Efficient bulk scale synthesis of popular pesticide synthon: tetrachlorothiophene

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ABSTRACT

Broad spectrum pesticides are molecules which act across a range of pests. The popular class of compounds with this property are thiacloprid, nitenpyram, ethaboxam, silthiofam, 3,3,4,4-tetrachloro tetrahydro thiophene etc. Interestingly, all these compounds possess at least one heterocyclic ring like thiophene, furan, and imidazole etc. in their structure. Among the synthons available for synthesis of neonicotinoids, tetrachlorothiophene is unique. The bulk-scale synthesis of tetrachlorothiophene is reported only by cyclization of hexachloro-1,3-butadiene. The reaction yields of synthesis of this synthon are around 45%. We report silica-coated magnetic nanoparticles as a generic catalyst for this cyclization reaction yielding tetrachlorothiophene. The yield improvement is 50–60% more compared to original yield. The distillate crystallization in methanol yielded >98% pure compound compared to typical 90–92% in conventional process. The proposed reaction uses reusable silica-coated 40 nm size magnetic nanoparticles and the catalyst itself is of low cost and reaction conditions are mild.

1. Introduction

Discovery of nicotinergic neuronal pathway in insects can be called a breakthrough for creation of new generation pesticides [1–3]. The class of compounds which inhibit this pathway are called neonicotinoids [4,5] and have been responsible for creation of broad spectrum pesticides. The organophosphorous [6,7], carbamates [8,9], and chloro compounds [10–12] etc. have always been active against a set of pests or a class of pests and the single pesticide [13] for controlling many pests was realized only through neonicotinoids [14,15]. The logic was that nicotinergic neuronal pathway [16–19] is common across all pests or insects and these compounds have minimal toxicity toward mammalian acetyl choline esterase enzyme [20,21]. The specificity is hypothesized to be originating from the heterocyclic compounds present in the pesticide structure. The recent trend with environmental protection agencies worldwide has been to recommend usage of only certain class of compounds which have minimal toxicity to humans, animals, avian, and aquatic organisms [22,23]. These heterocyclic compounds have low toxicity profile [24–27] and yet the cost of these pesticides remains a concern [28]. This originates from the reason that the heterocyclic ring structures usually have low reaction yields [29–32]. Our group is focused on creating heterogeneous
nanomaterials catalysts for synthesis of heterocyclics [33]. In this direction, we report an efficient synthetic route for “tetrachlorothiophene.” The synthetic methods for this molecule are sparse and often there are no bulk scale suppliers for the same. The technical challenge in synthesis of tetrachlorothiophene is the cyclization reaction of hexachloro 1,3-butadiene with presence of bulky chloro groups. The process and inert catalysis we report is simple, economical, and scalable.

Catalyst for heterocyclic ring compound formation are numerous. Most of these are based on heterogeneous transition metal [34,35], catalyst and minimal examples of heterogeneous catalysts. Lately magnetic nanomaterial catalysts is receiving significant interest worldwide. The nanomaterial catalysis can be generally classified in to specific and non-specific. The specific catalyst simulate homogeneous catalyst having functional groups and the magnetic particles facilitate easy isolation. The non-specific magnetic nanoparticles increase the surface area and is minimally used for heterocyclic ring cyclization reactions.

2. Experimental methods

Chemicals and reagents: Hexachloro 1,3-butadiene, methanol, and sulfur were obtained from E-Merck, India. All the glassware like vigeux column, oil bath, and distillation setup are procured from Tensil, Bangalore, India. The oil free vacuum pump is obtained locally with capacity to provide 0.5 mm Hg vacuum. The tetrachlorothiophene analytical standard is procured from Sigma-Aldrich. 13C NMR was recorded on a 125 MHz Bruker instrument and the GC-MS is used for mass spectral analysis. The IR Spectra were recorded on a Shimadzu (IRAffinity-1) instrument. SEM and TEM images were recorded at central instrumentation facility and CENSE labs of Indian Institute of Science (IISc) Bangalore, India and VIT University, Vellore, India.

