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Modified Biginelli Reaction: Synthesis of Pyrimidoquinoline Derivatives

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Compounds having quinolone and pyrimidine skeleton plays an important role in the medicinal chemistry. The objective of the present work was to modify the Biginelli reaction by using heterocylic ketones under microwave condition. We have demonstrated new synthetic route of quinolone fused 1,4-dipyrimidines by the reaction of 6-methyl-4-hyrdoxyquinolin-2(1*H*)-one (**1**), substituted aromatic aldehydes (**2a-g**) with phenyl urea (**3**). The structure of these newly synthesized compounds was characterized IR, NMR, Mass spectral and elemental analysis.

Keywords: Microwave, Quinoline, Beginelli reaction, Pyrimido, Aldehyde.

INTRODUCTION

Now a day, microwave irradiation has been used for a variety of applications including organic synthesis [1-4], wherein chemical reactions are accelerated by selective absorption of microwave energy by molecules. The results on this microwave approach are described for the synthesis of a variety of nitrogen heterocyclic compounds such as acridines, quinolines, naphthyridines and ring fused pyrazolo, pyrano, pyrimido derivatives [5-9]. Microwave irradiation also utilized the synthesis of some quinoline framework natural products like, montanine, edulitine, folimine, *etc*. [10-13].

The nitrogen heterocyclic compounds and their derivatives possess numerous biological activities [14-16]. The presence of quinoline skeleton in the framework of various biologically active compounds with antiasthmatic [17], antibacterial [18], antifungal [19], antimalarial [20], antitumour [21], anti-inflammatory [22] activities continue to promote their synthetic efforts. The recent literature reveals that 1,4-dihydropyrimidine derivatives exhibit good biological activities such as antimicrobial [23], antiviral [24], anti-HIV [25] and anticancer [26,27] activities. In the literature some methods are available for the synthesis of quinoline compounds containing 1,4-dihydropyrimidines. Recently, we reported the synthesis of various pyrimidoquinoline derivatives, including quinoline fused 1,4-dihydropyridines under microwave condition [8,28-31]. Due to the potential interest in finding new versatile procedures, 1,4-dihydropyrimidoquinolines synthesized from 6-methyl-4-hyrdoxyquinolin-2(1*H*)-one, substituted aromatic aldehydes, phenylurea *via* Biginelli reaction under microwave irradiation.

EXPERIMENTAL

Melting points were determined using Boetieus micro heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrophotometer. ^1H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer using TMS as an internal reference (chemical shifts in δ, ppm). Elemental analyses were performed on Perkin Elmer CHN-analyzer. Mass spectra were recorded on Shimadzu GCMS-QP5050A (70 eV) mass spectrometer. Reactions were monitored using thin layer chromatography (TLC) carried out on Merck silica gel 60 F254 pre-coated glass plates. The visualization was achieved under staining with iodine. All reactions were performed in a microwave reactor modified for synthesis.

Preparation of 1,4-diphenyl-9-methyl-1,4-dihyrdo-pyrimido-[5,4-*c*]quinolin-2,5(3*H*,6*H*)-diones (4a-g): A mixture

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of 6-methyl-4-hydroxyquinolin-2(1*H*)-one (**1**) (0.105 g, 0.0006 mol), aromatic aldehydes (**2a-g**) (0.0006 mol), phenyl urea (**3**) (0.0816 g, 0.0006 mol) and 10 mL of dimethyl sulphoxide (DMSO) was taken in a 100 mL round bottom flask. Then round bottom flask fitted with water condenser placed in microwave oven and heated at the power 580 W for specified time. The completion of the reaction was monitored for every 1 min by the TLC. After completion of the reaction, the mixture was poured into ice. The formed product was filtered, washed well with water, dried and purified by column chromatography.

TABLE-1
SYNTHESIS OF 1,4-DIPHENYL-1,4-DIHYDROPRIMIDO[5,4-*c*]QUIONOLINES

Entry	Solvent	Power (watt)	Time (min)	Yield (%)
1	No	320	12	0
2	No	580	12	13
3	DMF	320	10	55
4	DMF	580	10	55
5	THF	320	9	62
6	THF	580	8	65
7	Piperidine	320	9	60
8	Piperidine	580	8	65
9	DMSO	320	6	86
10	DMSO	580	4	97

Spectral data

9-Methyl-1-phenyl-4-(*o*-chlorophenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5 (3*H*,6*H*)-dione (4a): Time: 4 min. Yield: 0.2436 g (97.73 %), m.p.: 270 ºC; IR (KBr, ν_{max}, cm^{-1}): 3203-3336 (>NH) 1685 (>C=O), 1645 (>C=O); ^{1}H NMR (DMSO-d_6) δ, ppm: 2.38 (s, 3H, C_9-CH_3) 6.31 (s, 1H, C_4-H), 6.90-7.50 (m, 11H, Ar-H), 8.49 (s, 1H, C_{10}-H), 12.08 (s, 1H, NH), 13.09 (s, 1H, NH); MS (*m/z*): 415 ($M^{+\bullet}$), 417 ($M^{+\bullet}$+2). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_3O_2Cl$: C, 69.40 (69.37); H, 4.37 (4.31); N, 10.12 (10.18).

