Remarkable catalytic activity of silica nanoparticle in the bis-Michael addition of active methylene compounds to conjugated alkenes

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A R T I C L E   I N F O

A B S T R A C T

We have demonstrated the remarkable catalytic activity of silica nanoparticles (NPs) in the unusual bis-Michael addition of active methylene compounds to conjugated alkenes at room temperature. The catalyst silica NPs were reused up to seven runs without appreciable loss of catalytic activity.

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In recent years, nanoparticles (NPs) have attracted tremendous attention in catalysis because of their improved efficiency under mild and environmentally benign conditions in the context of 'Green' synthesis.[1,2] Due to their enormously large and highly reactive surface area, NPs have potential to exhibit superior catalytic activity in comparison to bulk counterparts.[3] Commonly used metallic/bi-metallic nanocatalysts[4–8] are expensive and toxic. Moreover, unsupported nanoparticles are usually unstable, and the coagulation of the nanoparticles during reaction is frequently unavoidable.[9] Thus, until now, the investigation of native nanoparticles as catalysts has been rare, although it is an important tool to gain a fundamental understanding of catalysis.[10] Recently, we have reported a native silica NPs catalyzed anti-Markovnikov addition of thiols to alkenes and alkynes.[11] This observation motivated us to explore the use of silica NPs in useful synthetic reactions, such as carbon–carbon (C–C) bond formation.

The Michael addition is one of the most useful C–C bond-forming reactions with wide synthetic applications in organic synthesis.[12,13] This reaction is conventionally catalyzed by strong bases that often lead to undesirable side reactions.[14] A number of reagents[15–23] have been developed for the mono-Michael addition reaction. To date, a few reagents, such as ruthenium complex[24] and basic ionic liquid,[25,26] have been reported for the bis-Michael

addition of active methylene compounds to conjugated carboxylic esters and nitriles. Moreover, these reagents failed to initiate the bis-Micheal addition of active methylene compounds to conjugated ketones even at elevated temperature. Thus, there is a demand for the development of a milder reagent for a general bis-Michael addition of active methylene compounds to α,β-unsaturated ketones, esters, and nitriles in a single step.

In this study, we are highly motivated to evaluate the catalytic activity of native silica NPs in a Michael addition. Unexpectedly, we observed remarkable catalytic activity of native silica NPs in an unusual bis-Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles (Scheme 1). Interestingly, no mono addition product was obtained in all the cases studied herein.

Silica NPs were synthesized using the well-established Stober method[27] that involved basic hydrolysis and condensation reaction

E^1, E^2 = COMe, COOEt, CN etc
X = COMe, COOMe, CN etc
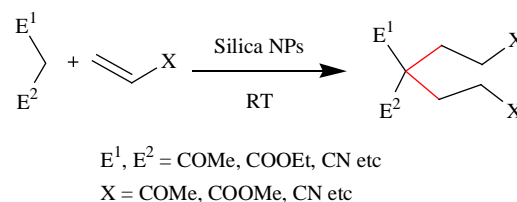
Scheme 1. Silica NPs catalyzed bis-Michael addition of active methylene compounds to conjugated alkenes.

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E-mail addresses: subanerj@mail.ucf.edu (S. Banerjee), ssantra@mail.ucf.edu (S. Santra).

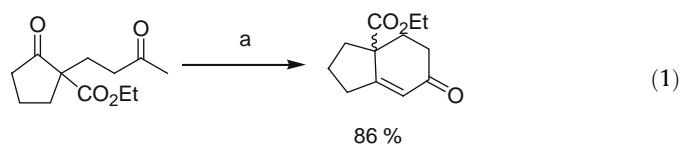of tetraethoxyorthosilane (TEOS) in 1:1 (V/V) water–ethanol mixture at room temperature. Silica NPs of different sizes were synthesized by simply adjusting the water to ethanol ratio. The silica NPs were characterized by transmission electron microscopy (TEM) (Fig. 1). The catalytic activity of these silica NPs has been tested in the Michael addition of active methylene compounds to conjugated alkenes.

