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Selective Protection of Carbonyl Compounds over Nano-sized Nickel Catalysts

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Abstract An efficient method for the preparation of 1,3-dithiolanes of aliphatic and both activated and deactivated aromatic carbonyl compounds with 1,2-ethanedithiol in the presence of a catalytic amount of inexpensive, easily recyclable, monodispersed, chemoselective Ni-nanoparticles having high TON and TOF is reported. An efficient method for the chemoselective thioacetalization of ketones in the presence of aldehydes using Ni-nanoparticles is also reported in this article. Our reaction is kinetically controlled and the method is relatively expedient, avoids the use of cost-prohibitive reagents, high temperatures and leads to excellent yield.

Keywords Dithiolanes · Ni-nanoparticles · Monodispersed · Recyclable · TON · TOF

1 Introduction

The protection of carbonyl functionality as a dithioacetal or a thioketal is important in the multistep total synthesis of complex natural and non-natural products. Among carbonyl protecting groups, 1,3-dithiolanes, 1,3-oxathiolanes, and 1,3-dithianes are important as they are inherently stable under both mildly acidic and basic conditions [1]. In addition, these are also utilized as masked acyl anions [2] or masked methylene functional groups [3] in carbon–carbon bond forming reactions. This ‘umpolung’ or inversion of polarity is an integral step of many multistep organic syntheses. Several methods for the preparation of thioacetals, dithiolanes, or dithianes derivatives from carbonyl compounds such as p-TsOH [4] in refluxing benzene (removing the water as an azeotrope with benzene), BF_3–OEt_2 [5], $ZnCl_2$ [6], SO_2 [7], TMSCl–NaI [8], TMSOTf [9], $AlCl_3$ [10], $TiCl_4$ [11], $Cu(OTf)_2$–SiO_2 [12], $SOCl_2$–SiO_2 [13], $ZrCl_4$–SiO_2 [14], $NiCl_2$ [15], $Bi(NO_3)_3$ [16], $Bi(OTf)_3$ [17], LiBr [18], $LiBF_4$ [19], $InCl_3$ [20], molecular I_2 [21], 5 M $LiClO_4$ [22] have been reported. Although some of these methods have been carried out under mild reaction conditions, most of them require [7, 13] reflux temperature [4, 17], long reaction times and use expensive and not readily available reagents [17]. They also suffer from a tedious work-up procedure [10, 11, 13] and require the use of stoichiometric reagents [4, 6]. Some of the methods mentioned above are incompatible with other protecting groups and fail to protect deactivated aromatic substrates [14]. Interestingly, only a few methods are known for chemoselective protection of aldehydes in the presence of ketones [12, 13, 15, 18–22]. Finally, the main disadvantage of almost all the existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, there is further scope in exploring mild, chemoselective and efficient methods for thioacetalization of carbonyl compounds. As a part of our continuing interest in the development of new synthetic methodologies; an efficient method for the chemoselective thioacetalization of aliphatic and both activated and deactivated aromatic carbonyl compounds using Ni-nanoparticles as catalyst under N_2 atmosphere at room temperature is reported here. We have recently used Ni-nanoparticles for the oxidative coupling of thiols to

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their corresponding disulphide [23], chemoselective reduction of aldehydes [24] and condensation of alcohols with thiols to give thioethers [25]. These useful results encouraged us to study the effect of the Ni-nanoparticles in the thioacetalization of carbonyl compounds. Nickel-nanoparticles are particularly attractive as they are inexpensive, gives relatively high yields under mild conditions and the time required is also less as compared to the traditional catalysts.

