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GREEN APPROACH FOR THE EFFICIENT SYNTHESIS OF BIGINELLI COMPOUNDS PROMOTED BY CITRIC ACID UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

Wide range of synthesis of 3,4-dihydropyrimidinones (Biginelli compounds) derived from divergent aldehydes, β-keto esters and urea or thiourea under solvent-free conditions was efficiently performed by citric acid (0.5 equiv.) at 80 ^{0}C with good to excellent yields.

Key words: *Citric acid; aldehyde; β-keto ester; urea or thiourea; Biginelli compounds.*

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons.[1] One such important MCR that belongs in this category is the venerable Biginelli dihydropyrimidine synthesis since its discovery by Biginelli in 1893.[2] Being important building blocks and versatile synthons, 3,4-dihydropyrimidinones are highly featured in organic synthesis due to their attractive pharmacological properties, including calcium channel blockers, antihypertensive agents, α-1a-antagonists, HIV gp-120-CD4 inhibitors (crambine and betzellidine alkaloids), antiviral, antitumour, antibacterial activities and neuropeptide Y(NPY) antagonists.[3] Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones continues to attract the attention of researchers. Several improved procedures for the preparation of DHPMs ('Biginelli compounds') have recently been reported, including traditional Bronsted acids,[4] pleothra of Lewis acids,[5] ionic liquids,[6] microwave irradiation,[7] solid phase reagents,[8] polymer-supported catalysts,[9] heterpopoly acids,[10], heterogeneous catalysts,[11] and organo acids.[12] Recently, we reported the bismuth triflate catalyzed efficient synthesis of Biginelli compounds in acetonitrile *at room temperature for the first time* according to literature reports.[5d] However, some of the newer reported methods including ours also suffer from unsatisfactory yields especially in the case of substituted aromatic aldehydes, cumbersome product isolation procedures and use of harsh solvents based on MSDS data which concerns for environmental pollution. More importantly, use of heavy metals as catalysts will be subjected to the contamination of dihydropyrimidinones, which is extremely important when concerning about synthesizing active pharmaceutical ingredients. Thus, despite all these improvements made by several groups, the search for better promoter still continues to be desirable especially in terms of cost-effectiveness, readily or commercial availability and environmentally benign solvent-free procedures.

One promising approach to environmentally consciousness in chemical research and industry augments to minimize or completely eliminate the use of harmful organic solvents in organic syntheses. This is because organic reactions run under solvent-free conditions are advantageous because of their enhanced selectivity, efficiency, ease of manipulation, and cleaner product formation as well as toxic or often volatile solvents are avoided.[13] Thus, a paradigm shift from

using solvents toward solvent-free reactions not only simplifies organic synthesis but also improves process conditions for large-scale synthesis.

In a continuation of our recent efforts to develop new synthetic routes for carbon-carbon and carbon-heteroatom bond formation,[14] herein we disclose the first example of an efficient synthetic protocol for the preparation of 3,4-dihydropyrimidinones using citric acid as an organopromoter under essentially solvent-free conditions (Scheme 1). Citric acid is a relatively strong organic acid. Citric acid and its salts are widely used because they are nontoxic, relative noncorrosiveness, safe to handle, and easily biodegraded.

EXPERIMENTAL

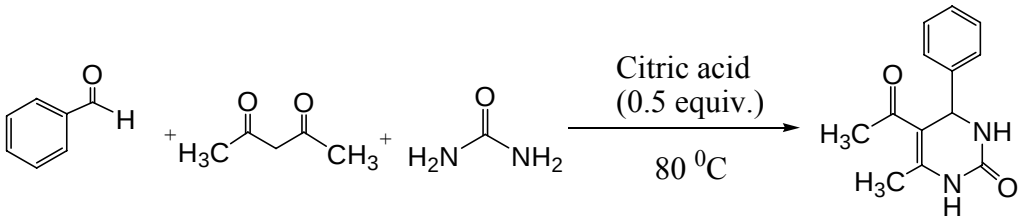
General remarks: Melting points were recorded on Sd. fine 9100 Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin–Elmer model 683 or 1310 spectrometers and are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded as solutions in $CDCl_3$, or DMSO (d_6) and chemical shifts reported in parts per million (ppm) on a Varian Gemini 200 MHz or AV 300 MHz, instrument using tetramethylsilane (TMS) as an internal standard. Low-resolution mass spectra were recorded on VG 7070H Micromass mass spectrometers. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60F-254 on glass). Percentage yields are given for compounds.

