97
1d		**2d**	4.0	85	1.4	84
1e		**2e**	3.5	97	1.0	97
1f		**2f**	3.5	78	1.0	89
1g		**2g**	3.0	84	2.0	82
1h		**2h**	3.5	81	1.0	87
1i		**2i**	1.0	84	1.2	81
1j		**2j**	0.5	84	1.3	97
1k		**2k**	0.5	81	1.5	83
1l		**2l**	0.5	84	1.3	87
1m		**2m**	3.0	82	1.0	87

[a] Yields of pure products; [b] Products are characterized by spectral analysis.

with 100% power) for a specified time (Table 1). After completion of the reaction (TLC), the product was extracted with ethyl acetate (2 × 10 mL). Removal of the solvent under reduced pressure gave crude product which was purified by column chromatography (pet. ether: ethyl acetate = 9:1).

Spectroscopic data of some selected compounds: **2f:** I.R. (cm^{-1}): 680, 730, 790, 810, 950, 1022, 1120, 1202, 1353, 1440, 1484, 1560, 1679, 2871, 2944, 3020; ^1H NMR: 1.25-1.85 (m, 6H); 3.92 (t, 2H); 4.37 (d, 2H); 4.71 (t, 1 H); 6.26 (m, 1H); 6.65 (d, 1H); 7.24 (m, 5H).

2g: I.R. (cm^{-1}): 845, 950, 1025, 1097, 1260, 1365, 1450, 2856, 2933; ^1H NMR: 0.7-0.85 (m, 9H); 1.2-1.6 (m, 14H); 2.0-2.1 (m, 1H); 3.4 (t, 2H); 3.8-3.9 (m, 1H); 4.75 (br, 1H).

2h: I.R. (cm^{-1}): 740, 820, 880, 940, 970, 1034, 1058, 1080, 1120, 1210, 1320, 1352, 1450, 1498, 2870, 2948; ^1H NMR: 1.25-1.74 (m, 6H); 3.56 (m, 1H); 3.92 (dd, 1H); 4.51 (d, 1H); 4.65 (t, 1H); 4.72 (d, 1H); 7.31 (m, 5H).

General Procedure for Deprotection of Tetrahydropyranyl Ethers

A mixture of THP ether (5 mmol) and $FeSO_4$ (1 mmol) with two drops of water was irradiated by microwaves for the time period indicated in the Table 1. After completion of the reaction (TLC) the product was extracted with ethyl acetate (2 × 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography (pet. ether: ethyl acetate = 9:1).

1m: I.R. (cm^{-1}): 702, 740, 1011, 1025, 1203, 1450, 1510, 1605, 2975, 3041, 3410; ^1H NMR ($CDCl_3$, 300 MHz): 4.3 (d, 2H, CH_2); 4.7 (s, 1H, OH); 4.9 (m, 1H); 5.5 (d, 1H); 7.2 (s, 5H, Ar-H).

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Key Words

$FeSO_4$; Catalyst; THP ethers; Alcohols.

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