



A SIMPLE AND ECONOMIC SYNTHESIS OF 5-(AMINOMETHYL)-4-(SUBSTITUTED PHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES.

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ABSTRACT A Simple and Economic Synthesis of 5-(aminomethyl)-4-(substituted phenyl)-6-methyl, 3,4-dihydropyrimidin-2(1H)-ones by using 5-amido-4-(substituted phenyl), 6-methyl, 3,4-dihydropyrimidin-2(1H)-ones and Lithium Aluminium Hydride in presence of completely dry THF. Lithium aluminium hydride has been found to be effective reducing agent. Different amides can be efficiently reduced with lithium aluminium hydride (LAH) to the corresponding Mannich bases.

KEYWORDS : Lithium Aluminium Hydride, Dry THF, 5-amido-4-(substituted phenyl)- 6-methyl-3,4-dihydropyrimidin-2(1H)-ones etc.

Introduction: Drug discovery may also require fundamental research into biological and chemical nature of the diseased state.

Drugs are the versatile molecule used as medicines or as components in medicine to diagnose cure, mitigate, treat or prevent disease. Medicinal Chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful medicines. The discovery of a new drug not only requires a design process but also the synthesis of the drug, a method of administration, the development of tests and procedures to establish how it operates in the body and its safety assessment. These and other aspects of drugs design and discovery require input from specialists from many other fields and so medicinal chemists need to have outline knowledge of the relevant aspects of these fields.

The Azetidin-2-ones, commonly known as β -lactams, are well known heterocyclic compounds among the organic and medicinal chemists mainly because of their antimicrobial and diverse pharmacological activities. The β -lactam antibiotics are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity^{1,2}. The most widely used antibiotics such as the Penicillins, Cephalosporins, Carumonam, Aztreonam, Thienamycin and the Nocardicins contains β -lactam (azetidin-2-one) ring³. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules, 2-azetidinones have played an important role in medicinal chemistry.

Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity⁴. Azetidinones are of great biological interest, especially as it possess antidepressant⁵, anticonvulsant⁶, cholesterol absorption inhibitors⁷, antimicrobial⁸, anti tubercular⁹, antiviral¹⁰ and antifungal¹¹ activity. Schiff bases have received more attention mainly because of their wide biological activities including anti-tumor¹², antibacterial¹³, fungicidal¹⁴, anti-inflammatory¹⁵, antiviral¹⁶, herbicidal¹⁷, antipyretic¹⁸ and anticonvulsant¹⁹. Schiff bases and their cyclization to produce β -lactam derivatives of biological significance²⁰.

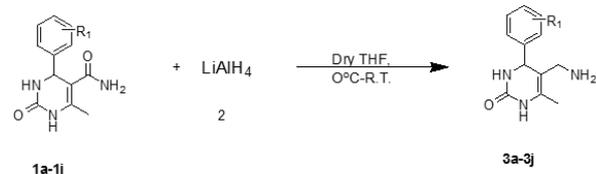
In recent years, renewed interest has been focused on the synthesis and modification of β -lactam ring to obtained compounds with diverse pharmacological activities like antitubercular²¹, anticonvulsant²², antibacterial²³, antidiabetic²⁴, anticancer²⁵, cholesterol absorption inhibitors²⁶, sedative²⁷, anti-HIV²⁸, antiparkinsonian²⁹ and anti-inflammatory³⁰. It also possess enzyme inhibitor³¹, hypoglycemic³² and human leucocytase elastase inhibitor activity³³.

Result and Discussion : In the presence of completely dry THF, the Lithium aluminium hydride easily reduces different amides into corresponding primary amines. In this communication, the reaction is occurs in between 5-amido-4-(substituted phenyl), 6-methyl, 3,4-dihydropyrimidin-2(1H)-ones (1)(0.01 mol) and Lithium aluminium

hydride (2) (0.05 mol) in presence of completely dry THF at 0°C, stirred it well for 1 h then allow it to stirred at room temperature for 4-5 hours in an inert atmosphere. After completion of reaction, the reaction mixture was poured over the crushed ice (10-20 g) and stirred it, the solid product were filtered, washed with acidified water and subsequently dried it.

