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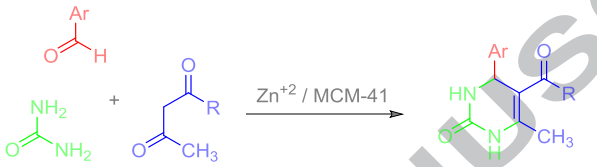

Ar = 2-Furyl, 5-Methyl-2-furyl, 2-Thienyl, 3-Thienyl, 2-Naphthyl
R = OMe, OEt, OBu, Ph

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ABSTRACT

The three component Biginelli condensation of various aryl aldehydes, 1,3-dicarbonyls and urea was investigated in the presence of free or MCM-41 supported $ZnNO_3$. The pyrimidone products, which were obtained under solvent-free conditions, were evaluated for antibacterial and antifungal activities as well as their cytotoxicities.

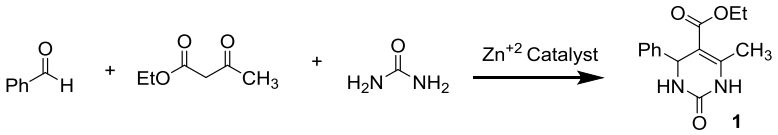
1. Introduction

The three component condensation of an aromatic aldehyde, urea, and a 1,3-dicarbonyl compound, known as the Biginelli reaction, offers an efficient methodology for the synthesis of 3,4-dihydropyrimidine-2-ones.[1] Interesting synthetic and pharmacological properties and the commercial availability or easy preparation of the individual building blocks have resulted in the remarkable popularity of this acid catalyzed reaction.[2] Development of various synthetic modifications such as the utilization of heterogeneous reusable catalysts and solvent free conditions have considerable advantages for overcoming some of the drawbacks of the classical Biginelli reaction, such as harsh conditions, long reaction times and low to moderate yields with certain substrates.[3] The incorporation of metal species onto heterogeneous surfaces such as mesostructure materials can improve the facile diffusion of bulky reactants and efficient interaction in their nano-size pores.[4] Therefore, these systems can promote the reaction without the use of solvent and minimise waste production. MCM-41 (Mobil Composition of Matter) is a mesoporous material with a high surface area which has been modified by various metallic ions, and widely utilized as a suitable support in many metal catalyzed reactions.[5] Among the potential Lewis acids which promote multicomponent reactions, Zn^{2+} based systems are interesting due to being efficient, inexpensive and environmentally benign.[6] In this work, we report the use of Zn^{2+} incorporated MCM-41 for the Biginelli reaction and a comparison with other Zn^{2+}species. We also report the $ZnNO_3$ promoted Biginelli reaction with 3-benzyloxy-2-formyl-4-pyrone (prepared from kojic acid), which represents the first report of this reaction incorporating the 4-pyrone skeleton. Finally, the evaluation of antibacterial and antifungal activities as well as the cytotoxicity data of selected pyrimidone derivatives is presented.

2. Results and discussion

We began by examining the Biginelli condensation between benzaldehyde, urea and ethyl acetoacetate in the presence of various Zn^{2+} species under solvent free conditions (Table 1). The well known $ZnCl_2$ catalyzed condensation gave product **1** in 90% yield (Entry 1), while substitution for the same amount of $Zn(NO_3)_2.6H_2O$, gave the product in higher yield and shorter time (Entry 2). To study the catalytic systems containing MCM-41, we first examined the activity of the mesoporous material in this reaction (Entries 3-5). Because the synthesis of MCM-like materials is typically based on the self assembly of ionic or non-ionic surfactant micelles on the silica skeleton, the organic template can be removed by calcination or extraction techniques.[7] Testing of both catalyst types (calcinated and with template), resulted in low yields of product due to the low acidity of the heterogeneous solid (Entries 3-5). In order to improve the activity of the silica materials, we attempted to disperse zinc cations onto the porous support using two methods: direct synthesis (DS) and wet

Table 1. Zn^{2+} Catalyzed Biginelli reaction at solvent free conditions



Entry	Catalyst	Amount of cat.	Time	Yield (%)
1	$ZnCl_2$	10% mol	20 min	90
2	$Zn(NO_3)_2.6H_2O$	10% mol	15 min	91
3	MCM-41 (Calcinated)	0.01 gr	2 h	40
4	MCM-41 (Calcinated)	0.02 gr	2h	47
5	MCM-41 (with template)	0.02 gr	5 h	36
6	$Zn(NO_3)_2.6H_2O$ /MCM-41/Calcinated/(WI)	0.02 gr	20 min	92
7	$Zn(NO_3)_2.6H_2O$ /MCM-41/Extracted/(WI)	0.02 gr	5 h	77
8	$Zn(NO_3)_2.6H_2O$ /MCM-41/Calcinated/(DS)	0.02 gr	1 h	78
9	$ZnCl_2$/MCM-41/Calcinated/(WI)	0.02 gr	3 h	49
10	$ZnCl_2$/MCM-41/Extracted/(WI)	0.02 gr	3 h	43
11	$Zn(NO_3)_2.6H_2O$ /MCM-41/Calcinated/(WI) (Recycled)	0.02 gr	25 min	84

