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An efficient microwave assisted synthesis of novel pyrimidine-5-carboxamides

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ABSTRACT

Synthesis of a series of pyrimidines **(4a-j)** was achieved from different acetoacetamides, 4-(2,4-dinitrophenoxy)phenyl aldehyde and urea using microwave irradiation within 5-10 min. with high yields. The structures of the products were supported by FT-IR, PMR and mass spectral data.

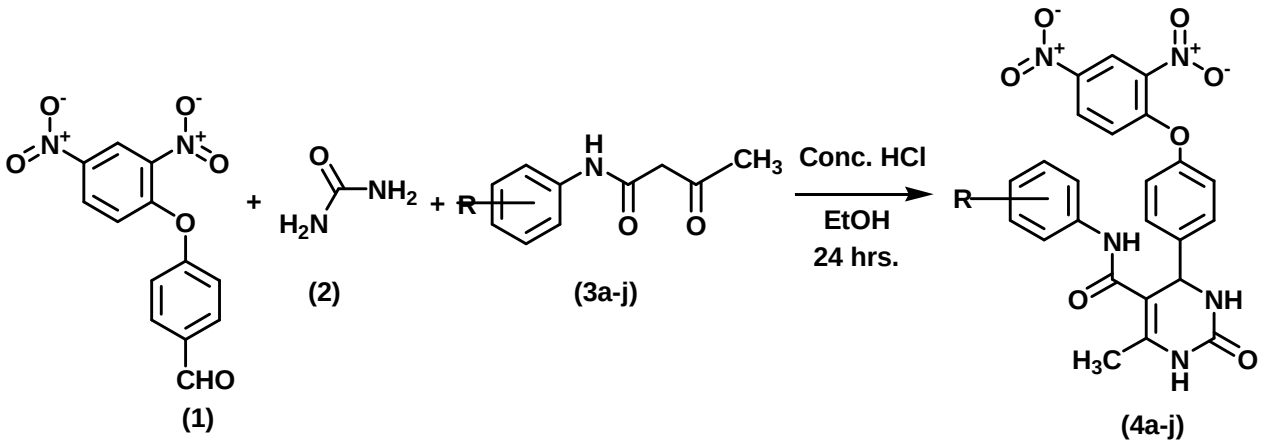
KEYWORDS

Pyrimidines;
Acetoacetamides;
Microwave assisted synthesis.

INTRODUCTION

Pyrimidine and its derivatives have been studied for over a century due to their variety of important chemical and biological applications. Pyrimidine derivatives are of interest because of their pharmacological properties[1-13] including antiviral[2], antihypertensive[4], antitumour[5], antibacterial[6-10] and effects.

Several synthetic strategies have been reported for the preparation of pyrimidine derivatives[5,13-18]. Most of these are based on modification of the classical one-pot Biginelli reaction[5,14-17] and in some cases on more complex multi-step processes involving harsh reaction conditions and long reaction times[18,19]. One major drawback of the classical Biginelli protocol is the low yield that is frequently encountered when using sterically more demanding aldehydes or 1, 3-dicarbonyl compounds[19,20]. The development of simple synthetic



Scheme 1

routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Application of microwave irradiation in achieving this task has been the focus of considerable attention in recent years and is becoming an increasingly popular technology.

In view of these observations, we have developed a new microwave assisted protocol for the synthesis of novel pyridmidines **(4a-j)** with the advantage of short reaction time, high yield and environmentally friendliness (Scheme 1).

EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on BRUKUR spectrophotometer (400MHz). Chemical shifts are expressed in units relative to TMS signal as internal reference. IR spectra were recorded on FT-IR SHIMADZU-FT-IR 8400 spectrophotometer on KBr pallets. Mass spectra were recorded on GCMS QP2010 Gas Chromatograph SHIMADZU. Thin Layer Chromatography (TLC) was performed on silica gel-G using hexane:ethyl acetate solvent system.