The product was recrystallized from ethanol to afford pure 5-(aminomethyl)-4-(substituted phenyl)- 6-methyl, 3,4-dihydropyrimidin-2(1H)-ones (3a-3j). And these results are summarized in Table-I.

Reaction:



Scheme 1:

5-(aminomethyl)-4-(substituted phenyl), 6-methyl, 3,4-dihydropyrimidin-2(1H)-one

Where R₁ = a) -H, b) 4-OCH₃, c) 4-NO₂, d) 4-Br, e) 4-Cl, f) 4-OC₂H₅, g) 3-Cl, h) 2-Cl, i) 2-F, j) 2-OC₂H₅

Table I : Analytical data of synthesized 5-(aminomethyl)-4-(substituted phenyl)- 6-methyl-3,4-dihydropyrimidin-2(1H)-ones

Sr. No.	Comp. No.	R ₁	Reaction time	M.F.	M.W.	Yield	M.Pt (°C)
1	3a	H	4	C ₁₂ H ₁₅ ON ₃	217	60%	232 °C
2	3b	p-OCH ₃	4.50	C ₁₃ H ₁₇ O ₂ N ₃	247	65%	224 °C
3	3c	p-NO ₂	4.50	C ₁₂ H ₁₄ O ₃ N ₄	262	69%	210 °C
4	3d	p-Br	3.50	C ₁₂ H ₁₄ ON ₃ Br	295.9	72%	218 °C
5	3e	p-Cl	4	C ₁₂ H ₁₄ ON ₃ Cl	251.5	70%	235 °C
6	3f	p-OC ₂ H ₅	4	C ₁₄ H ₁₉ O ₂ N ₃	261	65%	220 °C

7	3g	m-Cl	4.50	C ₁₃ H ₁₄ ON Cl	251.5	62%	221 °C
8	3h	o-Cl	4.20	C ₁₂ H ₁₄ ON Cl	251.5	78%	225 °C
9	3i	o-F	4.30	C ₁₂ H ₁₄ ON F	235	73%	228 °C
10	3j	o-OC ₂ H ₅	4.10	C ₁₄ H ₁₉ O ₂ N ₃	261	68%	230 °C

Experimental Section: The melting points of all synthesized compounds were recorded using open capillaries and are uncorrected. The IR spectra were recorded on a PERKIN ELMER Spectrophotometer in the frequency range 4000-400 cm⁻¹ in Nujol mull and as KBr pellets. ¹H NMR spectra were recorded on BRUKER ADVANCE II 400 spectrometer with TMS as internal standard using DMSO as solvents. All the compounds are synthesized in R. B. Flask by using water condenser and refluxed for several times. Purity of the compounds were checked on pre coated silica-G plates by TLC.

Chemicals (Reagents) used in the synthesis of 5-(aminomethyl)-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones, were of AR grade.

General Procedure : The equimolar amount of 5-amido-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (1a-lj) (0.01 mol) and Lithium aluminium hydride (2) (0.05 mol) in presence of completely dry THF at 0°C, stirred it well for 1 h then allow it to stirred at room temperature for 4-5 hours in an inert atmosphere. After completion of reaction, the reaction mixture was poured over the crushed ice (10-20 g) and stirred it, the solid product were filtered, washed with acidified water and subsequently dried it.

The product was recrystallized from ethanol to afford pure 5-(aminomethyl)-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (3a-3j).

Spectroscopic data of Representative 5-(aminomethyl)-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones :

1. 5-(aminomethyl)-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-1): m.p 232°C ,IR(KBr) :[cm⁻¹] 3422, 1000, 1683, 1367, 708 ; PMR (DMSO-d6) :6.0(1H,bs,NH),7.3(4H,m,ArH),6.2(1H,bs,NH),2.26(3H,s,CH₃),8.7(2H,t,NH₂).

