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Full Paper

Synthesis and characterization of 12-methyl-7-phenylbenzo[*h*]naphtho[*b*][1,6]naphthyridin-8-one derivatives

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ABSTRACT: *A simple and efficient procedure has been described for the synthesis of 12-methyl-7-phenylbenzo[h]naphtho[b][1,6]naphthyridin-8-ones 3a-g by the multi-component reaction of 4-hydroxy-6-methylquinolin-2(1H)-one* ***1*** *with 1-naphthylamine 2 and a variety of aldehydes under microwave irradiation condition. The structures of the newly synthesized compounds were confirmed by analytical and spectral (IR, NMR, and Mass) data.*

Keywords*: condensation; microwave; naphthyridine; naphthylamine; quinoline*

Introduction

Recently there has been an increased interest in the synthesis of naphthyridine and their application in medicinal chemistry as quinoline bioisosteres. The main driving force towards the synthesis of naphthyridine is the search for compounds of therapeutic importance [1, 2]. A large number of derivatives of the naphthyridines and related systems are synthesized for chemotherapeutic and pharmacological evaluation. 1,6-Naphthyridine derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activities such as antibacterial activities [3, 4], antitumor activities [5], antifungal activities [6], muscle relaxant activity [7] and insecticidal activity [8]. Some of the biological active 1,6-naphthyridines compounds are depicted in Figure 1.

Multi-Component Reactions (MCRs) play an increasingly important role in organic

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and medicinal chemistry for their high degree of atom economy, convergence, productivity, high selectivity, ease of extraction, excellent yield and broad application in combinatorial chemistry [9-12]. The variation of two or more compounds of the reaction can make available a large number of compound and increase chemical diversity [13, 14]. Recently, microwave induced rate acceleration technology has become a powerful tool in organic synthesis, due to the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction time [15-18].

By knowing advantages of multi-component reactions, we wished to synthesize some naphthyridine based nitrogen heterocycles using microwave irradiation coupled with MCR. For this, we have chosen 4-hydroxy-6-methylquinolin-2(1*H*)-one as one of the components.

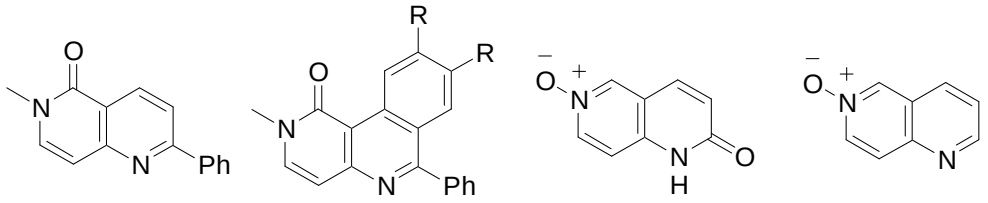


Figure 1. Some 1,6-naphthyridines.

Material and Methods

Melting points (mp) were determined using Boetieus micro-heating table and are uncorrected. IR (KBr, cm^{-1}) spectra were obtained on Shimadzu-8201 spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker AMX-400 spectrometer (400 MHz) 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. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used.

General Procedure for synthesis of 12-methyl-7-(substituted)phenylbenzo[h] naphtho[b][1,6] naphthyridin-8-ones (3a-g)

A mixture of 1-naphthylamine (0.001 mol), 4-hydroxy-6-methylquinolin-2(1*H*)-ones (1, 0.001 mol), respective aromatic aldehydes (0.001 mol) and 5 drops of TEA was taken in a 100 mL beaker and irradiated in a microwave oven at an output of about 320 W for the specified time (Table 1). The completion of the reaction was tested by TLC, and after completion of the reaction, the mixture was poured in to chilled water. The formed product was filtered, dried and purified by column chromatography using the solvents petroleum ether and ethyl acetate.

12-methyl-7-phenylbenzo[h]naphtho[b][1,6]naphthyridin-8-one (3a)

IR (KBr, cm^{-1}): 1544, 1604 (CN), 1643 (>C=O), 2800-3200 (-NH). ^1H NMR (DMSO-d_6): δ_H 2.50 (s, 3H, C_{12}-CH_3), 6.68 (s, 1H, C_7-H), 6.71-8.11 (m, 13H, Ar-H), 9.02 (s, 1H, C_{13}-H), 11.01 (s, 1H, NH), 11.18 (s, 1H, NH). Ms (*m/z*): 388. Anal. Calculated for $C_{27}H_{20}N_2O$; C 83.51, H 5.15, N 7.22%, Found C 83.46, H 5.09, N 7.20%.

