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Microwave assisted one-pot pseudo four-component synthesis of 2,4,6-trisubstituted pyridines using γ -MnO₂ nanoparticles

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Abstract This work described an efficient, one-pot pseudo four-component synthesis of 2,4,6-triarylpyridines. This reaction was performed under microwave irradiation and solvent-free conditions in the presence of γ -MnO₂ nanoparticles. Herein 2,4,6-triarylpyridines were synthesized via a simple reaction between benzyl alcohols, acetophenone, and ammonium acetate in the presence of γ -MnO₂ nanoparticles in good to excellent yields. Eco friendly, excellent yields of the product, short reaction times, inexpensive and readily available starting material are the main advantages of this method. *Graphical abstract*



Keywords Multi-component reaction \cdot Microwave \cdot Nano γ -MnO₂ \cdot Triarylpyridine \cdot Benzyl alcohols

Introduction

The nitrogen containing heterocyclic systems are one of the most important motifs in natural products and many synthetic compounds of pharmaceutical interest. Pyridine heterocycles are part of the most interesting heterocyclic organic compounds which represent chemical and pharmacological interest such as antiviral [1], antitumor [2], anticancer [3, 4], antibacterial [5, 6], and other biological activity [7–19]. Pyridines and their nucleoside analog showed intense cytotoxicity against several human cancer cell [20], influential and selective farnesyltransferase inhibitions [21], and inhibitors of HCV NS5B polymerase inhibitions [22], as well as antimicrobial [23] and antimycobacterial activities [24].

Transition metals oxide nanoparticles such as MnO₂ nanoparticles could catalyze organic reactions efficiently in a mild and environment friendly manner [25-31]. Use of minimum of reagent and energy, high yield of products easy reaction, simple work-up procedure and minimize byproduct, efficiency and recyclability are the main advantages of these catalysts. In recent decades many synthetic methods have been developed for the preparation of MnO₂ nanoparticles for example: reduction of potassium permanganate with aniline at ambient condition [32], use of hydrothermal method with longer hydrothermal reaction time [33, 34], by the incipient wetness impregnation method [2], by hydrothermal treatment and sequential thermal decomposition without employing any template or surfactant [35], via a facile quick-precipitation procedure at a low temperature (about 83 °C) without using any templates or surfactants [36] and by an sodium dodecyl sulphate (SDS)-assisted hydrothermal treatment method [37] or by reaction between $MnSO_4$, $(NH_4)_2S_2O_8$, and Na₂SO₄ [38].

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Scheme 1 ArCH₂OH + Ar' CH_3 + NH_4OAc $MaOH, nano \gamma-MnO_2$ 1 2 MW 600 W3 min Ar' Ar'

As part of our study aimed at developing efficient and straightforward methods to prepare organic compounds from readily available building blocks and simple catalyst [39–45], herein we report a simple and efficient method for the synthesis of 2,4,6-trisubstituted pyridines using γ -MnO₂ nanoparticles as catalyst, under microwave and solvent-free conditions (Scheme 1).

Results and discussion

Aryl alcohol, acetophenone, and ammonium acetate in the presence of air and nano γ -MnO₂ under microwave irradiation produced 2,4,6-triphenylpyridines **3a–3k** in 78–95 % yields (Table 1). This reaction was carried out as a pseudo four-component reaction under microwave and solvent-free conditions.

The ¹H NMR spectrum of **3f** exhibited two triplets at $\delta = 7.45$ and 7.54 ppm due to the 8 CH groups, a doublet of doublet signal at 7.74 with ${}^{3}J_{\text{FH}} = 8.7$ and ${}^{3}J_{\text{HH}} = 7.2$ Hz is due to the two CH groups and one singlet at 7.85 ppm is due to the two CH groups of pyridine ring. One distinctive doublet at 8.22 ppm with J = 7.2 Hz is due to the four *ortho* CH of phenyl groups.

A mechanistic pathway for the reaction is provided in Scheme 2, it is reasonable to assume that the first step may involve oxidation of benzyl alcohol **1** to corresponding nano γ -MnO₂ activated aryl aldehyde **4** by O₂ and then condensation with nano γ -MnO₂ activated acetophenone will form nano γ -MnO₂ activated chalcone **5**. The reaction of an ammonia molecule with a nano γ -MnO₂ activated chalcone **5** and Michael addition of another ammonia to a second nano γ -MnO₂ activated chalcone **5** leading to 2,4diaryl-1-azadiene **6** and 1:1 adduct **7**. Azadiene **6** and adduct **7** probably undergo a formal [4+2] cycloaddition reaction to form tetrahydropyridine intermediate **8**. Elimination of OH⁻ and nano γ -MnO₂ gives dihydropyridine intermediate **9**. Finally oxidative removal of benzylamin forms 2,4,6-triarylpyridine **3** (Scheme 2).

