Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Nanomaterial assisted bulk scale synthesis of 2-methyl-6-nitroquinoline

M. Chandrappa a,b, Korrapati Swathi c, S. Girish Kumar b, Phani Kumar Pullela a,b,*

a Department of Chemistry, CMR Institute of Technology, Bengaluru 560037, India
b Department of Chemistry, School of Engineering and Technology, Bengaluru 560043, India
c Kallam Haranadha Reddy Institute of Technology, NH-5, Chowdavaram, Guntur 522019, India

Abstract
Quinolines are an interesting class of moieties with various medicinal chemistry uses. The most prominent is their ability to be used as the last line of therapy for bacterial and viral infections including recent COVID-19. The synthesis of quinoline is through a cyclization reaction and overall reaction yields are about 20%. The bulky ring and the associated crowding of functional groups limit the catalyst options. In this publication, the use of Fe3O4@SiO2 for enhancing yield improvements, especially for heterocyclics is reported. The use of the 40 nm sized silica functionalized magnetite nanoparticles seems to help in both condensation and cyclization steps of representative 2-methyl-6-nitroquinoline. Reaction time reduction due to surface enabled catalysis of nanoparticles is 110 min to 80 min. The reaction yield has doubled due to the presence of catalyst and the mechanism suggests this drastic result is due to stabilization of unstable intermediate on the acidic surface of the silica coating. This near homogeneous catalysis of 40 nm sized, silica functionalized, magnetite nanoparticles have far reaching applications in bulk drug industry for drugs like chloroquine & hydroxychloroquine, the two essential drugs for prophylactic use for COVID-1.

1. Introduction
1.1. Applications of quinolines
Quinolines, as a functional group, is associated with antimalarials [1]. There are very few chemical functional groups which have vector level toxicity, and quinolines are one of them. Quinolines are also used for other purposes like pesticides [2], insecticides [3], anticancer, antibacterial, antiviral, retroviral, antimicrobial [4], antihistamines (antiallergic) [5], tuberculosis effective drugs [6] etc. Quinolines and quinazolines are considered as the last line of protection for tuberculosis, the bacteria which is resistant for most antibiotics.[7]. Malaria-resistant to quinolines in the 1960s has resisted the scientific community to use quinolines as antibiotics. However, most strains of multidrug resistant (MDR) and extensively drug resistant (XDR) of mycobacterium still respond to quinolines and they are used as injectables to save lives [8]. The observation of medicinal chemistry leads has suggested that the quinoline toxicity for vectors extends to cancer cells, parasites, microbes, bacteria, virus and this broad spectrum activity has led to almost 40 clinical leads based on quinolines at different stages of development [9]. The topical creams and cosmetics applications are evolving with special attention to the minimisation of microbial growth in pimples. The other applications like antipsychotic drugs [10], blood thinning agents [11], anti-inflammatory agents [12], lung and liver infection prevention, antidepressants, antihypertension etc. are under development and the process chemistry that involve yield improvements in quinoline synthesis are a necessity. The structures of antimalarials are shown in Scheme 1.

1.2. Synthesis of quinolines
Quinolines lead by chloroquine is a choice for antimalarials [13]. The molecule surprisingly has toxicity for almost all plasmidium strains and even after chloroquine-resistant versions evolved, the newer generation drugs are still based on quinoline ring [14]. Quinolines are usually synthesised by Friedlander reaction. This reaction has been used for over a century, but it is still the most
previously reported metal catalysts are very few. Solid-state acidic catalysts, like zeolites etc. also catalyse the quinoline synthesis, but their practical use in process chemistry is minimal. Yet, process chemistry solutions which can cut the production costs.

d) Nanomaterial catalysis is a potential possibility, and we need innovations in this direction to reduce production chemistry costs and improve the purity of the reaction product.

