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ORIGINAL PAPER

Chemoselective trimethylsilylation of alcohols catalyzed by saccharin sulfonic acid

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Abstract Saccharin sulfonic acid was easily prepared by the reaction of saccharin with neat chlorosulfonic acid at room temperature. This reagent is efficiently able to catalyze the chemoselective trimethylsilylation of alcohols with hexamethyldisilazane in the presence of amines and thiols.

Keywords Saccharin · Saccharin sulfonic acid · Alcohols · Trimethylsilylation · Hexamethyldisilazane

Introduction

Trimethylsilylation is one of the most important and popular methods for protecting the alcoholic hydroxyl group during a multistep synthesis [1, 2]. Generally, the formation of silyl ethers carried out by treatment of alcohols with silyl chlorides or silyl triflates in the presence of stoichiometric amounts of a base such as 4-(*N,N*-dimethylamino) pyridine [3], Li_2S [4], and sometimes a nonionic super base catalyst [5]. However, some of these methods suffered from drawbacks such as lack of reactivity or the difficulty in removing amine salts drived from the reaction of by-produced acids and cobases during the course of the reaction.

Hexamethyldisilazane (HMDS) is an expensive and commercially available reagent used for the silylation of alcohols. Its handling does not need special precaution, and workup of the reaction mixture is not time consuming because the by-product of the reaction is ammonia, which is easily removed from the reaction mixture. However, the low silylating power is considered the main drawback for the application of HMDS. To overcome this restriction, a variety of catalysts has been reported; of them, sulfonic acids [6], N,N',N',N'''-tetramethyltetra-2,3-pyridinoporphyrazinato copper (II) [7], poly(*N*-bromobenzene-1,3-disulfonamide) (PBBS) [8], trichloroisocyanuric acid [9], sulfonic acid-functionalized silica [10], $Al(HSO_4)_3$ [11], $ZrCl_4$ [12], silica triflate [13], and $Fe(HSO_4)_3$ [14] are examples. Although these procedures are an improvement, most of them suffer from disadvantages such as long reaction times, forceful reaction conditions, low selectivity, tedious workup, and use of toxic or expensive reagents.

Results and discussion

In continuation of our ongoing research program on the development of new methods for protecting the alcoholic hydroxyl group [11–17], we found that saccharin reacts with neat chlorosulfonic acid to give saccharin sulfonic acid (SaSA) (I) during an easy and clean reaction. The method needs no special workup procedure, because hydrochloric acid (HCl) gas is evolved from the reaction vessel immediately (Scheme 1).

On the basis of the structure of SaSA**,** we anticipated that this reagent would act as an efficient catalyst in reactions that need the use of acidic reagents to speed up. Therefore, we were interested in using SaSA for promoting trimethylsilylation (TMS) of alcohols with HMDS (Table 1, Scheme 2).

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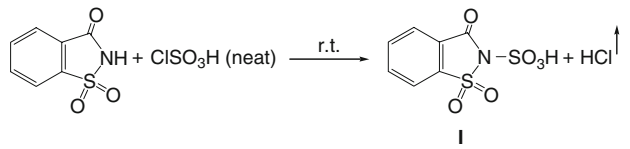


Scheme 1

A wide range of various alcohols, including benzylic, primary, secondary, and tertiary ones, underwent TMS with HMDS in the presence of catalytic amounts of SaSA at room temperature in good to high yields.

Primary benzylic alcohols (including electron releasing or withdrawing groups) and aliphatic alcohols were trimethylsilylated with excellent yields (Table 1, entries 1–15). The protection of benzylic, cyclic, and linear secondary alcohols were satisfactory subjected as well (Table 1, entries 16–21). Interestingly, 1-adamantanol, as a model of the hindered tertiary alcohols, was converted to the corresponding trimethylsilyl ether under the same reaction conditions (Table 1, entry 22). Because of the stability of amines and thiols under the selected reaction conditions (Table 1, entries 23, 24), the selective silylation of alcohols in the presence of the above-mentioned substrates was investigated (Table 1, entries 25, 26).

To illustrate the efficiency of the proposed method, Table 2 compares some of our results with some of those reported for the relevant reagents in the literature [9, 10, 14], which demonstrates its significant superiority.

In conclusion, SaSA, which can be easily prepared by the reaction of saccharin and neat chlorosulfonic acid, is efficiently able to catalyze the chemoselective trimethylsilylation of alcohols in the presence of amines and thiols. The short reaction times, reagent availability, high product yields, and easy workup are among the other advantages of this new method, which make this procedure a useful and attractive addition to the available methods. We are exploring further applications of SaSA for other types of functional group transformations.

Experimental

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical companies. IR spectra were recorded with a Shimadzu FT-IR 500 spectrophotometer using KBr pellets. Elemental analysis of SaSA was done with a GmbH VarioEL III analyzer and obtained results agreed favorably with calculated values. All of the trimethylsilyl ethers are known compounds and were characterized on the basis of their spectroscopic data (infrared and nuclear magnetic resonance), by comparison with those reported in literature [12, 18–21], and also by regeneration of the corresponding alcohols. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates.

