Silica-promoted facile synthesis of thioesters and thioethers: a highly efficient, reusable and environmentally safe solid support

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An efficient, mild and rapid procedure for the acylation and alkylation of aromatic and aliphatic thiols mediated on a silica gel surface at room temperature is described. The protocol allows the protection of thiols under neutral heterogeneous conditions without requiring any bases or Lewis acids, and the silica gel used as the promoter can be recycled for several runs without any loss of activity.

Introduction

Acylation and alkylation of thiols are essential transformations in organic synthesis and often used for protection of thiols.[1] These reactions are also familiar in several biological phenomena.[2] For example, S-acylation is the post-translational attachment of fatty acids to cysteine residues and is common among integral and peripheral membrane proteins.[3] S-Acylated peptides have many potential uses for elucidating the biophysical, structural and other properties of numerous S-acylated proteins of mammalian cells.[4] Peptides are commonly S-acylated by using alkyl or aryl thioester derivatives of palmitic acid.[5] The acylation of thiols is routinely carried out by using acid anhydrides or acid chlorides in the presence of nucleophilic tertiary amines such as triethylamine or pyridine along with 4-(dimethylamino)pyridine[6] or the less basic Bu_3P.[7] Several Lewis acid catalysts, such as $LiClO_4$,[8a] $MgBr_2$,[8b] $CoCl_2$,[8c] $Sc(OTf)_2$,[8d] $Sc(NTf_2)_3$,[8e] $Bi(OTf)_3$,[8f] $Cu(OTf)_2$,[8g] TMSOTf,[8h] $InCl_3$,[8i] and heteropoly acids[8j] *etc.* have been employed for acylation of thiols. Ruthenium(III) chloride has also been used for acylation of thiols in the presence of ionic liquids.[8k]

On the other hand, thioethers are a useful class of organic compounds and find versatile applications as key reagents in organic synthesis, bio-organic, heterocyclic and medicinal chemistry.[9] Plenty of synthetic methods exist for the preparation of alkyl or aryl sulfides,[10] including transition metal-catalyzed hetero-cross-couplings between aryl halides and thiols.[10e] The classical methods involve, however, the reaction of thiol with an alkyl halide in the presence of a strong base.[10f,g]

With the advent of solid-phase organic synthesis,[11] various inorganic oxides have been used for S-acylation or S-alkylation reactions. For example, acylation of thiols using anhydrides or carboxylic acids have been induced by Ac_2O–Py/basic alumina,[12a] montmorillonite K-10 and KSF,[12b,c] zeolite H-FER,[12d] heteropoly acid catalysts ($H_6P_2W_{18}O_{62}\cdot 24H_2O$)[12e] and yttria–zirconia-based Lewis acids.[12f] Similarly, solid supports such as hydrotalcite clays,[13a] $ZrCl_4$ dispersed on dry silica gel,[13b] KF/alumina,[13c] and K_2CO_3/alumina with microwaves[13d] have been used to promote S-alkylations.

Lewis acids are efficient catalysts but most of them cause strongly acidic waste streams during the work-up of the product, and some are also quite expensive. Although heterogeneous catalysts are useful on several occasions, most of them are either strongly basic or acidic in nature. Towards the development of greener protocols, Ranu *et al.*[14] reported acylation of alcohols, amines and thiols with acyl chlorides or anhydrides without solvent or catalyst, the product being distilled out directly from the reaction vessel. The reaction of thiophenol and acetyl chloride in a neat mixture at room temperature was, however, not successful in our hands. In view of the above limitations, there is growing demand for environmentally friendly, versatile, non-corrosive and reusable solid supports for the preparation of thioesters and thioethers.

Silica is a class of inexpensive and non-corrosive neutral solid that has been used as an efficient heterogeneous support for a variety of organic reactions.[15] Recently, we have developed a highly selective protocol for N-alkylation of amines promoted by silica gel.[16] Both mono- and bis-alkylations of primary amines can be selectively performed on a silica gel surface under different conditions. The remarkable efficiency of silica gel for selective N-alkylation of amines prompted us to undertake other reactions promoted by silica gel. In this communication, we describe a highly efficient and expeditious protocol for the acylation or alkylation of thiols using acyl chlorides or alkyl halides respectively, catalyzed by silica gel under mild and solvent-free conditions. No other catalyst or solvent was required and the reactions were carried out at ambient temperature.