2. Experimental methods

2.1. Synthesis and characterization of Fe₃O₄@SiO₂

2.1.1. Synthesis of Fe₃O₄ by Co-precipitation (sol-gel) method

Synthesis of Fe₃O₄ magnetic nanoparticles: In a dry 1.5L four necked RB flask, 9.5 g (0.1 mol) of NaNO₃ and 5 g (0.0125 mol) of NaOH are added and dissolved in 600 mL of water (solution X). The solution X is heated to 90 °C for 45 min with occasional swirling. The argon is bubbled through the solution X for enabling continuous mixing and the mixture is brought to room temperature. In another container 6.95 g (0.25 mol) of FeSO₄ dissolved about 60 mL of distilled water having 10 mM H₂SO₄ (Solution Y). Solution Y is add solution X at the rate of 20 mL/min. the particles are formed as the solution are mixed and Argon gas at 1L/hr is continued for about 4 h at 90 °C. The heated liquid is cooled to room temperature and transferred to a beaker. The formed magnetic nanoparticles are washed multiple times and stored for further use in distilled water.

2.1.2. Silica coating on magnetic nanoparticles

An ethanolic solution comprising of 25% water is taken in a 1L container and pH is changed to 12 using 10 N Sodium hydroxide solution. Fe₃O₄ nanoparticles are added to the above basic ethanolic solution and sonicated for about an hour. About 12.5 mL of TEOS (0.033 mol) is added above sonicated solution slowly at 1 mL/min and stirred for an hour. The Fe₃O₄ particles coated with silica layer are separated using external barium ferrite magnet, washing with distilled water for further use. The removal of ionic impurities is performed by heating to 90 °C at 30 using 0.3 M trisodium citrate and then ageing with 0.5 M tris. The former solution is at pH 6 and later solution is at pH of 8 and ideally remove both iron impurities and unreacted components. The overall synthesis of silica functionalized magnetic nanoparticles is given in Fig. 1. The overall yield of SMNP in this method vary from batch to batch, overall yield is 4 to 5 g.

2.1.3. Characterization of silica functionalized magnetic nanoparticles

The IR spectra is used for understanding batch to batch consistency and the SEM images to judge the morphology and size. Fig. 2 shows the SEM image 40 nm silica functionalized nanoparticles. Fig. 3 shows the IR Spectra, clearing detailing batch to batch consistency. The peaks indicative of silica functionalization. The 1000–1200 cm⁻¹ peak implies consistency in silica coating and is characteristic for the Si-O bond. The 40 nm sized particles in SEM are typical in undergoing partial aggregation and has consistency in size and performance.

3. Synthesis of 2-methyl-6-nitroquinoline

3.1. Chemicals and reagents

4-nitroquinoline and crotonaldehyde are procured from Sigma Aldrich and solvents were obtained from Merck Pvt Ltd. The chemicals are used without any further purification. The magnetic nanoparticles with silica coating are used after drying for overnight at 120 °C overnight.
3.2. Synthesis of 2-methyl-6-nitroquinoline

1.5 g of 4-nitroaniline (11 mmol) was dissolved concentrated HCl under reflux at 105°C. A 0.95 g of crotonaldehyde (14 mmol) is added drop wise at 100 mL/2hr rate and the reaction mixture is heated for an hour. Then the reaction mixture is cooled to 25°C (or room temperature) and neutralized with 11 N NaOH solution and the acquired product is obtained as whitish yellow precipitate and the same is recrystallized from methanol to remove the reactants. The light yellow color solid has melting point 164°C and yield is 47%.

Fig. 1. Diagrammatic representation of Fe₃O₄@SiO₂ Synthesis: Synthesis of nanoparticles using ferrous sulphate heptahydrate, NaNO₃ as starting materials and sodium hydroxide as reducing agent. The NaNO₃ in equilibrium with FeSO₄ generates in situ which allows nanoparticle formation.

Fig. 2. SEM analysis of silica functionalized magnetic nanoparticles.

