

CHEAP AND EFFICIENT PROTOCOL FOR THE ONE- POT MULTICOMPONENT SYNTHESIS OF DIHYDROPYRIMIDINONE DERIVATIVES USING SILICA NANOPARTICLES AS REUSABLE CATALYST

*Javid Monjezi¹, Maziar Noei² and Abbas Shirmardi Dezaki¹

¹Department of Chemistry, Masjed-Soleiman Branch, Islamic Azad University (I.A.U), Masjed-Soleiman, Iran

²Department of Chemistry, College of Chemistry, Mahshahr Branch, Islamic Azad University (I.A.U), Mahshahr, Iran

*Author for Correspondence

ABSTRACT

Multicomponent reactions have been successfully adopted by the chemists for the synthesis of a library of biologically active molecules. A one-pot practical synthesis of 3, 4-dihydro-pyrimidin-2(1H)-ones has been developed using silica nanoparticles (SiO₂- NPs) as reusable catalyst. The advantages of using SiO₂- NPs are: ease to synthesize from readily available and inexpensive materials and stability at elevated temperatures.

Keywords: Combinatorial Chemistry, Calcium Channel Antagonists, Anti-Hypertensive, Biginelli Reactions and Multi-Component Reactions

INTRODUCTION

Dihydropyrimidinones (DHPMs) have a wide range of biological activities, acting as calcium channel antagonists, anti-hypertensive, anti-bacterial, and anti-inflammatory agents, while also possessing cytotoxic activity. For example, the anti-cancer agent Monastrol (Figure 1) has been shown to specifically affect mitosis via a new mechanism consisting of the specific and reversible inhibition of the motility of the motor protein, mitotic kinesin. At the same time, (R)-SQ 32926 has been found to have potent anti-hypertensive activity. It has also been indicated that alkaloids isolated from marine sources containing dihydropyrimidine unit demonstrate interesting biological activity (Roberts and Strauss, 2005; Domling *et al.*, 2000; Vedachalam *et al.*, 2010; Lorpithaya *et al.*, 2008; Gorityala *et al.*, 2009).

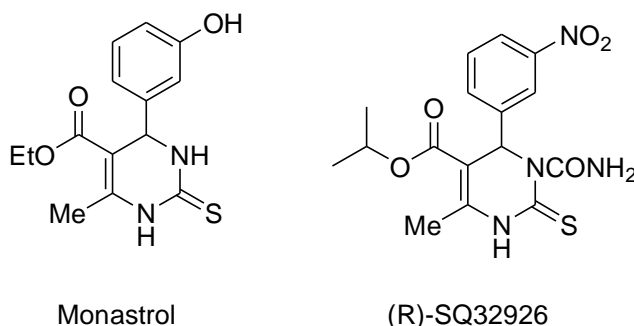
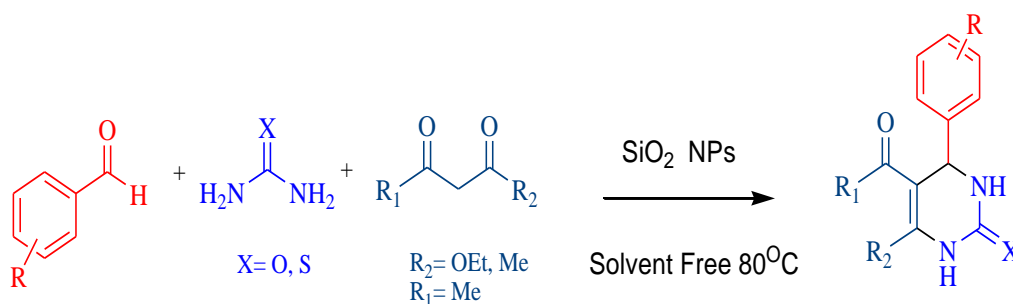


