



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 associated with this dihydropyrimidine scaffold. In this account, we highlight recent developments in the Biginelli reaction in areas such as solid-phase synthesis, combinatorial chemistry, and natural product synthesis.

The newly synthesized different amide derivatives of the 3,4, dihydropyrimidinon-2(1H)-one were well monitored 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.

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

Introduction :

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.¹⁻⁵ Multicomponent reaction strategies 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 portions of all the components.¹⁻⁵ The search and discovery for new MCRs on one hand⁶, 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 Biginelli dihydropyrimidinone synthesis. In 1893, Italian Chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethyl acetoacetate, aldehyde and urea⁷. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol 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





Biginelli Dihydropyrimidine synthesis again C. Oliver Kappe proposed a new tricks for the same dihydropyrimidine synthesis from an old dog⁸. The heterocyclic system constitute privileged substructures and are present in a large number of compounds with remarkable biological activity⁹. 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 throughput biological screening¹⁰.

Multicomponent synthesis of tetrahydropyrimidinethiones via condensation four component aromatic aldehyde, enaminone, aromatic amine and thiourea also affords products with excellent diastereo selectivity at room temperature¹¹. 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 derivatives¹². More recently, appropriately functionalized DHPMs have emerged as for example, orally active antihypertensive agents¹³⁻¹⁵ or α_1 adrenoceptor-selective antagonists¹⁶.

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 arrest¹⁷. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated¹⁷. Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs¹⁸.

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

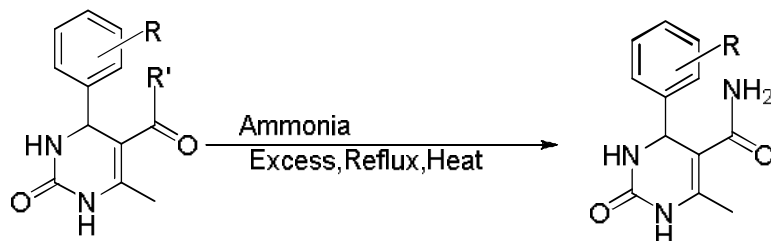
In this communication, we report the use of ammonia for the synthesis of amide from the 3,4-dihydropyrimidin-2(1H)-ones. As in the trial case, the 3,4-dihydropyrimidin-2(1H)-ones (0.75 gm) and the 15-20 ml of ammonia mixed thoroughly, and the reaction mixture refluxed on water bath. After the completion 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 increase the yield of product.

Reaction:



Where R'=OCH₃ or OC₂H₅

R=Ph or alkyl group

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 Bruker 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 recrystallized by using ethanol.

Spectroscopic Data of Different Amides :

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

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

2.34(3H,s,CH₃),1.16(3H,t,COCH₂CH₃).

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





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 ₆ H ₅	OEt	O	3.50	90%	189 °C	DMSO
2	4(NO ₂)-C ₆ H ₄	OEt	O	3.40	90%	202 °C	DMSO
3	4(OCH ₃)-C ₆ H ₄	OEt	O	3.10	92%	212 °C	DMSO
4	4(Br)-C ₆ H ₄	OEt	O	3.30	90%	201 °C	DMSO
5	4(OH)-C ₆ H ₄	OEt	O	3.45	83%	235 °C	DMSO
6	4(Cl)-C ₆ H ₄	OEt	O	4.00	92%	222 °C	DMSO
7	2(Cl)-C ₆ H ₄	OEt	O	3.50	90%	213 °C	DMSO
8	4(OC ₂ H ₅)-C ₆ H ₄	OEt	O	3.20	90%	192 °C	DMSO
9	4(F)-C ₆ H ₄	OEt	O	3.50	85%	198 °C	DMSO
10	4(I)-C ₆ H ₄	OEt	O	3.50	80%	209 °C	DMSO
11	3(NO ₂)-C ₆ H ₄	OEt	O	3.25	89%	197 °C	DMSO
12	3(Br)-C ₆ H ₄	OEt	O	3.30	84%	213 °C	DMSO

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References :

