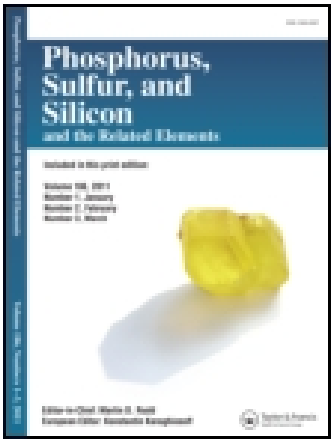

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A Convenient One-Pot Synthesis of Some New 3-(2-Phenyl-6-(2-thienyl)-4-pyridyl)hydroquinolin-2-ones Under Microwave Irradiation and Their Antimicrobial Activities

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A CONVENIENT ONE-POT SYNTHESIS OF SOME NEW 3-(2-PHENYL-6-(2-THIENYL)-4-PYRIDYL) HYDROQUINOLIN-2-ONES UNDER MICROWAVE IRRADIATION AND THEIR ANTIMICROBIAL ACTIVITIES

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A series of 3-(2-phenyl-6-(2-thienyl)-4-pyridyl)hydroquinolin-2-ones 4a–o were synthesized in high yields by a one–pot cyclocondensation reaction under Kröhnke's reaction conditions using 2-chloro-3-formyl quinoline 1a–c, 2-acetyl thiophene 2, and various N-phenacylpyridinium bromides 3a–e in a mixture of ammonium acetate and acetic acid by microwave irradiation. All the compounds have been characterized by elemental analysis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectral analysis. These compounds have been screened for their antimicrobial activities.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords 2-Acetyl thiophene; anti-microbial activity; 2-chloro-3-formyl quinoline; Kröhnke reaction condition; microwave irradiation; various *N*-phenacylpyridinium bromides

INTRODUCTION

The polysubstituted pyridines are prominent building blocks in supramolecular chemistry with their π-stacking and directional H-bonding ability.[1,2] The pyridyl heterocyclic core is also a widespread subunit in numerous natural products and pharmaceuticals.[3,4] These facts provide the basis for the development of new efficient synthetic pathways for pyridines. Polysubstituted pyridines have been synthesized using an enormous number of preparative approaches such as [5+1]-type Hantzsch synthesis from 1,5-diketone and nitrogen derivatives,[5,6] [3+3]-type cyclization of chalcones and iminophosphoranes,[7] [4+2] reactions of unsaturated imines with enolates,[8] and [3+2+1]-type cyclization of α,β-unsaturated compounds with α-substituted ketones and a nitrogen source.[9] Among these approaches, the latter approach is the most frequently employed. The two-step Kröhnke synthesis[10–12] via condensation of α,β-unsaturated ketones with pyridinium salts in the presence of a mixture of ammonium acetate and acetic acid gives a variety of polysubstituted pyridines and has distinct advantages over the other routes. The drawback of this

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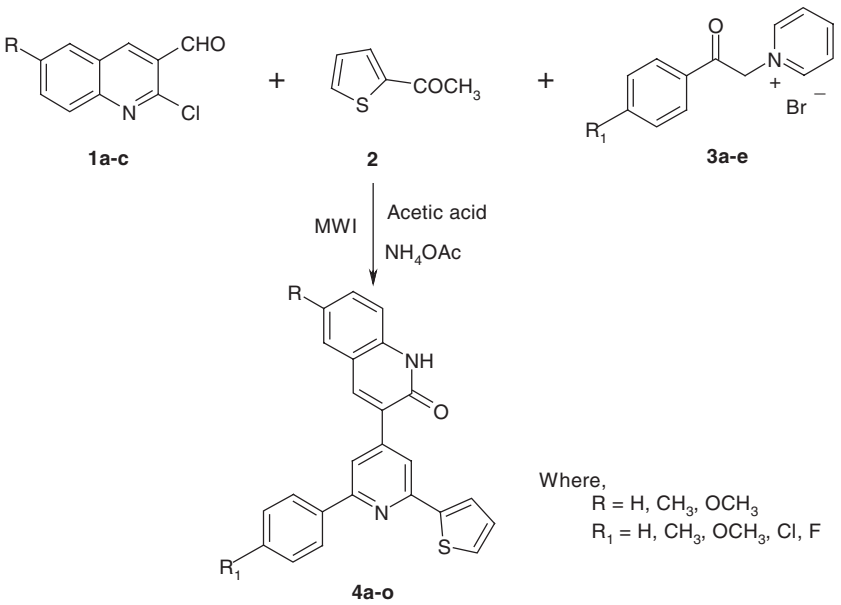
method is that pyridinium salts and α,β-unsaturated ketones have to be prepared first. To overcome this problem Chao-Guo Yan and his coworkers[13] have described a simple but effective modification of the Kröhnke's synthesis of pyridines in one-pot reactions of *N*-phenacylpridinium bromide with aromatic aldehydes and acetophenone in the presence of ammonium acetate and acetic acid under microwave irradiation to give polysubstituted pyridine derivatives. A literature survey reveals that a number of pyridine[14,15] derivatives have been synthesized by Kröhnke reaction conditions using various aldehydes, but not a single reference has been found where 2-chloro-3-formyl quinoline is used. We report in this article biologically active new pyridine derivatives containing quinoline moiety by Kröhnke reaction conditions utilizing this heterocyclic aldehyde[16–18] by microwave irradiation.

