Ultrasound-accelerated synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones with ceric ammonium nitrate †

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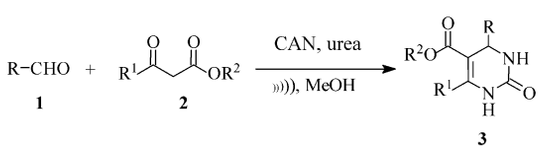
Ceric ammonium nitrate efficiently catalyzes the three component condensation of an aldehyde, β-ketoester and urea in methanol to afford the corresponding dihydropyrimidinones in excellent yields under sonication. Other oxidants such as manganese triacetate and Oxone were also found to catalyze this transformation under similar conditions.

Introduction

4-Aryldihydropyrimidinones are known to exhibit a wide range of biological activities[1] such as antiviral, antitumor, antibacterial and antiinflammatory properties. In addition, these compounds have emerged[2] as potent calcium channel blockers, antihypertensives, α_{1a}-adrenergic antagonists and neuropeptide antagonists. Furthermore, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in many marine natural products,[3] including batzelladine alkaloids, which have been found to be potent HIV gp-120-CD_4 inhibitors. The simple and direct method, originally reported by Biginelli,[4] for the synthesis of dihydropyrimidinones often suffers from low yields of products in the case of substituted aromatic and aliphatic aldehydes.[5] Subsequent multi-step syntheses[6] produced somewhat higher yields but these lack the simplicity of the original one-pot Biginelli protocol. Therefore, the Biginelli reaction continues to attract the attention of researchers in the hope of discovering milder and efficient procedures for the synthesis of dihydropyrimidinones. Recently, several improved procedures have been reported[7] using Lewis acids as well as protic acids as promoters. However, in spite of their potential utility, many of these methods involve expensive reagents, stoichiometric amount of catalysts, strongly acidic conditions, longer reaction times, high temperatures, unsatisfactory yields and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the useful Biginelli reaction. Recently, ultrasound has become a very useful tool in organic synthesis.[8] It has been used to enhance reaction rates in a large number of classical organic reactions.[9] Even though ultrasound has been used extensively in organic synthesis, it has not been employed to improve the one-pot Biginelli reaction. In recent years, ceric ammonium nitrate has emerged as a powerful one-electron transfer catalyst[10] in many carbon–carbon bond forming reactions. It has also been widely used in carbon–hetero atom bond formation. However, the use of CAN as a catalyst in the synthesis of pyrimidinones under neutral conditions has not been reported. In this report we describe an ultrasound-accelerated synthesis of pyrimidinones using a catalytic amount of ceric ammonium nitrate under sonic waves.

Results and discussion

The reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of CAN in methanol under sonication resulted in the formation of 3,4-dihydropyrimidin-2(1*H*)-one in 92% yield. Similarly, the treatment of several aromatic, aliphatic and heterocyclic aldehydes with ethyl acetoacetate and urea gave the corresponding dihydropyrimidinones in excellent yields (Scheme 1).



Scheme 1

The cyclocondensation proceeded smoothly under sonication to give the products in high to quantitative yields. Owing to the vibrational energy of the water, the bath temperature reached 55–60 °C under sonication. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted well under sonication to give the corresponding dihydropyrimidinones in high yields with high purity. Acid-sensitive aldehydes like 2-furaldehyde and phenylacetaldehyde worked well without the formation of any side products, which are generally observed under strongly protic or Lewis acidic conditions. Another important feature of this procedure is the survival of a variety of functional groups such as olefins, ethers, esters, nitro groups and halides under the present reaction conditions.

In addition to its simplicity and milder reaction conditions, this method is even effective with aliphatic and α,β-unsaturated aldehydes, which normally produce poor yields because of their decomposition or polymerization under strongly acidic conditions. Unlike the reported methods, the present procedure does not require any additives or acidic promoters[7e] or anhydrous conditions. The procedure not only preserves the simplicity of the Biginelli reaction but also gives excellent yields of the products.

The reaction rates and yields were dramatically enhanced by ultrasound. The rate enhancement under ultrasound may be attributed to the cavitation[9] and the activation of the catalyst by sonic waves. In the absence of sonic waves, the products were formed in moderate yields (55–70%) in the presence of 10% CAN in refluxing methanol after a long reaction time (8–12 h). However, the reaction did not proceed in the absence of ceric