Results and discussion

Preliminary optimization of the S-acylation with the aid of silica gel was tested with thiophenol and various acylating agents. Commercially available silica gel (–325 mesh gel for TLC, from SRL, India) was activated by heating under vacuum at 150 °C until bubbling ceased, and then cooled to room temperature under vacuum. In a typical procedure, a mixture of thiophenol and acylating agent in the ratio of 1 : 1.5 was added to the activated silica gel (500 mg $mmol^{-1}$) and the solid mixture was stirred at room temperature in the presence of air. The composition of the products was checked by taking a small amount of the solid reaction mixture in methanol and analyzing it by HPLC. The results are shown in Table 1. We

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Table 1 HPLC analyses [a]of the reaction of thiophenol with various acylating agents promoted on silica gel [b]in air at room temperature

			Relative percentages		
Entry	Acylating agent	Time/min	Acylated product[c]	Disulfide	Unreacted thiol
1	Acetic anhydride	30	0	9.78	90.22
2	Acetic anhydride	60	0	10.66	89.34
3	Acetic anhydride	120	0	10.91	89.09
4	Acetic acid	30	0	71.19	92.81
5	Acetic acid	60	0	7.86	92.14
6	Acetic acid	120	0	8.99	91.01
7	Acetyl chloride	30	78.19	5.37	16.44
8	Acetyl chloride	60	92.02	6.01	1.97
9	Acetyl chloride	120	93.29	6.71	0
10	Benzoyl chloride	30	97.02	2.98	0

[a] HPLC column: C_{18} (3.5 mm; 4.6 × 75 mm); solvent: MeOH and flow rate: 0.5 mL min^{-1}. [b] The silica gel was TLC grade with a –325 mesh particle size. [c] Peak areas were calibrated on the basis of initial run of a mixture of authentic samples of equimolar concentration.

observed that thiophenol can be acetylated efficiently with acetyl chloride by simple stirring of the solid mixture for 2 h at room temperature, producing *S*-phenyl ethanethioate in 93% yield (Table 1, entry 9). Neither acetic anhydride (Table 1, entries 1–3) nor acetic acid (Table 1, entries 4–6) were effective for a similar conversion. We further examined the reaction of thiophenol with benzoyl chloride, and found the reaction to be complete within 30 min, producing *S*-phenyl benzothioate in 97% yield (Table 1, entry 10).

After observing the facile conversion of thiophenol into the S-acetylated derivatives with acetyl chloride on the surface of silica gel at room temperature, we decided to carry out the same reaction with other inorganic supports. The results are summarized in Table 2. Silica gel was found to be a much better choice for promoting the S-acetylation reaction. While neutral alumina yielded the thioester in 64% yield (Table 2, entry 4), bentonite or molecular sieves afforded considerable amounts of disulfide (Table 2, entries 5–8). On the other hand, use of powdered talc did not result in significant amounts of the desired product (Table 2, entries 9–10). In order to check the necessity of the presence of silica, a mixture of thiophenol and acetyl chloride was magnetically stirred at room temperature for up to 2 h, and there was no trace of *S*-phenyl ethanethioate by HPLC analysis (Table 2, entries 11–13). Thus, the optimized reaction conditions used pre-activated silica gel (500 mg $mmol^{-1}$) and stirring the heterogeneous mixture for 2 h at room temperature.

To generalize the reaction procedure, we carried out S-acylation of several aromatic and aliphatic thiols with different acid chlorides in presence of the activated silica gel (Table 3). A smooth conversion was observed in each case, affording the desired products in good to excellent yields. A series of aryl thiols reacted with acetyl and benzoyl chloride to afford the corresponding thioesters in 85–97% yields (Table 3, entries 1, 2 and 4–6), whereas naphthalene-2-thiol gave the corresponding thioester in 65% yield (Table 3, entry 3). Aliphatic thiols also furnished corresponding thioesters using benzoyl chloride or bromide (Table 3, entries 7–10). 2-Chloroacetyl chloride gave the corresponding S-acylated product bearing the terminal chloride group (Table 3, entries 11–12). Other acyl chlorides like phenyl acetyl chloride, cinnamoyl chloride and iodobenzoyl chloride also gave thioesters readily (Table 3, entries 13–19). Bis-acyl chlorides such as oxalyl chloride, succinyl chloride, glutaryl chloride or bis-thiol (ethane-1,2-dithiol) afforded bis-acylations in fairly good yields (Table 3, entries 20–24). Thus, silica gel (TLC grade) could be used as an efficient heterogeneous surface for promoting S-acylation of both aromatic and aliphatic thiols at ambient temperature in absence of any additional catalysts, such as Lewis acids or strong bases.