Fig. 3. IR spectra of silica functionalized magnetic nanoparticles of different batches and compared with non-silanized magnetic nanoparticles.
3.3. Silica magnetic nanoparticle enabled synthesis of 2-methyl-6-nitroquinoline

1.5 g of 4-nitroaniline (11 mmol) was dissolved concentrated HCl under reflux at 105 °C in presence of Fe3O4@SiO2 particles. A 0.95 g of crotonaldehyde (14 mmol) is added drop wise at 100 mL/2hr rate and the contents of the reaction is refluxed for 1 h. Then the reaction is cooled to room temperature and Fe3O4@SiO2 particles are isolate prior to sodium hydroxide neutralization using external magnet. Later the reaction mixture is neutralized with 11 N NaOH solution and the acquired product is obtained as whitish yellow precipitate and the same is recrystallized from methanol to remove the reactants. The light yellow color solid has melting point 164 °C and yield is 81%. The synthesis reaction is shown in Scheme 2. Yield: 81% (16.7 g), m.p.: 165 °C. The reaction of 2-methyl-6-nitroquinoline synthesis was shown in Scheme 2.

Spectral analysis: Mass: [M + H]: 190, 1H NMR (CDCl3, 300 MHz); 8.75, (d, J = 2.7, 1H, quinoline5H) 8.45 (dd, J = 9.3 Hz, J = 3.6 Hz, 1H, quinoline7H), 8.23(d, J = 8.7 Hz, 1H, quinoline3H) 8.13 (d, J = 9.0 Hz, 1H, quinoline4H), 7.45(d, J = 8.4 Hz, 1H, quinoline8H), 2.80 (s, 3H, methyl protons). 13C NMR: 25.9, 77.3, 123.1, 124.1, 124.5, 130.6, 137.9, 145.2, 150.2, 163.5. Anal.Calc. for C10H9N2O2: C, 63.8; H, 4.28; N, 14.9. Found: C, 62.5; H, 3.98; N, 15.2.

4. Results and discussion

4.1. Importance of quinoline synthesis

Quinoline synthesis has received minimal chemical interest in catalysis area, and the catalysis is mostly non-specific, non-metal neutral heterogeneous catalyst. The yield improvements are minimal, and low yields characterize the condensation reactions followed by cyclisation. The transition metal and rare earth metal catalyst are spares, and even they have a minimal role when deactivating substitution like nitro group one present. 2-methyl-6-nitroquinoline was synthesized by the catalytic method, it was explained the synthesis in Scheme 3.

4.2. Proof for a reduction in reaction time via Fe3O4@SiO2 nanoparticles as catalyst

Functionalized nanomaterials are increasingly playing a pivotal role in modern-day organic synthesis. The mechanism and the way these nano sized particles increased yields are as also well documented. Unlike transition metal or rare earth metal catalysis, the nanomaterials bound to reaction intermediates is only hypothesized and cannot be characterized by any of the existing spectroscopic methods. This often is the reason for an indirect proof generation as evidence. In quinoline case, we characterized with and without reaction catalyst using a graph with x-axis as the time generation as evidence. In quinoline case, we characterized with microscopic methods. This often is the reason for an indirect proof

4.3. Proof for yield improvement of quinoline synthesis

The non-catalysed reaction has resulted in a 47% overall reaction yield. The reaction yields differ significantly from batch to batch, and often it was puzzling even though reaction condition is almost the same. The possible reason hypothesized in literature is the hindrance of water from condensation acting as an inhibitor for cyclisation. Interestingly none of the quinolone synthesis reactions is reported in anhydrous solvents, and the yield improvement has more molecular level mechanics then the by-product related inhibition. When we used Fe3O4@SiO2, the yield is improved almost 50% from the original yield. The bulk batch to batch consistency in yields is addressed and possible mechanism was shown in Scheme 3. The Fe3O4@SiO2 is present in the reaction throughout till the product isolation and hence is part of catalysis of both condensation and cyclisation. Our previous publications in this domain have proved that Fe3O4@SiO2 can aid in both condensation and cyclisation [19,20].

