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AN EFFICIENT ONE POT THREE COMPONENT SYNTHESIS OF 4-ARYL-6-(3-COUMARINYL) PYRIMIDIN-2 (*1H*)-ONES UNDER SOLVENT FREE CONDITIONS

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ABSTRACT

Silica gel supported zirconyl chloride octahydrate was found to be an efficient and recyclable catalyst for the synthesis of a series of biologically important molecules in high turnover numbers and rates. Substituted 4-aryl-6-(3-coumarinyl) pyrimidin-2 (*1H*)-ones can be prepared in high yield and purity by direct reaction via., cyclocondensation of urea and 3-acetylcoumarin with substituted aldehydes in the presence of a catalytic amount of $ZrOCl_2.8H_2O/SiO_2$ as Lewis acid and at ambient temperature under solvent-free conditions. The synthesized compounds **4(a-e)** were characterized by IR, NMR and Mass spectral analysis.

Key words: Zirconyl chloride octahydrate, 3-acetylcoumarin, Silicagel, Urea.

INTRODUCTION

Coumarins are important naturally occurring plant constituents, many of which exhibit a broad spectrum of biological activity[1-4] e.g., antitumor, anti-HIV, anti-oxidant, anticoagulant, antimicrobial, as well as inhibition of steroid 5a-reductase and platelet aggregation. In addition, coumarins are widely used as additives in food and cosmetics, dispersed fluorescent, optical brighteners, and tunable laser dyes[5-7].

Pyrimidinones are important heterocyclic compounds, which have been well documented in the literature because of their biological value[8]. Some of the pyrimidinones have emerged as integral backbones of several calcium-channel blockers and anti-hypertensive, anti- bacterial and anti-inflammatory agents[9], the batzelladine alkaloids

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containing 3,4-dihydropyrimidine-2 (1H)-one (DHPM) isolated from marine sources were found to inhibit the binding of HIV envelop protein gp-120 to human CD_4 cells[10]. The most common route to DHPMs involves the cyclocondensation of aromatic aldehydes, acetoacetate and urea in the presence of HCl as catalyst. This is one of the most representative multi component reactions (MCRs), which is well known as the Biginelli reaction.[11] Recently, Heravi et al.[12], reported the synthesis of 4,6-diarylpyrimidin-2 (*1H*)-ones (DAPMs) using TMSCl and sulfamic acid as a green and reusable catalyst, Khosropour et al.[13], used $Bi(TFA)_3$ immobilizedd on [nbpy]$FeCl_4$ and concentrated HCl in ionic liquid [BMIM]BF_4 was used by Hui et al.[14] to promote this reaction. Other reported methods for the synthesis of DAPM s from urea and 1, 3-diphenyl-propenone or 1, 3-diphenyl-propynone or 1,3-diphenyl-propane-1,3-dione require NaOEt/Et_3N or cyanourictrichloride/CF_3SO_3Zn as catalysts[15-18]. However most of these reported methods suffer from one or more drawbacks such as use of stoichiometric amounts of catalysts, use of expensive reagents (like TMSCl) and prolonged reaction time.

In recent years, MCRs have become modern synthetic protocols for the one pot synthesis of a wide variety of organic molecules[19], because of ease of readily available and in expensive catalysts under a solvent–free, resource effective and environmentally acceptable process could be an ideal synthesis[20].

The importance of zirconium as homogeneous catalyst has already been cited in literature in the number of biologically and pharmacologically significant organic transformation[21-26] $ZrOCl_2.8H_2O$ is relatively non toxic and in expensive to air. Our present work is directed to immobilize zirconium complex onto the common solid support in order to combine the properties such as catalyst reuse. The support material plays a critical role in the performance of the resulting supported reagent catalyst. Silica gel support was chosen due to its high surface area, excellent stability (chemical and thermal) good accessibility and ease of functionalization of the surface groups[27,28]. The catalyst does not need activation and is recycled many times under the same conditions with fresh reactants to yield, similar results with out significant loss of activity.

