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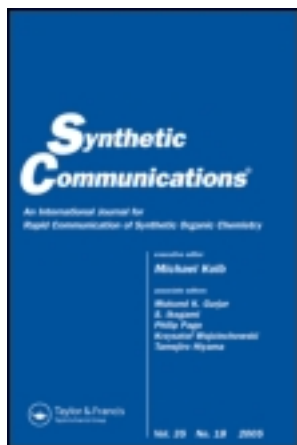
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Efficient and Selective Formation of Mixed Acetals by Nafion-H SAC-13 Silica Nanocomposite Solid Acid Catalyst

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ABSTRACT

Various types of hydroxy compounds can readily be converted to the corresponding mixed acetals with dialkoxymethanes in the presence of SAC-13 solid superacid. The transformation is almost instantaneous, product acetals are isolated in good to excellent yields, and the catalyst can be reused with minor loss of activity. Comparative studies were also carried out with *p*-toluenesulfonic acid and $\text{BF}_3 \cdot \text{OEt}_2$.

Key Words: Dialkoxymethanes; Hydroxy compounds; Mixed acetals; Nafion SAC-13; Protecting groups; Superacid.

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INTRODUCTION

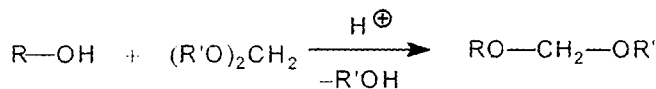
The use of solid catalysts in organic synthesis and in the industrial manufacture of chemicals is of increasing importance, because they provide green alternatives to homogeneous catalysts. This is particularly important in acid catalysis, where solid acids can be the safe alternatives of such hazardous and corrosive materials as hydrofluoric acid (HF), sulfuric acid, and nitric acid.

Nafion resins, that is, perfluorinated resinsulfonic acid-based ion-exchanged polymers, have been widely used in organic synthesis.^[1,2] Recently, a new type of Nafion, a silica nanocomposite material, has become commercially available (SAC-13, the product of Aldrich). Increased activity of such Nafion silica nanocomposites has been reported,^[3,4] which results from the large surface area ($150\text{--}500\text{ m}^2\text{ g}^{-1}$) and the presence of small ($<100\text{ nm}$) Nafion particles entrapped in the porous silica framework. SAC-13 has recently been found to be an efficient catalyst in acylations^[5,6] and the hetero-Michael addition.^[7]

We have chosen to test this catalyst in the preparation of mixed acetals, which have a number of utilizations in organic synthesis. Namely, they are used in the synthesis of isochromans and phtalans,^[8] and may also be used as aldehyde^[9] or ester equivalents.^[10] Most important is the common practice of protecting alcohols as methoxymethyl ethers prepared in an acid-catalyzed process.^[11] The reagents employed for this purpose could be either chloromethyl methyl ether or dimetoxymethane. The use of the latter is more desirable because of the strong carcinogenicity of chloromethyl methyl ether.^[12–15] Higher homologs, however, are rarely applied in synthesis protocols.^[16] A further example is our recent paper describing the use of higher dialkoxymethanes in the *N*-alkoxymethylation of carboxamides.^[17] Solid acids, including Nafion-H, have also been applied in this process.^[14,16]

RESULTS AND DISCUSSION

We found that when applying Nafion-H SAC-13 silica nanocomposite solid acid catalyst in the transformation of various primary and secondary alcohols (open chain and cyclic compounds and a sterol) with four different dialkoxymethanes (dimethoxy-, diethoxy-, diisopropoxy-, and dibutoxymethane), the desired mixed acetals are rapidly formed at reflux temperature (Sch. 1, Table 1). Following the original observation given in Ref.^[14], reactions were run for 10 h (primary alcohols) and 16 h (secondary alcohols). In later experiments, gas chromatography (GC) and thin-layer chromatography (TLC) analyses indicated the disappearance of the starting alcohol in a short time. In fact, product formation is almost instantaneous, and complete

*Scheme 1.*

conversions are usually achieved in 5 min. The reaction is an $\text{S}_{\text{N}}2$ -type substitution of the protonated acetal by the reacting alcohol (Sch. 2, route *a*).

