Silica nanoparticles as a reusable catalyst: a straightforward route for the synthesis of thioethers, thioesters, vinyl thioethers and thio-Michael adducts under neutral reaction conditions

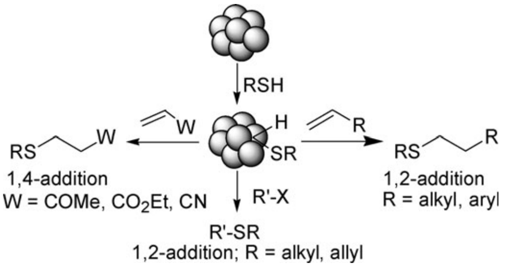
Subhash Banerjee,*[a] Jayanta Das,[ab] Richard P. Alvarez[a] and Swadeshmukul Santra*[abc]

Received (in Gainesville, FL, USA) 12th August 2009, Accepted 29th September 2009
First published as an Advance Article on the web 16th November 2009
DOI: 10.1039/b9nj00399a

A simple and straightforward route for the synthesis of thioethers, thioesters, vinyl thioethers and thio-Michael adducts has been demonstrated using silica nanoparticles (NPs) as a reusable catalyst *via* the 1,2-addition of thiols to alkenes, alkynes and alkyl/acyl halides, and the 1,4-addition of thiols to conjugated alkenes at room temperature.

Thioethers and thioesters play important roles in biological and chemical processes,[1] and also serve as useful building blocks for various organosulfur compounds.[2] Therefore, the synthesis of these compounds in a "green" and "straightforward" way would be of great importance. Traditionally, these compounds are synthesized by the addition of thiolate anions to organic halides,[3–15] alkenes and alkynes[16–19] by using different reagents and catalysts such as BuLi,[3] phase transfer catalysts,[4] metal complexes,[5–7] organometallic sulfides,[8–10] clay materials,[11] trifluoroacetic acid,[12] CSF-Celite,[13] thiomolybdates,[14] ionic liquids,[15] refluxing in benzene[17] and water.[18] However, most of these protocols involve the use of a strong base, highly toxic and expensive catalysts, and hazardous organic solvents. Thus, the development of a robust and general procedure for the synthesis of thioethers and thioesters *via* the 1,2-addition of thiols to alkyl/acyl halides, alkenes and alkynes, and the 1,4-addition of thiols to conjugated alkenes involving a simple, non-toxic and neutral catalyst would be attractive to address these limitations.

Recently, we have observed the remarkable inherent catalytic activity[20,21] of silica NPs. These NPs efficiently catalyzed the anti-Markovnikov addition of thiols to alkenes, leading to linear thioethers. These observations prompted us to explore the potential of this catalyst for other related reactions. In this paper, we report the application of silica NPs to the synthesis of thioethers and thioesters by the 1,2-addition of thiols to alkyl and acyl halides, and the 1,4-addition of thiols to conjugated alkenes. To highlight the importance of this study, we also report a summary of our previous results on anti-Markovnikov additions (Scheme 1).



Scheme 1

The silica NPs were synthesized using the well known Stober method,[22] which involves the base-catalyzed condensation of tetraethyl orthosilicate (TEOS) in a 1 : 1 ethanol–water mixture. The reaction mixture was centrifuged, washed with ethanol and the particles characterized by transmission electron microscopy (TEM) (Fig. 1). The average size of these particles was found to be in the range 150–250 nm. These silica NPs were used for the synthesis of thioethers through the 1,2-addition of thiols to alkenes, alkynes and alkyl halides. For the anti-Markovnikov addition,† the alkene or alkyne was added to a mixture of the thiol and the silica NPs, and the reaction mixture stirred at room temperature until completion of the reaction (TLC). The results are summarized in Table 1.

