One-pot synthesis of 5-carboxanilide-dihydropyrimidinones using etidronic Acid

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Abstract
A combination of a modified Biginelli reaction and an etidronic acid prompted a cyclocondensation reaction providing 5-carboxanilide-dihydropyrimidinones in good to excellent yields.

Keywords: Biginelli reaction, etidronic acid, cyclocondensation, 5-carboxanilide-dihydropyrimidinones, excellent yields

Introduction

Pyrimidines have been subjected to a large number of different modifications in order to obtain derivatives having different biological properties. Several groups have studied the chemistry and pharmacological properties of pyrimidine derivatives.[1-14] Pyrimidines have been found to have a broad range of biological effects including antiviral, antitumor, antibacterial, anti-inflammatory,[1] antihypertensive,[2] cardiovascular,[3] calcium channel blocking[4], and neuropeptide Y (NPY) antagonistic activity.[15] The versatile biological properties of pyrimidine derivatives prompted us to take up this project to synthesize some novel derivatives using a cyclocondensation reaction of a 1,3-diketone, an aldehyde, and urea.

The synthetic methodology used to generate DHPMs has been well documented and has typically involved variations of the original Biginelli reaction.[1,16-18] The reports by Kappe and Falsone[11-19] describe the synthesis of these compounds via a one pot condensation utilizing polyphosphate ester (PPE)[19] to generate 5-carboxylate DHPMs, however, 5-carboxanilide-dihydropyrimidinones using etidronic acid were not exemplified.

Etidronic acid [(1-hydroxyethylidene)bisphosphonic acid] is a phosphonic acid and is also known as a bisphosphonate having a molecular formula $C_2H_8O_7P_2$. The two PO_3 (phosphonate)

groups are covalently linked to a single carbon atom.[20] It is different from PPE and polyphosphoric acid (PPA).

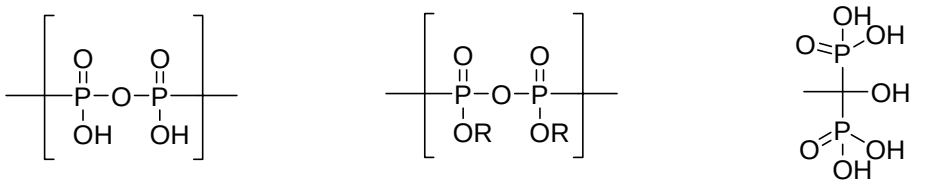


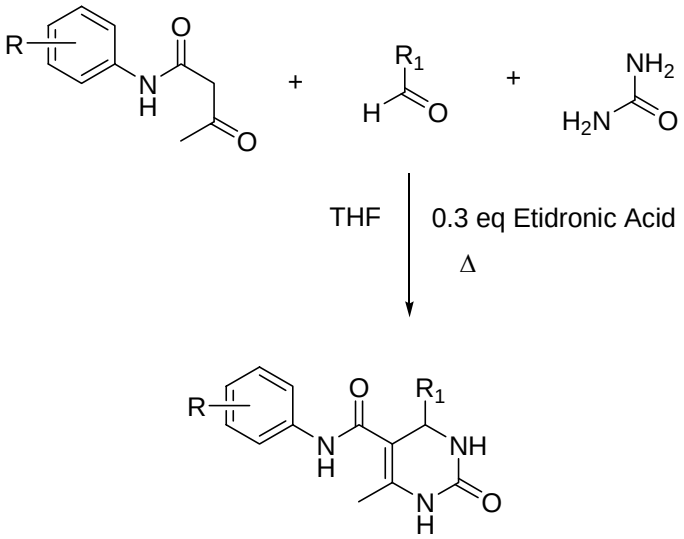
Figure 1

Reports have shown that polyphosphate ester (PPE), when used in an aprotic solvent such as THF, can serve as a desicant,[19] and simple benzamides can be dehydrated to their corresponding benzonitriles using this reagent.[21] Etidronic acid can also serve as a desicant. Our plan was to investigate whether etidronic acid could serve as a suitable reagent to form 5-carbanilide-DHPMs. In principle, etidronic acid should be strong enough as desicant to dehydrate a diketone, an aldehyde and urea to give the desired DHPMs, while being mild enough (Figure 1) to allow the use of functionally sensitive aldehydes.