The transformation is less straightforward for more hindered and tertiary alcohols. The reaction of 2-methylhexan-2-ol (data not shown) is nonselective, giving a range of products in low yields. In contrast, 1-phenylethanol (Entry 18) and adamantan-1-ol (Entry 20) undergo etherification. As observed in the early study with Nafion-H,^[14] this transformation can be highly selective for the latter compound and was attributed to steric hindrance. It may be surmised, however, that the reacting alcohol, in these cases, undergoes protonation to form the corresponding stable benzylic or tertiary carbocation. These, then, are attacked by the nonprotonated acetal; that is, an $\text{S}_{\text{N}}1$ -type substitution takes place (Sch. 2, route *b*). Benzyl alcohol, which can also give the stable benzylic carbocation, however, is a nonhindered alcohol and exhibits the usual selectivity to form the corresponding mixed acetals in high yields (Entry 7). This behavior clearly indicates the role of steric hindrance in ether formation.

As data in Table 1 show, the best yields of the mixed acetals can be achieved in almost all cases with diisopropoxy- and dibutoxy-methanes, particularly for primary alcohols. This is attributed to the fact that in these cases, reactions are carried out without solvent, in an excess of the reagent, at the boiling point of the corresponding formal. In contrast, the boiling points of dimethoxymethane (42°C) and diethoxymethane (89°C) are much lower, which does not allow for the reactions to be carried out at the optimum temperatures. However, when an appropriate cosolvent is used, yields can be increased substantially. In the reaction of dimethoxymethane, benzene proved to be the ideal solvent for primary alcohols, whereas toluene appears to be the solvent of choice when working with diethoxymethane (Entries 1, 4, and 7), particularly for secondary alcohols (Entries 9 and 12).

Catalyst recycling was also studied. It was found that SAC-13 maintains high activity even after five consecutive runs (an activity drop of about 5–10% was observed), provided the catalyst is washed with a polar solvent (ethanol) after each successive run.

According to the results of comparative studies with traditional catalysts in the homogeneous phase, *p*-toluenesulfonic acid gives results similar to SAC-13, except that the reaction time is somewhat longer (30 min). In contrast, yields and selectivities with $\text{BF}_3 \cdot \text{OEt}_2$ are usually inferior to

Table 1. Formation of mixed acetals (data indicate isolated yields).

Entry	R	Catalyst	R'			
			Me	Et	iPr	Bu
1	1-Octyl	SAC-13	62/96 ^a	85/89 ^b	100	100
2		<i>p</i> -TsOH	81	85	100	100
3		BF ₃ ·OEt ₂	77	86	96	Nonselective
4	2-Phenylethyl	SAC-13	70/94 ^a	85/86 ^b	99	100
5		<i>p</i> -TsOH	84	85	99	100
6		BF ₃ ·OEt ₂	91	90	84	Nonselective
7	Benzyl	SAC-13	62/90 ^a	87	91	98
8		<i>p</i> -TsOH	27/81 ^a	89	99	99
9	2-Octyl	SAC-13 ^a	68/72 ^b	58/79 ^b	89	88
10		<i>p</i> -TsOH ^a	66	58	94	83
11	Cyclohexyl	BF ₃ ·OEt ₂	57	66	82	Nonselective
12		SAC-13 ^a	76/78 ^b	70/83 ^b	88	85
13		<i>p</i> -TsOH ^a	89	68	92	86
14		BF ₃ ·OEt ₂	61	75	94	Nonselective

15	Cholesteryl	SAC-13 ^a	77	70	97	83
16		<i>p</i> -TsOH ^a	80	79	86	58
17		BF ₃ · OEt ₂	78	67	17	81
18	1-Phenylethyl	SAC-13 ^a	5(81 ^c + 6 ^d)	32	0(20 ^c + 21 ^e + 59 ^e)	42(58 ^c)
19		<i>p</i> -TsOH ^a	4(76 ^c + 14 ^d)	71	85(8 ^c + 7 ^d)	84(16 ^c)
20	1-Adamantyl	SAC-13 ^f	3(93 ^c)	7	10(77 ^c)	20(6 ^c)
21		<i>p</i> -TsOH ^f	33(3 ^c)	7	48(2 ^c)	16(5 ^c)
22		BF ₃ · OEt ₂	5	9	14(50 ^c)	0(53 ^c)

^aReaction in benzene cosolvent.