A number of alkenes participated in this reaction to provide linear thioethers. All the reactions were performed at room temperature to produce linear thioethers in high yield (85–98%) after short reaction times (0.5–1.5 h). It was observed that the addition of thiophenol to cyclohexene was unsuccessful in absence of the catalyst. The additions of thiols to alkenes were inconsistent when using amorphous silica as a catalyst, and only 50% phenylsulfanylethylbenzene was

---

† A typical experimental procedure for the anti-Markovnikov addition of olefins to thiols (entry 6, Table 1): Styrene (104 mg, 1 mmol) was added to a mixture of thiophenol (110 mg, 1 mmol) and silica NPs (~2–3 mg, 1 wt%) under neat conditions. The reaction mixture was stirred for 0.5 h at room temperature until completion (TLC). Extraction with ethyl acetate followed by evaporation of the solvents lead to the crude product in an almost pure form. Purification by short column chromatography over silica gel (hexane–ethyl acetate, 95 : 5) provided 2-phenylsulfanylethylbenzene (209 mg, 98%) as a colorless liquid. The product was characterized by ^{1}H NMR and IR spectroscopy, and the results compared with reported data.[20] This procedure was followed for all of the reactions listed in Table 1.

[a] *NanoScience Technology Center, University of Central Florida, 12424 Research Parkway, Suite 400, Orlando, FL 32826, USA. E-mail: ocsb2009@yahoo.com*
[b] *Department of Chemistry, University of Central Florida, 12424 Research Parkway, Suite 400, Orlando, FL 32826, USA*
[c] *Biomolecular Science Center, University of Central Florida, 12424 Research Parkway, Suite 400, Orlando, FL 32826, USA. E-mail: ssantra@mail.ucf.edu*

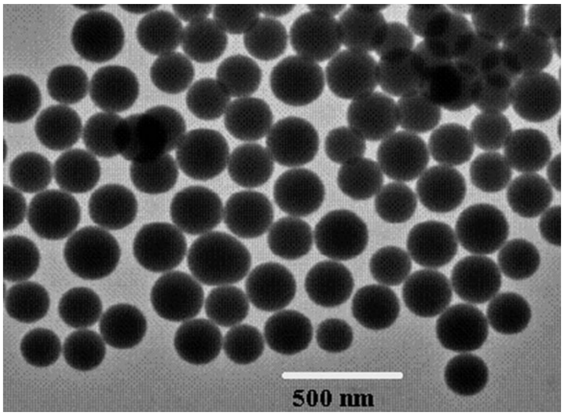
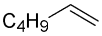
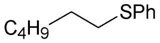
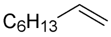
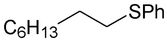
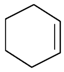
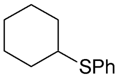
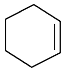
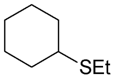
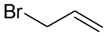
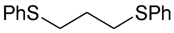
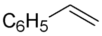
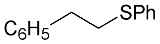
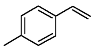
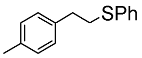
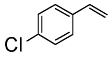
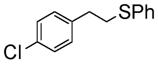
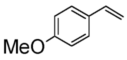
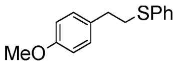
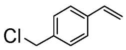
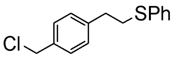
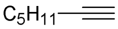
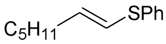
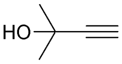
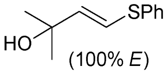
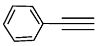
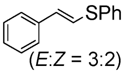


Fig. 1 A TEM image of the silica NPs.

isolated by the addition of thiophenol to styrene. The addition of thiophenol to 1-chloromethyl-4-vinylbenzene was highly selective in nature (entry 10, Table 1). The reactive chloromethyl group in the molecule remained intact, even after the use of two equivalents of thiophenol, which could be further functionalized.

