IRON (III) PHOSPHATE DIHYDRATE – CATALYZED ONE-POT SYNTHESIS OF DIHYDROPYRIMIDINONES AND THIONES : AN IMPROVED PROCEDURE FOR THE BIGINELLI REACTION

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Abstract : A fast and high yielding one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones with various aliphatic and aromatic aldehydes using $FePO_4.2H_2O$ as heterogeneous catalyst was carried out in acetonitrile.

Key words : Dihydropyrimidinones, Iron (III) phosphate dihydrate Biginelli Reaction, One-Pot Synthesis

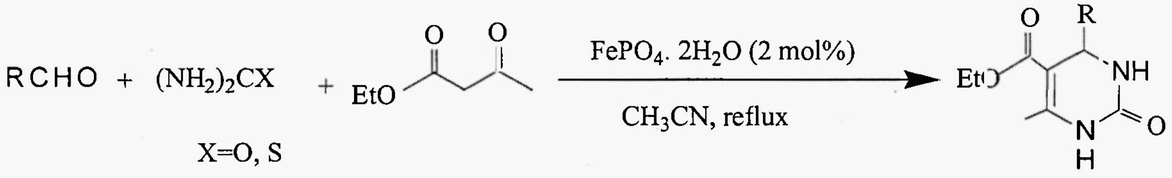
Introduction

Recently, the interest in synthesis of 3,4-dihydropyrimidin-2(1H)-ones(denoted as Biginelli compounds) and their derivatives is increasing tremendously because of their therapeutic and pharmalogical properties and also because of interesting biological activities of several marine alkaloids witch contain the dihydropyrmidine nucleus[1-4]. Strategies for the dihydropyrimidine nucleus involves one-pot to multistep approaches. The classical Biginelli synthesis is a one-pot condensation using β-dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea in ethanol solution containing catalytic amounts of acid[5]. This method often provides low to moderate yields of the desired target molecules. In recent years, many improved procedures have been reported for the preparation of DHPMs,using $InBr_3$[6], $InCl_3$[7], $LiClO_4$[8], $NiCl_2. 6H_2O$[9], p-TsOH[10], $LaCl_3. 6H_2O$[11], $Bi(OTf)_3$[12], $BF_3 .OEt_2$[13], NBS[14] as catalyst. However , many of these protocols suffer from drawbacks such as the use of expensive and highly acidic catalysts and also need prolonged reaction times. One the other hand, ferric phosphate is very cheap and safe catalyst that has been prepared using $Fe_2(SO4)_3$ and disodium phosphate[15]. Ferric phosphate is not harmful to human health[16].

Chemically, ferric phosphate is very stable and will not dissociate unless in the presence of concentrated acid, which is not present in natural surroundings, because of its low solubility in the aqueous agro ecosystem, there is little contamination beyond treated areas. The none-toxicity in all documented cases,except for as a molluscicide, make ferric phosphate consistent with organic farming and a good candidate as benign reagent.

Results and Discussions

We are interested in catalytic Biginelli reaction[17], herein we wish to report a simple, efficient and safe method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones using $FePO_4.2H_2O$ in acetonitrile as solvent. Several activated and deactivated aromatic and aliphatic aldehydes under reaction conditions gave the corresponding dihydropyrimidines and thiones in good yields. The experimental procedure is very simple, convenient and has the ability to tolerate a variety of other functional group such as methoxy, nitro, halide, and olefins under the reaction conditions. Thiourea was used as one of the ingredients with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1H)-thiones (Table-1, Scheme-1).



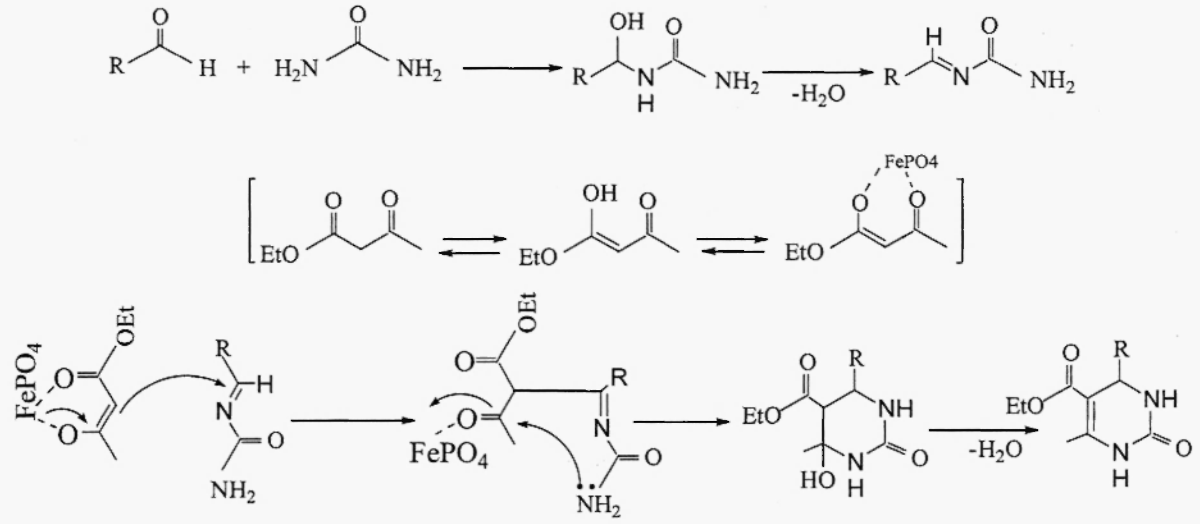
Scheme-1

The reaction may proceed through the acylimine intermediate (formed in situ by reaction of the aldehyde with urea), which is stabilized by the iron and the subseque addition of the β-ketoester enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding dihydropyrmidines (Scheme-2).

