One-Pot Synthesis of Dihydropyrimidin-2(*1H*)-ones Catalyzed by Ceric (IV) Ammonium Nitrate (CAN) under Solvent Free Conditions

Eman A. Ahmed*, Mounir A. A. Mohamed and Ahmed M. M. El-Saghier

Chemistry Department, Faculty of Science, Sohag University, 82524 Sohag, Egypt
abdala_15@yahoo.com; mounir_abbas@yahoo.com; el_saghier@yahoo.com

Abstract: Abstract: An efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones or thiones is described using ceric ammonium nitrate (CAN) as a catalyst in the reaction of an aromatic aldehyde, β-ketoester and urea or thiourea under solvent free conditions in terms of excellent yields and very short reaction time.
[Eman A. Ahmed, Mounir A. A. Mohamed and Ahmed M. M. El-Saghier. **One-Pot Synthesis of Dihydropyrimidin-2(*1H*)-ones Catalyzed by Ceric (IV) Ammonium Nitrate (CAN) under Solvent Free Conditions.** *J Am Sci* 2012;8(8):815-818]. (ISSN: 1545-1003). http://www.jofamericanscience.org.122

Keywords: Biginelli reaction, 3,4-dihydropyrimidin-2(1*H*)-ones, solvent free conditions, ceric ammonium nitrate (CAN).

1. Introduction

Many of 3,4-dihydropyrimidin-2(*1H*)-ones and their derivatives which named Biginelli compounds are medically important as calcium channel blockers, antihypertensive agents, α-1_a-adrenergic receptor antagonist, anti-inflammatory and antimicrobial.[1-4] Also, their structures have been found in some natural marine alkaloids which reported to inhibit binding of HIVgp-120 to CD4 cells opening a new field in AIDS therapy.[5]

Cerium(IV) ammonium nitrate (CAN) is a convenient and widely used catalyst for affecting a broad spectrum of synthetic transformations because it has many advantages such as: solubility in water, inexpensiveness, eco-friendly nature, simplicity in handling and convenient work-up.[6,7] CAN has long been used in organic synthesis as both oxidant and Lewis acid for functional-group conversion and promotion of bond-forming reactions.[8,9]

2. Experimental

All melting points were determined on a Koffler melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker avance 300 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm), IR spectra were obtained on a Bruker FT-IR ISS 25 spectrophotometer (KBr, ν_{max} in cm^{-1}) and mass spectra were recorded on Shimadzu Qp-2010 Plus (EI 70 eV) instrument.

General Procedure for synthesis of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(*1H*)-one and 3,4-dihydropyrimidin-2(*1H*)-thione (1-20):

A mixture of aromatic aldehyde (10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea or thiourea (15 mmol) and ceric ammonium nitrate (10 mmol%) was heated with stirring at 80-90 ^oC for appropriate time (Table 1). The progress of reaction was monitored by TLC, after completion of the reaction, crushed ice was added, the solid product was filtered off, washed with ice-cold water, dried and recrystalized from ethanol. The structures of the new synthesized compounds were established on the basis of their spectral data (IR, ^{1}HNMR and MS spectra).

Spectroanalytical data for new compounds : 5-Ethoxycarbonyl-6-methyl-4-(3,4-dihydroxyphenyl)-3,4-dihydropyrimidin-2(*1H*)-one (10):

IR(KBr):3400, 3312,1670 Cm^{-1} **:** ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.10(t, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.90(q, 2H, - CH_2-O), 4.80 (s, 2H, 2OH), 5.30 (s,1H, CH-Ar), 6.50-7.00 (m, 3H, CH arom.), 8.50 (s,1H,NH), 9.40(s,1H, NH): MS (EI 70 eV, 200 °C): m/z (%) =292 (64), 263 (100) [M], 247 (27), 219 (44), 183 (81), 176 (20), 155 (79), 136 (79), 109 (60), 77 (38), 69 (39).

