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Green Synthesis of Pyrimido[4,5-*b*]quinolin-2,4(1*H*,3*H*)-ones.

Vetrivel Nadaraj[1], Senniappan Thamarai Selvi[2]*, Maharajan Abirami[3] and Thangaian Daneil Thangadurai[4].

[1]Department of Chemistry, Tamilnadu College of Engineering, Coimbatore-641659, Tamil Nadu, India.
[2]Department of Chemistry, L.R.G. Govt. Arts College for Women, Tirupur-641 604, Tamil Nadu, India.
[3]Department of Chemistry, Sri Ramakrishna Engineering College, Coimbatore-641022, Tamil Nadu, India.
[4]Department of Nanotechnology, Sri Ramakrishna Engineering College, Coimbatore-22, Tamil Nadu, India.

ABSTRACT

Pyrimidine and fused pyrimidine plays an important role in the medicinal chemistry. Due to interesting activity of various substituted pyrimidines as biological agents considerable attentions have focused on this class. In the present communication, we have reported synthetic studies of fused pyrimidines extensively by the reaction of various substituted 2-chloroquinolin-3-carboxylic acids with phenyl urea. The structure of these newly synthesized compounds was characterized by standard spectroscopic and analytical techniques.

Keywords: quinoline, urea, pyrimidine, solvent-less

Corresponding author

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INTRODUCTION

The heterocyclic compounds and their derivatives possess various pharmacological properties and treating for various diseases [1]. Heterocyclic skeleton having nitrogen and sulfur are the most fascinated compound by scientists due to their diverse biological activities [2-5]. Among them, nitrogen heterocyclic compounds like, pyrimidines and quinolines plays a vital role in the medicinal research, because it posses promising antitumor [6, 7], anti-inflammatory [8, 9], antimicrobial [10, 11], analgesic [12], macrophage activation [13] and anti-HIV activities [14, 15]

In recent years, environment-friendly reaction processes have extensively been studied from the stand point of green chemistry [16, 17]. The development of environmentally improved new synthetic routes, which are need to reduce the amount of toxic waste and by- product arising from chemical processes requires increasing emphasis on the use of less toxic and environ-mentally compatible materials [18, 19]. In recent years, the interest in microwave assisted reaction is increasing as green reaction media for synthetic organic chemistry [20, 21]. Due to the potential interest in finding more new versatile procedures, a microwave-assisted efficient method for the synthesis of biologically active compounds such as pyrimidoquinoline, in one-step would be highly valuable and desirable.

EXPERIMENTAL SECTION

Melting points (mp) 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 d, 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.

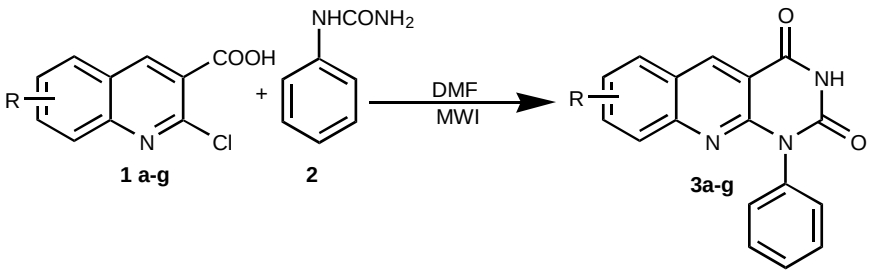
Preparation of 1-phenylpyrimido[4,5-*b*]quinolin-2,4(1*H*, 3*H*)-diones (3a-g)

General procedure: A mixture of 2-chloroquinoline-3-carboxylic acid (**1a-g**), phenyl urea and 5 drops of N,N-dimethylformamide (DMF) was taken in a 100 ml beaker and mixed well. Then the content of the beaker was irradiated under microwave oven at the power 320 W for specified time (**Table 1**). 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.

RESULTS AND DISCUSSION

With the aim to develop more efficient processes, reduce the number of separate reaction steps, and minimize byproducts for the synthesis of pyrimidoquinoline, and in continuation of our previous work [22, 23] on the development of new and efficient methods for the preparation of heterocyclic compounds, a convenient, practical, inexpensive, rapid procedure for the preparation of pyrimido[4,5-b]quinoline derivatives **3a-g** was reported (**Scheme 1**).

