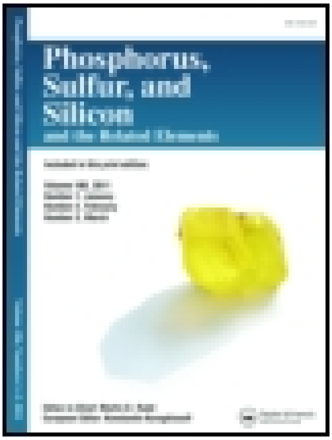

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Silica Triflate as an Efficient Reagent for the Chemoselective Formylation of Alcohols

Farhad Shirini [a] , Katayoun Marjani [b] , Hossein Taherpour Nahzomi [a c] & Mohammad Ali Zolfigol [d]
[a] Department of Chemistry , Guilan University , Rasht, Iran
[b] College of Chemistry , Teacher Training University , Tehran, Iran
[c] Teacher Training University , Iran
[d] Department of Chemistry , Bu-Ali Sina University , Hamadan, Iran

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Farhad Shirini
Department of Chemistry, Guilan University, Rasht, Iran

Katayoun Marjani
College of Chemistry, Teacher Training University, Tehran, Iran

Hossein Taherpour Nahzomi
Department of Chemistry, Guilan University, Rasht, Iran; and
Teacher Training University, Iran

Mohammad Ali Zolfigol
Department of Chemistry, Bu-Ali Sina University, Hamadan, Iran

Silica triflate, as a new and stable silica-based reagent, is prepared by a reaction of silica gel with trifluoromethane sulfonyl chloride at room temperature. This reagent can be used for the efficient and selective formylation of alcohols in the presence of phenols in a relatively short reaction time and high yields under heterogeneous reaction conditions.

Keywords Formylation; heterogeneous reaction conditions; silica triflate; silica gel; trifluoromethane sulfonyl chloride

Because of the importance of formate esters as useful synthetic reagents and intermediates,[1] formylation of the hydroxyl group is considered one of the most widely used transformations in organic chemistry.[2,3] Despite these uses and considerable potential, the formyl protecting group has been rather overlooked. This is partly due to the fact that efficient formylation procedures under mild conditions are not available. The direct esterification of alcohols with carboxylic acids

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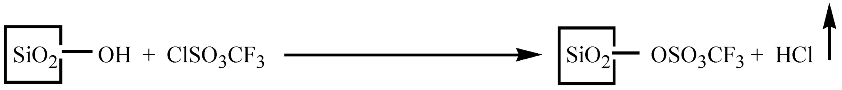
Address correspondence to Farhad Shirini, Department of Chemistry, Guilan University, Rasht, Guilan, 41335-1914, Iran. E-mail: shirini@guilan.ac.ir

is a reversible process that needs to eliminate water from the reaction mixture to drive the process to completion; thus the method is generally avoided. The acid halide or anhydride procedure is unsuitable for formylation because formyl halides and anhydride are unstable. Several formylation procedures have been reported over the years. These are based on formylation with formic acid in the presence of a dehydrating agent (Ac_2O,[4] DCC,[5] and 1,1'-oxalyldiimidazole[6]), transesterification with methyl/ethyl formate (catalyzed by silica-gel supported metal sulphate)[7] $Ce(OTf)_4$,[8] $Cu(NO_3)_2.3H_2O$,[9] PPh_3/CBr_4,[10] $KCoW_{12}O_{40}.3H_2O$,[11] TMSOTf,[12] $Cu(OTf)_2$,[13] $Sc(OTf)_3$,[14] $In(OTf)_3$,[15] $Bi(OTf)_3$,[16] Chloral,[17] $Al(HSO_4)_3$,[18] and $Mg(HSO_4)_2$.[19] Most of these methods, however, use uncommon and in some cases moisture sensitive or thermally unstable reagents that need to be prepared before use, in some cases, by multistep procedures employimg expensive catalysts. Many of these methods also suffer from some of the following limitations: elevated temperatures, long reaction times, inert atmosphere, separation of the spent or deformylated reagent, acidic reaction conditions or work-up, side reactions, and moderate yields.

In recent years our research group, as many others, focused on the development of the application of silica gel and its new derivatives in organic chemistry. Along these studies we have reported that these reagents are able to be used efficiently in many organic reactions.[20] In continuation of these studies we have found that trifluoromethane sulfonyl chloride reacts with silica gel, in an easy, clean, and immediate reaction, to give silica triflate (**I**) and HCl gas as the only products (Scheme 1).



