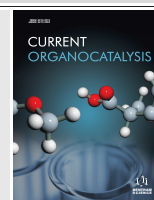




A Versatile Method for the Protection of Carbonyl Compounds by Camphor Sulfonic Acid



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Abstract: Background: Carbonyl groups are important functional groups and they play a key role in organic chemistry. This group needs to be protected in multistep synthesis against various reagents for a counter-reaction. The effort towards developing an efficient methodology for the protection of carbonyl functional group is always a demanding reaction. The protection of carbonyl compounds for inhibiting their chemical reactivity is an important operation in chemistry. In this paper, camphor sulfonic acid-catalysed protection of various carbonyl compounds is developed. This method is simple, environmentally friendly and yields products in high yields.

Method: Commercially available camphor sulfonic acid is used as organo-catalyst for the protection of carbonyl functionality. This catalyst is also employed for the protection of carbonyl functionality as thioacetal/mixed ketal in excellent yield. The newly synthesized compounds are characterized using ¹H NMR, ¹³C NMR and IR spectroscopy.

Result: A diverse carbonyl functional group is protected in excellent yield under mild reaction conditions.

Conclusion: We have developed an efficient organocatalysed protection method of carbonyl functionality applicable to wide range of substrates.

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1. INTRODUCTION

The chemistry of carbonyl group is very fascinating because it reacts with a wide range of reagents with or without any activation. To develop an effective synthesis, protection of carbonyl group is required in some examples. Therefore, methods are developed for the protection of carbonyl compounds and various protective groups can be used [1]. Acetal, 1-3-dioxalane, mixed ketal and thioketal are the widely used protective groups. Aldehydes and ketones are the most common groups that are protected by these methods. Importantly, these protective groups can also be removed to regenerate the original starting compounds. In many examples, the protected compounds are used as the key intermediates for the synthesis of natural products [2].

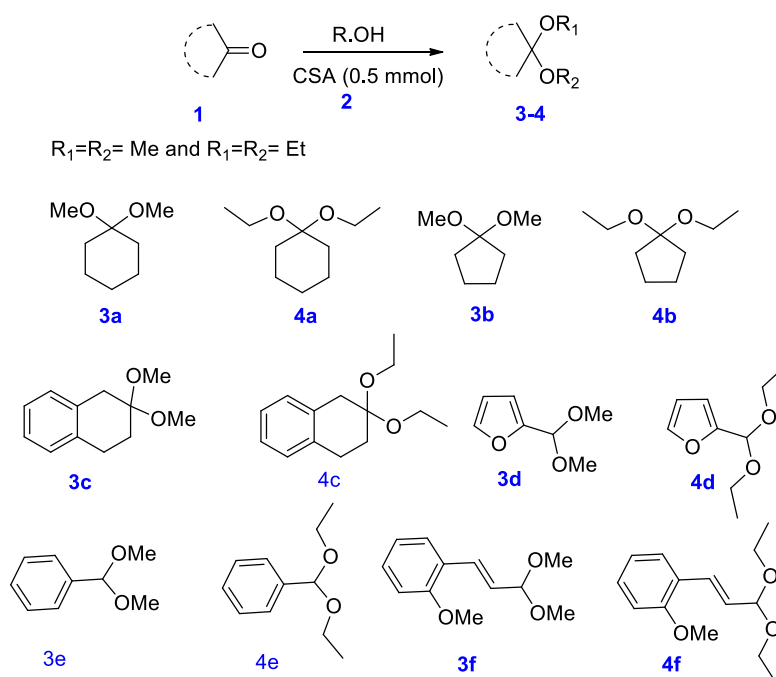
Protection of carbonyl compounds requires acidic catalysts in most of the instances. An efficient and general method for the protection of carbonyl groups is required. There are some limitations of the available methods. For example,

some conditions require high temperature with stoichiometric or excess reagents and moreover many of the methods are not applicable to all protective groups: acetal, ketal, thioketal or mixed ketal. A particular reagent can be extremely good for the preparation of acetal, this may not be suitable for ketal formation. Considering the importance of the protective group chemistry, catalytic version has developed. Our group reported a new iodine-catalyzed acetalization and thioketalization method of aldehydes and ketones with outstanding chemoselectivity. During the course of the investigation, we have developed a simple, mild and economically feasible camphor sulfonic acid-catalysed protection of carbonyl compounds as acetal, ketal, thioketal and mixed ketal.