Figure 1: Biologically Active Dihydropyrimidinones

The 'greening' of global chemical manufacturing by minimizing energy consumption and waste production has become a major concern to organic chemists in present years, A robust, efficient, and cost effective chemical process is normally considered important in pharmaceutical synthesis (Hota *et al.*, 2009). Currently, one-pot, multi-component synthesis are practiced extensively due to their prowess to minimize reaction time, the number of steps, energy consumption, waste production, and to maximize synthetic efficiency and environmental benignity (Khazaei *et al.*, 2013). One of the major industrial

Research Article

disadvantages of performing homogeneously catalyzed reactions is the difficulty of separating the catalyst from the product and reusing the expensive catalyst (Hota *et al.*, 2009; Khazaei *et al.*, 2013). These problems are of significant environmental and economic concerns in organic syntheses. Heterogeneity of the existing homogeneous catalysts by immobilization of the catalyst on insoluble surfaces can provide a simple solution to this problem (Mamani *et al.*, 2010; Davarpanah *et al.*, 2013). Multicomponent reactions (MCRs) are important in organic and medicinal chemistry. Also in combinatorial chemistry, they are predicted to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product, thus avoiding complicated purification operations and allowing savings of both solvents and reagents (Kiasat and Davarpanah, 2010). An important class of heterocyclic compounds in the pharmaceutical is 3, 4-dihydro-pyrimidin-2(1H)-ones (Salehi *et al.*, 2003; Niknam *et al.*, 2007; Zeng *et al.*, 2012; Nasr-esfahani *et al.*, 2011; Rafiee and Shahebrahimi, 2012; Tayebie *et al.*, 2012; Quan *et al.*, 2009; Kolosov *et al.*, 2009; Tajbakhsh *et al.*, 2012; Xu *et al.*, 2007; Timoshenko *et al.*, 2011; Biginelli, 1893; Sedova *et al.*, 2009). They are very well known for their wide range of biological activities as calcium channel blockers, (Kalita and Phukan, 2007; Singh *et al.*, 2008) antihypertensive agents and neuropeptide Y antagonists. Therefore, the development of a high throughput method for the synthesis of DHPMs is a topic of current interest for organic and medicinal chemists. A wide variety of reaction conditions have been published for the synthesis of DHPMs in solution and under solvent-free conditions (Davarpanah *et al.*, 2013; Kiasat and Davarpanah, 2010; Salehi *et al.*, 2003; Niknam *et al.*, 2007; Zeng *et al.*, 2012). However, there are still some drawbacks to the reported catalytic systems including the requirement for large amounts of catalyst, long reaction times, and low yields of product, drastic reaction conditions, and generation of large amount of toxic waste. This finding prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of DHPMs under simpler experimental set up and eco-friendly conditions. In this paper, we report SiO₂- NPs -catalyzed synthesis of DHPMs via a one-pot three component condensation of aldehydes, β -ketoester such as methyl or ethyl acetoacetate and urea under solvent free condition (Scheme 1).



Scheme 1

MATERIALS AND METHODS

General:

The chemicals were purchased from Merck, Fluka and Aldrich chemical companies. The reactions were monitored by TLC (silica-gel 60 F254, *n*-hexane:ethyl acetate). IR spectra were recorded on an FT-IR Shimadzu- 470 Spectrometer and the ¹H NMR spectra were obtained on a Bruker-Instrument DPX-400 Avance 2 model. Mass spectra were recorded on a Shimadzu GC-MS QP 100 Ex spectrometer. All of the products (except novel compounds) were characterized by comparison of their spectra and physical data, with those reported in the literature.

Typical procedure for the preparation of 3, 4-dihydropyrimidin-2(1H)-ones/thiones:

A mixture of aromatic aldehyde (1.0mmol), ethyl acetoacetate (1.0mmol), urea or thiourea (2mmol), and SiO₂- NPs (5% mole) was heated at 80 °C for the time shown in Table 3. After complete consumption of aromatic aldehyde as judged by TLC (using *n*-hexane–ethyl acetate as eluent), the mixture was washed with distilled water to separate the excess of urea or thiourea. The crude product was dissolved in hot

Research Article

ethanol. The hot solution was separated by filtration and allows reaching to room temperature. All isolated products gave satisfactory spectral data (^1H NMR and ^{13}C NMR) and compared with those reported in literature.

