Cerium (IV) Ammonium Nitrate as an Efficient Lewis Acid for the One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their Corresponding 2-(1*H*) Thiones

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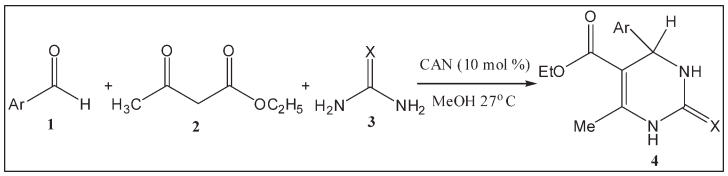
Received July 7, 2009
DOI 10.1002/jhet.259
Published online 22 February 2010 in Wiley InterScience (www.interscience.wiley.com).



A simple and highly efficient procedure for the Biginelli condensation reaction of aldehydes, β-ketoesters, urea, or thiourea catalyzed by Ceric ammonium nitrate (CAN) as a Lewis-acid at ambient temperature is described. The procedure proved to be simple and of high yield.

J. Heterocyclic Chem., **47**, 284 (2010).

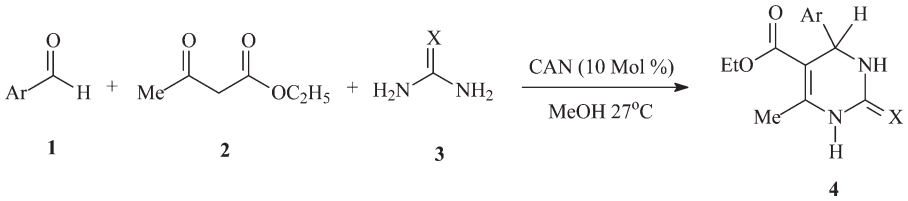
INTRODUCTION

Dihydropyrimidines (DHPMs) and their derivatives are class of heterocycles that posses a wide range of biological and therapeutic properties. They act as calcium channel blockers, antihypertensive agents, and α-la-antagonists and neuropeptide Y (NPY) antagonists [1–3]. Furthermore, several bioactive isolated marine alkaloids, in particular, the batzelladine alkaloids were found to contain 2-amino-1,4-dihydropyrimidine carboxylate core that have been found to be potent HIV gp-120-CD4 inhibitors [4–6]. They also have known to posses antibacterial, antiviral, antitumor and anti-inflammatory activities [7,8]. Thus, a synthesis of these heterocyclic molecules has been of much importance in current years.

The most simple and direct method for their synthesis was first reported by Biginelli [9] since more than 100 years ago; it involves a three one-pot condensation of benzaldehyde, ethyl acetoacetate, and urea under strong acidic conditions with a low yield. In the past 10 years, several one-pot methodologies for the synthesis of DHPM derivatives were developed. This involves the use of several catalysts such as lanthanide triflates [10], $ZrCl_4$ [11], VCl_3 [12], PPh_3 [13], $InBr_3$ [14], GaX_3 [15], H_3BO_3 [16], $KAl(SO_4)_2{\cdot}12H_2O$ supported on silica [17], $Y(NO_3)_3{\cdot}6H_2O$ [18], $Ce(NO_3)_3{\cdot}6H_2O$ [19], $CeCl_3$ and InCl3 [20], Nafion-H [21]. Microwave heating [22], ultrasound irradiation [23], and ionic liquids [24] were also performed as green techniques for their synthesis. Very recently, an efficient synthesis of DHPMs utilizing CaF_2 in refluxing EtOH [25], $Cu(NH_2SO_3)_2$ in refluxing acetic acid [26] and the use of etidronic acid catalyst [27] were reported. However, many drawbacks were associated with such synthesis such as the use of expensive reagents, strong acidic conditions, long reaction times, and low to moderate yields. Consequently, there is a need to develop a new efficient and simple method using inexpensive and environmentally benign catalyst. Ceric ammonium nitrate (CAN) was tested as an alternative catalyst. It is worth mentioning that the $CeCl_3{\cdot}7H_2O$ or $Ce(NO_3)_3{\cdot}6H_2O$ catalyzed synthesis of DHMPs suffers from some drawbacks such as the use of fairly high amounts of catalysts (100–20 mol %) or heating at 80°C.