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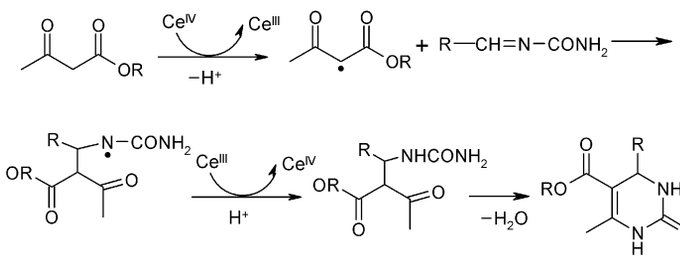
Table 1 Ceric ammonium nitrate catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones[a] under sonication[b]

Compound **3**	R	R^1	Time[c]/h	Yield[c] (%)	Observed melting point/°C[d] (literature)[11]
a	C_6H_5	CH_3	3.5 (5.0)	92 (88)	201–203 (203)
b	4-ClC_6H_4	CH_3	4.0 (6.5)	89 (85)	212–213 (214)
c	$C_6H_5CH_2$	CH_3	6.0 (6.0)	91 (87)	194–195 (195–196)
d	3,4-$(MeO)_2C_6H_3$	CH_3	3.0 (4.5)	90 (92)	176–177 (177)
e	4-$MeOC_6H_4$	CF_3	4.0 (5.0)	88 (80)	154–155 (156–157)
f	3,4-$Cl_2C_6H_3$	CH_3	5.0 (7.5)	90 (83)	221–223 (223)
g	2-Naphthyl	CH_3	4.5 (6.0)	84 (78)	247–249 (248)
h	4-MeC_6H_4	CF_3	5.0 (8.0)	88 (81)	168–170 (—)
i	4-$NO_2C_6H_4$	CH_3	7.0 (9.5)	85 (73)	206–208 (208)
j	3,4-Methylenedioxyphenyl	CF_3	4.5 (4.0)	90 (85)	220–221 (—)
k	Cyclohexyl	CH_3	3.5 (5.0)	87 (80)	235–236 (235–237)
l	Cinnamyl	CH_3	4.0 (5.5)	85 (82)	241–243 (242–244)
m	Thienyl	CH_3	3.5 (3.0)	90 (78)	206–208 (208)
n	Furfuryl	CH_3	3.0 (4.5)	87 (73)	205–206 (205)
o	Hexyl	CH_3	3.5 (4.0)	85 (77)	152–153 (151–152)
p	4-*N*,*N*-$(CH_3)_2NC_6H_4$	CH_3	4.0 (6.0)	88 (70)	256–257 (257–258)
q	3,4,5-$(MeO)_3C_6H_2$	CH_3	3.5 (4.5)	90 (85)	216–218 (217–219)

[a] $R^2 = C_2H_5$ for all compounds. [b] All products were characterized by ^1H NMR, IR and mass spectra and also by comparison of their physical characteristics with those of the authentic compounds.[11] [c] Yields and reaction times with Oxone are indicated in parentheses. [d] Melting points are uncorrected.



Scheme 2

ammonium nitrate, even under thermal conditions. The efficacy of other oxidants such as manganese(III) acetate and $FeCl_3$ was studied for this reaction. Among these catalysts, CAN was found to be superior in terms of conversion and reaction time. Similar results were also obtained using 10% Oxone in methanol under identical reaction conditions and the results are presented in Table 1. Furthermore, manganese(III) acetate worked well when acetic acid was used as solvent. Thus, this procedure provides easy access to substituted pyrimidinones with a wide variety of substitution patterns. Several examples illustrating this novel and rapid procedure for the synthesis of dihydropyrimidinones are summarized in Table 1. The best results were obtained with CAN when methanol was used as solvent, because radical generation from CH acidic substrates takes place in methanol at low temperatures. The reaction may proceed through a single-electron transfer with initial formation of a β-ketoester radical[12] that adds to the imine intermediate, as shown in Scheme 2.

In summary we have presented an ultrasound-accelerated synthesis of dihydropyrimidinones using a catalytic amount of ceric ammonium nitrate under neutral reaction conditions. Mild reaction conditions, improved yields, enhanced reaction rates, greater selectivity, compatibility with various functional groups, operational simplicity, an inexpensive catalyst and simple experimental/product isolation procedures are the main advantages of this procedure over existing ones for the synthesis of pyrimidinones.

Experimental

Melting points were recorded on a Büchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer with KBr optics. ^1H and ^{13}C NMR spectra were recorded on a Varian-Gemini-200 spectrometer in DMSO-d_6 using TMS as an internal standard. Mass spectra were recorded on a Finnigan-MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. TLC was monitored on 0.25 mm E. Merck pre-coated silica gel plates (60F-254). The CAN used for the reactions was purchased from Aldrich Co. and was used without purification. The Bransonic model 2210R-DTH ultrasound was operated at 335 W (47 KHz).