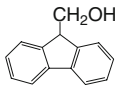
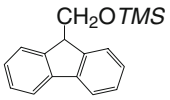
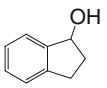
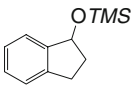
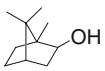
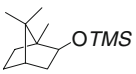
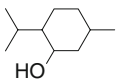
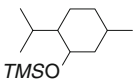
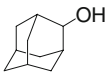
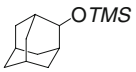
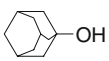
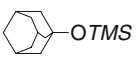
Saccharin sulfonic acid (SaSA, I, $C_7H_5NO_6S_2$)

A 500-cm^3 suction flask charged with 17.1 g saccharin (0.1 mol) was equipped with a constant pressure-dropping funnel containing 11.65 g chlorosulfonic acid (0.1 mol) and a gas inlet tube for conducting HCl gas over an adsorbing solution, i.e. water. Chlorosulfonic acid was added dropwise over a period of 10 min, and the reaction mixture was stirred slowly in an ice bath for 10 min. The mixture was then heated to room temperature and stirred for an additional 30 min. The mixture was triturated with 10 cm^3 *n*-hexane and filtered. The solid residue was

Table 1 Chemoselective trimethylsilylation (TMS) of alcohols

Entry	Substrate	Product	Time/min	Yield/%[a]
1	2-Cl–Ph–CH_2OH	2-Cl–Ph–CH_2OTMS	5	92
2	4-Cl–Ph–CH_2OH	4-Cl–Ph–CH_2OTMS	5	95
3	4-Br–Ph–CH_2OH	4-Br–Ph–CH_2OTMS	10	90
4	2-Br–Ph–CH_2OH	2-Br–Ph–CH_2OTMS	10	95
5	2-Me–Ph–CH_2OH	2-Me–Ph–CH_2OTMS	5	92
6	4-Me_3C–Ph–CH_2OH	4-Me_3C–Ph–CH_2OTMS	5	90
7	3-NO_2–Ph–CH_2OH	3-NO_2–Ph–CH_2OTMS	15	95
8	2-NO_2–Ph–CH_2OH	2-NO_2–Ph–CH_2OTMS	15	87
9	3-MeO–Ph–CH_2OH	3-MeO–Ph–CH_2OTMS	10	90
10	3-$PhCH_2O$–Ph–CH_2OH	3-$PhCH_2O$–Ph–CH_2OTMS	20	85
11	3,4-Cl_2Ph–CH_2OH	3,4-Cl_2Ph–CH_2OTMS	5	94

Table 1 continued

Entry	Substrate	Product	Time/min	Yield/%[a]
12			10	89
13	Ph–CH_2CH_2OH	Ph–CH_2CH_2OTMS	10	95
14	Ph–$CH_2CH_2CH_2OH$	Ph–$CH_2CH_2CH_2OTMS$	10	92
15	Ph–CH(Me)CH_2OH	Ph–CH(Me)CH_2OTMS	10	90
16	Ph–CH(OH)–Ph	Ph–CH(*OTMS*)–Ph	10	92
17	4-Cl–Ph–CH(OH)–Ph	4-Cl–Ph–CH(*OTMS*)Ph	5	90
18			10	80
19			30	90
20			35	92
21			20	87
22			20	90
23	4-Me–Ph–NH_2	4-Me–Ph–NH*TMS*	10	0
24	4-Br–Ph–SH	4-Br–Ph–S*TMS*	10	0
25	4-Cl–Ph–CH_2OH	4-Cl–Ph–CH_2OTMS	10	95
	+	+		+
	4-Br–Ph–SH	4-Br–Ph–*STMS*		0
26	2-Cl–Ph–CH_2OH	2-Cl–Ph–CH_2OTMS	10	92
	+	+		+
	4-Me–Ph–NH_2	4-Me–Ph–NH*TMS*		0

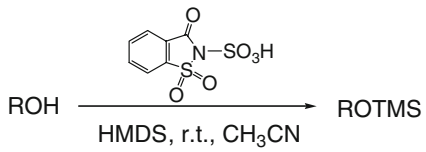
Products were identified spectroscopically and also by the conversion of the silyl ethers to the parent alcohols

[a] Isolated yield

washed with 10 cm^3 *n*-hexane and dried under vacuum. Saccharin sulfonic acid was obtained as a white solid (22.59 g, 90%), which was stored in a capped bottle. M.p.: 110–112 °C; FTIR: $\bar{\nu} = 3,100$, 2,976, 1,726, 1,593, 1,462, 1,340, 1,292, 1,180, 1,130, 1,068, 1,007, 885, 853, 760, 706, 584, 519, 455 cm^{-1}.

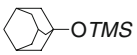
General procedure

To a solution of 1 mmol substrate and 25 mg SaSA (0.1 mmol) in 3 cm^3 CH_3CN, 120 mg HMDS (0.75 mmol) were added dropwise within 5 min, with stirring at room temperature. After completion of the reaction (TLC), the



Scheme 2

Table 2 Comparison of some of the results obtained by the silylation of alcohols with hexamethyldisilazane (HMDS) in the presence of saccharin sulfonic acid (SaSA) (**I**) with some of those reported by trichloroisocyanuric acid (**II**) [9], sulfonic acid-functionalized silica (**III**) [10], and $Fe(HSO_4)_3$ (**IV**) [14]

Entry	Product	Time/min/yield/%			
		I	**II**	**III**	**IV**
1	2-NO_2–Ph–CH_2O*TMS*	15/95		360/90	30/85
2	Ph–CH(O*TMS*)–Ph	10/92	180/95	60/98	50/75
3	Ph–CH_2CH_2O*TMS*	10/95	180/90	40/100	
4		20/90	720/95	240/85	150/70

solvent was evaporated, and 5 cm^3 *n*-hexane was added. The mixture was filtered through a silica-gel pad and filter cake was washed with 5 cm^3 *n*-hexane. Evaporation of the solvent gave almost pure product(s). Further purification proceeded by bulb to bulb distillation under reduced pressure or recrystallization to afford pure silyl ether.

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