Initially, we selected the Michael addition of malononitrile to methyl vinyl ketone (MVK) as a model reaction for investigation of different reaction parameters. The results are summarized in Table 1. We have observed that only 10 wt % of silica NPs were sufficient to push the reaction forward. In absence of catalyst, the Michael addition reaction did not progress at all. The general experimental procedure[29] for the bis-Michael addition reaction is given below.

We have also screened effect of different solvents with varying polarity and protic nature. It was observed that water proved to be the best choice for the Michael addition reaction over any organic solvents such as tetrahydrofuran and toluene. It was also observed that the rate of the Michael addition reaction increased with decreasing particle size. We have used ~50 nm silica NP for all reactions.
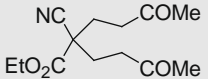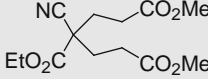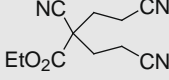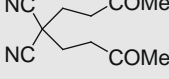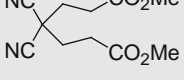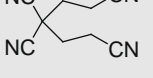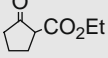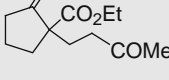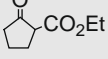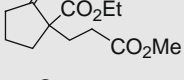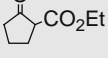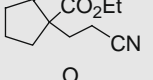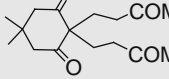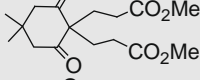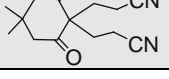
To explore the generality and scope of the bis-Michael addition reaction, the reaction of various active methylene compounds and conjugated alkenes was carried out under optimized conditions. The results are summarized in Table 2.

Interestingly, all open-chain and cyclic active methylene compounds (with two active α-C–H) such as a ethyl acetoacetate, diethyl malonate, ethyl cyanoacetate, 5,5-dimethyl-1,3-cyclohexadione, and malononitrile participated in bis-Michael additions with MVK, methyl acrylate, and acrylonitrile to produce the corresponding bis-adducts exclusively in high yields. These products are very useful synthons, two representative examples of conversion of these adducts to annulated bicyclic and tricyclic conjugated ketones are shown below (Eqs. 1 and 2).

Figure 1. TEM image of silica NPs (size ~ 50 nm).

Table 1
Optimization of reaction conditions

Entry	Reaction medium	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	H$_2$O[b]	10	2	95
2	H$_2$O[b]	0	24	0
3	Neat	10	6	70
4	Ethanol	10	8	77
5	THF	10	12	25
6	Toluene	10	12	20

[a] Isolated yield.
[b] Reactions were carried out in 0.5 ml H$_2$O.

$$(1)$$

86 %

Table 2
Silica NP catalyzed Michael addition of active methylene compounds to conjugated alkenes

Entry	Active methylene compound	Conjugated alkene	Product	Time (h)	Yield[a] (%)	Ref.
1	MeOC, EtO$_2$C	Me, O	MeOC, COMe, EtO$_2$C, COMe	3.5	85	28a
2	MeOC, EtO$_2$C	OMe, O	MeOC, CO$_2$Me, EtO$_2$C, CO$_2$Me	6.0	78	26
3	MeOC, EtO$_2$C	CN	MeOC, CN, EtO$_2$C, CN	3.5	82	28b
4	EtO$_2$C, EtO$_2$C	OMe, O	EtO$_2$C, CO$_2$Me, EtO$_2$C, CO$_2$Me	6.0	81	26
5	EtO$_2$C, EtO$_2$C	CN	EtO$_2$C, CN, EtO$_2$C, CN	4.0	86	28c

Table 2 (*continued*)

