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Potassium phosphate or silica sulfuric acid catalyzed conjugate addition of thiols to α,β-unsaturated ketones at room temperature under solvent-free conditions

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Abstract—Potassium phosphate and silica sulfuric acid have been found to be useful and highly efficient catalysts for conjugate addition of thiols to α,β-unsaturated ketones under solvent-free conditions, at room temperature. Silica sulfuric acid (SSA) was found to be suitable for electron-deficient enones while potassium phosphate was found to effect thia-Michael addition with both, electron-deficient as well as electron-rich conjugated ketones.

Conjugate addition of thiols to α,β-unsaturated ketones to form a carbon–sulfur bond constitutes a key reaction in biosynthetic processes as well as in organic synthesis.[1,2] It is known that the resultant β-sulfido carbonyl compounds serve as starting materials for the generation of β-acylvinyl cation equivalents[3] and homoenolate equivalents.[4] The reaction is also important to organic chemists as a protecting strategy for double bonds as the olefin can be very easily regenerated by the removal of the sulfur moiety through Cu(I)-induced elimination or by oxidative elimiation.[5,6] Consequently, a large number of methods have been reported for 1,4-conjugate addition of thiols to electron-deficient olefins.[7] The reaction has been investigated using Lewis acids such as $Hf(OTf)_3$,[8a] $Bi(OTf)_3$,[8b] $Cu(BF_4)_2$,[8c] $InBr_3$,[8d] $Bi(NO_3)_3$,[8e] I_2.[8f] Quite recently, bis(trifluoromethansulfon)imide[9a] and Nafion SAC-13[9b] have been reported as efficient Bronsted acids and $H_3PW_{12}O_{40}$[9c] as a heteropoly acid catalyst for this reaction. In addition, ionic liquids like $(Bmim)PF_6/H_2O$[10a] and molten tetrabutylammonium bromide[10b] have been employed as efficient catalysts-reaction media in the thia-Michael addition reaction. However, the use of toxic and expensive metal precursors limit the use of Lewis acids as catalysts, while those involving the use of Bronsted acids or basic catalysts need an aqueous work-up for the separation of catalysts. Furthermore, in many cases, yields as well as selectivities are far from satisfactory due to side reactions.[11] Thus, the development of a simple but highly efficient method for the thia-Michael addition reaction is desirable. Herein, we report the use of potassium phosphate as well as silica sulfuric acid as highly useful catalysts for the addition of thiols to α,β-unsaturated ketones, at room temperature, under solvent-free conditions.

In the last few years, the use of silica sulfuric acid (SSA)[12] as a reusable, heterogeneous, solid Bronsted acid catalyst has received much attention.[13–17] From our laboratory, we have investigated SSA catalyzed, chemoselective tetrahydropyranylation of alcohols over phenols,[18a] chemoselective dithioacetalization of aldehydes over ketones,[18b] chemoselective conversion of aldehydes to acylals[18c] as well as the synthesis of α-aminonitriles.[18d] These earlier studies with SSA prompted us to test the efficacy of silica sulfuric acid in the conjugate addition of thiols to α,β-unsaturated ketones.

Cyclohexenone and thiophenol were chosen as a model enone and thiol. The reaction of an equimolar (2 mmol, each) mixture of cyclohexenone and thiophenol in the

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Keywords: Michael addition; Chalcones; Conjugated enones; Silica sulfuric acid; Potassium phosphate; Thiols; α,β-Unsaturated ketones.

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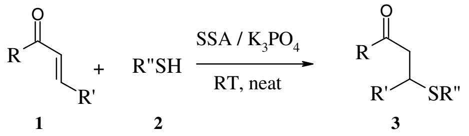
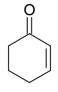
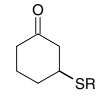
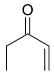
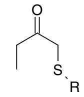
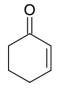
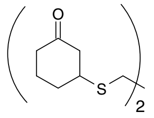
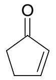
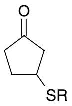
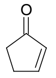
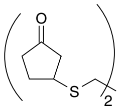
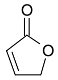
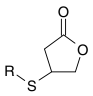


Scheme 1.

presence of silica sulfuric acid (0.2 g, 25 mol %) proceeded via an exothermic reaction and afforded the corresponding 1,4-addition product (TLC) in an 89% yield, in a very short time, (10 min) at room temperature, in the absence of an organic solvent (Scheme 1).