RESULTS AND DISCUSSION

A solvent-free or solid state reaction obviously reduces pollution, and brings down handling costs due to simplification of experimental procedure, work up technique and saving in labour. These would be especially important during industrial production. Interest in the environmental control of chemical processes has increased remarkably during three decades ago (Over the past three decades) as a response to public concern about the use of hazardous chemicals. Therefore, to improve the effectiveness of this method in preventing chemical waste, it is important to investigate its optimal conditions. For establishing the simple and suitable conditions to prepare DHPMs using SiO_2 -NPs as a solid catalyst, upon treatment of benzaldehyde (1mmol), ethyl acetoacetate (1mmol) and urea (2mmol) was chosen as a model reaction. At first, we found that in the absence of the catalyst, the reaction did not proceed even at a high temperature (Table1).

Table 1: Catalyst Optimized with Various Amounts of SiO_2 - NPs under Solvent-Free Conditions at 80°C

| Entry | Catalyst mol% | Time/min | Yield ^a (%) |
|-------|---------------|----------|------------------------|
| 1 | - | 300 | 10 ^b |
| 2 | 1 | 180 | 65 |
| 3 | 2 | 120 | 75 |
| 4 | 4 | 50 | 81 |
| 5 | 5 | 30 | 92 |
| 6 | 6 | 30 | 92 |

^a Isolated Yields. ^b Not Completed

After examining the various amounts of SiO_2 -NPs according to Table 1 and a wide range of temperatures (Table 2), it was found that the condensation reaction can be efficiently carried out by adding 5mol% of the catalyst at 80°C under solvent-free conditions in a short time span of 40 min. The use of excessive amounts of the catalyst does not increase the yield and reaction rate.

Table 2: Temperature Optimized At Several Thermal Conditions Using SiO_2 - NPs (5 Mol %)

| Entry | Temperature $^\circ\text{C}$ | Time/min | Yield ^a (%) |
|-------|------------------------------|----------|------------------------|
| 1 | 30 | 300 | 65 |
| 2 | 60 | 70 | 75 |
| 3 | 70 | 45 | 87 |
| 4 | 80 | 30 | 92 |
| 5 | 100 | 30 | 80 |

^a Isolated Yields.

In order to evaluate the generality of this model reaction, we prepared a range of DHPMs under optimized reaction conditions. In all case aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in high yields and short reaction times. As shown in Table 3, the type of aromatic aldehyde had no significant effect on the reaction. The structure of the products was established from their IR spectral data and comparison of their melting points with those of authentic samples. Also, the structure of some products was confirmed by ^1H NMR spectral data.

Research Article

Table 3: Solvent-Free Synthesis of DHPMs Using SiO₂- NPs (5 Mol %) At 80 °C

| Entry | R | X | R ₂ | Time (min) | Yield ^a (%) | M.P.(°C) ^b |
|-------|-------------------------|---|----------------|------------|------------------------|-----------------------|
| 1 | Ph- | O | OEt | 30 | 92 | 203-205 |
| 2 | Ph- | S | OEt | 30 | 90 | 206-208 |
| 3 | 4-O ₂ N- Ph- | O | OEt | 30 | 85 | 209-211 |
| 4 | 4-O ₂ N- Ph- | S | OEt | 30 | 85 | 200-203 |
| 5 | 3-O ₂ N- Ph- | O | Et | 40 | 78 | 227-229 |
| 6 | 3-O ₂ N- Ph- | S | Et | 40 | 78 | 205-207 |
| 7 | 4-Cl-Ph- | O | OEt | 30 | 94 | 210-212 |
| 8 | 2-Cl-Ph- | O | OEt | 35 | 89 | 214-216 |
| 9 | 4-Cl-Ph- | O | Me | 30 | 90 | 205-207 |
| 10 | 4-CH ₃ OPh | O | OEt | 40 | 83 | 201-203 |
| 11 | 4-CH ₃ OPh | O | Me | 40 | 78 | 191-193 |
| 12 | 4-CH ₃ OPh | S | Me | 60 | 85 | 152-153 |
| 13 | Ph- | S | Me | 35 | 87 | 220-222 |
| 14 | 4-F-Ph- | O | OEt | 35 | 88 | 181-183 |

^a Isolated Yields, ^b Products were characterized by comparison of their spectroscopic data (NMR and IR) and melting points with those reported in the literature.