2. RESULTS AND DISCUSSIONS

The acetal and ketals are prepared in the presence of acids using trialkyl orthoformate or alcohol [3]. A few methods are developed that do not require acid-catalysts. Some reactions under mildly acidic conditions are also developed. Some selective ketalization of carbonyl compounds is performed with lanthanides and metal-catalysts. However, many of these methods are nonselective. In contrast, lanthanides work well with specific molecules and this method is not general.

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Scheme 1. Camphor sulphonic acid mediated protection of carbonyl compounds.

Table 1. Acetal synthesis catalyzed by camphor sulphonic acid.

Entry	Acetal/Ketal	R ₁ /R ₂	R ₁ /R ₂	Catalyst	Time (h)	Yield (%) ^a
1	3a	4a	Me/Me	Et/Et	0.5 mol% 0.6mol%	1 2 70(3a) 75(4a)
2	3b	4b	Me/Me	Et/Et	0.5 mol% 0.6mol%	1,5 2 75(3b) 80(4b)
3	3c	4c	Me/Me	Et/Et	0.5 mol% 0.6mol%	2 3 80(3c) 75(4c)
4	3d	4d	Me/Me	Et/Et	0.5 mol% 0.6mol%	3 4 75(3d) 70(4d)
5	3e	4e	Me/Me	Et/Et	0.5 mol% 0.6mol%	1 2 80(3e) 70(4e)
6	3f	4f	Me/Me	Et/Et	0.5 mol% 0.6mol%	2 3 75(3f) 75(4f)

a: crude yield and characterized by NMR spectroscopy.

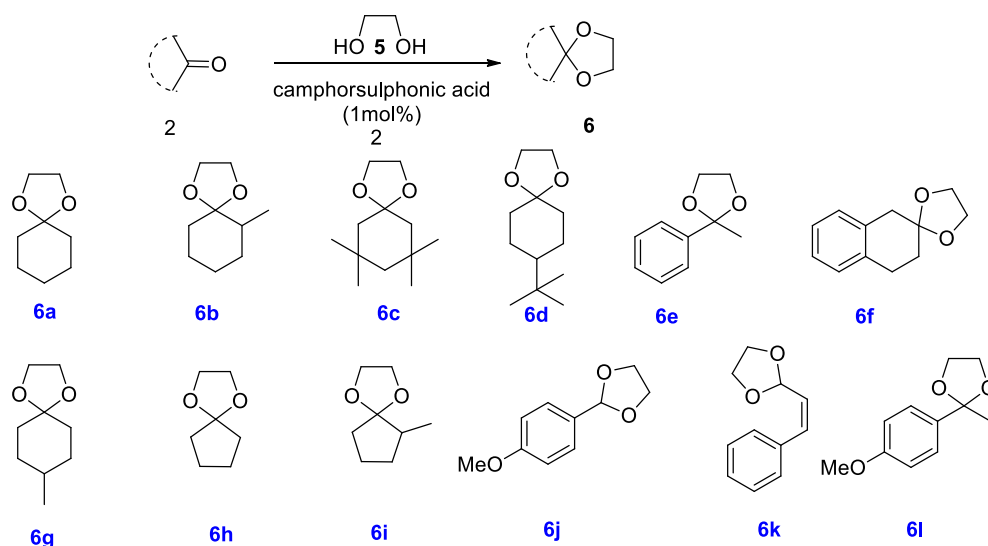
For this reason, generally mild and effective method is necessary. Methods that can overcome the limitations of lanthanides and acid catalysis are desirable. Bismuth salts as environmentally friendly reagents have been clearly established. A facile and convenient molecular iodine-catalyzed protection for various carbonyl compounds as ketals in high yield is reported. Aldehydes were protected as acetals by using catalytic amounts of iodine and methanol or ethanol.

The desired compounds were obtained in excellent yield; the rate of reaction was found to be extremely fast. We also found that camphor sulphonic acid is an excellent catalyst for the protection of carbonyl compounds (**1** to **3-4**) as catalyst (Scheme 1, Table 1). Different types of carbonyl compounds gave acetals by this method. In general, this method was fast, but reversible in nature.

Our method was tested for the preparation of 1,3-dioxalane derivatives (Scheme 2) and the data is shown in Table 2. The method proceeds equally well irrespective of the nature of the carbonyl compounds.