4.4. Catalyst optimization for the synthesis of quinoline

The optimization of silica functionalized magnetic nanoparticles (catalyst) concentration for the quinoline synthesis was done in our lab. The catalyst optimization of Fe3O4@SiO2 nanoparticles was done for the quinoline derivative. The overall reaction yield was calculated for every batch, on yield basis the catalyst ratio for the reaction was optimized. In this case 6% (w/w) of the catalyst is given greater yields, 6% (w/w) catalyst is optimal ratio for the reaction. The ratio of Fe3O4@SiO2 catalyst taken concerning reagents. After optimization of catalyst ratio, we have developed a process for the bulk scale synthesis of quinoline derivative using the 6% catalyst (w/w) and the catalyst ratio and the improvement in yield was given in Table 1.

4.5. Mechanism for 2-methyl-6-nitroquinoline synthesis

The mechanism of the Doebner-Miller synthesis of quinolines has been the topic of many researchers, leading to the currently accepted mechanism which involves an aldol condensation producing an α,β-unsaturated aldehyde followed by Michael addition of the aromatic amine. The reaction was carried out with crotonaldehyde, 4-nitroaniline in the presence of silica functionalized nanocatalyst. The Fe3O4@SiO2 is initiated of α, β-unsaturated

![Scheme 2](image-url)
aldehyde for the reaction and stabilizes the intermediate. The Fe$_3$O$_4$@SiO$_2$ catalyst provides its surface area for cyclisation through Michael addition. The possible mechanism for the complete synthesis for the 2-methyl-6-nitroquinoline is shown in Scheme 3.

**Scheme 3.** Mechanism for synthesis of 2-methyl-6-nitroquinoline: The reaction mechanism with silica functionalized magnetic nanocatalyst for the synthesis of 2-methyl-6-nitroquinoline.

**5. Conclusion**

Nanomaterial assisted bulk synthesis of 2-methyl-6-nitroquinoline has reached applications in bulk drug synthesis. The yield improvement and possibility of reduction in reaction time are possible take away from the study. The 40 nm sized nanomaterials are increasingly receiving interest and this study

**Table 1**

Optimization of catalyst (Fe$_3$O$_4$@SiO$_2$) ratio for the synthesis of 2-methyl-6-nitroquinoline on a small scale.

| Batch No | Fe$_3$O$_4$@SiO$_2$ w/w ratio | Reaction yield |
|----------|-------------------------------|----------------|
| 1        | 1%                            | 45%            |
| 2        | 2%                            | 49%            |
| 3        | 3%                            | 56%            |
| 4        | 4%                            | 62%            |
| 5        | 5%                            | 74%            |
| 6        | 6%                            | 81%            |
| 7        | 7%                            | 79%            |
| 8        | Without Fe$_3$O$_4$@SiO$_2$    | 47%            |
paves way for usage of functionalized nanomaterials at the 40 nm size. The reaching of saturation yield in shorter time can be explored further for drugs like stavudine, which often suffer from the decomposition of the product formed during reaction.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Acknowledgement**

This project is funded by Department of Science and Technology, DST Nanomission project, SR/NM/NT-1034/2015(G).

**References**

[1] R. Sharma, S. Patil, P. Maurya, Drug discovery studies on quinoline-based derivatives as potential antimalarial agents, SAR QSAR Environ. Res. 25 (2014) 189–203.

[2] J. Ramírez-Prada, S.M. Robledo, I.D. Vélez, M.del P. Crespo, J. Quiroga, R. Abonia, A. Montoya, L. Svetaz, Z.-H. Shen, C.-X. Tan, J.-Q. Weng, T.-M. Xu, H.-Y. Huang, Synthesis and in vivo fungicidal activity of some new quinoline derivatives against rice blast, Pest Manag. Sci. 73 (2017) 1900–1907.