9-Methyl-1-phenyl-4-(*m*-chlorophenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5-(3*H*,6*H*)-dione (4b): Time: 6 min, Yield: 0.198 g (79.43 %) m.p.: 194 °C; IR (KBr, ν_{max}, cm^{-1}): 3154-3320 (>NH), 1708 (>C=O), 1645 (>C=O); ^{1}H NMR (DMSO-d_6) δ, ppm: 2.32 (s, 3H, C_9-CH_3), 6.28 (s, 1H, C_4-H), 6.72-8.09 (m, 11H, Ar-H), 8.72 (s, 1H, C_{10}-H), 11.43 (s, 1H, NH), 12.06 (s, 1H, NH). MS (*m/z*): 415 ($M^{+\bullet}$), 417 ($M^{+\bullet}$+2). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_3O_2Cl$: C, 69.40 (69.31); H, 4.37 (4.35); N, 10.12 (10.09).

9-Methyl-1-phenyl-4-(*p*-chlorophenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5-(3*H*,6*H*)-dione (4c): Time: 4 min. Yield: 0.215 g (86.25 %), m.p.: 158 °C; IR (KBr, ν_{max}, cm^{-1}): 3305-3324 (>NH), 1716 (>C=O), 1648 (>C=O); ^{1}H NMR (DMSO-d_6) [δ, ppm]: 2.36 (s, 3H, C_9-CH_3), 6.24 (s, 1H, C_4-H), 6.88-7.96 (m, 11H, Ar-H), 8.69 (s, 1H, C_{10}-H), 11.40 (s, 1H, NH), 12.18 (s, 1H, NH); MS (*m/z*): 415 ($M^{+\bullet}$), 417 ($M^{+\bullet}$+2). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_3O_2Cl$: C, 69.40 (69.35); H, 4.37 (4.34); N, 10.12 (10.09).

9-Methyl-1-phenyl-4-(*p*-nitrophenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5-(3*H*,6*H*)-dione (4d): Time: 4 min. Yield: 0.246 g (92.47 %), m.p.: 172 °C; IR (KBr, ν_{max}, cm^{-1}): 3189-3320 (>NH), 1718 (>C=O), 1635 (>C=O), 1573, 1398; ^{1}H NMR (DMSO-d_6) δ, ppm: 2.39 (s, 3H, C_9-CH_3), 6.21 (s, 1H, C_4-H), 6.91-8.12 (m, 11H, Ar-H), 8.72 (s, 1H, C_{10}-H), 11.440 (s, 1H, NH), 12.048 (s, 1H, NH). MS (*m/z*): 426 ($M^{+\bullet}$). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_4O_4$: C, 67.61 (67.58); H, 4.26 (4.25); N, 13.15 (13.09).

9-Methyl-1-phenyl-4-(*m*-nitrophenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5(3*H*,6*H*)-dione (4e): Time: 9 min. Yield: 0.238 g (93.15 %), m.p.: 166 ºC; IR (KBr, ν_{max}, cm^{-1}): 3315-3331 (>NH), 1720 (>C=O), 1640 (>C=O), 1556, 1380; ^{1}H NMR (DMSO-d_6) δ, ppm: 2.39 (s, 3H, C_9-CH_3), 6.21 (s, 1H, C_4-H), 6.91-8.12 (m, 11H, Ar-H), 8.72 (s, 1H, C_{10}-H), 11.440 (s, 1H, NH), 12.048 (s, 1H, NH). MS (*m/z*): 426 ($M^{+\bullet}$). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_4O_4$: C, 67.61 (67.55); H, 4.26 (4.21); N, 13.15 (13.12).

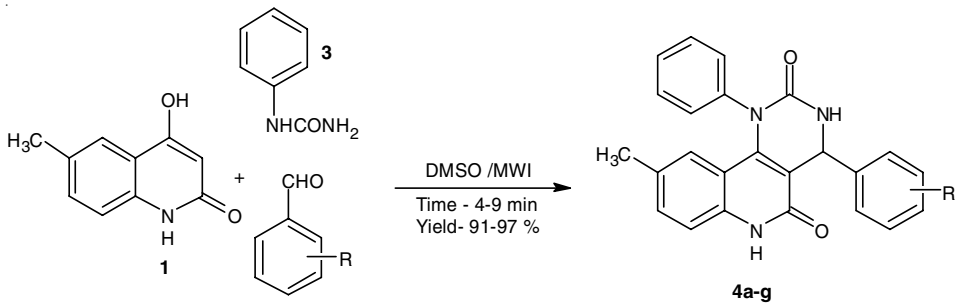
9-Methyl-1-phenyl-4-(*p*-hydroxyphenyl)-1,4-dihydropyrimido[5,4-*c*]quinolin-2,5(3*H*,6*H*)-dione (4f): Time: 4 min. Yield: 0.221 g (92.78 %), m.p.: 162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3312-3328 (>NH), 1721 (>C=O), 1642 (>C=O); ^{1}H NMR (DMSO-d_6) δ, ppm: 2.32 (s, 3H, C_9-CH_3), 6.27 (s, 1H, C_4-H), 6.82-7.91 (m, 11H, Ar-H), 8.87 (s, 1H, C_{10}-H), 11.14 (s, 1H, NH), 12.00 (s, 1H, NH); MS (*m/z*): 397 ($M^{+\bullet}$). Elemental analysis (%) calcd. (found) for $C_{24}H_{19}N_3O_3$: C, 72.59 (72.52); H, 4.82 (4.75); N, 10.58 (10.51).