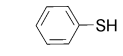
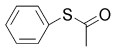
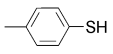
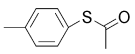
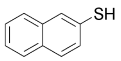
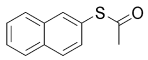
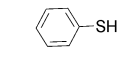
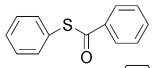
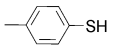
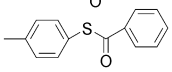
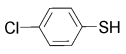
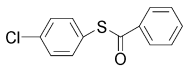
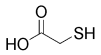
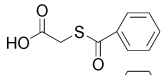
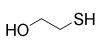
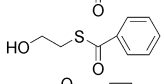
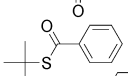
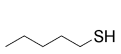
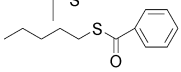
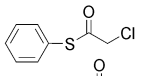
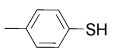
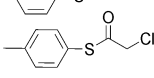
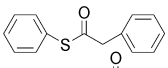
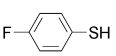
To broaden the scope of using the heterogeneous surface, we then studied S-alkylation of thiols in presence of silica gel. Generally, thiols are alkylated with alkyl halides in presence of a strong base. In the case of aryl or vinyl halides, however, transition metal-catalyzed C–S coupling reactions are more common.[10e] Our studies included the reaction of a variety of thiols with different alkyl halides in the presence of silica, and the results are shown in Table 4. Both aryl and alkyl thiols reacted efficiently with activated alkyl halides (benzyl chloride or iodobenzyl bromide, allyl chloride or bromide, and

Table 2 Reaction of thiophenol with acetyl chloride without solvent on various inorganic solid supports at room temperature

			Relative percentages		
Entry	Solid support[a]	Time/min	Acetylated product[b]	Disulfide	Unreacted thiophenol
1	Silica	60	92.02	6.01	1.97
2	Neutral alumina	30	25.80	14.80	59.39
3	Neutral alumina	60	58.38	14.95	28.67
4	Neutral alumina	120	63.99	15.56	20.45
5	Bentonite	30	56.39	43.61	0
6	4 Å MS	30	16.01	73.10	10.89
7	4 Å MS	60	17.80	74.06	8.14
8	4 Å MS	120	19.82	75.16	5.02
9	Talc	30	37.94	7.56	54.50
10	Talc	60	38.96	9.39	51.64
11	Neat	30	0	4.86	96.14
12	Neat	60	0	6.94	93.06
13	Neat	120	0	7.09	92.91

[a] Solid support used 500 mg $mmol^{-1}$. [b] Percentage compositions were based on HPLC analyses on column: C_{18} (3.5 mm; 4.6 × 75 mm); solvent: MeOH and flow rate: 0.5 mL min^{-1}.

Table 3 S-Acylation of thiols using various acylating agents promoted on silica[a] in air at room temperature

Entry	Thiol	Acylating agent	Time/h	Product[b]	Yield (%)[c,d]
1			1.5		92
2			2		93
3			4		65
4			0.5		97
5			3		85
6			2.5		87
7			6		65
8			4		68
9			5		85
10			3		82
11			3		87
12			3		85
13			2.5		82
14			2.5		87
15			5		89
16			7		68
17			5		72
18			7		60
19			10		65
20			1.5		74
21			1.5		73
22			1.5		69
23			4		72
24			5		72

[a] 500 mg mmol^{-1} silica gel was used. [b] Products were characterized by IR, ^{1}H- and ^{13}C-NMR spectroscopy. [c] Yields refer to isolated pure products. [d] Disulfide (~5%) was isolated for benzenethiol and 4-methylbenzenethiol.

Table 4 S-Alkylation of thiols promoted by silica surface[a] at room temperature

Entry	Thiol	Alkyl halide	Time/h	Product[b]	Yield (%)[c]
1			5		90
2			6		92
3			10		89
4			5		85
5			4.5		88
6			4		80
7			4		81
8			6		75
9			7		81
10			6		84
11			6		77
12			10		68
13			4		78
14			6		78
15			12		71
16			8		68
17			18		75
18			14		76
19			8		78

[a] 500 mg mmol^{-1} silica gel was used. [b] Products were characterized by IR, ^{1}H- and ^{13}C-NMR spectral data. [c] Yields refer to isolated pure products.

