

# Silica sulfuric acid as a reusable heterogeneous catalyst for the diastereoselective Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furan: facile synthesis of $\gamma$ -butenolides

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**Abstract** Silica sulfuric acid was found to be an efficient catalyst for the vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furan with various aldehydes with good diastereoselection. The reaction proceeds rapidly in THF, affording the corresponding 5-(arylhydroxymethyl)furan-2(5*H*)-ones in good yields. This method offers significant advantages such as experimental simplicity, and recoverability and reusability of the catalyst.

**Keywords** 2-(trimethylsilyloxy)furan · Aldehydes · Diastereoselectivity ·  $\gamma$ -Butenolides · Vinylogous Mukaiyama aldol reaction

## Introduction

The Mukaiyama aldol reaction is one of the most important carbon–carbon bond-forming processes in organic synthesis [1, 2]. The catalytic coupling of 2-(trimethylsilyloxy)furan (TMSOF, **2**) with aldehydes **1** by means of a vinylogous Mukaiyama aldol reaction has emerged as an important method to provide 5-(arylhydroxymethyl)furan-2(5*H*)-ones ( $\gamma$ -butenolides) **3** [3]. The butenolide moiety substituted at the  $\gamma$ -position by a chain bearing hydroxyl groups is an important structural subunit in many natural products and biologically active compounds [4–7] such as muricatacin, L-factor, sapinofuranone, isocalpalide B, cardiobutanolide, etc. (Fig. 1). Various lanthanide triflates have been reported for the vinylogous Mukaiyama aldol reaction; however,

the cost of the triflates restricts their use [8–11]. Enantioselective versions of these reactions have been known by use of chiral mediators. Racemic examples of the vinylogous Mukaiyama aldol reaction are known employing Lewis acids such as SnCl<sub>4</sub>, ZnCl<sub>2</sub>, TiCl<sub>4</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, SiCl<sub>4</sub> or silyl triflates [12–20]. Recently, Bi(OTf)<sub>3</sub>·4H<sub>2</sub>O [22] has been used for the vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furan. In view of the versatility of this reaction, there is still a need to develop a new catalytic system that can be recyclable.

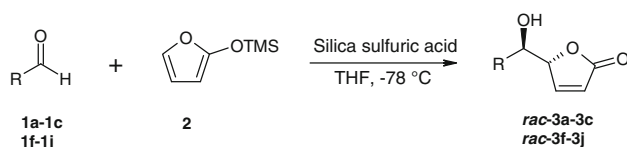
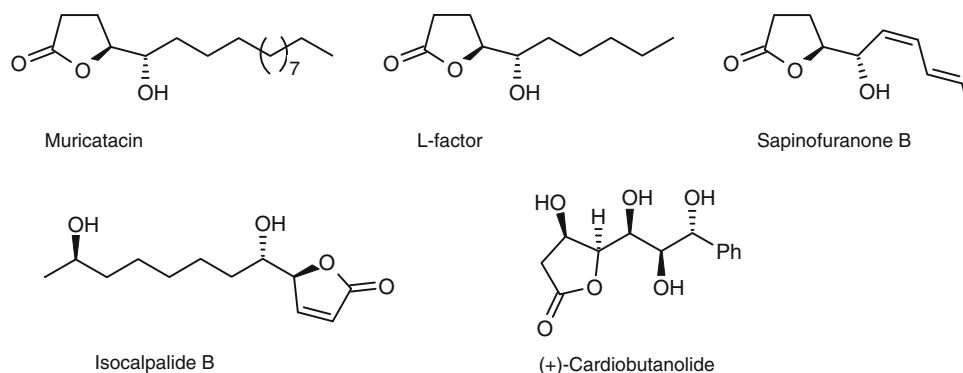
Heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions, and minimization of chemical waste as compared with their liquid-phase counterparts. The use of solid acids such as silica sulfuric acid (SSA) [23–26] for synthesizing organic intermediates and fine chemicals is attracting increasing attention, also making a field of intense research activity [27].

