Heterogeneous acidic catalysts for the tetrahydropyranylation of alcohols and phenols in green ethereal solvents

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Abstract

The application of heterogeneous catalysis and green solvents to the set up of widely employed reactions is a challenge in contemporary organic chemistry. We applied such an approach to the synthesis and further conversion of tetrahydropyranyl ethers, an important class of compounds widely employed in multistep syntheses. Several alcohols and phenols were almost quantitatively converted into the corresponding tetrahydropyranyl ethers in cyclopentyl methyl ether or 2-methyltetrahydrofuran employing NH_4HSO_4 supported on SiO_2 as a recyclable acidic catalyst. Easy work up of the reaction mixtures and the versatility of the solvents allowed further conversion of the reaction products under one-pot reaction conditions.

Introduction

Due to their general stability to a wide range of reagents and ease of removal, tetrahydropyranyl (THP) ethers are widely employed in multistep organic synthesis for the protection of hydroxy derivatives [1,2]. In addition, they can be converted into a wealth of useful functional groups [2,3], and found employment as fragrances or pro-fragrances in everyday life [4-7]. Although a lot of work has been devoted to the search of low impact, heterogeneous and recyclable catalysts to promote THP ethers synthesis [2,8-14], to the best of our knowledge no

attention was dedicated to their employment in low impact solvents.

From this point of view, it is worth noting that although ethers are the solvents of choice for reactions involving highly polar nucleophilic reagents such as organolithium and organomagnesium compounds or aluminium hydrides, tetrahydropyranylation reactions are usually run in hydrocarbons, chloroalkanes or dipolar aprotic solvents [1,2,8-15], thus affording a paradig-

matic example of the ironic Murphy's Law of Solvents, recently stated by Jessop et al. [16]: "The best solvent for any process step is bad for the next step".

Starting from these premises and following our interest in the development of reaction procedures in low impact solvents [17,18], we report here on the tetrahydropyranylation of alcohols and phenols in cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF) in the presence of heterogeneous acidic catalysts. Indeed, both CPME [19-22] and 2-MeTHF [21-25] are characterized by relatively high boiling points, a narrow explosion range, hydrophobicity, easy drying and recovery possibilities. Additionally, CPME is produced via a 100% atom economical reaction [19,20], whilst 2-MeTHF is accessible from renewable resources [21,23]. Finally, it is worth noting that besides being moderately irritant, both solvents are characterized by low toxicities and are considered negative for genotoxicity and mutagenicity [26-28]. Due to these environmentally friendly characteristics, CPME and 2-MeTHF appear as versatile green alternatives to ethereal solvents such as tetrahydrofuran, dioxane, diethyl ether or methyl *tert*-butyl ether.

Aiming to the development of a particularly practical and environmentally friendly procedure to the generation of THP ethers, we devoted our efforts to the employment of heterogeneous acidic catalysts [29,30] in order to set up conditions allowing easy processing of the reaction mixtures and, possibly, the recovery and recycling of the catalyst.

Results and Discussion

Taking 2-phenylethanol (**1a**) as a model compound, we investigated its conversion into the corresponding THP ether **3a** by reacting 4 M solutions of this alcohol with a slight excess (1.1 equiv) of 3,4-dihydro-2*H*-pyran (**2**, DHP) in the presence of several acidic heterogeneous catalysts (Scheme 1 and Table 1). The recovered reaction mixtures were very simply elaborated by filtering the catalyst followed by evaporation of the solvent in vacuo.

Scheme 1: Synthesis of THP ether **3a**.
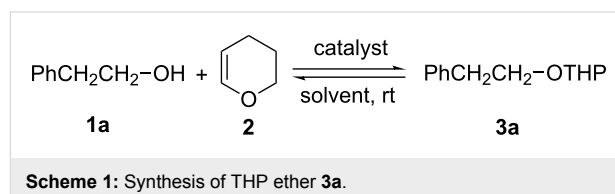
No reaction occurred in both solvents in the absence of an acidic catalyst as well as in the presence of several ammonium salts, i.e., NH_4Cl, NH_4Br and $NH_4H_2PO_4$ (Table 1, entries 1–4). On the other hand, inorganic salts with a relatively higher acidity, i.e., NH_4HSO_4, $NaHSO_4$ and $KHSO_4$ [31], as well as Amberlyst 15 and Montmorillonite K10, efficiently promoted practically quantitative conversion of the starting material into the corresponding tetrahydropyranyl ether **3a** within a few hours in both solvents (Table 1, entries 5–9).