Encouraged by this initial success, the reactions were then performed between a variety of α,β-unsaturated cyclic as well as acyclic ketones with different thiols under solvent-free conditions, at room temperature. The results summarized in Table 1 highlight the general applicability of this reaction. It was noticed that the reactions of thiols with enones such as cyclohexenone, cyclopentenone and ethyl vinyl ketone yielded the desired thia-Michael addition products rapidly (10–25 min) and in an excellent yields (73–96%). In addition, the reaction between cyclohexenone and ethane-1,2-dithiol yielded the double Michael addition product in excellent yield (91%). However, when the reaction was extended towards chalcones, the expected thia-Michael addition products were obtained in very poor yields (15–20%) and attempts to increase the yields by increasing the amount of catalyst, time as well as temperature of the reaction mixture were unsuccessful. Thus, the conjugate addition of thiols to enones must been governed by electronic as well as steric effects. Certainly, due to steric hindrance as well as the π-resonance effect of phenyl groups, chalcones become less electrophilic

Table 1. Potassium phosphate/silica sulfuric acid (SSA)-catalyzed Michael addition of thiols to α,β-unsaturated ketones

Entry	Enone	Thiol	Product[a]		Time (min)		Yield[b] (%)	
	1	**2**	**3**		SSA	K$_3$PO$_4$	SSA	K$_3$PO$_4$
A	 **1a**	**2a**		**3aa**	10	30	89	85
		2b		**3ab**	10	—	94	—
		2c		**3ac**	20	25	94	81
		2d		**3ad**	10	39	95	90
		2e		**3ae**	15	25	93	90
		2f		**3af**	15	—	73	—
B	 **1b**	**2a**		**3ba**	15	60	93	95
		2b		**3bb**	15	—	95	—
		2c		**3bc**	15	35	86	95
		2d		**3bd**	25	30	94	98
		2e		**3be**	30	40	90	95
		2f		**3bf**	15	—	91	95
C	 **1a**	**2g**		**3ag**	10	55	91	84
D	 **1d**	**2a**		**3da**	NP	25	—	89
E	 **1d**	**2g**		**3dg**	NP	30	—	72
F	 **1e**	**2d**		**3ed**	70	30	26	79

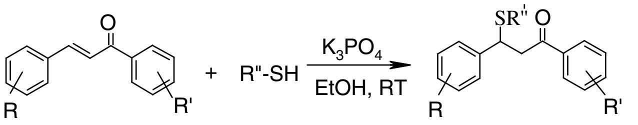
2a: thiophenol; **2b**: *p*-methylthiophenol; **2c**: *p*-chlorothiophenol; **2d**: benzylthiol; **2e**: *n*-butanethiol; **2f**: cyclohexylthiol; **2g**: ethane-1,2-dithiol.

[a] All products showed satisfactory spectroscopic data. (IR, ^{1}H NMR).

[b] Yields refer to pure, isolated products.

and make the conjugate addition difficult. From these observations, it was concluded that though silica sulfuric acid was an efficient solid acid catalyst for thia-Michael addition to electron-deficient and sterically unhindered conjugated enones, it was unsuitable as a catalyst for sterically hindered conjugated enones. This led us to the development of an alternative and more general protocol for the Michael addition of thiols to chalcones using an inexpensive, highly efficient and easy to handle catalyst.

From a mechanistic viewpoint, for the successful conjugate addition of thiols to chalcones, it is essential that C_β be sufficiently electrophilic. It is known that the use of a metal salt as catalyst allows the metal ion to form a strong coordinate bond with the carbonyl oxygen and thereby makes C_β sufficiently electrophilic to assist the thia-Michael addition (Scheme 2). Furthermore, for a strong coordinate bond, the metal ion must be sufficiently oxophilic which is the case if the counter anion of the metal salt is highly electron-withdrawing. In line with these requirements, Chakraborti et al.[19] have demonstrated the usefulness of triflates as well as perchlorates of group I and II elements as efficient catalysts for the conjugate addition of thiols to chalcones. With this in mind, it was surmised that the easily available, inexpensive, nontoxic, potassium phosphate[20] might serve as an efficient catalyst in the thia-Michael addition reaction. This is because (i) potassium phosphate has a strong electron-withdrawing counter anion, namely PO_4^{3-} to make the K^+ ion oxophilic enough to form a strong coordinate bond with the oxygen atom of the enone and thereby make C_β sufficiently electrophilic, and (ii) potassium phosphate is basic enough to deprotonate thiols having pK_a values in the range 7–11[21] to convert them to their conjugate bases and assist the thia-Michael addition. Thus, we evaluated the catalytic efficiency of potassium phosphate in the thia-Michael addition reaction.



