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# Environmentally Friendly Tetrahydrofuranylation of Alcohols Using $NaHSO_4$–$SiO_2$ under Solvent-free Conditions

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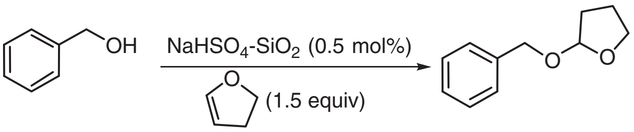
A simple, environmentally friendly, and efficient tetrahydrofuranylation of alcohols has been developed using $NaHSO_4$–$SiO_2$ (0.5 mol %) as a catalyst under solvent-free conditions to yield corresponding THF ethers in good to excellent yields.

The protection of alcohols as 2-tetrahydrofuranyl (THF) ether is a well-established protocol in organic synthesis.[1,2] THF ethers like their homologues relative and extensively studied 2-tetrahydropyranyl (THP) ethers are tolerant to a range of alkaline and organometallic reagents.[3,4] THF ethers are more preferable protecting groups than THP ethers since they can be deprotected under very mild acidic conditions.[3] This difference in labiality to acidic conditions allows selective deprotection of THF ethers in the presence of THP ethers in organic synthesis strategies.[1,3,5,6] However, the wide application of THF ethers as orthogonal protecting groups is hampered by the limited number of tetrahydrofuranylation protocols reported in the literature. This is mainly due to the reagents employed being expensive, toxic, commercially unavailable, corrosive, incompatible with sensitive functional groups as well as the need for chlorinated solvents.[7,8] The reagent systems reported include: $BrCCl_3$/2,4,6-collidine/THF,[3] $Al(OTf)_3$/DHF/DCM,[4] 2-chlorotetrahydrofuran/$Et_3N$,[5] $CrCl_2/CCl_4$/THF,[6] $VCl_3$/THF/$CCl_4$,[7] Mn(0)/THF/$CCl_4$,[8] $(ON^+)$(Salen)ruthenium(II) complex/2,3-dihydrofuran (DHF)/DCM,[9] $Ph_2CHCO_2$-DHF/TsOH/$CCl_4$,[10] CAN/THF,[11] $PhI(OAc)_2$/THF,[12] $(n\text{-}Bu_4N^+)_2S_2O_8^-$/THF,[13] *tert*-butylperoxy-$\lambda^3$-iodane/$CCl_4$/THF,[14] acetonyltriphenylphosphonium bromide (ATPB)/$CH_2Cl_2$,[15] *p*-TsCl/NaH/THF,[16] and $FeCl_3$/THF/UV.[17] Unlike in the tetrahydropyranylation of alcohols, the use of efficient acid catalysts for tetrahydrofuranylation has received very little attention in the literature.[4] Herein, we report a novel, inexpensive, solvent-free, high yielding, and simple protocol using $NaHSO_4$ supported on silica gel as a catalyst in order to address some of the tetrahydrofuranylation issues.

$NaHSO_4$ supported on silica gel has gained interest in organic synthesis as a viable and alternative acid catalyst for a number of transformations due to its low cost, ease of preparation, mildness, recoverability, reusability, and insensitivity to moisture. It has been applied as a catalyst in the opening of epoxides into $\beta$-hydroperoxy alcohols;[18] synthesis of trisubstituted quinolines,[19] $\beta$-enaminones,[20] *N*-acylsulfonamides,[21] aryl-14*H*-dibenzo[*a*,*j*]xanthenes,[22] amidoalkylnaphthols,[23] and coumarins;[24] selective monoacetylation of unsymmetrical diols;[25] and the Ferrier rearrangement of glycals.[26]

In our first attempt in developing a solvent-free $NaHSO_4$-catalyzed tetrahydrofuranylation, a solvent-free solution of benzyl alcohol and DHF was treated with 0.5 mol % of $NaHSO_4$–$SiO_2$ (3.0 mmol $NaHSO_4$/g)[25] to afford the corresponding THF ether in 90% yield in 5 min at room temperature (Scheme 1). Reducing the catalyst loading to 0.2 mol % resulted in a sluggish reaction and low yields.



**Scheme 1.** Tetrahydrofuranylation of benzyl alcohol.

Variation in the total amount of DHF revealed that 1.5 equivalents were sufficient to fully convert the alcohol into the desired THF ether. Treatment of various primary and secondary alcohols in this way provided efficient access to the desired THF ethers.[27] While tertiary alcohols were difficult to protect, the reactions proceeded remarkably well with the other alcohols.

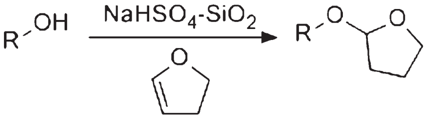
In all cases, complete conversion of the starting alcohol was achieved in a short reaction time, and good to excellent yields (67–91%) of the ethers were obtained (Table 1). Products were identified by $^1H$ and $^{13}C$ NMR spectroscopy after chromatographic purification. Interestingly, no aqueous workup was required as reaction mixtures were directly loaded onto silica gel for chromatographic purification. The reaction conditions are tolerant of a range of acid-sensitive groups such as allyl (Table 1, Entry 6), propargyl (Table 1, Entry 7), and ether linkages (Table 1, Entry 2).

Investigation of the recovery and reusability of the catalyst was carried out using benzyl alcohol as a model substrate. The catalyst was recovered quantitatively by simple filtration, washed with diethyl ether, and then reactivated at 100 °C for 30 min in an oven. The catalyst was reused at least three times without lose of activity (1st use 90%, 2nd use 90%, and 3rd use 92%).

