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Ammonium chloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions

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Abstract—Ammonium chloride as a very inexpensive and readily available reagent, and efficiently catalyzes one-pot, three component, Biginelli condensation reactions of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones in high yields at 100°C.

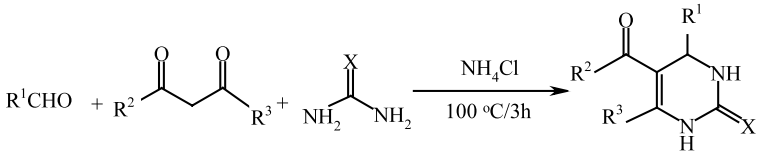
It is well known that 3,4-dihydropyrimidin-2-(1*H*)-ones and related compounds exhibit a wide range of biological activities[1] such as antiviral, antitumor, antibacterial and antiflammatory properties. In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature[2] and in potent HIVgp-120-CD_4 inhibitors.

Recently, many synthetic methods for preparing these compounds have been reported including classical conditions, with microwave and ultrasound irradiation and by using Lewis acids as well as protic acid promoters such as: zirconium(IV) chloride,[3] indium(III) bromide,[4] ytterbium(III)-resin,[5] 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphorate ($BMImPF_6$),[6] ceric ammonium nitrate (CAN),[7] $Mn(OAc)_3{\cdot}2H_2O$,[8] lanthanide triflate,[9] indium(III) chloride,[10] lanthanum chloride,[11] H_2SO_4,[12] HOAc,[13] montmorillonite KSF,[14] polyphosphate ester (PPE),[15] BF_3–OEt_2/CuCl/HOAc,[16] and conc. HCl.[17,18]

However, in spite of their potential utility, many of these methods involve expensive reagents, strongly acidic conditions, long reaction times, high temperatures and stoichiometric amounts of catalysts, and give unsatisfactory yields. Therefore, the discovery of a new and an inexpensive catalyst for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones under neutral and mild conditions is of prime importance.

In connection with our previous work on solid state organic transformations[19–21] using ammonium chloride as a catalyst,[22] we wish to report the results obtained from a study of the preparation 3,4-dihydropyrimidin-2-(1*H*)-ones with NH_4Cl as a very inexpensive and easily available catalyst under neutral and solvent-free conditions (Scheme 1).

The procedure gives the products in good yields and avoids problems associated with solvent use (cost, handling, safety and pollution). Decreased reaction times are also realized because of the increased reactivity of the reactant in the solid state and the fact that the other reaction product, water, evaporates at the reaction temperature of 100°C.



R^1= Alkyl and Aryl
R^2= Alkyl-O and Alkyl
R^3=Methyl, Phenyl and 2-Thienyl

X= O, S

(1-26)

Scheme 1.

Keywords: Biginelli reaction; dihydropyrimidinones; ammonium chloride; one-pot condensation; solvent-free.
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Table 1. Ammonium chloride-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions at 100°C

DHMP	R1	R2	R3	X	Yield (%)[a]	Mp (°C)	
						Found	Reported
1	C_6H_5	OEt	Me	O	90	200–202	201–203[b]
2	4-OMe-C_6H_4	OEt	Me	O	84	199–201	199–201[b]
3	4-Cl-C_6H_4	OEt	Me	O	83	209–211	210–212[b]
4	4-NO_2-C_6H_4	OEt	Me	O	83	205–207	207–210[b]
5	3-NO_2-C_6H_4	OEt	Me	O	80	225–227	226–228[c]
6	2-Cl-C_6H_4	OEt	Me	O	85	216–218	215–218[c]
7	2-Me-C_6H_4	OEt	Me	O	81	207–208	208–210[d]
8	CH_3	OEt	Me	O	42	186–188	189–190[e]
9	C_3H_7	OEt	Me	O	78	155–157	153–155[f]
10	C_4H_9	OEt	Me	O	65	154–156	157–158[b]
11	C_6H_5	OMe	Me	O	92	207–209	207–210[b]
12	4-NO_2-C_6H_4	OMe	Me	O	79	234–236	235–237[b]
13	4-OMe-C_6H_4	OMe	Me	O	90	192–193	191–193[b]
14	4-Cl-C_6H_4	OMe	Me	O	85	204–206	204–207[g]
15	2-Cl-C_6H_4	OMe	Me	O	85	252–253	–
16	3-NO_2-C_6H_4	OMe	Me	O	80	279–280	–
17	C_6H_5	Me	Me	O	79	232–235	233–236[b]
18	4-OMe-C_6H_4	Me	Me	O	86	177–179	178–180[b]
19	4-NO_2-C_6H_4	Me	Me	O	83	229 (dec.)	230 (dec.)[b]
20	C_6H_5	OEt	Me	S	88	205–206	205–207[c]
21	4-OMe-C_6H_4	OEt	Me	S	86	138–140	140[h]
22	3-NO_2-C_6H_4	OEt	Me	S	78	206–207	206–207[c]
23	C_6H_5	OBn	Me	O	80	165–166	–
24	4-OMe-C_6H_4	OBn	Me	O	75	186–187	–
25	C_6H_5	CF_3	2-Thienyl	O	89	98–101	99–102[b]
26	C_6H_5	OEt	Ph	O	77	158–160	157–159[g]

[a] Isolated yield.
[b] Ref. 9.
[c] Ref. 15.
[d] Ref. 4.
[e] Ref. 24.
[f] Ref. 23.
[g] Ref. 16.
[h] Ref. 11.