Typical experimental procedure for the synthesis of 1,2,3,4 tetrahydropyrimidine-5-carboxamides

A mixture of urea (2 mmol), 4-(2,4-dinitrophenoxy)phenyl aldehyde (1 mmol), acetoacetamide (1 mmol) in absolute alcohol (5 ml) in the presence of catalytic amount of conc. HCl was irradiated in a microwave oven operating medium power (480 watts) for appropriate time. Progress of the reaction was monitored by thin layer chromatography using ethyl acetate:hexane (2:8) solvent system. After completion of reaction, the reaction mixture was allowed to stand at room temperature overnight. The crystalline product separated was recrystallized from absolute alcohol.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4a)

M. p. 221 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 2.02), (s, 1H, -CH) (δ 5.43), (s, 1H, -NH) (δ 5.96), (s, 1H, -NH) (δ 5.99), (d, 3H, Ar-H) (δ 7.20 to 8.23), (m, 7H, Ar-H) (δ 7.02 to 7.67), (s, 1H, Ar-H) (δ 7.67), (s, 1H,-NH) (δ 9.70). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc), Alkane: (-CH3(C-H str. (asym.)2945, C-H str.(sym.)2750, C-H def.(asym.)1469, C-H def.(sym.)1344. Aromatic (C-H str.)3110, Aromatic Ring (C=C str.)1525, C-H (i.p def.) 1074, C-H (o.p. def.) 754). Pyrimidine[(C-N-C(str.v)1344, (C-N(str.v)1278, (N-H,(str.)1600], Nitro: (N-O 1370), Chloro (C-Cl str.(sym,)661. Mass (m/z):523(M-1) Elemental Analysis: C, 55.02; H, 3.46; Cl, 6.77; N, 13.37; O, 21.38 found: C, 54.72; H, 3.26; Cl, 6.47; N, 13.22; O, 21.23.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(4-florophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4b)

M. p. 202 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 1.18), (s, 1H, -CH) (δ 5.56), (s, 1H, -NH) (δ 5.88), (s, 1H, -NH) (δ 6.05), (d,3H, Ar-H) (δ 7.29 to 8.03), (m,7H, Ar-H) (δ 7.01 to 7.62), (s, 1H, Ar-H) (δ 7.71), (s, 1H, -NH) (δ 9.81). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc), Alkane: (-CH3(C-H str.(asym.)2939, C-H str.(sym.)2725, C-H def.(asym.)1452, C-H def.(sym.)1338). Aromatic(C-H str.3105, C=C str. 1532, C-H (i.p def.)1069, C-H (o.p. def.) 786). Pyrimidine[C-N-C(str.v)1339, C-N(str.v)1274, N-H,(str.)1598]. Nitro: (N-O 1365), Fluoro (C-F str.(sym,)658. Mass (m/z): 507(M-1) Elemental Analysis: C, 56.81; H, 3.58; F, 3.74; N, 13.80; O, 22.07 found: C, 56.78; H, 3.50; F, 3.69; N, 13.75; O, 22.01.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(4-methylphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4c)

M. p. 198 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 1.19), (s, 3H, -CH3) (δ 2.14), (s, 1H, -CH) (δ 5.06), (s, 1H, -NH) (δ 5.81), (s, 1H, -NH) (δ 5.92), (d, 3H, Ar-H) (δ 7.11 to 8.35), (m, 7H, Ar-H) (δ 7.01 to 7.64), (s, 1H, Ar-H) (δ 7.64), (s, 1H, -NH), (δ 9.92). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc). Alkane: (-CH3(C-H str.(asym.)2975, C-H str.(sym.)2722, C-H def.(asym.)1456, C-H def.(sym.)1342). Aromatic(C-H str.3099, C=Cstr.1520,C-H (i.p def.)1068, C-H (o.p. def.) 796). Pyrimidine[C-N-C(str.v)1341, C-N(str.v)1271, N-H,(str.)1596]. Nitro: (N-O 1379). Mass (m/z):503(M-1) Elemental Analysis: C, 59.64;

H, 4.20; N, 13.91; O, 22.25 found: C, 59.54; H, 4.11; N, 13.68; O, 22.22.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(4-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4d)

