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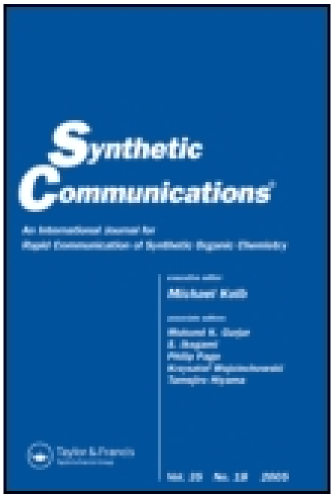

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

MICROWAVE ACCELERATED TETRAHYDROPYRANYLATION AND DETETRAHYDROPYRANYLATION OF ALCOHOLS, PHENOLS, AND THIOLS CATALYZED BY HYDRATED ZIRCONIA

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Published online: 12 Dec 2006.

To cite this article: Anil S. Gajare , Dhananjay P. Sabde , Murlidhar S. Shingare & Radhika D. Wakharkar (2002) MICROWAVE ACCELERATED TETRAHYDROPYRANYLATION AND DETETRAHYDROPYRANYLATION OF ALCOHOLS, PHENOLS, AND THIOLS CATALYZED BY HYDRATED ZIRCONIA, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:10, 1549-1555, DOI: 10.1081/SCC-120004145

To link to this article: http://dx.doi.org/10.1081/SCC-120004145

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SYNTHETIC COMMUNICATIONS, 32(10), 1549–1555 (2002)

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ABSTRACT

A solvent free and expeditious method for tetrahydropyranylation and detetrahydropyranylation of alcohols, phenols and thiols is described using hydrated zirconia and 3,4-dihydro-2H-pyran (DHP). A comparison of this microwave-accelerated reaction with conventional heating condition is also presented.

Key Words: Tetrahydropyranylation; Detetrahydropyranylation; Hydrated zirconia; Microwave accelerated; Alcohols; Thiols

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The tetrahydropyranylation is one of the most frequently used methods for protection of hydroxyl groups[1] because of the remarkable stability of tetrahydropyranyl ethers towards a variety of reaction conditions. Tetrahydropyranylation of alcohols is one of the methods of choice to protect hydroxyl groups in a multi-step organic synthesis, and a variety of reagents[1] are reported for the same. Ongoing research in other laboratories has disclosed the use of new reagents for the tetrahydropyranylation of alcohols and their detetrahydropyranylation such as protic acids[2a] (HCl and PTSA), Lewis acids and pyridinium *p*-toluenesulfonate.[2b]

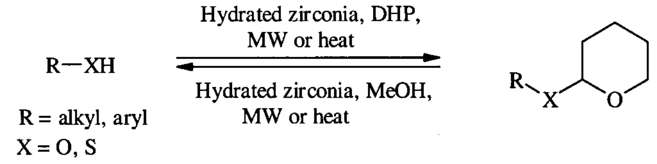
More recently, ion exchange resins (amberlyst H-15[2c] and Nafion[2d]), clay materials, (montmorillonite K-10,[2e] H-Y Zeolite[2f]) $ZnCl_2$,[2g] tetra-*n*-butylammonium peroxydisulfate,[2h] CuCl,[2i] zirconium sulfophenyl phosphonate[2j] and H-Rho[2k] have also been employed for the protection of alcohols as THP ethers. Generally, aqueous acids such as acetic acid, HCl, boric acid etc., are used for the cleavage of THP ethers. The weaker acids invariably require higher temperatures. Other known reagents for hydrolysis of THP ethers are Amberlyst H-15,[3a] $MgBr_2$,[3b] Me_2AlCl,[3c] $(NCSBu_2Sn)O$,[3d] MeOH/HCl,[3e] $NaBH_3CN/BF_3{\cdot}OEt_2$,[3f] PhPBr,[3g] DDQ[3h] and LiCl in H_2O-DMSO[3i] etc. However, some of these procedures suffer from expensive reagents, high temperature, and strongly acidic conditions. Heterogeneous catalysts in the recent years have shown enormous potential in the synthesis of fine chemicals because of their shape selectivity, thermal stability,[4a] reusability,[4b] tailor made acidic and basic properties and environment friendly nature.

