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THREE-COMPONENT SYNTHESIS OF 6-ARYL-4-METHYL-2-OXO-1,2,3,6-TETRAHYDROPYRIMIDINE-5-(N-ARYL)CARBOXAMIDES

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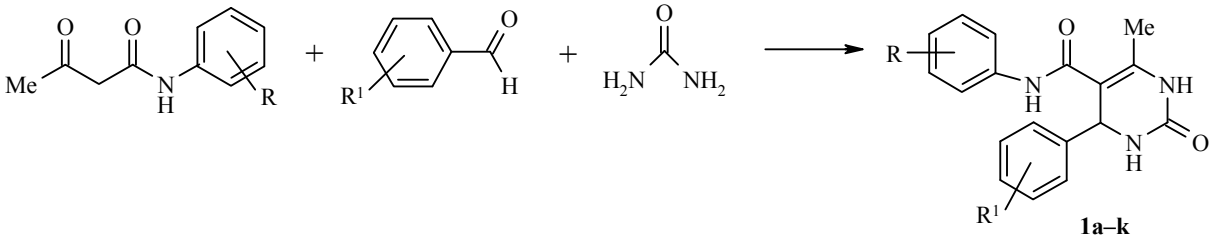
A three-component synthesis using acetoacetanilides and a mixture of an aromatic aldehyde and urea yields 6-aryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-(N-aryl)carboxamides.

Keywords: N-arylamides, 6-aryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-(N-aryl)carboxamides, urea, three-component synthesis.

Different variants of carrying out the Biginelli reaction have been reported in the literature. However, these basically deal with the interaction of acetylpyruvate esters with urea and aromatic aldehydes [1-4]. We have previously shown that 6-aryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-(N-aryl)carboxamides are formed in the reaction of acetylacetic acid N-arylamides with a mixture of an aromatic aldehyde and thiourea [5].

In continuing this investigation we have, for the first time, carried out a three-component condensation of acetoacetanilides, urea, and aromatic aldehydes which give the 6-aryl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-(N-aryl)carboxamides **1a-k**. In the course of this study it was found that the reaction occurs without solvent at 120-150ºC over 5-7 min.



1a–k

1 a–e R = H, **a** R^1= H, **b** R^1 = 4-NO_2, **c** R^1 = 4-Cl, **d** R^1 = 3-NO_2, **e** R^1 = 2-Cl; **f–h** R = 2-Me, **f** R^1 = H, **g** R^1 = 3-NO_2, **h** R^1 = 2-OMe; **i** R = 2,4-Me_2, R^1 = H; **j,k** R = 2-MeO, **j** R^1 = H, **k** R^1 = 4-Cl

Compounds **1a-k** are colorless, crystalline materials which are soluble in chloroform, DMF, and DMSO, and with heating in ethanol or acetic acid, but insoluble in water.

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The IR spectra of compounds **1a-k** show absorption bands for amide stretching at 1660-1680, the C=C bonds at 1600-1620, and NH bonds at 3150-3200 cm^{-1}.

The ^1H NMR spectra of the compounds are characterized by the presence of signals for the aromatic protons together with the associated methyl group protons singlet at 1.79-2.15 ppm, a doublet at 5.20-5.67 ($J_{1,6}$ = 1.8-2.4 Hz) for the H-6 proton, two signals for the N(3)–H proton at 8.12-8.98, two doublets at 7.05-7.84 for the pyrimidine ring N(1)–H proton, and a singlet at 8.74-9.78 ppm for the NH group proton.

The position of the N(1)–H proton signal was established in a series of experiments with suppression of the resonance frequency of the side chain NH protons, the N(1)–H and N(3)–H protons. Suppression of the resonance frequency for the N(1)–H proton caused the H-6 proton signal to become a singlet. Two signals for the H-3 proton were seen in DMSO solution which points to the existence of the compound in two tautomeric forms with two closely placed signals for OH and NH group protons.

The mass spectrum of compound **1i** shows a molecular ion peak at 335 for M^+ with fragment ion peaks having *m/z* 121 for $[Me_2C_6H_3NH]^+$ and 77 for $[Ph]^+$ thus confirming this structure.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument using vaseline oil and ^1H NMR spectra of a Bruker 500 spectrometer (500 MHz) using DMSO-d_6 with TMS as internal standard. Mass spectra were obtained on a Finnigan MAT Incos-50 instrument with ionization energy 70 eV.

Compounds 1a-k (General Method). A mixture of the acetoacetanilide (0.01 mol), the benzaldehyde (0.01 mol), and urea (0.01 mol) was held for 5-7 min at 120-150ºC until evolution of gas ceased. The reaction mixture was then cooled, treated with ethanol, and the crystals formed were filtered off and recrystallized from alcohol.