12-methyl-7-(o-chlorophenyl)benzo[h]naphtho[b][1,6]- naphthyridin-8-one (3b)

IR (KBr, cm^{-1}): 1569, 1604 (CN), 1641 (>C=O), 2800-3260 (-NH). ^1H NMR (DMSO-d_6): δ_H 2.45 (s, 3H, C_{12}-CH_3), 6.41 (s, 1H, C_7-H), 7.01-8.22 (m, 13H, Ar-H), 13.40 (bs, 2H, 2NH). Ms (*m/z*): 422. Anal. Calculated for $C_{20}H_{19}N_2OCl$; C 76.78, H 4.50, N 6.64%, Found C 76.75, H 4.47, N 6.60%.

12-methyl-7-(p-chlorophenyl)benzo[h]naphtho [b][1,6]- naphthyridin-8-one (3c)

IR (KBr, cm^{-1}): 1559, 1610 (CN), 1648 (>C=O), 2830-3258 (-NH). ^1H NMR (DMSO-d_6): δ_H 2.50 (s, 3H, C_{12}-CH_3), 6.42 (s, 1H, C_7-H), 6.92-8.32 (m, 13H, Ar-H), 11.10 (s, 1H, NH), 11.22 (s, 1H, NH). Ms (*m/z*): 422. Anal. Calculated for $C_{20}H_{19}N_2OCl$; C 76.78, H 4.50, N 6.64%, Found C 76.77, H 4.46, N 6.60%.

12-methyl-7-(m-chlorophenyl)benzo[h]naptho[b][1,6]- naphthyridin-8-one (3d)

IR (KBr, cm^{-1}): 1560, 1618 (CN), 1645 (>C=O), 2860-3280 (-NH).^1H NMR (DMSO-d_6): δ_H 2.68 (s, 3H, C_{12}-CH_3), 6.62 (s, 1H, C_7-H), 6.72-8.30 (m, 13H, Ar-H), 11.10 (bs, 2H, 2NH). Ms (*m/z*): 422. Anal. Calculated for $C_{20}H_{19}N_2OCl$; C 76.78, H 4.50, N 6.64%, Found C 76.78, H 4.48, N 6.62%.

12-methyl-7-(p-hydroxyphenyl)benzo[h]naphtho[b][1,6]- naphthyridin-8-one (3e)

IR (KBr, cm^{-1}): 1564, 1614 (CN), 1643 (>C=O), 2890-3250 (-NH).^1H NMR (DMSO-d_6): δ_H 2.43 (s, 3H, C_{12}-CH_3), 6.48 (s, 1H, C_7-H), 6.92-8.10 (m, 13H, Ar-H), 11.10 (s, 2H, 2NH), 11.44 (s, 1H, OH). Ms (*m/z*): 404. Anal. Calculated for $C_{27}H_{20}N_2O_2$; C 80.20, H 4.95, N 6.93%, Found C 80.18, H 4.92, N 6.90%.

12-methyl-7-(o-hydroxyphenyl)benzo[h]naphtho[b][1,6]- naphthyridin-8-one (3f)

IR (KBr, cm^{-1}): 1560, 1604 (CN), 1646 (>C=O), 2800-3300 (-NH).^1H NMR (DMSO-d_6): δ_H 2.58 (s, 3H, C_{12}-CH_3), 6.48 (s, 1H, C_7-H), 7.11-8.20 (m, 13H, Ar-H), 11.21 (s, 2H, 2NH), 11.39 (s, 1H, OH). Ms (*m/z*): 404. Anal. Calculated for $C_{27}H_{20}N_2O_2$; C 80.20, H 4.95, N 6.93%, Found C 80.15, H 4.90, N 6.91%.

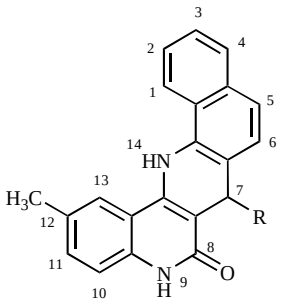
12-methyl-7-(m-nitrophenyl)benzo[h]naphtho[b][1,6]- naphthyridin-8-one

(3g)

IR (KBr, cm^{-1}): 1569, 1618 (CN), 1648 (>C=O), 2890-3380 (-NH).^{1}H NMR (DMSO-d_6): δ_H 2.64 (s, 3H, C_{12}-CH_3), 6.48 (s, 1H, C_7-H), 7.08-8.18 (m, 13H, Ar-H), 11.18 (s, 2H, 2NH). Ms (*m/z*): 433. Anal. Calculated for $C_{27}H_{19}N_3O_2$; C 74.83, H 4.39, N 9.70%, Found: C 74.80, H 4.35, N 9.65%.