Results and Discussion

After extensive optimization, we found that the single step reaction could be carried out in a general and efficient one-pot process to afford a variety of 5-carboxanilide-DHPMs. As outlined in Table 1, addition of 0.3 equiv of etidronic acid to a reaction mixture containing a 1:1:1.5 ratio of aldehyde/acetoacetanilide/urea in THF, at 75 °C for 1 hr, was optimal for the formation of 5-carboxanilide-DHPMs without affecting the anilide group in yields typically exceeding 70%.

A variety of substituted aromatic, aliphatic and hetero-aromatic aldehydes, with either electron-donating or electron-withdrawing groups, provided favorable results in this reaction. For example, 5-carboxanilide-dihydropyrimidinones generated from 4-nitro benzaldehyde and 2-furyl aldehyde afforded the corresponding products in greater than 90% yield. Aliphatic aldehydes were equally amenable to these conditions with *n*-butyraldehyde providing the 5-carboxanilide-dihydropyrimidinone in 95 to 97% yield. Halogenated aromatic substitution at the 4-position of the DHPM could also be achieved using this methodology, albeit in significantly lower yields (compound 2, 4 and 7).



Scheme 1. Sunthetic approach towards 5-carboxanilide-4-substituted dihydropyrimidinones.

All the synthesized compounds were characterized using IR, Mass, ^{1}H NMR, ^{13}C NMR and elemental analysis. In the mass spectral study, the molecular ion peak was observed in agreement with the molecular weight of the respective compound. In the ^{1}H NMR spectral study, two characteristic signals of –NH of the dihydropyrimidine ring system were observed between 8.5 to 10 δ ppm. The chiral proton at the C4 position exhibited a signal at 5-5.5 δ ppm as a singlet. The –NH proton of the carboxanilide group was observed at 8-8.5 δ ppm as a singlet. The ^{13}C NMR spectra were consistent with the proposed structure. There are two carbon signals found at 163 to 165 δ ppm for the amide carbon (CONH). The reason of having more carbon signals than expected could be due to two isomers may existing because of a restricted rotation around the amide functional group. IR spectra showed a secondary amine (-NH) group in the range of 3200 to 3400 cm^{-1} and a carbonyl (-C=O) group near 1690 cm^{-1}.

Table 1. A general one-pot Biginelli reaction to generate 5-carboxanilide-4-substituted dihydropyrimidinones

Entry	R	R1	Yield[a](%)
1	3-CF_3	Phenyl	79
2	3-CF_3	3-Cl Phenyl	69
3	3-CF_3	2-Furyl	90
4	3,4-dichloro	3-Cl Phenyl	73
5	3,4-dichloro	4-NO_2 Phenyl	92
6	3,4-dichloro	n-propyl	97
7	4-NO_2	4-F Phenyl	72
8	4-NO_2	4-OCH_3Phenyl	85
9	4-NO_2	n-propyl	95

[a]Isolated yields after purification.

Conclusion

In summary, a new method for the preparation of 5-carboxanilide-DHPMs was discovered that utilizes a multicomponent coupling reaction catalyzed by etidronic acid, with a rapid and high yielding cyclocondensation to afford the corresponding DHPMs. The use of etidronic acid was well tolerated with a range of aldehydes and ketones. In addition, this methodology is cost effective and amenable to large-scale syntheses.

Experimental Section

General Procedures. Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Fluka, Sigma Aldrich, Merck and Rankem and used without further purification.

5-Carboxanilide-tetrahydropyrimidines. General Procedure

A mixture of an appropriate aldehyde (10 mmol, 1.0 equiv), *N*-phenyl-3-oxobutanamide (10 mmol, 1.0 equiv), urea (15 mmol, 1.5 equiv) and etidronic acid (5.0 mmol, 0.5 equiv) in THF (10 mL) was heated in a sealed tube for 1 hr at 75 °C. The reaction mixture was cooled to room temperature and poured onto ice (100 g). The resulting precipitate was collected by vacuum filtration and the solid was washed with water followed by a small amount of methanol and diethyl ether. The solid was recrystallized from ethanol to yield N-phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxamide derivatives as a white to pale yellow solid in 70-95 % yield.

