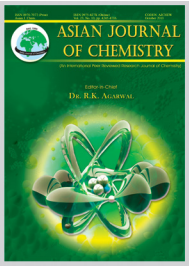
Asian Journal of Chemistry; Vol. 24, No. 8 (2012), 3751-3753

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Silica Gel-Supported Poly Phosphoric Acid Catalyzed One-Pot Multi-Component Synthesis of 2,4,6-Triarylpyridines under Solvent-Free and Microwave Irradiation Conditions

NASER MONTAZERI*, KHALIL POURSHAMSIAN, ROYA KALANTARIAN and MOHAMMAD MEHDI KIA

Department of Chemistry, Faculty of Sciences, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

*Corresponding author: Fax: +98 192 4274409; Tel: +98 192 4274415; E-mail: montazer50@toniau.ac.ir

(*Received*: 27 September 2011; *Accepted*: 26 March 2012) AJC-11231

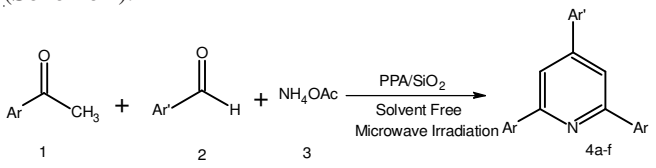
A simple, green and efficient protocol is developed in which silica gel-supported poly phosphoric acid (PPA-SiO_2) is employed as a solid acid catalyst in solvent-free and microwave irradiation conditions for the synthesis of various 2,4,6-triarylpyridines from acetophenones, aryl aldehydes and ammonium acetate. The salient features of the reaction include gool yields, relatively short reaction time and mild reaction conditions. The method is environmentally friendly and does not require solvents.

Key Words: Silica gel-supported poly phosphoric acid, 2,4,6-Triarylpyridines, Solvent-free, Microwave irradiation, Acetophenones, Environmentally friendly.

INTRODUCTION

Microwave irradiation has proved to be an efficient method of heating that cause to some facilities in performing reaction and improvement of yields[1,2]. The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development[3-6]. By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assemble in a fraction of time required by classical thermal methods. Pyridines possess a broad spectrum of biological activity. In many enzymes of living organisms it is the prosthetic pyridine nucleotide (NADP) that is involved in various oxidation-reduction processes[7]. Other evidence of the potent activity of pyridine in biological system is its presence in the important vitamins niacin and pyridoxine (vitamin B_6)[8]. Also, pyridines are very useful intermediates for the development of molecules of pharmaceutical and biological interest. Substituted pyridines derivatives have found applications in diverse therapeutic areas including antituberculosis, antibacterial, antiinflammatory, antiasthmatic, antidepressant and potent HIV protease inhibitor[9-13]. In addition to the pyridine ring is ubiquitous in agrochemicals such as fungicides[14], bactericides and herbicides[15]. 2,4,6-Triarylprydines have been synthesized by reaction of N-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of ammonium acetate[16,17]. However, the pyridinium salts and the unsaturated ketones have to be synthesized first, so this method is relatively expensive. More recently, several new improved methods and procedures for preparation of 2,4,6-triarylpyridines have been reported, for example solvent-free reaction of chalcones with ammonium acetate[18], reaction of α-ketoketene dithioacetals with methyl ketones in the presence of NH_4OAc[19], reaction of N-phosphinylethanimines with aldehydes[20], solvent-free reaction between acetophenones, benzaldehydes and NH_4OAc in the presence of various catalysts, for example $HClO_4$-SiO_2[21], preyssler type heteropolyacid[22] and I_2[23] and the one-pot reaction of acetophenones, benzaldehydes and NH_4OAc without catalyst under microwave irradiation[24]. However, several of these methods are associated with expensive and highly acidic catalysts, long reaction times, unsatisfactory yields and difficult product isolation. Therefore, the development of simple efficient, clean, good-yielding and environmentally friendly approaches using new catalyst for the synthesis of these compounds is an important task for organic chemists. Recently solid-supported reagents, such as silica gel-supported acid have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling[25-27]. Although, the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no reported in the literature on the use of poly phosphoric acid-SiO_2 in synthesis of 2,4,6-triaryl pyridines under microwave irradiation conditions. In continuation of our interest in

finding new environmentally benign methods for the synthesis of various heterocyclic compounds[28-33] and use of various solid acid for organic transformations[34], herein we want to report for first time, a new and efficient synthesis of 2,4,6-triarylpyridines in the presence of poly phosphoric acid-SiO_2 as a solid catalyst under microwave irradiation conditions (**Scheme-I**).



