



Synthesis and Applications of Silica Supported Dichlorotriazine (Si-DCT) in Nucleophilic Scavenging

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ABSTRACT

A new method for heterogeneous nucleophilic scavenging with silica supported dichlorotriazine (Si-DCT, **2**) is described. The Si-DCT was prepared by immobilized commercial grade silica gel with 3-aminopropyltrimethoxysilane, followed by reacting with cyanuric chloride. The applications of Si-DCT in removal of unwanted nucleophilic impurities from reaction mixture were demonstrated. It was shown that excess amines from sulfonamide and amide syntheses can be completely removed by adding Si-DCT and filtering off the solid. The desired products were obtained in high yields and purities without any further purification steps.

Keywords: silica gel, scavenger resins, supported reagents, solid-supported scavenger.

1. INTRODUCTION

Solid-supported scavenging is a new purification technique that uses solid-bound reagents to selectively react with excess reagents and/or reaction byproducts [1]. The impurities once bound to the solid-support can be removed by filtering out of the reaction mixture, leaving high purity product in the solution [2]. This technique can therefore greatly facilitate reaction workup and purification processes in organic synthesis. Using solid-supported scavenger is also environmental benign since lesser amount of organic solvents is required, in comparison with the classical purification methods such as solvent extraction and column chromatography [1-2].

Solid supports for preparing insoluble scavenging reagents can be divided into two major categories; polystyrene based and silica gel based [1]. Cross-linked polystyrene resins are the most commonly used supports since they have long been used in typical solid-phase

organic syntheses [2]. Recently, silica gel has been considered as a new alternative material for the reaction scavenging purpose [3]. This is to overcome limitation of polystyrene based resins which are often more expensive, having lower loading and undesirable swelling properties [4].

Unlike the polymeric supports, silica gel is less expensive. It is rigid insoluble material with high mechanical and thermal stability. Silica gel also does not swell in any organic solvent, thus it can be used in various reaction mediums [5]. Moreover, silica gel has a large surface area (typically 200-800 m²/g), thus allows high density of functional groups to be immobilized on its surface.

With our previous interest in the chemistry of trichloro-1,3,5-triazine [6], this has led us to explore the possibility of using silica gel as a support to produce a new type of silica gel based nucleophilic scavenger. Polystyrene and poly

(ethylene glycol) (PEG) supported dichlorotriazine had already been prepared [7-9]. Both materials were shown to be very effective in scavenging a variety of nucleophiles such as amines, alcohols and thiols.

To the best of our knowledge, silica supported dichlorotriazine has not yet been explored as solid-support scavenger. In this paper, we therefore describe the synthesis of silica supported dichlorotriazine (Si-DCT, **2**) and illustrate its application in scavenging excess amines nucleophiles in the synthesis of model sulfonamide and amide.

2. MATERIALS AND METHODS

2.1 Chemicals and Instruments

All solvents and chemicals were obtained from commercial sources and used without prior purification. Cyanuric chloride and benzoyl chloride were obtained from Aldrich. 3-Aminopropyltriethoxysilane, ninhydrin, benzene sulfonylchloride, morpholine, *n*-butylamine, diisopropyl ethylamine were purchased from Fluka. Silica gel (70-230 mesh, 60 Å) and TLC aluminium sheets silica gel 60 F 254 were obtained from MERCK. UV absorptions were measured with a UV – VIS Spectrophotometer, U-2000 Holiba. GC-MS spectra were obtained from an Agilent 6890 (GC)/ HP 5975 (MS) GC-MS system with HP-5MS 5% phenyl methyl siloxane column. The injector and detector temperatures were 250 °C and 260 °C respectively. Oven temperature was programmed at 10 °C /min from 80 °C to 240 °C. NMR measurements were conducted on a Bruker *AVANCE*TM (400 MHz for ¹H) using chloroform-*d* (CDCl₃) as the solvent. Chemical shift values (δ) are reported in ppm using tetramethylsilane as an internal standard. Coupling constants (*J*) are expressed in Hz and the abbreviation s, d, m, and br represent splitting pattern as singlet, doublet, multiplet and broad NMR peak, respectively.

2.2 Preparation of Chemically Modified Silicas

Chemical modification of the silica surface

was carried out using a standard coupling procedure [10] as outlined in Scheme 1. The silica gel was first reacted with 3-aminopropyltriethoxysilane and the resulting aminated silica **1** was then linked to cyanuric chloride under basic conditions.