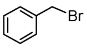
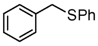
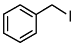
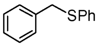
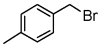
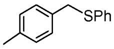
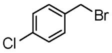
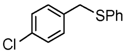
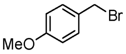
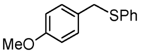
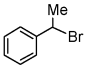
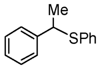
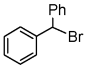
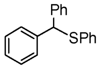
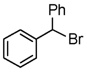
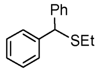
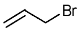
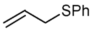
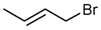
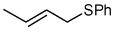
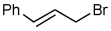
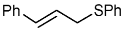
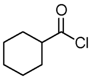
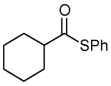
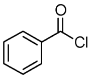
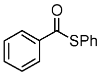
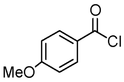
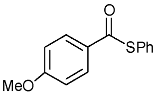
These NPs also promoted the addition of thiols to alkynes, leading to vinyl thioethers in high yields (85–96%) at room temperature. The results for the addition of thiols to alkynes are represented by entries 11–13 in Table 1. Interestingly, we observed 100% anti-Markovnikov addition, and no Markovnikov adducts were isolated in any case studied herein. Alkyl, allyl and acyl halides were also thiolated by this catalyst at room temperature to produce thioethers and thioesters, respectively (Table 2). In a simple experimental

Table 1 The silica NP-catalyzed anti-Markovnikov addition of thiols to alkenes and alkynes

Entry	Thiol	Alkene	Product	Time/h	Yield (%)[a]	Ref.
1	PhSH			1.5	87	20
2	PhSH			1.5	85	20
3	PhSH			1.0	88	20
4	EtSH			1.5	85	20
5	PhSH (2 equiv.)			1.0	86	20
6	PhSH			0.5	98	20
7	PhSH			0.5	94	20
8	PhSH			0.5	90	20
9	PhSH			0.5	90	20
10	PhSH			0.5	96	20
11	PhSH		 (*E*:*Z* = 1:1)	1.0	85	20
12	PhSH		 (100% *E*)	1.0	85	20
13	PhSH		 (*E*:*Z* = 3:2)	0.5	96	20

[a] The yield refers to those pure isolated products characterized by spectroscopic (^{1}H NMR and IR) data.

Table 2 The silica NP-catalyzed addition of thiols to alkyl, allyl and acyl halides

Entry	Thiol	RX	Product	Time/h	Yield (%)[a]	Ref.
1	PhSH			20	85	15
2	PhSH			1.5	88	15
3	PhSH			1.0	92	23
4	PhSH			1.5	90	24
5	PhSH			1.5	92	15
6	PhSH			1.5	89	15
7	PhSH			1.0	87	15
8	EtSH			2.0	85	15
9	PhSH			1.0	95	15
10	PhSH			1.5	90	15
11	PhSH			1.5	90	15
12	PhSH	MeCOCl	MeCOSPh	2.0	85	15
13	PhSH			2.0	86	15
14	PhSH			1.5	90	15
15	PhSH			1.5	90	15

[a] The yield refers to those pure isolated products characterized by spectroscopic (^{1}H NMR and IR) data.

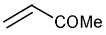
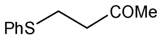
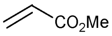
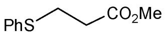
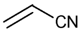
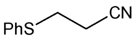
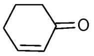
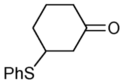
procedure,‡ the alkyl or acyl halide was added to a mixture of thiol and the silica NPs (5 wt%), and the reaction mixture was stirred at room temperature until completion of the reaction (TLC). The reactions of thiols with alkyl halides proceeded faster in water in comparison to other solvents. The addition of thiophenols to acyl halides were carried out in neat reaction conditions. This simple procedure turned out to be applicable to a number of substituted benzyl and allyl halides, and we achieved 80–95% yields of thioethers within 2 h. To investigate the nature of the addition of thiols to allylic halides, we performed the reaction of thiophenol with crotyl bromide. The 1,2-addition product was isolated exclusively and no 1,4-adduct was obtained (entries 10 and 11 in Table 2). The catalyst was found to be very effective for the synthesis of thioesters. Both alkyl and aryl acid chlorides were converted to their corresponding thioesters by a reaction with thiophenol in the presence of silica NPs under neat conditions (entries 12–15, Table 2).