Ceric ammonium nitrate catalyzed synthesis of pyrimidinones

General procedure. *Method A.* A homogeneous solution of aldehyde (5 mmol), ethyl acetoacetate (5 mmol), urea (10 mmol) and ceric ammonium nitrate (10% w/w of aldehyde) in methanol (15 ml) was sonicated (Bransonic model 2210R-DTH) for the appropriate time (see Table 1). The reaction temperature was raised to 55–60 °C after sonication for 3–7 h. On completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and the resulting solid was filtered under suction and recrystallized from hot methanol to afford the pure product.

Method B. A mixture of aldehyde (5 mmol), ethyl acetoacetate (5 mmol), urea (10 mmol) and Oxone (10% w/w of aldehyde) in methanol (15 ml) was sonicated (Bransonic model 2210R-DTH) for the appropriate time (see Table 1). The reaction temperature was raised to 55–60 °C after sonication for 3–7 h. On completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and the resulting solid was filtered under suction and recrystallized from hot methanol to afford pure product.

Compound 3c. Solid, mp 194–195 °C; ^1H NMR (DMSO-d_6): δ 1.25 (t, 3H, $J = 6.8$ Hz), 2.25 (s, 3H), 2.60–2.70 (m, 2H), 4.15 (q, 2H, $J = 6.7$), 4.25 (m, 1H), 7.10–7.25 (m, 6H), 8.80 (br s, NH); EIMS: *m*/*z* 274 (M^+), 183, 155, 137, 91; IR (KBr): ν 3248, 3117, 2975, 1724, 1652, 1495, 1287, 1226, 1092, 778 cm^{-1}.

Analysis calcd. for $C_{15}H_{18}N_2O_3$ (274.318) C, 65.68; H, 6.61; N, 10.21. Found: C, 65.7; H, 6.63; N, 10.24%.

Compound 3d. Solid, mp 176–177 °C; ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3H, J = 7.0 Hz), 2.30 (s, 3H), 3.80 (s, 6H), 4.05 (q, 2H, J = 7.0 Hz), 5.25 (s, 1H), 6.80 (m, 2H), 6.85 (m, 1H), 7.25 (br s, NH), 8.95 (br s, NH); EIMS: m/z 320 (M^+), 292, 276, 247, 232, 183, 155, 137, 97, 69; IR (KBr): ν 3253, 3118, 2956, 1723, 1682, 1654, 1519, 1461, 1237, 1139, 1095, 790 cm^{-1}. Analysis calcd. for $C_{16}H_{20}N_2O_5$ (320.342) C, 59.99; H, 6.29; N, 8.74. Found: C, 60.05; H, 6.30; N, 8.76%.

Compound 3h. Solid, mp 168–170 °C; ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 6.8 Hz), 2.20 (s, 3H), 4.05 (q, 2H, J = 6.9 Hz), 5.20 (d, 1H, J = 2.0 Hz), 7.25 (br s, NH), 7.30–7.42 (m, 4H), 9.0 (br s, NH); IR (KBr): ν 3243, 1705, 1689 cm^{-1}; EIMS: m/z 228 (M^+). Analysis calcd. for $C_{15}H_{17}N_2F_3O_3$ (330.305) C, 54.55; H, 5.19; N, 8.48; F, 17.26. Found: C, 54.57; H, 5.20; N, 8.47; F, 17.28%.

Compound 3j. Solid, mp 220–221 °C; ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 6.9 Hz), 4.05 (q, 2H, J = 6.9 Hz), 5.20 (d, 1H, J = 2.1 Hz), 6.05 (s, 2H), 6.70 (m, 3H), 7.25 (br s, NH), 9.0 (br s, NH); IR (KBr): ν 3245, 1700, 1690 cm^{-1}; EIMS: m/z 358 (M^+). Analysis calcd. for $C_{15}H_{15}N_2F_3O_5$ (360.28) C, 50.0; H, 4.20; N, 7.78; F, 15.82. Found: C, 50.05; H, 4.27; N, 7.76; F, 15.85%.

Compound 3k. Solid, mp 235–236 °C; ^{1}H NMR (DMSO-d_6): δ 1.05 (m, 4H), 1.25 (t, 3H, J = 6.8 Hz), 1.45 (m, 3H), 1.75 (m, 4H), 2.3 (s, 3H), 4.15 (m, 3H), 6.15 (br s, NH), 8.45 (br s, NH); EIMS: m/z 266 (M^+), 183, 137, 155, 40; IR (KBr): ν 3236, 3118, 2920, 2850, 1726, 1702, 1647, 1450, 1230, 1095, 789 cm^{-1}. Analysis calcd. for $C_{14}H_{22}N_2O_3$ (266.338) C, 63.14; H, 8.33; N, 10.82. Found: C, 63.17; H, 8.35; N, 10.80%.

