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Synthesis and Characterization of Different Amides Via Biginelli

Chemistry

KEYWORDS : Phosphoric acid , ammonia , one-pot synthesis, Biginelli reaction etc.

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ABSTRACT

P. Biginelli in 1893 reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1H)-ones (DHMPs) via three component condensation reaction of an aromatic aldehyde, urea and the ethyl acetoacetate. The yields of the dihydropyrimidinones obtained via this novel protocol are significantly higher than those utilizing the conventional ethanol / HCl method. A simple and economic synthesis of 3,4-dihydropyrimidin-2(1H)-ones by using phosphorus pentaoxide. The phosphorus pentaoxide can be converted into the phosphoric acid. The phosphorus pentaoxide has been found to be mild and efficient reagent for the synthesis of dihydropyrimidinones and its corresponding thioanalogs in refluxing ethanol. These are become popular in the world of synthetic organic chemistry due to their activities such as antibacterial, anti-viral, anti-inflametory. A series of the new 5-amido-4(phenyl)-6-methyl,3,4-dihydropyrimidin-2(1H)-ones have been synthesized by using the 5-ethoxycarbonyl-4(phenyl)-6-methyl,3,4-dihydropyrimidin-2(1H)-ones and the excess amount of the ammonia. The different compounds of this series can be synthesized by using one-pot multicomponent synthesis. The newly synthesized different amide derivatives of the 3,4, dihydropyrimidin-2(1H)-one were well monitor by using TLC plates. And these synthesized compounds were well characterized by 1H-NMR spectral studies. The results of such compound have been discussed in this paper. In the conclusion, we have developed a simple, quick a one pot multicomponent synthesis and characterization of different amide via Biginelli.

Introduction :

The synthesis of dihydropyrimidinones and their thio-analogous have become more popular in the world of synthetic organic chemistry due to their activities such as antibacterial, antiviral, antihypertensive, anti-inflammatory, antitumor[1]. Although the mechanism of Biginelli reaction has been debated for a number of years, most researchers now agree on the following sequence of steps, as proposed by Kappe[2]. The Biginelli reaction produces a 3,4-dihydropyrimidinone, an example of class of compounds exhibiting the pharmacological activity. Recently some marine alkaloids possess dihydropyrimidin-5-carboxylate core have been shown to exibit interesting biological activities such as potent HIV-gp-120-CD4 inhibitors as well as anti HIV agent [3]. An efficient synthesis of dihydropyrimidin-2(1H)-ones using the phosphorus pentaoxide was studied by Deshmukh and etal [4]. And thus we have requires the development of new protocol for high yield and the use of inexpensive reagent, which requires shorter time and with easier work-up procedure, A few method involves the use of ionic crystals.[5].

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. [6-10] In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portion of all the components.[6-10] The search and discovery for new MCRs on one hand[11], and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. The recent advances in the Biginelli Dihydropyrimidine synthesis again C. Oliver Kappe proposed a new tricks for the same dihydropyrimidine synthesis from an old dog[11]. The heterocyclic system constitute privileged substructures and are present in a large number of compounds with remarkable biologicl activity [12]. Although, the MCR strategy is a highly desirable approach in drug discovery development in the context of rapid identification, structural diversification and optimization of biologically active lead compounds of potential therapeutic importance within a short span of time which can generate large number of libraries of heterocyclic compounds with the aid of high through put biological screening .

Result & Discussion:

The phosphoric acid is an on expensive reagent acts as an acid & the dehydrating reagent also. In the presence of the phosphoric acid the Biginell Reaction Satisfactory fulfilled the entire above requirements. The phosphoric acid increases in the acidic condition of the reaction mixture & due to which the rate of the reaction is increases which leads to shorter reaction time.

In this communication, we report the used of phosphoric acid for one pot multicomponent synthesis of 3,4 – dihydropyrimidinones. As in the trial case, benzaldehyde (1.06 gm, 10 m moles), ethyl acetoacetate (1.30 gm , 10 m moles), urea (1.80 gm,30 m moles)and phosphoric acid (0.5 gm, 30.54 m moles) urea mixed thoroughly & the reaction mixture refluxed on water bath. After the completion of the reaction, the mixture was poured on the crushed ice (100 gm) after the stirring the desired dihydropyrimidinones separated out as a white solid in the quantitative yield.(Scheme – 1) However excess addition of phosphoric acid does not increases the yield of product.