***N*-(3-(Trifluoromethyl)phenyl)-4-phenyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (1).** Mp 208–210°C; Yield – 79%. IR (KBr): 3289, 3276, 3234, 3010, 2956, 1689, 1672, 1554, 1345, 1220, 1108, 789 cm^{-1}; ^{1}H NMR: δ = 10.17 (s, 1H, NH), 9.95 (s, 1H, NH), 8.39 (s, 1H, NH), 8.09–7.27 (m, 9H, Ar), 5.46 (s, 1H, CH), 1.61 (s, 3H, CH_3); Mass: *m/z* = 375 [M^+]; ^{13}C NMR (400 MHz, DMSO) δ 14.13 (CH_3), 51.12 (C4), 108.73 (C5), 120.54, 121.16, 125.81, 126.19, 127.34, 128.50, 128.68, 130.08, 130.31, 130.36, 132.17 and 133.00 (CAr.), 125.71 (CF_3), 134.08 (C-C4, Ar), 137.34 (C-NH, Ar), 146.35 (C6), 151.05 (C2, CO), 164.35 ($CONH_2$); Anal. Calcd for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30; N, 11.20. Found: C, 60.77; H, 4.28; N, 11.21.

***N*-(3-(Trifluoromethyl)phenyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (2).** Mp 216–218°C; Yield – 69%. IR (KBr): 3408, 3298, 3271, 3088, 2928, 1672, 1654, 1506, 1442, 1334, 1122, 792 cm^{-1};^{1}H NMR: δ = 10.14 (s, 1H, NH), 9.98 (s, 1H, NH), 8.45 (s, 1H, NH), 8.09–7.22 (m, 8H, Ar), 5.46 (s, 1H, CH), 1.64 (s, 3H, CH_3); Mass: *m/z* = 409 [M^+]; Anal. Calcd for $C_{19}H_{15}ClF_3N_3O_2$: C, 55.69; H, 3.69; N, 10.25. Found: C, 55.62; H, 3.67; N, 10.22.

***N*-(3-(Trifluoromethyl)phenyl)-4-(furan-2-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (3).** Mp 222–224°C; Yield – 90%. IR (KBr): 3290, 3282, 3271, 3088, 2856, 1690, 1672, 1376, 1222, 1022, 756 cm^{-1}; ^{1}H NMR: δ = 10.04 (s, 1H, NH), 9.97 (s, 1H, NH), 8.40 (s, 1H, NH), 7.84–6.79 (m, 7H, Ar), 4.96 (s, 1H, CH), 1.73 (s, 3H, CH_3); Mass: *m/z* = 365 [M^+]; Anal. Calcd for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.85; H, 3.84; N, 11.49.

***N*-(3,4-Dichlorophenyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4).** Mp 192–194°C; Yield – 73%. IR (KBr): 3450, 3209, 3072, 2847, 1691, 1676, 1600, 1510, 1425, 1342, 1172, 1023, 769 cm^{-1}; ^{1}H NMR: δ = 9.70 (s, 1H, NH), 8.92 (s, 1H, NH), 8.42 (s, 1H, NH), 7.94–7.15 (m, 7H, Ar), 5.00 (s, 1H, CH), 1.73 (s, 1H, CH_3); Mass: *m/z* = 410 [M^+]; Anal. Calcd for $C_{18}H_{14}Cl_3N_3O_2$: C, 52.64; H, 3.44; N, 10.23. Found: C, 52.61; H, 3.45; N, 10.21.