Our process is eco-friendly and environmentally benign as it does not require elevated temperature, harsh acids or bases and produces a high yield with excellent chemoselectivity. The reaction time was observed to be relatively small and this process can be applied to a variety of aliphatic, aromatic, cyclic and heterocyclic aldehydes and ketones. Moreover, it is a one pot synthesis and has an easy work up and product isolation procedure. In typical cases when metal salts and other complexes were used as catalysts, an excessive amount of catalysts (usually in grams) was needed. This was normally eliminated as 'waste product' and often had a propensity to be toxic. The quantity of catalyst that we use here has been significantly reduced to a microgram scale. Hence, these have far lesser chances of being toxic. As far as the toxicity of Ni-nanoparticles are concerned, there are reports in which Ni-nanoparticles have been used for various applications including in vivo and in vitro treatment of living cells/organisms and no evidence of toxicity has been reported for low dosage [26–28].

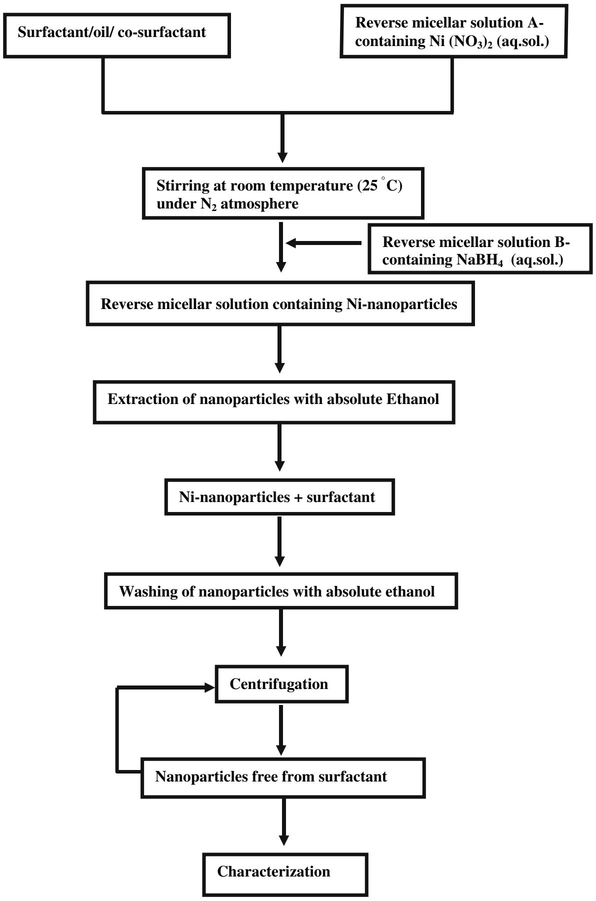
2 Experimental

2.1 General Remarks

All reactions were carried out at an ambient temperature in oven-dried glassware. The materials were purchased from Sigma-Aldrich and Merck and were used without any additional purification. All reactions were monitored by thin layer chromatography (TLC) on gel F254 plates. The silica gel (250–400 meshes) for column chromatography was purchased from Spectrochem Pvt. Ltd. India. ^{1}H-NMR (300 MHz.) and ^{13}C-NMR (300 MHz) spectra were recorded on a Bruker Spectrospin 300 MHz spectrometer in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C NMR as internal references). MS were recorded on TOF-Mass spectrometer Model No. KC455. Melting points were recorded on Buchi melting point 540 instruments. The size and morphology of Ni-nanoparticles were characterized with the help of transmission electron microscope (TEM, FEI Philips Morgani 268D model; Acc. voltage: 100 kV with magnification: upto 2,80,000×) and Quasi Elastic Light Scattering instrument (QELS, photocor-FC, model-1135 P). The metallic nature of the particles was confirmed with UV-spectrophotometer (Shimadzu).