2.1. Synthesis of silica-coated magnetic nanoparticles (Fe₃O₄@SiO₂)

2.1.1. Synthesis of magnetic nanoparticle (Fe₃O₄)

Synthesis of magnetic nanoparticles was done using modified Stobers method [33,36–41] and the same is reported elsewhere[33]. About 5 g of sodium nitrate and 3 g of sodium hydroxide were taken in a 500 mL round bottom flask and 400 mL of distilled water was added. The solution was degassed with argon and the solution is heated on a water bath at 90°C for 30 min and the mixture was cooled to ≤60°C. Then, 4.2 g ferrous sulfate was taken in a separate beaker, to this ferrous sulfate solution, 1 mL of 0.5 M sulfuric acid was added and dissolved and diluted up to 50 mL. This ferrous sulfate solution was added to the above mixture drop by drop with a constant flow rate. The formation of black magnetite nanoparticles (MNP) was observed in the reaction flask. Mixture was degassed for 5 min and heated at 90°C for 4 h under argon atmosphere. The hot reaction mixture was transferred into a 1000 mL beaker and placed on magnet for 15 min. The MNPs settled down and the resultant clear supernatans was decanted. Distilled water was added to remove unreacted sodium hydroxide, the solution was swirled and allowed the contents to settle down and supernatant was discarded. The particles were washed till the pH of the medium reached pH below 8 and indicated complete removal of unreacted sodium hydroxide.

2.1.2. Silica functionalization of magnetic nanoparticle (Fe₃O₄@SiO₂)

About 350 mL of ethanol and 100 mL of water were taken in a beaker, the MNPs was added from above step 2.1.1 and the pH was adjusted to 12 using sodium hydroxide. The suspension was sonicated for 60 min to remove aggregates. About 4 mL of tetra ethyl orthosilicate (dissolved in 8 mL of ethanol) was added to the above solution. Sonication was continued further for one hour. The sonicated Fe₃O₄@SiO₂ solution was allowed to settle on magnet for 30 min and supernatant was discarded. The particles are washed with distilled water (5 × 100 mL) till the pH reached below 8. Figure 1 shows the procedure of silanization of MNPs.

2.1.3. Removal of traces of Fe²⁺ and Fe³⁺

The MNP synthesized by this method could have traces of Fe³⁺ or Fe²⁺ ions which could cause unwanted reactions in conventional organic synthesis. The traces of unreacted Fe³⁺ and Fe²⁺ ions were removed by refluxing in 0.1 M citrate buffer (pH 6) and 5 mM tris buffer containing 1 mM EDTA (pH 8). For citrate wash, silanized magnetic nanoparticles (Fe₃O₄@SiO₂) were mixed with 100 mL of 0.1 M citrate buffer pH 6 and heated at 90°C for 30 min. After the solution was cooled, the silanized magnetic nanoparticles were separated using magnet and washed with distilled water (3 × 100 mL). For Tris-EDTA wash, silanized magnetic nanoparticle (Fe₃O₄@SiO₂) were mixed with 100 mL of 5 mM tris, 1 mM EDTA pH 8, and heated at 90°C for 30 min. The silanized magnetic nanoparticles were separated using magnet and water wash is given (3 × 100 mL). The Fe₃O₄@SiO₂

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NaNO₃ + NaOH + FeSO₄ → Fe₃O₄

Figure 1. Synthesis of Fe₃O₄@SiO₂ magnetic nanoparticles: The process is based on modified Stober process and is a combination of (a) Precipitation method for Fe₃O₄ nanoparticles and (b) Sol-gel method for coating of SiO₂ on Fe₃O₄ nanoparticles. The modifications for Stober process include, using stream of N₂ for mixing, slow aging, and controlled addition to obtain consistent size of 40 nm sized particles and elimination of calcination.
were stored in distilled water and prior to use, Fe₃O₄@SiO₂ were separated using magnet and dried in oven at 250 °C for 24 h. The obtained Fe₃O₄@SiO₂ at this stage are around 40 nm in size. Figure 2 shows IR spectra before and after silanization [33,42,43]. The SEM and TEM images were shown in Figures 3 and 4.

