DE GRUYTER OPEN

ACTA CHEMICA IASI, ***24_1****, 20-28 (2016)*

DOI: 10.1515/achi-2016-0002

CLEAN SYNTHESIS OF PYRANO[2,3-*D*]PYRIMIDINES USING ZNO NANO-POWDERS

Nariman Maleki, Zahra Shakarami,* Saeid Jamshidian and Maryam Nazari

Department of Chemistry, Faculty of Sciences, Najafabad Branch, Islamic Azad University, P.O. Box: 517, Najafabad, Esfahan, Iran

Abstract: ZnO nano-powders were used for the one-pot synthesis of pyrano[2,3-*d*]pyrimidines *via* the solvent-free multi-component reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile, in good to excellent yields of products.

Keywords: multi-component reaction; 1,3-dimethylbarbituric acid; pyrano[2,3-*d*]pyrimidines; ZnO nano-powders

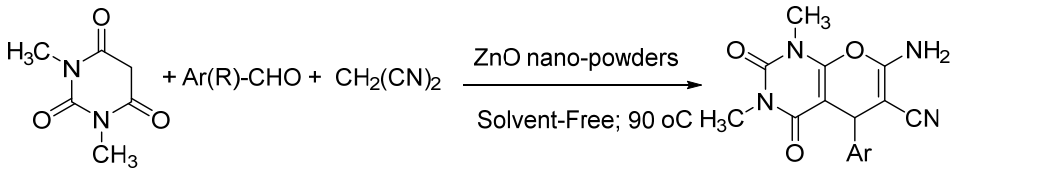
Introduction

Nitrogen- and oxygen-containing heterocyclic compounds are of considerable interest, as they are a class of natural and synthetic compounds that possess a great variety of biological and pharmaceutical activities.[1-12] For example, pyrano[2,3-*d*]pyrimidines are important structural components of both natural and synthetic biologically active compounds. Pyrano[2,3-*d*]pyrimidines show antitumor,[13] hepatoprotective,[14] antibronchitic[15] and anti-AIDS activity.[16]

* Zahra Shakarami, *e-mail*: shakaramizahra87@gmail.com

Among all the reported methods for the entitled compounds, the multi-component condensation reaction of aromatic aldehydes, barbituric acid derivatives and malononitrile has gained significant attention in the scientific community. Many different bases were proved to be viable catalysts for this reaction. However, the established reaction systems based on the use of homogeneous catalysts are often plagued by many intrinsic problems including corrosion, difficulty of catalyst recycling and the generation of waste.[17-23]

Thus, the discovery of new synthetic methodologies that facilitate the preparation of organic compounds is of great interest. One approach to address the abovementioned challenges involves the development of new environmentally friendly catalysts for the condensation reaction. Therefore, the scope of the present work was to achieve the multi-component condensation reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile to afford pyrano[2,3-*d*]pyrimidines by using ZnO nano-powders as a green, environmentally friendly catalyst (Scheme 1).



1: Ar = Ph
2: Ar = 4-MePh
3: Ar = 4-Cl-Ph
4: Ar = 3-NO_2Ph
5: Ar = 2,4-diClPh
6: Ar = 4-BrPh
7: Ar = 4-FPh
8: Ar = 3-ClPh

Scheme 1. Preparation of pyrano[2,3-*d*]pyrimidines using ZnO nano-powders.

Results and Discussion

The morphological evolution of the catalyst was investigated using SEM images of the sample and the results are revealed in Figure 1. As shown in Figure 1, the particles of ZnO nano-powders are relatively

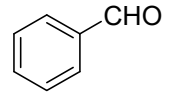
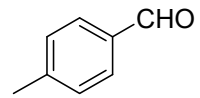
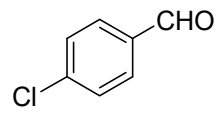
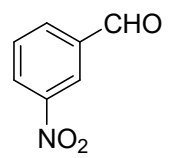
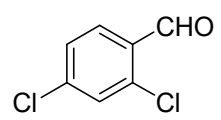
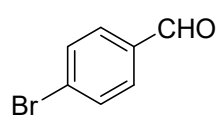
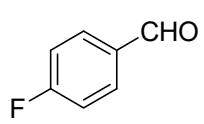
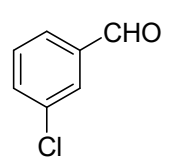
homogeneous in size and shape, and are uniform spheres having less than 100nm in size.

Figure 1. FE-SEM micrograph of ZnO nano-powders.

The catalytic activity of the prepared nano-powders was examined in the condensation reactions of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile, in order to afford pyrano[2,3-*d*]pyrimidines in better yields (Table 1). The progress of the reaction was monitored by TLC. After completion, reaction work-ups afforded the pure products in good yields (Table 1, Compound numbers 1-8).

The reactions worked well with almost all the aldehydes. However, aromatic aldehydes bearing electron withdrawing groups showed better reactivity, therefore the reactions were completed in a shorter time.

