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An Economic and Green Prospect for the Synthesis of Dihydropyrimidinones Using Microwave and Solid Acid Catalyst under Solvent Free Condition-A Comparative Study

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Abstract – Cyclocondensationof β-ketoesters, aromatic aldehyde and urea is a key step for synthesis of 3,4-hydropyrimidin-2-(1H)one. In this work we report a very simple procedure for this conversion by using reusable, heterogeneous acidic media silica sulphuric acid in solvent free condition using microwave with high efficiency.

Keywords: Cyclocondensation, Solvent free reaction, Solid silica based sulfonic acid, 3, 4-Dihydropyrimidin-2-(1H)ones, Microwave irradiation.

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INTRODUCTION

MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [1-4]. MW-assisted chemistry has blossomed into a useful technique for a variety of applications in drug discovery [5] and organic synthesis. Dihydropyrimidinones belong to an important class of heterocyclic compounds with pharmacological and biological properties. DHPs act as potent vasodilators, antihypertensives, antiatherosclerotics, antitumor, antimutagenic, and antidiabetic agents [6-12]. They are also useful as cognition enhancers, neuroprotectants, and platelet antiaggregatory agents [13, 14]. Biginelli reaction is one of the most studied reactions in the area of multicomponent reactions [15]

The application of Brönsted and Lewis acids such as silica-based nanocatalysts and silica sulphuric acid (SSA) as heterogeneous catalysts in organic transformations is very important to avoid wastes as well as improving the greenness of the processes [16-17]. In the recent years, has shown immense potentiality as an efficient and easily retrievable solid catalyst in various important organic syntheses under solvent-free conditions [18].

Herein we wish to report a green methodology for the construction of 3, 4- Dihydropyrimidin-2-(1*H*)ones, using SSA as a solid-supported acid catalyst under solvent-free conditions.Various catalysts have been used to catalyse this reaction like protic acids [19], Lewis acids [20], heterogeneous acidic catalyst [21] and reagents like iodine [22] NBS [23] etc. But many of these protocols are still suffering from different drawbacks such as longer reaction time, high catalyst loading, expensive reagents, corrosive reagents and low yields of products.

RESULTS AND DISCUSSION:

The model reaction to synthesize 1e by the reaction of ethyl acetoacetate, benzaldehyde and urea was investigated with different amounts of solid silica-based sulfonic acid (0-5 mol %). And the best results were obtained (95% yield) with 3% of catalyst. Then the reactions were carried out at different MW power (250-900W) and different time of irradiation (5-8 min). The maximum yield (95%) was obtained in 7min at 900W.

Table-1: Comparision of present work with earlier work

Entry	Catalyst	Conventional Time (in min)	synthesis Yield (%)	MW assisted synthesis Time (in min)	Yield (%)	Reference
1	$KAl(SO_4)_2.12H_2O$ supp. silica gel	240	92	-	-	[24]
2	$HClO_4$-SiO_2	20	98	-	-	[25]
3	C-SO_3H	25	95	-	-	[26]
4	Zirconia based solid acid	40	90	-	-	[27]
5	KSF-Montmorillonite	48h	82	-	-	[28]
6	$H_7[PMo_8V_4O_{40}]$	6h	92	-	-	[29]
7	$H_3PMo_{12}O$	-	-	5	80	[30]
8	SiO_2-Pr-SO_3H	-	-	6-7	95	-

The results of present study were compared with those of earlier reported (Table-1). It can be seen that the best results in terms of time and yield are obtained using the present protocol.

EXPERIMENTAL:

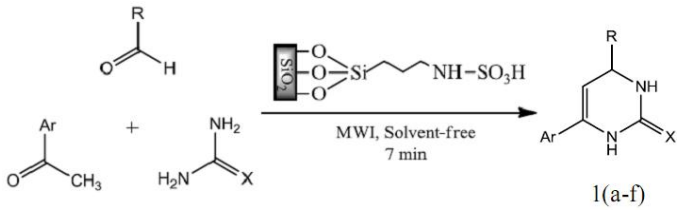
Materials and method: Silica gel (K100, 0.063–0.200 mm) was purchased from Merck (Germany) and 3-aminopropyltrimethoxy silane from Aldrich Chemical Company. All melting points were determined on a perfit melting point apparatus and areuncorrected. 1H NMR spectra were registered on a Brucker DPX-200NMR spectrometer (200 MHz) in CDCl3+DMSO-*d*6 using tetramethylsilane as an internal standard and IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs. Mass spectral data was recorded on Jeol JMS D-300 mass spectrometer at 70 eV. All yields refer to the isolated yields.

PREPARATION OF CATALYST:

Solid silica-based sulfonic acid:

To a mixture of 3-aminopropylsilica (5 g) in chloroform (20 mL) chlorosulfonic acid (1 g, 0.6 mL) was added dropwise at 00 C. After addition was complete, the mixture was stirred for 2 h until HCl gas evolution stopped. Then, the mixture was filtered and washed with ethanol (30 mL) and dried at room temperature to obtain silica solid-based sulfonic acid as a cream powder (5.13 g). Sulfur content of the samples determined by conventional elemental analysis was 9.29%.