Conditions: benzaldehyde (3 mmol), ethyl acetoacetate (3 mmol), urea (4.5 mmol), 80 ^{o}C.

impregnation (WI) techniques. The catalyst formed by introduction of the metal into the calcinated silica materials (after complete removal of the organic template) by the wet impregnation method,[8] gave the highest yield and its efficacy was comparable to free $ZnNO_3$ (Entry 6). Replacing the thermal calcination step with extraction, gave a catalytic system with relatively poor activity (Entry 7). Furthermore, the direct synthesis method consisting of addition of the metal catalyst into the reaction mixture at the beginning of preparation process,[9] also produced a lower yield (Entry 8). Despite the proven high catalytic activity of $ZnCl_2$, impregnation onto the hexagonal channels of MCM-41, led to a decrease in effectiveness (Entries 9,10). Therefore, we focused on an optimized system based on supported $ZnNO_3$ (Entry 6) which showed acceptable activity even when recycled (Entry 11).

This catalyst was found to have the highest metal loading (14.61%) relative to other species as determined by Energy dispersive X-ray (EDX) (Table 2). Estimation of the acidity of the active catalytic sites at loaded species of $Zn(NO_3)_2$ was performed using the Hammett indicator method[10] which showed the highest acidity for our selected system (Table 2, Entry 4). For determination of the basic strength of the catalyst the following Hammett indicators were used: bromothymol blue (H_-=7.2), phenolphthalein (H_-=9.3) and alizarine yellow (H_-=11.0). H_- function defined by Eq. (1), where [BH] and [B^-] are the concentration of the indicator and its conjugate base respectively, and pKBH is the logarithm of the dissociation constant of the indicator used:

$$H_- = pKBH + \log[B^-]/[BH] \quad \text{Eq. (1)}$$

A 0.1 N solution of benzoic acid in anhydrous methanol was used for titration of each catalyst sample, see ESI for details.[11]

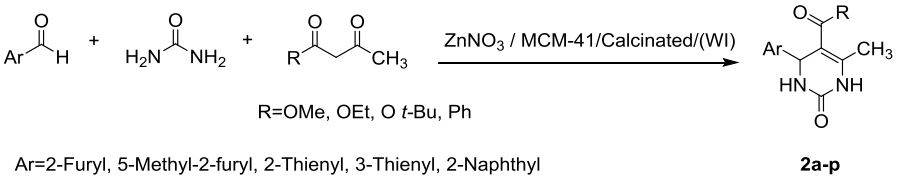
We next examined this catalytic system with thiophene, furan and 2-naphthyl carbaldehydes to obtain the products **2a-p** (Table 3). Additionally we utilized 5-benzyloxy-2-formyl-4-pyrone **3** (prepared from commercially available kojic acid [12]) as an aldehyde partner in the Biginelli condensation reaction (Table 4). Treatment with urea and various 1,3-dicarbonyls in the presence of a supported $ZnNO_3$ species, resulted in only trace conversion, even at higher temperatures and longer times. However, the use of free $ZnNO_3$ gave the corresponding Biginelli products in acceptable yields (Table 4). Interestingly, the use of $ZnCl_2$ under solvent free conditions, produced a complex mixture of products which could not be isolated.

Table 2. Basicity and percent of metal loading on MCM-41.