Table 1. Preparation of pyrano[2,3-d]pyrimidines using ZnO nano-powders as catalysts (0.25 mmol).

Compound Number	Aldehyde	Time (h)	Yield (%)[a]	M.p.[°C][lit. M.p.][Ref.]
1		3	89	219-222 [219-222][22]
2		4	78	203-205 [202-203][22]
3		2.5	86	210-212 [239-241][22]
4		1.5	98	201-203 [204][23]
5		4	78	251-253 [211-212][23]
6		2	89	209-211 [235][23]
7		2.5	96	234-236 [229-232][22]
8		2.3	83	223-225 [247-248][23]

[a]Isolated yield; All product were characterized on the basis of their NMR analysis.

Experimental

All reagents were purchased from Merck or Sigma-Aldrich and used without further purification. Field Emission Scanning Electron Microscope

(FE-SEM) images were obtained on HITACHI S-4160. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel Polygram SIL G/UV 254 plates.

Preparation of ZnO nano-powders

To a solution of $ZnCl_2$ (30 mmol in 100 mL water), 50 mL of hexane and subsequently 50 mL of ethanol was added. The mixture was stirred for 10 min. Then, an aqueous solution of ammonia (10% V/V) was added to the solution drop-wise under vigorous magnetic stirring. The mixture was stirred continuously for 10 min. The resulting precipitate was washed with water several times and dried in an oven at 100 °C for 1 h, followed by calcination at 500 °C for 2 h.

General procedure

A mixture of aldehyde (1 mmol), 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol), and ZnO nano-powders (0.25 mmol) was heated at 90°C and maintained until completion (for reaction times, see Table 1). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was dissolved in hot EtOH. The catalyst was removed by simple filtration. The solvent was then concentrated and the crude products were purified by crystallization from EtOH. The spectral data of selected compounds is given below:

7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile **(Table 1, Entry 1):** ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.04 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.31 (s, 1H, CH), 7.16 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.34-7.38 (m, 4H).

7-amino-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-5-p-tolyl-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile **(Table 1, Entry 2):** ^{1}H-NMR (400

MHz, DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 4.27 (s, 1H, CH), 7.07 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 2H, NH_2).

7-amino-5-(2,4-dichlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile **(Table 1, Entry 5):** ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.06 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 4.87 (s, 1H, CH), 7.48 (s, 2H, NH_2), 7.54-7.75 (m, 3H, ArH).

Conclusions

In summary, a high-yielding one-pot condensation reaction of 1,3-dimethylbarbituric acid, aromatic aldehydes and malononitrile for the synthesis of pyrano[2,3-*d*]pyrimidines using ZnO nano-powders as catalysts was developed. Various aromatic aldehydes afforded the corresponding products is high yields.

Acknowledgements

The authors are indebted to the Islamic Azad University, Najafabad Branch for financial support of this research.

References

1. Ghashang, M.; Kargar, M.; Shafiee, M. R. M.; Mansoor, S. S.; Fazlinia, A.; Esfandiari, H. CuO Nano-structures Prepared in Rosmarinus Officinalis Leaves Extract Medium: Efficient Catalysts for the Aqueous Media Preparation of Dihydropyrano [3, 2-c] chromene Derivatives. *Recent Pat. Nanotech.* **2015**, *9*, 204-211.

2. Ghashang, M.; Mansoor, S. S.; Mohammad Shafiee, M. R.; Kargar, M.; Najafi Biregan, M.; Azimi, F.; Taghrir, H. Green chemistry preparation of MgO nanopowders: efficient catalyst for the synthesis of thiochromeno [4, 3-b]

pyran and thiopyrano [4, 3-b] pyran derivatives. *J. Sulfur Chem.* **2016**, *37*, DOI: 10.1080/17415993.2016.1149856.

3. Ghashang, M.; Mansoor, S. S.; Aswin, K. Thiourea dioxide: An efficient and reusable organocatalyst for the rapid one-pot synthesis of pyrano [4, 3-b] pyran derivatives in water. *Chin. J. Catal.* **2014**, *35*, 127-133.

4. Baziar, A.; Ghashang, M. Preparation of pyrano [3, 2-c] chromene-3-carbonitriles using ZnO nano-particles: a comparison between the Box–Behnken experimental design and traditional optimization methods. *React. Kinet. Mechan. Catal.* **2016**, *117*, DOI: 10.1007/s11144-016-1013-x.

5. Ghashang, M. $ZnAl_2O_4$–Bi_2O_3 composite nano-powder as an efficient catalyst for the multi-component, one-pot, aqueous media preparation of novel 4H-chromene-3-carbonitriles. Res. Chem. Intermed. **2016**, *42*, 4191-4205.

6. Dehbashi, M.; Aliahmad, M.; Mohammad Shafiee, M. R.; Ghashang, M. Nickel-doped SnO_2 Nanoparticles: Preparation and Evaluation of Their Catalytic Activity in the Synthesis of 1-amido Alkyl-2-naphtholes. *Synth. React. Inorg. Metal-Org. Nano-Metal Chem.* **2013**, *43*, 1301-1306.

