Synthesis of different Amide from the 3,4-Dihydropyrimidin-2(1H)-one by using ammonia as a solvent via Biginelli.

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Abstract:

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.

In 1893, P. Biginelli 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. In the past decades, this long-neglected multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties assoiated with this dihydropyrimidine scaffold. In this account , we highlight recent developments in the Biginelirection in areas such as solid-phase synthesis, ombinatorial chemistry, and natural product synthesis.

The newly synthesized different aide derivatives of the 3,4, dihydropyrimidinon-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 coumpound have been discussed in this paper.

Keywords: 3,4-Dihydropyrimidinone, amide, ammonia etc.

Introduction:

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. [1-5] Multicomponent reactions stragies offer significant advantages over the conventional linear type synthesis. 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.[1-5] The search and discovery for new MCRs on one hand[6], and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations.

One such MCR that belongs in the latter category is the venerable Biginellidihydropyrimidinone synthesis. In a893, Italian Chemist PietroBiginelli reported on the acid catalysedcyclocondensation reaction of ethyl acetoacetate, aldehyde and urea[7]. The reaction was carried out by simply heating a mixture of the three components dissolved in etanol with a catalytic amount of HCl at reflux temperature.

The product of this novel one-pot, three component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1H)-ones. The recent advances in the

BiginelliDihydropyrimidine synthesis again C. Oliver Kappe proposed a new tricks for the same dihydropyrimidine synthesis from an old dog[8]. The heterocyclic system constitute privileged substructures and are present in a large number of compounds with remarkable biologicl activity [9]. 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 coumpounds of potential therapeutic importance within a short span of time which can generate large number of libraries of heteroyclic compounds with the aid of high through put biological screening[10].

Multicomponent synthesis of tetrahydropyrimidinethiones via condensation four component aromatic aldehyde ,enaminone, aromatic amine and thiourea also affords products with excellent diastereoselectivity at room temperature[11] . In the past decades, a broad range of the biological effects, including antiviral, antitumor, antibacterial and anti-inflammatory activities , has been ascribed to these partly reduce pyrimidine derivatives[12]. More recently, appropriantely functionalized DHPMs have emerged as for example, orally active antihypertensive agents[13-15] or α1a adrenoceptor-seletive antagonists[16].

A very recent highlight in this context has been the identification of the structurally rather simple DHPMs monastrol as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest[17]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with intresting biological activities containing the dihydropyrimidine-5-carboxylate core have recently ben isolated[17]. Monastrol Specifically inhibits the mitotic kinesin Eg5 motor protein and can be considred as a new lead for the development of anticancer drugs[18].

The intense activity in the field of dihydropyrimidine chemistry during the past decade.From both academic and industrial laboratories. In this account, recent developments in the long-neglected Biginelli Reaction are reviewed, with special emphasis placed on novel synthetic methodology from our laboratory, in addition to solid-phase and stereoselective DHPM synthesis.

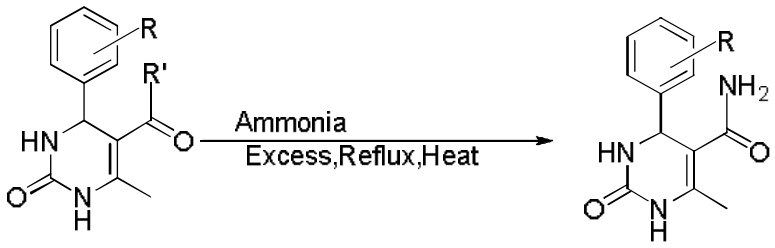
Result and Discussion:

The Phosphuric acid act as a dehydrating agent and act as a acid. In the presence of phosphuric acid the Biginelli reaction satisfactorily fulfilled the entire above requirements. The ammonia act as a solvent, when the excess of ammonia is react with the dihydropyrimidinone, then the ethoxy group from the dihydropyrimidinone is react with ammonia and that group is replaced by $-NH_2$ group. So in this way formation of different amide derivatives takes-place.

In this communication, we report the use of ammonia for the synthesis of amide from the 3,4-dihydropyrimidin-2(1H)-ones. As in the trial case, the 3,4 dihydropyrimidin-2(1H)-ones (0.75gm) and the 15-20 ml of ammonia mixed thoroughly , and the reaction mixture refluxed on water bath. After the completion of the reaction mixture , the mixture was poured into the crushed ice.(100 gm), after the stirring, the desired amide product separated out as a white solid in the

quantitative yield. (Scheme-I). The same reaction then attempted with the variable quantities of ammonia. However excess addition of ammonia does not increases the yield of product.

Reaction:



Where R'=OCH_3 or OC_2H_5

R=Ph or alkyl group

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

Entry	R	R'	X	Time(hrs)	% Yield	M.P.(oC)	Solubility
1	C_6H_5	OEt	O	3.50	90%	189 ^oC	DMSO
2	4(NO_2)-C_6H_4	OEt	O	3.40	90%	202 ^oC	DMSO
3	4(OCH_3) -C_6H_4	OEt	O	3.10	92%	212 ^oC	DMSO
4	4(Br)-C_6H_4	OEt	O	3.30	90%	201 ^oC	DMSO
5	4(OH)-C_6H_4	OEt	O	3.45	83%	235 ^oC	DMSO
6	4(Cl)-C_6H_4	OEt	O	4.00	92%	222 ^oC	DMSO
7	2(Cl)-C_6H_4	OEt	O	3.50	90%	213 ^oC	DMSO
8	4(OC_2H_5)-C_6H_4	OEt	O	3.20	90%	192 ^oC	DMSO
9	4(F)-C_6H_4	OEt	O	3.50	85%	198 ^oC	DMSO
10	4(I)-C_6H_4	OEt	O	3.50	80%	209 ^oC	DMSO
11	3(NO_2)-C_6H_4	OEt	O	3.25	89%	197 ^oC	DMSO
12	3(Br)-C_6H_4	OEt	O	3.30	84%	213 ^oC	DMSO

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:

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.

Spetroscopic Data of Different Amides :

1.5-amido-4(phenyl)6-methyl,3,4-dihydropyrimidin-2(1H)-one (entry 1) : M.P.(189 ^{O}C)

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 ^{O}C)

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

Acknowledgement:-

The authors are very thankful to the Principal of G. S. Science, Arts and Commerce College, Khamgaon, for providing the necessary facilities in the Laboratory and also to, CDRI, Lucknow for providing the spectral analysis.

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