

Microwave-assisted Solventless Biginelli Reaction Catalyzed by Montmorillonite Clay-SmCl₃ · 6H₂O System

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Abstract: 4-Aryl/alkyl-3, 4-dihydro-2(1H)-pyrimidone esters and 5-acetyl-4-aryl/or alkyl-6-methyl- 3, 4-dihydropyrimidin-2(1)-ones were synthesised efficiently using montmorillonite clay- SmCl₃ · 6H₂O system promoted by microwave irradiation in solventless condition.

Keywords: Microwave, samarium trichloride, montmorillonite, Biginelli reaction, pyrimidone.

Many 4-aryl-3, 4-dihydro-2(1H)-pyrimidone (DHPMS) esters and 5-acetyl-4-aryl/or alkyl- 6-methyl-3, 4-dihydropyrimidin-2(1)-ones are of pharmacological important compounds because of their promising biological effects, including antiviral, antibacterial, antitumor, anti-inflammatory activities¹. Recently they were found to be as calcium channel modulators², antihypertensive agents³ and α_{1a} -antagonists⁴. Some alkaloids recently isolated from marine sources with interesting biological activities also possess the dihydropyrimidinone-5-carboxylate core⁵. Most notably among these are the batzelladine alkaloids which have been found to be potent HIVgp-120-CD4 inhibitors⁶. Therefore synthesis of this type of heterocyclic compounds is of much current importance. The most simple and straightforward procedure, reported by Biginelli more than 100 years ago⁷, involves the three component condensation in one-pot, but the yield is usually low. Much effort has been made recently to improve and modify this reaction. Lanthanide triflate⁸, lanthanum chloride⁹, indium chloride¹⁰ and acidic clay montmorillonite KSF¹¹ were used to replace the strong protic acid in the classic Biginelli reaction; glacial acetic acid¹² and polyphosphate ester¹³ were used as promoter in the microwave assisted condensation. High yields were claimed in most above mentioned reactions.

Microwave irradiation organic reactions become popular in recent years owing to the higher reaction rates, simpler, more safe and environment friendly reaction conditions, which may be suitable to be applied in large scale production¹⁴. Samarium salts can promote a variety of condensation reactions¹⁵ and SmCl₃ is cheaper than triflate salts. Clay montmorillonite is a good catalyst-carrier. Montmorillonite can also be modified to satisfy the different reactions. We herein wish to report a protocol of synthesis of

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4-aryl-3, 4-dihydro-2(1H)-pyrimidone esters and dihydropyrimidinones using SmCl₃ deposited montmorillonite clay in the microwave-assisted solvent-free conditions.

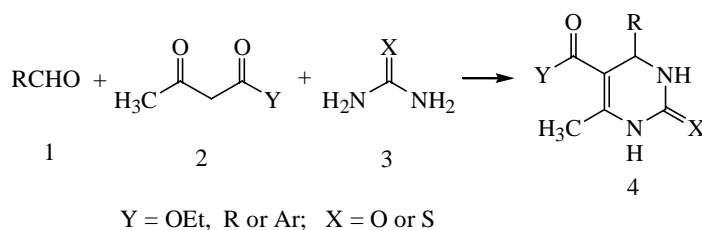


Table 1 The yield and mp. of **4a~4m**

Entry	R	Y	X	Catalyst	Yield(%) *	mp. (°C)	Ref.
4a	Ph	OEt	O	SmCl ₃	90	202	12
4b	2-NO ₂ -C ₆ H ₄	OEt	O	SmCl ₃	89	206-208	16
4c	4-NO ₂ -C ₆ H ₄	OEt	O	SmCl ₃	82	208	12
4d	<i>n</i> -Pr	OEt	O	SmCl ₃	81	153-155	17
4e	3-CH ₃ -C ₆ H ₄	OEt	O	SmCl ₃	89	218-222	
4f	4-CH ₃ -C ₆ H ₄	OEt	O	SmCl ₃	91	170-171	12
4g	4-Br-C ₆ H ₄	OEt	O	SmCl ₃	86	202-206	
4h	4-Cl-C ₆ H ₄	OEt	O	SmCl ₃	88	213	12
4i	Ph	CH ₃	O	SmCl ₃	87	233-236	8
4j	4-NO ₂ -C ₆ H ₄	CH ₃	O	SmCl ₃	90	230	8
4k	4-CH ₃ -C ₆ H ₄	CH ₃	O	SmCl ₃	84	161-162	
4l	<i>n</i> -Pr	CH ₃	O	SmCl ₃	82	142-145	
4m	Ph	Ph	O	SmCl ₃	89	214-216	18
4n	4-NO ₂ -C ₆ H ₄	Ph	O	SmCl ₃	93	236-239	
4o	<i>n</i> -Pr	Ph	O	SmCl ₃	80	212-216	
4p	Ph	CH ₃	S	SmCl ₃	78	220-222	10
4q	<i>n</i> -Pr	CH ₃	S	SmCl ₃	75	138-142	
4a	Ph	OEt	O		50		
4i	Ph	CH ₃	O		0		
4m	Ph	Ph	O		0		

* Isolated yields

We investigated the effect of the molar ratios of reagents and the influence of MW irradiation on a neat mixture of aldehyde, β -dicarbonyl compound, urea(thiourea) and montmorillonite clay/SmCl₃ in the modified Biginelli reaction and found following optimum conditions. The ratio of aldehyde, β -dicarbonyl compound and (thio)urea was 1:1:1.5. The mixture was mixed with montmorillonite clay/SmCl₃ (10:1) and subjected to microwave irradiation at 40% power in a 700W microwave oven for 3 min (successive irradiations of 30-40s with cooling intervals of 1 min, the temperature being 80-90°C).