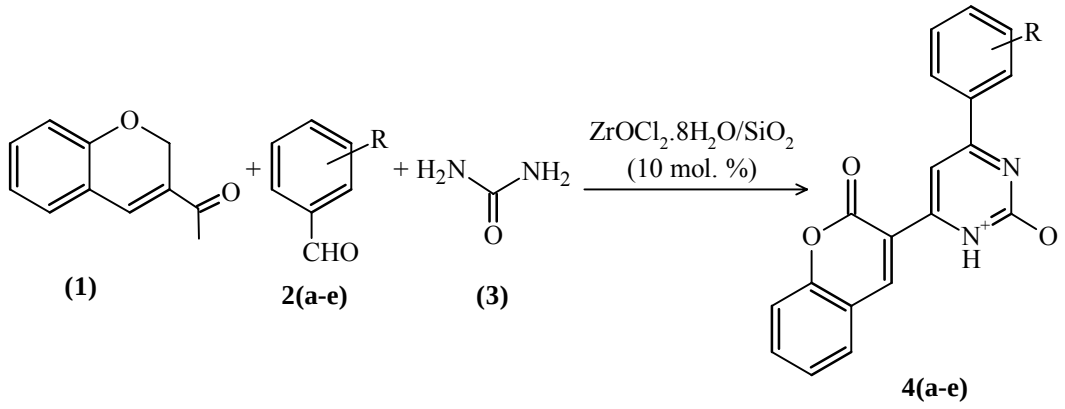
In continuing effort in our laboratory to development of efficient and new methodology systems for various organic transformations, an active on going research area and the scope for further improvement towards milder reaction conditions[29]. We are reporting a solvent–free protocol for the synthesis of 4-aryl-6-(2-oxo-*2H*-chromen-3-yl) pyrimidin-2(*1H*)-ones, via cyclocondensation of urea and 3-acetylcoumarin with substituted aldehydes using $ZrOCl_2.8H_2O/SiO_2$ as a catalyst. Excellent yields of title compounds upto 96% was achieved within 8-15 min.

EXPERIMENTAL

Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on Simadzu FTIR-8400 spectrometer using KBr pellets. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6 on a Bruker AVANCE 300 instrument with the TMS as an internal standard. All the chemical shifts values were recorded as δ ppm. Mass spectra (EI-MS) were taken on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV. CHN analysis was carried out on Carlo Erba E A 1108 automatic analyzer. The progress of each reaction was monitored and purity of the compounds was checked by thin layer chromatography.

General procedure for the synthesis of 4-aryl-6-(2-oxo-*2H*-chromen-3-yl) pyrimidin 2 (*1H*)-ones

A mixture 3-acetyl coumarin **1** (1 mmol), substituted aromatic aldehyde **2 (a-e)** (1 mmol), urea **3** (1.5 m mol) and $ZrOCl_2.8H_2O/SiO_2$ (0.27 g, 10 mol %) was mixed well and heated on a pre heated hot plate for 8-15 min at 80^{o}C. (At the end of the reaction the liquefied reaction mixture suddenly becomes solid). The reaction progress was monitored by TLC. Water (5 mL) was added into the flask, stirred for several minutes, and then filtered through a sintered funnel to afford the crude products, which were purified by recrystallization from hot ethanol. After completion of the reaction, the catalyst was filtrated, washed by chloroform and dried for 1 h and reused for four runs. As it has been shown in Table 3, the reactions were carried out without observation of appreciable loss in catalyst activity.



(1) **2(a-e)** **(3)** **4(a-e)**

Scheme 1

4(a-e) : **4-Aryl-6-(2-Oxo-*2H*-Chromen-3-yl) Pyrimidin-2 (*1H*)-ones**

Table 1: Optimization of the reaction conditions for the synthesis of 4-(p-methoxy phenyl)-6-(2-oxo-*2H*-chrome-3-yl) pyrimidin-2 (*1H*)-one (4b)[a]

Entry	Solvent	$ZrOCl_2.8H_2O/SiO_2$ Catalyst (mol. %)	Temp. (^oC)	Time	Yield %[b]
1	CH_3CN	20	80	2.5 h	65
2	Solvent-free	--	100	45 min	20
3	Solvent free	20	100	20 min	78
4	Solvent free	10	100	10 min	84
5	Solvent free	10	80	10 min	96
6	Solvent free	5	80	10 min	70

[a] 3-acetylcoumarin (1 m mol), p-methoxy benzaldehyde (1 m mol) and urea (1.5 m mol)
[b] Yield of isolated products

Table 2: $ZrOCl_2.8H_2O/SiO_2$ (10 mol %) catalyzed three component cyclo condensation of aldehyde and urea with 3-acetylcoumarin 4(a-e)