Zirconia[5] in its pure and modified form has been employed in many industrial processes. Recently we have reported the Friedel Crafts acylation of aromatic compounds and reduction of azobenzenes by using hydrated zirconia[6]. The preparation methods and pretreatment temperature are found to affect the activity of ZrO_2. The ZrO_2 calcined at relatively low temperatures has been found responsible for the high selectivity and longer catalyst life for particular reactions. The high activity of ZrO_2 is attributed to its acid base bifunctional properties.

Various microwave accelerated organic transformations under solvent free conditions have been reported[7] to date. Microwave assisted heterogeneous reactions[8] coupled with the various solid inorganic supports have attracted researchers because of the simplicity, greater stability and rapid synthesis of variety of organic compounds.[9] The enhanced reaction rates, formation of pure products in high yields and the ease of manipulation are the salient features of the microwave approach, along with the use of mineral supported reagents or catalysts. Recently solvent free microwave assisted reactions[10] have gained more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure with a possibility of upscaling the reaction on a preparative scale and helps the induction of reaction under dry conditions.

RESULT AND DISCUSSION

In this communication we report the microwave-accelerated tetrahydropyranylation of alcohols, phenols and thiols catalyzed by hydrated zirconia (Scheme 1). This method has distinct advantages over the other existing methods viz. mild reaction conditions, absence of solvent, shorter reaction time, easy and quick isolation of the product and excellent yields.



Scheme 1.

Generality of the present procedure of tetrahydropyranylation has been exhibited by protection of a wide range of hydroxy compounds, such as primary, secondary, tertiary, allylic, acetylenic alcohols, phenolic and poly functional compounds with dihydropyran under mild conditions. The highly acidic catalyst *p*-toluenesulfonic acid, Nafion-H is known to produce polymeric byproducts.[2d] The hydrated zirconia does not exhibit the strong acidic sites therefore the acid sensitive groups such as ketal and sillyl ethers (Table 1, Entries 1 and 2) were found intact under the reaction conditions. Allylic and acetylenic alcohols could be protected without isomerization of double or triple bonds under the reaction conditions, and the resulting ethers were isolated as the only products (Table 1, Entries 3 to 7). Reaction of dihydropyran with bulky substrates (Entries 13–16) easily protected the hydroxy group with quantitative yield. Thiols could be protected as tetrahydropyranyl thiol ethers without occurrence of dimerization of thiols (Entries 17–22) in excellent yield. A selective protection of alcoholic function (Entry 8) in case of 2-mercapto ethanol could be achieved with one mole DHP.

Table 2 demonstrates an equally efficient reversal of tetrahydropyranylation reaction under similar conditions (Scheme 1). In the presence of hydrated zirconia the removal of the THP group has been carried out rapidly in methanol at reflux temperature (Table 2). As in the case of the

Table 1. Tetrahydropyranylation of Alcohols, Phenols, and Thiols Catalyzed by Hydrated Zirconia

		Thermal		Microwave	
Entry	Substrate	Time (min)	Yield[a]	Time (min)	Yield[a]
1	4-(2-methyl-1,3-dioxolan-2-yl)phenol	80	82	7	90
2	4-hydroxy-1-phenyl-1-trimethylsilyl ether	90	85	7	92
3	Allyl alcohol	90	70	7	80
4	Dimethyl allyl alcohol	90	80	7	85
5	Propargyl alcohol	90	85	7	95
6	*t*-Butylanol	80	75	7	85
7	Chloro ethanol	50	90	3	97
8	2-Mercapto ethanol	60	82	5	86
9	Cinnamyl alcohol	100	80	10	85
10	Geraniol	110	73	7	87
11	(-)Menthol	80	75	10	81
12	Cyclohexanol	–	–	7	80
13	Phenyl ethyl alcohol	100	80	15	93
14	Cholesterol	70	95	7	98
15	Phenol	60	87	7	98
16	α-Naphthol	80	85	7	95
17	Thiophenol	90	80	10	88
18	4-Chloro thiophenol	90	80	10	88
19	4-Methyl thiophenol	80	85	–	–
20	4-Methoxy thiophenol	100	87	10	90
21	Benzyl mercaptan	100	91	–	–
22	Furfuryl mercaptan	100	82	10	89

