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Razi University

Faculty of Chemistry
Department of Organic Chemistry

M.Sc. Thesis

Title of Thesis

**Application of silica sulfuric acid in Acylation, Formylation and
Thioacetalization**

Supervisors:

Prof. M. M. Khodaei

Dr. A. Alizadeh

By:

Ziba Akbaripanah

August 2009

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اساتید راهنما:

پروفسور محمد مهدی خدایی

دکتر عبدالحمید علیزاده

نگارش:

زیبا اکبری پناه

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Ziba Akbaripanah

Evaluated and approved by thesis committee: as *Very good*

M. M. Khodaei M. M. Khodaei, Ph. D., Prof. of Organic Chemistry (Chairman)

A. Alizadeh A. Alizadeh, Ph. D., Assist. Prof. Of Organic Chemistry

H. Adibi H. Adibi, Ph. D., Assist. Prof. of Organic Chemistry

K. Bahrami K. Bahrami, Ph. D., Assist. Prof. of Organic Chemistry

August 2009

Dedicated To:

My Dear Parents

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Abstract

In this thesis, acylation reactions and N-formylation of amines and thioacetalization of carbonyl compounds have been investigated.

Acylation of phenols, amines and thiols containing both electron-withdrawing and electron-donating groups were carried out with acetic anhydride in the presence of silica sulfuric acid at room temperature under solvent-free conditions, and esters, amides and thioesters were obtained in good yields at short reaction times.

In continue, N-formylation of amines containing both electron-withdrawing and electron-donating groups are carried out with formic acid in the presence of silica sulfuric acid at 50-60 °C, and produced formamide products in excellent yields at short reaction times.

Finally, thioacetalization of carbonyl compounds in the presence of silica sulfuric acid, was carried out with 1,2-ethanedithiol at 60 °C under solvent-free conditions, in short reaction times and high yields.

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Chapter One

Introduction

1.1. A review on advantages of silica sulfuric acid

Solid acids have many advantages such as ease of handling, decreasing reactor and plant corrosion problems, and environmentally safe disposal.^{1, 2} Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes.³ On the other hand, reduction the amount of sulfuric acid and/or simplification in handling procedures is required for risk reduction, economic advantage and environment protection. Green chemistry has been defined as a set of principles that reduce or eliminate the use or generation of hazardous substances.

In addition, there is current research and general interest in heterogeneous systems because of their importance in industry and in developing technologies.⁴ Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. These reactions are effected by the reagents immobilized on the porous solid supports and have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier work-up.⁵ Both silica sulfuric acid (SSA) and silica chloride (SC) are solid acids which can be used for different organic functional group transformations either as reagent or as catalyst under heterogeneous conditions.

Recently, has demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimisation of chemical wastes as compared to the liquid phase counterparts. In continuation of studies on the application of inorganic acidic salts has found that silica gel reacts with chlorosulfonic acid to give a white powder which was named "silica sulfuric acid" (SSA).⁶

It is interesting to note that the reaction is easy and clean without any work-up procedure, because HCl gas is evolved from the reaction vessel immediately.⁷ However, we hoped that SSA would be a superior proton source compared to other reported solid supported acids or acidic resins, such as polystyrene sulfonic acid and Nafion-H (Nafion has the handicap of low surface area which renders it unrealistic for practical use)² for running reactions under heterogeneous conditions.

1.2. A review on preparation of esters, amides and thioesters

Acetylation of phenols and thiols is usually carried out by using acid anhydrides or acyl chlorides in the presence of protic acids,⁸ various Lewis acid catalysts or basic reagents such as 4-(dimethylamino)pyridine [DMAP]⁹⁻¹⁰ and tributylphosphine.¹¹

The protection of phenols and amines as their acylated derivatives¹² is a straightforward approach due to the feasibility of regeneration of the parent compound by nucleophilic deprotection.¹³ Acylation is normally achieved by treatment with anhydrides in the presence of suitable catalyst. Various organic (e.g., Bu₃P) and inorganic (e.g., halides, triflate and tetrafluoroborate of transition, rare earth and alkali metals) catalysts have been employed for this purpose.¹²

