CHAPTER 1

INTRODUCTION

1.1 Common base reagents in organic synthesis

In organic synthesis, bases are commonly used as reagents in the reactions involving hydrogen transfer such as Michael addition, Knoevenagel condensation, alkylation, acylation and sulfonation. Tertiary amines such as triethylamine (TEA), *N*-methyl morpholine (NMM), quinoline, *N*,*N*-diisopropylethylamine (DIPEA or DIEA), methylpyridine and dimethylamine are often used as base reagents since lone pair electrons of nitrogen can bind with proton leading to the formation of quaternary ammonium salt [1-2]. Especially, diisopropylethylamine or so called Hünig's base, DIPEA or DIEA, is a tertiary amine commonly used in organic synthesis as a base. Because the nitrogen atom is shielded by the two isopropyl groups and an ethyl group, only a proton is small enough to easily fit. Thus this compound is a good base but a poor nucleophile, which makes it a useful organic reagent. Typical applications for Hünig’s base include chemical reactions such as acylation, elimination and alkylation of secondary amines with alkyl halogenides, where the respective halogen acid is generated in the course of the reaction. The halogen acid reacts with the nitrogen function of Hünig’s base and ammonium salts form accordingly. Without Hünig’s base, some of the synthesized tertiary amine would take on the role of proton scavenger and hence reduce the yield. Although it must be strong, the auxiliary base must not be nucleophilic enough to act as an alkylating agent in its own right. Hünig’s base meets all the requirements for an auxiliary base. Its nucleophilicity is low due to steric hindrance, enabling its use in chemical reactions as a strong base and “proton sponge”. Unwanted secondary reactions do not occur because, unlike similar reagents such as di- and triethylamine which have both nucleophilic and basic properties, Hünig’s base is not capable of replacing the intended reaction partner due to its built-in steric hindrance. So far, DIEA has been successfully applied in various reactions [3].

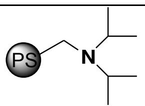
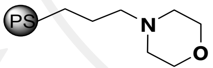
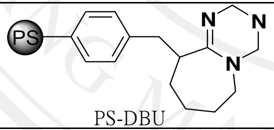
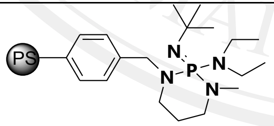
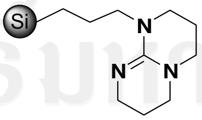
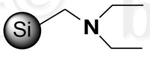
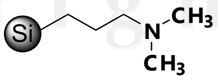
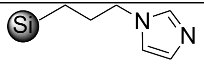
Generally, excess amount of base is usually required in reaction to facilitate the completion of reaction. This then leads to time-consuming purification process and tedious extractive work up. To overcome such limitations, various base reagents were immobilized on to solid support to facilitate their isolation from crude reaction mixture.

1.2 Solid supported base reagents

Solid-supported base reagents in organic synthesis have been used in wide range of applications. Table 1.1 provides a list of solid-supported bases which are weak base (entry 1, 2, 6, 7, 8, 9) and strong base (entry 3, 4, 5) and their applications. Polymer and silica gel were used as solid supports. For example, in 1995, Gooding and co-workers [4] have prepared a polymer-supported diisopropylethylamine (PS-DIEA). The use of PS-DIEA afforded the completion of conversion to the desired mesylate in 95 % isolated yield. Reaction work-up required filtration and rinsing of the resin, followed by removal of the solvent and excess methansulfonyl chloride *in vacuo*, which greatly simplified over aqueous extraction when triethylamine was used as base.

In 2001, Marsh and co-workers [5] synthesized high loading polymer resins having trichlorotriazine core structure and functionalized with morpholine to form PS-NMM. It was used as proton scavenger in the synthesis of *N*-Benzyl-4-chloro-benzamide from benzylamine and acid chloride. It was found that PS-NMM can be used as an effective proton scavenger and products can be obtained in high yield without further purifications.

Table 1.1 Solid-supported base reagents and their applications

Entry	**Structure**	**Application**	**Solid support**	**Reference**
1	 PS-DIEA	Alkylation, sulfonation	Polymer	[9, 4]
2	 PS-NMM	Alkylation, sulfonation proton scavanger	Polymer	[5]
3	 PS-DBU	Alkylation, sulfonation	Polymer	[10]
4	 PS-BEMP	Alkylation, sulfonation	Polymer	[11]
5	 Si-TBD	Alkylation, esterification, dehalogenation, williamson ether synthesis	Silica	[12]
6	 Si-TEA	Alkylation, Knoevenagel, sulfonation	Silica	[6]
7	 3-(Dimethylamino)propyl-functionalized silica gel	Catalyst in Michael reaction, Knoevenagel reactions, alkane oxidation, acid scavenger	Silica	[7, 8]
8	 3-(1-Imidazol-1-yl)propyl-functionalized silica gel	Catalytic cyclization reactions Tertiary amine for acid removal	Silica	[13]