Ceric ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a broad spectrum of synthetic transformations due to its many advantages such as solubility in water and various organic solvents, inexpensiveness, ecofriendly nature, uncomplicated handling, fast conversions, and convenient work-up procedure which make CAN a potent catalyst in organic synthesis. Although DHMPs has been previously synthesized utilizing CAN as one electron oxidant [28] under ultrasound irradiation, we found that there is no need for sonification as the reaction proceeds smoothly at ambient temperature. Also, we do believe that CAN acts as a Lewis acid catalyst because of the applicability of our protocol for the synthesis of DHMP thiones. The use of CAN as a Lewis-acid catalyst in C—N bond formation

Scheme 1



in heterocyclic chemistry is somehow limited [29]. Thus, in continuation to our efforts in the synthesis of azoles and azines [30,31] *via* simple and high-yielding protocol, we report herein and for the first time a novel three component one-pot synthesis of Biginelli 3,4-dihydropyrimidine-2(1H)-ones and 2-(1H)-thiones in high yields *via* the reaction of aromatic aldehydes, ethyl acetoacetate, urea, or thiourea using CAN as catalyst at ambient temperature.

RESULTS AND DISCUSSION

When aryl aldehydes **1** was treated with ethyl acetoacetate **2** and urea or thiourea **3** in MeOH (10 mL) in the presence of CAN (10 mol %) at ambient temperature (27°C), and the reaction mixture was left overnight, the dihydropyrimidinones/thiones **4** were obtained in a high yield (cf. Scheme 1). The optimization of the reaction was investigated. For this goal, we explored the effect of catalyst molar ratio and solvent effect on the overall yield. Our investigation clearly revealed that addition of (10 mol %) of CAN to the reaction mixture containing 1:1:1.2 molar ratio of 1:2:3 at ambient temperature was optimal for the formation of the condensation products. In addition, MeOH was found to be the best solvent among those tested (H_2O, EtOH, THF).

To study the scope of the procedure, a variety of aromatic, heteroaromatic, and α,β-unsaturated aldehydes were utilized. In all cases, the reaction proceeds smoothly in a high yield with a slight decrease in the yield when the aryl substituent involves a strong electron donating group. However, attempts to apply this to simple aliphatic aldehydes were unsuccessful (Table 1).

A proposed mechanism to account for the formation of 4 is demonstrated in Scheme 2.

Table 1

CAN catalyzed one-pot synthesis of Biginelli 3,4-dihydropyridin-2(1*H*)-ones and their corresponding 2-(1*H*)-thiones.

Entry	Ar	X	Yield (%)	mp (°C) Found	mp (°C) Lit.
4a	C_6H_5	O	95	202–203	201–204 [26]
4b	4-$CH_3OC_6H_4$	O	93	203–205	204–206 [26]
4c	4-$CH_3C_6H_4$	O	94	213–215	212–213 [26]
4d	3-$NO_2C_6H_4$	O	96	225–227	226–228 [26]
4e	4-ClC_6H_4	O	93	212–214	212–214 [5]
4f	2-Furyl	O	88	204–206	205–207 [5]
4g	$C_6H_5CH{=}CH$	O	84	241–242	241–243 [28]
4h	C_6H_5	S	94	207–209	207–209 [26]
4i	4-$CH_3OC_6H_4$	S	92	150–152	150–152 [32]
4j	4-$NO_2C_6H_4$	S	93	108–110	109–111 [32]