9-Methyl-1,4-diphenyl-1,4-dihydropyrimido[5,4-*c*]-quinolin-2,5-(3*H*,6*H*)-dione (4g): Time: 6 min. Yield: 0.220 g (96.23 %), m.p.: 178 °C, IR (KBr, ν_{max}, cm^{-1}): 3151-3336 (>NH), 1734 (>C=O), 1643 (>C=O); ^{1}H NMR(DMSO-d_6) [δ, ppm]: 2.37 (s, 3H, C_9-CH_3), 6.41 (s, 1H, C_4-H), 7.18-7.93 (m, 11H, Ar-H), 8.42 (s, 1H, C_{10}-H), 11.62 (s, 1H, NH), 12.58 (s, 1H, NH). MS (*m/z*): 381 ($M^{+\bullet}$). Elemental analysis (%) calcd. (found) for $C_{24}H_{18}N_3O_2$: C, 75.59 (75.56); H, 5.03 (5.01); N, 11.02 (10.58).

RESULTS AND DISCUSSION

In this communication, an elegant methodology of modified Biginelli reaction for derive pyrimidoquinoline derivatives from 6-methyl-4-hydroxyquinolin-2(1*H*)-one (**1**). Our recent approaches of modified Biginelli reaction, to synthesize pyrimidoquinolines under microwave condition [29,30]. The Biginelli reaction are modified by using cyclic ketone like dimedone, cyclohexan-1,3-diketone instead of linear ketone [32,33]. We are using heterocyclic ketones such as 4-hydroxyquinolin-2(1*H*)-one to synthesis various pyrimidoquinolines.

By employing a reaction of 6-methyl-4-hydroxyquinolin-2(1*H*)-one (**1**), substituted benzaldehyde (**2a-g**) and phenyl urea (**3**), the reaction conditions were optimized under microwave irradiation (**Scheme-I**). The reaction was first carried out in the absence of the solvent and it was found that the reaction did not proceed and trace amount (Table-1, entry 1 & 2). We demonstrated the effect of various solvents such as DMSO, piperidine, DMF and THF under the same reaction conditions. The DMSO solvent condition afforded the products in higher yield and shorter reaction time (Table-1). The optimized condition extends to derivatives of target compound. The IR spectrum of target compound **4a** showed absorptions at 1685 and 1645 cm^{-1} for carbonyl groups and broad absorption band at 3336-3203 cm^{-1} for >NH groups. The ^{1}H NMR spectrum registered two singlets at δ 12.08 and 13.09 for two



a R = *o*-Cl, **b** R = *m*-Cl, **c** R = *p*-Cl, **d** R = *p*-NO_2, **e** R = *m*-NO_2, **f** R = *p*-OH, g R = H

Scheme-I: Synthesis of pyrimido[5,4-*c*]quinolines (**4a-g**)

NH groups; a multiplet in the region δ 6.90-7.50 for eleven aromatic protons and three singlets at δ 6.31, 8.49, 2.38 for C_4-, C_9 and methyl protons respectively.

The mass spectrum showed a molecular ion peak at *m/z* 415 [M^+] and 417 [M^++2]. The analytical values: C, 69.40; H, 4.37; N, 10.12 % (calcd.); C, C, 69.37; H, 4.31; N, 10.18 % (Found) agreed well with the molecular formula, $C_{24}H_{18}N_3O_2Cl$. From all the above spectral values we confirmed the compound **4a** as 9-methyl-1-phenyl-4-(*o*-chlorophenyl)-1,4-dihydro-pyrimido-[5,4-*c*]quinolin-2,5(3*H*,6*H*)-dione.

Conclusion

In conclusions, 6-methyl-4-hydroxyquinolin-2(1*H*)-ones are efficient precursor for synthesis of variety of novel ring fused quinolines. Moreover, the target compounds 1,4-dihydro-pyrmido[5,4-*c*]quinolones were prepared from 6-methyl-4-hydroxyquinolin-2(1*H*)-one, phenyl urea and aromatic aldehydes *via* Biginelli reaction. The notable features of this protocol, easy work of the products, mild reaction condition and moderate to excellent yields, short reaction times and cleaner reaction.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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