4 **5** **6**

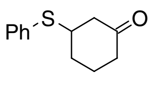
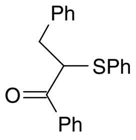
Scheme 2.

trans-1,3-Diphenylpropenone **4a** and thiophenol were selected as model substrates and ethanol as the solvent. To a stirred solution of **4a** (2 mmol) and thiophenol (2 mmol) in ethanol (5 mL) was added potassium phosphate (0.05 g, 25 mol %). An exothermic reaction took place which was completed in 10 min at room temperature and furnished the desired thia-Michael addition product **6a** (91%), as characterized by comparison of the mp and the spectral data with that reported.[22] The generality of the protocol was investigated by reacting a variety of chalcones possessing electron-donating as well as electron-withdrawing groups with various thiols to furnish the corresponding thia-Michael addition product (Scheme 1) in acceptable yields (78–98%). The results are summarized in Table 2. As expected, the reaction between thiols as well as dithiol with enones such as cyclohexenone, cyclopentenone and ethyl vinyl ketone also yielded the corresponding Michael addition products in excellent yields (Table 1). It is interesting to note that there was no formation of a disulfide as a side

Table 2. Potassium phosphate-catalyzed Michael addition of thiols to chalcones

Entry	R	R′	R″	Time (min)	Yield (%)
a	H	H	Ph	10	91
b	H	H	*n*-Bu	15	80
c	Cl	H	*n*-Bu	10	96
d	Cl	H	4-Cl C_6H_4	5	96
e	Cl	H	Ph	5	91
f	F	H	$PhCH_2$	10	78
g	F	OMe	4-Cl C_6H_4	8	93
h	F	H	Ph	10	84
i	Cl	CH_3	4-Cl C_6H_4	8	98
j	Cl	CH_3	*n*-Bu	15	82
k	F	H	4-Cl C_6H_4	10	84
l	F	H	*n*-Bu	20	92

Table 3. Comparison of the catalytic efficacy of SSA/K_3PO_4 with other catalysts

Entry	Product	Cat. (mol %)	Solvent	Time (h)	Yield (%)	Ref.
1		$InBr_3$ (10)	CH_2Cl_2	24	74	8d
2		$Bi(NO_3)_3$ (15)	CH_2Cl_2	4	65	8e
3		$Bi(OTf)_3$ (5)	CH_3CN	1.5	72	8b
4		$Zn(ClO_4)_2$ (1)	Neat	5[a]	90	19
5		$H_3PW_{12}O_{40}$ (1)	Neat	5[a]	95	9c
6		(Bmim)PF_6	(Bmim)PF_6	10[a]	95	10a
7		$(Bu)_4N^+Br^-$	$(Bu)_4N^+Br^-$	30	92	10b
8		Iodine	Neat	3	97	8f
9		**SSA**	Neat	15	89	—
10		**K_3PO_4**	Neat	10	91	—
11		$Zn(ClO_4)_2$	Neat	1.5	87	19
12		(Bmim)PF_6	(Bmim)PF_6	15	95	10a
13		$InCl_3$	EtOH	1	95	22
14		**SSA**	C_2H_5OH	24	15	—
15		**K_3PO_4**	C_2H_5OH	25[a]	91	—

[a] Time in minutes.

product even though potassium phosphate catalyzed oxidative coupling of thiols to disulfides has already been reported.[21]

When the catalytic efficiency of potassium phosphate was compared with other reported catalysts (Table 3), it was revealed that potassium phosphate is better suited for this reaction for the reasons of low cost, ease of availability, yields, reaction temperature as well as work-up procedure. In all cases, on completion of the reaction, chloroform was added, the catalyst was filtered, washed with chloroform and the solvent was removed to yield the almost pure thia-Michael addition product.[24]

In summary, we have described herein the usefulness of silica sulfuric acid as well as potassium phosphate as highly efficient and cost effective catalysts for the thia-Michael addition reaction under solvent-free conditions, (except chalcones) at room temperature. Short reaction times, high yields, and avoidance of anhydrous conditions should make this protocol a useful alternative to existing methods.

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24. *General procedure*: A mixture of α,β-unsaturated ketone (2 mmol), thiol (2 mmol) and SSA (0.2 g, 25 mol %)/K_3PO_4 (0.05 g, 25 mol %) was stirred at room temperature for the appropriate time (Table 1 or 2). On completion of the reaction (TLC), chloroform (20 mL) was added and the reaction mixture was filtered. The catalyst was washed with chloroform (2 × 10 mL). Evaporation of the solvent followed by short column chromatography over silica gel (petroleum ether/ethyl acetate, 95:5, v/v) afforded pure thia-Michael adducts, which were characterized by spectral methods.

    Spectral data: 4-[benzylthio]-dihydrofuran-2[3*H*]-one[23] (**3ed**, Table 1): IR (neat): 2924, 1789 1602, 794, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.4 (1H, AB q, $J = 18$ Hz, 7 Hz), 2.73 (1H, AB q, $J = 18$ Hz, 7 Hz), 3.45 (1H, q, $J = 7$ Hz), 3.79 (2H, s), 4.04 (1H, AB q, $J = 10$ Hz, 7 Hz), 4.36 (1H, AB q, $J = 10$ Hz, 7 Hz), 7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 35.35, 36.05, 37.95, 72.93, 127.57, 128.63, 128.80, 137.31, 174.91.