The reported methodologies suffer from one or more of the following disadvantages: (i) potential health hazard [DMAP is highly toxic (e.g., intravenous LD50 in the rat: 56 mg/kg)]¹⁴ and Bu₃P is flammable (flash point: 37 °C),¹⁵ need to use halogenated solvents), (ii) difficulty in handling (Bu₃P) undergoes aerial oxidation and triflates are moisture sensitive, (iii) high cost of the catalysts (e.g., triflates), (iv) requirement of special efforts to prepare the catalysts [Bi(OTf)₃,¹⁶ Nafion-H, yttria-zirconia, AlPW₁₂O₄₀, and Mn(haacac)Cl], (v) the lack of atom economy (use of excess of acetylating agents), (vi) stringent reaction conditions and the requirement of longer reaction times, (vii) in many cases the reported acylation methodologies are applicable to alcohols only and not suitable for acid-sensitive substrates and (viii) few catalysts are reported for acylation of challenging substrates such as electron deficient and sterically hindered phenols, sterically hindered alcohols and electron deficient as well as sterically hindered amines. Thus, there is a need for development of a suitable catalyst for acylation of challenging substrates.¹⁷

The acylation of alcohols and phenols, amines and thiols is one of the most useful and versatile transformations in organic synthesis.¹² In addition, the protection of hydroxyl functionality as acetate is preferred due to its ease of introduction, stable under mild acidic reaction conditions and also eases of removal by mild alkaline hydrolysis.¹⁸ Acetylation of hydroxy groups is an often used protection technique because of the ease of formation as well as mild conditions for deprotection.¹²

On the other hand, protic and Lewis acids, such as *p*-toluene sulfonic acid, zinc chloride and cobalt chloride, are well known to catalyze the acylation reaction using acetic anhydride as acetylation agent.¹⁹⁻²¹ Recently, research has been directed to overcome the

above problems which culminated in the development of insoluble solid acids, such as montmorillonite K₁₀, KSF and molecular sieves as catalysts.²²⁻²⁶

Some of the reported methods work well on primary or secondary alcohols only and fail to protect tertiary alcohols or less reactive phenols. A few of these methods also suffer from side reactions such as dehydration and rearrangement and might not be fully compatible for the acylation reactions with substrates bearing acid-sensitive groups. Thus, simple, efficient, and mild methods are still desirable.²⁷

In recent years there has been a tremendous upsurge of interest in various chemical transformations performed under heterogeneous catalysis.²⁸⁻³⁰ However, the practice of expensive and toxic metal precursors limits the use of these methods and they become unsuitable in the context of green chemistry. Furthermore, many of these methods are applicable for the acetylation of alcohols only. Lack of chemoselectivity and reusability of some of these reported catalysts made us think about the development of a mild and efficient methodology. Keggin type heteropolyacids and their salts are a class of highly acidic solid acid catalysts made up of heteropolyanion having metal-oxygen octahedral as the basic structural unit.³¹

Among the various protecting groups used for this purpose, acyl is one of the most common groups in view of its easy introduction, being stable to the acidic reaction conditions, and also easily removable by mild alkaline hydrolysis.³²

Acylation of such functional groups is often necessary during the course of various transformations in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products. Although numerous methods to achieve acylation reactions are known, newer methods continue to attract attention for their experimental simplicity and effectiveness.³³

Thioesters are usually prepared by condensation of a thiol and an acid chloride and they have widespread applications in synthetic chemistry as precursors to aldehydes, ketones, acids, esters, lactones, amides, lactams and heterocycles.³⁴ Surprisingly, in view of the diverse chemistry this functional group offers, it has attracted scant interest from combinatorial chemists.³⁵ Due to the importance of thioesters, various chemical and enzymatic methods have been developed for their synthesis directly from carboxylic acids³⁶ or acid chlorides.³⁷ The conversion of alkyl halides to thioesters using potassium thioacetate is well reported in the literature.³⁸

A free SH group can be protected as thioether, thioester or, after oxidation, as disulfide, from which it can be regenerated by reduction.³⁹ Thioesters are formed and

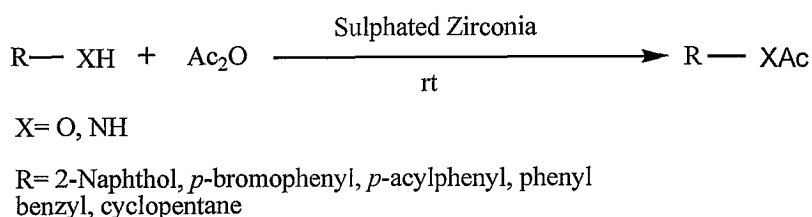
cleaved in the same way as oxygen esters; they are more reactive against nucleophilic substitution⁴⁰ and used as 'activated esters'. The yields and reaction conditions depend on the solvent, the basic catalyst and the acidity of thiol.³⁹

