

An Efficient Synthesis of 5-Alkoxy carbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones Catalyzed by KSF Montmorillonite

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Abstract: A mild and efficient catalytic method for synthesis of 5-alkoxy carbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones using KSF montmorillonite as catalyst is described.

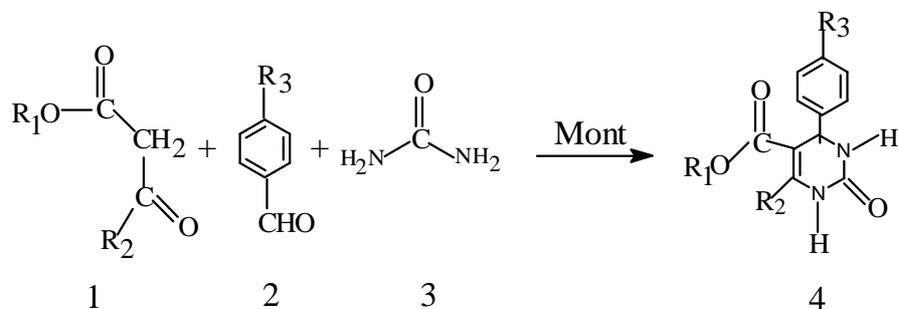
Keywords: Biginelli reaction, dihydropyrimidinones, Montmorillonite

Introduction

4-Aryl-3,4-dihydropyrimidin-2(1H)-ones **4** ("Biginelli compounds", DHPMs) have been reported to possess diverse biological activities such as antiviral, antibacterial, antihypertensive and anti-tumor effects [1-3]. More recently, DHPMs have emerged as the integral backbones of several calcium channel blockers [4]. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have been isolated [5]. Consequently a great need still exists for versatile and simple processes whereby compounds **4** may be formed under very mild conditions. However, Biginelli's initial one-pot method of refluxing a β -keto ester **1**, aryl aldehyde **2** and urea **3** with a catalytic amount of acid frequently afforded low (20-60%) yields of the desired target molecules **4** [6]. This has led to the recent disclosure of several improved reaction protocols for the synthesis of DHPMs, either by modification of the classical one-pot Biginelli approach itself [7-10], or by the development of novel, but more complex multistep strategies [11,12]. In addition, several combinatorial approaches towards DHPMs **4** have been reported [13,14].

Montmorillonite clays have been widely used in organic synthesis due to their ready availability, ease of set up and of work up, mild experimental condition and high yield and selectivity. Recently,

Bigi [15] reported that the Biginelli reaction could be performed under solventless conditions using KSF montmorillonite, although the procedures described suffer limitations such as long reaction times and moderate yields. Our group has exploited the catalytic potential of montmorillonite for various synthetic organic transformations [16]. While optimizing the reaction conditions of the Biginelli reaction, we found that treatment of β -keto ester, aryl aldehyde and urea with KSF montmorillonite in methanol afforded DHPMs in good to excellent yields (Table 1).



Results and Discussion

Our results show that it is necessary to control the molar ratio of the reactant. When the molar ratio of β -keto ester (1): aryl aldehyde (2): urea (3) is 1:1:1.2, our method produced higher yields. The same reaction when run in methanol gave better yields than in tetrahydrofuran. A variety of montmorillonites, including montmorillonite K 10 and montmorillonite KSF showed catalytic activity for Biginelli reaction, although montmorillonite KSF reagent proved superior to montmorillonite K 10.

Table 1. Experimental results and physical data of dihydropyrimidinones 4.

entry	R ₁	R ₂	R ₃	Yield(%)				m.p. (°C) (literature) [7]
				A ^a	B ^b	C ^c	D ^d	
1	Et	Me	Me	88				213-4
2	Et	Me	Cl	93	56	92	76	214-5(213-5)
3	Et	Me	NO ₂	89	54	91		209-11(208-11)
4	Et	Me	OMe	82	37	85	79	200-2(201-3)
5	Et	Me	H	92	71	94	82	205-6(202-4)
6	Et	Ph	H	80	10	70	75	158-9(157-9)
7	Me	Me	H	90	42	88		211-3(209-12)

^a Method A: New reaction conditions(montmorillonite KSF in methanol, reflux 8-10h).

