

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

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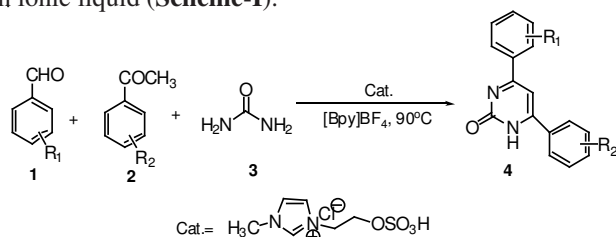
An efficient, one-pot, three-component cyclocondensation reaction of aromatic aldehydes, aromatic ketone and urea catalyzed by 1-methyl-3-[2-(sulfooxy)ethyl]-1H-imidazol-3-ium chloride is developed to give 4,6-diarylpyrimidin-2(1H)-ones.

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 CDCl₃ 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

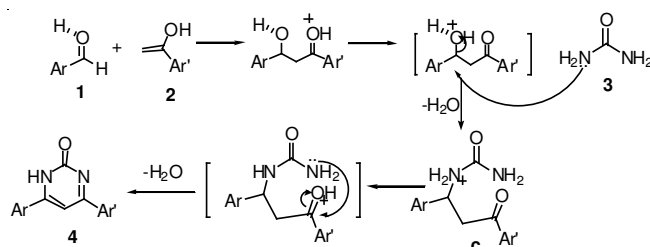
^aReaction condition: 4-nitroacetophenone (1 mmol), 3,4-dimethoxybenzaldehyde (1 mmol) and urea (4 mmol) in [Bpy]BF₄ at different temperature for 6 h catalyzed by 0.4 mol % of **I**. ^bNo reaction.

TABLE-3
SYNTHESIS OF **4a**^a

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.

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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).