Several groups have reported the utility of silica as support for base reagent. 3-(Dimethylamino)propyl-functionalized silica gel can be used in alkylation and Knoevenagel reaction [6-7]. In 2004, Jackson and co-workers [8] applied base catalysts immobilised on silica coated reactor walls in continuous flow systems in the catalysis of conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds. Flowcell plates with a silica coating were prepared and *N*,*N*-dimethyl-3-aminopropyl groups were tethered to this support using *N*,*N*-dimethyl-3-aminopropyltrimethoxysilane. These catalytic surfaces had been shown to be active as base catalysts for both Knoevenagel and Michael reactions with good yields and consistent continuous conversions.

The success of any solid-supported reagents depends on the properties of the solid support in many critical ways. Several new interesting of solid supports was investigated over the past year. Solid materials that are commonly used as solid supports in heterogeneous reagent are silica and polymers [14]. The definition for solid support purposes of solid material consist of; insoluble in water and common organic solvents and has sufficient thermal stability, high surface area and ease for surface functionalized, allowing them to be readily separated (by filtration, centrifugation, etc.) from excess reagents, soluble reaction by-products, or solvents [15]. Polymers and silica are widely used as solid support for the preparation of solid-supported reagents due to their high surface area and insoluble in any organic solvents [16-21]. Despite these solid materials have some disadvantages such as ability to recycle reagents on solid support is not assured, reactions may run more slowly due to diffusion constraints, and stability of the support material can be poor under harsher reaction conditions [22].

Recently, magnetic nanoparticles have been considered as the new alternative material for solid-supported reagents. These supports become more popular due to their high specific surface and ease of chemical modification or attachment with reagents. Moreover, magnetic nanoparticles do not swell and dissolved in any organic solvents; they are either well dispersed in a liquid with a nanoparticles size distribution to imply homogeneous properties [23] and easily removed by external magnet [24-25]. Due to the advantages of this protocol, magnetic nanoparticles-supported reagents will be obtained and can be applied in solution phase organic synthesis. This strategy can fasten purification step and enable parallel synthesis of structurally diverse compound. Magnetic nanoparticles support reagent was applied as catalyst in a variety of reaction of organic synthesis such as oxidation of phenolic and aniline compound [26], preparation of large ring compounds [27], aldol condensations, nucleophilic addition, acrylations [28] and Heck reaction [29]. These protocols showed high catalytic activity, good stability than the artificial catalyst. Moreover, the catalysts can be reused several times. From literature review have no any groups reported magnetic nanoparticle functionalize with base solution for use as base reagent.

1.3 General procedure for preparation of magnetic nanoparticles

The particle size and shape, the size distribution, the surface chemistry and consequently the magnetic properties of the particles are critical factors affecting for their applications. Clearly all important factors are controlled by the procedure of preparation and the using process conditions. Several techniques are available to facilitate production of magnetic nanoparticles with specific physical and chemical properties such as co-precipitation of iron salt [30-33], thermal decomposition of iron precursors [34], hydrothermal method, techniques under oxidizing conditions [35] and sol-gel transition [36]. The most general procedure which have been employed by several groups was co-precipitation method. Co-precipitation method is related to convenience, efficiency, and possibility to easily synthesize the major type of iron oxide nanoparticles, magnetite (Fe_3O_4) nanoparticles in solution. The reaction principle is simply as: $Fe^{2+} + 2Fe^{3+} + 8OH^{-} \rightarrow Fe(OH)_2 + 2Fe(OH)_3 \rightarrow Fe_3O_4 + 4H_2O$. There are the main methods for the synthesis in solution of magnetite spherical particles in the nanometer range. In the first, ferrous hydroxide suspensions are partially oxidized with different oxidizing agents [37, 38]. For example, spherical magnetite particles of narrow size distribution with mean diameters between 30 and 100 nm can be obtained from Fe(II) salt and base. The other method consists in ageing stoichiometric mixtures of ferrous and ferric hydroxides in aqueous media, yielding spherical magnetite particles homogeneous in size [39]. It has been shown that by adjusting the pH and the ionic strength of the precipitation medium, it is possible to control the mean size of the particles. The size decreases as the pH and the ionic strength in the medium increases [32,40]. The production of large quantities of magnetic nanoparticles with narrow size distribution remains a significant challenge for these methods.