Synthesis of 4,6-diaryl-3,4-dihydropyrimidin-2(1H)-ones 1(a-f)



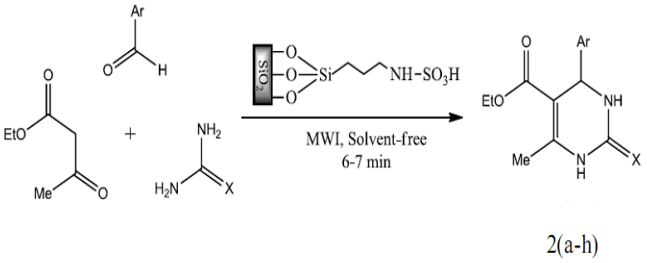
Scheme-1

Table-3: Physical data of 4,6-diaryl-3,4-dihydropyrimidin-2(1H)-ones 1(a-f)

Entry	R	Ar	Product[a]	Yield[b] (%)	M.P (0°C) Found	Reported[c]
1	5-CH_3-C_4H_2S	C_4H_3S	1a	92	241-243	-
2	4- (CH_3O)C_6H_4	C_6H_5	1b	89	257-259	259-261
3	C_6H_5	C_6H_5	1c	91	234-236	233-235
4	4-(Cl)-C_6H_4	C_6H_5	1d	87	264-266	267-269
6	1- CH_3-C_4H_3N	C_4H_3S	1e	86	227-229	-
7	5-CH_3-C_4H_2O	C_4H_3S	1f	90	223-225	-

aReaction conditions*: aldehyde (1 mmol), cyclic keto ester (1 mmol), urea/thiourea (1.5 mmol), solid silica-based sulfonic acid (3 mmol) in microwave irradiation of 900W at 90oC under solvent free condition. bIsolated yields. cProducts were characterized by comparison of their physical and spectroscopic data with those reported in the literature (Anil et al., 2007)*

Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones /thiones 1 (a-h)



Scheme-2

Table-4. Physical data of 3,4-dihydropyrimidin-2-(1H)-ones /thiones2 (a-h)

Entry	R	Ar	Product[a]	Yield[b] (%)	M.P (0°C) Found	Reported[c]
1	3-$CH_3C_4H_2O$	O	2a	93	217-219	-
2	3-CH_3-C_4H_2S	O	2b	91	217-219	-
3	4-NO_2-C_6H_4	O	2c	92	212-214	211-213
4	4-Cl-C_6H_4	O	2d	89	215-217	213-215
5	C_6H_5	O	2e	95	206-208	205-207
6	3-NO_2-C_6H_4	S	2f	87	205-207	204-205
7	4-OCH_3-C_6H_4	S	2g	91	153-155	151-153
8	C_6H_5	S	2h	89	208-210	209-211

aReaction conditions: aldehyde (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea/thiourea (2.5 mmol), solid silica based sulfonic acid (3 mmol) in microwave irradiation 990W at 90oC under solvent free condition. bIsolated yields. cProducts were characterized by comparison of their physical and spectroscopic data with those reported in the literature (AtulChaskaret al., 2009; Hitendraet al., 2007)

The reusability of the catalyst was also investigated. For this purpose, the same model reaction to synthesize the compound 2e was again studied under the optimized conditions. After completion of the reaction, the catalyst was filtered, washed with worm ethanol, dried at 1000C under vacuum for 2 h and reused for the same reaction process. As shown in Fig. 1, the catalyst could be reused for eight times without reduction in the catalytic activity of the catalyst.

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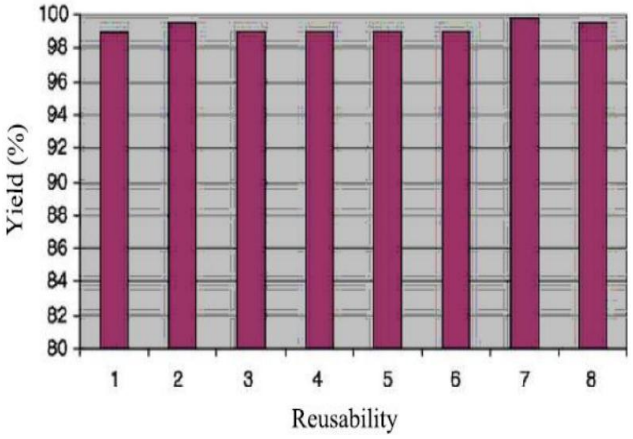

Fig. 1. Reusability of Solid silica-based sulfonic acid

CONCLUSION:

The demand for green and economic synthetic methods in the fields of healthcare and fine chemicals pose significant challenges to the synthetic chemical community. This objective can be achieved, in part, through the development of solvent free protocols using MW heating. The synthesized products show antihypertensive and calcium channel blocking activity.

REFERENCES:

[1] X. Yu, X. Pan and J. Wu, *Tetrahedron*, 67, 6, 2011, 1145-1149.