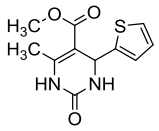
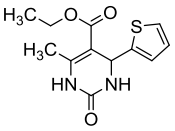
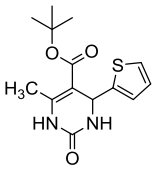
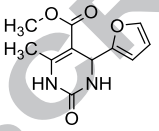
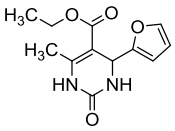
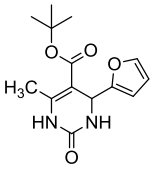
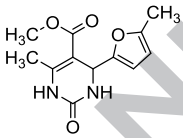
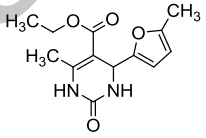
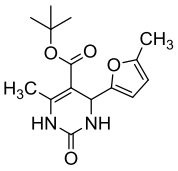
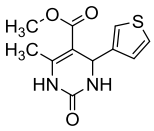
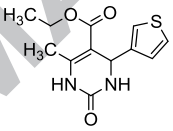
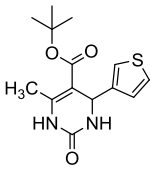
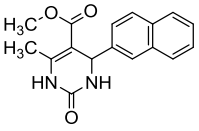
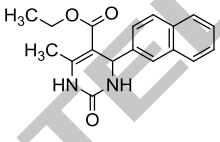
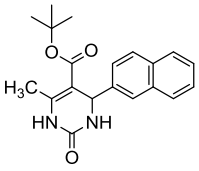
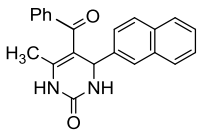
Entry	Catalyst	Basicity (mmol/g)	Metal loading (%)
1	$Zn(NO_3)_2$/MCM-41/Template/(DS)	5.16	10.50
2	$Zn(NO_3)_2$/MCM-41/Calcinated/(DS)	1.13	11.29
3	$Zn(NO_3)_2$/MCM-41/Extracted/(WI)	2.74	12.54
4	$Zn(NO_3)_2$/MCM-41/Calcinated/(WI)	0.97	14.61

The antimicrobial activity of twelve compounds were investigated by the disk diffusion method and the antibacterial and antifungal activities are presented in Table 5. These revealed that the compounds possessed weak to moderate antimicrobial activity, with compound **2d** possessing a furan ring and methoxycarbonyl group showing higher antimicrobial activity in both the bacterial and fungal test strains. Moreover, this compound exhibited higher activity against Staphylococcus aureus and Candida kefyr than Escherichia coli.

Table 3. Catalytic Biginelli reactions in the presence of $ZnNO_3$/MCM-41.



2a-p

Product	Yield	Product	Yield	Product	Yield	Product	Yield
	**2a** 93%		**2b** 85%		**2c** 77%		**2d** 78%
	**2e** 80%		**2f** 76%		**2g** 88%		**2h** 87%
	**2i** 76%		**2j** 79%		**2k** 82%		**2l** 69%
	**2m** 91%		**2n** 84%		**2o** 81%		**2p** 86%

Conditions: aldehyde (3 mmol), urea (4.5 mmol), 1,3-dicarbonyl (3 mmol), cat (0.06 g), 80 °C, 3-6 h.

Table 4. Yields of Biginelli products obtained from aldehyde **3**.

3 **4a-e**

Entry	R	Product **4** (Yield %)
1	OCH_3	**4a** (57)
2	OCH_2CH_3	**4b** (67)
3	$OC(CH_3)_3$	**4c** (50)
4	CH_3	**4d** (66)
5	Ph	**4e** (80)

Conditions: aldehyde **3** (1.3 mmol), urea (1.9 mmol), 1,3-dicarbonyl (1.3 mmol), $Zn(NO_3)_2.6H_2O$ (0.036 g, 10% mol), 80 °C, 24 h.

Table 5. Antimicrobial activity of selected compounds.

Compound	Zone of inhibition (mm)		
	Escherichia coli	*Staphylococcus aureus*	*Candida kefyr*
2a	7.6	8	6.4
2d	**12**	**14.4**	**14**
2e	6.4	7	7
2f	7	6.4	6.8
2g	6.8	7.2	7
2h	7	7	7
2i	7	7.4	6.4
2j	7	7	7
2k	7.3	6.4	7
2l	7.1	6.8	6.4
2m	9	9	9
4e	8.4	7	7

The cytotoxicity studies and inhibitory effects of the selected compounds were also studied using MDA-MB-231 and MCF7 cell lines and the cytotoxicity was evaluated using the MTT assay, an approach which is generally applied to measure mitochondrial activity to quantify cell growth or cell death. To assess the *in vitro* cytotoxicity of selected Biginelli products, cell viabilities of human breast cancer cell lines (MDA-MB-231) under 48 h incubation with different concentrations of compounds (4000, 2000, 1000, 500, 250, 50 and 25 μg/mL) were studied using the MTT assay. As seen in Figure 1, compounds **2p**, **2l** and **2b** showed inhibitory activities against MDA-MB-231. However, the degree of inhibition of **2l** was stronger (IC_{50}=2000 μg/mL) than **2p** and **2b** (IC_{50}=4000 μg/mL). The cell viabilities for other compounds, revealed the nontoxic effects on MDA-MB-231 breast cancer cell lines. Similar results were obtained for MCF7 cell lines.

