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A GREEN APPROACH TO THE SYNTHESIS OF 2,3-DIHYDROPYRIMIDIN-2(1*H*)-ONES BY URONIUM HYDROGENSULFATE UNDER SOLVENT-FREE CONDITIONS

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Abstract- 3,4-Dihydropyrimidin-2(1*H*)-ones and –thiones are synthesized in high yields by a one-pot condensation of an aldehyde, a β-dicarbonyl compound with hydrogensulfate salt of urea or thiourea under solvent-free conditions.

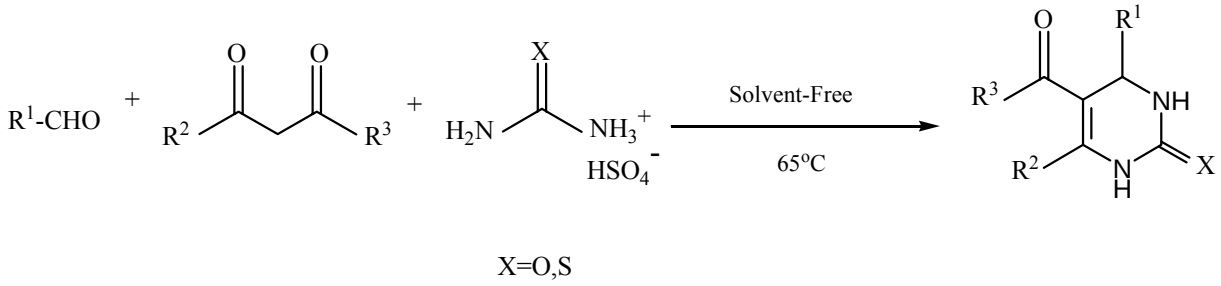
3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogues (Biginelli compounds, DHPMs) represent an important heterocyclic system which are becoming increasingly sufficient due to their therapeutic and pharmacological properties, such as antiviral, antibacterial, and hypertensive, as well as efficacy as potent calcium channel blockers, α_{1a} adrenergic antagonists, and neuropeptide Y(NPY) antagonists.[1,2] Also the anti-HIV activity in some marine natural products containing the DHMPs skeleton is observed.[3]

The Biginelli reaction, first described more than a century ago, was a one-pot but low yielding (often 20-50%) condensation of β-dicarbonyl compounds with aromatic aldehydes and urea under strongly acidic conditions.[4] Subsequent multistep syntheses produced somewhat higher yields but lacked the simplicity of one-pot, one step synthesis.[5]

The art of performing efficient chemical transformation by coupling three or more components in a single operation by a catalytic process avoiding stoichiometic toxic reagents, large amount of solvents and expensive purification techniques, represents a fundamental target of modern organic synthesis.[6] Thus Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest and several

improved procedures have recently been reported.[7-19] However some of these newer reported methods also suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedure, applicability for only aromatic aldehydes, and environmental pollution.[7-12, 19] Consequently, there are scopes for further renovation toward milder reaction conditions, use of environmentally benign reagents, variations of substituents in all three components, and better yields.

Herein, we describe a novel, green, and high yielding protocol for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones and –thiones by the reaction of aromatic and aliphatic aldehydes with β-dicarbonyl compounds in the presence of uronium- or thiouronium hydrogensulfate which act both as the substrate and the pormoter (Scheme 1). Uronium hydrogensulfate is a very cheap and stable solid material that its application in synthetic methodology has already been reported.[20]



Scheme 1

The reaction of various types of aldehydes and β-dicarbonyls with hydrogensulfate salt of urea- or -thiourea under solvent-free conditions resulted in the formation of dihydropyrimidin-2-ones and -thiones. The reactions proceeded smoothly at 65˚C and were completed within 2-4 hours. Table 1 shows the generality of this protocol, which is equally effective for urea and thiourea, and also for aromatic and aliphatic aldehydes. Under this condition, the yields were significantly better in comparison with the classical Biginelli procedure. Several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *ortho-, meta- or para-* positions afforded high yields of products. An important feature of this procedure is the survival of a variety of functional groups such as alkoxy groups, nitro groups, hydroxy groups, halogeno groups, etc. under the reaction conditions. Another advantage of this method is its efficiency for the high yield synthesis of DHPMs from aliphatic aldehydes (Entries 12, 13). 3,4-Dihydropyrimidin-2(1*H*)-thiones, which are also of interest because of their biological activities, are synthesized with similar success. For example monastrol, a mitoic kinesin Eg5 motor portein inhibitor and potential new lead for the development of anticancer drugs,[21] was obtained in 91% yield (Entry 25) . A bis-dihydropyrimidinone compound was also synthesized by a pseudo five-component reaction that could be an