Effect of the amount of the phosphoric acid on the yield of 3,4-dihydropyrimidin-2(1H)-one was investing by using amount of phosphoric acid.

In this (Scheme-II) again the excess amount of the addition of ammonia does not affect the yield of reaction.

As per our observation 100 mg phosphoric acid gives 30-40 % yield, 200 mg of phosphoric acid gives 55-60% yield, 300 mg gives 60-70 % yield ,400mg gives 75-80% yield while 500mg of phosphoric acid gives 85-90% yield in the refluxing ethanol. Using the optimized quantity of the phosphoric acid was extended to a variety of aldehyde including aromatic, aliphatic, as well as heterocyclic aldehydes to afford corresponding dihydropyrimidinones in the excellent yields. The versatility of the method was then checked by using thio urea instead of urea to prepare dihydropyrimidinones & by replacing EAA with MAA. Which gave the corresponding DHPMs. Both these variations did not affect appreciably the yield as well as case of work up procedure. And these result are summarized in Table -1

Reaction:

Scheme: I

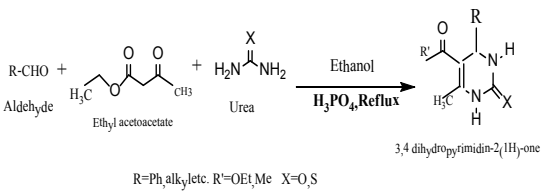
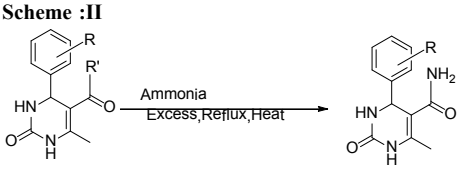


Table:1 Data for the synthesis of corresponding 3,4-dihydropyrimidin-2(1H)-one in the presence of phosphoric acid :

Entry	R	R'	X	Time (hrs)	% Yield	M.P.(oC)
1	C_6H_5	OEt	O	1.0	95%	203-204(204) ^oC
2	$4(NO_2)$-C_6H_4	OEt	O	1.0	95%	207-208(210) ^oC
3	$3(OCH_3)$ -C_6H_4	OEt	O	1.45	89%	189-190(190) ^oC
4	$4(OC_2H_5)$-C_6H_4	OEt	O	1.45	90%	196-197(195) ^oC
5	4(Cl)-C_6H_4	OEt	O	0.5	95%	217-218(210) ^oC
6	C_6H_5	Me	O	1.50	90%	207-208(210) ^oC
7	$4(NO_2)$-C_6H_4	Me	O	3.0	80%	188-189(190) ^oC
8	4(OH)-C_6H_4	Me	O	3.30	80%	209 ^oC
9	4(OCH3)-C_6H_4	OEt	O	1.5	90%	203 ^oC
10	4(Br)-C_6H_4	OEt	O	2.0	92%	216 ^oC
11	2(Cl)-C_6H_4	OEt	O	1.20	88%	218 ^oC
12	4(F)-C6H4	OEt	O	1.40	86%	207 ^oC

Scheme :II



Where R'=OCH_3 or OC_2H_5

R=Ph or alkyl group

Table:2 Data for the synthesis of different amide from 3,4-dihydropyrimidin-2(1H)-one :

Entry	R	R'	X	Time(hrs)	% Yield	M.P.(oC)
1	C_6H_5	OEt	O	3.50	90%	189 ^oC
2	$4(NO_2)$-C_6H_4	OEt	O	3.40	90%	202 ^oC
3	2(Cl)-C_6H_4	OEt	O	3.50	90%	213 ^oC
4	$4(OC_2H_5)$-C_6H_4	OEt	O	3.20	90%	192 ^oC
5	4(OH)-C_6H_4	OEt	O	3.45	83%	235 ^oC
6	4(Cl)-C_6H_4	OEt	O	4.00	92%	222 ^oC
7	$4(OCH_3)$ -C_6H_4	OEt	O	3.10	92%	212 ^oC
8	4(Br)-C_6H_4	OEt	O	3.30	90%	201 ^oC
9	$3(NO_2)$-C_6H_4	OEt	O	3.25	89%	197 ^oC
10	3(Br)-C_6H_4	OEt	O	3.30	84%	213 ^oC