Entry	R	product	Time (min)	Yield (%)
a	H	4a	12	94
b	-O Me	4b	10	96
c	-3-NO_2	4c	8	92
d	-CH_3	4d	15	90
e	-Br	4e	10	94

Table 3: Recycling and reusing of the catalyst

Entry	Runs	Aldehyde	Time/min	Yield[a] %
1	Fresh	2b	10	96
2	First	---	10	96
3	Second	---	10	92
4	Third	---	10	91

[a] Isolated yield

Charectarization of compounds

6-(2-Oxo-2*H*-chromen-3-yl)-4-phenyl pyrimidin-2-(1*H*)-one (4a): m.p. 212-214^{o}C; IR (KBr): 3370, 3095, 2986, 2850, 1720, 1692, 1607 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.2-7.8 (m, 9H, Ar-H), 8.52 (s, 1H, coumarin-H), 7.48 (s, 1H, C^{5}-H); 8.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 96.5, 121.5, 122.3, 125.6, 125.8, 126.8, 128.4, 128.9, 129.2, 130.5, 131.1, 133.2, 142.0, 156.3, 159.5; MS (m/z): 317 (M+H). Anal. Calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.10; H, 3.78; N, 8.80.

4-(p-Methoxyphenyl-6-(2-Oxo-*2H*-chromen-3-yl)-pyrimidin-2-(*1H*)-one (4b): m.p. 242-246^{o}C; IR (KBr): 3375, 3095, 2988, 2855, 1738, 1690, 1617 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.85 (s, 3H, -OCH$_3$), 7.04 (dd, 2H, Ar-H), 7.41 (t, 1H, Ar-H), 8.62 (s, 1H, coumarin-H), 7.52 (s,1H, C^{5}-H), 7.72-7.80 (m, 4H, Ar-H), 7.93 (dd, 1H,Ar-H), 7.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 55.6, 96.5, 114.4, 121.5, 122.3, 125.6, 125.8, 126.8, 128.4, 130.2, 130.5, 142.0, 150.2, 159.5, 163.0, 164.6; MS (m/z): 347 (M+H). Anal. Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.20; H, 4.02; N, 7.98.

4-(3-Nitrophenyl-6-(2-Oxo-*2H*-chromen-3-yl)-pyrimidin-2-(*1H*)-one (4c): m.p. 282 -284^{o}C; IR (KBr): 3405, 3115, 2998, 2859, 1728, 1692, 1614 cm-1; ^{1}H NMR (DMSO-d_6): δ 7.02 (dd, 2H, Ar-H), 7.42 (t, 1H, Ar-H), 8.54 (s,1H, coumarin-H), 7.88 (s, 1H, C^{5}-H), 7.2-7,42 (m, 3H, Ar-H), 7.47 (s, 1H, Ar-H), 7.92 (dd, 1H, Ar-H), 8.94 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 96.5, 121.5, 122.3, 123.4, 124.1, 125.8, 125.5, 126.8, 128.4, 129.8, 130.5, 134.1, 135.3, 142.0, 148.5, 150.2, 156.3, 159.5, 164.6; MS (m/z): 362 (M+H). Anal. Calcd. $C_{19}H_{11}N_3O_5$: C, 63.16; H, 3.07; N, 11.63. Found: C, 63.10; H, 3.02; N, 11.58.

4-(p-Tolyl)-6-(2-Oxo-*2H*-chromen-3-yl)-pyrimidin-2-(*1H*)-one (4d): m.p. 202-204^{o}C; IR (KBr): 3395, 3109, 2998, 2859, 1710, 1688, 1604 cm-1; ^{1}H NMR (DMSO-d_6): δ 2.38 (s,3H, CH$_3$), 6.92 (dd, 2H, Ar-H), 7.12 (t, 1H, Ar-H), 8.52 (s, 1H, coumarin-H), 7.78 (s,1H, C^{5}-H), 7.4-7,42 (m, 4H, Ar-H), 7.88 (dd, 1H,Ar-H), 8.58 (s,1H,NH); ^{13}C NMR (DMSO-d_6): δ 24.3, 96.5, 121.5, 122.3, 125.5, 125.8, 126.8, 128.4, 129.1, 129.2, 130.2, 130.5, 140.7, 142.0, 150.2, 156.3, 159.5, 164.6; MS (m/z): 330 (M+H). Anal. Calcd. $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.74; H, 4.20; N, 8.40.

