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Nafion-catalyzed preparation of benzhydryl ethers

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Abstract—Nafion-H is found to be an efficient and recyclable catalyst for the preparation of diphenylmethyl ethers of alcohols. Published by Elsevier Science Ltd.

The selective protection of alcohols as diphenylmethyl (DPM) ethers is commonly used in organic synthesis.[1] DPM ethers are relatively inexpensive to prepare, stable towards a variety of reagents and are also found as an integral part of several pharmacologically active compounds.[2] Several reagents are available for the preparation of DPM ethers such as diphenylmethyl diazomethane or diphenylmethyl phosphate-trifluoroacetic acid,[3] diphenylmethyl chloride or bromide in the presence of a base,[4] diphenylmethanol in the presence of concentrated sulfuric[5]or *p*-toluenesulfonic acid,[6] xenon difluoride,[7] ytterbium triflate-ferric chloride[8] and iron salts.[9] These methods require a high catalyst to substrate ratio, longer reaction times, and larger amounts of solid supports which results in generation of waste. Thus there is a need for an efficient metal- or support-free catalyst for the preparation of DPM ethers, preferably using a solid acid. Nafion-H, a perfluorinated sulfonic acid resin, represents such a useful solid acid catalyst for a variety of organic transformations.[10] The high catalytic activity of Nafion-H, its selectivity and ease of separation from the reaction mixture as well as its regeneration renders it a very attractive candidate.[10] As part of an ongoing research program to develop greener chemical transformations,[11] herein, we report an efficient Nafion-catalyzed preparation of DPM ethers of alcohols at moderate temperature.

In the present method, a mixture of alcohol and diphenylmethanol was warmed in the presence of a catalytic amount of Nafion-H in acetonitrile, unless otherwise indicated, to afford the corresponding DPM ether. After completion of the reaction, the organic solvent containing the crude product was simply decanted off and the solvent evaporated. The crude product was purified by column chromatography using hexane/ethyl acetate as eluent. The formation of DPM ethers starting from benzhydrol and benzyl alcohol was examined under a variety of reaction conditions. Initially, the identification of appropriate solvent and the reaction temperature were optimized. The reaction delivered highest yield in acetonitrile compared to ethyl acetate and methylene chloride. The reaction was almost complete in 3 h at 80°C affording DPM ether (93%), while the reaction at room temperature was slower, providing ~60% in 3 h and 95% overnight. Next, the catalyst to substrate ratio was optimized. The reaction worked well at a catalyst to substrate ratio of 50 mg/1 mmol. At lower ratios, such as 50 mg/10 mmol, the reaction slowed down considerably and equal amounts of self-condensed ether of benzhydrol was formed overnight along with unreacted benzhydrol.

Having established acetonitrile as the reaction solvent, 80°C as the reaction temperature and 50 mg/1 mmol catalyst to substrate ratio, the method was extended to a variety of hydroxyl compounds and the results are summarized in Table 1. For these rapid reactions, the reactivity trend for different alcohols was found to be primary>secondary>tertiary. This chemoselective feature of the method became apparent when DPM ethers of benzylic alcohols and primary alcohols were formed in high yields with only trace amount of dibenzhydryl ether (<5%). The reactions involving secondary (entries 4 and 5) and tertiary alcohols (entry 6), however, proceeded relatively slow and the amount of dibenzhydryl ether was also increased in these cases.

Keywords: alcohols; diphenylmethyl ethers; Nafion-H.

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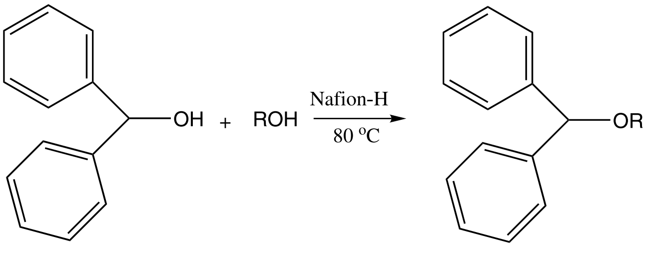
Table 1. Nafion-catalyzed preparation of DPM ethers from alcohols



Entry	Alcohol	Time (h)	Yield% (isolated)
1	1-Hexanol	2	78
2	1-Hexanol	3	91
3	1-Pentanol	2	76
4	2-Pentanol	4	42
5	3-Pentanol	4	35
6	2-Methyl-2-propanol	3	<5
7	Cyclohexanol	2	51
8	Cyclohexylmethanol	2	75
9	Benzyl alcohol	1	85
10	Benzyl alcohol	2	92
11	4-Fluorobenzyl alcohol	1	89
12	2-Fluorobenzyl alcohol	1	83
13	2-Bromobenzyl alcohol	1	90
14	2-Chlorobenzyl alcohol	1	81
15	3-Chlorobenzyl alcohol	1	87
16	4-Chlorobenzyl alcohol	1	89
17	Allylic alcohol	2	67

The recyclability of the catalyst was investigated for the reaction between benzhydrol and benzyl alcohol. After completion of the reaction, a simple decantation of the organic liquid afforded the product and the catalytic amount of Nafion could be utilized for subsequent preparation of DPM ethers. The procedure was repeated eight times for the reaction of benzhydrol and benzyl alcohol without any significant loss of activity as the catalyst remained active even after the eighth cycle (82% yield).

The preparation of DPM ethers of benzyl alcohol is representative of the general procedure employed. Nafion-H (150 mg) [Nafion®, NR 50, Fluka], benzhydrol (3 mmol), and benzyl alcohol (3.3 mmol) in acetonitrile (4.5 mL) were mixed in a 25 ml round bottom flask and stirred at 80°C. The progress of the reaction was monitored by TLC examination. Upon completion of the reaction, the organic solvent containing the crude product was decanted, the catalyst washed, and the solvent removed under reduced pressure on a rotary evaporator. The pure product was isolated by column chromatography using eluent, hexane/ethyl acetate (85%). All the DPM ethers are known compounds and were characterized by GC and ^{1}H NMR.

In conclusion, the present preparative method is an efficient and practical alternative to the preparation of DPM ethers of alcohols. The operational simplicity, the absence of solid supports and of inorganic salts, and the catalyst recyclability makes this high yield methodology an attractive alternative to the existing methods.

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