In order to improve the yields, we performed reactions using different quantities of reagents. The best results were obtained with a 0.5:1:1:1.5 ratio of ammonium chloride, aldehyde, 1,3-dicarbonyl compound and urea or thiourea.

As can be seen from Table 1, aldehydes, 1,3-dicarbonyl compounds and urea or thiourea in the presence of NH_4Cl gave the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones under neutral conditions in good yields after 3 h. Even aliphatic aldehydes, which normally show extremely poor yields in the Biginelli reaction,[23] gave 42–78% yields of the corresponding dihydropyirimidin-2-(1*H*)-ones **8**, **9** and **10** (Table 1). Furthermore, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted well, giving moderate to excellent yields.

In summary, we have developed an economically and environmentally friendly procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones with short reaction times. This involves the use of NH_4Cl as a very inexpensive and easily available catalyst and neutral and solvent-free conditions.

Experimental

Ammonium chloride-catalyzed synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one, (4d) under solvent-free conditions

A mixture of 4-nitrobenzaldehyde (0.30 g, 2 mmol), ethyl acetoacetate (0.26 g, 2 mmol), urea (0.18 g, 3 mmol) and NH_4Cl (0.05 g, 0.8 mmol) was heated with stirring at 100°C for 3 h. After cooling, the reaction mixture was washed with cold water (2×50 mL) and residue recrystallized from ethyl acetate:*n*-hexane (1:3) to afford the pure product **4** (0.51g, 1.7 mmol, 83%). Mp 205–207°C; IR (KBr) (ν_{max}, cm^{-1}): 3215, 1731, 1707, 1641; ^1H NMR (DMSO-d_6): δ_H 1.07 (3H, t, ^3J 6.8 Hz, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, ^3J 5.4 Hz, OCH_2), 5.27 (1H, s, CH), 7.50 (2H, d, ^3J 7.3 Hz, arom.), 7.87 (1H, s, NH), 8.20 (2H, d, ^3J 7.2 Hz, arom.), 9.33 (1H, s, NH); ^{13}C NMR: δ_C 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5; MS (*m*/*z*,%) 305 (M^+, 25), 276 ($M^+-C_2H_5$, 92), 260 ($M^+-C_2H_5CO_2$, 20), 183 (100).

All the products (except **15**, **16**, **23** and **24**) are known compounds which were characterized by IR and ^1H

NMR spectral data and their mp's compared with literature reports.

5-Methoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one*, *15. Mp 252–254°C; IR (KBr) (ν_{max}, cm^{-1}): 3210, 3090, 1683, 1639; ^1H NMR (DMSO-d_6): δ_H 2.28 (3H, s, CH_3), 3.44 (3H, s, OCH_3), 5.60 (1H, s, CH), 7.26–7.39 (4H, m, arom.), 7.70 (1H, s, NH), 9.31 (1H, s, NH); ^{13}C NMR: δ_C 18.2, 51.2, 51.9, 98.2, 128.2, 129.1, 129.9, 132.1, 141.9, 149.9, 151.9, 166.0; MS (*m*/*z*,%) 281 (M^+, 29), 265 (M^+–CH_3, 62), 221 (M^+–CH_3CO_2H, 27), 169 (100).

5-Methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one*, *16. Mp 279–281°C; IR (KBr) (ν_{max}, cm^{-1}): 3340, 3200, 3088, 1690, 1631; ^1H NMR (DMSO-d_6): δ_H 2.27 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 5.29 (1H, s, CH), 7.61–8.12 (4H, m, arom.), 7.90 (1H, s, NH), 9.37 (1H, s, NH); ^{13}C NMR: δ_C 18.4, 51.4, 53.8, 98.6, 121.4, 122.8, 130.7, 133.4, 147.2, 148.3, 150.1, 152.3, 166.1; MS (*m*/*z*,%) 292 (M^++H, 25), 232 (M^+–CH_3CO_2, 92),169 (100).

5-Benzyloxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one*, *23. Mp 165–167°C; IR (KBr) (ν_{max}, cm^{-1}): 3345, 3218, 3100, 1703, 1637; ^1H NMR (DMSO-d_6): δ_H 2.26 (3H, s, CH_3), 5.00 and 5.04 (2H, AB-system, ^3J 12.7 Hz, OCH_2), 5.16 (1H, d, ^3J 2.9 Hz, CH), 7.13–7.30 (10H, m, arom.), 7.72 (1H, s, NH), 9.23 (1H, s, NH), ^{13}C NMR: δ_C 18.3, 54.4, 65.3, 99.2, 126.7, 127.8, 128.0, 128.2, 128.7, 128.9, 137.0, 145.1, 149.7, 152.4, 165.5; MS (*m*/*z*,%) 322 (M^+, 45), 231 (M^+–$C_6H_5CH_2$, 19), 187 (M^+–$C_6H_5CH_2CO_2$, 20), 77 (100).

5-Benzyloxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one*, *24. Mp 186–188°C; IR (KBr) (ν_{max}, cm^{-1}): 3340, 3210, 3100, 1695, 1630, 1603; ^1H NMR (DMSO-d_6): δ_H 2.25 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 4.99 and 5.04 (2H, AB system, ^3J 12.7 Hz, OCH_2), 5.12 (1H, s, CH), 6.83–7.27 (9H, m, arom.), 7.68 (1H, s, NH), 9.21 (1H, s, NH), ^{13}C NMR: δ_C 18.3, 53.8, 55.5, 65.2, 99.5, 114.2, 127.9, 128.0, 128.2, 128.7, 137.0, 137.3, 149.4, 152.4, 159.0, 165.6.

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