Good results were also obtained with a 25 wt % dispersion of NH_4HSO_4 over SiO_2 ($NH_4HSO_4@SiO_2$, Table 1, entries 10 and 11). Additionally, the supported catalyst, which can be stored in a desiccator for several months with no detrimental effects, is particularly easy to recover and was recycled up to 4 times with no evident loss of activity (Table 1, entry 10). Its robustness was further assessed by the good qualitative matching between the IR spectra of the fresh and recycled cata-

Table 1: Synthesis of 2-(2-phenylethoxy)tetrahydro-2*H*-pyran (**3a**).

entry	solvent	catalyst (%)	3a/1a (%)[b]
1	CPME or 2-MeTHF	none	<5:>95
2	CPME or 2-MeTHF	NH$_4$Cl	<5:>95
3	CPME or 2-MeTHF	NH$_4$Br	<5:>95
4	CPME or 2-MeTHF	NH$_4$H$_2$PO$_4$	<5:>95
5	CPME or 2-MeTHF	NH$_4$HSO$_4$	94:6
6	CPME	NaHSO$_4$	93:7
7	CPME	KHSO$_4$	93:7
8	2-MeTHF	Amberlyst 15	>95:<5
9	CPME or 2-MeTHF	Montmorillonite K10[c]	>95:<5
10	CPME	NH$_4$HSO$_4$@SiO$_2$[d,e]	>95:<5
11	2-MeTHF	NH$_4$HSO$_4$@SiO$_2$	>95:<5
12	CPME	NH$_4$HSO$_4$@SiO$_2$[f]	93:7

[a]All reactions were run at rt during 4 h in the presence of the catalyst (3 mol % of **1a**, unless otherwise indicated). [b]As determined by ^{1}H NMR analyses of crude reaction mixtures; no other product was detected besides **1a**. [c]**1a**/catalyst = 3 wt %. [d]Comparable results were obtained after 4 times recycling of the catalyst. [e]No reaction was observed in the presence of a comparable amount of carefully dried SiO$_2$. [f]3 mol ‰ of **1a**.

lysts (see Supporting Information File 1, Figure S1). Additionally, it is worth noting that a comparable result was obtained by reducing the amount of catalyst to one tenth (3 mol ‰ of **1a**, Table 1, entry 12).
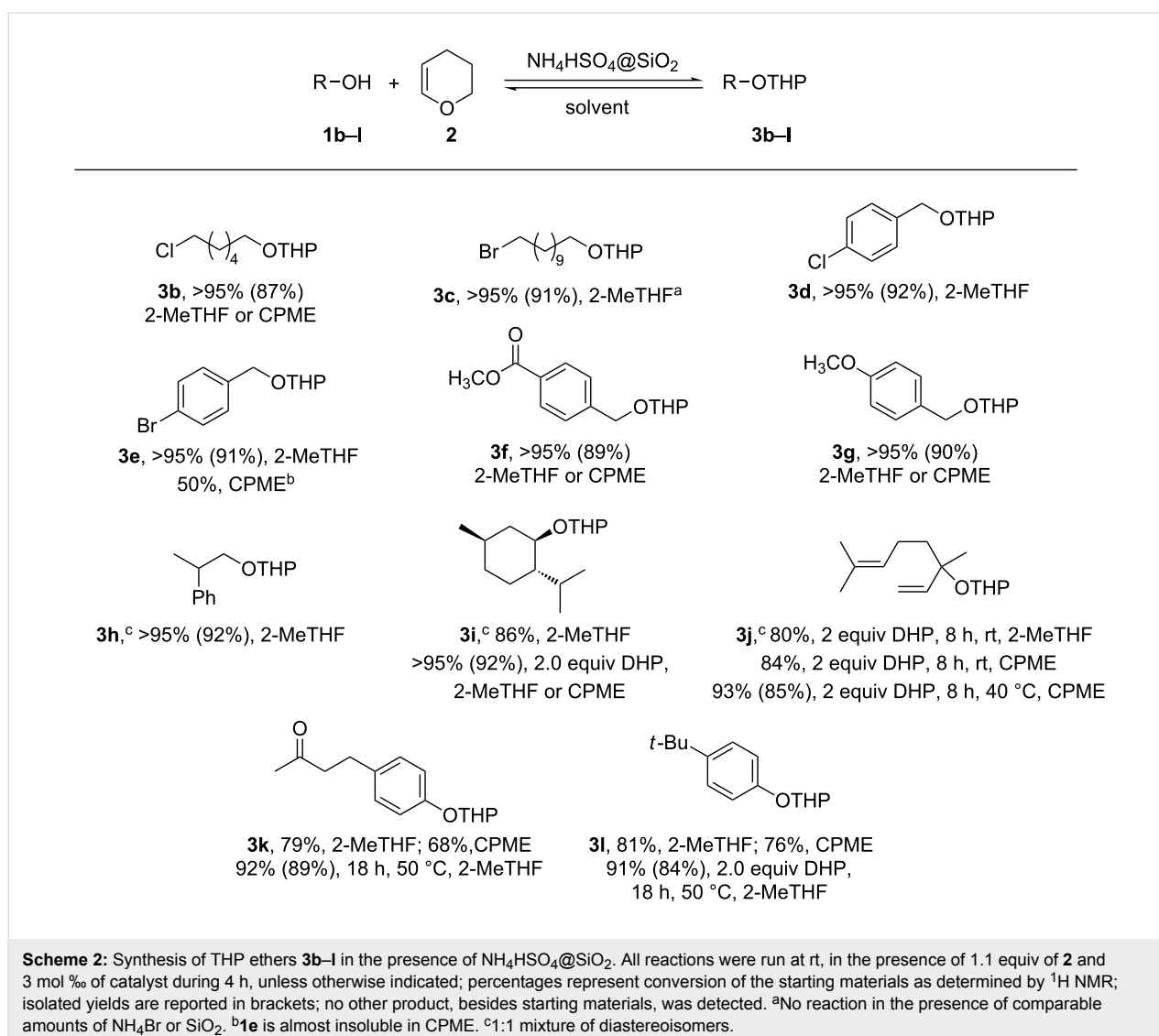
Finally, both CPME and 2-MeTHF proved stable towards such an acidic supported catalyst, as established by the absence of any decomposition product within the reaction mixtures, as determined by ^{1}H, ^{13}C NMR and gas-liquid chromatography analyses [32].