So that many methods have been reported for their preparation.⁴¹ The related thioesters (thiol esters) have received much less attention.⁴² Despite the fact that thioesters are suitable intermediates for several functional group manipulations and C-C bond-forming reactions.⁴³

1.2.1. Sulphated Zirconia

Ratnam et al. reported the preparation of sulphated zirconia, which is active towards the *O* or *N*-acylation of alcohols, phenols and amines with acid anhydride as an acylating agent under solvent free conditions. Sulphated zirconia prepared by the treatment of a high surface area zirconia ($320\text{m}^2\text{ g}^{-1}$) with 1N H_2SO_4 shows a strong acidity after calcinations at 893 K. The sulphated zirconia obtained by sulphation has 14.5 wt. % S just after oven drying and 1.8 wt. % S after calcination at 893 K.

The described methodology illustrates a very simple acylation procedure, with wide applicability, extending the scope to benzylic, primary, secondary, tertiary, and cyclic alcohols. Sterically hindered and electron deficient phenols and amines are efficiently acylated under similar conditions and solvent free conditions⁴⁴ (Scheme 1.1).

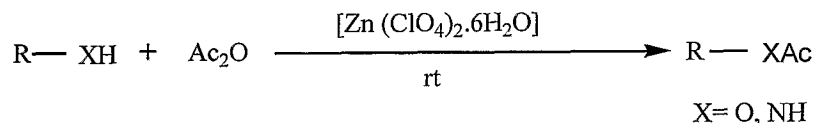


Scheme 1.1

1.2.2. Zinc perchlorate hexahydrate [$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$]

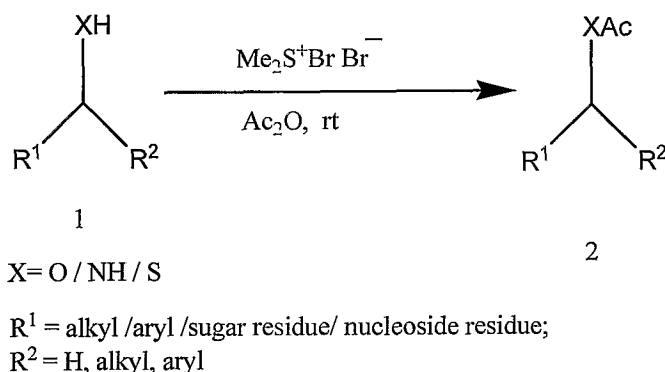
Shivani et al. have reported that commercially available zinc perchlorate hexahydrate [$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$] was found to be a highly efficient catalyst for acylation of electron deficient phenols, sterically hindered alcohols and electron deficient and sterically hindered amines. The acetylated derivatives were obtained in excellent yields under solvent-free conditions and at room temperature. However, the reaction of highly electron

deficient and sterically hindered phenol, e.g., 2,4-dinitrophenol required heating at 80 °C. The catalyst was found to be of general use with respect to other acylating agents such as propionic, *iso*-butyric, pivalic, benzoic and chloroacetic anhydrides.¹⁷



1.2.3. Bromodimethylsulfonium bromide

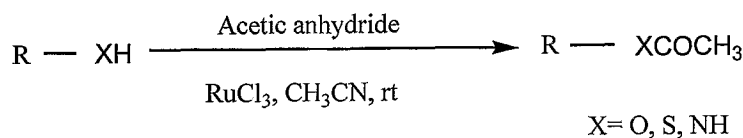
Khan et al. realized that bromodimethylsulfonium bromide, which can generate HBr in the reaction medium on reaction with alcohol, might be a very useful pre-catalyst for the acetylation reactions. Various alcohols and phenols, amines, thiols and thiophenols can be transformed easily to the corresponding acetate derivatives, on treating with two equivalents of acetic anhydride in the presence of 5 mol% bromodimethylsulfonium bromide pre-catalyst at room temperature in good yields⁴⁵ (Scheme 1.2).