Scheme-I

EXPERIMENTAL

All reagent and solvents were purchased from commercial sources and used as received. The poly phosphoric acid-SiO_2 was prepared according to the literature[35]. Melting points were recorded on an electrothermal type 9100 melting points apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks.The ^{1}H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

Preparation of the catalyst (PPA-SiO_2): Poly phosphoric acid (2.1 g) was charged in the round-bottom flask and $CHCl_3$ (100 mL) was added. After the mixture was stirred at 50 ºC for 1 h. SiO_2 (200-400 mesh, 4.9 g) was added to the solution and the mixture was stirred for another 1 h. The $CHCl_3$ was removed with rotary evaporator and the resulting solid was dried in vacuum at room temperature for 3 h[35].

Recycling and reusing of the catalyst: The catalyst was recovered by filtration, dried at 100 ºC under vacuum for 2 h and reused in another reaction. The catalyst could be reused at least three times with only slight reduction in the catalyst activity of the catalyst.

General procedure for the synthesis of 2,4,6-triarylpyridines 4a-g using PPA-SiO_2 as a catalyst: A mixture of acetophenone derivative **1** (2 mmol), arylaldehyde **2** (1 mmol), ammonium acetate **3** (1.3 mmol) and PPA-SiO_2 (10 mg) as catalyst was placed in a 100 mL beaker. The beaker was covered with a stemless funnel and then irradiation in the microwave oven for 5 min with power of 600 W. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and boiling ethanol was added. The catalyst was filtrated and the filtrate was concentrated to give the solid product that was washed with water and recrystallized from *n*-hexane to give pure products **4a-g**. The structure of the products were confirmed by ^{1}H NMR and IR spectroscopy and comparison with authentic samples prepared by reported methods[18].

RESULTS AND DISCUSSION

Developing a simple, ecofriendly reaction protocol for the synthesis of heterocyclic compound is an attractive area of research in both academic and pharmaceutical[36].

Hence, the challenge for sustainable environment calls for the use of clean procedures, which can avoid the use of harmful solvents. The chemists are, therefore, more interested in seeking new processes involving solvent-free reactions which are devoid of pollution with low cost and simplicity in processing[37,38]. Therefore, due to the increasing demand in modern organic processes for avoiding expensive purification, we decided to investigate the efficiency of PPA-SiO_2 as catalyst in the synthesis of 2,4,6-triarylpyridines under solvent-free and microwave irradiation conditions. To find the optimum quantity of PPA-SiO_2, the synthesis of compound **4a** was used as a model reaction. Therefore, a mixture of acetophenone (2 mmol), 4-nitrobenzaldehyde (1 mmol) and NH_4OAc (1.3 mmol) in the presence of various amount of the PPA-SiO_2 was irradiated in the microwave oven under solvent-free conditions at 600 W(Table-1).

TABLE-1
EFFECT OF PPA-SiO_2 AMOUNT ON THE MODEL REACTION[a]

Entry	Catalyst (mg)	Time (min)	Yield (%)[b]
1	None	15	None
2	5	5	71
3	10	5	79
4	15	4	69
5	20	4	65
6	25	4	65

[a]2 mmol acetophenone, 1 mmol 4-nitrobenzaldehyde and 1.3 mmol ammonium acetate in the presence of various amount of PPA-SiO_2 under solvent-free and microwave irradiation conditions at 600 W.
[b]Isolated yields.

It was found that the yield of compound **4a** was strongly affected by the catalyst amount. The results show clearly that PPA-SiO_2 is an effective catalyst for this transformation and in the absence of the catalyst (entry1, Table-1) the reaction did not take place, indicating that the catalyst are necessary for the reaction. It is found that the yield of product **4a** was improved and the reaction time was shorted as the amount of the catalyst was increased to 10 mg, whereas further increase in catalyst amount was found to have an inhibiting effect on formation of the product (entry 4-6, Table-1). The model of reaction was also examined in various solvents and under solvent-free conditions in the presence of 10 mg of PPA-SiO_2. The yield of the reaction under solvent-free conditions was the highest and the reaction time was shortest (entry 1, Table-2).

TABLE-2
SYNTHESIS OF COMPOUND **4a** IN THE PRESENCE OF PPA-SiO_2 IN DIFFERENT SOLVENTS[a]

Yield (%)	Time (min)	Solvent	Entry
79	5	None	1
69	8	CH_2Cl_2	2
63	11	CH_3CN	3
59	8	H_2O	4
Trace	8	EtOH	5

[a]2 mmol acetophenone, 1 mmol 4-nitrobenzaldehyde, 1.3 mmol ammonium acetate and 10 mg PPA-SiO_2 in different solvents and solvent-free conditions at 600 W.
[b]Isolated yields.