[2] C. Kalinski, H. Lemoine, J. Schmidt, C.Burdack, J. Kolb and M. Umkehrer, *Synthesis*, 24, 2008, 4007-4011.

[3] V. Polshettiwar and R. S. Varma, *Curr. Opin. Drug Discovery Dev*., 10, 2007, 723–737.

[4] B. Ganem, *Accounts of Chemical Research*, 42, 2009, 463-472.

[5] L. A. Wessjohann, D. G. Rivera and O. E. Vercillo, *Chem. Rev.*, 109, 2009, 796-814.

[6] D. J. Vugts, M. M. Koningstein, R. F. Schmtiz, F. J. J. kanter, M. B. Groen and R. V. A. Orru,*Eu J.*, 12, 27, 2006, 7178-7189.

[7] B. R. P. Kumar, G. Sankar, R. B. N. Baig and S. Chandrashekaran, ,*Eu. J. Med. Chem.*, 44, 10, 2009, 4192-4198.

[8] H. A. Stefani, C. B. Oliveira, R. B. Almeida, C. M. P. Pereira, R. C. Braga, R.Cella, V. C. Borges, L. Savegnago and C. W. Nogueira, ,*Eu. J. Med. Chem.*, 41, 4, 2006, 513-518.

[9] D. L. Silva, F. S. Reis, R. M. Dandara, A. L. T. G. Ruiz, J. E. Carvalho, A. A. Sabino, L. V. Modolo and A. Fatima, *Bioorg.& Med. Chem.*, 20, 8, 2012, 2645-2650.

[10] D. Russowski, R. F. S. Canto, S. A. A. Sanches, M. G. M. D'Oca, A. D. Fatima, R. A. Pilli, L. K. Kohn, M. A. Antonio and J. E. D. Carvalho, *Bioorg. Chem.*, 34, 4, 2006, 173-182. [11] B. Jank, T. Pernat and C. O. Kappe, Molecules, 5, 3, 2000, 227-239.

[12] D. Vo, W. C. Matome, M. Ramesh, N. Iqbal, M. W. Wolowyk, S. E. Howlett,E. Knaus, Eu. *J.Med. Chem.*, 38, 1995, 2851.

[13] R. A. Janis, D. J. Triggle, *J. Med. Chem.*, 25, 1983, 775.

[14] R. H. Bocker, F. P. Guengerich, *J. Med. Chem.*, 28, 1986, 1596. [15]P. Biginelli and P. Gazz, *ChimItal*, 23, 1893, 360- 416

[16] C. O. Kappe, *Eu. J. of Med. Chem.,* 35, 12, 2000, 1043-1052.

[17] (a) A. Corma, and H. Garcia, *Adv. Synth. Catal*. 348, 2006, 1391–1412; (b) A. Corma, and H. Garcia, *Chem. Rev.*, 103, 2003, 4307–4366; (c) A. Corma and H. Garcia *Chem. Rev.,* 102, 2002, 3837–3892.

[18]. J. Azizian, A. R Karimi, Z. Kazemizadeh, A. A. Mohammadi, M. R. Mohammadizadeh, *Synthesis*, 2005, 1095–1098.

[19] A. Kamal and A. A. Qureshi, *Tetrahedron*, 19, 4, 1963, 513- 520.

[20] D. Bandyopadhyay, S. Maldonado and B. K. Banik, *Molecules*, 17, 3, 2012, 2643-2662. [21] B. Vijayakumar and G. R. Rao, *J. of Porous Materials*, 19, 4, 2012, 491-497.

[22] R. S. Bhosale, S. V. Bhosale, S. V. Bhosale, T. Wangb and P. K. Zubaidhaa, *Tetra. Lett.* 45, 2004, 9111-9113.

[23] H. Hazarkhani and B. Karimi, *Synthesis*, 8, 2004, 1239-1242.

[24] F. Shirini, K. Marjani, and H. T. Nahzomi, *ARKIVOC*, 2007, 51-57.

[25] M. Maheswara, S. H. Oh, K. Kim and J. Y. Do, *Bull. Korean Chem. Soc.*, 29, 9, 2008.

[26] V. Mirkhani, M. Moghadam, S. Tangestaninejad, I. Mohammadpoor-Baltork

and M. Mahdavi, J. *Iran. Chem. Soc*., 8, 3, 2011, 608-615.

[27] B. M.,Reddy, P. M. Sreekanth, P. Lakshmanan, *J. Mol.Catal. A: Chem.*, 237, 93, 2005.

[28] H. Lin, J. Ding, X. Chen and Z. Zhang, *Molecules*, 5, 2000, 1240-1243.

[29] J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetra. Lett.* 41, 2000, 9075–9078.

[30] H. Salehi1, S. Kakaei, S.J. Ahmadi, M. A. F. Zareh, S. M. Sadat Kiai, H. R. Pakoyan and H. Tajik Ahmadi, *Journal of Applied Chemical Researches*, 4, 14, 2010.