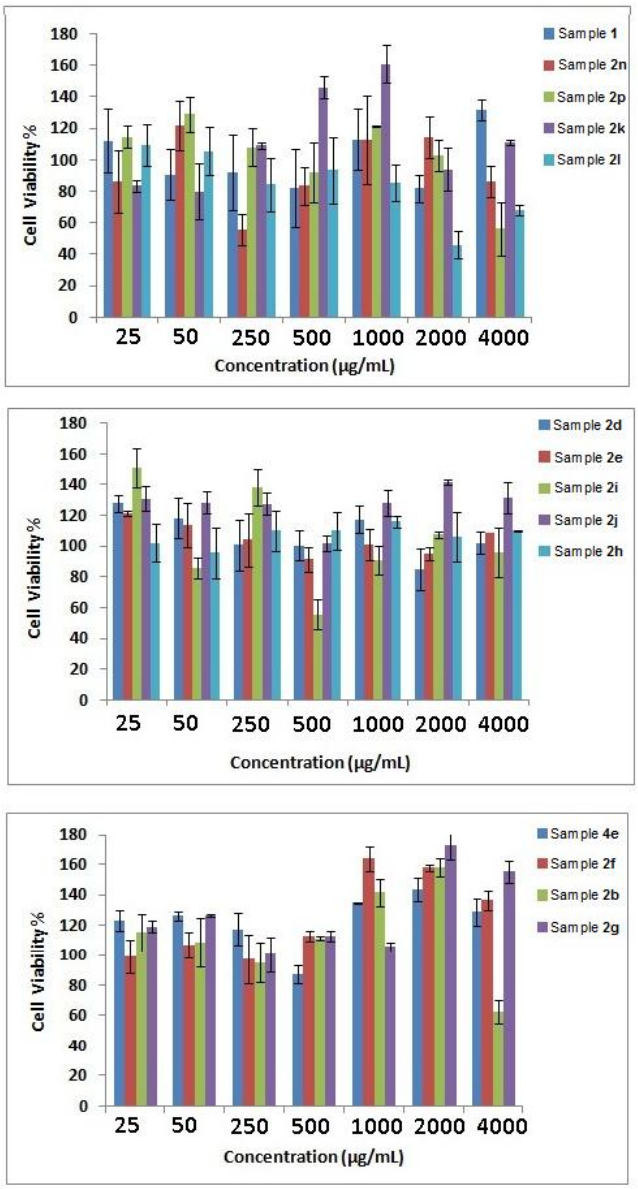


Figure1. Cytotoxicity data of selected compounds against the MDA-MB-231 cell line.

3. Conclusion

In summary we have reported the solvent free Biginelli reaction in the presence of free or MCM-41 incorporated $ZnNO_3$. The easy workup and high yields of products as well as the reusability of the solid catalyst were the advantages of our method. These reactions were examined with furan, thiophene and naphthyl carbaldehydes which were catalyzed in the presence of $ZnNO_3$ impregnated on calcinated MCM-41. Reaction of 3-benzyloxy-2-formyl-4-pyrone (prepared from kojic acid) was optimized in the presence of free $ZnNO_3$. Antimicrobial studies of the products showed relatively good activity for the derivative obtained from furfural and methyl acetoacetate. The cytotoxicity studies and inhibitory effects of selected products using MDA-MB-231 and MCF7 cell lines, showed inhibitory activities for compounds **2b**, **2l** and **2p**, and nontoxic effects of other derivatives.