Having established the ideal reaction, the synthesis scope of the reaction was further evaluated with different aldehydes and the results of present studies are summarized in Table-3. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in good yields. As expected,

TABLE-3
SYNTHESIS OF 2,4,6-TRIARYLPYRIDINES (**4a-g**)

Entry	Ar	Ar'	Products	Time (min)	Yields (%)	m.p. (ºC)
1	C_6H_5	4-$NO_2C_6H_4$	**4a**	5	79	198-200 (Lit.[18] 195-197)
2	*p*-$MeOC_6H_4$	4-$NO_2C_6H_4$	**4b**	4	83	142-144 (Lit.[18] 143-144)
3	*p*-MeC_6H_4	4-ClC_6H_4	**4c**	6	80	201-202 (Lit.[18] 199-200)
4	*p*-$MeOC_6H_5$	4-ClC_6H_4	**4d**	4	82	114-115 (Lit.[18] 115-116)
5	C_6H_5	4-ClC_6H_4	**4e**	2	81	126-127 (Lit.[18] 125-127)
6	C_6H_5	4-MeC_6H_4	**4f**	7	76	124-125 (Lit.[18] 123-124)
7	C_6H_5	2-MeC_6H_4	**4g**	10	72	121-123 (Lit.[18] 120-122)

[a]All products were characterized by use of IR and ^{1}H NMR spectral data and comparison of their melting points with those of authentic samples.
[b]Isolated yields.

presence of an electron-withdrawing group in the arylaldehyde improved the rate and yield of the reaction due to enhanced electrophonic reactivity of the carbonyl group (entry 1-5, Table-3). Whereas arylaldehydes possessing electron-donating groups afforded the corresponding 2,4,6-triarylpyridines in slightly lower yields (entry 6,7, Table-3).

Recycling studies were carried out in order to evaluate the catalytic activity of PPA-SiO_2. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature and boiling ethanol was added. The catalyst was filtrated and the recycled catalyst washed with *n*-hexane, dried and reused for the same reaction process. The catalyst could be reused at least three times with only slight reduction in the catalytic activity (79 % for 1set use; 78 % for 2nd use; 76 % for 3rd use).

Conclusion

In summary, a new application of silica gel-supported poly phosphoric acid (PPA-SiO_2) as an effective, very cheap and non-toxic catalyst for the synthesis of many 2,4,6-triarylpyridines, based on the condensation of acetophenons, arylaldehydes and ammonium acetate under mild reaction conditions is presented. This method considerations because it little waste. The availability and stability of the catalyst, the simple work-up procedure, good yields, relatively short reaction times under mild reaction conditions and recyclable catalyst, make this method a valid contribution to the existing methodologies.

ACKNOWLEDGEMENTS

The authors gratefully acknowledged the financial support from the Research Council of Islamic Azad University, Tonekabon Branch.