2.2.1 Silica Pretreatment

Silica gel (20 g) was added with a mixture of nitric acid and sulfuric acid (1:1, 150 ml), followed by sonicating for 10 min. The mixture was then refluxed for 3 h, and washed with deionized water until pH ~ 7. The pre-purified silica gel was then oven dried at 120 °C for 24 h and kept in desiccator.

2.2.2 Synthesis of 3-Amino functionalized Silica **1**

3-aminopropyltriethoxysilane (10 ml) was dissolved in 100 ml of toluene in a round-bottomed flask. Whilst the solution was stirred vigorously, 10 g of the pretreated silica gel was slowly added. After sonicating for 10 min, the reaction mixture was refluxed for 3 h. The silica gel was then rinsed with toluene, followed by methanol and acetone respectively to obtain silica **1**. The silica **1** was oven dried at 80 °C for 12 h and kept in desiccator. The amount of the amino group on silica was 0.78 mmol/g, estimated from quantitative ninhydrin test [11].

2.2.3 Synthesis of Silica Supported Dichlorotriazine (Si-DCT, **2**)

Cyanuric chloride (5 equiv) was added as a powder into a 100 ml round-bottomed flask containing amino functionalized silica **1** (5 g), diisopropylethylamine (10 equiv) and dichloromethane (20 ml). After stirring for 1 h at 0 °C, the reaction was completed as indicated by negative ninhydrin test of the resulting silica. This silica supported dichlorotriazine (Si-DCT, **2**) was then filtered and washed with dichloromethane, followed by water and acetone, respectively. The silica **2** was kept dry under desiccator. The loading capacity of dichlorotriazine moiety on Si-DCT **2**, calculated from the starting aminated silica **1**, was 0.70 mmol/g.

2.3 Synthesis of Sulfonamide 3 [12]

Benzenesulfonyl chloride (0.0882 g, 0.50 mmol) was added into a stirred solution containing morpholine (0.0520 g, 0.60 mmol), Na_2CO_3 (0.1050 g) and CH_2Cl_2 (3 ml). After the reaction was completed, Si-DCT, **2** (0.285 g, 2 equiv with respect to the excess morpholine) was added. After 10 min of stirring, the solution was filtered and the solid was washed with CH_2Cl_2 . The filtrate was concentrated by evaporation under reduced pressure to give **3** as a white solid 0.1095 g (96% yield). R_f 0.44 (20 % ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.76 (m, 2H), 7.63 (m, 1H), 7.56 (m, 2H), 3.74 (t, $J = 4.8$ Hz, 4H), 3.00 (t, $J = 4.8$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 135.9, 133.7, 129.7, 128.5, 66.7, 46.6. GC-MS (M^+) cal'd for $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{S}$ 227, found 227.

2.4 Synthesis of Amide 4

Benzoyl chloride (0.0700 g, 0.50 mmol) was added into a stirred solution containing 59 ml (0.60 mmol) of *n*-butylamine, Na_2CO_3 (0.1050 g) and CH_2Cl_2 (3 ml). After the reaction was completed, Si-DCT, **2** (0.285 g, 2 equiv with respect to the excess *n*-butylamine) was added. After 10 min of stirring, the solution was filtered and washed with CH_2Cl_2 . The filtrate was concentrated by evaporation under reduced pressure to give **4** as colorless oil 0.0865 g (98 % yield). R_f 0.40 (80% ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.75 (m, 2H), 7.48 (m, 1H), 7.41 (m, 2H), 6.31 (br s, 1H), 3.44 (q, $J = 7.2$ Hz, 2H), 1.60 (p, $J = 7.6$ Hz, 2H), 1.40 (s, $J = 7.2$ Hz, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 135.2, 131.5, 128.8, 127.1, 40.1, 32.1, 20.5, 14.1. GC-MS (M^+) cal'd for $\text{C}_{11}\text{H}_{15}\text{NO}$ 177, found 177.