2.2 Preparation of Nickel-nanoparticles

A chemical method involving reduction of Ni^{2+} ions to Ni (0) in a reverse micellar system was employed to prepare the Nickel-nanoparticles (Scheme 1). Poly (oxyethylene) (tetra methyl butyl)-phenyl ether, commercially known as Triton X-100 (TX-100) was used as the surfactant and hexanol was used as a co-surfactant. Cyclohexane is used as the solvent (continuous phase), and aqueous solution of salts is used as the dispersed phase (water core in which particle formation occurs). The reverse micelles were prepared by dissolving TX-100 in cyclohexane (usually 0.08–0.15 M of TX-100 solution). A typical preparative method is as follows: to a set volume of 100 mL (0.1 M TX-100 solutions in cyclohexane), 900 μL of Ni $(NO_3)_2$ aqueous solution (2% w/v) and hexanol (q.s.) was added to prepare an optically clear reverse micellar solution (RM-1). To another 100 mL (0.1 M TX-100 solution in



Scheme 1 Block diagram preparation procedure of Nickel-nanoparticles

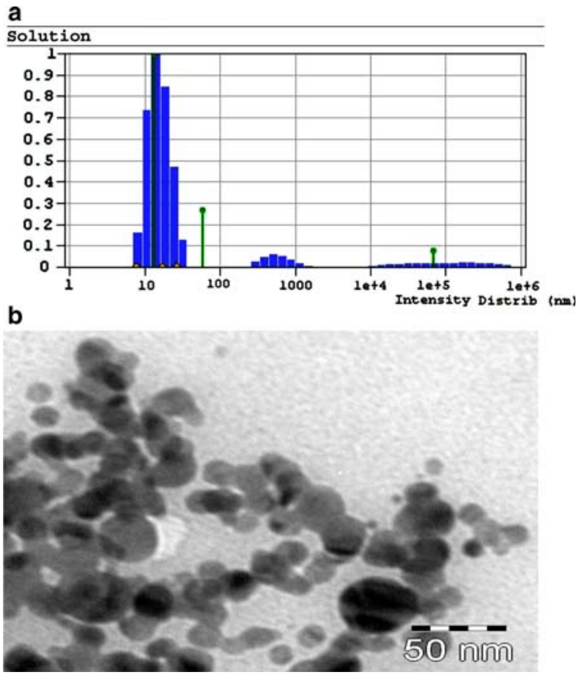


Fig. 1 (**a**) QELS data of Ni-nanoparticles: Plot of population distribution in percentile versus size distribution in nanometer. (**b**) TEM image of Ni-nanoparticles showing the population density of the nanoparticles. The scale bar corresponds to 50 nm in the TEM image

cyclohexane), $NaBH_4$ alkaline solution (5% w/v in 2% NaOH w/v aq. solution) and hexanol (q.s.) was added to obtain RM-2. To the prepared reverse micellar aqueous solution of Ni $(NO_3)_2$ (2% w/v) (RM-1), another reverse micellar $NaBH_4$ alkaline solution (5% w/v in 2% NaOH w/v aq. solution) (RM-2) was added dropwise with constant stirring in a nitrogen atmosphere. Under nitrogen atmosphere, the resulting solution was stirred for 3 h to allow complete Ostwald ripening (particle growth). The nickel nanoparticles were extracted by adding absolute ethanol to the reverse micellar solution containing Ni-nanoparticles followed by centrifugation at 3,000–4,000 rpm for 10 min. By varying the water content parameter W_0 (defined as the molar ratio of water to surfactant concentration, $W_0 = [H_2O]/[\text{surfactant}]$) the size of the nanoparticle could be controlled. The sizes of the Nickel-nanoparticles prepared at $W_0 = 5$ were confirmed as 14–18 nm through Quasi Elastic Light Scattering (QELS) data Fig. 1a and Transmission Electron Microscopy (TEM) Fig. 1b. The Ni-nanoparticles prepared were round in shape and black in color (colloidal state).

