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Facile One-Pot Synthesis of Diversely Substituted Tetrahydroquinolines

Nirali S. Mewada
Department of Chemistry, Government Science College, Gandhinagar, Gujarat, India

ABSTRACT

A facile one-pot synthesis of novel 4-quinolinyl substituted 2-alkoxy-5,6,7,8--tetrahydroquinoline-3-carbonitriles by microwave-assisted reactions of cyclohexanone and arylidene malononitriles in presence of sodium in the corresponding alcohols is described. All the newly synthesized compounds were characterized by various spectroscopic techniques and by elemental analyses. The newly synthesized compounds were evaluated for their antimicrobial activities.

Keywords: Tetrahydroquinolines, Quinolyl, Antimicrobial Activity

I. INTRODUCTION

As a privileged fragment, quinoline is a ubiquitous subunit in many quinoline-containing natural products with remarkable biological activities[1,2].

Recently, the 5,6,7,8-tetrahydroquinolines have drawn considerable attention due to their interesting pharmacological applications as RET tyrosine kinase inhibitors [3], anti-HIV [4,5], anti-fungal [6], anti-cancer [7], C5a receptor antagonists agents [8].

Literature survey revealed that most of the reported literature describe the synthesis of 1,2,3,4-tetrahydroquinoline nucleus [9-11] and concise methods to access usefully functionalized 5,6,7,8-tetrahydroquinolines are scarce in the literature [12].
In view of these observations and as part of a continuing effort in our laboratory towards the development of new methods for the expeditious synthesis of biologically active heterocyclic compounds,[13] we report herein, a simple and efficient microwave-assisted synthesis of novel 4-quinolinyl substituted 2-alkoxy 5,6,7,8-tetrahydroquinoline-3-carbonitriles.

All the newly synthesized compounds were evaluated for their antibacterial and antifungal activity. The biological activity of the synthesized compounds was compared with reference standard drugs.

II. METHODS AND MATERIAL

All reagents were of analytical grade and used directly. All the melting points were determined in open glass capillary and are uncorrected. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel-G coated aluminum plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation. The synthesized compounds were purified by recrystallization and/or column chromatography. The IR spectra were recorded on BRUKER TENSOR Series using KBr pellets. 1H NMR spectra were recorded on 300 MHz BRUKER ULTRASHIELD using DMSO-d_6 as a solvent and TMS as an internal reference and chemical shift values were expressed in δ ppm.

General procedure for synthesis of 4-quinolinyl substituted 2-alkoxy 5,6,7,8-tetrahydroquinoline-3-carbonitriles (3a-e)

A mixture of cyclohexanone **1** (2.5 mmol), arylidene malononitrile **2a-e** (2.5 mmol) in the appropriate alcohol (15 mL) containing sodium (0.05 g) was irradiated under microwaves at 300 W for an appropriate time. The separated solid was collected, washed with water and then with methanol affording the corresponding **3a-e** in good purity.

2-Methoxy-4-(2-chloro-6-fluoroquinolin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile 3a.

Yield: 93%; m.p. 178-180 ^{o}C; IR (KBr, cm^{-1}): 2219, 1640, 1263, 1092; ^{1}H NMR (DMSO-d$_6$, δ / ppm): 1.53-1.60 (m, 2H), 1.68-1.78 (m, 2H), 2.71-2.78 (m, 2H), 2.05-2.12 (m, 1H), 2.34-2.42 (m, 1H), 3.81 (3H, s), 7.74-7.77 (m, 1H), 7.11-7.16 (m, 1H), 7.30-7.33 (m, 1H), 8.00 (s,1H); MS (m/z): 367 (M+).

2-Methoxy-4-(2,7-dichloroquinolin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile 3b.

Yield: 95%; m.p. 193-195 ^{o}C; IR (KBr, cm^{-1}): 2228, 1612, 1288, 1052; ^{1}H NMR (DMSO-d$_6$, δ / ppm): 1.52-1.79 (m, 4H), 2.02-2.15 (m, 1H), 2.35-2.41 (m, 1H), 2.75-2.85 (m, 2H), 3.80 (3H, s), 8.04-8.07 (d, 1H), 7.51-7.54 (m, 1H), 7.77-7.78 (d, 1H), 8.17 (s,1H); MS (m/z): 384 (M+).

2-Methoxy-4-(2,6-dichloroquinolin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile 3c.

Yield: 91%; m.p. 214-216 ^{o}C; IR (KBr cm^{-1}): 2222, 1608, 1262, 1061; ^{1}H NMR (DMSO-d$_6$, δ / ppm): 1.63-1.78 (m, 4H), 2.74-2.81 (m, 2H), 2.02-2.13 (m, 1H), 2.37-2.41 (m, 1H), 3.72 (3H, s), 7.79-7.83 (d, 2H), 7.40-7.42 (m, 1H), 7.17-7.19 (d,1H); MS (m/z): 384 (M+).

2-Methoxy-4-(2-chloro-6-bromoquinolin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile 3d.