- 1 **Armstrong, R.W.;** Combs, A.P.; Tempest, P.A.; Brown, S.D.; Keating, T.A. Multiple component condensation strategies for combinational library synthesis. *Acc. Chem. Res.* 1996,29,123-131.
- 2 **Ugi,I.; Domling, A.; Horl, W.** Multicomponent Reactions in organic chemistry. *Endeavour* 1994,18,115-122.
- 3 **Dax, S.L.; McNally, J.J.; Youngman, M.A.** Multi-component Methodologies in solid phase organic synthesis. *Curr.Opin.Chem.Biol.* 1999,6,255-270.
- 4 **Tietze, L.F.; Lieb, M.E.** Domino Reactions for library synthesis of small molecules in combinatorial chemistry. *Curr.Opin.Chem. Biol.* 1998,2,363-371.
- 5 **Domling, A.** Isocyanide Based Multi component Reactions in combinatorial chemistry. *Comb. Chem..high throughput screening* 1998,1,1-22.
- 6 **Weber, L; Illgen, k; Almstetter, M.** Discovery of New Multicomponent Reactions with combinatorial Methods. *Synlett* 1999,3,366-374.
- 7 **Biginelli, P.** Aldehyde- Urea Derivatives of Aceto- and oxalo acetic acids. *Gazz.Chim. Ital.* 1893,23,360-413.
- 8 **Kappeoliver C. ;** Recent Advances in the Biginelli Dihydropyrimidine synthesis, *Acc. Chem.. Res.* 2000,33,879-888.
- 9 **Eicher T, Hauptmanns,** The chemistry of Heterocycles, 2nded, Wiley-VCH: Weinheim, Germany, 2003,pp 3/6.





10 **Armstrong R W , Combs A P, Tempest P A , Brown S D, Keating T A**, Acc. Chem. Res.; 1996,29,123. Ugi I , Pure Appl. Chem., 2001,73,187. Domling A, Ugi I, Angewandte Chemie International Edition., 2000,39,3151.

11 **Wan, J-P.; Wang.C.; pan. Y.** Tetrahedron 2011,67,922.

12 **Kappe, C.O.** 100 years of the Biginelli Dihydropyrimidine synthesis. Tetrahedron 1993,49, 6937-6963.

13 **Atwal, K.S.; Swanson, B.N.; Unger. S.E; Floyd, D.M.; Moreland, S; Hedberg, A; O' Reilly, B.C.** 3-CARBAMOYL-4-ARYL-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic Acid Esters as orally Effective Antihypertensive Agents. J. Med.chem. 1991,34,806-811.

14 **Rovnyak , G.C.; Atwal, K.S.; Hedberg A; Kimball, S.D.; Moreland, S, Gougoutas, J.Z; O' Reilly , B.C.; Schwartz, J; Malley, M.F.** Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic Acid Ester, Potent Antihypertensive Agent. J. Med.chem. 1992,35,3254-3263.

15 **Grover, G.J.** and et al., s. pharmacologic profile of the Dihydropyrimidine calcium channel Blockers SQ32,926. J. Cardiovasc. pharmacol. 1995,26,289-294.

16 **Nagarathnam, D.; Miao, S.W.; Lagu, B.; Chiu, .; Fang, J.; Dhar,; T.G.M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M.R.; Zhang, C.; Chang, R.S.L.; Broten, T.P.; Ransom, R.W.; Schorn, T. W.; Chen, T.B.; O'malley, S.; Kling, P.; Schnrck, K.; Benedesky, R.; Harrell, C.M.; Vyas, K.P.; Gluchowski, C.** Design and synthesis of novel Adrenoceptor-selective Antagonists. Structure-Activity Relationship in Dihydropyrimidones. J. Med. Chem. 1999.

17 **Mayer, T.U.; Kapoor, T.M.; Haggarty, S.J.; King R.W.; Schreiber, S.L.; Mitchison, T.J.** small- molecule INHIBITOR OF mitotic spindle Bipolarity Identified in a phenotype-Based Screen. Science 1999, 286,971-974.

18 **Heys, L; Moore, C.G.; Murphy, P.J.** the Guanidine metabolites of ptilocaulis spiculifer and Related Compounds, Isolation and synthesis, Chem. Soc. Rev. 2000,29,57-67.

