RESEARCH LETTER

Chemoselective acetylation of amines and thiols using monodispersed Ni-nanoparticles

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We report here a method by which Ni-nanoparticles can be used efficiently to catalyze the acetylation of a variety of amines and thiols under ambient conditions at room temperature. However in a competitive reaction, the thiol was acetylated selectively while the amine remained almost unaffected. The demonstrated chemoselectivity could have multiple potential synthetic applications. Some of the major advantages of this method are high yields, selectivity, short reaction times (<40 min), ease of operation, and compatibility with other protecting groups. Additionally, the process reported is environmentally benign.

Keywords: Ni-nanoparticles; acetylation; thiols; amines; heterogeneous catalyst

Introduction

The acetylation of amines and thiols is one of the most useful and versatile transformations in organic synthesis (1,2). The protection of such functional groups is often necessary during the course of various transformations in multi-step synthesis, often in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids, and natural products. An example of the use of acetylation for varied purposes could be found extensively in peptide synthesis (3). Protection of amino group is sometime essential due to medicinal value, e.g. preparation of paracetamol from 4-aminophenol. It is also used for detection of the presence of hydroxyl or amino group in a compound. The acetylation of amines or thiols is usually performed with acid anhydrides or acetyl chlorides in the presence of amine bases such as triethylamine or pyridine along with 4-(dimethylamino) pyridine along with 4-(dimethylamino) pyridine (which acts as a co-catalyst) or 4-pyrrolidinopyridine (4). Sometimes tributylphosphine is also employed as a less basic catalyst for acetylation reactions, particularly for substrates that are relatively sensitive to strong bases (5). In literature, several methods have been developed for the preparation of acetate from the corresponding alcohol or phenol or thiol using various metal salts, such as CoCl2 (6), ZnCl2 (7), RuCl3 (8), TiCl4–AgClO4 (9), LiClO4 (10), Mg(ClO4)2 (11), Zn(ClO4)2·6H2O (12), and some triflates such as Sc(OTf)3 (13), Me3SiOTf (14), In(OTf)3 (15), Cu(OTf)2 (16), Ce(OTf)3 (17), and Bi(OTf)3 (18) catalysts or stoichiometric reagents.

Recently, it was reported that I2 is also a useful catalyst for acetylation of alcohols under solvent free conditions. Although perchlorates (19–21) have been found to be effective catalysts for this transformation, they suffer from a serious drawback in the sense that as some of the perchlorates are highly explosive in nature (22). In addition, Mg(ClO4)2 has to be anhydrous in order to obtain an optimal yields (23). The other methods based on triflates (24–29) and I2 have several disadvantages as they have long reaction times, require dry reaction conditions (30–32), and invariably require arduous aqueous work-up and chromatographic separation procedures. Besides, the reagents are expensive and some of them are difficult to handle.

Although numerous methods could be found in the literature which give good yields of the acetylated products, contemporary organic synthesis is constantly striving for discovery and design of reagents that could potentially be selectively efficacious and not affect other sensitive protecting groups. The work in the field of metal nanoparticles as catalysts in synthetic organic chemistry has gained much interest since they have a large surface-volume ratio (33–35). The application of Ni-nanoparticles as catalysts in organic synthesis has hardly been explored. The use of Ni-nanoparticles has several advantages as compared to the traditional catalysts. Besides being inexpensive, we have been able to use them in the past to give high yields of desired products under mild conditions in a relatively short time.

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As a part of our continuing interest in the development of new synthetic methodologies (36–41), herein we report an efficient method for the selective acetylation of various amines and thiols (Scheme 1). We hypothesized that Ni-nanoparticles might be a useful catalyst for acetylation reactions based on various observations. Ni-nanoparticles have been used previously for the oxidative coupling of thiols to give the corresponding disulfide (42), condensation of alcohols with thiols to thioethers (43), and chemoselective reduction of aldehydes (44). These useful results encouraged us to study if the same Ni-nanoparticles could be implemented further for acetylation reaction. Here, we report the acetylation of amines and thiols by employing acetic anhydride in the presence of a catalytic amount of Ni-nanoparticles as catalyst at room temperature.

Our process is economic and eco-friendly (green) as it does not require elevated temperature, harsh acids or bases, produces high yield with excellent chemo selectivity and significantly reduces the reaction time. Moreover, it is applicable to a variety of aliphatic, aromatic, cyclic, and heterocyclic substrates. In addition, it is a one pot synthesis, it does not require inert atmosphere and has an easy work-up and product isolation from the catalyst. Traditionally when metal salts and other complexes were used as catalysts, an excessive amount of catalysts (usually in grams) was found in the form of waste after the reaction. In certain cases, this might be toxic. In our methodology, we have significantly reduced the amount of catalyst several folds to microgram levels (less chances of exhibiting toxicity). As far as toxicity of Ni-nanoparticles is concerned there are many 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 at a low dosage (45,46). Therefore, we claim that our method is environmentally benign and less toxic.