Yield: 89%; m.p. 204-206 ^{o}C; IR (KBr, cm^{-1}): 2220, 1585, 1278, 1064; ^{1}H NMR (DMSO-d$_6$, δ / ppm): 1.61-1.75 (m, 4H), 2.74-2.80 (m, 2H), 2.08-2.15 (m, 1H), 2.32-2.41 (m, 1H), 3.75 (3H, s), 7.90-7.91 (d, 1H), 7.09-7.15 (m, 2H), 8.13 (s, 1H); MS (m/z): 428 (M+).

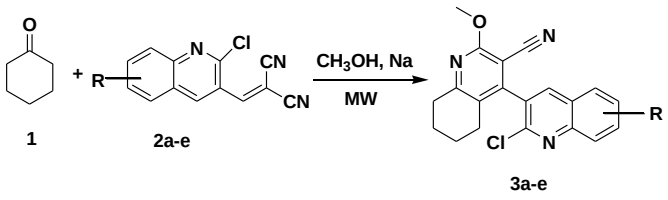
2-Methoxy-4-(2-chloro-6-nitroquinolin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile 3e.

Yield: 88%; m.p. 202-204 ^{o}C; IR (KBr, cm^{-1}): 2224, 1622, 1276, 1066; ^{1}H NMR (DMSO-d$_6$, δ / ppm): 1.63-1.76 (m, 4H), 2.69-2.76 (m, 2H), 2.08-2.17 (m, 1H), 2.31-2.43 (m, 1H), 3.83 (3H, s), 8.04-8.07 (d, 1H), 7.51-7.54 (m, 1H), 7.77-7.78 (d, 1H), 8.17 (s,1H); MS (m/z): 394 (M+).

III. RESULTS AND DISCUSSION

Chemistry:

Herein, we report the efficient and rapid microwave-assisted one-pot synthesis of novel 4-quinolinyl substituted 2-alkoxy tetrahydroquinoline-3-carbonitriles. Treatment of cyclohexanone **1** with arylidene malononitriles **2** in corresponding alcohols in presence of sodium under microwave irradiation at 300 W afforded the 4-quinolinyl substituted 2-alkoxy 5,6,7,8-tetrahydroquinoline-3-carbonitriles **3a-e** in excellent yields (88-95%) in very short time **(Scheme 1)** as compared to the conventional heating producing lower yields after long reaction times (9-15 h).



Scheme-1

Code	R	Time (min.)	Yield %
3a	6-F	8	93
3b	7-Cl	11	95
3c	6-Cl	12	91
3d	6-Br	9	89
3e	6-NO_2	10	88

All the newly synthesized 2-methoxy-5,6,7,8-tetrahydroquinolines **3a-e** were cHracterized by IR, ^{1}H NMR, mass spectroscopic techniques and elemental analyses. The IR spectra of **3a-e** revealed the appearance of confirmatory bands characteristics of stretching vibrations of 2228-2219 cm^{-1} (-CN), 1640-1585 cm^{-1} (C=N) groups. Furthermore, asymmetric and symmetric stretching vibration bands of ether (C-O-C) linkage were also obtained in IR spectra in the range of 1288-1262 cm-1 and 1092-1052 cm^{-1} respectively, which confirmed the presence of 2-methoxy group. The ^{1}H NMR spectra of compounds **3a-e** showed confirmatory signals in the range of δ 3.72 - δ 3.83 ppm as a singlet for (-OCH_3), which confirmed the structure.

Antimicrobial screening

All the synthesized compounds **3a-e** exhibited moderate to good antimicrobial activity. Compound **3c** showed the highest activity against all the bacteria and fungi. Compounds **3b** and **3e** also showed fairly good antibacterial activity as compared to the standard drugs Ampicillin and Chloramphenicol. Compounds **3a** and **3e** exhibited good antifungal activity against A. niger as compared to the standard Griseofulvin. Results of antimicrobial evaluation are summarized in **Table-1**.

Table-1. Antimicrobial Evaluation of 3a-e.

No.	R	Zone of Inhibition in mm				
		S.p.	S.a.	E.c.	B.s.	A.n.
3a	6-F	12	12	10	08	16
3b	7-Cl	14	14	13	13	11
3c	6-Cl	15	15	16	14	17
3d	6-Br	13	13	10	10	12
3e	6-NO_2	14	14	13	14	16
	Ampicillin	16	18	16	18	-
	Chloramphenicol	18	16	19	16	-
	Ciprofloxacin	23	17	20	19	-
	Griseofluvin	-	-	-	-	20

IV. CONCLUSION

We have reported a new and efficient microwave-assisted synthesis of novel 4-quinolinyl substituted 2-alkoxy 5,6,7,8-tetrahydroquinoline-3-carbonitriles from cyclohexanone and arylidene malononitriles. Considering the availability of the starting materials, the simple reaction procedure, simple work-up and the robust nature of this chemical process provides a very straightforward route to construct various highly functionalized tetrahydroquinoline-3-carbonitriles.

The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against standard strains. These results make them interesting lead molecules for further synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise towards the pursuit of discovering novel classes of antimicrobial agents. Further studies to acquire more information concerning structure–activity relationships are in progress.

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