2.3 Typical Methods for Thioacetalization of Carbonyl Compounds

A solution of carbonyl compound (5 mmol) in 5 mL acetonitrile was stirred with 1,2-ethanedithiol (5.2 mmol) and 600 μL of Ni-nanoparticle (14 ± 3 nm, 10 mol%) were added at 25 °C under N_2 atmosphere. The mixture was stirred for 20 min at 25 °C, and the progress was monitored by TLC using hexane: dichloromethane as an eluent. Following completion of the reaction, the crude reaction mixture was centrifuged at 6,000 r.p.m. for 10 min to remove the Ni-nanoparticles for reuse and then diluted with ethyl acetate (30 mL) and washed with water (3 × 10 mL) followed by aqueous sodium thiosulphate (2 × 10 mL, 10%). The organic layer was dried over anhydrous sodium sulfate (Na_2SO_4) followed by evaporation of solvent using a rotavapour under reduced pressure. The crude products were subjected to column chromatography using silica gel eluent (95% hexane and 5% ethyl acetate) which gave the thioacetylated product in excellent yield. Structural assignments of the products were based on their ^1H NMR, CHNSO, FT–IR and mass analyses. The analysis of complete spectral and compositional data revealed the formation of a thioacetylated product.

2.4 Typical Procedure for the Recycling of the Ni-nanoparticles (Catalyst)

After completion of the reaction, the reaction mixture was centrifuged at 4,000–6,000 r.p.m. for 10 min, which precipitated the Ni-nanoparticles as solid pellet at the bottom of the centrifuge tube. The nanoparticles were washed with acetonitrile 3–4 times to confirm the complete removal of any residual material. The particles were than redispersed in the desired solvent for further catalytic reaction cycles. The same process was repeated after each reaction cycle to isolate and reuse the Ni-nanoparticles as catalyst.

3 Results and Discussion

Thioacetalization reactions were carried out using various aliphatic, aromatic, and heterocyclic aldehydes and ketones with 1,2-ethanedithiol, in the presence of Ni-nanoparticles (14 ± 3 nm, 10 mol%) in acetonitrile at room temperature under N_2 atmosphere. All of these reactions gave the corresponding 1,3-dithiolanes in relatively high yields (21 showed the lowest yield of 68%). The results of these studies are tabulated in Table 1 and the reaction mechanism is shown in Fig. 2.

It is clear from the mechanism, that the corresponding methyl ketones show a lower yield as compared to the aldehydes (Table 1, Entry-1 and 13; 11 and 21 can be chosen as representative examples of aromatic and aliphatic carbonyl compounds for proving this point). This might have been because of steric factors (the extra bulk imposed by the methyl group on the attaching thiol

Table 1 Ni-nanopartcles catalysed selective dithioacetalization of carbonyl compounds[a]