Scheme 1.2

1.2.4. RuCl₃ / CH₃CN

Kanta De has been applied a mild and efficient method for acylation of alcohols, phenols, thiols, and amines using a catalytic amount of ruthenium chloride in acetonitrile at room temperature. Similarly, several primary and secondary alcohols underwent the acetylation reactions in excellent yields (Scheme 1.3). Interestingly, tertiary alcohols are acetylated smoothly with no side product.²⁷



Scheme 1.3

1.2.5. In (OTf)₃

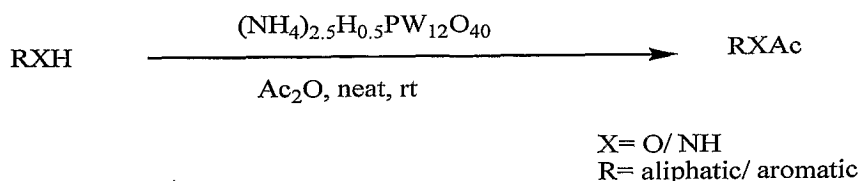
Chakraborti et al. reported the use of In(OTf)₃ as catalyst for the acetylation.⁴⁶ The larger negative H_0 value of -14.1 of triflic acid⁴⁷ suggests that metal triflates should be very strong Lewis acids and thus might lead to competitive side reactions (e.g. rearrangement, dehydration, etc.) for acid sensitive substrates.

They reasoned that the use of an In (III) salt derived from a weaker protic acid should make the catalyst less susceptible to moisture and circumvent the problem of side reactions for acid-sensitive substrates. Although metal triflates have been claimed to be the most effective acylation catalysts, the high cost, susceptibility to moisture and commercial non-availability (in some cases) do not make the metal triflates popular for use in large scale synthesis. In a model reaction of 2-hydroxynaphthalene (1.0 mmol) with Ac₂O (1 equiv), the acetylation was complete in 2 min under neat conditions at room temperature affording a 95% yield in the presence of InCl₃ (0.1 mol %). The InCl₃ was recovered and further used without significant loss of its catalytic activity.

1.2.6. Ammonium salt of 12-tungstophosphoric acid

((NH₄)_{2.5}H_{0.5}PW₁₂O₄₀)

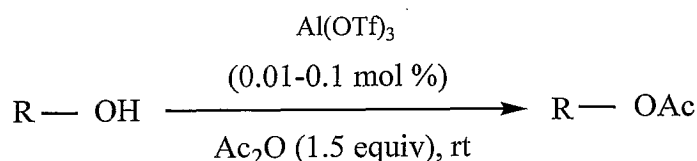
The ammonium salt of 12-tungstophosphoric acid ((NH₄)_{2.5}H_{0.5}PW₁₂O₄₀) was employed for the acetylation of a variety of alcohols, phenols and amines under solvent-free conditions at 30 °C (Scheme 1.4). This method showed preferential selectivity for the acetylation of the amino group in the presence of hydroxyl group.. *Satam et al.* have tested the catalytic activity of various salts for the transesterification of soybean oil. The salts of 12-tungstophosphoric acid were prepared by standard procedure and the catalytic activity was studied at the reflux temperature of methanol-oil mixture.⁴⁸



Scheme 1.4

1.2.7. Al(OTf)₃

Kamal et al. reported that a number of alcohols, phenols and thiophenols can be acetylated with acetic anhydride in excellent yields, in the presence of 0.1 mol % of Al(OTf)₃ at room temperature under solvent-free conditions in short times (10–40 s) (Scheme 1.5). Encouraged by the success of this reaction various primary, secondary, benzylic and cyclic alcohols and phenols were subjected to acylation in excellent yields.⁴⁹



Scheme 1.5

Other catalysts available in the literature for such acylation reactions are: DMAP⁵⁰ and Bu₃P⁵¹ and Lewis acids such as CoCl₂,⁵² Sc(OTf)₃,⁵³ Sc(NTf₂)₃,⁵⁴ TMSOTf,⁵⁵ Bi(OTf)₃,⁵⁶ Cu(OTf)₂,⁵⁷ TaCl₅,⁵⁸ zeolites,⁵⁹ clays,⁶⁰ Nafion-H,⁶¹ yttria-zirconia,⁶² LiClO₄,⁶³ InCl₃,⁶⁴ and In(OTf)₃.⁶⁵

1.3. Applications of esters, amides and thioesters

Protection of functional groups plays an important role in the synthesis of complex organic molecules such as natural products. Acetylation have found increasing attention as highly familiar protocols.⁶⁶ Organic esters represent an important family of intermediates widely employed in the synthesis of fine chemicals, drugs, plasticizers, perfumes, food preservatives, pharmaceuticals and chiral auxiliaries.^{12, 67} The acylation of alcohols, phenols and amines is one the most frequently used transformations in organic synthesis.⁶⁸ It also provides an efficient route for protecting –OH groups during oxidation, peptide coupling and glycosidation reactions.^{12, 69}