methyl iodide) to afford the desired S-alkylated products in 65–92% yield (Table 4, entries 1–14). Benzylation of thioglycolic acid or 2-mercaptoethanol was performed selectively so as to afford the desired thioethers bearing free carboxyl or alcoholic functionalities respectively (Table 4, entries 15–16). Use of non-activated alkyl halides, however, required longer times (14–18 h) for thioether formation (Table 4, entries 17–18). Bis-alkylations were observed with 1,2-dichloroethane (entry 18) and with ethane-1,2-dithiol (entry 19) in good yields. In a typical procedure, a mixture of thiol and alkyl halide in a ratio of 1 : 1.2 was intimately mixed with activated silica gel and stirred at room

Table 5 Recycling experiments using thiophenol and acetyl chloride promoted over silica surface[a]

Run	Yield of *S*-phenyl ethanethioate (%)[b]
1	92
2	90
3	90
4	91
5	88
6	91
7	90

[a] 500 mg mmol $^{-1}$ of silica gel was used. [b] Yield refers to isolated pure product.

temperature for the required time to obtain the corresponding thioethers in 68–92% yield after purification.

Finally, the advantage of using the silica gel in the above reactions was examined by its recovery and reuse after the first run. Accordingly, after the reaction, ether was added to the reaction mixture and the silica gel was filtered off and washed successively with methanol (× 2), acetone (× 1), and then activated by heating under vacuum (150 °C/1 mmHg for 1 h). Gratifyingly, it was found that the recovered silica can be reused for seven consecutive runs, without any significant loss of activity (Table 5).

Solid-phase mediated reactions are generally governed by the nature and availability of the functional groups on the solid surface. Silica gel is a porous, amorphous form of silica and is radically different from other silica-based materials due to its unique internal structure. It is composed of a vast network of interconnected microscopic pores. The surface of silica is composed of silanol (≡SiOH) groups and siloxane bridges (≡SiOSi≡), and their concentrations depend greatly on the temperature of the pretreatment.[17] It is known that upon heating, silanols condense to produce siloxane bridges, and that at higher temperatures, the numbers of accessible silanol groups per nm^2 of silica surface decrease. Since silanol groups are believed to be responsible for the Lewis or Brønsted acidity of silica, partial dehydroxylation and forming more siloxane bridges might result in even poorer acidity of the pre-activated silica.[18] Although several solid supports including modified silica with distinctly acidic or basic characters have been employed for S-alkylation of thiols,[11-13] the use of pre-activated silica gel (pH of 10% aqueous solution is ~7) to promote S-acylation and S-alkylation is, to the best of our knowledge, reported here for the first time.

Conclusion

Based on the above discussions, we can conclude that commercially available silica gel (used for TLC) can be used as a cheap source of solid supports to synthesize thioethers and thioesters in an expeditious way. The reaction procedures are operationally straightforward, mild, and environmentally friendly, and moreover the solid support is reusable. No major modifications of silica or dispersion with other catalysts (such as Lewis acids or bases) are required to promote the reactions. Since S-acylation/alkylation reactions are often used in synthesis, and medicinal and biological chemistry, the reaction procedure, being endowed with so many attractive features, could find application as an alternative 'green' reaction methodology. Explorations of further applications of silica gel are underway in our laboratory.

Experimental†

General procedure for S-acylation

A mixture of thiol (2 mmol) and acyl chloride (3 mmol) was intimately mixed with pre-activated silica gel (1 g) (TLC grade, –325 mesh, from SRL, India) and stirred with a magnetic stirrer bar for a period in the range 30 min to 10 h. After the reaction was complete, the solid mixture was washed with diethyl ether (3 × 10 mL) and the solid was filtered off. The filtrate was concentrated and passed through a short column of silica gel. The desired product was pure by TLC, characterized by spectral (IR, ^{1}H- and ^{13}C-NMR) data, and compared to the values in the literature.[8k,19]

General procedure for S-alkylation

A similar procedure was followed for alkylation of thiol (2 mmol) with alkyl halide (2.4 mmol) over silica (1 g) at room temperature for the time given in Table 3. The product obtained after purification on a short column of silica gel was characterized by spectral (IR, ^{1}H- and ^{13}C-NMR) data, and compared to the values in the literature.[13a,b]