Recently, the synthesis of organic compounds assisted by microwaves[19,20] has become an improved technique due to greater selectivity, rapid transfer of energy, significant practical simplicity, and pure products. Compared with classical heating, microwave-assisted organic synthesis is characterized by spectacular acceleration, higher yields, milder reaction conditions, and shorter reaction times as well as allowing synthesis to become environmentally benign, improving many processes.[21,22] The coupling of microwave technology with one-pot multicomponent condensation reactions has received significant attention,[23] since two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. This leads to reduction of time and energy and constitutes overall an economical way of developing new pharmaceutically important compounds.[24]

RESULTS AND DISCUSSION

Under microwave irradiation, 2-chloro-3-formyl quinoline **1a–c**, 2-acetyl thiophene **2**, and *N*-phenacylpyridinium bromide **3a–e** in the presence of ammonium acetate and acetic acid reacted smoothly to give **4a–o** in high yield (78–90%). The required 2-chloro-3-formyl quinoline **1a–c** was prepared by Vilsmeier–Haack reaction,[25] and *N*-phenacylpyridinium bromide **3a–e** was prepared by the procedure in the literature.[26]

The formation of compounds **4a–o** involves the Kröhnke mechanism (see Scheme S1, available online in the Supplemental Materials). The reaction is homogeneous and proceeds via 2-chloro-3-formyl quinoline **1a–c**, reacted first with 2-acetyl thiophene **2** to form an α,β-unsaturated ketone (**4I**). **4I** is further reacted with *N*-phenacylpyridinium bromide **3a–e** to give 1,5-diketone derivatives (**4II**). The cyclization of **4II** occurs with ammonia, and finally the pyridine cation is eliminated with the formation of 3-(2-phenyl-6-(2-thienyl)-4-pyridyl) hydroquinolin-2-ones[27,28] **4a–o**. During the course of the reaction, 2-chloro quinoline is converted into 2-quinolones,[29] The structures of compounds **4a–o** were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra. The IR spectra of **4a** exhibited absorptions at 3180 for –NH–, 3010 for aromatic C−H stretching, 1655 for (carbonyl group), and 1420–1600 cm^{-1} for C=C aromatic and C=N stretching of pyridine. The ^{1}H NMR of **4a** showed a singlet at δ 12.12 for –NH– proton and aromatic protons resonate as multiplets at 7.21–8.54. The ^{13}C NMR spectrum of **4a** showed signals at δ 128.89 (−CH−C−S−), 131.65 (−CO−C−), 138.84 (−NH−C−), 140.15 (−N=C−C−), 145.32 (=N−C−C-S−), 146.40 (−CO−C−C=), 152.10 (−C−N−), 156.03 (−C=N−), 115.43–139.42 for aromatic carbon, and the carbonyl carbon was observed at 161.10. The structure was further confirmed by its mass spectral studies. It gave a molecular ion peak at *m/z* 381 (M+1) corresponding to the molecular formula $C_{24}H_{16}N_2OS$ (Scheme 1). All the compounds were screened for their antibacterial and antifungal activities using ciprofloxacin, ampicillin, and griseofulvin as standard drugs.