2. 5-(aminomethyl)-4-(4-methoxy-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-2): m.p 224°C ,IR(KBr) :[cm⁻¹] 3378, 1017, 1685, 1466, 686 ; PMR (DMSO-d6) :5.2(1H,bs,NH),7.2(4H,m,ArH),7.5(1H,bs,NH),2.3(3H,s,CH₃),8.5(2H,t,NH₂).

3. 5-(aminomethyl)-4-(4-nitro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-3): m.p 210°C ,IR(KBr) :[cm⁻¹] 3406, 1079, 1647, 3104, 1586, 736 ; PMR (DMSO-d6) :7.6(1H,bs,NH),8.2(4H,m,ArH),5.3(1H,bs,NH),2.1(3H,s,CH₃),8.7(2H,t,NH₂).

4. 5-(aminomethyl)-4-(4-bromo-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-4): m.p 218°C ,IR(KBr) :[cm⁻¹] 3406, 1041, 1601, 1394, 541 ; PMR (DMSO-d6) :8.6(1H,bs,NH),7.5(4H,m,ArH),5.2(1H,bs,NH),2.0(3H,s,CH₃),6.9(2H,t,NH₂).

5. 5-(aminomethyl)-4-(4-chloro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-5): m.p 235°C ,IR(KBr) :[cm⁻¹] 3020, 1237, 1759, 1536, 749 ; PMR (DMSO-d6) :8.6(1H,bs,NH),7.3(4H,m,ArH),5.2(1H,bs,NH),2.0(3H,s,CH₃),6.8(2H,t,NH₂).

6. 5-(aminomethyl)-4-(4-ethoxy-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-6): m.p 220°C ,IR(KBr) :[cm⁻¹] 3022, 1041, 1759, 1446, 756 ; PMR (DMSO-d6) :8.5(1H,bs,NH),6.8(4H,m,ArH),5.1(1H,bs,NH),2.0(3H,s,CH₃),7.1(2H,t,NH₂).

7. 5-(aminomethyl)-4-(3-chloro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-7): m.p 221°C ,IR(KBr) :[cm⁻¹] 3429, 1377, 1642, 1572, 688 ; PMR (DMSO-d6) :5.2(1H,bs,NH),7.3(4H,m,ArH),8.6(1H,bs,NH),2.0(3H,s,CH₃),6.9(2H,t,NH₂).

8. 5-(aminomethyl)-4-(2-chloro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-8): m.p 225°C ,IR(KBr) :[cm⁻¹] 3451, 1113, 1687, 1431, 743 ; PMR (DMSO-d6) :5.6(1H,bs,NH),7.3(4H,m,ArH),8.6(1H,bs,NH),2.0(3H,s,CH₃),6.8(2H,t,NH₂).

9. 5-(aminomethyl)-4-(4-fluoro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-9): m.p 228°C ,IR(KBr) :[cm⁻¹] 3408, 1284, 1686, 1581, 750 ; PMR (DMSO-d6) :5.4(1H,bs,NH),7.2(4H,m,ArH),8.6(1H,bs,NH),2.0(3H,s,CH₃),6.9(2H,t,NH₂).

10. 5-(aminomethyl)-4-(2-chloro-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.(entry-10): m.p 230°C ,IR(KBr) :[cm⁻¹] 3418, 1040, 1674, 1473, 746 ; PMR (DMSO-d6) :8.5(1H,bs,NH),6.8(4H,m,ArH),5.4(1H,bs,NH),2.56(3H,s,CH₃),7.2(2H,t,NH₂).

In the conclusion, we have developed a simple quick and efficient method or the synthesis of 5-(aminomethyl)-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones by using Lithium aluminium hydride and dry THF. Apart from its Simplicity, the important advantage of the present protocol is the ability to tolerate variations in all the three components of the reaction. To the best of our knowledge, this is one of the quickest, economical and simple alternatives towards the synthesis of the 5-(aminomethyl)-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones. This introduces another important use of Lithium aluminium hydride in the synthetic Organic Chemistry.

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