NOTE

Three-Component One-Pot Synthesis of 4,6-Diarylpyrimidin-2(1H)-ones Catalyzed by 1-Methyl-3-[2-(sulfooxy)ethyl]-1H-imidazol-3-ium Chloride

YU WAN¹, LIANG-FENG CHEN², HAI-YING WANG², LING-LING ZHAO², SHU-YING HUANG²,
GUI-XIANG LIU², SHU-NING YUE², WEN-LI ZHANG² and HUI WU^{1,2,*}

¹Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Xuzhou 221116, P.R. China

²School of Chemistry and Chemical Engineering, Jiangsu Normal University, Xuzhou 221116, P.R. China

*Corresponding author: Fax: +86 516 83500164; Tel: +86 516 83403163; E-mail: wuhui72@yahoo.com.cn

(Received: 8 June 2012;

Accepted: 14 May 2013)

AJC-13489

An efficient, one-pot, three-component cyclocondensation reaction of aromatic aldehydes, aromatic ketone and urea catalyzed by 1-methyl-3-[2-(sulfooxy)ethyl]-1H-imidazol-3-ium chloride is developed to give 4,6-diarylpyrimidin-2(1H)-ones.

Key Words: Synthesis, 4,6-Diarylpyrimidin-2(1H)-ones, 1-Methyl-3-[2-(sulfooxy)ethyl]-1H-imidazol-3-ium chloride.

Pyrimidinones is an important class of heterocycles due to their relevance to various biological, pharmaceutical and therapeutic activities¹, such as anticancer, anti HIV, antibacterial, antimalarial, antihypertensive, sedative, anticonvulsant, anti-thyroid, antihistaminic activities²⁻⁴. They are mostly used as calcium channel blockers^{5,6}, α -antagonists⁷ and neuropeptide-antagonists⁸.

Biginelli⁹ first reported the one-step synthesis of 3,4-dihydropyrimidin-2(1H)-one in alcohol using strong mineral acid. Soon afterwards, various methods were reported concerning the synthesis of pyrimidine derivatives. Few one-pot syntheses have been published using different catalysts such as chlorotrimethylsilane¹⁰, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ ¹¹, $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \cdot 18\text{H}_2\text{O}$ ¹², sulfamic acid¹³, $\text{Bi}(\text{TFA})_3$ immobilized in $[\text{nbpy}]\text{FeCl}_4$ ¹⁴, 2,4,6-trichloro-1,3,5-triazine¹⁵, etc.

Herein, a novel catalyst synthesized in our lab, 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride (**I**) was firstly used to promote the simple preparation of 4,6-diarylethenes pyrimidin-2(1H)-ones *via* an efficient one-step three-component reaction of aromatic aldehyde, aromatic ketone and urea in ionic liquid (**Scheme-I**).

Scheme-I: Synthesis of 4,6-diarylpyrimidin-2(1H)-ones

All melting points are uncorrected and were measured on XT5 melting point apparatus. The ¹H and ¹³C NMR spectra were run on a Bruker Advance DMX 400 spectrometer in CDCl_3 using TMS as internal standard. Mass spectra were obtained on a Bruker MicroTOF-QII instrument. The IR spectra were obtained in potassium bromide pellets with a Bruker 27FTIR-Tensor using KBr optics.

Synthesis of 4,6-diarylpyrimidin-2(1H)-ones¹⁶: The mixture of aromatic aldehyde (1 mmol), aryl ketone (1 mmol) urea (4 mmol), ionic liquid (2 mL) and **I** (0.4 mol %) were stirred at 90 °C for the given time. After the completion (monitored by TLC), the mixture was diluted with water. The crude solid was filtered and washed with 95 % EtOH and then recrystallized with 95 % EtOH/DMF (1/4) to provide the pure product **4** (**Scheme-I**).

Initially, to optimize the reaction condition, the effects of solvents, reaction time and temperature on the yield of **4b** were evaluated and the results were summarized in Table-1. It was found that ionic liquid afforded better yield than other solvents. $[\text{Bpy}]\text{BF}_4$ was better than $[\text{Bmim}]\text{BF}_4$ may be due to its more suitable polarity and acidity to dissolve the reactants. The appreciable amount of catalyst was 0.4 mol %. However, the increasing of catalytic loading could not enhance the yield of the product (Table-1, entry 7). Subsequently, the best temperature was investigated. The results in Table-2 indicated the optimal temperature was 90 °C.

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes and aromatic ketone (Table-3).

TABLE-1
SYNTHESIS OF **4b** UNDER DIFFERENT CONDITIONS^a

Entry	Solvent	Catalyst (mol %)	Time (h)	Isolated yield (%)
1	CH ₃ COCH ₃	0.4	12	Nr ^b
2	EtOH	0.4	12	NP ^c
3	DMF	0.4	12	Nr ^b
4	CH ₃ CN	0.4	12	NP ^c
5	THF	0.4	12	Nr ^b
6	[Bmim]BF ₄	0.4	6	79
7	[Bpy]BF ₄	0.4	6	88
8	[Bpy]BF ₄	0.6	6	87
9	[Bpy]BF ₄	0.5	6	88
10	[Bpy]BF ₄	0.3	6	74
11	[Bpy]BF ₄	0.2	6	62
12	[Bpy]BF ₄	0.1	6	53

^aReaction condition: 3,4-dimethoxybenzaldehyde (1 mmol), 4-nitroacetophenone (1 mmol), and urea (4 mol) in 2 mL of different solvents at 90 °C using 0.4 mol % of **I** as catalyst. ^bNo reaction. ^cNo desired products.