Entry	Active methylene compound	Conjugated alkene	Product	Time (h)	Yield[a] (%)	Ref.
6	NC, EtO$_2$C (methylene)	CH$_2$=CH–COMe	NC, EtO$_2$C, COMe, COMe	4.0	85	28d
7	NC, EtO$_2$C	CH$_2$=CH–OMe (acrylate)	NC, EtO$_2$C, CO$_2$Me, CO$_2$Me	5.0	80	26
8	NC, EtO$_2$C	CH$_2$=CH–CN	NC, EtO$_2$C, CN, CN	4.5	79	26
9	NC, NC	CH$_2$=CH–COMe	NC, NC, COMe, COMe	2.0	95	26
10	NC, NC	CH$_2$=CH–OMe	NC, NC, CO$_2$Me, CO$_2$Me	2.5	92	26
11	NC, NC	CH$_2$=CH–CN	NC, NC, CN, CN	2.5	94	26
12	cyclopentanone-CO$_2$Et	CH$_2$=CH–COMe	cyclopentanone, CO$_2$Et, COMe	3.0	90	26
13	cyclopentanone-CO$_2$Et	CH$_2$=CH–OMe	cyclopentanone, CO$_2$Et, CO$_2$Me	5.0	85	26
14	cyclopentanone-CO$_2$Et	CH$_2$=CH–CN	cyclopentanone, CO$_2$Et, CN	4.5	87	26
15	dimedone (dimethyl cyclohexane-1,3-dione)	CH$_2$=CH–COMe	dimedone, COMe, COMe	3.0	90	28f
16	dimedone	CH$_2$=CH–OMe	dimedone, CO$_2$Me, CO$_2$Me	4.0	85	28g
17	dimedone	CH$_2$=CH–CN	dimedone, CN, CN	4.0	90	28g

[a] Yields refer to those of pure isolated products characterized by spectroscopic data.

$$\text{(dimedone bis-adduct, COMe/COMe)} \xrightarrow{a} \text{(HO, bicyclic enone)} \qquad (2)$$

75 %
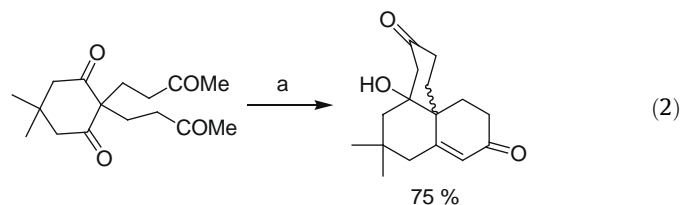
Reagents (a): Pyrrolidine and acetic acid in ethyl acetate.

The use of 1 equiv (or less) of conjugated alkene in these reactions did not produce any monoaddition product, only the bis-adducts were isolated in proportionate yields. The formation of bis-adducts in one step with methyl acrylate, and acrylonitrile was reported previously in two procedures.[24–26] However, these reagents are not applicable as they failed to initiate the bis-Michael addition of conjugated ketones even at elevated temperatures. Other restrictions involved long reaction times (48–96 h) at 50–70 °C[24] and low isolated yields (24–89%). Interestingly, the silica NPs
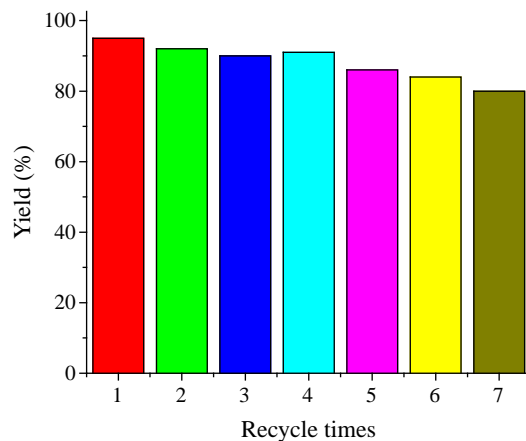
Figure 2. Recycle of the catalyst.
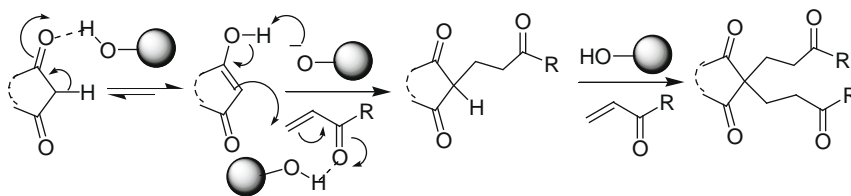
Scheme 2. Plausible mechanism for silica NP catalyzed bis-Michael addition.