[3] F. Zajdel, A. Partyka, K. Marcinek, A.J. Bojarski, M. Pawlowski, A. Wesołowska, Quinoline- and isoquinoline-sulfonamide analogs of aripiprazole: novel antipsychotic agents?, Future Med. Chem. 6 (2014) 57–75.

[4] M.M. Ghorab, M.S. Alsaid, Anti-breast cancer activity of some novel quinoline derivatives, Acta Pharm. 65 (2015) 271–283.

[5] M. Xu, T. Wagerle, J.K. Long, G.P. Lahm, J.D. Barry, R.M. Smith, Insecticidal quinoline and isoquinoline isoxazolines, Bioorganic Med. Chem. Lett. 24 (2014) 4026–4030.

[6] S. Mukherjee, M. Pal, Medicinal chemistry of quinolines as emerging anti-inflammatory agents: an overview, Curr. Med. Chem. 20 (2013) 4386–4410.

[7] J.J. Casal, S.E. Asís, Natural and synthetic quinoline derivatives as anti-tuberculosis Agents, Austin Tuberc. Res. Treat. 2 (2017) 2–4.

[8] C.M.M. Gómez, V.V. Kouznetsov, Recent developments on antimicrobial quinoline chemistry, in: Microb. Pathog. Strateg. Comb. Them Sci. Technol. Educ., FORMATEX, 2013, pp. 666–677.

[9] S. Singh, G. Kaur, V. Mangla, M.K. Gupta, Quinoline and quinolones: Promising scaffolds for future antimycobacterial agents, J. Enzyme Inhib. Med. Chem. (2015).

[10] P. Zajdel, A. Partyka, K. Marcinek, A.J. Bojarski, M. Pawlowski, A. Wesołowska, Quinoline- and isoquinoline-sulfonamide analogs of aripiprazole: novel antipsychotic agents?, Future Med. Chem. 6 (2014) 57–75.

[11] M.M. Ghorab, M.S. Alsaid, Anti-breast cancer activity of some novel quinoline derivatives, Acta Pharm. 65 (2015) 271–283.

[12] L. Paloque, P. Verhaeghe, M. Casanova, C. Castera-Ducros, A. Dumètre, L. Mbatchi, S. Hutter, M. Kraiem-M'Rabet, M. Laget, V. Remusat, P. Rathelot, N. Azas, P. Vanelle, Discovery of a new antileishmanial hit in 8-nitroquinoline series, Eur. J. Med. Chem. 54 (2012) 75–86.

[13] G.C. Muscia, M. Bolini, J.P. Carnevale, A.M. Bruno, S.E. Asís, Microwave-assisted Friedländer synthesis of quinolines derivatives as potential antiparasitic agents, Tetrahedron Lett. 47 (2006) 8811–8815.

[14] J.B. Bharate, R.A. Vishwakarma, S.B. Bharate, Metal-free domino one-pot protocols for quinoline synthesis, RSC Adv. 5 (2015) 42020–42053.

[15] Y. Xie, L. Li, Microwave-assisted α-halogenation of 2-methylquinolines with tetrabutylammonium iodide and 1,2-dichloroethane (1,2-dibromoethane), Tetrahedron Lett. 55 (2014) 3892–3895.

[16] G. Nagendrappa, Organic synthesis using clay and clay-supported catalysts, Appl. Clay Sci. 53 (2011) 106–138.

[17] M. Chandrappa, K. Kumar, P.K. Pullela, Critical Modification to Bulk Scale Synthesis of 2-Amino-5-carboethoxy-4-hydroxypyrimidine, Asian J. Chem. 29 (2017) 2119–2122.

[18] M. Chandrappa, G. V.S. Reddy, R. Fazlur, B.N. Murthy, P.K. Pullela, S.G. Kumar, Fe3O4@SiO2 magnetic nanoparticles for bulk scale synthesis of 4′-chloro-2′-5′,6′-terpyridine, Chem. Pap. 71 (2017) 2445–2453.