Scheme 1

EVALUATION OF ANTIMICROBIAL ACTIVITY

The in vitro antimicrobial activity of compounds **4a–o** was carried out against 24-h old cultures of three bacteria: *Escherichia coli* as Gram-negative bacteria and *Bacillus substilis* and *Staphylococcus aureus* as Gram-positive bacteria, and two fungi: *Aspergillus niger* and *Rhizopus oryzae* by the disc-diffusion method.[30,31] (For full details regarding antimicrobial activity, see the Supplemental Materials online and Table S1.)

EXPERIMENTAL

All melting points were taken in open capillaries and are uncorrected. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was run using TLC aluminum sheets silica gel 60 F_{254} (Merck). Elemental analysis (% C, H, N) was carried out by a Perkin Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using solvent peak as the internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. The microwave oven (700 W) used was a modified microwave oven (RAGA's Electromagnetic Systems).

Preparation of 3-(2-Phenyl-6-(2-thienyl)-4-pyridyl)hydroquinolin-2-ones 4a–o

2-Chloro-3-formyl quinoline (0.5 g, 0.0026 mol), 2-acetyl thiophene (0.28 mL, 0.0026 mol), *N*-phenacylpyridinium bromide (0.72 g, 0.0026 mol), ammonium acetate (2.0 g, 0.026 mol), and acetic acid (5 mL) were charged in a 25 mL round bottom flask.

Table I Substitutes on compounds **4a–o**

Compound	R	R_1
4a	H	H
4b	CH_3	H
4c	OCH_3	H
4d	H	CH_3
4e	CH_3	CH_3
4f	OCH_3	CH_3
4g	H	OCH_3
4h	CH_3	OCH_3
4i	OCH_3	OCH_3
4j	H	Cl
4k	CH_3	Cl
4l	OCH_3	Cl
4m	H	F
4n	CH_3	F
4o	OCH_3	F

The flask was heated for 4–6 min at 118°C under microwave irradiation (at 420 W). The reaction was monitored by TLC; after the completion of reaction, the reaction mixture was cooled to room temperature and stirred for 30 min, and the resulting solid was collected by filtration and washed with water. The crude product was purified by leaching in an equimolar mixture of chloroform and methanol (20 mL) to obtain the pure solid sample **4a–o**. A sample characterization is given, and the remainder of the data are found in the Supplemental Materials online.

3-(2-Phenyl-6-(2-thienyl)-4-pyridyl)hydroquinolin-2-one 4a

A pale yellow solid**,** mp 295–296°C, yield: (90%). Anal. Calcd. for $C_{24}H_{16}N_2OS$ (380.47): C, 75.76; H, 4.23; N, 7.36. Found: C, 75.61; H, 4.36; N, 7.54%. IR (KBr): 3180 (N−H stretching), 3010 (aromatic C−H stretching), 1655 (>C=O stretching), 1420–1600 (C=C aromatic and C=N stretching of pyridine), 690 (C−S stretching) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.21–8.54 (15H, m, Ar−H), 12.12 (1H, s, NH) ppm; ^{13}C NMR: δ 115.43, 117.20, 118.62, 119.71, 122.65, 125.91, 127.13, 128.96, 129.07, 129.21, 129.27, 129.75, 139.42 (−C−Ar−), 128.89 (−CH−C−S−), 131.65 (−CO−C−), 138.84 (−NH−C−), 140.15 (−N=C−C−), 145.32 (=N−C−C−S−), 146.40 (−CO−C−C=), 152.10 (−C−N−), 156.03 (−C=N−), 161.10 (−CO−NH−) ppm; Mass: *m/z*: 381 (M+1).

CONCLUSION

A simple and efficient, one-pot procedure has been followed for the generation of polysubstituted pyridines with microwave assistance. The method allows the introduction of various substituted alkyl and aryl groups into the 2-, 4-, and 6-positions of pyridine. It can be concluded from Table I that among all the compounds, **4e** and **4m** showed good antibacterial activity against the tested organisms *E. coli* and *S. aureus*, while compounds **4d** and **4m** showed good antibacterial activity against the tested organism *B. subtilis*. The compounds **4h**, **4l**, and **4m** against the tested organism *R. oryzae* and compounds **4d** and **4n** against the tested organism *A. niger* showed good antifungal activity, while the remaining

compounds of the series were moderately active against the tested organisms *E. coli*, *S. aureus*, *B. subtilis*, *A. niger*, and *R. oryzae.*

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