2. Results and discussion

All the reactions were carried out at room temperature and they proceeded with high efficiency. Our method is very mild and compatible with a wide range of functional groups (Tables 1 and 2). Although the exact mechanism for this reaction Ni-nanoparticles is not entirely clear, we postulate that the (Scheme 2) catalytic acetylation is initiated by coordinating carbonyl group of acetic anhydride to the Ni-nanoparticles. This coordination of carbonyl groups to the on the surface of the catalyst enhances its electrophilic character. This activated carbonyl group is attacked by heteroatom (N or S) of the substrate (nucleophilic amine or thiol), to produce the corresponding acetate.

Aromatic and aliphatic amines were successfully acetylated using Ni-nanoparticles (Table 1). It is expected from the mechanism that aromatic amines substituted with electron-withdrawing groups should react slower than amines substituted with electron-donating groups. Our results confirm this expectation as aromatic amines substituted by electron-withdrawing groups (Table 1, entry 4, 6) react less rapidly as compared to those that are substituted otherwise (Table 1, entry 2, 3); however, it is remarkable that there is no significant difference in the absolute times for these differentially substituted compounds. Indeed, even an aromatic amine that is sterically hindered by an electron-withdrawing nitro group (ortho position) was acetylated in a very high yield (Table 1, entry 6, 9). We suspected that this was because of the efficacy of the catalysts used. To test this, we carried out control experiments in the absence of a catalyst. We found that the reaction did not proceed at all and the starting materials remained intact.

Aliphatic and aromatic thiols were also acetylated in high yields (Table 2). However, even in these cases when a control experiment was conducted in the absence of a catalyst, the reaction did not proceed at all and intact starting materials were isolated.

Finally, in a competitive acetylation reaction using equimolar mixture of aniline and thiophenol, the thiophenol was acetylated selectively while the amine remained almost unaffected producing the corresponding thiamide. (Scheme 3) This selective acetylation of primary thiols over primary amines by this process is one of the considerable synthetic
importances. This shows the high chemoselectivity of the reaction toward $-\text{SH}$ group.

Thus, it is thus apparent from our data (Tables 1 and 2) that all aliphatic, aromatic, and heteroaromatic amines and thiols underwent the acetylation reaction smoothly. While the sterically hindered amines required a slightly longer time when compared with others, the yields were very good in every case.

### 2.1. Solvent effect

In order to elucidate the role of the solvents, various solvents were used in order to evaluate the scope and limitations of the reaction. It was found that Ni-nanoparticles catalyzed acetylation reaction were faster in acetonitrile rather than in other solvents, such as dichloromethane, chloroform, and tetrahydrofuran (Table 3). Interestingly, the reaction was extremely slow in tetrahydrofuran.

![Chemical structure](image1)

**Table 1. Protection (acetylation) of aliphatic, aromatic, and heteroaromatic amines using 10 mol% Ni-nanoparticles**

| Entry | Amine | Time (h) | Product | Yield (%)$^a$ |
|-------|-------|----------|---------|--------------|
| 1     | $\text{NH}_2$ | 0.75     | $\text{NHAc}$ | 92           |
| 2     | $\text{NH}_2\text{Br}$ | 0.08     | $\text{NHAc}\text{Br}$ | 96           |
| 3     | $\text{NH}_2\text{Cl}$ | 0.08     | $\text{NHAc}\text{Cl}$ | 98           |
| 4     | $\text{HOOC}$ | 0.16     | $\text{HOOC}\text{NHAc}$ | 90           |
| 5     | $\text{NH}_2$ | 0.25     | $\text{NHAc}$ | 87           |
| 6     | $\text{NH}_2\text{NO}_2$ | 0.17     | $\text{NHAc}\text{NO}_2$ | 88           |
| 7     | $\text{N}$ | 0.41     | $\text{N}\text{NHAc}$ | 91           |
| 8     | $\text{CH}_3\text{-CH}_2\text{-NH}_2$ | 0.26     | $\text{CH}_3\text{-CH}_2\text{-NHAc}$ | 82           |
| 9     | $\text{H}_3\text{CO}$ | 1.0      | $\text{H}_3\text{CO}\text{NHAc}$ | 79           |
| 10    | $\text{NH}_2\text{NO}_2$ | 1.0      | $\text{NHAc}\text{NO}_2$ | 94           |

$^a$Acetonitrile was used as solvent in all the reactions.