5-Ethoxycarbonyl-6-methyl-4-(3,4-dihydroxyphenyl)-3,4-dihydropyrimidin-(*1H*)-thione (20):

IR(KBr):3397, 3317,3247, 1670 Cm^{-1}**:** ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.20(t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.80(q, 2H, -CH_2-O), 4.80 (s, 2H, 2OH), 5.30 (s,1H, CH-Ar), 6.50-7.00 (m, 3H, CH arom.), 8.40 (s,1H,NH), 9.40(s,1H, NH) : MS (EI 70 eV, 200 °C): m/z (%) =309 (18), 308 (28), 308 (80), 279 (54), 262 (54), 234 (74), 219 (26), 200 (26), 198 (100) [M], 174 (32), 171 (58), 153 (31), 136 (22), 118 (31), 110(19),77(49), 67 (50).

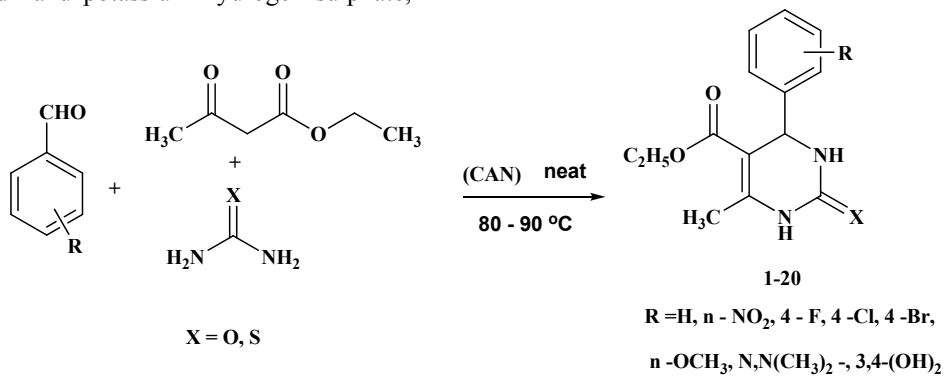
3. Results and Discussion

The original one-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones was firstly reported by Pietro Biginelli in 1893 performing the three components cyclocondensation reaction of ethyl

acetoacetate, benzaldehyde and urea under Bronsted acid catalysis.[10]

In recent years, attention of this reaction has increased rapidly and several modified procedures have been reported to improve the efficiency of the Biginelli dihydropyrimidine synthesis. For example modifications by using Lewis acids such as ytterbium triflate[11], bismuth triflate[12], cupric chloride[13], manganese triacetate,[14] copper(Π)triflate,[15] ferric chloride,[16] nickel chloride[16] and zirconium(iv)chloride,[17] as well as by using Bronsted acids such as *p*-toluenesulphonic acid[18], silica sulphuric acid[19] and potassium hydrogen sulphate,[20] or using basic condition via phase transfer catalysis.[21] In our survey, CAN was used as a catalyst in Biginelli reaction in presence of methanol as a solvent under sonication for 3-7 h.[22]

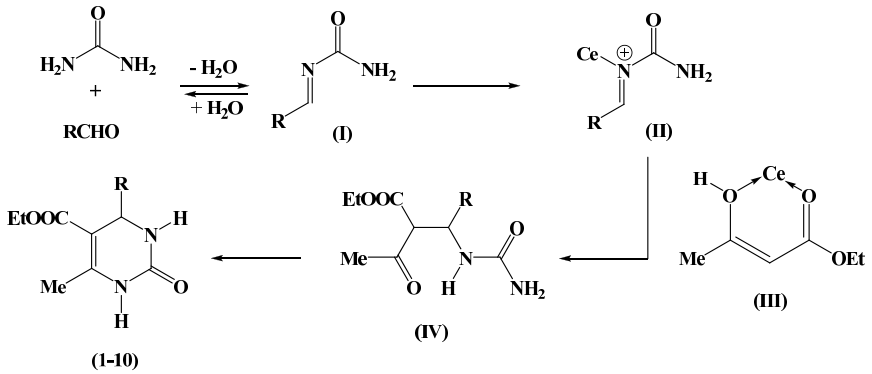
In continuation of our interest in the synthesis of fused pyrimidines,[23] herein we report a simple, efficient, very short time path (30-110 sec) and high yielding procedure for the one-pot, three component synthesis of some 3,4-dihydropyrimidin-2(*1H*)-one derivatives **1-20** using ceric ammonium nitrate (CAN) as a catalyst under solvent-free conditions through the Biginelli reaction (Scheme 1).