Table-1 : $FePO_4.2H_2O$, catalyzed Synthesis of Dihydropyrimidones and thiones in acetonitrile.

Entry	Aldehyde	X	Product	Time(Min)	M. P. (°C)		Yield%[a]
					Observed	Founded	
1	PhCHO	O	4a	15min	202-204	200-202[18]	91
2	4-Cl- phCHO	O	4b	30min	214-216	215-216[18]	88
3	3-Nitro- phCHO	O	4c	20min	225-220	215-216[19]	85
4	4-MeO- phCHO	O	4d	80min	202-204	215-216[20]	88
5	PhCH=CHCHO	O	4e	30min	158-160	157-159[21]	93
6	$CH_3CH_2CH_2CHO$	O	4f	90min	152-154	153-155[9b]	89
7	$(CH_3)_2CHCHO$	O	4h	90 min	171-174	170-172[9b]	85
8	PhCHO	S	4i	135min	209-211	170-172[20]	82
9	4-MeO-PhCHO	S	4j	150min	153-156	170-172[20]	90
10	4-Cl-PhCHO	S	4k	130min	191-195	192-195[20]	92

a)Isolated yields



Scheme-2

Experimental

Preparation of 3,4-dihydropyrimidin-2(1H)-ones and thiones: A typical procedure . In three neck round bottomed flask , benzaldehyde (5 mmol, 0.507^{cc}), ethyl acetoacetate (5 mmol, 0.5^{cc}), urea(7.5mmol, 0.45g), $FePO_4.2H_2O$(0.05 mmol 0.009^{g}) in acetonitrile (4cc) was stirred at reflux temperature for 15 min (Table 1).Upon completions of the reaction, as indicated by TLC(eluent: n-hexane: ethylacetate, 4:1), the solvent was removed under reduced pressure, the residue was poured on crushed ice and filteres to give crude the product, witch was purified by recrystallization from MeOH.

Conclusions

In conclusion a mild, simple, efficient and eco-friendly protocol has been presented for the Biginelli reactions in the presence of iron(III) phosphate dehydrate that provides dihydropyrimidinone and thiones derivatives in excellent to high yields.

References

1. X. Ma, C. Qian, L. Wong, M. Yang, *J. Org. Chem.* **65**:3864 (2000) and references cited therein.
2. E.H. Hu, D.R. Siddler, U.H. Dolling, *J. Org. Chem.* **63**:3454 (1998).
3. B.B. Snider, Z. Shi, *J. Org. Chem.* **58**:3828 (1993).
4. W.M.F. Fabian, M.A. Semones, *Tetrahedron*, **53**:2803 (1997).
5. C.O. Kappe, *Tetrahedron*, **49**:6937 (1993).
6. N.Y. Fu, Y.F. Yuan, Z. Cao, S.W. Wang, J.I. Wang, C. Poppe, *Tetrahedron*, **58**:4801 (2002).
7. B. Ranu, A. Hajra, U. Jana, *J. Org. Chem.* **65**:6270 (2000).
8. J.S. Yadav, B.V.S. Reddy, R. Srinivas, C. Venugopal, T. Ramalingam, *Synthesis* 1341 (2001).
9. a) J. Lu, H. Ma, *Synlett.* 63 (2000). (b) J. Lu, Y. Bai, *Synthesis*, 466 (2002).
10. T. Jin, S. Zhang, Ti. Li, *Synth.Commun.* **32**:1847 (2002).

11. J. Lu, Y. Bai, Z. Wang, B. Yang, H. Ma, *Tetrahedron Lett.* **41**:9075 (2000).
12. R. Varala, H.M. Alam, S.R. Adapa, *Synlett.* 64 (2003).
13. E.H. Hu, D.R. Sider, U.H. Dolling, *J. Org. Chem.* **63**:3454 (1998).
14. H. Hazarkhani, B. Karimi, *Synthesis*, 1239-1242 (2004).
15. *Comprehensive inorganic chemistry*, V.3: 1042 (1979).
16. *TAP report for Ferric phosphate* (July 2004).
17. (a) M. Tajbakhsh, B. Mohajerani, M.M. Heravi, A.N. Ahmadi, *J. Mol. Cata. A: Chemical*, **236**:216-219 (2005); (b) M.M. Heravi, F. Derikvand, F. Bamoharram, *J. Mol. Cata. A: Chemical*, **242**:173-175 (2005).
18. M. Gohain, D. Prajapati, Sandhu, S. Jagir, *Synlett.* 235 (2004).
19. C.O. Kappe, D. Kumar, R.S. Varma, *Synthesis* 1799 (1999).
20. A.S. Paraskar, G.K. Dewkar, A. Sudalai, *Tetrahedron Lett.* **44**:3305 (2003).
21. H. Hazarkhani, B. Karimi, *Synthesis* 1239 (2004).

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