### 2.2. Recyclability of the catalyst

The Ni-nanoparticles could be recycled by separating them from the reaction mixture by mild centrifugation and used as a catalyst for the same reaction again to check the change in their catalytic activity. It was observed that with the increasing number of cycles of the reaction, the catalytic activity of the Ni-nanoparticles decreased and it was nearly lost after fourth cycle. The relation between the number of cycles of the reaction and the catalytic activity in terms of yield is shown in Figure 1.

### 3. Experimental

#### 3.1. General remarks

All reactions were carried out 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 and $^{13}$C-NMR spectra were recorded on a Bruker Spectrospin 300 MHz spectrometer in CDCl$_3$ (with Trimethylsilane (TMS) for $^1$H-NMR and CDCl$_3$ for $^{13}$C-NMR as internal references). Mass spectra were recorded on TOF-Mass spectrometer Model No. KC455. Melting points were recorded on Buchi melting point 540 instruments.

### 3.2. General procedure for acetylation reaction

Acetic anhydride (2 mmol) was added drop wise to a solution of the amine or thiol (1 mmol) and Ni-nanoparticles (10 mol%) in acetonitrile (5 mL) at

| Entry | Reactant (thiol) | Product | Time (h) | Yield (%) |
|-------|-----------------|---------|----------|-----------|
| 1     |                  |         | 0.08     | 97        |
| 2     |                  |         | 0.18     | 94        |
| 3     |                  |         | 0.2      | 91        |
| 4     |                  |         | 0.36     | 94        |
| 5     |                  |         | 0.16     | 83        |
| 6     | CH$_3$-(CH$_2$)$_7$-SH | CH$_3$-(CH$_2$)$_7$-SAc | 0.5 | 81        |
| 7     |                  |         | 1.0      | 82        |
| 8     |                  |         | 0.18     | 89        |

$^a$Acetonitrile was used as solvent in all the reactions.

Scheme 3. Competitive acetylation using equimolar mixture of aniline and thiophenol.

| Table 2. Protection (acetylation) of aliphatic, aromatic thiols using 10 mol% Ni-nanoparticles$^a$. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Entry | Reactant (thiol) | Product | Time (h) | Yield (%) |
|-------|-----------------|---------|----------|-----------|
| 1     |                  |         | 0.08     | 97        |
| 2     |                  |         | 0.18     | 94        |
| 3     |                  |         | 0.2      | 91        |
| 4     |                  |         | 0.36     | 94        |
| 5     |                  |         | 0.16     | 83        |
| 6     | CH$_3$-(CH$_2$)$_7$-SH | CH$_3$-(CH$_2$)$_7$-SAc | 0.5 | 81        |
| 7     |                  |         | 1.0      | 82        |
| 8     |                  |         | 0.18     | 89        |

Note: 2 mmol of acetic anhydride added to thiophenol and aniline, respectively, in 5 mL solvent, having 10 mol% of Ni-nanoparticles (20 nm), stirring at room temperature. $^a$The conversion was determined by $^1$H-NMR analysis of the crude product.

| Table 3. Solvent effect on Ni-nanoparticles catalyzed acetylation of amine and thiols at room temperature. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Solvent | Thiophenol | Aniline | Time | Conversion$^a$ (%) | Time | Conversion$^a$ (%) |
|---------|------------|---------|------|-------------------|------|-------------------|
| THF     | 1 h        | 22      | 1 h  | 30                |
| CH$_2$Cl$_2$ | 1 h    | 60      | 1 h  | 60                |
| CHCl$_3$ | 1 h        | 45      | 1 h  | 76                |
| $n$-C$_6$H$_6$ | 1 h | 30      | 1 h  | 30                |
| CH$_3$CN | 35 min     | 85      | 30 min | 90             |
Supplementary data (procedural details of synthesis of Ni-nanoparticles and its characterization data) associated with this article can be found, in the online version.

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Figure 1. Recycling of Ni-nanoparticles for acetylation reaction.
Note: 2 mmol of acetic anhydride added to thiophenol and aniline, respectively, in 5 mL acetonitrile, having 10 mol% of Ni-nanoparticles (20 nm), stirring at room temperature.

4. Conclusion

In conclusion, Ni-nanoparticles acted as an efficient catalyst for the acetylation of aliphatic and aromatic thiols and amines. A variety of amines and thiols have been acetylated rapidly using catalytic amount of the catalyst. Our method is very quick (<40 min) and avoids the use of expensive reagents, elevated temperature, and leads to improved yield. Additional applications of this technique are currently under investigation.

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