Scheme 1

Initially we studied a model reaction employing benzaldehyde, ethyl acetoacetate and urea in the presence of four different molar ratios of CAN (2, 5, 10 and 15 mol %) in order to investigate the catalytic efficiency of CAN, and to establish the optimum quantity of this catalyst and our study has revealed that 10 mol% of the catalyst was the optimum ratio. Synthesis of 3,4-dihydropyrimidine-2(*1H*)-ones **1-10** and 3,4-dihydropyrimidine-2(*1H*)-thiones **11-20** has been depicted in Scheme 1. Further reactions of aromatic aldehydes were carried out under the same experimental reaction conditions and the results of these reactions were summarized in Table 1.

Although different mechanistic pathways have been previously proposed,[24,25] we believe that the reaction may proceed through an initially N-acylimine (**I**) formed from the reaction of the aldehyde and urea, Scheme 2. The coordination of the lone-pair of the nitrogen atom in the N-acylimine (**I**) with the Lewis acid CAN could lead to the *in situ* formation of N-carbamoyliminum ion (**II**) which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate (**III**) affording the open chain intermediate (**IV**). Finally, intramolecular cyclization with loss of H_2O molecule, producing the 3,4-dihydropyrimin-2(*1H*)-ones **1-10**.



Scheme 2

The IR and ^{1}H-NMR spectral data of the obtained compounds **1-20** were compatible with the proposed structures as well as the melting points were in accordance with those reported in literature.

In conclusion, we have developed a simple, eco-friendly and efficient method for the synthesis of a variety of dihydropyrimidin-2(*1H*)-ones as biologically active compounds *via* improved Biginelli-type reaction catalyzed by CAN. This method does not involve the use of toxic solvents thus; it is an environmentally friendly process.

Table 1: Analytical and experimental data of the obtained compounds **1-20**.

Comp. No.	Substitution R	Substitution X	Molecular formula	Melting point (°C) Found	Melting point (°C) reported	Time (sec)	Yield (%)
1	H	O	$C_{14}H_{16}N_2O_3$	203-205	204-206 [21]	60	96
2	2-nitro	O	$C_{14}H_{15}N_3O_5$	218-219	216-218 [21]	80	92
3	3-nitro	O	$C_{14}H_{15}N_3O_5$	223-225	225-227 [21]	70	97
4	4-Fluoro	O	$C_{14}H_{15}FN_2O_3$	185-187	186-188 [21]	50	88
5	4-chloro	O	$C_{14}H_{15}ClN_2O_3$	206-208	207-209 [21]	90	97
6	4-bromo	O	$C_{14}H_{15}BrN_2O_3$	210-212	215 [22]	100	94
7	4- methoxy	O	$C_{15}H_{18}N_2O_4$	199201	203 [22]	80	93
8	2-methoxy	O	$C_{15}H_{18}N_2O_4$	246-248	255-257 [26]	70	98
9	4-N,N-dimethyl	O	$C_{16}H_{21}N_3O_3$	238-240	230-232 [27]	100	96
10	3,4-dihydroxy	O	$C_{14}H_{16}N_2O_5$	230-232	---	100	97
11	H	S	$C_{14}H_{16}N_2O_2S$	203-204	206 [22]	70	87
12	2-hydroxy	S	$C_{14}H_{16}N_2O_3S$	205207	206-208 [21]	90	95
13	3-nitro	S	$C_{14}H_{15}N_3O_4S$	200-202	206-207 [15]	110	89
14	4-fluoro	S	$C_{14}H_{15}FN_2OS$	184-186	191-192 [28]	100	86
15	4-chloro	S	$C_{14}H_{15}ClN_2O_2$ S	190-192	183-184 [28]	100	90
16	4-bromo	S	$C_{14}H_{15}BrN_2O_2S$	192-19	195-196 [29]	100	92
17	4- methoxy	S	$C_{15}H_{18}N_2O_3S$	143-145	141-143 [21]	90	92
18	2- methoxy	S	$C_{15}H_{18}N_2O_3S$	200-202	201-202 [29]	90	98
19	4-N,N-dimethyl	S	$C_{16}H_{21}N_3O_2S$	206-208	209-210 [17]	110	96
20	3,4-dihydroxy	S	$C_{14}H_{16}N_2O_4S$	226-228	---	100	95