4-(p-Bromophenyl)-6-(2-Oxo-*2H*-chromen-3-yl)-pyrimidin-2-(*1H*)-one (4e): m.p. 292-294^{o}C; IR (KBr): 3398, 3119, 3005, 2869, 1718, 1680, 1614 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.04 (dd, 2H, Ar-H), 7.16 (t, 1H, Ar-H), 8.63 (s, 1H, coumarin-H), 7.90 (s, 1H, C^{5}-H), 7.48-7,52 (m, 4H, Ar-H), 7.86 (dd, 1H, Ar-H), 8.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 96.5, 121.5, 122.3, 125.4, 125.5, 126.8, 128.4, 130.5, 131.4, 131.8, 132.2, 142.0, 150.2, 156.3, 159.5, 164.6; MS (m/z): 395 (M+H). Anal. Calcd. $C_{19}H_{11}N_2O_3$: C, 57.74; H, 2.81; N, 7.09. Found: C, 57.72; H, 2.82; N, 7.05.

RESULTS AND DISCUSSION

A series of pyrimidin-2(*1H*)-ones were synthesized as illustrated in **Scheme 1**. The compounds **4 (a-e)** were synthesized by acid catalyst $ZrOCl_2.8H_2O/SiO_2$ condensation of 3-acetyl coumarin **1**, substituted aromatic aldehyde **2 (a-e)** and urea **3** by a modification of the Bigenilli reaction in good yields (90-96%).

We started our investigation with 3-acetylcoumain **1**, anisaldehyde **2b** and urea **3** as model substrates to screen the experimental conditions. The results are summarized in Table 1. First, the reaction was carried out by treating one equivalent of each of 3-acetylcoumain **1**, anisaldehyde **2b** and 1.5 equivalent of urea **3** at reflux in acetonitrile in the presence of $ZrOCl_2.8H_2O/SiO_2$ (20 mol%) to get the expected product **4b** after 2.5 hr in 65% yield. In an attempt to improve the yields and owing to the benefits of solvent free conditions, the same reaction was performed in the absence of solvent and in the absence of catalyst but gave no product at 100°C even after 45 min. On addition of 20 mol % of $ZrOCl_2.8H_2O/SiO_2$ to this mixture, rapidly induced cyclocondensation produced **4b** in good yield (84%, Table 1, entry 4) within 10 min.

It was observed that the mixture which was initially in a liquid state and suddenly solidified during the course of heating to a light green solid mass (monitored by TLC). The solid mass was washed with cold water, then washed with diethyl ether, dried and recrystallized from ethanol to get 4-(p-methoxyphenyl)-6-(2-oxo-*2H*-chromen-3-yl)pyrimidin-2 (*1H*)-one **(4b)**. The effect of the reaction temperature on the yield of the product was evaluated (80°C to 100°C). The yield of **4b** reached a maximum of 96% at 80°C after 10 min, indicating that ketone reacts rapidly with aldehyde and urea to form 4-aryl-6-(2-oxo-*2H*-chromen-3-yl) pyrimidin-2(*1H)*-ones when the reaction is carried out with 10 mol% of catalyst. Less than 10 mol% of catalyst (5 mol%) led to poorer yields 69% after longer reaction times and more than 6 to 9 mol% could not improve the yield. These results encouraged us to further investigate the formation of 4-aryl-6-(2-oxo-2H-chromen-3-yl) pyrimidin-2 (1H)-ones **4 (a-e)** from a variety of aldehydes and urea with 3-acetylcoumarin **(Scheme 1)**. In this study, the araldehydes containing both electron withdrawing and electron releasing substituents were found to active toward cyclocondensation as their reactions were compared in a short time to afford excellent yield of the desired products (Table 2). The structures of **4 (a-e)** were characterized by Infrared (IR), ^{1}H NMR, ^{13}C NMR and mass spectrophotometer.

In conclusion, we have successfully developed an environmentally benign method for the synthesis of 4-aryl-6-(2-oxo-*2H*-chromen-3-yl) pyrimidin-2 (*1H*)-ones via the multi component reactions of different aldehydes, and urea with 3-acetyl coumarin under non-

toxic, inexpensive and efficient catalyst $ZrOCl_2.8H_2O/SiO_2$ was employed. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields.