(I)

SCHEME 1

We anticipated that silica triflate, as a new triflate derivative, would be able to accelerate the formylation of alcohols as the other reported triflates[14,15] (Scheme 2).

A variety of alcohols including primary, secondary, tertiary, and benzylic ones were converted to their formate esters in a single step by mixing the alcohol, formic acid, and silica triflate in refluxing hexane in good to high yields (Table I). The formylation of allylic alcohols was not clean and gave a complex mixture of products along with the unreacted

$$\mathrm{ROH} \xrightarrow[\text{Hexane, reflux.}]{\mathrm{HCO_2H}\ /\ \text{silica triflate}} \mathrm{ROCHO}$$

SCHEME 2

alcohol, so this method is not suitable for the formylation of these kinds of alcohols (Table I). Phenols remained unreacted under these conditions, indicating that the reaction could be selective for the formylation of alcohols in the presence of phenols. The selectivity was demonstrated by competitive reactions, in which equimolar mixtures of an alcohol and a phenol were subjected to formylation, whereby the alcohols were completely formylated and the phenols were mostly recovered unchanged (Table II).

We have found that silica triflate is a reusable catalyst, and even after five runs for the formylation of alcohols, the catalytic activity of the reagent was almost the same as the freshly used catalyst. The stability of the composition of the reagent was demonstrated by its IR spectra, which were the same before and after the reactions.

It should be noted that the formylation reaction did not proceed using silica gel and trifluoromethane sulfonyl chloride alone or by the separate addition of these reagents to the reaction mixture (Table 1). These results indicate that SiOTf is the reagent responsible for the catalytic activity observed.

In order to show the efficiency of the present method, Table III compares some of the results with some of those reported in the literature.[11,19]

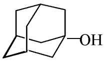
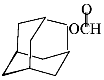
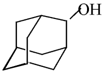
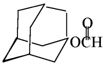
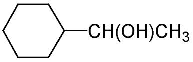
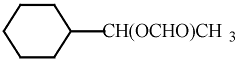
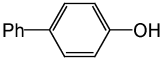
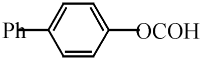
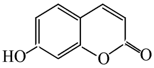
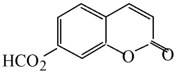
In conclusion this article reports the synthesis of a new triflate derivative based on silica gel and its applications in the efficient formylation of alcohols. Mild reaction conditions, simplicity of the procedure, short reaction times, good to high yields of the products, heterogeneous reaction conditions, and general applicability for primary through tertiary alcohols make this method a useful addition to the existing methodologies. Work on the effect of silica triflate on other types of organic reactions is currently ongoing in our laboratory.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck (Darmstadt, Germany), and Aldrich Chemical Companies. Products were characterized by their

TABLE I Formylation of Alcohols[a]

Substrate	Product	Substrate (mmol): Catalyst (mg) [b]	Time (min)	Yield[c] (%)
2-$ClC_6H_4CH_2OH$	2-$ClC_6H_4CH_2OCOH$	1:60	10	95
4-$ClC_6H_4CH_2OH$	4-$ClC_6H_4CH_2OCOH$	1:60	10	90
4-$BrC_6H_4CH_2OH$	4-$BrC_6H_4CH_2OCOH$	1:120	8	92
2-$NO_2C_6H_4CH_2OH$	2-$NO_2C_6H_4CH_2OCOH$	1:120	60	80
3-$NO_2C_6H_4CH_2OH$	3-$NO_2C_6H_4CH_2OCOH$	1:120	60	85
4-$NO_2C_6H_4CH_2OH$	4-$NO_2C_6H_4CH_2OCOH$	1:120	60	80
2-Pyridyl methanol	2-Pyridyl methyl formate	1:60	5	90
3-Pyridyl methanol	3-Pyridyl methyl formate	1:60	4	93
$C_6H_5CH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2CH_2OCOH$	1:60	10	95
$C_6H_5CH(CH_3)CH_2OH$	$C_6H_5CH(CH_3)CH_2OCOH$	1:60	12	90
$C_6H_5CH_2CH(OH)CH_3$	$C_6H_5CH_2CH(OCOH)CH_3$	1:60	11	95
		1:90	8	90
		1:90	11	87
		1:90	5	90
(-)-Menthol	(-)-Menthyl formate	1:90	8	95
$(CH_3)_3COH$	$(CH_3)_3COCOH$	1:90	3	90
$C_6H_5CH{=}CHCH_2OH$	$C_6H_5CH{=}CHCH_2OCOH$	1:120	20	—[d]
C_6H_5OH	C_6H_5OCOH	1:60	30	0[e]
		1:60	40	0[e]
2-Naphthol	2-Naphthyl formate	1:60	15	0[e]
		1:60	20	0[e]
4-$ClC_6H_4CH_2OH$	4-$ClC_6H_4CH_2OCOH$	1:60	15	0[e,f]
2-$NO_2C_6H_4CH_2OH$	2-$NO_2C_6H_4CH_2OCOH$	1:60	15	0[e,g]
$C_6H_5CH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2CH_2OCOH$	1:60	15	0[e,h]