The protection of ketones, and aldehydes as thioketals was usually carried out in the presence of acids [4]. Many other methods were reported in the literature, such as magnesium or zinc triflates titanium tetrachloride, Nafion-H and lanthanum chloride. But, the chemoselectivity between these groups was reported with, Amberlyst-15 catalyst, silica gel-thionyl chloride, indium trichloride and ceric ammonium nitrate. Long reaction time, reflux temperature, unwanted side reactions and non-selectivity were some of the limitations of acid-catalyzed thioketalization of carbonyl compounds.

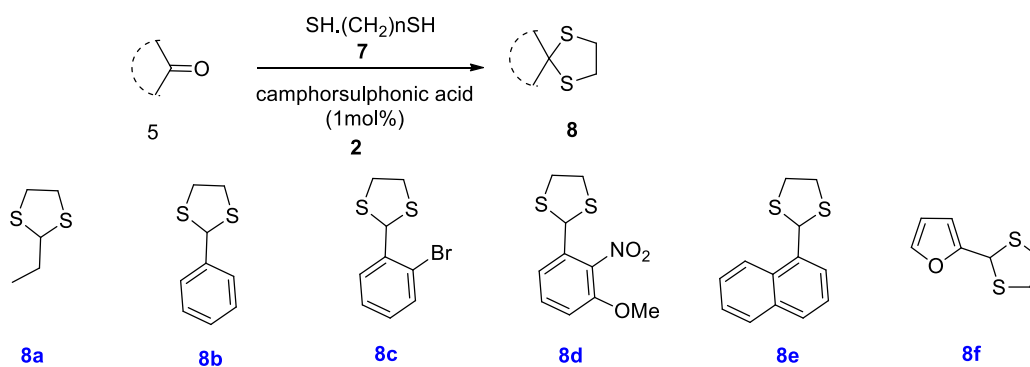
We discovered that the thioketalization of numerous carbonyl compounds can be performed with camphor sulphonic acid as catalysts in high yields (**5** to **8**). Toward the goal, several aromatic aldehydes on reaction with 1, 3-propane thiol and ethane thiol in the presence of camphor sulphonic acid (10 mol%) in dry THF as the solvent at room temperature (Scheme 3). Within a few hours, thioketal reaction was completed and the product was obtained in excellent yield



Scheme 2. Camphor sulphonic acid mediated protection of carbonyl compounds as cyclic acetal.

Table 2. Camphorsulphonic acid-catalyzed synthesis of cyclic ketal.

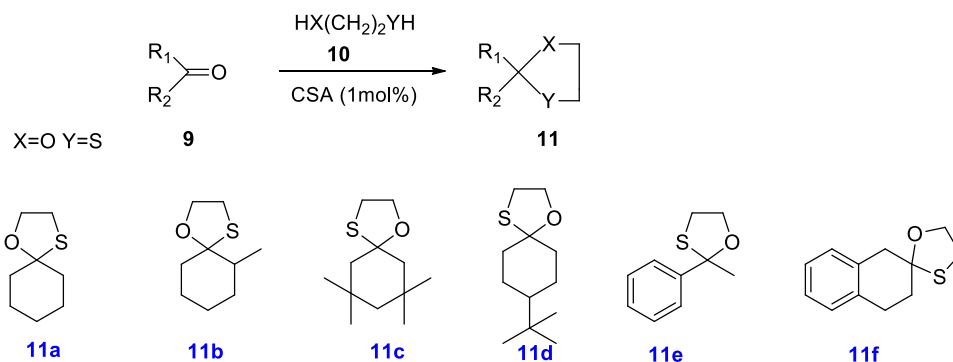
Entry	Carbonyl Compound(s)	Ketal/Acetal	Time (h)	Yield ^a
1	Cyclohexanone	6a	10	80%
2	1-Methyl-cyclohexanone	6b	12	75%
3	3,3,5,5-Tetramethyl-cyclohexanone	6c	15	70%
4	4-tertbutyl-cyclohexanone	6d	14	80%
5	Acetophenone	6e	13	90%
6	b-tetralone	6f	11	80%
7	4-Methyl-cyclohexanone	6g	12	75%
8	Cyclopentanone	6h	10	80%
9	1-Methyl-cyclopentanone	6i	12	70%
10	p-Methoxybenzaldehyde	6j	12	70%
11	Cinnamaldehyde	6k	10	75%
12	p-Methoxy-acetophenone	6l	12	80%



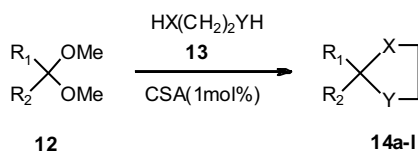
Scheme 3. Camphor sulphonic acid mediated protection of carbonyl compounds as cyclic thioacetal.