Results and Discussion

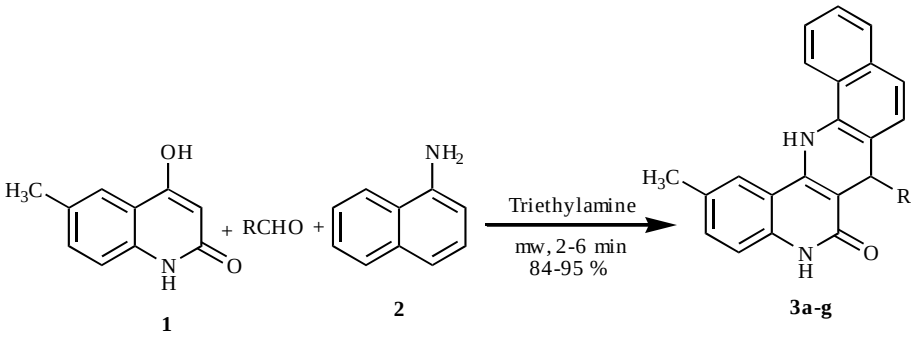
The reaction started with the reactants heterocyclic diketone such as 4-hydroxy-6-methylquinolin-2(1*H*)-one (**1**). Accordingly, the reaction was carried out by irradiating a mixture of 4-hydroxy-6-methylquinolin-2(1*H*)-one (**1**), benzaldehyde, 1-naphthylamine (**2**) and five drops of triethylamine (TEA) in a beaker inside the microwave oven at an output of about 320 W for 3 min (TLC check). After the irradiation, the reaction mixture was poured into ice water, which gave a white product, **3a** in 94% yield. The solid obtained was filtered and purified by column chromatography using the solvents petroleum ether and ethyl acetate. The products were characterized on the basis of their IR, ^{1}H NMR, mass spectroscopic and analytic data.



3a

IR spectrum of **3a** showed carbonyl absorption band at 1643 cm^{-1} for carbonyl group, NH absorption appeared broad band in the region 2800-3200 cm^{-1} and other absorptions at 1604, 1544 $cm.^{-1}$ The ^{1}H NMR spectrum of the product **3a** showed three singlets at δ 2.50, 6.68 and 9.02 due to methyl, C_7 and C_{13} protons. Other thirteen aromatic protons registered an unresolved multiplet in the region δ 6.71-8.11 and also registered two singlets at δ 11.01 and 11.18 for two NH protons. The mass spectrum showed a molecular ion peak at *m/z* 388 ($M^{\cdot+}$). The elemental analysis of **3a** corroborated the proposed molecular formula $C_{27}H_{20}N_2O$; Calcd.: C 83.51, H 5.15, N 7.22%; Found: C 83.46, H 5.09, N 7.20%. From all the above spectral values we confirmed the compound **3a** as 12-methyl-7-phenylbenzo [*h*]naphtho[*b*][1,6] naphthyridin-8-one (Scheme 1). A series of other derivatives (**3b-g**) were also prepared using different aldehydes like *o*-chlorobenzaldehyde, *m*-chlorobenzaldehyde, *p*-chlorobenzaldehyde, *m*-nitrobenzaldehyde, *p*-hydoxybenzaldehyde and *o*-

hydroxybenzaldehyde (Table 1) (Scheme 1).



3a: R = C_6H_5, **3b**: R = *o*-Cl C_6H_5, **3c**: R = *p*-ClC_6H_5, **3d**: R = *m*-ClC_6H_5, **3e**: R = *o*-OHC_6H_5, **3f**: R = *p*-OHC_6H_5, **3g**: R = *m*-$NO_2C_6H_5$,

Scheme 1. Synthetic route of compound **3a-g**.