[a] Products were characterized by their physical constants, in comparison with authentic samples and IR and NMR spectroscopy.

[b] Reaction is performed in the presence of 1.2 mmol of formic acid.

[c] Isolated yield.

[d] Mixture of products.

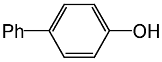
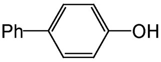
[e] The starting material was recovered intact.

[f] Reaction was performed in the presence of silica gel.

[g] Reaction was performed in the presence of trifluoromethane sulfonyl chloride.

[h] Reaction was performed in the presence of a mixture of trifluoromethane sulfonyl chloride and silica gel.

TABLE II Competitive Formylation of Alcohols and Phenols

Substrates	Phenol:Alcohol:Cat. (mg)[a]	Time (min)	Yield (%)[b]
 + 4-$ClC_6H_4CH_2$ OH	1:1:60	10	0 + 90
 + $C_6H_5CH_2CH_2CH_2$ OH	1:1:150	10	0 + 95
C_6H_5OH + 4-$ClC_6H_4CH_2$ OH	1:1:60	10	0 + 90
C_6H_5OH + $C_6H_5CH_2CH_2CH_2$ OH	1:1:60	10	0 + 92

[a] Reaction is performed in the presence of 1.2 mmol of formic acid.
[b] Isolated yield.

physical constants, comparison with authentic samples, and IR and NMR spectroscopy.

Preparation of Silica Triflate

A 500-mL suction flask, charged with 18.0 g silica gel (type 60, 15–40 μm), was equipped with a constant pressure-dropping funnel containing trifluoromet-hane sulfonyl chloride (8.426 g, 0.05 mol) and a gas inlet tube for conducting HCl gas over water. Trifluoromethane sulfonyl chloride was added dropwise over a period of 30 min with slow

TABLE III Comparison of Some of the Results Obtained by the Formylation of Alcohols Using Formic Acid in the Presence of Silica Triflate, with Some of Those Reported for $KCoW_{12}O_{40}.3H_2O$[11] and $Mg(HSO_4)_2$[19]

	Time (min)/Yield (%)		
Substrate	Silica Triflate	$KCoW_{12}O_{40}.3H_2O$	$Mg(HSO_4)_2$
(-)-Menthol	8/92	60/81	—
4-$ClC_6H_4CH_2$ OH	10/95	45/97	480/85
$C_6H_5CH_2CH_2CH_2$ OH	10/95	30/94	60/80

stirring at r.t. Gas was evolved from the reaction vessel immediately. After the addition was complete, the mixture was shaken for 30 min. The reaction mixture was washed with 50 mL of dry CH_2Cl_2 and dried under vacuum. Silica triflate was obtained as a white solid (20.4–20.6 g), which was stored in a capped bottle. In order to determine the amount of active triflate content of the reagent, the produced HCl from the previously discussed reaction was titrated with 0.1 M aq NaOH. The results from several runs showed the formation of 0.018–0.020 mol of HCl; therefore, the amount of active triflate was determined to be 1 mmol per 1.04–1.08 g silica triflate; IR (KBr): 1255, 1230 ($\upsilon_{S=O}$), 1130, 1010 (υ_{C-F}), 955, 820, 650, 530, 500 cm^{-1}.

General Procedure

A mixture of alcohol (1 mmol), formic acid (0.055 g, 1.2 mmol), and silica triflate (0.06–0.12 g) in hexane (4 mL) was heated at reflux. The progress of the reaction was monitored by GC or TLC. After completion of the reaction, the mixture was filtered, and the solid residue was washed with *n*-hexane (3 mL). The solvent was removed under reduced pressure. Water (20 mL) was added to the residue, and the product was extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (2×10 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave almost pure products (Table I). Further purification was carried out by column chromatography on silica gel to afford pure formate.

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