Compound 3l. Solid, mp 241–243 °C; ^{1}H NMR (DMSO-d_6): δ 1.05 (t, 3H, J = 7.0 Hz), 2.50 (s, 3H), 3.95 (q, 2H, J = 7.0 Hz), 4.25 (d, 1H, J = 6.0 Hz), 6.05 (dd, 1H, J = 16.4 and 1.8 Hz), 6.2 (d, 1H, J = 16.4 Hz), 7.25 (m, 5H), 7.45 (d, NH, J = 1.7 Hz), 8.95 (br s, NH); EIMS: m/z 286 (M^+), 252, 224, 196, 149, 84; IR (KBr): ν 3335, 3242, 3098, 2978, 1689, 1642, 1492, 1373, 1218, 1121, 785. Analysis calcd. for $C_{16}H_{18}N_2O_3$ (286.229) C, 67.12; H, 6.34; N, 9.78. Found: C, 67.15; H, 6.37; N, 9.80%.

Compound 3m. Solid, mp 206–208 °C; ^{1}H NMR (DMSO-d_6): δ 1.25 (t, 3H, J = 7.0 Hz), 2.30 (s, 3H), 4.10 (q, 2H, J = 7.0 Hz), 5.50 (d, 1H, J = 2.2 Hz), 6.85 (m, 2H), 7.15 (m, 1H), 7.30 (br s, NH), 8.90 (br s, NH); IR (KBr): ν 3245, 1720, 1690 cm^{-1}; EIMS: m/z 266 (M^+). Analysis calcd. for $C_{12}H_{16}N_2O_3S$ (268.33) C, 53.7; H, 6.0; N, 10.44; S, 11.95. Found: C, 53.78; H, 6.05; N, 10.47; S, 11.97%.

Compound 3n. Solid, mp 203–205 °C; ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 6.8 Hz), 2.25 (s, 3H), 4.15 (q, 2H, J = 6.8 Hz), 5.20 (br s, 1H), 6.10 (m, 1H), 6.25 (m, 1H), 7.30 (m, 1H), 7.40 (br s, NH), 9.10 (br s, NH); IR (KBr): ν 3242, 1710, 1685 cm^{-1}; EIMS: m/z 250 (M^+). Analysis calcd. for $C_{12}H_{16}N_2O_4$ (252.268) C, 57.13; H, 6.39; N, 11.10. Found: C, 57.15; H, 6.40; N, 11.13%.

Compound 3o. Solid, mp 151–153 °C; ^{1}H NMR (DMSO-d_6): δ 0.95 (t, 3H, J = 6.8 Hz), 1.25–1.40 (m, 9H), 1.55 (m, 2H), 2.30 (s, 3H), 4.15 (m, 2H), 4.25 (m, 1H), 6.05 (br s, NH), 8.55 (br s, NH); EIMS: m/z 253 (M^+), 209, 183, 155, 137, 91, 40; IR (KBr): ν 3249, 2933, 1730, 1646, 1433, 1331, 1288, 1086, 779 cm^{-1}. Analysis calcd. for $C_{13}H_{22}N_2O_3$ (254.327) C, 61.39; H, 8.72; N, 11.01. Found: C, 61.40; H, 8.75; N, 11.08%.

Compound 3p. Solid, mp 256–257 °C; ^{1}H NMR (DMSO-d_6): δ 1.25 (t, 3H, J = 6.8 Hz), 2.30 (s, 3H), 3.05 (s, 6H), 4.05 (q, 2H, J = 6.8 Hz), 5.20 (d, 1H, J = 2.1 Hz), 6.65 (d, 2H, J = 8.0 Hz), 7.15 (br s, NH), 7.20 (d, 2H, J = 8.0 Hz), 8.90 (br s, NH); IR (KBr): ν 3243, 1725, 1673 cm^{-1}; EIMS: m/z 303 (M^+). Analysis calcd. for $C_{16}H_{23}N_3O_5$ (305.375) C, 62.93; H, 7.59; N, 13.76. Found: C, 62.91; H, 7.60; N, 13.75%.

Compound 3q. Solid, mp 216–218 °C; ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, J = 7.0 Hz), 2.35 (s, 3H), 3.85 (s, 9H), 4.05 (q, 2H, J = 7.0 Hz), 5.25 (br s, 1H), 6.50 (m, 2H), 7.05 (br s, NH), 8.85 (br s, NH); IR (KBr): ν 3240, 1717, 1680 cm^{-1}; EIMS: m/z 350 (M^+). Analysis calcd. for $C_{17}H_{24}N_2O_6$ (352.384) C, 57.44; H, 6.86; N, 7.95. Found: C, 57.50; H, 6.89; N, 7.97%.

Acknowledgements

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