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REFERENCES

1. R. O. Kennedy and R. D. Thornes, Coumarins: Biology, Applications and Mode of Action, Wiley (1997).
2. G. Chichester Cravotto, G. M. Nano, G. Palmisano and S. Tagliapietra, Tetrahedron Asymmetry, **12**, 707 (2001).
3. C. J. Wang, Y. J. Hsieh, C. Y. Chu, Y. L. Lin and T. H. Tseng, Cancer Lett., **183**, 163 (2002).
4. G. H. Fan, W. Mar, M. K. Park, E. Wook Choi, K. Kim and S. Kim, Bioorg. Med. Chem. Lett., **11**, 2361 (2001).
5. R. D. H. Murray, J. Mendez and S. A. Brown, The Natural Coumarins: Occurrence, Chemistry and Biochemistry, Wiley, New York (1982).
6. M. Zahradnik, The Production and Application of Fluorescent Brightening Agents, Wiley, New York (1992).
7. M. Maeda, Laser Dyes, Academic, New York (1984).
8. C. O. Kappe, Tetrahedron, **49**, 6937 (1993).
9. K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd and M. F. Malley, J. Med. Chem., **33**, 2629 (1990).
10. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh and D. J. Faulkner, J. Org. Chem., **60**, 1182 (1995).
11. P. Biginelli, Gaz. Chim. Ital., **23**, 360 (1893).
12. M. M. Heravi, L. Ranjbar, F. Derikvand and B. Alimadadi, Mol. Divers, **12**, 191 (2008).
13. A. R. Khosropour, B. I. Mahammed-poor and H. Ghorobankhani, Catal. Commun., **7**, 713 (2006).

14. W. Hui, C. Xiu-mei, W. Yu, Y. Limg, X. Hai-qiang, X. Hui-hong, P. Li-ling, M. Rui and Y. Cai-hui, J. Chem. Res. Synop., **12**, 711 (2008).

15. S. Goswami, S. Jana, S. Dey and A. K. Adak, Aust. J. Chem., **60(20)**, 120 (2007).

16. E. K. Dora, B. Dash and C. S. Panda, J. Heterocycl. Chem., **20(3)**, 691 (1983).

17. J. Nasielski, A. Standaert and R. Nasielski-Hinkens, Synth. Commun., **21(7)**, 901 (1991).

18. F. C. Baddar, F. H. Ai-Hajjar and N. R. E1-Rayyers, J. Heterocycl. Chem., **13(2)**, 257 (1976).

19. For Recent Reviews on Multicomponent Reactions, a) A. Domling, Chem. Rev., **106**, 17-89 (2006); b) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekenth and L. Balagopal, Acc. Chem. Res., **36**, 899-907 (2003); c) R. V. A. Orru and M. de Greef, Synthesis, **10**, 1471 (2003).

20. P. A. Wender, S. L. Handy and D. L. Wright, Chem. Ind. (London), 765 (1997).

21. H. Firouzabadi, N. Iranpoor, M. Jafarpour and A. Ghaderi, J. Mol. Catal. A. Chem., **253**, 249 (2006).

22. B. E.- Sis, A. Abdolla, M. M. Hashemi and M. Zirak, Eur. J. Org. Chem., **22**, 5152 (2006).

23. Y. Wu, L. N. He, Y. Du, J. Q. Wang and C. X. Miao, W. Li, Tetrahedron, **65**, 6204 (2009).

24. A. K. Chakraborti and A. Kondaskar, Tetrahedron Lett., **44**, 8315 (2003).

25. S. Bhagat and A. K. Chakraborti, J. Org. Chem., **72**, 1263 (2007).

26. A. K. Chakraborti and R. Gulhane, Synlett., 627 (2004).

27. P. M. Price, J. H. Clark and D. J. Macquarrie, J. Chem. Soc., Dalton Trans, 101 (2000).

28. R. K. Sharma, S. Mittal and M. Koel, Crit. Rev. Anal. Chem., **33**, 183 (2003).

29. B. Prasanna, B. Srinivas, S. Kanakraj, V. Amarnath and G. V. P. Chandramouli, E.- J. Chem., **9(4)**, 1676 (2012).

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