We have also tested the catalytic activity of silica NPs in Michael additions, *i.e.* the 1,4-addition of thiols to conjugated alkenes. It was observed that silica NPs efficiently catalyzed the 1,4-addition of thiophenol to conjugated ketones, carboxylic esters and nitriles under solvent-free conditions; the results are summarized in Table 3. The 1,4-addition

---

‡ A typical experimental procedure for the 1,2-addition of thiols to alkyl halides (entry 1, Table 2): Benzyl bromide (170 mg, 1 mmol) was added to a mixture of thiophenol (110 mg, 1 mmol) and silica NPs (~15 mg, 5 wt%) in water (0.5 mL). The reaction mixture was stirred for 2.0 h at room temperature until completion of the reaction (TLC). Extraction with ethyl acetate followed by evaporation of the solvents lead to the crude product, which was purified by short column chromatography over silica gel (hexane–ethyl acetate, 95 : 5) to provide 2-phenylsulfanylethylbenzene (170 mg, 85%). This procedure was followed for all of the reactions listed in Table 2. The procedure was also followed for the synthesis of thioesters (Table 2), but all of these reactions were carried out under neat conditions (without water). All of the products in Table 1, Table 2 and Table 3 are known and were characterized from their spectroscopic (^{1}H NMR and IR) data in comparison with reported values (references are given in the respective tables).

Table 3 The 1,4-addition of thiophenol to conjugated alkenes

Entry	Thiol	Conjugated alkene	Product	Time/min	Yield (%)[a]	Ref.
1	PhSH			5	98	25
2	PhSH			5	98	25
3	PhSH			5	86	25
4	PhSH			5	95	25

[a] The yield refers to those pure isolated products characterized by spectroscopic (^{1}H NMR and IR) data.

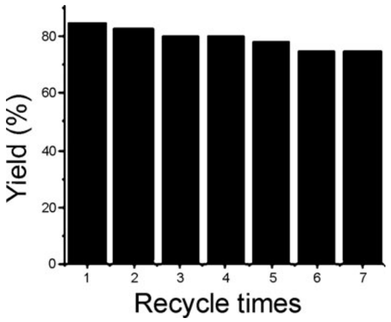
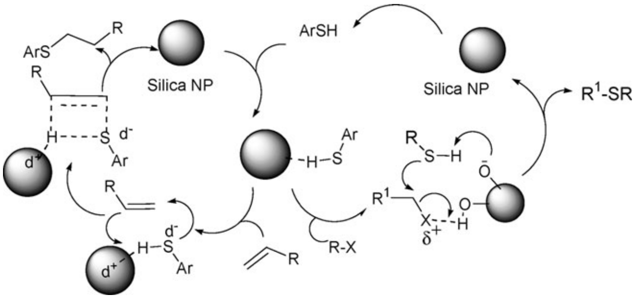


Fig. 2 The reuse of silica NPs in the synthesis of 2-phenylsulfanylethylbenzene.



Scheme 2 A plausible reaction mechanism.

reactions were very fast (5–6 min) at room temperature and no solvents were required.

Finally, after each reaction, the catalyst was recovered, washed with ethanol and dried for reuse. The catalyst was reused seven times with minimal loss of catalytic activity. Fig. 2 shows the variation of yield of 2-phenylsulfanylethylbenzene (entry 6, Table 1) with the number times the silica NPs were recycled.

The silica NPs play a major role in these reactions. A comparison of the reactivity of different reagents in the anti-Markovnikov addition of thiophenol to styrene is presented in Table 4.

Under neutral pH conditions, a silica NP's surface consists of silanol groups partly in their neutral form (Si–OH) and partly in their deprotonated (SiO^-) form. Here, we speculate that SiO^- polarizes the SH hydrogen of thiols with the Si–OH-promoted elimination of halide ion or acetate ion (Scheme 2). To establish grounds for this speculation, we synthesized vinyl silica NPs and observed that the reactivity of the catalyst was reduced by one third compared to that of silica NPs. This observation establishes the role of the surface groups of the silica NPs.