M. p. 191 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 2.23), (s, 3H, -CH3) (δ 3.34), (s, 1H, -CH) (δ 5.21), (s,1H,-NH) (δ 5.96), (s, 1H, -NH) (δ 5.99), (d, 3H, Ar-H) (δ 7.06-8.53), (m, 7H, Ar-H) (δ 7.07 to 7.66), (s, 1H, Ar-H) (δ 7.69), (s, 1H, -NH) (δ 9.90). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc). Alkane: (-CH3(C-H str.(asym.)2968, C-H str.(sym.)2720, C-H def.(asym.)1446, C-H def.(sym.)1348). Aromatic(C-H str.3114, C=Cstr.1529, C-H (i.p def.)1073, C-H (o.p. def.) 801). Ether(C-O-C str.(asym.)1240, C-O-C str.(sym.) 1022). Pyrimidine[C-N-C(str.v)1348, C-N(str.v)1272, N-H,(str.)1592]. Nitro: (N-O1389). Mass (m/z):519(M-1) Elemental Analysis: C, 57.80; H, 4.07; N, 13.48; O, 24.64 found: C, 57.74, H, 4.01; N, 13.34; O, 24.44.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(3-chloro,4-chloro-phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4e)

M. p. 202 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 2.12), (s, 1H, -CH) (δ 5.23), (s, 1H, -NH) (δ 5.88), (s, 1H, -NH) (δ 6.02), (d, 3H, Ar-H) (δ 7.09 to 8.40), (m, 6H, Ar-H) (δ 7.10 to 7.60), (s, 1H, Ar-H) (δ 7.61), (s, 1H, -NH) (δ 9.72). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc), Alkane: (-CH3(C-H str.(asym.)2941, C-H str.(sym.)2752, C-H def.(asym.)1463, C-H def.(sym.)1345). Aromatic(C-H str.3114, C=Cstr.1526, C-H (i.p def.)1077, C-H (o.p. def.) 784). Pyrimidine[C-N-C(str.v)1345, C-N(str.v)1288, N-H,(str.)1610]. Nitro: (N-O 1365), Fluoro (C-F str.(sym,)651), Chloro(C-Cl str.(sym,)661). Mass (m/z):541(M-1) Elemental Analysis: C, 53.20; H, 3.16; Cl, 6.54; F, 3.51; N, 12.92; O, 20.67, found: C, 53.12; H, 3.11; Cl, 6.24; F, 3.45; N, 12.83; O, 20.62.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4f)

M. p. 189 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 2.00), (s, 1H, -CH) (δ 5.38), (s, 1H, -NH) (δ 5.62), (s, 1H, -NH) (δ 5.94), (d, 3H, Ar-H) (δ 7.12 to 8.46), (m, 6H, Ar-H) (δ 7.06 to 7.67), (s, 1H, Ar-H) (δ 7.68), (s, 1H,-NH) (δ 9.88). FT-IR (frequency range: 4000-400cm^{-1}KBr-Disc), Alkane: (-CH3(C-H str.(asym.)2954, C-H str.(sym.)2755, C-H def.(asym.)1465,C-H def.(sym.)1344). Aromatic(C-H str.3118, C=Cstr.1524, C-H (i.p def.)1079, C-H (o.p. def.) 783). Pyrimidine[C-N-C(str.v)1342, C-N(str.v)1282, N-H,(str.)1613]. Nitro: (N-O 1365), Chloro (C-Cl str.(sym,)667) Mass (m/z):523(M-1) Elemental Analysis: C, 55.02; H, 3.46; Cl, 6.77; N, 13.37; O, 21.30, found: C, 55.00; H, 3.11; Cl, 6.24; F, 3.45; N, 13.23; O, 20.60.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4g)

M. p.181 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 1.18), (s, 1H, -CH) (δ 5.28), (s, 1H, -NH) (δ 5.74), (s, 1H, -NH) (δ 5.99), (d, 3H, Ar-H) (δ 7.04 to 8.50), (m, 5H, Ar-H) (δ 7.120 to 7.65), (s, 1H, Ar-H) (δ 7.56), (s, 1H, Ar-H) (δ 7.42), (s, 1H, -NH) (δ 9.85). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc), Alkane: (-CH3(C-H str.(asym.)2951, C-H str.(sym.)2742,.C-H def.(asym.)1471, C-H def.(sym.)1355). Aromatic(C-H str.3124, C=Cstr.1528, C-H (i.p def.)1072,C-H (o.p. def) 782). Pyrimidine[(C-N-C(str.v)1353, C-N(str.v)1287, N-H,(str.)1622]. Nitro: (N-O 1365), Chloro(C-Cl str.(sym,)657) Mass (m/z):551(M-1) Elemental Analysis: C, 55.02; H, 3.46; Cl, 6.77; N, 13.37; O, 21.30, found: C, 55.00; H, 3.14; Cl, 6.21; F, 3.40; N, 12.83; O, 21.25.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(2-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4h)