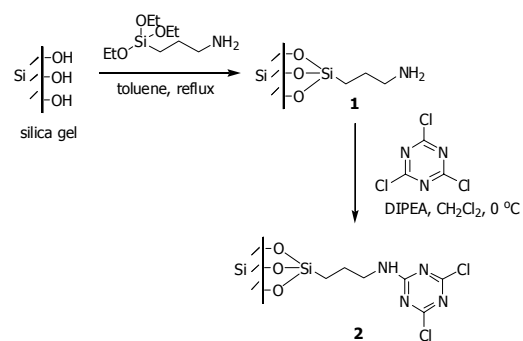
3. RESULTS AND DISCUSSION

3.1 Synthesis of Silica Supported Dichlorotriazine (Si-DCT, **2**)

Silica supported dichlorotriazine (Si-DCT) **2** was synthesized as outlined in Scheme 1. Commercial grade silica gel was first pretreated

with a mixture of $\text{HNO}_3/\text{H}_2\text{SO}_4$ to remove traces of metal impurities. 3-Aminopropyl-triethoxy-silane was immobilized on silica surface by silylation reaction using a standard procedure [10]. An excess of cyanuric chloride was then added to the aminated silica **1** at 0 °C to ensure a single site substitution of a chlorine atom on the triazine core [13]. Negative ninhydrin test of the obtained silica **2** after one hour reaction indicated the completion of the reaction. The loading capacity of the dichlorotriazine group on **2** was 0.70 mmol/g, estimated from the original loading of the amino group in **1**.

Scheme 1.



3.2 Scavenging Reactions of Si-DCT, **2**

The two chlorine atoms of Si-DCT **2** can be sequentially displaced by any nucleophiles. However, increasing the degree of substitution to the triazine core will gradually reduce its reactivity toward $\text{S}_{\text{N}}\text{Ar}$ reactions. As a result, nucleophilic scavenging selectivity of **2** can be achieved based on the strength of nucleophiles and reaction conditions [14].

To study the reactivity of **2**, series of its reactions with various nucleophiles were examined. TLC analysis was used to follow these scavenging events. In these experiments, reactive nucleophiles in dichloromethane (Figure 1) were individually mixed with **2** (2 equiv with respect to the nucleophiles). Na_2CO_3 was used as base in the scavenging reaction. It was found that primary and secondary amines (**a-e**) reacted rapidly with **2**, as indicated by the disappearance of the amines within 20

minutes after adding **2**. However, weaker nucleophiles such as aromatic amines (**f-g**) and alcohols (**h-i**) reacted with **2** rather slowly.

They required longer reaction times (>1 h) and/or reactions at elevated temperature to achieve a complete removal.

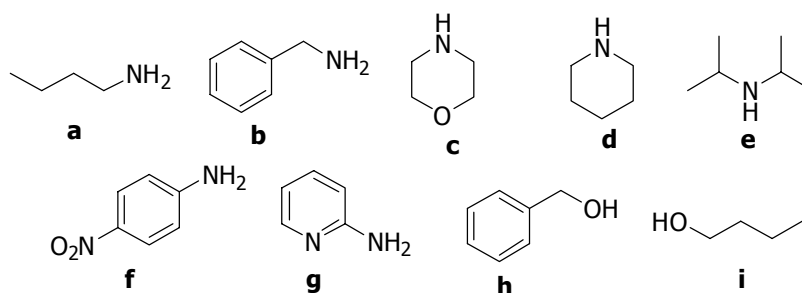
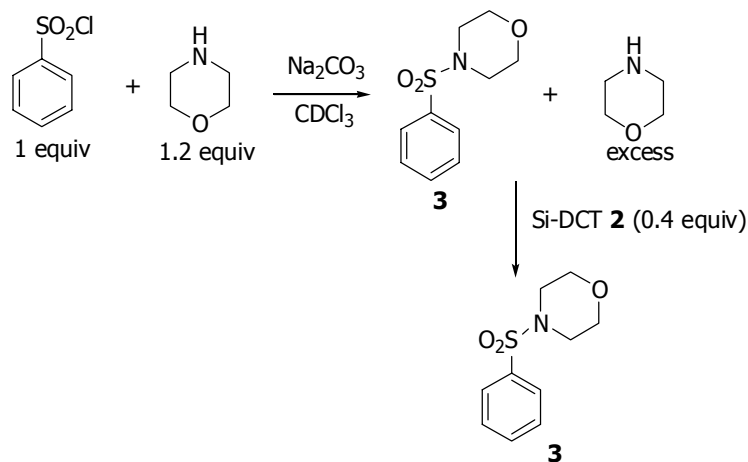


Figure 1. Nucleophiles.