^b Method B: Classical Biginelli conditions (cat.H₂SO₄ in EtOH, reflux 18h)[6]

^c Method C: Hu improved conditions (BF₃·OEt₂/CuCl in THF, reflux 18h)[7]

^d Method D: Bigi improved conditions (montmorillonite KSF without solvent at 130°C for 48h) [15]

Our approach not only preserved the simplicity of Biginelli's one-pot reaction, but also consistently provided excellent yields of dihydropyrimidinones 4, regardless of the keto ester or aldehyde substituents tested. Montmorillonite KSF has many advantages over catalysts like $\text{BF}_3 \cdot \text{OEt}_2 / \text{CuCl}$ such as ease of handling, low cost and elimination of metal wastes (use of an environmentally-friendly catalyst). When compared to Bigi's conditions (Table 1), our method consistently produced higher yields and required shorter reaction times. Detailed work on the mechanism of the transformation is still in progress.

Conclusions

We have presented a mild and efficient catalytic method for synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones using KSF montmorillonite as catalyst.

Experimental

General

Melting points were determined using a XT 4A melting point apparatus and were uncorrected. The ^1H - and ^{13}C -NMR spectra were acquired on a Bruker Avance 300 spectrometer in DMSO with TMS as internal standard. IR spectra were recorded on a Nicolet Axatar IR 360 spectrometer. Elemental analysis data were taken on a Perkin-Elmer 240C elemental analytical instrument.

Syntheses

A mixture of β -keto ester (20mmol), aryl aldehyde (20mmol), urea (24mmol) and montmorillonite KSF (0.6g) was refluxed in dry methanol (15mL). The completion of the reaction was monitored *vide* tlc. Montmorillonite KSF filtered off and methanol was removed under reduced pressure. The product was crystallised from ethanol. The results were summarized in Table 1. All the products except entry 1 are known compounds, which were satisfactorily characterised by melting point, ^1H -NMR, ^{13}C -NMR and IR spectra.

Entry 1 (88% yield) mp 213-4°C, IR(KBr) 3245, 3114, 2981, 2942, 1725, 1706, 1650 cm^{-1} ; ^1H -NMR (DMSO- d_6) δ 9.13 (s, 1H), 7.66 (d, $J=3.11\text{Hz}$, 1H), 7.09 (m, 4H), 5.08 (d, $J=3.11\text{Hz}$, 1H), 3.95 (q, $J=7.03\text{Hz}$, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 1.08 (t, $J=7.03\text{Hz}$, 3H); ^{13}C -NMR (DMSO- d_6) δ 165.5, 152.3, 148.2, 142.1, 136.4, 129.0, 126.3, 99.6, 59.3, 53.8, 20.8, 17.9, 14.2. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.42; H, 6.65; N, 10.16.

References

1. McKinstry, D. W.; Reading, E. H. *J. Franklin Inst.* **1944**, 237, 422-431.
2. Matsuda, T.; Hirao, I. *Nippon Kagaku Zasshi* **1965**, 86, 1195-1197.
3. Kato, T. *Japn. Kokai Tokkyo Koho JP* **1984**, 59,190,974.
4. Takatani, T.; Takasugi, H.; Kuno, A.; Inoue, Z. *Japn. Kokai Tokkyo koho JP* **1987**, 62 ,252,775.
5. Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, 117, 1657-2658.
6. Biginelli, P. *Gazz. Chim. Ital.* **1893**, 23, 360.
7. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, 63, 3454-3457.
8. Kappe, C. O.; Falsone, F. S. *Synlett* **1998**, 718.
9. Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 10, 1799-1803.
10. Lu, J.; Ma, H. *Synlett* **2000**, 1, 63-64.
11. O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, 26, 1185.
12. Shutalev, A. D.; Kishko, E. A.; Sivova, N.; Kuznetsov, A. Y. *Molecules* **1998**, 3, 100.
13. Studer, A.; Hadida, S.; Ferrito, R.; Kim, S. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, 275, 823.
14. Lewandowski, K.; Murer, P.; Svec, F.; Frechet, J. M. *J. Chem. Soc. Chem. Commun.* **1998**, 2237.
15. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Letters* **1999**, 40, 3465-3468.
16. Lin, H. X.; Zhang, L. X.; Cheng, L. S. *Chin. Chem. Lett.* **1999**, 10(11), 915-916.

Samples Availability: Samples are available from the authors.