Experimental Section :

All the compounds are reported one and their melting points are matched with reported value. All the above products have been characterized by proton NMR. The 1H-NMR spectra were recorded by using DMSO solvent on a Brucker 300MHz spectrometer with tetra-methyl silane as an internal standard and the reaction was monitored by TLC using silica gel 60-F 254 plates.

General Procedure :

For Scheme-I, the mixture of an aldehyde(10mmoles), urea/thiourea (30mmoles), ethyl acetoacetate/ acetyl acetone (10mmoles) and the phosphoric acid (0.5 gm, 3.54 mmoles) in a 250 ml round bottom flask refluxed on water bath , cooled and the reaction mixture was poured on crushed ice. The separated solid was then filtered, washed with pet ether, dried and recrystalized using ethanol.

For Scheme-II, The mixture of an dihydropyrimidinones(0.75 gm) and ammonia (15-20 ml) in a 250ml round bottom flask and refluxed on water bath, cooled the flask and the given mixture is added into the crushed ice (100gm).

The separated solid was then filtered, washed with pet ether, then dry the product and recrystalized by using ethanol.

Spectroscopic Data of Different Compounds :-

Scheme-I (Spectroscopic Data of Representative DHPMs)

1) 5-Ethylcarbonyl-4(phenyl)-6-methyl,3,4-dihydropyrimidine-2(1H)-one (Entry 1):- m.p.203-204^{0}c (Lit m. p. 204^{0}c) PMR (DMSO) : 5.3 (1H,bs,NH), 7.39(5H,m,ArH),8.24(1H, bs, NH),2.34(3H,SCH_3),1.16 (3H,t,$COCH_2CH_3$).

2) 5-Ethylcarbonyl4-(4-nitrophenyl)-6-methyl-3,4 dihydropyrimidin-2(1H)-one (Entry 2):m. p.207-208^{0}c (Lit. m. p. 210^{0}c) PMR (DMSO) :5.1 (1H,bs,NH),7.2 (5H,m,ArH), 9.1 (1H,bs,NH), 2.25(3H,S,CH_3), 1.12(3H,t,$COCH_2CH_3$).

3) 5-Ehoxycarbonyl-4-(4-ethoxyphenyl)-6-methyl-3,4 dihyropyrimidin-2(1H)-one (Entry 4) : m. p. 196-197^{0}c (Lit. m. p. 195^{0}c) PMR(DMSO): 5.1, (1H,bs,NH), 7.1 (5H, m, ArH), 9.1(1H,bs,NH), 2.5(3H,S,CH_3), 1.12(3H,t,$COCH_2CH_3$).

4) 5-Ethoxycarbonyl-4-(2-Chlorophyenyl) -6 methyl- 3,4 dihydropyrimidin-2 (1H) –one (Entry 9): m. p. 217-218^{0}c (Lit. m. p. 210^{0}c) PMR(DMSO): 5.6, (1H,bs, NH), 7.3 (5H,m,ArH), 9.2 (1H bs, NH) ,2,29 (3H, S,CH_3), 101 (3H,t, $COCH_2CH_3$).

Scheme-II (Spectroscopic Data of Different Amides)

1) 5-amido-4(phenyl)6-methyl,3,4-dihydropyrimidin-2(1H)-one (entry 1) : M.P.(189 ^oC)

PMR(DMSO):5.3(1H,bs,NH),7.39(5H,m,ArH),8.24(1H,bs,NH),

2.34(3H,S,CH_3),1.16(3H,t,$COCH_2CH_3$).

2) 5-amido-4(4-methoxy phenyl)6-methyl,3,4-dihydropyrimidin-2(1H)-one (entry 3) :M.P.(212 ^oC)

PMR (DMSO):5.1(1H,bs,NH),7.1(5H,m,ArH),

9.1(1H,bs,NH),2.5(3H,s,CH3),1.12(3H,t,COCH2CH3

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