Due to the ease of the preparation from particularly cheap starting materials, the ease of handling and its high activity, we further investigated the ability of NH$_4$HSO$_4$@SiO$_2$ to catalyze the synthesis of different THP ethers in low impact ethereal solvents. Accordingly, the reactions were performed in the presence of 3 mol ‰ of the catalyst and were successfully applied

to the synthesis of a series of THP ethers of functionalized and non-functionalized alcohols and phenols, including some known fragrances (**3g–j** and **3l**) [4-7], as illustrated in Scheme 2.

Conversions exceeding 95% were achieved under the mild conditions illustrated in Scheme 2 with primary aliphatic and benzylic alcohols **1b–h**. A notable exception is the low conversion of 4-bromobenzyl alcohol **1e** in CMPE, most probably due to the low solubility of the starting material in this solvent. This disadvantage was easily overcome by performing the reaction in 2-MeTHF.

More demanding conditions (2.0 equiv of **2**) were required to obtain good conversions of a secondary alcohol, i.e, (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol ((−)-menthol, **1i**). The reaction afforded an almost 1:1 mixture of only two diastereoiso-

Scheme 2: Synthesis of THP ethers **3b–l** in the presence of NH$_4$HSO$_4$@SiO$_2$. All reactions were run at rt, in the presence of 1.1 equiv of **2** and 3 mol ‰ of catalyst during 4 h, unless otherwise indicated; percentages represent conversion of the starting materials as determined by ^{1}H NMR; isolated yields are reported in brackets; no other product, besides starting materials, was detected. [a]No reaction in the presence of comparable amounts of NH$_4$Br or SiO$_2$. [b]**1e** is almost insoluble in CPME. [c]1:1 mixture of diastereoisomers.

mers as determined by ^{1}H and ^{13}C NMR analysis of the crude reaction mixture, thus suggesting that it occurs with no epimerization at C1.

This result was confirmed by submitting compound **3i** to acid-catalyzed deprotection with H_2SO_4@SiO_2 (25 wt % [33] as depicted in Scheme 3). Alcohol **1i**, was recovered as a single stereoisomer, identical to the commercially available starting material, as determined by ^{1}H and ^{13}C NMR analysis of the crude reaction mixture (see Supporting Information File 1).

Scheme 3: Deprotection of THP ether **3i**.
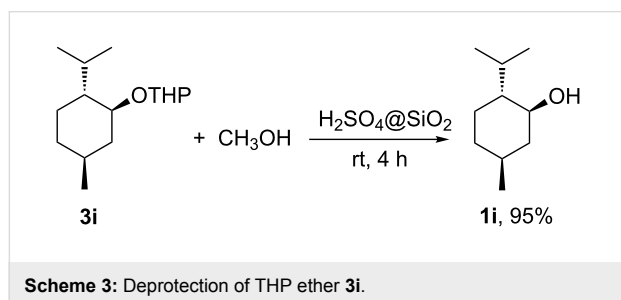
Finally, the tetrahydropyranylation of a tertiary alcohol **1j** as well as of phenols **1k** and **1l** required, besides the employment of 2.0 equiv of DHP, relatively longer reaction times and higher temperatures. It is worth noting that under our mild reaction conditions we did not observe any isomerisation of the acid-sensitive allylic alcohol **1j** [34].