Corresponding author
Mounir A. A. Mohamed
Chemistry Department, Faculty of Science, Sohag University, 82524 Sohag, Egypt
mounir_abbas@yahoo.com;

References

1. Tabern, D. L.; Volwiler, E. H. Sulphur-containing barbiturate hypnotics, J. *Am. Chem. Soc.* **1935**, *57*: 1961.
2. Atwal, K. S.; Rovyak, G. C.; Reilly, B. C. O.; Schwartz, J. Substituted 1,4-dihydropyrimidinones. 3. Synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidinones *J. Org. Chem.* **1989**, *54*: 5898-5907.
3. Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab-initio, semiempirical and X-ray crystallographic studies, *Tetrahedron*, **1997**, *53*:2803-2816.
4. Grover, G. I.; Dzwonzyk, S.; McMullen, D. M. ; Normadin, D. E.; Paraham, C. S.; Steph, P.G.; Moreland, S. Pharmacologic Profile of the Dihydropyrimidine Calcium Channel Blockers SQ 32,547 and SQ 32,946, *J. Cardiovasc. Pharmacol.* **1995**, *26*: 289-294.
5. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrossi, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westly, J. W.; Potts, B. C. M. Novel Alkaloids from the sponge Batzella sp: inhibitors of HIV gp 120-human Cd4 Binding *J. Org. Chem.* **1995**, *60*:11821188.
6- Sadek K. U., Alnajjar A., Mekheimer R. A., Mohamed N. K., Mohamed H. A. Cerium(IV) Ammonium Nitrate (CAN) Mediated Reactions IV: A Highly Efficient Synthesis of N,N'-diarylsubstituted Formamidines in Water at Ambient Temperature, *Green and Sustainable Chemistry*, **2011**, 1: 92-97.
7- Mekhalifa A., Metter R. Heal W. Chen B. Unexpected Formation of N,N-Disubstituted Formamidines from Aromatic Amines, Formamidines and Trifluroacetic Anhydride. *Tetrahedron*, **2006**, 62(24):5617-5625.
8- Devery J. J., Mohanta P. K., Casey B. M. Flowers R. A. Facile Route to Tetrasubstituted Pyrazoles Utilizing Ceric Ammonium Nitrate, *Synlett.*, **2009**, 9: 1490-1494.
9- a) Molander G. A. Application of lanthanide reagents in organic synthesis, *Chem. Rev.*, **1992**, 92: 29-68.