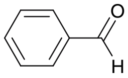
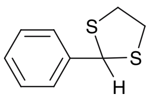
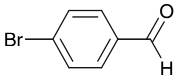
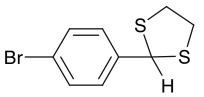
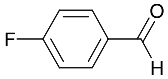
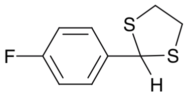
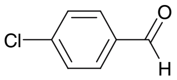
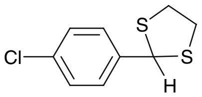
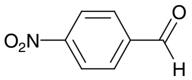
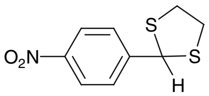
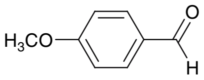
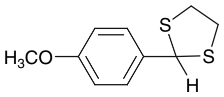
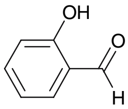
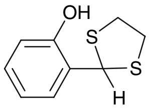
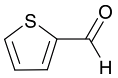
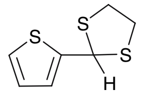
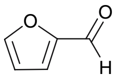
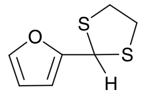
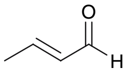
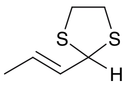
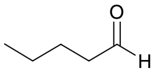
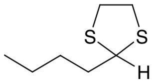
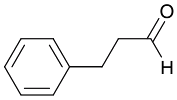
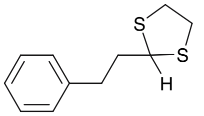
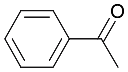
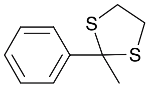
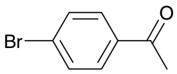
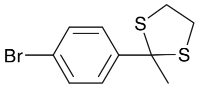
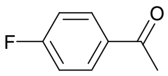
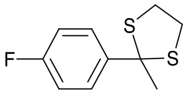
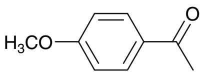
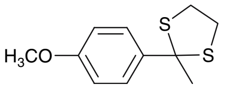
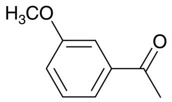
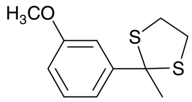
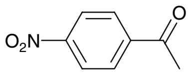
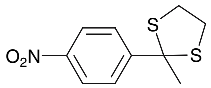
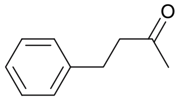
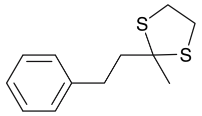
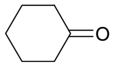
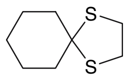
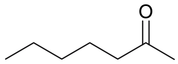
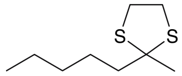
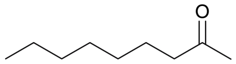
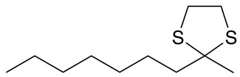
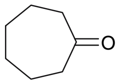
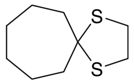
Entry	Substrate	Product	Time (min)	Yield (%)[b,c]
1.			20	96
2.			22	92
3.			22	92
4.			20	91
5.			25	93
6.			22	90
7.			20	87
8.			45	79
9.			45	76
10.			25	87
11.			25	84
12.			35	79
13.			20	92
14			22	90
15.			20	92
16.			24	91

Table 1 continued

Entry	Substrate	Product	Time (min)	Yield (%)[b,c]
17.			25	89
18.			23	94
19.			30	73
20.			22	89
21.			20	68
22.			20	72
23.			25	89

[a] Reaction condition: Carbonyl compound (5 mmol), 1,2-ethanedithiol (5.2 mmol), Ni-nanoparticles (14 ± 3 nm, 10 mol%), 25 °C, solvent (5 mL), stirred under N_2 atmosphere

[b] Confirmed by comparison with authentic samples (FT–IR, TLC, M.P/B.P.)

