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Selective synthesis of unsymmetrical ethers from different alcohols catalyzed by sodium bisulfite

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ABSTRACT

An efficient method for the preparation of unsymmetrical ethers from alcohols catalyzed by sodium bisulfite is reported. The procedure enables the direct dehydration of primary, secondary, and tertiary benzylic alcohols with aliphatic alcohols in the absence of solvent to selectively produce unsymmetrical ethers in high yields with low catalyst loading. No symmetrical ethers are generated in the reactions. The etherification of a chiral secondary benzyl alcohol with butanol exclusively yields racemic ethers, suggesting that the reaction involves a carbocation intermediate mechanism.

1. Introduction

Ether bond formation is of great importance in organic synthesis. The classical synthetic methods for ethers include Williamson ether synthesis,[1] dehydration coupling of alcohols,[2] as well as reductive etherification of carbonyl compounds.[3] Williamson ether synthesis is the most widely used protocol for the preparation of both symmetrical and unsymmetrical ethers. However, it requires the conversion of a hydroxyl group into a good leaving group, such as halogen or tosyl, and the reaction needs to be carried out in the presence of a strong base, which does not allow for substrates bearing basic-intolerant groups.[4] The method is also less effective for secondary and tertiary halides (tosylates) due to the competition of elimination reactions. In addition, the usage of halides, together with the production of waste salts, is environmentally less desirable.

The direct preparation of ethers from alcohols is more environmentally friendly. In this context, symmetrical ethers can be readily generated by acid-catalyzed condensation of alcohols.[5] However, traditionally, unsymmetrical ethers can be prepared only from the reaction of a tertiary alcohol with a primary or secondary alcohol. Because the reactions involve the formation of carbocation intermediates from the tertiary alcohols, they always suffer from the competition of the elimination reactions, which are in many cases, even more favorable. In the past decades, a variety of transition metal[6] or Lewis acid[7] catalyzed cross-coupling reactions of different alcohols have been reported. In 2002, Kobayashi et al. described that Brønsted acid (dodecylbenenesulfonic acid) catalyzed the reactions of benzyl alochols with dodecanol to afford the corresponding benzyl dodecyl ethers.[8] In this paper, we describe that the cross-coupling reactions of two different alcohols can be catalyzed by sodium bisulfite to selectively afford unsymmetrical ethers (Scheme 1).

$$\mathrm{R^1OH} \quad + \quad \mathrm{R^2OH} \xrightarrow{\mathrm{NaHSO_3\ (cat.)}} \mathrm{R^1OR^2}$$

R^1: benzylic (primary, secondary, tertiary)
R^2: alkyl (primary, secondary)

Scheme 1. $NaHSO_3$-catalyzed formation of unsymmetrical ethers from discrete alcohols.

2. Results and discussion

2.1. Optimization of the reaction condition

In the initial study, we investigated the straightforward etherification of *p*-methoxybenzyl alcohol **1a** with *n*-BuOH **2a** under the

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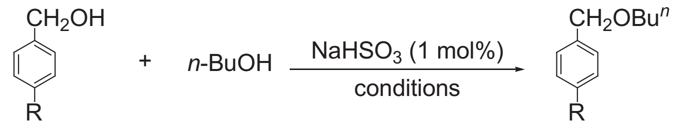
catalysis of 1 mol % of $NaHSO_3$ (Table 1). No formation of the unsymmetrical ether was detected when the reaction was performed in CH_2Cl_2, toluene, THF or CH_3CN, and the starting materials were recovered completely (entries 1–4). In $MeNO_2$, the reaction could give rise to 4-methoxybenzyl ether **3a** in 46% yield after refluxing for 14 h (entry 5). However, in the absence of additional solvent, the reaction could produce **3a** in 82% isolated yield after heating at 100 °C for 1 h (entry 6). No etherification occurred at lower temperature (60 °C) and the starting materials were recovered (entry 7). In the case of benzyl alcohol or *para*-nitrobenzyl alcohol, the corresponding ethers could not be obtained even the reaction time was prolonged to 6 (entry 8) or 16 h (entry 9).

Table 1
Optimization on the $NaHSO_3$-catalyzed etherification of benzylic alcohol **1** with *n*-BuOH[a]



1 **2a** **3**

Entry	R	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	OMe	CH_2Cl_2	1	Reflux	NR[c]
2	OMe	$PhCH_3$	1	Reflux	NR[c]
3	OMe	THF	1	Reflux	NR[c]
4	OMe	CH_3CN	1	Reflux	NR[c]
5	OMe	CH_3NO_2	14	Reflux	46
6	OMe	—	1	100	82
7	OMe	—	1	60	NR[c]
8	H	—	6	110	NR[c]
9	NO_2	—	16	110	NR[c]

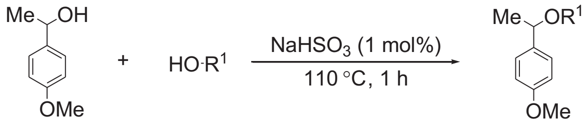
[a] Unless otherwise noted, the reactions were performed with *p*-methoxybenzyl alcohol (2.0 mmol), *n*-BuOH (8.0 mmol), and $NaHSO_3$ (1 mol %) in 5 mL of solvent.
[b] Isolated yield.
[c] No reaction.