efficiently catalyzed the bis-addition of MVK, methyl acrylate and acrylonitrile within a reasonable time period (2–6 h) at room temperature with high yields (78–95%). This observation is highly significant in the context of establishing a simplified method of forming two C–C bonds in a single step. We anticipate that these adducts, containing important functional groups (e.g., ketones, esters, and nitriles) will find wide-spread synthetic applications. We have demonstrated a two-step synthesis of 10-hydroxy-8,8-di-methyl-tricyclo[8.4.0.01,6]tetradec-5-ene-4,12-dione, (Eq. 2) form 5,5-dimethyl-1,3-cyclohexadione, in which a bis-Michael addition was the key step.

To evaluate the stability of the catalytic activity and the potential for recycling, we completed several catalytic cycles. In each cycle, the reaction mixture was centrifuged, and the NPs were washed with ethanol and dried under vacuum to remove the residual solvent. The particulate nature of the used catalyst was confirmed by TEM. The catalyst could be reused for seven times with a minimal loss of activity (Fig. 2).

The reason for this unusual behavior of the silica NP toward bis-Michael addition is unknown at this stage. We believe that silica surface chemistry plays an important role in this reaction. At neutral pH, silica NPs are present in partly de-protonated, providing both the –Si–OH and –Si–O⁻ groups on the NP surface. The –Si–OH group stabilizes the enol form of active methylene compounds and polarizes the conjugated alkene via H-bonding with carbonyl oxygen. The Si–O⁻ promotes the nucleophilic attack of the enolized active methylene compound (Scheme 2).

In conclusion, we have successfully demonstrated remarkable catalytic activity of silica NPs in the Michael addition of active methylene compounds to conjugated alkenes under neutral reaction conditions. In particular, we were able to develop a robust protocol for the bis-addition of α,β-unsaturated ketones with active methylene compounds in one step. The present synthesis strategy is simple and straight-forward, and catalyst silica NP is stable, easy to synthesize, and reusable. Certainly, this observation provides great promise toward additional useful applications.

Acknowledgments

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29. General experimental procedure for the silica nanoparticle catalyzed Michael addition of active methylene compounds to conjugated alkenes: Representative example for the Michael addition of malononirile to methyl vinyl ketone (Table 2, entry 9): Methyl vinyl ketone (140.18 mg, 2 mmol) was added to a mixture of malononitrile (66 mg, 1 mmol) and silica NP (∼5 mg, 10 wt %) in water (0.5 mL), and the mixture was stirred for 2 h until completion of reaction (TLC). Ethyl acetate (10 mL) was added to the reaction mixture and was stirred for 5 min. The reaction mixture was centrifuged, precipitate catalyst was washed with ethanol and finally dried for subsequent runs. The organic layer was separated by separating funnel, dried over anhydrous Na_2SO_4, and evaporated the solvent to leave crude product, which was purified by short column chromatography over silica gel (ethyl acetate/hexane 1:9) to provide pure bis-Michael adduct, 2,2-bis-(3-oxo-butyl)-malononitrile as brownish solid in excellent yield (195 mg, 95%). The product was characterized by its IR and ^{1}H NMR and ^{13}C NMR spectroscopic data, and was compared with reported[28a] one.