CONCLUSION

In this study, we presented a simple, powerful and clean method for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via three-component coupling reactions, under solvent free conditions at 80 °C was investigated. This environmentally friendly route offers several advantages including high yield, short reaction time, simple work-up procedure, and ease of separation as well as the ability to tolerate a wide variety of substitutions in the reagents.

ACKNOWLEDGMENTS

We are grateful to the Research Council of, Masjed-Soleiman Branch, Islamic Azad University for financial support of this investigation.

REFERENCES

- Biginelli P (1893)**. Aldehyde-urea derivatives of aceto- and oxaloacetic acids. *Gazzetta Chimica Italiana* **23** 360-413.
- Davarpanah J, Kiasat AR, Noorizadeh S and Ghahremani M (2013)**. Nano magnetic double-charged diazoniabicyclo[2.2.2]octane dichloride silica hybrid: Synthesis, characterization, and application as an efficient and reusable organic-inorganic hybrid silica with ionic liquid framework for one-pot synthesis of pyran annulated heterocyclic compounds in water. *Journal of Molecular Catalysis A: Chemical* **376** 78-89.
- Domling A and Ugi I (2000)**. Multicomponent Reactions with Isocyanides. *Angewandte Chemie International Edition* **39**(18) 3168-3210.
- Gorityala BK, Lorpitthaya R, Bai Y and Liu X-W (2009)**. ZnCl₂/alumina impregnation catalyzed Ferrier rearrangement: an expedient synthesis of pseudoglycosides. *Tetrahedron* **65**(29-30) 5844-5848.
- Hota SK, Chatterjee A, Bhattacharya PK and Chattopadhyay P (2009)**. A green chemical approach for the N-alkylation of aldoximes to form nitrones in organized aqueous media and their in situ cycloaddition with olefins. *Green Chemistry* **11** 169-174.
- Kalita HR and Phukan P (2007)**. CuI as reusable catalyst for the Biginelli reaction. *Catalysis Communications* **8**(2) 179-182.
- Khazaei A, Zolfigol MA, Mokhlesi M and Rostamian R (2013)**. Nano-sphere silica sulfuric acid: novel and efficient catalyst in the one-pot multi-component synthesis. *Journal of the Iranian Chemical Society* **10**(6) 1297-1301.
- Kiasat AR and Davarpanah J (2013)**. Fe₃O₄@silica sulfuric acid nanoparticles: An efficient reusable nanomagnetic catalyst as potent solid acid for one-pot solvent-free synthesis of indazolo[2,1-

Research Article

b]phthalazine-triones and pyrazolo[1,2-b]phthalazine-diones. *Journal of Molecular Catalysis A: Chemical* **373** 46-54.

Kolosov MA, Orlov DV, Beloborodov DA and Dotsenko VV (2009). A chemical placebo: NaCl as an effective, cheapest, non-acidic and greener catalyst for Biginelli-type 3,4-dihydropyrimidin-2(1H)-ones (-thiones) synthesis. *Molecular Diversity* **13**(1) 5-25.

Lorpitthaya R, Xie ZH, Kuo JL and Liu X-W (2008). Stereo controlled Intramolecular Aziridination of Glycals: Ready Access to Aminoglycosides and Mechanistic Insights from DFT Studies. *Chemistry - A European Journal* **14**(5) 1561– 1570.

Mamani L, Sheykhani M, Heydari A, Faraji M and Yamini Y (2010). Sulfonic acid supported on hydroxyapatite-encapsulated- γ -Fe₂O₃ nanocrystallites as a magnetically Brønsted acid for N-formylation of amines. *Applied Catalysis A: General* **377**(1-2) 64-69.