Table 1. Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and -thiones by the Condensation of Aldehydes, β-Dicarbonyls and Uronium- or Thiouronium Hydrogensulfate under Solvent-Free Conditions

Entry	R^1	R^2	R^3	X	Time (h)	Yield[a] (%)	Mp(°C)[b] Found	Mp(°C)[b] Reported
1	C_6H_5	Me	OEt	O	2	93	205-207	202-204[19]
2	2-NO_2-C_6H_4	Me	OEt	O	2.5	92	207-209	206-208[12]
3	2-CH_3O-C_6H_4	Me	OEt	O	2	96	261-263	262[15]
4	3-O_2N-C_6H_4	Me	OEt	O	3	92	223-225	227-229[13a]
5	3-HO-C_6H_4	Me	OEt	O	3	91	161-163	164-166[9]
6	4-O_2N-C_6H_4	Me	OEt	O	3	96	209-211	208-211[19]
7	4-Cl-C_6H_4	Me	OEt	O	3.5	95	212-214	213-215[19]
8	4-CH_3O-C_6H_4	Me	OEt	O	2.5	89	203-204	201-203[19]
9	4-F-C_6H_4	Me	OEt	O	3	90	185-187	185-186[19]
10	3,4-$(CH_3O)_2$-C_6H_3	Me	OEt	O	2	90	176-177	178[7]
11	C_6H_5-CH=CH	Me	OEt	O	2	96	231-233	232-235[8]
12	*n*-C_3H_7	Me	OEt	O	2	91	157-159	157-158[16]
13	*n*-C_6H_{13}	Me	OEt	O	2	89	150-153	151-152[7]
14	C_6H_5	C_6H_5	OEt	O	4	91	155-158	157-159[19]
15	C_6H_5	Me	OMe	O	2	93	208-210	209-212[19]
16	4-Cl-C_6H_4	Me	OMe	O	3	94	205-207	204-207[19]
17	4-O_2N-C_6H_4	Me	OMe	O	3	92	235-236	235-237[19]
18	2,4-$(Cl)_2$-C_6H_3	Me	OMe	O	2.5	95	250-253	254-255[8]
19	4-CH_3O-C_6H_4	Me	OMe	O	3	83	165-168	168-170[19]
20	C_6H_5	Me	Me	O	2	87	237-238	233-236[18]
21	4-CH_3O-C_6H_4	Me	Me	O	3	81	166-167	168-170[9]
22	4-O_2N-C_6H_4	Me	Me	O	3	90	231(dec)	230(dec)[8]
23	C_6H_5	Me	OEt	S	2	91	208-211	209-211[11]
24	3-O_2N-C_6H_4	Me	OEt	S	3	93	206-208	203-205[13a]
25	3-HO-C_6H_4	Me	OEt	S	3	90	185-186	184-186[16]
26	C_6H_5	Me	Me	S	2	92	187(dec)	185(dec)[17]
27	4-CHO-C_6H_4	Me	OEt	O	4	85	>290	>300[14]
28[c]	C_6H_5	Me	OEt	O	6	45	205-207	202-204[19]

[a]Isolated yield (65°C).

[b]Products were characterized by comparison of their spectroscopic data (^{1}H-NMR and IR spectrum) and mps with those reported in the literature.

[c]The reaction was performed in the absence of uronium hydrogensulfate

interesting model compound for new generation of biologically active molecules (Entry 27). Entry 28 shows the promotion effect of uronium hydrogensulfate in the Biginelli reaction.

In conclusion, we have described a highly efficient solvent-free modification of the Biginelli multicomponent reaction that allows the assembly of structurally divers DHPM derivatives. Mild reaction conditions, high yields, elimination of solvent or solid support, and the stability and cheapness of the reagent are features of this new procedure. The work-up procedure is very simple and green, including washing the reaction mixture with water followed by recrystallization of the product from EtOH. Another advantage of this environmentally benign and safe protocol is the use of uronium and thiouronium hydrogensulfate that acts as both the promoter and the source of one of the substrates. Moreover, this method has the ability to tolerate a wide variety of substituents in all three components.

EXPERIMENTAL

Products are known compounds and were characterized by comparison IR and ^{1}HNMR spectra and melting points were essentially identical with those of authentic samples. Melting points were measured on an Electrothermal 9100 apparatus and are not corrected. IR spectra were measured on a Shimadzu IR-470 spectrophotometer. ^{1}HNMR spectra were run on a Bruker 500 DRX AVNCE spectrometer. Yields refer to isolated products.