To stress the usefulness of a tetrahydropyranylation reaction performed in a green ethereal solvent and in the presence of a heterogeneous acidic catalyst, we realized two one-pot procedures employing either 2-MeTHF or CPME as a solvent.

Accordingly, the mixture obtained by reacting **1f** with 1.1 equiv of **2** and 3 mol ‰ of NH_4HSO_4@SiO_2 in 2-MeTHF under dry

Ar was filtered and dropwise added to a vigorously stirred freshly prepared solution of EtMgBr in the same solvent at rt. Aqueous work-up and flash chromatography afforded the desired tertiary alcohol **4fa** in 78% yield (Scheme 4).

Under similar conditions, protection of **1f** in CPME, followed by filtration and dropwise addition of the resulting solution to a suspension of $LiAlH_4$ in the same solvent, afforded the mono-protected diol **4fb** in almost quantitative yield (Scheme 5).
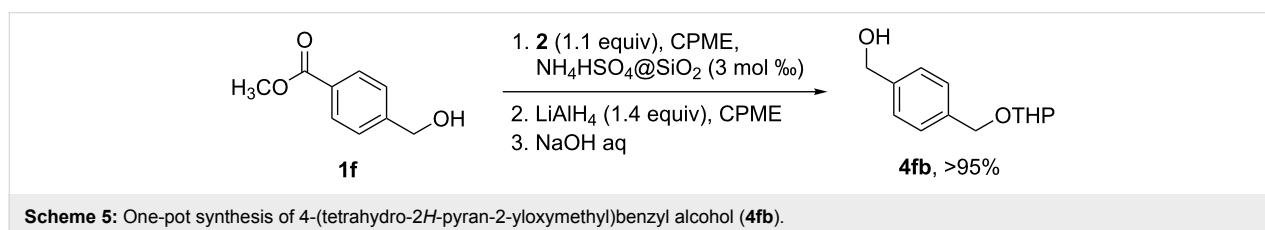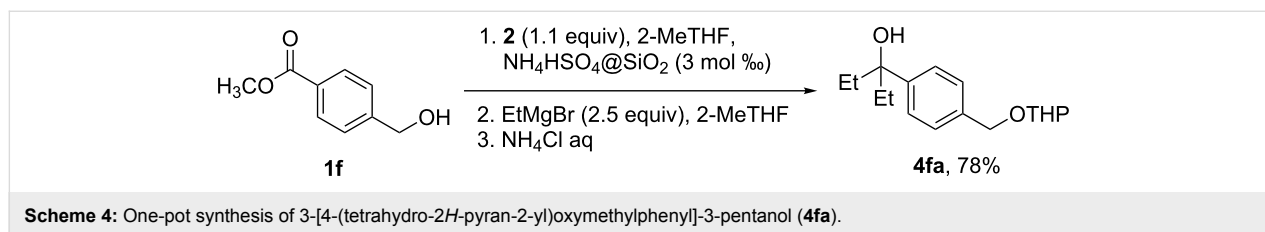
Conclusion

The above reported results show that several heterogeneous acidic catalysts efficiently promote the tetrahydropyranylation of an alcoholic model compound in low impact ethereal solvents under mild conditions. Further investigations show that NH_4HSO_4@SiO_2, easily prepared from inexpensive starting materials, successfully catalyzes the protection of a variety of functionalized and non-functionalized alcohols and phenols, including an optically pure alcohol with no detrimental effects on its stereochemistry. Due to a particularly simple work-up procedure, NH_4HSO_4@SiO_2 can be easily recovered and recycled several times. The easy removal of the acidic catalyst from the reaction mixtures and the versatility of the employed solvents allowed the successful further conversion of the reaction products with strong nucleophiles under one-pot conditions.

Supporting Information

Supporting Information File 1
Full experimental details, copies of IR spectra of fresh and recycled NH_4HSO_4@SiO_2 and copies of ^{1}H and ^{13}C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-141-S1.pdf]

Scheme 4: One-pot synthesis of 3-[4-(tetrahydro-2*H*-pyran-2-yl)oxymethylphenyl]-3-pentanol (**4fa**).

Scheme 5: One-pot synthesis of 4-(tetrahydro-2*H*-pyran-2-yloxymethyl)benzyl alcohol (**4fb**).

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32. As a note of caution it is worth noting that reactions run in 2-MeTHF under more demanding conditions (40 °C, 8 h), led to the formation of minor amounts of peroxides (<5 mg/L) as semiquantitatively evaluated with a commercially available kit (Quantofix®, measuring range 0.5–25 mg·L^{-1} H_2O_2). Accordingly, such reactions were safely run under an inert atmosphere.
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