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References

1. (a) Qu, H.; Li, X.; Mo, F.; Lin, X. *Beilstein J. Org. Chem.* **2013**, *9*, 2846–2851; (b) Wan, J. P.; Pan, Y. J. *Chem. Commun.* **2009**, *45*, 2768–2770; (c) Shen, Z. L.; Xu, X. P.; Ji, S. J. *J. Org. Chem*. **2010**, *75*, 1162–1167; (d) Chitra, S.; Devanathan, D.; Pandiarajan, K. *Eur. J. Med. Chem.* **2010**, *45*, 367–371. (e) Liu, Q.; Xu, J.; Teng, F.; Chen, A.; Pan, N.; Zhang, W. *J. Heterocycl. Chem*. **2014**, *51*, 741–746.
2. (a) Lal, J.; Gupta, S. K.; Thavaselvam, D.; Agarwal, D. D. Bioorg. Med. Chem. Lett. 2012, 22, 2872–2876; (b) Lusch, M. J.; Tallarico, J. A. *Org. Lett*. **2004**, *6*, 3237-3240; (c) Hegedüs, A.; Hell, Z.; Vígh, I. *Synth. Commun*. **2006**, *36*, 129–136; (d) Shen, Z. L.; Xu, X. P.; Ji, S. J. *J. Org. Chem*. **2010**, *75*, 1162–1167; (e) Srivastava, V. P.; Yadav, L. D. S. *Tetrahedron Lett*. **2010**, *51*, 6436–6438. (f) Azizian, J.; Mohammadi, M. K.; Firuzi, O.; Mirza, B.; Miri, R. *Chem. Biol. Drug Des*. **2010**; *75*, 375–380. (g) Chitra, S.; Devanathan, D.; Pandiarajan, K. *Eur. J. Med. Chem*. **2010**, *45*, 367–371.
3. (a) Panda, S. S.; Khanna, P.; Khanna, L. *Current Org. Chem*. **2012**, *16*, 507-520; (b) Karade, H. N.; Sathe, M.; Kaushik, M. P. *Molecules* **2007**, *12*, 1341-1351; (c) Lee, K. Y.; Ko, K. Y. *Bull. Korean Chem. Soc*. **2004**, *25*, 1929-1931. (d) Atar, A. B.; Jeong, Y. T. *Mol. Divers*. **2014**, *18*, 389-401.
4. (a) Shobha, D.; Chari, M. A.; Mano, A.; Selvan, S. T.; Mukkanti, K.; Vinu, A. *Tetrahedron* **2009**, *65*, 10608–10611. (b) Cai, M.; Xu, Q.; Sha, J. *J. Mol. Catal, A-Chem*. **2007**, *272*, 293–297; (c) Oskooie, H. A.; Heravi, M. M.; Karimi, N.; Monjezy, M. H. *Synth. Commun*. **2011**, *41*, 826–831.
5. (a) Tamaddon, F.; Moradi, S. *J. Mol. Catal. A-Chem*. **2013**, *370*, 117. (b) Iwanami, K.; Sakakura, T.; Yasuda, H. *Catal. Commun*. **2009**, *10*, 1990–1994. (c) Thitsartarn, W.; Gulari, E.; Wongkasemjit, S. *Appl. Organometal. Chem*. **2008**, *22*, 97–103; (d) Parida, K. M.; Rath, D.; Dash, S. S. *J. Mol. Catal. A-Chem*. **2010**, *318*, 85–93; (e) Iwanami, K.; Seo, H.; Choi, J. C.; Sakakura, T.; Yasuda, H. *Tetrahedron* **2010**, *66*, 1898–1901.
6. (a) Tamaddon, F.; Moradi, S. *J. Mol. Catal. A- Chem*. **2013**, *370*, 117-122. (b) Sun, Q.; Wang, Y. Q.; Ge, Z. M.; Cheng, T. M.; Li, R. T. *Synthesis* **2004**, *7*, 1047–1051; (c) Wang, C. F.; Jiang, H.; Gong, H.; Wang, M.; Wang, Z. C. *Chin. J. Org. Chem*. **2006**, *26*, 333-336.
7. Derylo-Marczewska, A.; Gac, W.; Popivnyak, N.; Zukocinski, G.; Pasieczna, S. *Catal. Today* **2006**, *114*, 293–306.
8. Parida, K. M.; Dash, S. S. *J. Mol. Catal. A-Chem* **2009**, *306*, 54-61.
9. (a) Selvaraj, M.; Pandurangan, A.; Seshadri, K. S.; Sinha, P. K.; Lal, K. B. *Appl. Catal. A-Gen*. **2003**, *242*, 347–364; (b) Savidha, R.;

Pandurangan, A.; Palanichamy, M.; Murugesan, V. *J. Mol. Catal. A-Chem*. **2004**, *211*, 165–177.

10. Carvalho, L.; Abreu, W.; Silva, M.; Lima, J.; Oliveira, J.; Matos, J.; Moura, C.; E. Moura, E. *J. Braz. Chem. Soc*. **2013**, *24*, 550-557.
11. Tanabe, K.; Yamaguchi, T. *J. Res. Inst. Catal*. 1964, 11, 179-184.
12. (a) Ghasemi, Z.; Kalantar Esfangare, H. *Heterocycl. Commun*. **2015**, *21*, 37–41; (b) Shahrisa, A.; Ghasemi, Z. *Chem. Heterocycl. Compd*. **2010**, *46*, 30-36.

Supplementary Material

Spectra and characterization data (IR, ^{1}H, and ^{13}C NMR) of compounds (**2a-p**) and also (**4a-e**), the preparation and analytical data of the catalysts, as well as the procedures for biological studies are available via the Internet at www.sciencedirect.com.