Nasr-esfahani M., Hoseini S. J., Mohammadi F (2011). Fe₃O₄ Nanoparticles as an Efficient and Magnetically Recoverable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones under Solvent-Free Conditions. *Chinese Journal of Catalysis* **32**(9-10) 1484-1489.

Niknam K, Zolfigol MA, Hossieninejad Z and Daneshvar N (2007). Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-one Using Metal Hydrogen Sulfates M(HSO₄)_n as Catalyst under Solvent-Free Conditions. *Chinese Journal of Catalysis* **28**(7) 591-595.

Quan ZJ, Da YX, Zhang Z and Wang XC (2009). PS-PEG-SO₃H as an efficient catalyst for 3,4-dihydropyrimidones via Biginelli reaction. *Catalysis Communications* **10** 1146–1148

Rafiee E and Shahebrahimi S (2012). Nano Silica with High Surface Area from Rice Husk as a Support for 12-Tungstophosphoric Acid: An Efficient Nano Catalyst in Some Organic Reactions. *Chinese Journal of Catalysis* **33**(7-8) 1326-1333.

Roberts BA and Strauss CR (2005). Toward Rapid, “Green”, Predictable Microwave-Assisted Synthesis. *Accounts of Chemical Research* **38**(8) 653–661.

Salehi P, Dabiri M, Zolfigol MA and Bodaghifard MA (2003). Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Letters* **44**(14) 2889-2891.

Sedova VF, Krivopalov VP and Shkurko OP (2010). Synthesis of substituted 3,4-dihydropyrimidin-2(1H)-ones and pyrimidin-2(1H)-ones by the Biginelli reaction with 3,5-Di-tert-butyl-4-hydroxybenzaldehyde. *Russian Journal of Organic Chemistry* **45**(10) 1535-40.

Singh BK, Mishra M, Saxena N, Yadav GP, Maulik PR, Sahoo MK, Gaur RL, Murthy PK and Tripathi RP (2008). Synthesis of 2-sulfanyl-6-methyl-1,4-dihydropyrimidines as a new class of antifilarial agents. *European Journal of Medicinal Chemistry* **43**(12) 2717-2723.

Singh K, Arora D, Poremsk E, Lowery J and Moreland RS (2009). N1-Alkylated 3,4-dihydropyrimidine-2(1H)-ones: Convenient one-pot selective synthesis and evaluation of their calcium channel blocking activity. *European Journal of Medicinal Chemistry* **44**(5) 1997–2001.

Tajbakhsh M, Ranjbar Y, Masuodi A and Khaksar S (2012). A Simple and Environmentally Benign Protocol for Biginelli Reactions Catalyzed by Silica-Bonded S-Sulfonic Acid. *Chinese Journal of Catalysis* **33**(9-10) 1542-45

Tayeb R, Maleki B and Ghadamgahi M (2012). Ammonium Dihydrogen Phosphate Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones. *Chinese Journal of Catalysis* **33**(4-6) 659-665.

Timoshenko VM, Markitanov YM and Shermolovich YG (2011). 2-Oxo-2-polyfluoroalkylethane-1-sulfones and -sulfamides in the Biginelli and ‘retro-Biginelli’ reactions. *Tetrahedron Letters* **52**(49) 6619-6622.

Vedachalam S, Zeng J, Gorityala BK, Antonio M and Liu X-W (2010). N-Heterocyclic Carbene-Catalyzed Intramolecular Aldehyde–Nitrile Cross Coupling: An Easy Access to 3- Aminochromones. *Organic Letters* **12** 352–355.

Xu D, Li H and Wang Y (2012). Highly enantioselective Biginelli reaction catalyzed by a simple chiral primary amine catalyst: asymmetric synthesis of dihydropyrimidines. *Tetrahedron* **68**(38) 7867-7872

Zeng Z, Wang LY, Cao Y and Luo YP (2012). Synthesis of 2-amide-3-carboxylate-4-aryl-4H-chromene derivatives. *Research on Chemical Intermediates* **38** 1751-176.