M. p. 211 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 2.18), (s, 1H, -CH) (δ 5.21), (s, 1H, -NH) (δ 5.54), (s, 1H, -NH) (δ 5.85), (d, 3H, Ar-H) (δ 7.13 to 8.25), (m, 7H, Ar-H) (δ 7.02 to 7.67), (s, 1H, Ar-H) (δ 7.78), (s, 1H, -NH) (δ 9.97). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc). Alkane: (-CH3(C-H str.(asym.)2934, C-H

str.(sym.)2729, C-H def.(asym.)1445, C-H def.(sym.)1335). Aromatic(C-H str.3145, C=Cstr.1524, C-H (i.p def.)1081, C-H (o.p. def.) 797). Pyrimidine[C-N-C(str.v)1332, C-N(str.v)1275, N-H,(str.)1999]. Nitro: (N-O 1374), Fluoro(C-F str.(sym,)668) Mass (m/z):507(M-1) Elemental Analysis: C, 56.81; H, 3.58; F, 3.74; N, 13.80; O, 22.07 found: C, 56.54; H, 3.25; F, 3.64; N, 13.72; O, 22.00.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(2-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4i)

M. p. 203 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 1.21), (s, 3H, -CH3) (δ 3.21), (s, 1H, -CH) (δ 5.42), (s, 1H, -NH) (δ 5.98), (s, 1H, -NH) (δ 5.94), (d, 3H, Ar-H) (δ 7.14 to 8.36), (m, 7H, Ar-H) (δ 7.11 to 7.65), (s, 1H, Ar-H) (δ 7.67), (s, 1H, -NH) (δ 9.99). FT-IR (frequency range: 4000-400 cm^{-1} KBr-Disc). Alkane: (-CH3(C-H str.(asym.)2972, C-H str.(sym.)2755, C-H def.(asym.)1455, C-H def.(sym.)1345). Aromatic(C-H str.3095, C=Cstr.1525, C-H (i.p def.)1064, C-H (o.p. def.) 794) .Pyrimidine[C-N-C(str.v)1345, C-N(str.v)1257, N-H,(str.)1594]. Nitro: (N-O 1378). Mass (m/z):503(M-1) Elemental Analysis: C, 59.64; H, 4.20; N, 13.91; O, 22.25 found: C, 59.44; H, 4.10; N, 13.63; O, 22.11.

4-(4-(2,4-dinitrophenoxy)phenyl)-*N*-(3.4-dichlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4j)

M. p. 192 °C; yellow crystals; ^{1}H NMR (DMSO, 400 MHz): δ ppm (s, 3H, -CH3) (δ 1.23), (s, 1H, -CH) (δ 5.11), (s, 1H, -NH) (δ 5.78), (s, 1H, -NH) (δ 5.98), (d, 3H, Ar-H) (δ 7.11 to 8.40), (m, 6H, Ar-H) (δ 7.14 to 7.64), (s, 1H, Ar-H) (δ 7.65), (s, 1H, -NH) (δ 9.74). FT-IR (frequency range: 4000-400cm^{-1}KBr-Disc). Alkane: (-CH3(C-H str.(asym.)2944, C-H str.(sym.)2754, C-H def.(asym.)1467,,C-H def.(sym.)1344). Aromatic(C-H str.3117, C=Cstr.1524, C-H (i.p def.)1074, C-H (o.p. def.) 787). Pyrimidine[C-N-C(str.v)1345, C-N(str.v)1284, N-H,(str.)1611]. Nitro: (N-O 1367), Fluoro(C-F str.(sym,)671), Chloro(C-Cl str.(sym,)664) Mass (m/z):557(M-1) Elemental Analysis: C, 51.63; H, 3.07; Cl, 12.70; N, 12.54; O, 20.06, found: C, 51.61; H, 3.05; Cl, 12.13; N, 12.25; O, 20.01.

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