2.2. Synthesis of tetrachlorothiophene

In synthesis of tetrachlorothiophene, 104 g of hexachloro-1,3-butadiene (0.4 moles) and 12.9 g of sulfur (0.4 moles) were taken in 2 liter, three necked flask was set up in an oil bath, and the flask was fitted with a stirrer and a vigreux column. The reagents were refluxed at 150°C for 12 h. By increase of temperature of oil bath to 240°C, the byproduct S₂Cl₂ was removed at the top of column from the refluxing reaction mixture. When distillation was stopped, attach a divac and flash distill the product out of reaction flask. Redistill the distillate in a packed column. Finally the distillate was crystallized from an equal volume of methanol. Melting point was reported as 28–30°C and it was observed at 28–29°C. Percentage Yield is 40%. ¹³C NMR (CDCl₃, 125 MHz): 119.6, 120.9. GCMS: m/z [M⁺] for C₄Cl₄S Calcd. 221.92, found 221.77. Elemental anal: C₄Cl₄S (%): C-21.65, Cl-63.90, and S-14.45. Found: C-21.23, Cl-64.03, and S-14.74.

2.3. Synthesis of tetrachlorothiophene using Fe₃O₄@SiO₂

Synthesis of silanized nanomaterial-assisted tetrachlorothiophene was similar to the procedure given above for synthesis of tetrachlorothiophene. A 5% (w/v) 40 nm silanized magnetic nanoparticles was added to the hexachloro-1,3-butadiene and sulfur solution. The solution is

Figure 2. IR spectra of magnetic nanoparticle before and after silanization: The IR Spectra of magnetic nanoparticles is an useful tool to maintain quality control during production of nanoparticles. The before and after silanization is an useful indication of process and the 1100–1250 cm⁻¹ peak reflect SiO₂ coating (Dark spectra).

Figure 3. SEM image of silanized 40 nm magnetic nanoparticles: The SEM Image shows two types of nanomaterial sizes. The most prevalent are around 40 nm and may be responsible for catalysis [33]. The 180 nm are the larger particles which aid in easy removal of particles from reaction medium.

Figure 4. TEM image of silanized 40 nm magnetic nanoparticles: The dark color is magnetic core and light colored layer surrounding black color is silica coating. The 40 nm nanoparticles provides more catalytic surface area for bulk scale synthesis.
stirred for 30 min at 150°C. After reaction is completed the Fe₃O₄@SiO₂ is removed by external barium ferrite magnet and continued with above reported workup. Melting point was reported as 28–30°C and it was observed at 28–29°C. Percentage yield is 75%. ¹³C NMR (CDCl₃, 125 MHz): 121.8, 120.4, GCMS: m/z [M⁺] for C₅Cl₄S Calc.221.92, Found: 222, Elemental anal: C₅Cl₄S (%): C-21.65, Cl-63.90, and S-14.45. Found: C-21.23, Cl-64.03, and S-14.74.

2.4. **Characterization of Fe₃O₄@SiO₂ nanoparticles**

The nanoparticles used in this study were characterized by SEM (Figure 3) and TEM (Figure 4). The SEM confirms that the particles are roughly of the 40 nm size and TEM confirms the uniform SiO₂ coating of particles. It is also interesting that these particles are non-calculated and the literature studies, as well as our group publications [32] suggest that nanoparticles less than 50–60 nm does not require calcination and the SiO₂ coating will be uniform at this size level. The sonication during silanization with TEOS was reported to yield magnetic nanoparticles with uniform SiO₂ coating and we could demonstrate the same at 100 g scale. The Figure 2 shows IR spectra 2 shows IR spectra before and after silanization [33,42,43]. Figures 3 and 4 shows SEM and TEM. Figure 5 shows the EDS spectra of silica-coated magnetic nanoparticles. The EDS spectra has confirmed that the particles consist of elements, Iron, Oxygen and Silicon and their ratios reflect the Fe₃O₄@SiO₂ structure.