2.2. Substrate adaptability

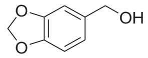
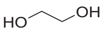
Under the optimized reaction conditions, we tested the reaction of **1a** with aliphatic primary, secondary, and tertiary alcohols **2a–g** in the absence of solvent (Table 2). In the case of primary and secondary alcohols, the $NaHSO_3$ catalyst was effective in promoting the reactions (entries 1–5). Notably, allyl alcohol **2f** also successfully reacted with **1a** to give desired ether **3f** (entry 6). 2-Butyl-4-methoxybenzyl ether **3g** has a fruity pear odor and is a potential fragrance compound.[7n] The unsymmetrical ether **3g** could be obtained in 70% yield after longer reaction time (entry 7). A scale-up reaction of 1.1 g **1a** with **2g** also gave **3g** in up to 72% isolated yield, which is comparable to that of small amount etherification. In the case of aliphatic alcohols with steric hindrance, such as *t*-BuOH, no unsymmetrical ether was obtained and the starting material remained.

We then explored the synthesis of unsymmetrical ethers from secondary benzyl alcohol **1b** and the results are summarized in Table 3. In the case of linear primary alcohols, unsymmetrical

Table 3
$NaHSO_3$-catalyzed etherification of 1-(4-methoxyphenyl)ethanol **1b**[a]

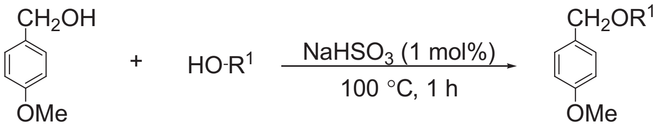


1b **2a–l** **4a–l**

Entry	Alcohol **2**		Ratio (**1b**:**2**)	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	$CH_3(CH_2)_3OH$	**2a**	1:4	110	1	**4a**	80
2	$CH_3(CH_2)_6OH$	**2b**	1:4	110	1	**4b**	85
3	$CH_3(CH_2)_{11}OH$	**2c**	1:1	110	1	**4c**	77
4	$CH_3(CH_2)_{17}OH$	**2d**	1:1	110	1	**4d**	85
5	$(CH_3)_2CH(CH_2)_2OH$	**2e**	1:4	110	1	**4e**	83
6	$CH_2{=}CHCH_2OH$	**2f**	1:10	90	14	**4f**	81
7	$CH_3CH(OH)CH_2CH_3$	**2g**	1:10	110	24	**4g**	75
8	$(CH_3)_2CHOH$	**2h**	1:10	90	14	**4h**	53
9	$(CH_3)_3COH$	**2i**	1:10	90	14	**4i**	NR[c]
10	CH_3OH	**2j**	1:10	60	14	**4j**	87
11[d]	CH_3OH 	**2k**	1:1	110	1	**4k**	87
12		**2l**	1:10	90	24	**4l**	72

[a] Unless otherwise noted, the reactions were performed with 1-(4-methoxyphenyl) ethanol (2.0 mmol), alcohol **2** (8.0 mmol), and $NaHSO_3$ (1 mol %) at 110 °C for 1 h.
[b] Isolated yields.
[c] No reaction.
[d] $NaHSO_3$ (0.3 mol %) was applied.

Table 2
$NaHSO_3$-catalyzed etherification of *p*-methoxybenzyl alcohol **1a**[a]



1a **2a–g** **3a–g**

Entry	Alcohol **2**		Ratio (**1a**:**2**)	Time (h)	Product	Yield[b] (%)
1	$CH_3(CH_2)_3OH$	**2a**	1:4	1	**3a**	82
2	$CH_3(CH_2)_6OH$	**2b**	1:4	1	**3b**	84
3	$CH_3(CH_2)_{11}OH$	**2c**	1:4	1	**3c**	86
4	$CH_3(CH_2)_{17}OH$	**2d**	1:1	3	**3d**	86
5	$(CH_3)_2CH(CH_2)_2OH$	**2e**	1:4	1	**3e**	82
6	$CH_2{=}CHCH_2OH$	**2f**	1:10	1	**3f**	87
7[c]	$CH_3CH(OH)CH_2CH_3$	**2g**	1:4	12	**3g**	70

[a] Unless otherwise noted, the reactions were performed with *p*-methoxybenzyl alcohol (2.0 mmol), alcohol **2** (8.0 mmol), and $NaHSO_3$ (1 mol %) at 100 °C for 1 h.
[b] Isolated yields.
[c] The reaction was carried out at 110 °C.