TABLE-2
SYNTHESIS OF **4b** AT DIFFERENT TEMPERATURE^a

Entry	T (°C)	Isolated yield (%)
1	r.t	Nr ^b
2	60	Nr ^b
3	80	64
4	90	88
5	100	88
6	110	86

^aReaction condition: 4-nitroacetophenone (1 mmol), 3,4-dimethoxybenzaldehyde (1 mmol) and urea (4 mmol) in [Bpy]BF₄ at different temperature for 6 h catalyzed by 0.4 mol % of **I**. ^bNo reaction.

TABLE-3
SYNTHESIS OF **4a**

Comp.	R ₁	R ₂	Time (h)	Isolated yield (%)
4a	2-OCH ₃	4-NO ₂	6	85
4b	3,4-(OCH ₃) ₂	4-NO ₂	6	88
4c	4-OCH ₃	4-NO ₂	5	86
4d	3-Br	4-NO ₂	6	87
4e	3-NO ₂	4-NO ₂	7	85
4f	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	4-NO ₂	6	86
4g	4-OH	4-NO ₂	6	84
4h	4-Br	4-Cl	6	85
4i	4-I	4-Cl	6	86
4j	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	4-Cl	7	87
4k	3,4-(OCH ₃) ₂	3-OH	6	86
4l	4-I	3-OH	6	87
4m	4-Cl	H	6	85
4n	4-OCH ₃	H	7	83

^aReaction condition: aromatic aldehydes (1 mmol), aromatic ketone (1 mmol) and urea (4 mmol) in 2 mL of [Bpy]BF₄ at 90 °C catalyzed by 0.4 mol % of **I**.

The possible reaction mechanism was proposed in **Scheme-II**. It is presumed that the reaction proceeds *via* initial Aldol addition of aromatic aldehyde with aryl ketone to give a chalcone, which addition with urea to give intermediate C. The cyclization and dehydration of C give products **4**.

Scheme-II

In summary, we report here a high yield one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones, from readily available aromatic aldehydes, aromatic ketones and urea catalyzed by 1-methyl-3-[2-(sulfooxy)ethyl]-1*H*-imidazol-3-ium chloride. This new protocol provides an environmentally benign route along with the associated advantages of simplicity of operation and higher atomic efficiency.

ACKNOWLEDGEMENTS

The authors are grateful to the foundation of the Priority Academic Program Development of Jiangsu Higher Education Institutions, Qing Lan Project in Jiangsu Province (No. 08QL001T), Key Basic Research Project in Jiangsu University (No. 10KJA430050), the Post-Graduate Innovation Project in Jiangsu Province (No. CXZZ12_0979) and the Natural Science Foundation of Jiangsu Normal University (No. 09XLA17, No. 09XLB05) for financial support.

REFERENCES

- P. Salehi, M. Dabiri, A.R. Khosropour and P. Roozbehniya, *J. Iran. Chem. Soc.*, **3**, 98 (2006).
- D. Russowsky, E.V. Benvenuti, G.S. Roxo and F. Grasel, *Lett. Org. Chem.*, **4**, 39 (2007).
- N. Rameshwar, T. Parthasarathy and A.R. Reddy, *Indian J. Chem.*, **47B**, 1871 (2008).
- T.B. Shah, A. Gupte, M.R. Patel, V.S. Chauhari, H. Patel and V.C. Patel, *Indian J. Chem.*, **48B**, 88 (2009).
- C.O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000).
- B. Gangadasu, P. Narender, B.C. Raju and V.J. Rao, *Indian J. Chem.*, **45B**, 1259 (2006).
- K.S. Atwal, B.N. Swanson, S.E. Umger and D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem.*, **34**, 806 (1991).
- S. Bartolini, A. Mai, M. Artico, N. Paesano, D. Rotili, C. Spadafora and G. Sbardella, *J. Med. Chem.*, **48**, 6776 (2005).
- G. Biginelli, *Chim. Ital.*, **23**, 360 (1893).
- L.Z. Wang, X.Q. Bian, H. Liu, Q. Sun and C.D. Wang, *J. Chem. Res.*, **34**, 694 (2010).
- Z. Pourghobadi and F. Derikvand, *Chin. Chem. Lett.*, **21**, 269 (2010).
- M.M. Heravi, F. Derikvand and L. Ranjbar, *Synth. Commun.*, **40**, 1256 (2010).
- M.M. Heravi, L. Ranjbar, F. Derikvand, B. Alimadadi and H.A. Oskooie, *Mol. Divers.*, **12**, 191 (2008).
- A.R. Khosropour, I. Mohammadpoor-Baltork and H. Ghorbankhani, *Catal. Commun.*, **7**, 713 (2006).
- A.R. Khosropour, B.I. Mohammadpoor and J. Mahbubeh, *Heterocycles*, **68**, 1551 (2006).
- H. Wu, Y. Wan, X.M. Chen, C.F. Chen, L.-L. Lu, H.-Q. Xin, H.-H. Xu, L.-L. Pang, R. Ma and C.-H. Yue, *J. Heterocycl. Chem.*, **46**, 702 (2009).