3. **Results and discussion**

3.1. **Conventional synthesis of Tetrachlorothiophene**

Hexachloro-1,3-butadiene and sulfur was heated at 150°C for 12 h. The temperature of reaction is increased to 240°C and the S₂Cl₂ is distilled out. Once the distillation of S₂Cl₂ stops, connect a divac and flash distill the tetrachlorothiophene. The crude tetrachlorothiophene is distilled against at 75–76 °C at 2 mm Hg and the product is crystallized by combining with equal volume of methanol. As the reaction does not use a separate solvent and the hexachloro 1,3-butadiene also acts as solvent, the product has a yield of about 40%. The published literature suggests that the cyclization step and slow reaction kinetics are the reason for low product yield for formation of thiophenes from substituted 1,3-butadienes. Insertion of sulfur and ring cyclization occurs through a nucleophilic attack of lone pair on the two terminal carbons. If not catalyzed, this non-homogeneous reaction condition always results in lesser yields [44,45].

| Sl No | Element | Weight (%) | Atomic (%) |
|-------|---------|------------|------------|
| 1     | O       | 35.88      | 63.10      |
| 2     | Si      | 9.23       | 9.25       |
| 3     | Fe      | 54.88      | 27.65      |

**3.2. Synthesis of Fe₃O₄@SiO₂ and related catalytic activity**

Magnetic nanoparticles are used widely for both specific and non-specific catalysis. Their use in conventional reactions as well as specialized metal catalyzed reactions is of good promise. As a group, the size of the nanomaterials in the range of 40–100 nm size have resulted in significant improvement in reaction yields. The exact mechanism of silica functionalized magnetic nanoparticles is still unknown and the hypothesis projected was that the smaller size of particles improves surface area similar to other solid state catalysts like montmorillonite clay [46–49], silica [50,51], and aluminum [52,53] etc. The acidic nature of silica is projected to be a reason for improved yield but Fe₃O₄@SiO₂ are also reported to be catalysts even in basic reaction mediums, raising questions on this theory. We recently reported that magnetic nanomaterials result in improved reaction yields for isoxazole [33] cyclization involving heterocyclic formation seem to have resulted in significantly higher reaction yields. The interaction of heteroatoms with silica surface during heterocyclic reactions is reported and the acidic surface tends to support heterocyclic formations [54–58]. There are numerous acidic catalysts [59,60], especially Lewis acids [61,62] which are reported to aid in reaction cyclization by stabilizing the heteroatom. The Fe₃O₄@SiO₂ nanoparticles may primarily have reaction catalysis due to their size and increase in surface area, but the role of acidic surface-hetero atom interaction may also have a role. The 40 nm size Fe₃O₄@SiO₂ were synthesized with few modifications of Stober synthesis involving sodium nitrate and ferrous sulfate. The capping of the particles was done with TEOS in ethanol system reported by us elsewhere [33]. All the reactions reported, here were done with 5% w/v of catalyst. As such catalytic activity of Fe₃O₄@SiO₂ particles is not.
3.3. Synthesis of tetrachlorothiophene with Fe$_3$O$_4$@SiO$_2$ as catalyst