4-Methyl-2-oxo-N,6-diphenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1a). Yield 58%; mp 246-248ºC (alcohol). IR spectrum, δ, cm^{-1}: 1600 (C=C), 1675 (CON), 3200 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, 4-CH_3); 5.32 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.44 (10H, m, 2 Ph); 7.48 (1H, d, $J_{1,6}$ = 2.4, H-1); 8.61 and 8.62 (1H, 2s, 3-NH and 2-OH); 9.43 (1H, s, NH). Found, %: C 70.48, 70.26; H 5.64, 5.49; N 13.82, 13.72. $C_{18}H_{17}N_3O_2$. Calculated, %: C 70.34; H 5.58; N 13.67.

4-Methyl-6-(4-nitrophenyl)-2-oxo-N-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1b). Yield 62%; mp 256-258ºC (alcohol). IR spectrum, δ, cm^{-1}: 1620 (C=C), 1680 (CON), 3200 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, 4-CH_3); 5.51 (1H, d, $J_{1,6}$ = 1.8, H-6); 7.39 (9H, m, Ph, $NO_2C_6H_4$); 7.76 (1H, d, $J_{1,6}$ = 1.8, H-1); 8.89 and 8.90 (1H, 2s, 3-NH and 2-OH); 9.63 (1H, s, NH). Found, %: C 61.49, 61.23; H 4.62, 4.48; N 15.79, 15.99. $C_{18}H_{16}N_4O_4$. Calculated, %: C 61.36; H 4.58; N 15.90.

6-(4-Chlorophenyl)-4-methyl-2-oxo-N-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1c). Yield 82%; mp 244-246ºC (alcohol). IR spectrum, δ, cm^{-1}: 1610 (C=C), 1660 (CON), 3150 (NH). ^1H NMR spectrum, δ, ppm (J, Hz): 2.02 (3H, s, 4-CH_3); 5.33 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.27 (9H, m, Ph, ClC_6H_4); 7.55 (1H, d, $J_{1,6}$ = 2.4, H-1); 8.77 and 8.79 (1H, 2s, 3-NH and 2-OH); 9.56 (1H, s, NH). Found, %: C 63.16, 63.39; H 4.79, 4.67; N 12.43, 12.18. $C_{18}H_{16}ClN_3O_2$. Calculated, %: C 63.25; H 4.72; N 12.29.

4-Methyl-6-(3-nitrophenyl)-2-oxo-N-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1d). Yield 72%; mp 262-264ºC (alcohol). IR spectrum, δ, cm^{-1}: 1600 (C=C); 1670 (CON); 3200 (NH). ^1H NMR spectrum, δ, ppm (J, Hz): 2.05 (3H, s, 4-CH_3); 5.45 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.46 (9H, m, Ph, $NO_2C_6H_5$); 7.66 (1H, d, $J_{1,6}$ = 2.4, H-1); 8.78 and 8.80 (1H, 2s, 3-NH and 2-OH); 9.50 (1H, s, NH). Found, %: C 61.20, 61.44; H 4.68, 4.49; N 16.04, 15.83. $C_{18}H_{16}N_4O_4$. Calculated, %: C 61.32; H 4.58; N 15.94.

6-(2-Chlorophenyl)-4-methyl-2-oxo-N-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1e). Yield 78%; mp 226-228ºC (alcohol). IR spectrum, δ, cm^{-1}: 1610 (C=C), 1680 (CON), 3200 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, 4-CH_3); 5.42 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.52 (9H, m, Ph, ClC_6H_4); 7.84 (1H, d, $J_{1,6}$ = 2.4, H-1). 8.65 and 8.66 (1H, 2s, 3-NH and 2-OH); 9.65 (1H, s, NH). Found, %: C 63.16, 63.39; H 4.79, 4.67; N 12.18, 12.43. $C_{18}H_{16}ClN_3O_2$. Calculated, %: C 63.25; H 4.72; N 12.29.

4-Methyl-N-(2-methylphenyl)-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1f). Yield 27%; mp 232-234ºC (alcohol). IR spectrum, δ, cm^{-1}: 1600 (C=C), 1675 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.79 (3H, s, 4-CH_3); 2.24 (3H, s, C$\underline{H}_3C_6H_4$); 5.30 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.42 (1H, d, $J_{1,6}$ = 2.4, H-1); 7.44 (9H, m, Ph, $CH_3C_6\underline{H}_4$); 8.54 and 8.56 (1H, 2s, 3-NH and 2-OH); 8.83 (1H, s, NH). Found, %: C 71.27, 70.93; H 5.85, 6.02; N 13.19, 12.97. $C_{19}H_{19}N_3O_2$. Calculated, %: C 71.01; H 5.96; N 13.07.