***N*-(3,4-Dichlorophenyl)-4-(4-nitrophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (5).** Mp 186–188°C; Yield – 92%. IR (KBr): 3284, 3228, 3117, 2933, 2854, 1693, 1666, 1622, 1442, 1338, 1238, 1128, 773 cm^{-1}; ^{1}H NMR: δ = 10.25 (s, 1H, NH), 9.85 (s, 1H, NH), 8.20-7.24 (m, 7H, Ar), 5.07 (s, 1H, CH), 1.62 (s, 3H, CH_3); Mass: *m/z* = 421 [M^+]; Anal. Calcd for $C_{18}H_{14}Cl_2N_4O_4$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.27; H, 3.31; N, 13.34.

***N*-(3,4-Dichlorophenyl)-4-propyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (6).** Mp 184–186°C; Yield – 97%. IR (KBr): 3286, 3272, 2976, 2842, 1684, 1456, 1361, 1222, 1072, 740 cm^{-1}; ^{1}H NMR: δ = 10.44 (s, 1H, NH), 9.57 (s, 1H, NH), 7.60-7.19 (m, 3H, Ar), 6.87 (s, 1H, NH), 4.95 (s, 1H, CH), 3.65–3.31 (m, 2H, CH_2), 2.61–2.14 (m, 2H, CH_2), 1.58–1.39 (m, 3H, CH_3), 0.94 (s, 3H, CH_3); Mass: *m/z* = 342 [M^+]; Anal. Calcd for $C_{15}H_{17}Cl_2N_3O_2$: C, 52.64; H, 5.01; N, 12.28. Found: C, 52.61; H, 4.96; N, 12.28.

***N*-(4-Nitrophenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (7).** Mp 262–264°C; Yield – 72%. IR (KBr): 3279, 3244, 3225, 3190, 2852, 1693, 1674, 1614, 1529, 1448, 1357, 1240, 758 cm^{-1}; ^{1}H NMR: δ = 9.97 (s, 1H, NH), 8.19 (s, 1H, NH), 8.16 (s, 1H, NH), 7.89–6.96 (m, 8H, Ar), 4.96 (s, 1H, CH), 1.68 (s, 3H, CH_3); Mass: *m/z* = 370 [M^+]; Anal. Calcd for $C_{18}H_{15}FN_4O_4$: C, 58.38; H, 4.08; N, 15.13. Found: C, 58.37; H, 4.04; N, 15.10.

***N*-(4-Nitrophenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro--6-methyl-2-oxopyrimidine-5-carboxamide (8).** Mp 210–212°C; Yield – 85%. IR (KBr): 3373, 3248, 3211, 3090, 1689, 1678, 1600, 1529, 1354, 1207, 1186, 840, 758 cm^{-1}; ^{1}H NMR: δ = 10.21 (s, 1H, NH), 8.91 (s, 1H, NH), 8.54 (s, 1H, NH), 8.18–6.84 (m, 8H, Ar), 4.89 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 1.74 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO) δ 14.73 (CH_3), 52.39 (C4), 58.93 (OCH_3), 108.66 (C5),

114.39, 114.63, 121.17, 121.54, 127.55, 128.57, 129.35 and 130.06 (CAr.), 131.88 (C-C4, Ar.), 134.25 (C-NH, Ar), 136.98 (C-NO_2), 145.00 (C6, C-CH_3), 157.05 (C2, C=O), 159.43 (C-OCH_3), 163.75 (CONH); Mass: *m/z* = 382 [M^+]; Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.66; H, 4.71; N, 14.63.

***N*-(4-Nitrophenyl)-4-propyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-pyrimidine-5-carboxamide (9).** Mp 222–224°C; Yield – 95%. IR (KBr): 3308, 3296, 3277, 2954, 2848, 2822, 1688, 1668, 1545, 1442, 1345, 1207, 1112, 786 cm^{-1}; ^1H NMR: δ = 9.03 (s, 1H, NH), 8.51 (s, 1H, NH), 8.25 (s, 1H, NH), 7.38–6.78 (m, 4H, Ar), 5.75 (s, 1H, CH), 3.16-3.13 (m, 2H, CH_2), 2.52–2.49 (m, 2H, CH_2), 1.98 (s, 3H, CH_3), 1.77–1.72 (m, 3H, CH_3); Mass: *m/z* = 318 [M^+];Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.57; H, 5.66; N, 17.57.

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