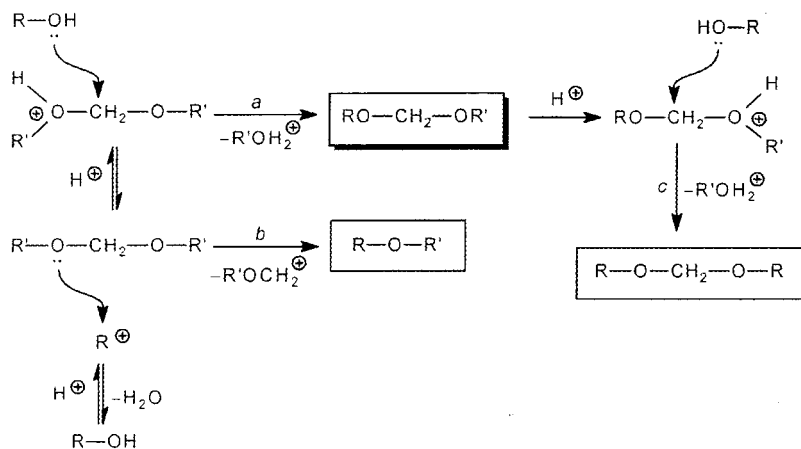
^bReaction in toluene cosolvent.

^cThe corresponding ether of the starting material.

^dStyrene.

^eUnidentified compounds.

^fReactions in chloroform cosolvent.



Scheme 2.

those found for the other two catalysts, particularly in the transformation with dibutoxymethane. This may be attributed to the high reaction temperature, which results in side reactions and the loss of the $BF_3 \cdot OEt_2$ catalyst due to its high volatility.

As mentioned, the selectivity of acetal formation is sensitive to reaction temperature. When working at higher temperatures, we observed the formation of symmetrical acetals (Table 2). As time dependence of product composition showed, this is a consecutive reaction step; that is, the initial product mixed acetals react further with a second molecule of alcohol (Sch. 2, route c).

In summary, we demonstrated that SAC-13 is a highly reactive and selective catalyst in the formation of mixed acetals in the reaction of alcohols with dialkoxymethanes. The fast reaction, easy handling, simple workup of

Table 2. Temperature dependence of selectivity of acetal formation in the transformation of 2-phenylethanol.

Temperature	Diisopropoxymethane		Dibutoxymethane	
	SAC-13	<i>p</i> -TsOH	SAC-13	<i>p</i> -TsOH
100°C	99	99	100	100
120°C	51/49 ^a	92/8 ^a	—	—
178°C	—	—	91/9 ^a	67/33 ^a

^aRatio of mixed acetal to symmetric acetal.

the reaction mixture and the possibility of recycling make this new solid acid the catalyst of choice in the title reaction.

EXPERIMENTAL

All compounds and catalysts were purchased from Aldrich and were of appropriate purity to be used without further purification. Reaction mixtures were analyzed by GC [HP 5890 GC, HP-1 column (50 m \times 0.32 mm \times 1.05 μ m) flame ionization detector] and TLC. Product identification was performed by means of gas chromatography-mass spectrometry (GC-MS) (HP 5890 GC coupled with a HP 5970 mass selective detector). In some cases, reaction mixtures were purified by column chromatography [silica gel (Merck 60, 0.040–0.063 mm), hexane-ethyl acetate (7 : 3)] and were analyzed by nuclear magnetic resonance (NMR) spectroscopy [Bruker DRX 500 spectrometer at 500 MHz, CDCl_3 as solvent and tetramethylsilane (TMS) as an internal reference].

General Acetalization Procedure

A stirred solution of the alcohol (2 mmol) and the dialkoxymethane (47 mmol) was stirred under reflux in the presence of SAC-13 (0.1 g) under a dry atmosphere.^[14] After completion of the reaction, the solid catalyst was filtered off and washed with dialkoxymethane (or with the corresponding cosolvent). Catalyst quantities in the homogeneous reactions were 8–10 wt% of *p*-toluenesulfonic acid (calculated for the alcohol) or 2.4 mmol of $\text{BF}_3 \cdot \text{OEt}_2$. The amounts of dialkoxymethanes were 47 mmol and 108 mmol, respectively. The workup procedure in these cases included neutralization with 10% NaHCO_3 and washing with brine followed by drying (Na_2SO_4). In reactions carried out in cosolvent (8 cm^3 of benzene, toluene or chloroform in the case of adamantanol), the quantity of dialkoxymethanes was decreased to 12 mmol.

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