Since $SiO_2$ is a well-known Lewis acid catalyst,[28] it was important to investigate whether the activity of the $NaHSO_4$–$SiO_2$ was the result of $SiO_2$ alone or a combination of the two. Thus, attempts were made to effect tetrahydrofuranylation of benzyl alcohol using $SiO_2$. However, formation of a new product was not detected from TLC analysis. The importance of $SiO_2$ was then tested by trying to effect tetrahydrofuranylation of benzyl alcohol in the presence of unsupported $NaHSO_4$ (0.5 mol %). The reaction provided the desired THF ether but at a relatively slower rate, 50 min (compared to less than 5 min in the case of supported $NaHSO_4$) proving it was the combination of $NaHSO_4$ and $SiO_2$ that contributed to the efficiency of the catalyst. This difference in the rate of the reaction is in accordance with results reported in the literature.[29] Nishiguchi and Taya reported that the silica gel serves as a "reaction field" increasing the surface area where the reagents and substances get adsorbed to react at a relatively faster rate.[29]

The protocol is superior to reported methods in terms of yield, catalyst loading, and reaction rate as can be seen from the results shown in Table 2. All the reported methods require an organic solvent, longer reaction time, and in most cases elevated

**Table 1.** Formation of THF ethers from alcohols using $NaHSO_4$–$SiO_2$



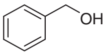
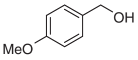
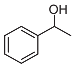
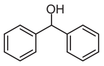
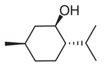
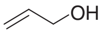
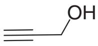
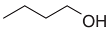
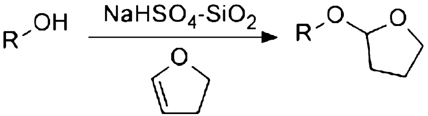
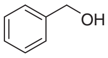
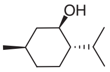
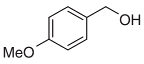
| Entry | Substrate | Time/min | Yield/% |
|---|---|---|---|
| 1 |  | 5 | 90 |
| 2 |  | 5 | 90 |
| 3 |  | 5 | 86 (1:1) |
| 4 |  | 5 | 85 |
| 5 |  | 5 | 90 |
| 6 |  | 5 | 67 |
| 7 |  | 5 | 75 |
| 8 |  | 5 | 81 |
| 9 |  | 5 | 91 |

**Table 2.** Comparison of $NaHSO_4$–$SiO_2$ with literature reported catalysts for the tetrahydrofuranylation of different alcohols



| Alcohol | Catalyst | Time | Yield /% | Ref. |
|---|---|---|---|---|
|  | $VCl_3$ | 2–4 h | 85 | 7 |
| | *tert*-butylperoxy-$\lambda^3$-iodane | 10 h | 77 | 14 |
| | Mn(0) | 4 h | 93 | 8 |
| | ATPB | 5 min | 94 | 15 |
| | $CrCl_2$ | 4–6 h | 95 | 6 |
| | $BrCCl_3$/2,4,6-collidine | 8–15 h | 87 | 3 |
| | $NaHSO_4$–$SiO_2$ | 5 min | 90 | *This work* |
|  | $VCl_3$ | 2–4 h | 90 | 7 |
| | Mn(0) | 15 h | 99 | 8 |
| | ATPB | 3 h | 97 | 15 |
| | $CrCl_2$ | 4–6 h | 85 | 6 |
| | $BrCCl_3$/2,4,6-collidine | 8–15 h | 60 | 3 |
| | $NaHSO_4$–$SiO_2$ | 5 min | 90 | *This work* |
|  | $VCl_3$ | 2–4 h | 86 | 7 |
| | $CrCl_2$ | 4–6 h | 95 | 6 |
| | $BrCCl_3$/2,4,6-collidine | 8–15 h | 71 | 3 |
| | $NaHSO_4$–$SiO_2$ | 5 min | 90 | *This work* |

temperature. On the contrary, the current method is efficient under solvent-free conditions at room temperature and reaction goes to completion in less than 5 min to provide comparable yields.

In conclusion, we have demonstrated that $NaHSO_4$ supported on silica gel under solvent-free conditions is an efficient catalyst for the tetrahydrofuranylation of alcohols. To the best of our knowledge, the shorter reaction time, low acid catalyst loading, and low cost and high stability of the catalyst, compatibility with a wide range of acid-sensitive groups and more interestingly the absence of organic solvents (both as solvents in the reaction and workup), make the method attractive in organic synthesis, being greener and superior to the already reported methods.

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26 H. H. Kinfe, F. M. Mebrahtu, K. Sithole, *Carbohydr. Res.* **2011**, *346*, 2528.

27 *Typical procedures*: (a) *Preparation of the $NaHSO_4$–$SiO_2$ catalyst*:[26] To a solution of 5 g (0.04 mol) of $NaHSO_4$ in 25 mL of water in a 100-mL round bottom flask was added 14 g of $SiO_2$ (column chromatographic grade, 60 Å, 200–400 mesh). After stirring the mixture for 15 min at room temperature, the solvent was removed in vacuo at 40 °C until a free-flowing white solid was obtained. The catalyst was further dried in an oven maintained at 120 °C for 48 h prior to use; (b) *Tetrahydrofuranylation of alcohols*: To a mixture of alcohol (1.67 mmol) and 2,3-dihydrofuran (2.5 mmol), $NaHSO_4$–$SiO_2$ (0.5 mol %) was added. The reaction mixture was stirred at room temperature until TLC analysis showed complete disappearance of the starting material. After completion of the reaction, the mixture was directly loaded onto a silica gel for chromatographic purification using 1:9 ethyl acetate:hexane eluent to afford corresponding THF ethers. The structure of the products were determined from their NMR spectra.

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