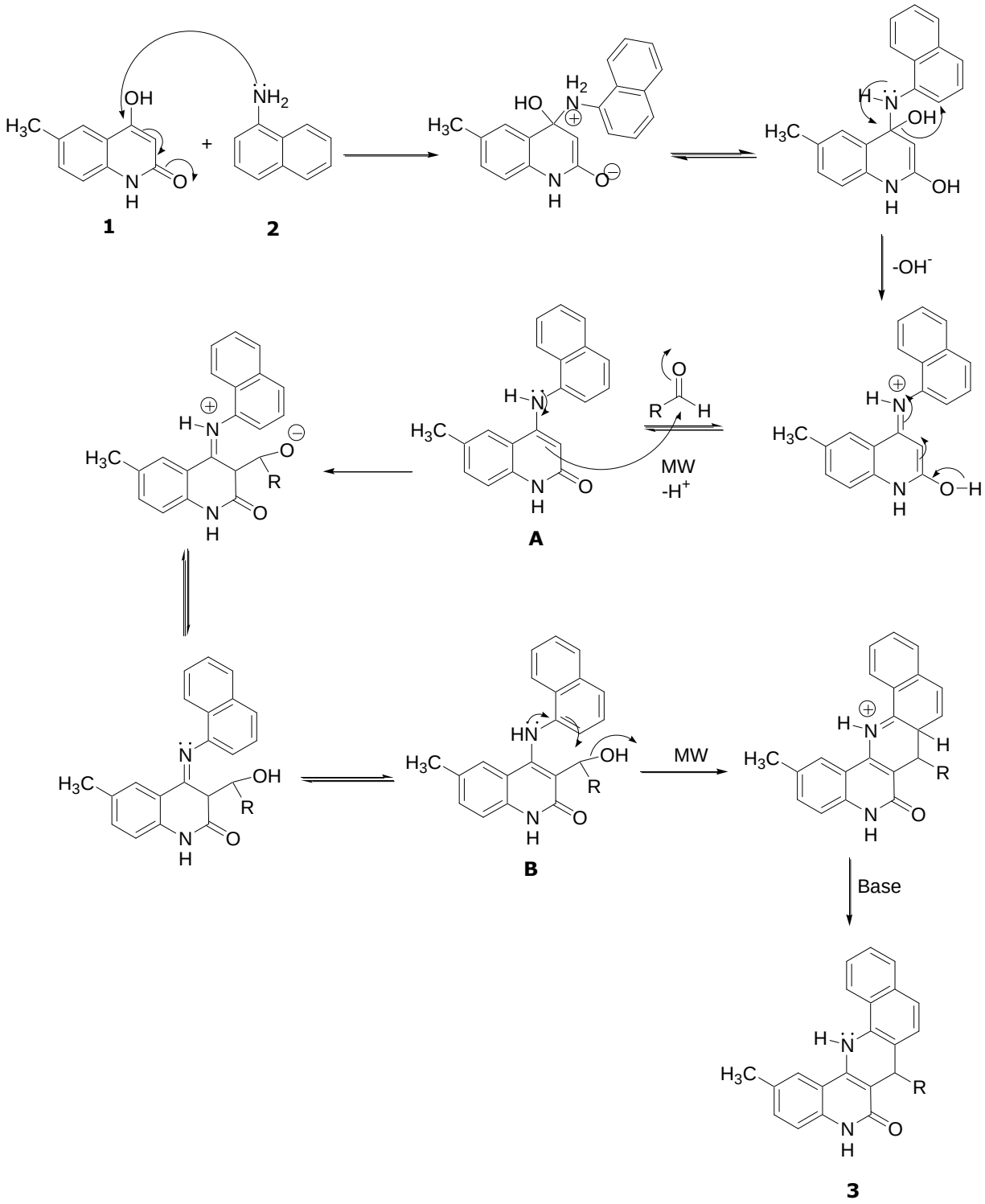
Table 1. Physical data of Synthesized of Compounds **3a-g**.

Compound	Reaction Time (min)	Yield (%)	mp °C
3a	3.0	94	250-252
3b	4.0	90	190-192
3c	2.0	92	> 300
3d	6.0	82	130-132
3e	2.0	90	> 300
3f	3.0	80	110-112
3g	2.0	89	260-264

The plausible mechanism (Scheme 2) proposed for the above reaction involves three steps. In the first step, condensation takes place between 4-hydroxy-6-methylquinolin-2(1*H*)-one (**1**) and 1-naphthylamine (**2**) to form intermediate enamine **A**. In the second step, the enamine **A** attack to aromatic aldehydes (addition reaction) to give intermediates **B**, which further undergoes dehydration reaction to give 1,6-naphthyridine **3** (Step 3).

Conclusion

In conclusion, we have developed an efficient and high yield protocol for synthesis of new 12-methyl-7-phenylbenzo[*h*]naphtho[*b*]naphthyridin-8-ones 3a-g by multi-component reaction of 4-hydroxy-6-methylquinolin-2(1*H*)-one, aldehydes and 1-naphthylamine in triethylamine by using microwave irradiation. These methods offer tremendous reduction in reaction time, operational simplicity, cleaner reaction, easier work-up and better yields and are environmentally co-friendly compared to conventional methods.



Scheme 2. Proposed mechanism of synthesized Compound 3.

Acknowledgments

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