A set of reactions with and without Fe$_3$O$_4$@SiO$_2$ as catalyst were done with reaction conditions mentioned in experimental section and as shown in Scheme 1. The 40 nm size Fe$_3$O$_4$@SiO$_2$ nanoparticles were added along with hexachloro-1,3-butadiene and sulfur. The nanoparticles were stirred in solution using an overhead stirrer. The reaction time was about 12 h for with and without catalyst. By maintaining same reaction conditions, any increase in reaction yield is a direct result of nanomaterial supported catalysis and can be attributed to Fe$_3$O$_4$@SiO$_2$ catalyst. Though we found reduction in reaction time also possible as a result of nanomaterial catalysis, in this case reaction yield improvement was more necessary. During the S$_2$Cl$_2$ removal at 240°C the Fe$_3$O$_4$@SiO$_2$ nanoparticles were left in solution, to avoid additional steps in the process. The product distillation was also done in nanoparticle presence and in both reaction scenarios, product was crystallized by mixing with 1:1 methanol. The notable observation is almost 50% improvement in reaction yield from the original. The yield improvement was confirmed with different batch sizes (5 g, 10 g, and 100 g). Each batch size was done in duplicates and the average yields with standard deviation are given in Table 1. The boiling point of product is 75–76°C at 2 mm Hg and is in agreement with literature reported boiling point [29].

Table 1. Reaction yield at different batch sizes. $n$ is the number of iterations done.

| S. No. | Scale (g) | Presence of Fe$_3$O$_4$@SiO$_2$ (%) | Absence of Fe$_3$O$_4$@SiO$_2$ (%) |
|--------|-----------|-------------------------------------|------------------------------------|
| 1      | 5         | 60 ± 2                              | 42 ± 2                             |
| 2      | 10        | 64 ± 4                              | 44 ± 1                             |
| 3      | 100       | 66 ± 3                              | 47 ± 3                             |

3.4. Mechanism of Fe$_3$O$_4$@SiO$_2$ and role of acidic surface of nanoparticles

The mechanism of thiophene formation from substituted thiophenes is reported in literature [63,64]. The reaction mechanism and role of nano catalyst is given in Scheme 2. There are three sites of possible interactions for silica surface. The elimination of chloride can be facilitated

Scheme 1. Synthesis of tetrachlorothiophene: The reaction involves condensation of hexachloro-1,3-butadiene with sulfur at elevated temperature for 12 h. The S$_2$Cl$_2$ is distilled off after the reaction and product is recovered by distillation at reduced pressure. To improve purity of obtained product, Vigreux column is used during distillation.
by acidic surface of silica apart from the stabilization of sulfur group. The pi bonds of the 1,3-butadiene allow initial insertion of sulfur atom and the nanoparticles seem to be aiding the removal of chlorines as $S_2Cl_2$.

### 3.5. Validation of catalysts by lowering reaction time

It is reported that conventional homogeneous and heterogeneous reaction that apart from yield improvement, lowering of reaction temperature and reaction time [65,66] are also possible. If the Fe$_3$O$_4$@SiO$_2$ is acting as a catalyst, it should be able to show these properties and these reported reactions were performed at gram scale. About 1 g sample is taken out at periodic intervals and the product yield is analyzed and are given in Table 2. The Table 2 suggests that the reaction yield improvement after 4 h could be the basis for catalysis. The initial spurt in yield is caused by facilitation of $S_2Cl_2$ elimination as that kind of elimination reactions are reported to be the rate limiting for thiophene derivative synthesis [67]. A detail analysis with "Design of experiments" varying reaction time and reaction temperature could provide further insights into the ideal reaction conditions for tetrachlorothiophene.

### 4. Conclusion

We report 40 nm sized Fe$_3$O$_4$@SiO$_2$ as a heterogeneous catalyst for improvement of reaction yields of tetrachlorothiophene. The near 50% yield improvement in this solvent-free reaction is significant and this thio-synthan is useful for synthesizing various pesticides and medicinal chemistry analogs. The reaction scale clearly suggests the possible use of these Fe$_3$O$_4$@SiO$_2$ nanoparticles in bulk drug/API industry.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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