## Results and discussion

Initially, the reaction of benzaldehyde with 2-(trimethylsilyloxy)furan was studied in the presence of a catalytic amount of silica sulfuric acid in THF at –78 °C and found to give 5-(hydroxyphenylmethyl)furan-2(5*H*)-one ( $\gamma$ -butenolide) in 93% yield (Scheme 1). Preliminary <sup>1</sup>H nuclear magnetic resonance (NMR) studies of the crude product revealed that the reaction provided *syn* diastereoselectivity (the *syn/anti* ratio was determined to be 91:9). Encouraged by this result, the scope of the reaction was explored with various aldehydes, as indicated in Table 1. A variety of aromatic aldehydes were used as coupling partners with TMSOF. Aldehydes containing electron-donating as well as electron-withdrawing substituents cleanly underwent

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**Fig. 1** Naturally occurring 5-(1-hydroxyalkyl)- $\gamma$ -butyrolactones



**Scheme 1**

reaction in isolated yields ranging from 86% to 93% and with good diastereoselectivities. This clearly indicates that variation in the electronic nature of the substituent on the aromatic ring has apparently no influence on the efficiency and diastereoselectivity of the reaction. The *syn/anti* relative stereodisposition of products was assigned based on known compounds [14, 19]. The present reaction conditions also work for  $\alpha,\beta$ -unsaturated aldehydes (Table 1, entry 9) as well as heteroaromatic aldehydes such as furfural. Aliphatic aldehydes can also serve as substrates in this reaction, giving the corresponding butenolides in lower yields with moderate diastereoselectivity when compared with aromatic aldehydes. Thus, the reaction of tridecanal and hexanal with TMSOF produced the corresponding butenolides **3d** and **3e** in 85% yield (Scheme 2).

Hydrogenation of these precursors using Pd/C led to the naturally occurring molecules muricatacin (**4**) and L-factor (**5**) in racemic form. Literature precedents for enantioselective versions of the reaction exist [27, 28].

The catalyst works under heterogeneous conditions and can easily be prepared from readily available  $\text{ClSO}_3\text{H}$  and silica gel [27]. It can be conveniently handled and removed from the reaction mixture. The catalyst was recycled three times without loss of activity. The salient features of the present method are mild reaction conditions, simple experimental procedure, high yields, good diastereoselectivities, and reusability of the catalyst. To our knowledge, this is the first report on synthesis of butenolides from aldehydes and TMSOF using a heterogeneous solid acid catalyst.

## Conclusions

Silica sulfuric acid proved to be an efficient heterogeneous catalyst for addition of TMSOF to aldehydes. The reaction is applied to synthesis of natural products such as muricatacin and L-factor in racemic form.

## Experimental

Starting materials were purchased from Aldrich Chemical Company, USA, and used as received. Evaporation of solvents was performed at reduced pressure using a Buchi rotary evaporator.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of samples in  $\text{CDCl}_3$  were recorded on a Bruker UXNMR FT-300 MHz (Avance) spectrometer. Mass spectra were recorded on a LC-MSD (Agilent technologies) spectrometer at 70 eV. Thin-layer chromatography (TLC) was performed on Merck 60 F-254 silica gel plates.

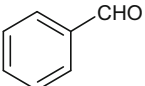
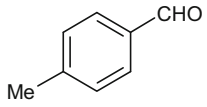
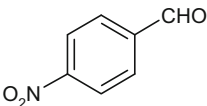
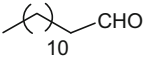
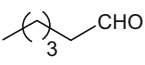
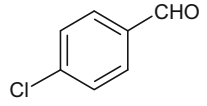
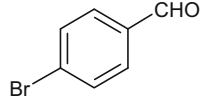
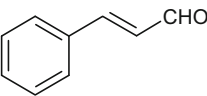
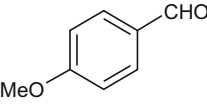
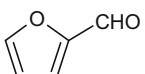
### Preparation of silica sulfuric acid

Silica sulfuric acid was prepared according to a previously reported procedure [27].