To illustrate the efficiency of **2** in nucleophilic scavenging, ^1H -NMR analysis was used to follow the progress of reaction of **2** with

morpholine in the synthesis of sulfonamide **3** as shown in Scheme 2.

Scheme 2.



In this experiment, excess amount of morpholine was added into an NMR tube containing a mixture of benzene sulfonyl chloride, Na_2CO_3 and CDCl_3 . The reaction was monitored by ^1H -NMR. After the reaction was completed, the remaining morpholine was

removed by adding Si-DCT **2** directly into the NMR tube. The tube was sonicated for three minutes and the NMR spectra were taken at every five minutes after adding **2**. The resulting NMR data was shown as a stack plot in Figure 2.

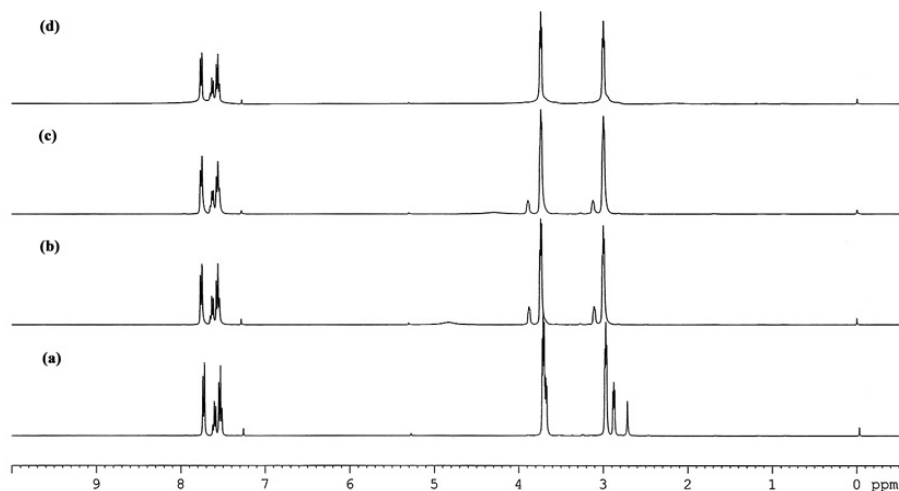
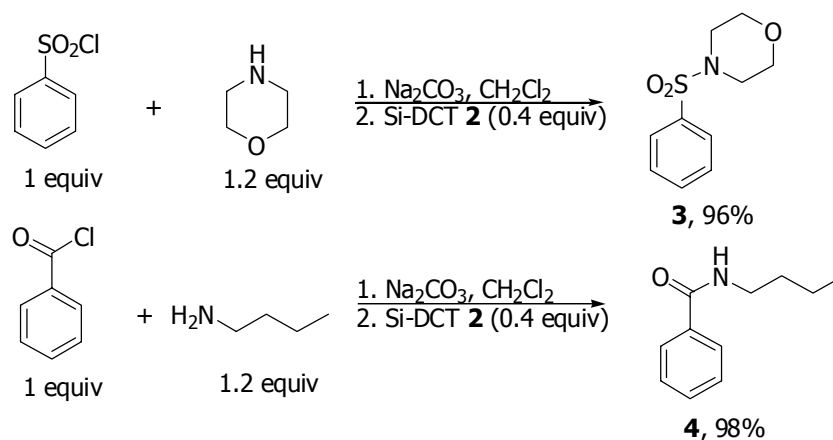


Figure 2. Stack plot of the NMR spectra of the reaction in Scheme 2; (a) crude reaction before adding **2**, (b) crude reaction after adding **2** for 5 min, (c) crude reaction after adding **2** for 10 min, (d) crude reaction after adding **2** for 15 min.

It was found that an excess morpholine in the reaction mixture was completely removed in 15 minutes, as indicated by the disappearance of NMR peaks at δ 3.70, 2.91 and 2.72. It was also noted that a presence of base

such as Na_2CO_3 is necessary for scavenging efficiency of **2**. This is to prevent salt formation of amines with HCl liberated in the $\text{S}_{\text{N}}\text{Ar}$ reaction.

Scheme 3.



To demonstrate the application of **2** in chemical syntheses, sulfonamide **3**, and amide **4** were prepared according to Scheme 3. It was found that by adding Si-DCT **2**, both **3**

and **4** were obtained in quantitative yield without any aqueous work up and/or column chromatography. GC-MS spectra of **3** and **4** were shown in Figure 3 and 4, respectively.