7. Ghashang, M. Zinc hydrogen sulfate promoted multi-component preparation of highly functionalized piperidines. *Lett. Org. Chem.* **2012**, *9*, 497-502.

8. Ghashang, M. Preparation and application of barium sulfate nano-particles in the synthesis of 2, 4, 5-triaryl and N-aryl (alkyl)-2, 4, 5-triaryl imidazoles. *Curr. Org. Synth.* **2012**, *9*, 727-732.

9. Shafiee, M. M. R.; Ghashang, M.; Fazlinia, A. Preparation of 1, 4-dihydropyridine derivatives using perchloric acid adsorbed on magnetic Fe_3O_4 nanoparticles coated with silica. *Curr. Nanosci.* **2013**, *9*, 197-201.

10. Taghrir, H.; Ghashang, M.; Biregan, M. N. Preparation of 1-amidoalkyl-2-naphthol derivatives using barium phosphate nano-powders. *Chin. Chem. Lett.* **2016**, *27*, 119-126.

11. Shafiee, M. R. M.; Mansoor, S. S.; Ghashang, M.; Fazlinia, A. Preparation of 3, 4, 5-substituted furan-2 (5H)-ones using aluminum hydrogen sulfate as an efficient catalyst. *C. R. Chim.* **2014**, *17*, 131-134.

12. Zare, M.; Ghashang, M.; Saffar-Teluri, A. BaO-ZnO nano-composite efficient catalyst for the photo-catalytic degradation of 4-chlorophenol. *Biointerface Res. Appl. Chem.* **2016**, *6*, 1049-1052.

13. Valderrama, J. A.; Colonelli, P.; Vasquez, D.; Gonzalez, M. F.; Rodriguez, J. A.; Theoduloz, C. Studies on quinones. Part 44: novel angucyclinone *N*-heterocyclic analogues endowed with antitumoral activity. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 10172–10181.

14. Furuay, S.; Ohtaki, T. Pyranopyrimidine derivatives, their production and use. *Eur. Pat. Appl.* **1994**, *EP*608565.

15. Bagley, M. C.; Hughes, D. D.; Lubinu, M. C.; Merrit, E. A.; Taylor, P. H.; Tomkinson, N. C. O. Microwave-assisted synthesis of pyrimidine libraries. *QSAR Comb. Sci.* **2004**, *23*, 859–867.

16. Nogueras, M.; Cobo, J.; Quijano, M. L.; Melguizo, M.; Shchez, A.; Melgarejob, M. Selective Synthesis of 6-Ribo- (and Xylo) Pyrano and Furano Aminopyridines. Anticancer and Anti-AIDS Activities. *Nucleosides Nucleotides* **1994**, *13*, 447–457.

17. Seeliger, F.; Berger, S. T. A.; Remennikov, G. Y.; Polborn, K.; Mayr, H. Electrophilicity of 5-benzylidene-1,3-dimethylbarbituric and -thiobarbituric acids. *J. Org. Chem.* **2007**, *72*, 9170–9780.

18. Khurana, J. M.; Vij, K. Nickel nanoparticles as semiheterogeneous catalyst for one-pot, three-component synthesis of 2-amino-4H-pyrans and pyran annulated heterocyclic moieties. *Synth. Commun.* **2013**, *43*, 2294-2304.

19. Azarifar, D.; Nejat-Yami, R.; Sameri, F.; Akrami, Z. Ultrasonicpromoted one-pot synthesis of 4H-chromenes, pyrano[2,3-d]pyrimidines, and 4H-pyrano[2,3-c]pyrazoles. *Lett. Org. Chem.* **2012**, *9*, 435-439.

20. Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Nikishin, G. I.; Zaimovskaya, T. A. Electrocatalytic multicomponent assembling of aldehydes, *N*-alkyl barbiturates and malononitrile: an efficient approach to pyrano[2,3-d]pyrimidines. *Mendeleev. Commun.* **2011**, *21*, 122–124.

21. Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. A novel three-component one-pot synthesis of pyrano[2,3-d]pyrimidines and pyrido[2,3-d]pyrimidines using microwave heating in the solid state. *Tetrahedron Lett.* **2003**, *44*, 8307–8310.

22. Elinson, M. N.; Ryzhkov, F. V.; Merkulova, V. M.; Ilovaisky, A. I.; Nikishin, G. I. Solvent-free multi-component assembling of aldehydes, *N,N′*-dialkyl barbiturates and malononitrile: fast and efficient approach to pyrano[2,3-*d*]pyrimidines. *Heterocycl. Commun.* **2014**, *20*, 281–284.

23. Khazaei, A.; Ranjbaran, A.; Abbasi, F.; Khazaei, M.; Moosavi-Zare, A. R. Synthesis, characterization and application of $ZnFe_2O_4$ nanoparticles as a heterogeneous ditopic catalyst for the synthesis of pyrano[2,3-*d*] pyrimidines. *RSC Adv.* **2015**, *5*, 13643-13647.