b) Nair V., Mathew J., Prabhakaran J. Carbon-carbon bond forming reactions mediated by cerium(IV) reagents, *Chem. Soc. Rev.* **1997**, 26: 127-132.
10. Biginelli, P. Derivati Aldeiduredici Degli Eteri Acetile Dossal-Acetico, *Gazz.Chim. Ital.* **1893**, *23*, 360-416.
11. Ma, Y.; Qian, C.; Wang, L.; Yang, M. Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent free conditions, *J. Org. Chem.* **2000**, *65*, 3864-3868.
12. Varala, R.; Alam, M. M.; Adapa, S. R. Bismuth Triflate Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2 (1*H*)-ones: An Improved Protocol for the Biginelli Reaction, *Synlett* **2003**, 67-70.
13. Gohain, M.; Prajapati, D.; Sandhu, J. S. A facile microwave induced one-pot synthesis of novel pyrimido[4,5-d]pyrimidines and pyrido[2,3-d]pyrimidines under solvent free conditions, *Synlett* **2004**, 235
14. kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. $Mn(OAc)_3 \cdot 2H_2O$- mediated three-component, one-pot, condensation reaction: an efficient synthesis of 4-aryl-substituted 3,4-dihydropyrimidin-2-ones, *Tetrahedron Lett.* **2001**, *42*: 7873.
15. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. $Cu(OTf)_2$: a reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones, *Teterahedron Lett.* **2003**, 44(16): 3305.
16- Lu J., Bay Y. Catalysis of the Biginelli reaction by ferric and nickel chloride hexahydrates. One-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones, *Synthesis* **2002**, 4:466-470.
17. Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R. Reddy, V. V. N. Zirconium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin- 2(1*H*)-ones, *Tetrahedron Lett.* **2002**, *43*:2657-59.
18. Jin, T.; Zhang, S.; Li, T. p-Toluenesulfonic acid-catalized efficient synthesis of dihydropyrimidines: Improved high yielding protocol for the Biginelli reaction, *Synth. Commun.* **2002**, 32(12), 1847-1851.
19. Salehi, P.; Dabiri, M.; Zolfigol, M.A.; Fard, M.A.B. Silica-sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones, *Tetrahedron Lett.* **2003**, *44*, 2889-2891.
20. Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhang, Q. A new Biginelli reaction procedure using potassium hydrogen sulfate as the promoter for an efficient synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones *Synlett* **2004**, 537- 539.
21. Ahmed, B.; Khan, R. A.; Habibullah; Keshari, M. An improved synthesis of Biginelli-type compounds via phase-transfer catalysis, *Tetrahedron Lett.* **2009**, *50*, 2889-2892.
22. Yadav, J. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. Ultrasound-accelerated synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones with ceric ammonium nitrate, *J. Chem. Sos. Perkin Trans.1*, **2001**, 1939-1941.
23- Mohamed M. A. A., Mahmoud N. F. H., El-Saghier A. M. M. Ceric(IV) a facile and eco-friendly catalysis in heterocyclic synthesis (II): A one-pot synthesis of pyrimido[4,5-d]pyrimidines through Biginelli reaction, *Chemistry Journal*, **2012**, 2(2), 101-105.
24- Folkers K., Johnson T. B. Researches on pyrimidines. CXXXVI. The mechanism of formation of tetrahydropyrimidines by the Biginelli reaction *J.Am. Chem. Soc.* **1933**, 55, 3784-3791.
25- Sweet F., Fissekis J. D. Synthesis of 3,4-dihydro-2(1)-pyrimidinones and the mechanism of the Biginelli reaction *J. Am. Chem. Soc.* **1973**, 95(26), 8741-8749.
26. Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. A catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2(*1H*)-one using 12-tungstophosphoric acid, *J. Molecular Catalysis A: Chemical,* **2005**, 242, 173-175.
27. Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones/thiones catalyzed by triphenylphosphoric acid *Teterahedron Lett.,* **2008**, 49, 6119-6121.
28. Shaabani, A.; bazgir, A.; Teimouri, F. Ammonium chloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones under solvent-free conditions, *Teterahedron Lett.,* **2003**,44(4), 857-859.
29. Chandark, H. S. ; Lad, N. P.; Upare, P. P. Recyclable amberlyst-70 as a catalyst for Biginelli reaction: An efficient one-pot green protocol for the synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones, *Catal. Lett.,* **2009**, 13(3-4), 469-473.

7/25/2012