Table 4 Comparison of results for the anti-Markovnikov addition of thiophenol to styrene using different reagents

Reagent	Time/conditions	Yield (%)
Benzene	24 h/RT 10 h/reflux	92
Neat	24 h/RT	30
Silica NPs	0.5 h/RT	98
Amorphous silica	12 h/RT	50
Water	1.5 h/RT	90

Conclusions

In conclusion, we have demonstrated a straightforward route for the synthesis of thioethers, thioesters and vinyl thioethers catalyzed by simple, neutral and stable silica NPs. The reactions are considerably fast. This present synthesis strategy offers several advantages, such as (1) mild reaction conditions (room temperature), (2) high isolated yields of thioethers and thioesters, (3) low cost, (4) the use of a non-toxic and neutral catalyst, (5) recyclability of the catalyst, and (6) aqueous reaction conditions. Moreover, this study demonstrates the potential of silica NPs as a catalyst in other organic reactions.

Acknowledgements

This work was partly supported by the National Science Foundation (NSF CBET-63016011 and NSF-NIRT Grant EEC-0506560). We are also pleased to acknowledge Dr S. Biswas for his help with the TEM.

References

1 M. E. Peach, Thiols As Nucleophiles, in *The Chemistry of the Thiol Group*, ed. S. Patai, John Wiley & Sons, London, 1979, pp. 721.
2 R. J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley & Sons, New York, 1996.
3 J. M. Yin and C. Pidgeon, *Tetrahedron Lett.*, 1997, **38**, 5953–5954.
4 A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, 1975, **97**, 2345–2349.

5 C. Goux, P. Lhoste and D. Sinou, *Tetrahedron Lett.*, 1992, **33**, 8099–8102.
6 C. J. Li and D. N. Harpp, *Tetrahedron Lett.*, 1992, **33**, 7293–7294.
7 P. C. B. Page, S. S. Klair, M. P. Brown, M. M. Harding, C. S. Smith, S. J. Maginn and S. Mulley, *Tetrahedron Lett.*, 1988, **29**, 4477–4480.
8 M. Gingras, T. H. Chan and D. N. Harpp, *J. Org. Chem.*, 1990, **55**, 2078–2090.
9 D. N. Harpp and M. Gingras, *J. Am. Chem. Soc.*, 1988, **110**, 7737–7745.
10 M. Kosugi, T. Ogata, M. Terada, H. Sano and T. Migita, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3657–3658.
11 T. S. Li and A. X. Li, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1913–1917.
12 L. S. Richter, J. C. Marsters and T. R. Gadek, *Tetrahedron Lett.*, 1994, **35**, 1631–1634.
13 S. T. A. Shah, K. M. Khan, A. M. Heinrich and W. Voelter, *Tetrahedron Lett.*, 2002, **43**, 8281–8283.
14 V. Polshettiwar, M. Nivsarkar, J. Acharya and M. P. Kaushik, *Tetrahedron Lett.*, 2003, **44**, 887–889.
15 B. C. Ranu and R. Jana, *Adv. Synth. Catal.*, 2005, **347**, 1811–1818.
16 P. Kumar, R. K. Pandey and V. R. Hegde, *Synlett*, 1999, 1921–1922.
17 S. Kanagasabapathy, A. Sudalai and B. C. Benicewicz, *Tetrahedron Lett.*, 2001, **42**, 3791–3794.
18 B. C. Ranu and T. Mandal, *Synlett*, 2007, 925–928.
19 C. G. Screttas and M. Michascrettas, *J. Org. Chem.*, 1979, **44**, 713–719.
20 S. Banerjee, J. Das and S. Santra, *Tetrahedron Lett.*, 2009, **50**, 124–127.
21 S. Banerjee and S. Santra, *Tetrahedron Lett.*, 2009, **50**, 2037–2040.
22 W. Stober, A. Fink and E. Bohn, *J. Colloid Interface Sci.*, 1968, **26**, 62–69.
23 G. Hua and J. D. Woollins, *Tetrahedron Lett.*, 2007, **48**, 3677–3679.
24 B. C. Ranu, S. Samanta and A. Hajra, *Synlett*, 2002, 987–989.
25 B. C. Ranu and S. S. Dey, *Tetrahedron*, 2004, **60**, 4183–4188.