General Procedure for the synthesis of 3,4-dihydropyrimidinones: In a typical experimental procedure, a mixture of aldehyde (1.0 mmol), α-methylene ketone (1.1 mmol), urea or thiourea (1.3 mmol) and citric acid (0.5 mmol) were taken into a round bottom flask under stirring and the reaction mixture heated at 80 ^{0}C for appropriate time. After completion of the reaction as monitored by TLC, to the reaction mixture, cold water was added and stirred for 10 minutes, then filtered and washed with water and dried in vacuum and the corresponding product was further recrystallized from ethanol.

All the compounds were known and characterized by IR, ^1H NMR, mass spectrometry and also by comparing their physical characteristics with those in the literature [4-12].

RESULTS AND DISCUSSION

Initially, we have studied the efficacy of chosen water-soluble organoacids (1 equiv. as standard) such as maleic acid, malonic acid, *p*-toluene sulphonic acid and citric acid for the model reaction using benzaldehyde (1 mmol), urea (1.5 mmol) and acetyl acetone (1.3 mmol) under solvent-free conditions at 80 ^{0}C to afford the corresponding dihydropyrimidinone (Scheme-1). Among the acids screened, citric acid was found to be the best promoter in terms of reaction times and yields (92% isolated yield), whereas other organoacids such as maleic acid, malonic acid, *p*-toluene sulphonic acid gave yields of 72%, 75% and 55% respectively. To the best of our knowledge, there are no earlier reports on the preparation of Biginelli compounds using citric acid. The optimum yields of the product were obtained when a ratio of aldehyde: urea: acetonyl acetone is in the following order respectively 1.0:1.3:1.1. Next, we studied the optimization of promoter loading. The reaction is found to be sluggish when carried out using 10 mol% (52%), 30 mol% (55%). And with 0.5 equiv. of promoter (96% isolated yield), it was found to be optimum. Increasing the promoter loading further did not improve the yields.



Scheme 1

With the optimized parameters in hand, we then proceeded to test the reactivity order of chosen structurally divergent 1,3-diketones for the reaction with benzaldehyde and urea or thiourea and the results are summarized in Table 1. The 1,3-diketones containing electron withdrawing groups such as $–CF_3$ or –Ph substitutents (entries 7-10, Table 1) have resulted in poor yields compared to the electron donating groups such as $–CH_3$ (entries 1-6, Table 1).

Intrigued by these observations, we have extended our studies to test the scope and generality of the present developed procedure to structurally divergent aldehydes and thus forming a mini-library of 3,4-dihydropyrimidinones and the results are summarized in Table 2. As can be seen from the data in Table 2, dihydropyrimidinones bearing aromatic rings with pharmacologically relevant substitution patterns can be obtained using citric acid in the present protocol without any transition metal contamination. All the compounds were known and well characterized by comparing their melting points, IR, ^1H NMR and mass spectral analyses (see Supporting Information for selected compounds). The dihydropyrimidinones were the only products obtained and the rest of the material was essentially starting material. Table 2 shows the generality of the present protocol, which is equally effective for urea and thiourea, and also for aromatic and aliphatic aldehydes.

Very important to note that this protocol has tolerance of acid sensitive aldehydes such as furfural (entries 21-22 and 49-50), 2-thiophene carboxaldehyde (entries 23-24) and cinnamaldehyde (entries 25-26 and 51-53) without formation of byproducts. Another important practical feature of this procedure is the survival of a variety of functional groups such as ether (entries 3-4 and 33-34), hydroxy (entries 11-16 and 39-44), halides (entries 17-18 and 45-46) under the optimized conditions.

The proposed mechanism for the citric acid-promoted synthesis of dihydropyrimidinones may tentatively be visualized to occur via a tandem sequence of reactions involving (i) formation of acylimine intermediate, formed by the reaction of the aldehyde and urea activated by citric acid through intermolecular hydrogen bonding, and subsequent addition of β-diketoester enolate to the acylimine followed by cyclodehydration to afford dihydroprimidin-2(*1H*)-one.

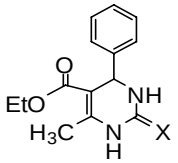
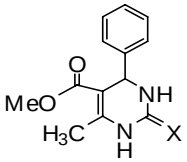
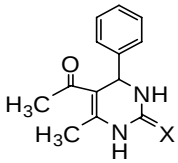
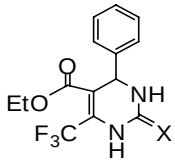
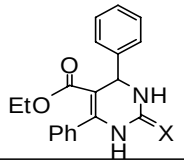
CONCLUSION

In summary, we have developed a novel and very simple protocol for the synthesis of 3,4-dihydroprimidin-2(*1H*)-ones under solvent-free conditions promoted by citric acid provided an efficient, eco-friendly, commercially available and economic promoter, and to the most important is devoid of product contamination by heavy metal traces for the large scale synthesis. We believe that this protocol will find useful applications for the needs of both academia as well as pharmaceutical industries.