[c] Determined by GC

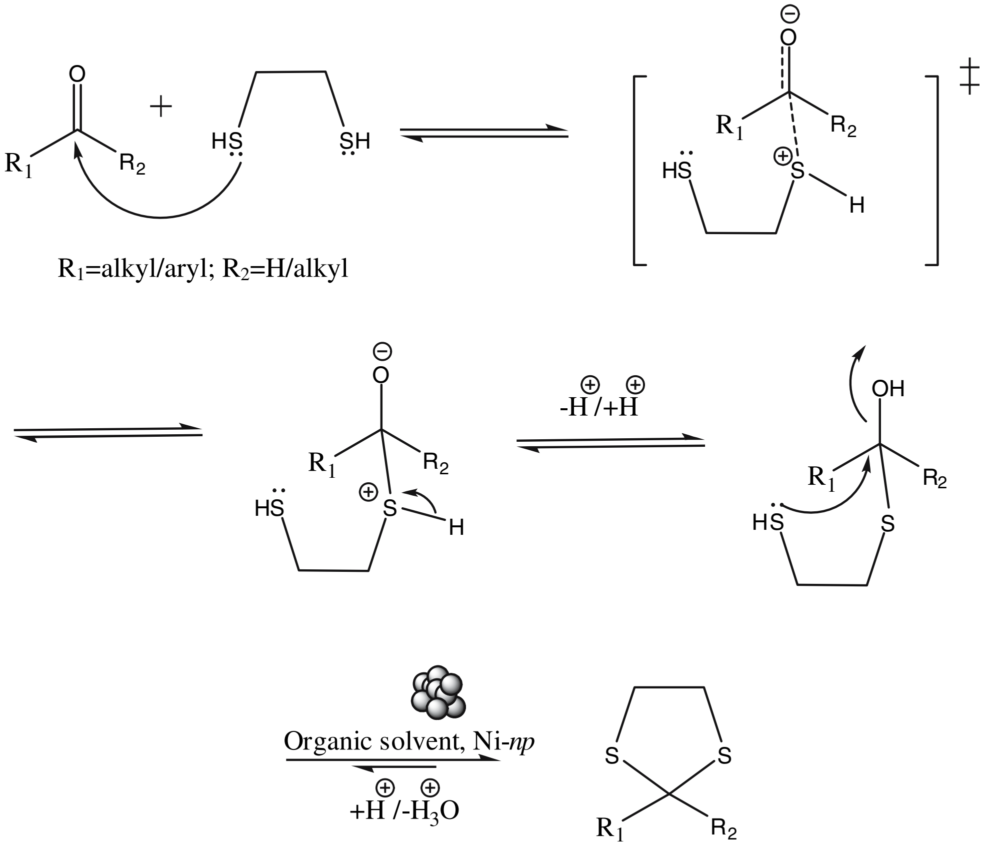
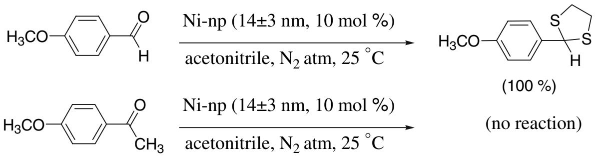


Fig. 2 Proposed mechanism for the protection of carbonyl compound using ethane dithiol over nano-sized Nickel catalyst

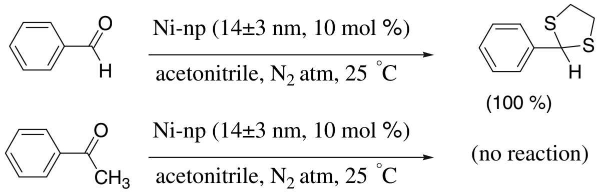
nucleophile), or electronic factors (the electron-donating inductive effect of methyl group renders the carbonyl carbon less electrophilic) or a combination of both. Amongst the aromatic carbonyl compounds, the reaction mechanism suggests that the electron withdrawing substituents would activate the benzene ring and thus increase the yield of the products. On the other hand, the electron donating substituents (Table 1, Entry-16 and 17) would show a slight decrease in the yield of the corresponding 1,3-dithiolanes. The experimental observations however show that electronics does not play a very significant role for this process as the differences in yields (~2%) are acceptable within the errors involved. Finally, for substituents at the *ortho* position, steric hindrance to the incoming nucleophile played a role in lowering the yield as well (Table 1, Entry-7).

Amongst the aliphatic carbonyl compounds, those with a more electrophilic carbonyl group showed a greater yield (Table 1, Entry-10 and 11). In general, the aromatic compounds showed a greater yield than the aliphatic or alicyclic compounds (Table 1, Entry-1 and 12). This might have been because of the absence of electronic stability of the corresponding transition states in aliphatic or alicyclic compounds by resonance.