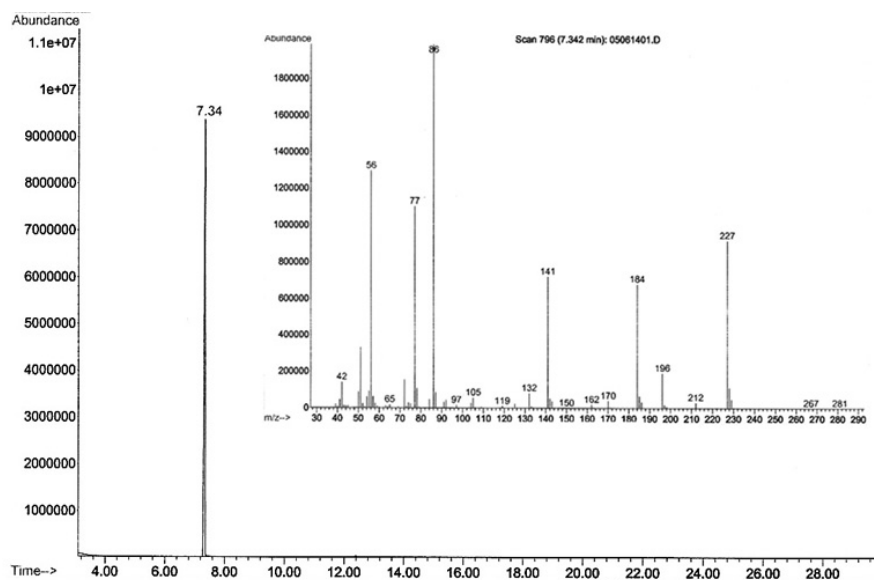


Figure 3. Gas chromatogram and mass spectrum of sulfonamide **3**.

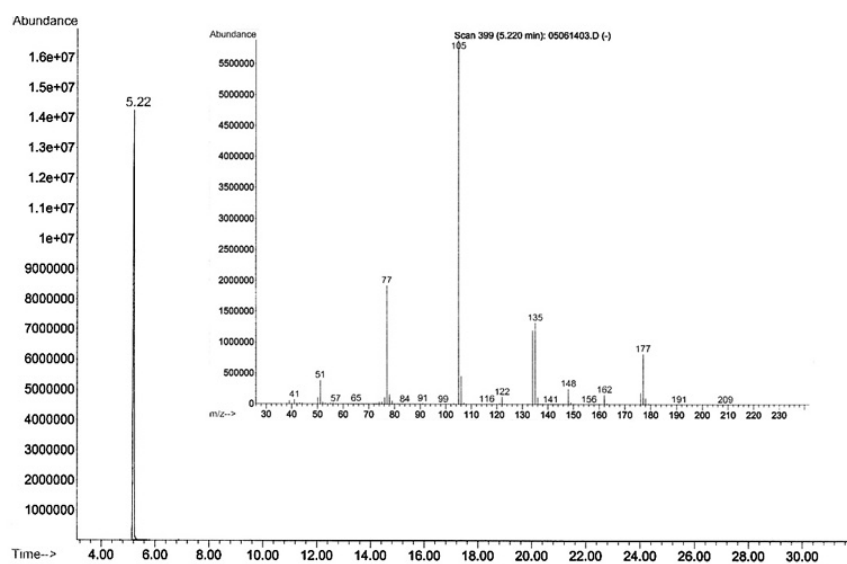


Figure 4. Gas chromatogram and mass spectrum of amide **4**.

4. CONCLUSIONS

Silica supported dichlorotriazine (Si-DCT, **2**) was successfully prepared from inexpensive starting materials. It was shown to be very effective agent in removal of unwanted nucleophilic impurities from reaction mixture. Excess amines from sulfonamide and amide syntheses can be completely removed by simply adding Si-DCT **2**, followed by filtering off the solid. The desired products were obtained

in high yields and purities. Thus, this technique can accelerate reaction workup as no any further purification steps was needed in comparison with the classical methods. In principle, **2** not only can be used as a nucleophilic scavenger, but also as a supported reagent in organic synthesis [15]. Research into expanding the scope of applications of **2** is currently being undertaken.

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