The presence of the phenolic/alcoholic hydroxyl and amino groups in a wide spectrum of biologically active compounds necessitates the manipulation of the chemical reactivity of these functional groups during the synthesis of multifunctional synthetic targets possessing one or more of these groups.¹⁷

Amides and organic esters represent an important family of intermediates widely employed in the synthesis of industrial chemicals, cosmetics and food additives.⁷⁰ Acylation of such functional groups is often necessary during the course of various transformation in a synthetic sequence, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids and natural products.³³ Among them, the conversion of hydroxyl or amino group into the corresponding acetate is essential due to its medicinal value, e.g. the preparation of paracetamol from 4-aminophenol as well as for confirmation of the presence of hydroxyl or amino group in a compound.⁷¹

Biologically-active thioesters play central roles in living cells serving as essential metabolic intermediates due to their ability to act as excellent intermediates for acyl group transfer reactions. In addition, biosynthesis of polyketides and nonribosomal polypeptides achieved via thioester intermediates of fatty acids and amino acids.⁷² Over the past 50 years, extensive chemical and enzymatic methods have been developed to synthesize various thioesters for probing mechanisms of numerous thioester-utilizing enzymes.⁷³

Sulphur compounds are of particular interest among the multiple constituents of food flavour because of their very powerful odours. A amount of some of them can have a considerable effect on food olfactory characteristics.

1.4. A review on preparation of formamides

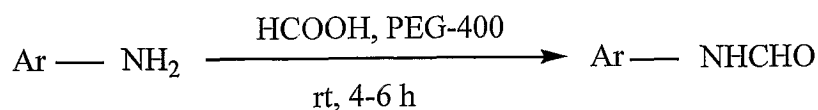
Various methods are available for N-formylation of amines.⁷⁴⁻⁸² Formamides are useful reagents in Vilsmeier formylation reactions.⁸³ Moreover, they are Lewis bases and can catalyze several organic transformations.⁸⁴

The synthesis of formamides by the way of N-formylation of amines using known and new formylating agents is documented.⁸⁵⁻⁸⁶

Formamides are Lewis bases, which are known to catalyze reactions such as allylation⁸⁷ and hydrosilylation⁸⁸ of carbonyl compounds. asymmetric allylation of aldehydes has been achieved with chiral formamides.⁸⁹ They have been used in the synthesis of formamidines⁹⁰ and isocyanides.

1.4.1. Polyethylene glycol

Das et al. have observed that the N-formylation of aniline can efficiently accomplished in this reaction medium by treatment with formic acid at room temperature.⁹¹

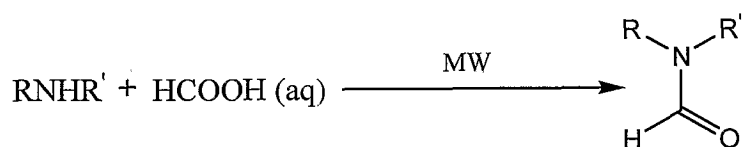


Scheme 1.6

A series of anilines were converted into the corresponding N-formyl amines in high yields (Scheme 1.6). No additional solvent or catalyst was used. Different functionalities such as alkyl, nitro, halogens and carbonyl remained intact. Anilines containing both electron-donating and electron-withdrawing groups underwent the conversion smoothly. Previously, the N-formylation of anilines having electron-withdrawing groups was found to be difficult.⁹² The present conversion is also chemoselective.

1.4.2. Microwave-induced organic reaction enhancement ('MORE') chemistry technique

Bose et al. tested 'MORE' chemistry approach for N-formylation with aq formic acid (80%). Microwave-induced organic reaction enhancement ('MORE') chemistry technique (open vessel; controlled microwave energy to stay below the boiling point of the reaction mixture) was used for the N-formylation of aliphatic and aromatic amines and amino heterocycles with aq formic acid (80%) on a multiple gram scale in a few minutes⁹³ (Scheme 1.7).



Scheme 1.7

1.4.3. The use of polymer (ion-exchange resin) and inorganic solid supported reagents

Desai et al. reported on the use of polymer (ion-exchange resin) and inorganic solid-supported reagents as a formylating agent to produce formamides starting from primary and secondary amines. Using an insoluble polymer or an inorganic solid-supported reagent as a formylating agent, microwave irradiation furnished the corresponding formamides in high yields, with reduced reaction time and solvent volume over the conventional approach⁹⁴ (Scheme 1.8).