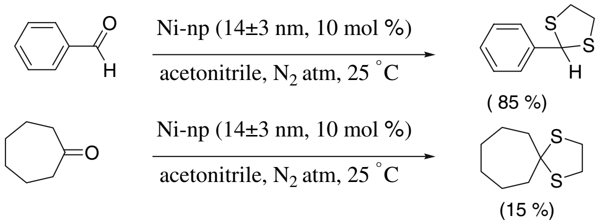
It is noteworthy that the aliphatic or alicyclic ketones did not undergo the reaction smoothly at room temperature (Table 1, Entry-19, 21 and 22). These ketones have a yield that is less than 75%. This might have been due to a combination of steric and electronic factors described above. This result prompted us to explore the chemoselective protection of aldehydes in the presence of ketones. The reaction of an equimolar amount of a carbonyl compound mixture that consists of various aromatic/heteroatomic/α, β-unsaturated aldehydes, and similar ketones was carried out with 1,2-ethanedithiol in the presence of Ni-nanoparticles (14 ± 3 nm, 10 mol%) under N_2 atmosphere at room temperature (Scheme 1, Table 1). In each case the corresponding dithioacetals were obtained in good to excellent yields in a short reaction time (~20 min). The products were purified by column chromatography using silica gel and the purity of the products was determined by GC analysis. In representative examples, when an equimolar amount of *p*-methoxybenzaldehyde and *p*-methoxyacetophenone were treated with 1,2-ethanedithiol in the presence of 10 mol% of Ni-nanoparticles (14 ± 3 nm), the *p*-methoxybenzaldehyde was converted to the corresponding 1,3-dithiolane in a 100% yield and *p*-methoxyacetophenone was found to remain unreacted (Scheme 2). In the case of a competition reaction of equimolar amounts of benzaldehyde and acetophenone (5 mmol each) with 1,2-ethanedithiol (5.2 mmol) in the presence of Ni-nanoparticles as catalyst (14 ± 3 nm, 10 mol%), benzaldehyde was converted to the corresponding 1,3-dithiolane quantitatively and acetophenone was again found to be unreacted (Scheme 3). In a third competitive reaction, we treated an equimolar amount of benzaldehyde and cycloheptanone with 1,2-ethanedithiol using identical procedures. The benzaldehyde reacted to produce an 85% yield while the cycloheptanone gave a yield of only 15% (Scheme 4).



Scheme 2



Scheme 3



Scheme 4

In all these cases, the aldehyde reacted in almost quantitative yields while the ketone remained unreacted. These reactions are kinetically controlled. The reaction time is only 20 min and thus equilibrium is not allowed to set in. The final step of the reaction mechanism is irreversible as the water which is eliminated separates out from the organic phase into an aqueous phase. In this way, our claim of having developed a gentle methodology for the chemoselective protection of aldehydes using 1,3-dithiolanes in the presence of ketones is justified.

3.1 Optimization of the Amount of Ni-nanoparticles in the Thioacetalization of Carbonyl Compounds

We observed that the catalyst concentration plays a major role in optimization of the product yield. On increasing the molar concentration of the Ni-nanoparticles (14 ± 3 nm) from 2 to 20 mol% for thioacetalization of aldehydes and ketones, it was observed that increased loading of the catalyst from 10 to 20 mol% gave almost

Table 2 Optimisation of the amount of Ni-nanoparticles for the formation of thioacetalized products

Mol% catalysts	Entry a (Table 1)		Entry d (Table 1)	
	Yield (%)[b]	Time (min)	Yield (%)[b]	Time (min)
2	72	20	68	20
5	81	20	76	20
10	96	20	92	20
15	93	20	91	20
20	91	20	91	20

[a] Reaction condition: Carbonyl compound (5 mmol), 1,2-ethanedithiol (5.2 mmol), Ni-nanoparticles (14 ±3 nm, 10 mol %), 25 °C, acetonitrile (5 mL), stirred under N_2 atmosphere