Table 3. Thioketalization with camphor sulfonic acid.

Entry	Carbonyl Compounds	Thiol(n)	Acetal	Time (h)	Yield
1	Propionaldehyde	2,3	8a	6	90%
2	Benzaldehyde	2,3	9b	7	86%
3	O-Bromobenzaldehyde	3	8c	6	80%
4	2-Nitro-3-Methoxybenzaldehyde	3	8d	6	90%
5	1-Naphthaldehyde	3	8e	6	70%
6	2-Furfuraldehyde	3	9f	6	80%

**Scheme 4.** Synthesis of mixed acetal/ketal.**Table 4.** Mixed ketal formation under camphor sulphonic acid.

Entry	Carbonyl Compound(s)	Mixed Ketal	Time (h)	Yield ^a
1	Cyclohexanone	11a	12	90%
2	1-Methyl-cyclohexanone	11b	12	75%
3	3,3,5,5-Tetramethyl-cyclohexanone	11c	14	70%
4	4-tertbutyl-cyclohexanone	11d	14	74%
5	Acetophenone	11e	10	80%
6	b-tetralone	11f	11	80%

**Scheme 5.**

(Table 3). This method was then applied for the protection of different ketones.

As an extension, preparation of mixed ketals was accomplished in good yield (**9** to **11**, Scheme 4). All types of carbonyl compounds were protected as mixed ketals (Table 4). However, this reaction requires longer reaction times.

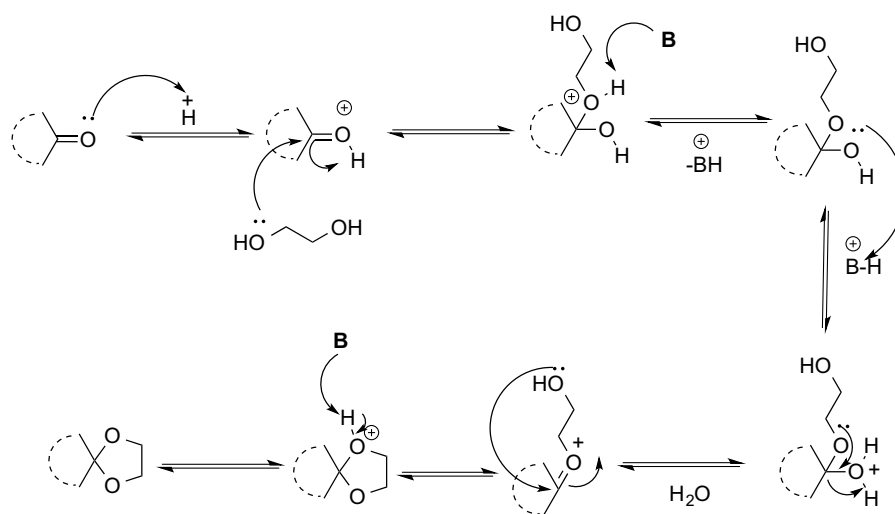
Since the present camphor sulfonic acid-catalyzed method was excellent, we performed transketalization reaction

with a few compounds. Transketalization is required in synthetic organic chemistry. This method required mixing acetals with ethane thiol or ethylene glycol in the presence of camphor sulfonic acid. Transketalization was completed within a few hours (Scheme 5, **12** to **14** and Table 5).

The mechanism of camphor sulfonic acid-catalyzed process was interesting (Scheme 6). A representative the example of ketal formation was shown here. The carbonyl compounds were protonated first and then a nucleophilic reaction by the oxygen of glycol was possible to form an intermediate in which the glycol unit was attached to the carbonyl group. The anion present in the medium acted as a base and removed the proton, further protonation, nucleophilic attack by the second hydroxyl group and deprotonation completed the cycle.

Table 5. Transketalization of carbonyl compounds.

R ₁	R ₂	14	X/Y=O	X/Y=S	X=O Y=S
H	Ph	14a-c	80	85	70
Ph	Ph	14d-f	70	70	75
2-Bromophenyl	H	14g-i	80	70	60
3-Bromophenyl	H	14j-l	75	70	65

**Scheme 6.** Mechanism for ketal formation with 1,2-diol.

CONCLUSION

The present Camphor sulfonic acid-catalyzed protection of carbonyl compounds groups is new and mild. This method can be applied to a wide range of substrates successfully. The yield of the protected products in most of the examples is excellent.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

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