### General experimental procedure for the silica sulfuric acid-catalyzed Mukaiyama aldol reaction of TMSOF with aldehydes

To a solution of the aldehyde **1** (1 mmol) in THF, silica sulfuric acid catalyst (20 mol%) was added and stirred for 10 min. Then the reaction mixture was brought to  $-78\text{ }^{\circ}\text{C}$ , and a solution of 2-(trimethylsilyloxy)furan (**2**, 1 mmol) in THF was added dropwise. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  until the reaction was completed as indicated by TLC. The mixture was filtered, and the catalyst was washed with a small amount of THF. The recovered catalyst can be used for further reactions. The filtrate was

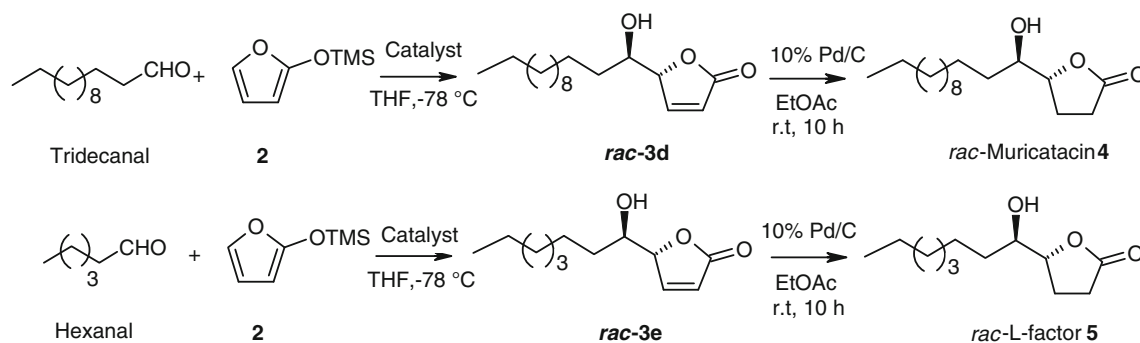
**Table 1** Silica sulfuric acid-catalyzed reactions of various aldehydes with 2-(trimethylsilyloxy)furan

Entry	RCHO 1	Product 3 <sup>a</sup>	Time (h)	dr ( <i>syn:anti</i> )	Yield (%) <sup>c</sup>
1		<b>3a</b> [21]	1.5	91:9	93
2		<b>3b</b> [21]	2.0	90:10	92
3		<b>3c</b> [20]	1.0	93:7	90
4		<b>3d</b> [27]	3.0	80:20	85
5		<b>3e</b> [28]	3.0	78:22	85
6		<b>3f</b> [21]	1.6	90:10	90
7		<b>3g</b> [20]	1.8	89:11	91
8		<b>3h</b> [21]	1.4	85:15	89
9		<b>3i</b> [21]	1.6	89:11	88
10		<b>3j</b> [21]	0.8	86:14	86

<sup>a</sup>All products were characterized by <sup>1</sup>H NMR, infrared (IR), and mass spectral data

<sup>b</sup>The diastereomeric ratio was determined based on <sup>1</sup>H NMR studies of crude products

<sup>c</sup>Yields refer to isolated yields of the mixture of *syn/anti* diastereomers



Scheme 2

concentrated under reduced pressure and purified by silica gel column chromatography to obtain the pure product **3**.

#### General procedure for the preparation of compounds **4** and **5**

To a stirred solution of **3e** (0.2 g, 1.08 mmol) in 10 cm<sup>3</sup> EtOAc, 10% Pd/C (50 mg) was added, and the reaction mixture was stirred under H<sub>2</sub> atmosphere for 10 h at room temperature and then filtered through Celite. The filtrate was concentrated under reduced pressure to yield compound **5** (0.18 g, 89%) as a colorless liquid. A similar procedure was used for the preparation of compound **4**.

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