ACKNOWLEDGEMENTS

Dr. Enugala and Dr. Varala thank Dr. J. S.Yadav, Director, IICT and CSIR, India for providing necessary facilities and funding.

Table 1: Comparision of the reaction rates of benzaldehyde and urea or thiourea with divergent acetoacetates.

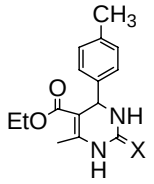
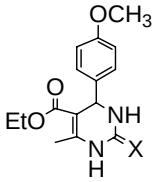
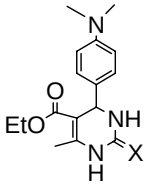
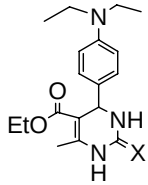
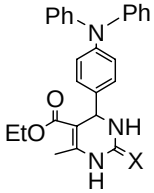
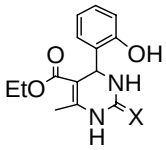
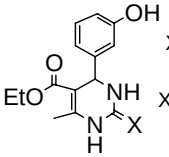
Entry	Product		Time (h)/ Yield (%)[a]	M.P (^{0}C) Found	M.P (^{0}C) Reported
1		X = O	1/98	202	200-202[4e]
2		X = S	1/99	202-203	202-204[4e]
3		X = O	1/97	210-213	210-213[4e]
4		X = S	1/98	221	221-222[4e]
5		X = O	1/92	228-229	230[12c]
6		X = S	1/95	220-221	220-222[5h]
7		X = O	3/45	160-162	New
8		X = S	3/62	164-165	New
9		X = O	2.5/64	158	158-159[5i]
10		X = S	2.5/76	184-186	183-185[5i]

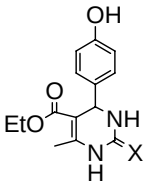
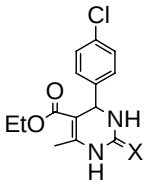
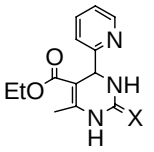
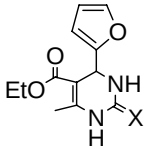
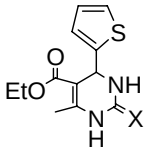
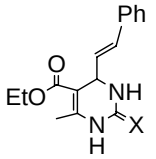
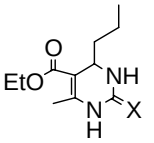
[a] Isolated Yields.

REFERENCES

1. For leading reviews on Multi Component Reactions, see: a) Multicomponent reactions, J. Zhu, H.Bienayme. Eds.; Wiley: Weinheim, 2005; (b) H. Bienayme, C. Hulme, G. Oddon, P. Schmitt. *Chem. Eur. J.* **6**, 3321 (2000); (c) A. Domling and I. Ugi, *Angew. Chem., Int. Ed.* **39**, 3168 (2000); (d) C. O. Kappe. *Acc. Chem. Res.* **33**, 879 (2000); (e) C. Simon, T. Constantieux and J. Rodriguez. *Eur. J. Org. Chem.* 4957, (2004).
2. P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893).
3. (a) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz and M. F. Malley. *J. Med. Chem.* **33**, 2629 (1990); (b) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Z. Gougoutas, A. Hedberg, M F. Malley, J. P. McCarthy, R. Zhang and S. Moreland. *J. Med. Chem.*, **38**, 119 (1995) and references therein; (c) T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber and T. J. Mitchison. *Science*, **286**, 971 (1999); (d) C. O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000).

Table 2: Citric acid mediated mini-library synthesis of divergent Biginelli compounds.