Scheme 1



3a R = H, **3b** R = 7-CH_3, **3c** R = 9-CH_3, **3d** R = 7-OCH_3, **3e** R = 9-OCH_3, **3f** R = 7-Cl, **3g** R = 7-Br

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Table 1: Spectral and analytical data of compounds 3a-g

Compd	Reaction Time (min)	Yield (%)	mp (°C)	IR (KBr) [ν_{max} cm^{-1}]	MS (70eV) $M^{1\cdot}$ (*m/z*)	Molecular formula	Analysis (%) Calcd. Found	^{1}H-NMR (DMSO-d_6) [δ, ppm]
3a	6	86	>300	3300-3160 (NH) 1718, 1665 (>C=O)	289	$C_{17}H_{11}N_3O_2$	C 70.59 70.52 H 3.84 3.80 N 14.53 14.49	12.33 (s, 1H, NH), 8.97 (s, 1H, C_5-H), 7.30-8.00 (m, 9H, Ar-H)
3b	5	87	260	3330-3190 (NH) 1715, 1660 (>C=O)	303	$C_{18}H_{13}N_3O_2$	C 71.29 71.22 H 4.32 4.28 N 13.86 13.81	12.30 (s, 1H, NH), 8.93 (s, 1H, C_5-H), 8.50 (s, 1H, C_6-H), 7.26-7.93 (m, 7H, Ar-H), 2.60 (s, 3H, C_7-CH_3)
3c	7	88	205	3320-3200(NH) 1717, 1662 (>C=O)	303	$C_{18}H_{13}N_3O_2$	C 71.29 71.20 H 4.32 4.26 N 13.86 13.79	12.34 (s, 1H, NH), 8.90 (s, 1H, C_5-H), 7.30-8.00 (m, 8H, Ar-H), 2.67 (s, 3H, C_9-CH_3)
3d	9	78	200	3295-3150 (NH) 1710, 1667 (>C=O)	319	$C_{18}H_{13}N_3O_3$	C 67.71 67.70 H 4.11 4.09 N 13.17 13.14	12.02 (s, 1H, NH), 8.91 (s, 1H, C_5-H). 7.28-8.15 (m, 8H, Ar-H), 3.89 (s, 3H, C_7-OCH_3)
3e	8	90	235	3350-3190 (NH) 1708, 1660 (>C=O)	319	$C_{18}H_{13}N_3O_3$	C 67.71 67.68 H 4.11 4.05 N 13.17 13.11	12.20 (s, 1H, NH), 8.87 (s, 1H, C_5-H). 7.38-8.26 (m, 8H, Ar-H), 3.88 (s, 3H, C_9-OCH_3)
3f	12	82	285	3290-3110 (NH) 1718, 1665 (>C=O)	323	$C_{17}H_{10}N_3O_2Cl$	C 63.16 63.15 H 3.12 3.09 N 13.00 12.91	12.30 (s, 1H, NH), 8.80 (s, 1H, C_5-H). 7.40-8.32 (m, 8H, Ar-H)
3g	12	70	233	3320-3230 (NH) 1712, 1664 (>C=O)	367	$C_{17}H_{10}N_3O_2Br$	C 55.59 55.55 H 2.75 2.69 N 11.44 11.41	12.28 (s, 1H, NH), 8.91 (s, 1H, C_5-H). 7.42-8.31 (m, 8H, Ar-H)

Substituted quinolin-3-carboxylic acid were initially synthesized from oxidation of 2-chloro-3-formylquinoline and corresponding substituted anilines. The title compounds (**3a-g**) were synthesized by refluxing 2-chloroquinolin-3-carboxylic acid (**1a**-**g**) with Phenyl urea (**2**) and catalytic amount of DMF under microwave irradiation (**Scheme 1**). The reaction was monitored by thin layer chromatography (TLC) and spots were visualized in iodine chamber. After completion of the reaction, the reaction mixture was poured into ice water. The yellow solid obtained was filtered, washed, dried and recrystalised from ethanol. All the synthesized compounds characterized by IR, NMR, Mass Spectra and analytical data.

In general, the IR spectral data of all the compounds showed characteristic peaks around 3300- 3160 cm^{-1} for >NH group, 1665, 1720 cm^{-1} for >C=O supports the formation of pyrimido[4,5-b]quinoline derivatives. Similarly, ^{1}H-NMR spectrum registered two singlet around δ 12.33 for >NH and δ 8.97 for C_5-H and multiplet appeared around δ 7.30-8.00 for aromatics protons. The mass spectrum showed a molecular ion peak at *m*/*z* at 289 (37%) and elemental analysis (Calcd: C, 70.59; H, 3.84; N,14.53. Found: C, 70.52; H, 3.80; N, 14.49) agreed with its molecular formula $C_{17}H_{11}N_3O_2$. From the above spectral data, the structure of the compound **3a-g** was confirmed as 1-phenylpyrimido[4,5-*b*]quinolin-2,4(1*H*, 3*H*)-dione.

CONCLUSIONS

In this context, we introduce an efficient procedure for synthesis of pyrimido[4,5-b]quiniolines, from 2-chloro-3-formylquinoline derivatives and phenyl urea under microwave irradiation without any solvent. The current method presents a simple and useful synthetic process for quinolines because of the high yield, short reaction time, straightforward and easy work-up procedure. Use of microwave irradiation as the novel source and efficient for organic synthesis.

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