The results, summarized in **Table 1**, indicated that this protocol is able to tolerate the structural variety. Both aromatic and aliphatic aldehydes have been subjected to this condensation very efficiently. Besides the β -ketone ester, β -diketone can also be employed without any decrease in yield. Thiourea has been used with similar success to provide the corresponding dihydropyrimidines. SmCl₃ • 6H₂O was used as Lewis

acid no special precaution was needed in handling. The catalyst can be reused for several times. When the reactions were proceeded without SmCl_3 , low yield was obtained for acyl acetate as a substrate, no product was detected for β -diketones (see Table 1).

In summary, a new and efficient modified Biginelli reaction has been described. The advantages of this environmentally benign reaction include the simple reaction set-up, high product yields, short reaction time and needless reaction solvents. In addition, the catalyst can be recovered and reused, so it is valuable in the economic point of view.

General Procedure: A mixture of aldehyde (1 mmol), β -dicarbonyl compound (1 mmol), (thio)urea (1.5 mmol) and montmorillonite clay (5g)/ $\text{SmCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5 mmol) was placed in a 50 mL glass flask. After the mixture was stirred for 30s with a spatula, the reaction container was irradiated in MW oven 6 times at 40% power of total 700W for 30s with 1 min cooling period after each irradiation. After the reaction was complete, the reaction mixture was soaked with methanol for half an hour and filtered off. The filtrate was concentrated in vacuum to afford the crude product. It could be purified by preparative TLC. The filtrating residue was catalyst and montmorillonite which can be reused.

References and Notes

1. C. O. Kappe, *Tetrahedron*, **1993**, *49*, 6937.
2. (a) G. C. Rovnyak, S. D. Kimball, B. Bever, *et al.*, *J. Med. Chem.* **1995**, *38*, 119. (b) K. S. Atwal, C. G. Rovnyak, S. D. Kimball, *et al.*, *J. Med. Chem.* **1990**, *33*, 2629. (c) H. Cho, M. Ueda, K. Shima, *et al.*, *J. Med. Chem.* **1989**, *32*, 2399.
3. (a) G. C. Rovnyak, K. S. Atwal, S. D. Kimball, *et al.*, *J. Med. Chem.* **1992**, *35*, 3254. (b) K. S. Atwal, B. N. Swanson, S. E. Unger, *et al.*, *J. Med. Chem.* **1991**, *34*, 806.
4. (a) D. R. Sidler, R. D. Larsen, M. Chartrain, *et al.*, PCT Int. Appl. WO 99 07695. (b) D. Nagarathnam, W. C. Wong, S. W. Miao, *et al.*, PCT Int. Appl. WO 97 17969.
5. B. B. Snider, Z. Shi, *J. Org. Chem.*, **1993**, *58*, 3828 and refs therein.
6. (a) A. D. Patil, N. V. Kumar, W. C. Kokke, *et al.*, *J. Org. Chem.*, **1995**, *60*, 1182. (b) B. B. Snider, J. Chen, A. D. Patil, *et al.*, *Tetrahedron Lett.*, **1996**, *37*, 6977. (c) A. V. Rama Rao, M. K. Gujar, J. Vasudevan, *J. Chem. Soc., Chem. Commun.*, **1995**, 1369.
7. P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360.
8. Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.*, **2000**, *65*, 3864.
9. J. Lu, Y. Bai, Z. Wang, *et al.*, *Tetrahedron Lett.*, **2000**, *41*, 9075.
10. B. C. Ranu, A. Hajra, U. Jana, *J. Org. Chem.*, **2000**, *65*, 6270.
11. F. Bigi, S. Carloni, B. Frullanti, *et al.*, *Tetrahedron Lett.*, **1999**, *40*, 3465.
12. J. S. Yadav, B. V. Subba Reddy, E. Jagan Reddy, T. Ramalingam, *J. Chem. Res.*, **2000**, 354.
13. C. O. Kappe, D. Kumar, R. S. Varma, *Synthesis*, **1999**, 1799.
14. D. Villemin, F. Caillot, *Tetrahedron Lett.*, **2001**, *42*, 639.
15. W. L. Bao, Y. M. Zhang, T. K. Ying, *Synth. Commun.*, **1996**, *26*, 503.
16. K. A. Kumar, M. Kasthuraiah, C. S. Reddy and C. D. Reddy, *Tetrahedron Lett.*, **2001**, *42*, 7873.
17. J. J. V. Eynde, N. Audiart, V. Canonne, *et al.*, *Heterocycles*, **1997**, *45*, 1967.
18. Y. F. Chi and Y. L. Wu, *Hua Xue Xue Bao*, **1956**, 184.
19. Representative data: **4k**: mp: 161-162°C; ^1H NMR ($\text{CDCl}_3 + \text{DMSO}-d_6$): 7.65 (s, br, 1H, NH), 7.20-7.13 (m, 4H), 5.67 (s, br, 1H, NH), 5.41 (d, 1H, $J = 2.03\text{Hz}$), 2.35 (s, 3H), 2.32 (s, 3H), 2.11 (s, 3H); IR(KBr): 3429, 3291, 2925, 1702, 1618 cm^{-1} ; MS (70 eV, EI): m/z (%): 244(23), 229(49), 201(17), 153(38). Elemental Analysis: Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83; H, 6.60; N, 11.47; Found. C, 68.60; H, 6.84; N, 11.69.

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