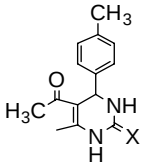
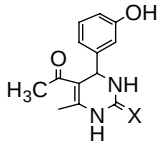
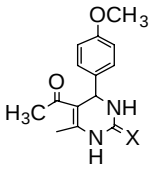
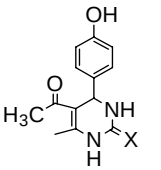
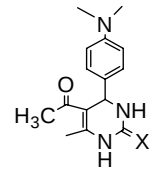
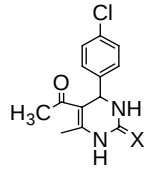
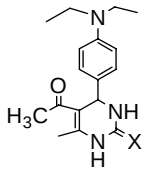
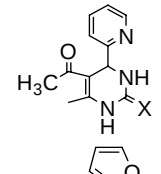
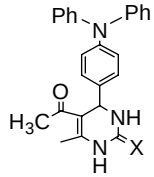
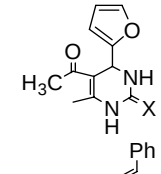
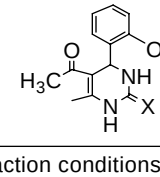
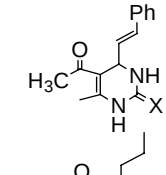
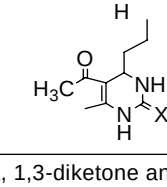
Entry	Product	Time (h)/ Yield (%)	MP (^{0}C) Found	MP (^{0}C) Reported
1	 X = O	1/68	215-216	215-216[5h]
2	X= S	2/73	214-216	214-215[4]
3	 X = O	1/79	203-205	201-203[5h]
4	X= S	3/84	156-158	150-152[10b]
5	 X = O	1/75	230-234	256-258[5h]
6	X= S	5/72	210-212	209-210[4]
7	 X = O	1/75	196-198	New
8	X= S	4/71	202-204	New
9	 X = O	1/71	133-135	New
10	X= S	5/92	190-192	New
11	 X = O	3/63	200-201	200-202[5g]
12	X= S	3/52	204-206	New
13	 X = O	1/56	170-174	164-166[5j]
14	X= S	3.5/48	190-193	185-186[5k]

Entry	Product	Time (h)/Yield (%)	MP (^{0}C) Found	MP (^{0}C) Reported
15	 X = O	2/76	230-234	237-238[12d]
16	X= S	1.5/88	202	202-203[12d]
17	 X = O	1/68	215-216	215-216[12d]
18	X= S	4/72	194-198	208-210[12d]
19	 X = O	5/56	203-205	New
20	X= S	5/63	224-226	New
21	 X = O	1/94	208-209	208-210[12d]
22	X= S	2/92	234-236	New
23	 X = O	2/58	205-206	207-208[12d]
24	X= S	3.5/62	239-241	New
25	 X = O	1.5/75	234-235	232-235
26	X= S	4/79	163-165	New
27	 X = O	2/58	172-174	New
28	X= S	2/61	107-111	New

Reaction conditions: 1:1.5: 1.3: 0.5 (aldehyde, urea or thiourea, 1,3-diketone and citric acid) at 80 ^{0}C.

[a]Yields refer to isolated pure products.

Table 2: Citric acid mediated mini-library synthesis of divergent Biginelli compounds.

Entry	Product	Time (h)/Yield (%)		MP (^{0}C) Found	MP (^{0}C) Reported	Entry	Product	Time (h)/Yield (%)		MP (^{0}C) Found	MP (^{0}C) Reported
29		X = O	1/73	229-230	New	**41**		X = O	3/61	204-208	New
30		X= S	2.5/86	226-228	New	**42**		X= S	2/76	240-243	New
31		X = O	1/99	166-167	166-168[12c]	**43**		X = O	2/71	244-245	245-246
32		X= S	1/84	172-175	New	**44**		X= S	4/88	246-248	New
33		X = O	1/75	213-214	New	**45**		X = O	1/60	206-208	206-208
34		X= S	5/79	152-155	New	**46**		X= S	3/78	209-211	208
35		X = O	1/71	145-147	New	**47**		X = O	5/74	224	224-225[5j]
36		X= S	4/76	133-135	New	**48**		X= S	5/62	172-175	New
37		X = O	1/84	189-191	New	**49**		X = O	2/84	210-212	210-212[5j]
38		X= S	5/90	242-245	New	**50**		X= S	1/91	240-242	New
39		X = O	2/96	204-208	New	**51**		X = O	1.5/93	230-232	New
40		X= S	4/98	240-243	New	**52**		X= S	2/97	160-162	New
						53		X = O	2/62	113-115	New
						54		X= S	2/78	118-119	New

Reaction conditions: 1:1.5: 1.3: 0.5 (aldehyde, urea or thiourea, 1,3-diketone and citric acid) at 80 ^{0}C.
[a]Yields refer to isolated pure products.

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