To optimize this reaction, the **3a** preparation was selected as a model, then the effects of nano γ -MnO₂ amounts and the effects of the other Lewis acids such as

Table 1 Pseudo four-component synthesis of 2,4,6-trisubstituted pyridines **3** in the presence of nano γ -MnO₂

Product	Ar	Ar'	Yield ^a /%
3a	Ph	Ph	95
3b	Ph	4-MePh	78
3c	Ph	2-MePh	86
3d	Ph	4-OMePh	83
3e	Ph	4-Cl-Ph	84
3f	Ph	4-F-Ph	79
3g	Ph	4-NO ₂ -Ph	78
3h	4-Me-Ph	4-Me-Ph	80
3i	4-Me-Ph	4-Cl-Ph	87
3j	4-Me-Ph	4-OMePh	85
3k	4-Me-Ph	Ph	89

^a Isolated yields

ZnO and ZnFe₂O₄ nanoparticles to the reaction yields were tested. Finally, the reaction temperature was optimized. The results of these experiments are displayed in the Tables 2 and 3. All of these tests were done in solvent-free conditions. The effect of microwave power to the reaction yields was tested and indicated in Table 2. As can be seen from Table 2, at low and high temperatures, the reaction yields were low. It may be because of low reaction rate and being incomplete at low temperatures and formation of the other byproducts at high powers. According to Tables 2 and 3, the highest yield was obtained in the presence of 10 mol% of nano γ -MnO₂ under microwave irradiation 600 W power for 3 min (Tables 2, 3).

Conclusion

In conclusion, we have developed a simple and efficient synthesis of 2,4,6-trisubstituted pyridines in the presence of γ -MnO₂ nanoparticles under microwave irradiation in solvent-free conditions. Excellent yields of products, short reaction times and mild reaction conditions, use of simple chemicals, eco-friendly, inexpensive and readily available starting chemicals, and high atomic economy are the main advantages of this method.



Table 2 Synthesis of 3a in the presence of various nano-catalysts under microwave irradiation power 600 W for 3 min

Entry	Nano ZnFe ₂ O ₄ / mol %	Nano α-Fe ₂ O ₃ / mol %	Nano γ-MnO ₂ / mol %	Yield ^a / %
1	0	0	0	6
2	0	0	1	17
3	0	0	2	23
4	0	0	4	40
5	0	0	6	66
6	0	0	8	85
7	0	0	10	95
8	0	0	12	95
9	0	0	10 ^b	35
10	10	0	0	80
11	0	10	0	78

^a Isolated yields

^b Commercial MnO₂

Experimental

All starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. γ -MnO₂ nanoparticles were synthesized via dissolving MnSO₄, (NH₄)₂S₂O₈, and Na₂-SO₄ with a molar ratio of 1:1:1 in deionized water at room temperature [36]. To confirm nano structure of nano γ -MnO₂ the SEM image were carried out (Fig. 1).

The progress of the reaction was monitored by TLC. Melting points were measured on an Electro-thermal 9100 apparatus. ¹H NMR and ¹³C NMR spectra (CDCl₃) were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.1 and 75.4 MHz, respectively. Elemental analyses for *C*, *H* and *N* were performed using a CHN-O-Rapid analyzer and the instrument model was Eager 300 for EA11112. The experiments were performed using a microwave oven

Table 3 Synthesis of 3a at various microwave powers and time in the presence of 10 mol % nano $\gamma\text{-}MnO_2$

Entry	Microwave power/W	Time/min	Yield ^a /%
1	100	2	23
2	180	2	35
3	300	2	46
4	450	2	54
5	600	2	67
6	600	3	95
7	600	4	93
8	900	2	72
9	900	3	65

^a Isolated yields



Fig. 1 SEM image of nano $\gamma\text{-MnO}_2,$ the average particle size was 36 nm

(ETHOS 1600, Milestone) with a maximum power of 900 W specially designed for organic synthesis.

General procedure for the synthesis of 2,4,6-trisubstituted pyridines 3a–3k

The reaction was carried out by first mixing benzyl alcohol 1 (1 mmol), acetophenone 2 (1 mmol), 0.040 g NaOH

(1 mmol), and 0.077 g ammonium acetate (1 mmol) in the presence of 0.001 g γ -MnO₂ nanoparticles (0.010 mmol) then heating them under microwave irradiation at 600 W for 3 min in solvent-free condition. Reaction monitoring by TLC clearly indicated formation of the corresponding 2,4,6-triarylpyridines. Upon completion, the reaction mixture was cooled to room temperature and γ -MnO₂ nanoparticles were separated by dissolving the reaction mixture in boiling ethanol and then it was centrifuged. After over flowing the solution the titled product was separated as a light yellow crystal in solution. The solvent was removed and the product was recrystallized from *n*-hexane–EtOAc (1:1). The structures of the isolated products **3a–3k** were confirmed by their ¹H and ¹³C NMR spectral data and their melting point values [39].

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