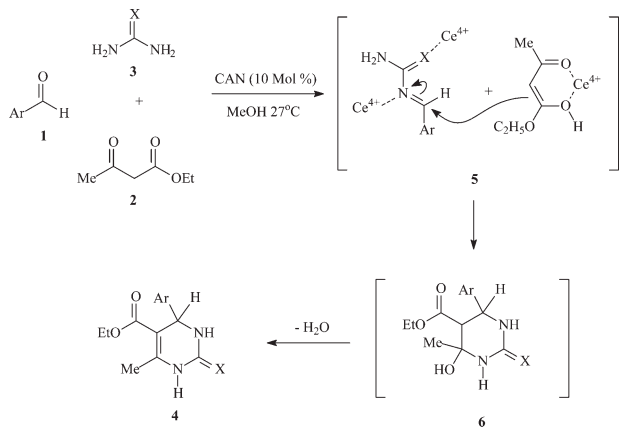
CONCLUSIONS

In conclusion, a catalytic amount of ceric ammonium nitrate (CAN) efficiently catalyzes the three component one-pot synthesis of Biginelli condensation product in MeOH at ambient temperature. The procedure proved to be simple, highly efficient, produces excellent yields which make it a useful and important addition to the well-known Biginelli reaction.

EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analyses were obtained on a LECO CHNS-932 Elemental Analyzer. Infrared spectra were recorded in KBr on a Perkin-Elmer 2000 FTIR system. ^{1}H-NMR and ^{13}C-NMR (DMSO-d_6) spectra were determined on a Bruker DPX spectrometer operating at 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR in DMSO-d_6 as solvents and TMS as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec Q MS 30 and MS 9 (AEI) spectrometers, with EI 70 eV.

Scheme 2



General procedure for the synthesis of compounds 4a–j. To a mixture of each of aldehyde 2a–i (10 mmol), ethylacetoacetate (10 mmol), urea or thiourea (12 mmol) dissolved in MeOH (20 mL), was added cerium IV ammonium nitrate (10 mol %). The reaction mixture was stirred at room temperature (27°C) overnight. Brine solution was then added to the mixture and the salt formed was collected by filtration and recrystallized from EtOH to afford pure samples of compounds **4a–j**.

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4a. Mp 201–203°C. IR (KBr): 3230 and 3200 (2NH), 1685 and 1664 (CO) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.12 (t, 3H, *J* = 7.2 Hz, CH_3), 2.32 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.2 Hz, CH_2), 5.09 (d, 1H, *J* = 4 Hz, pyrimidyl 4-H), 6.87 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.30 (t, 2H, *J* = 7.5 Hz, Ar-H), **6.35** (**t**, 2H, *J* = 7.5 Hz, Ar-H), 9.66 (**s**, 1H, NH), 10.44 (**s**, 1H, NH). ms (EI, 70 eV): m/z = **278** (M^+, 100). Anal. Calcd for $C_{14}H_{16}O_3N_2$ (260.29): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.62; H, 6.22; N, 10.78.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4b. Mp 203–205°C. IR (KBr): 3230 and 3204 (2NH), 1688 and 1664 (CO) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.10 (t, 3H, *J* = 7.2 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.00 (q, 2H, *J* = 7.2 Hz, CH_2), 5.09 (d, 1H, *J* = 3.2 Hz, pyrimidyl 4-H), 6.87 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.14 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.68 (**s**, 1H, NH), 9.15 (**s**, 1H, NH). ms (EI, 70 eV): m/z = 290 (M^+,100).Anal. Calcd for $C_{15}H_{18}O_4N_2$ (290.31): C, 62.05; H, 6.24; N, 9.64. Found: C, 61.85; H, 6.28; N, 9.66.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 4h. Mp 150–152°C. IR (KBr): 3230 and 3204 (2NH), 1688 and 1664 (CO) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO): δ = 1.12 (t, 3H, *J* = 7.1 Hz, CH_3), 2.29 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.00 (q, 2H, *J* = 7.1 Hz, CH_2), 5.08 (d, 1H, *J* = 3.5 Hz, pyrimidyl 4-H), 6.93 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.13 (d, 2H, *J* = 8.5 Hz, Ar-H), 9.26 (**s**, 1H, NH), 10.3 (**s**, 1H, NH). ms (EI, 70 eV): m/z = 306 (M^+, 100). Anal. Calcd for $C_{15}H_{18}O_3N_2S$ (306.38): C, 58.80; H, 5.92; N, 9.14; S, 10.47. Found: C, 58.78; H, 5.88; N, 9.12; S, 10.44.

Acknowledgments. This research was done by the financial support of the Public Authority for Applied Education and Training (Transform grant TS-06-14) of Kuwait.

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