1.4 Modification surface of magnetic nanoparticles

The surface properties of the magnetic nanoparticles are also important for their proper application; consequently many surface modification techniques for organic and inorganic materials have been developed. Magnetic nanoparticles are more reactive than bulk materials due to high surface, therefore these magnetic core nanomaterials need to be protected against corrosion. Coating also prevents the leaching of potentially toxic components during applications. This coating has to consider the nature of the coating and the ease of future functionalization to suit specific applications. Silica is one of the most commonly used material for coating on surface of magnetic nanoparticles [41]. Several reports have described the advantages of direct silanation for the modification of the particle surface because of the high density of surface functional groups and simple operation [42].

In general, silica coated magnetic particles is carried out as the hydrolysis of tetraethylorthosilane (tetraethoxysilane : TEOS), silica is an amorphous material with high meachaical strength [43]. It carried negative charge at pH < 3 because of the silanol groups (-Si-OH) on the surface. In order to modify the surface chemistry of silica, silylation can be carried out with use of functional alkoxysilane, such as 3-aminopropyltriethoxysilane (ATPES ; X = NH_2) (Figure 1.1). A typical silane coupling agent has the structure of $Y–(CH_2)n–Si–X_3$, where X represents the alkoxy or halide groups and Y, the organic functional groups, including amine, thiol, carboxylic, phosphate, vinyl, cyanide, and methacrylate. The $Si-X_3$ group hydrolyzes readily in the presence of water and catalyst to form silanol groups which couple with surface silanol groups. As a result, the organic functional groups (Y) remain reactive on the surface. This unique feature of silane coupling agents has made silanation a widely used method in modifying surface properties and introducing functional groups on particles [44]. Detailed studies by using XPS, diffuse reflectance FT-IR, and potential measurements revealed that the ethoxysilyl groups condensed each other and also with OH groups on the surface of magnetic nanoparticles [45].

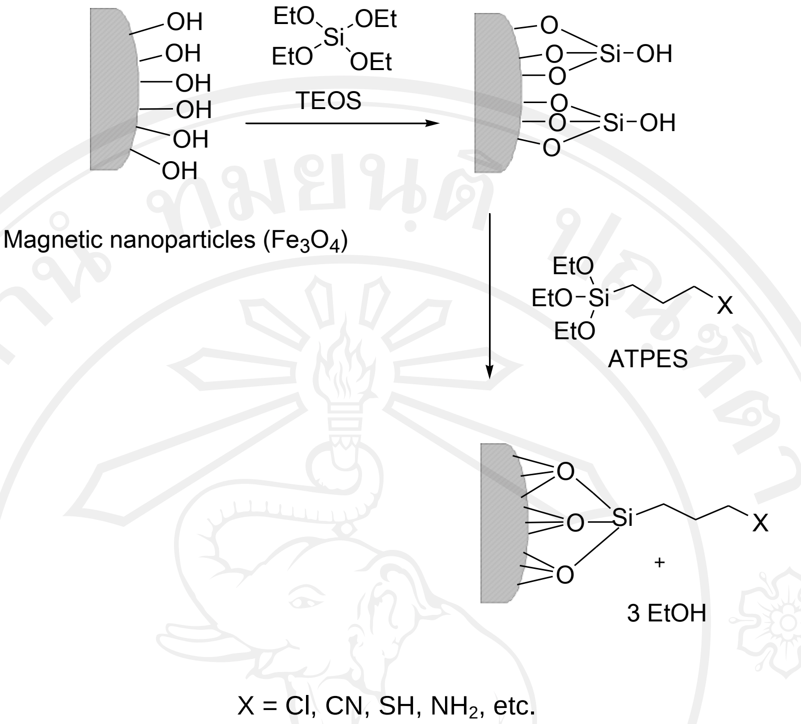


Figure 1.1 Silylation of a silica surface using triethoxysilane

1.5 Characterization of Solid supported reagents

Solid supported reagent can be characterized with several techniques, Fourier transform infrared spectra (FT-IR) is one of common spectroscopic technique. FT-IR is a type of determine the chemical functional groups in the sample. Difference functional groups absorb characteristic frequencies of IR radiation. The particles size and morphology of the sample is determined by scanning electron microscopy (SEM). This technique is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity.

In this study, magnetic silica nanoparticles supported base reagents and nonmagnetic silica supported base reagent were synthesize for comparison the efficiency of solid support. The selected solid support containing structure resemble *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine and methylpiperidine will be synthesized. These solid supported bases will be applied as base reagent in organic synthesis.

1.6 Aim of this research

1.6.1 To synthesize magnetic silica nanoparticles and nonmagnetic silica supported base reagents.

1.6.2 To optimize efficiency of magnetic silica nanoparticles and nonmagnetic silica supported base reagents and for use as base reagent in organic synthesis

1.6.3 To apply the magnetic silica nanoparticles supported base reagent in organic synthesis