General procedure for the synthesis of DHPMs

Aldehyde (1 mmol), the β-dicarbonyl compound (1 mmol), urea (or thiourea) (0.5 mmol), and uronium (or thiouronium) hydrogensulfate (1 mmol), were thoroughly mixed and heated at 65^{o}C under solvent-free conditions for the appropriate period of time (Table 1). After completion of the reaction as indicated by TLC analysis, the solid mixture was washed with cold water (15 mL) to remove the excess of urea or thiourea and also the acidic reagent and then filtered. The remaining crude product was recrystallized from EtOH.

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REFERENCES

1. (a) G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. MacCarthy, R. Zhang, and S. Moreland, *J. Med .Chem.,* 1995, **38**, 119. (b) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, and M. F. Malley, *J. Med. Chem.,* 1990, **33**, 2629. (c) K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, and B. C. O'Reilly, *J. Med. Chem.,* 1991, **34**, 806. (d) G. J. Grover, S. Dzwonczyk, D. M. McMullen, D. E. Normandin, C. S. Parham, P. G. Sleph, and S. Moreland, *J. Cardiovasc. Pharmacol.,* 1995, **26**, 289.

2. C. O. Kappe, *Eur. J. Med. Chem.,* 2000, **35**, 1043.

3. A. D. Patil, N. V. Kummar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mail, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley, and B. C. Potts, *J. Org. Chem.,* 1995, **60**, 1182.

4. P. Biginelli, *Gazz. Chim. Ital.,* 1893, **23**, 360.

5. K. S. Atwal, B. C. O'Reilly, J. Z. Gougoutas, and M. F. Malley, *Heterocycles,* 1987, **26**, 1189.

6. N. Mizzuno and M. Misono, *Chem. Rev.,* 1998, **98**, 199.

7. J. S. Yadav, B. V. S. Reddy, K. B. Reddy, K. S. Raj, and A. R. Prasad, *J. Chem. Soc., Perkin Trans. 1,* 2001, 1939.

8. Y. Ma, C. Qian, L. Wang, and M. Yang, *J. Org. Chem.,* 2000, **65**, 3864.

9. B. C. Ranu, A. Hajra, and U. Jana, *J. Org. Chem.,* 2000, **65**, 6270.

10. J. Lu, Y. Bai, Z. Wang, B. Yang, and H. Ma, *Tetrahedron Lett.,* 2000, **41**, 9075.

11. N. Y. Fu, Y. F. Yuan, Z. Cao, S. W. Wang, J. T. Wang, and C. Peppe, *Tetrahedron,* 2002, **58**, 4801.

12. K. A. Kumar, M. Kasthuraiah, C. S. Reddy, and C. D. Reddy, *Tetrahedron Lett.,* 2001, **42**, 7873.

13. (a) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodaghi Fard, *Tetrahedron Lett.,* 2003, **44**, 2889. (b) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodaghi Fard, *Heterocycles,* 2003, **60**, 2435.

14. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang, and Q. Zhuang, *Synlett,* 2004, 537.

15. F. S. Falsone and C. O. Kappe, *Arkivoc,* 2001, **2**, 1234.

16. J. J. V. Eynde, N. Audiart, V. Canonne, S. Michel, Y. V. Haverbeke, and C. O. Kappe, *Heterocycles,* 1997, **45**, 1967.

17. S. D. Sharma, V. Kaur, P. Bhutani, and J. Khurana, *Bull. Chem. Soc. Jpn.,* 1992, **65**, 2246.

18. F. Bigi, S. Carloni, B. Frullanti, R. Maggi, and G. Sartori, *Tetrahedron Lett.,* 1999, **40**, 3465.

19. E. H. Hu, D. R. Sidler, and U. H. Dolling, *J. Org. Chem.,* 1998, **63**, 3454.

20. M. A. Zolfigol, A. G. Choghamarani, A. Taqian-Nasab, H. Keypour, and S. Salehzadeh, *Bull. Korean Chem. Soc.,* 2003, **24**, 638.

21. (a) T. U. Mayer, T. M. Kapoor, S. Haggarty, R. W. King, S. L. Schreiber, and T. J. Mitchison, *Science,* 1999, **286**, 971. (b) A. Dondoni, A. Massi, and S. Sabbatini, *Tetrahedron Lett.,* 2002, **43**, 5913.