[a] Isolated by chromatographic purification and products were characterized by IR, ^{1}H, ^{13}C NMR and MS.

protection study, the selectivity has been studied for the depyranylation of ethers (Entries 1 and 2). All the products were purified by column chromatography and the corresponding tetrahydropyranyl ethers and alcohols were obtained in good to excellent yields.

EXPERIMENTAL

General procedure for the protection of alcohols: The alcohols, phenols or thiols (10 mmol), 3,4-dihydro-2H-pyran (20 mmol) and hydrated zirconia

Table 2. Detetrahydropyranylation of Alcohols, Phenols, and Thiols Catalyzed by Hydrated Zirconia

		Thermal		Microwave	
Entry	Substrate	Time (min)	Yield[a]	Time (min)	Yield[a]
1	4-(2-methyl-1,3-dioxolan-2-yl)phenol	80	75	7	80
2	4-hydroxy-1-phenyl-1-trimethylsilyl ether	90	70	7	87
3	Allyl alcohol	90	70	7	80
4	Dimethyl allyl alcohol	90	75	7	80
5	Propargyl alcohol	90	80	7	85
6	*t*-Butylanol	80	82	8	85
7	Chloro ethanol	80	80	7	90
8	2-Mercapto ethanol	70	85	10	92
9	Cinnamyl alcohol	65	85	10	75
10	Geraniol	50	70	7	80
11	(-)Menthol	50	75	7	90
12	Cyclohexanol	90	85	10	78
13	Phenyl ethyl alcohol	85	70	10	92
14	Cholesterol	75	90	10	95
15	Phenol	75	90	10	90
16	α-Naphthol	95	87	8	90
17	Thiophenol	80	85	8	85
18	4-Chloro thiophenol	90	85	8	85
19	4-Methyl thiophenol	100	82	7	82
20	4-Methoxy thiophenol	60	80	8	85
21	Benzyl mercaptan	75	70	8	75
22	Furfuryl mercaptan	80	70	8	75

[a] Isolated by chromatographic purification and products were characterized by IR, ^{1}H, ^{13}C NMR and MS.

(20% w/w) were added in a glass test tube and the reaction mixture was placed inside a household microwave oven and irradiated [14] for the specified time or heated in an oil bath at 80–100°C (see Table 1). On completion of the reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane (10 ml). The catalyst was removed by filtration and washed with dichloromethane (2 × 10 ml). Removal of the solvent under reduced pressure followed by chromatographic purification afforded products in good to excellent yields.

General procedure for the deprotection of alcohols: A solution of THP ether (10 mmol) with hydrated zirconia (20% w/w) in methanol (5–10 ml) were added in a glass test tube and the reaction mixture was placed inside a household microwave oven and irradiated[11] for the specified time or heated in an oil bath at 80–100°C (see Table 2). On completion of the reaction as indicated by TLC, the catalyst was removed by filtration and washed with methanol (2 × 10 ml). Removal of the solvent under reduced pressure followed by chromatographic purification afforded products in good to excellent yields.

Thus, a simple and efficient method for tetrahydropyranylation and its cleavage of a variety of alcohols, phenols and thiols has been explored using hydrated zirconia as a catalyst, thermally as well as under microwave irradiation.

ACKNOWLEDGMENTS

We wish to thank CSIR New Delhi for the award of Research Associateship to ASG and senior research fellowship to DPS.

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Received in the UK March 5, 2001

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