4-Methyl-N-(2-methylphenyl)-6-(3-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1g). Yield 64%; mp 225-227ºC (alcohol). IR spectrum, δ, cm^{-1}: 1620 (C=C), 1660 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82 (3H, s, 4-CH_3); 2.21 (3H, s, C$\underline{H}_3C_6H_4$); 5.46 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.48 (8H, m, $NO_2C_6\underline{H}_4$, $CH_3C_6\underline{H}_4$); 7.80 (1H, d, $J_{1,6}$ = 2.4, H-1); 8.98 and 8.99 (1H, 2s, 3-NH and 2-OH); 9.89 (1H, s, NH). Found, %: C 62.38, 62.18; H 4.82, 5.04; N 15.39, 15.18. $C_{19}H_{18}N_4O_4$. Calculated, %: C 62.29; H 4.95; N 15.29.

4-Methyl-N-(2-methylphenyl)-6-(2-methoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1h). Yield 59%; mp 210-212ºC (alcohol). IR spectrum, δ, cm^{-1}: 1600 (C=C), 1670 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.88 (3H, s, 4-CH_3); 2.10 (3H, s, C$\underline{H}_3C_6H_4$); 3.70 (3H, s, CH_3O); 5.67 (1H, d, $J_{1,6}$ = 2.4, H-6); 7.05 (1H, d, $J_{1,6}$ = 2.4, H-1); 7.17 (8H, m, $CH_3C_6\underline{H}_4$, $CH_3OC_6\underline{H}_4$); 8.64 and 8.65 (1H, 2s, 3-NH and 2-OH); 8.88 (1H, s, NH). Found, %: C 68.25, 68.48; H 6.12, 5.95; N 11.03, 12.12. $C_{20}H_{21}N_3O_3$. Calculated, %: C 68.36; H 6.02; N 11.96.

4-Methyl-N-(2,4-dimethylphenyl)-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1i) Yield 27%; mp 257-259ºC (alcohol). IR spectrum, δ, cm^{-1}: 1620 (C=C), 1680 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, 4-CH_3); 2.06 and 2.18 (6H, s, $(C\underline{H}_3)_2C_6H_3$); 5.38 (1H, d, $J_{1,6}$ = 2.5, H-6); 7.23 (8H, m, $(CH_3)_2C_6\underline{H}_3$, Ph); 7.26 (1H, d, $J_{1,6}$ = 2.5, H-1); 8.64 and 8.65 (1H, 2s, 3-NH and 2-OH); 8.89 (1H, s, NH). Found, %: C 71.51, 71.73; H 6.28, 6.42; N 12.41, 12.64. $C_{20}H_{21}N_3O_2$. Calculated, %: C 71.62; H 6.31; N 12.53.

4-Methyl-N-(2-methoxyphenyl)-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1j). Yield 58%; mp 175-177ºC (alcohol). IR spectrum, δ, cm^{-1}: 1600 (C=C); 1675 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 (3H, s, 4-CH_3); 3.64 (3H, s, CH_3O); 5.20 (1H, d, $J_{1,6}$ = 2.5, H-6); 7.51 (1H, d, $J_{1,6}$ = 2.5, H-1); 7.52 (9H, m, $CH_3OC_6\underline{H}_4$, Ph); 8.12 and 8.14 (1H, 2s, 3-NH and 2-OH); 8.74 (1H, s, NH). Found, %: C 67.51, 67.76; H 5.74, 5.52; N 12.36, 12.56. $C_{19}H_{19}N_3O_3$. Calculated, %: C 67.64; H 5.68; N 12.45.

6-(4-Chlorophenyl)-4-methyl-N-(2-methoxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1k). Yield 63%; mp 213-215ºC (alcohol). IR spectrum, δ, cm^{-1}: 1610 (C=C), 1680 (CON), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, 4-CH_3); 3.66 (3H, s, CH_3O); 5.24 (1H, d, $J_{1,6}$ = 2.5, H-6); 7.53 (8H, m, $CH_3OC_6\underline{H}_4$, $ClC_6\underline{H}_4$); 7.64 (1H, d, $J_{1,6}$ = 2.5, H-1); 8.34 (1H, s, NH); 8.87 and 8.89 (1H, 2s, 3-NH and 2-OH). Found, %: C 61.51, 61.26; H 4.98, 4.72; N 11.39, 11.21. $C_{19}H_{18}N_3ClO_3$. Calculated, %: C 61.38; H 4.88; N 11.30.

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