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Notes and references

† ^{1}H and ^{13}C NMR spectral data of selected compounds: *S*-*p*-Tolyl ethanethioate (Table 3, Entry 2): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 2.36 (3H, s, -CH_3); 2.38 (3H, s, -$COCH_3$); 7.20 (2H, d, J = 7.5 Hz, 2 Ar-H), 7.28 (2H, d, J = 7.5 Hz, 2 Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 21.3 (*p*-Me); 30.1 (acetyl Me); 124.5 (Ar-C); 130.0 (Ar-C); 134.4 (Ar-C); 139.7 (Ar-C); 194.6 (-CO-). *S*-*p*-Chlorophenyl benzothioate (Table 3, entry 6): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 7.37–7.48 (6H, m, Ar-H); 7.56–7.61 (1H, m, Ar-H); 7.99 (2H, d, J = 7.5 Hz, 2 Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 125.8 (Ar-C); 127.5 (Ar-C); 128.8 (Ar-C); 129.5 (Ar-C); 133.8 (Ar-C); 135.9 (Ar-C); 136.3 (Ar-C); 189.5 (-CO-). *S*-*p*-Tolyl 2-chloroethanethioate (Table 3, entry 12): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 2.37 (3H, s, *p*-Me); 4.25 (2H, s, -CH_2); 7.23 (2H, d, J = 8.1 Hz, 2 Ar-H); 7.30 (2H, d, J = 8.1 Hz, 2 Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 21.3 (*p*-CH_3); 47.9 (-CH_2); 122.9 (Ar-C); 130 (Ar-C); 134.5 (Ar-C); 140. 3 (Ar-C); 192.9 (-CO-). *S*,*S*-Diphenyl ethanebis(thioate) (Table 3, entry 20): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 7.47 (10H, s, 10 Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 125.4 (Ar-C); 129.6 (Ar-C); 130.2 (Ar-C); 134.4 (Ar-C); 187.0 (-CO-). *S*,*S*-Dipentyl ethanebis(thioate) (Table 3, entry 21): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 0.88–0.92 (6H, t, J = 6.9 Hz, 2 × terminal Me protons); 1.26–1.40 (8H, m, 4 × CH_2); 1.59–1.69 (4H, p, J = 6.9 Hz, 2 × CH_2); 2.94–2.99 (4H, t, J = 7.2 Hz, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ/ppm): 13.9 (-CH_3); 22.2 (-CH_2); 28.7 (-CH_2); 28.9 (-CH_2); 31.0 (-CH_2); 188.5 (-CO). 1,4-Dithiane-2,3-dione (Table 3, entry 22): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 2.59 (4H, s, 2 × CH_2). ^{13}C NMR ($CDCl_3$, δ/ppm): 39.9 (-CH_2); 116.5 (-CO-). Allyl (*p*-tolyl)sulfane (Table 4, entry 5): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 2.31 (3H, s, -CH_3); 3.49 (2H, d, J = 6.9 Hz, -CH_2); 5.02–5.11 (2H, m, =CH_2); 5.79–5.91 (1H, m, =CH); 7.09 (2H, d, J = 8.1 Hz, 2 × Ar-H); 7.25 (2H, d, J = 8.1 Hz, 2 × Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 21.0 (-CH_3); 37.9

(-CH_2); 117.4, 129.8, 130.7, 132.0, 133.8, 136.4 (aromatic and olefinic C). Allyl (*p*-fluorophenyl)sulfane (Table 6, entry 7): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.47 (2H, d, J = 6.9 Hz, -CH_2); 5.01–5.06 (2H, m, =CH_2); 5.77–5.91 (1H, m, =CH); 6.96–7.01 (2H, m, 2 × Ar-H); 7.32–7.37 (2H, m, 2 × Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 38.6 (-CH_2); 115.7, 116.0, 117.7, 133.2, 133.3, 133.6 (aromatic and olefinic C). (*p*-Methoxyphenyl)methyl sulfane (Table 4, entry 10): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 2.44 (3H, s, -CH_3); 3.79 (3H, s, -OMe); 6.85 (2H, d, J = 8.7 Hz, 2 × Ar-H); 7.27 (2H, d, J = 8.7 Hz, 2 × Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 18.1 (-CH_3); 55.4 (-OMe); 114.6 (Ar-C); 128.8 (Ar-C); 130.2 (Ar-C); 158.2 (Ar-C). 1,2-Bis(phenylthio)ethane (Table 4, entry 18): ^{1}H NMR ($CDCl_3$, δ/ppm relative to TMS): 3.08 (4H, s, -CH_2); 7.19–7.32 (10H, m, 10 × Ar-H). ^{13}C NMR ($CDCl_3$, δ/ppm): 33.3 (-CH_2); 126.6 (Ar-C); 129.0 (Ar-C); 129.9 (Ar-C); 134.9 (Ar-C).

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