[b] Determined by GC

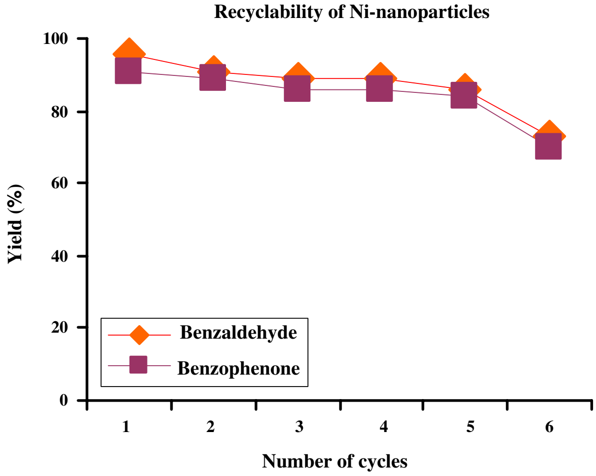


Fig. 3 Recyclability of Ni-nanoparticles catalysed dithioacetalization of carbonyl compounds. Reaction condition: carbonyl compound (5 mmol), 1,2-ethanedithiol (5.2 mmol), Ni-nanoparticles (14 ± 3 nm, 10 mol%), 25 °C, acetonitrile (5 mL), stirred under N_2 atmosphere. Determined by GC

same yield of product (Table 2). However, it appeared that a concentration of 10 mol% of Ni-nanoparticles is the suitable choice for the optimum yield of thioacetalized product (Table 3).

3.2 Solvent Effect

Various solvents were used in order to evaluate the scope and limitations of the reaction. Compounds **1**, **2** and **4** were selected and the reaction outlined above was carried out in the chosen solvents. Clearly, acetonitrile stands out as the solvent of choice, with its fast conversion and quantitative yield. In general, the polar aprotic solvents (acetonitrile and DMF) resulted in the best yields. The protic solvents (methanol and ethanol) gave the lowest yield as the thiol nucleophile was solvated and consequently its nucleophilicity decreased. The non-polar dicholoromethane gave an intermediary yield. Methanol and ethanol being completely miscible with water hindered the separation of water from the organic phase in the final step of the reaction. This might have also lead to a lower yield in methanol and ethanol (~60%).

3.3 Recyclability

The Ni-nanoparticles could be recycled by separating them from the reaction mixture by mild centrifugation. They could be used as a catalyst for the same reaction again and the change in their catalytic activity was studied. The relation between the number of cycles of the reaction and the catalytic activity in terms of yield is presented in the Fig. 3. It was observed that with the increasing number of cycles of the reaction, the catalytic activity of the Ni-nanoparticles slightly decreased. This might have been due to the slow oxidation of Ni-nanoparticles.

Table 3 Effect of solvents for the Ni-nanoparticles catalyzed thioacetalization of carbonyl compounds[a,b]

Solvent	Entry-1 (Table 1)		Entry-2 (Table 1)		Entry-4 (Table 1)	
	Time	Conversion (%)[c]	Time	Conversion (%)[c]	Time	Conversion (%)[c]
Dichloromethane	20	70	20	74	20	52
Methanol	20	58	20	62	20	50
Ethanol	20	65	20	71	20	55
Dimethylformamide	20	80	20	86	20	60
Acetonitrile	20	96	20	92	20	65

[a] Reaction condition: Carbonyl compound (5 mmol), 1,2-ethanedithiol (5.2 mmol), Ni-nanoparticles (14 ± 3 nm, 10 mol%), 25 °C, solvent (5 mL), stirred under N_2 atmosphere

[b] Confirmed by comparison with authentic samples (FT–IR, TLC, M.P/B.P.)

[c] Determined by GC

4 Conclusion

A simple, eco-friendly and efficient procedure for the synthesis of 1,3-dithiolanes from diverse carbonyl compounds with 1,2-ethane dithiol is reported for the first time by our research group using inexpensive, easily recyclable, monodispersed Ni-nanoparticles (14 ± 3 nm) as catalyst. Our method is very quick, avoids the use of expensive reagents, high temperatures and leads to improved products yields. The ambient conditions, high reaction rates, excellent product yields and easy work up procedures at room temperature not only make this methodology an alternative platform to the conventional acid/base catalyzed thermal process but also brings it under the umbrella of environmentally greener and safer synthetic procedures. Additional applications of this technique are currently under investigation.

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