REFERENCES

1. L. Perraux and A. Loupy, *Tetrahedron*, **57**, 9199 (2001).
2. P. Lidstrom, J. Tierneym, B. Wathey and J. Westman, *Tetrahedron*, **57**, 9225 (2001).
3. S. Caddick, *Tetrahedron*, **51**, 10403 (1995).
4. A.K. Bose, B.K. Banik and M.S. Mamhas, *Tetrahedron Lett.*, **36**, 213 (1995).
5. G.B. Jones and B.J. Chapman, *J. Org. Chem.*, **58**, 5558 (1993).
6. F. Matloubi-Moghaddam, A. Sharifi and M.R. Saidi, *J. Chem. Res.*, **5**, 338 (1996).
7. N.F. Agarwal, A. Goel and V.J. Ram, *J. Org. Chem.*, **68**, 2983 (2003).
8. J.A. Joule, G. Smith and K. Mills, Heterocyclic Chemistry, Chapman and Hall, London, edn. 3, pp. 72-119 (1995).
9. B. Vacher, B. Bonnaud, F. Funes, N. Jubault, W. Koek, M.B. Assie, C. Cosi and M. Kleven, *J. Med. Chem.*, **42**, 1648 (1999).
10. W.B. Choi, I.N. Houpis, H.R.O. Churchill, A. Molina, J.E. Lynch, R.P. Volante, P.J. Reider and A.O. King, *Tetrahedron Lett.*, **36**, 4457 (1995).
11. Y. Abe, H. Kayakiri, S. Satoh, T. Inoue, Y. Sawada, N. Inamura, M. Asano, I. Aramori, C. Hatori, H. Sawai, T. Oku and H. Tanaka, *J. Med. Chem.*, **41**, 4062 (1998).
12. Z.S. Song, M. Zhao, R. Desmond, P. Devine, D.M. Tschaen, R. Tillyer, L. Frey, R. Heid, F. Xu, B. Foster, J. Li, R. Reamer, R. Volante, E.J. Grabowski, U.H. Dolling and P.J. Reider, *J. Org. Chem.*, **64**, 9658 (1999).
13. G. Matolcsy, Pesticide Chemistry, Elsevier Scientific: Amsterdam Oxford, pp. 427-430 (1988).
14. W.J. Michaely and A.D. Gutman, in eds.: D.R. Baker, J.G. Fenyes, W.K. Moberg and B. Cross, In Synthesis and Chemistry of Agrochemicals, ACS Symposium Series 335 Chapter, American Chemical Society, Washington, Ch. 5 (1987).
15. G.W. Ware, Pesticides: Theory and Application Freeman: San Francisco, Oxford, p. 102 (1983).
16. F. Kröhnke, *Synthesis*, 24 (1976).
17. F. Kröhnke and W. Zecher, *Angew. Chem. In. Ed.*, **1**, 626 (1962).
18. M. Adib, H. Tahermansouri, S.A. Koloogani, B. Mohammadi and H.R. Bijanzadeh, *Tetrahedron Lett.*, **47**, 5957 (2006).
19. K.T. Potts, M.J. Cipullo, P. Ralli and G. Theodoridis, *J. Am. Chem. Soc.*, **103**, 3584 (1981).
20. T. Kobayashi, H. Kakiuchi and H. Kato, *Bull. Chem. Soc. (Japan)*, **64**, 392 (1991).
21. L. Nagarapu, A.R. Peddiraju and S. Apuri, *Catal. Commun.*, **8**, 1973 (2007).
22. M.M. Heravi, K.H. Bakhtiari, Z. Daroogheha and F.F. Bamoharram, *Catal. Commun.*, **8**, 1991 (1991).
23. Y.M. Rem and C. Cai, *Monatsh. Chem.*, **140**, 49 (2009).
24. S. Tu, T. Li, F. Shi, F. Fung, S. Zhu, X. Wei and Z. Zong, *Chem. Lett.*, **34**, 732 (2005).
25. A.R. Hajipour and A.E. Ruoho, *Tetrahedron Lett.*, **46**, 8307 (2005).
26. S. Kantevari, R. Bantu and L. Nagarapu, *J. Mol. Catal. A: Chem.*, **269**, 53 (2005).
27. H.R. Shaterian, A. Hosseinian and M. Ghashang, *Arkivoc*, **2**, 59 (2009).
28. N. Montazeri and K. Rad-Moghadam, *Chin. Chem. Lett.*, **19**, 1143 (2008).
29. K. Pourshamsian, N. Montazeri, K. Rad-moghadam and S. Ali-Asgari, *J. Heterocycl. Chem.*, **47**, 1439 (2010).
30. M. Bakavoli and M. Ghasemzadeh, *J. Heterocycl. Chem.*, **42**, 1021 (2005).
31. N. Montazeri, S. Khaksar, A. Nazari, S.S. Alavi, S.M. Vahdat and M. Tajbakhsh, *J. Fluorine Chem.*, **132**, 450 (2011).
32. N. Montazeri, *Asian J. Chem.*, **22**, 7432 (2010).
33. N. Montazeri and K. Rad-Moghadam, *Asian J. Chem.*, **18**, 1557 (2006).
34. N. Montazeri and K. Rad-Moghadam, *Phosphorus, Sulfur Silicon Rel. Elem.*, **179**, 2533 (2004).
35. T. Aoyama, T. Takido and M. Kodomari, *Synlett*, 2307 (2004).
36. I. Kanizsai, S. Gyonfalvi, Z. Szakonyi, R. Sillanpaa and F. Fulop, *Green Chem.*, **9**, 357 (2007).
37. M.A.P. Martins, C.P. Frizzo, D.N. Moreira, L. Buriol and P. Machado, *Chem. Rev.*, **109**, 4140 (2009).
38. K. Tanaka and F. Toda, *Chem. Rev.*, **100**, 1025 (2000).