Microwave-assisted one-pot synthesis of some new furo[2,3-*b*]quinolines using potassium carbonate under solvent-free conditions

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Abstract: A rapid, solvent-free microwave-assisted method has been developed for the synthesis of novel furoquinolines. The title compounds were achieved by the reaction between corresponding 2-hydroxy-3-formyl-quinolines (**1a**–**1c**) with chloroacetamide, ethylchloroacetate, and phenacylbromide in specially designed microwave (MW) oven for organic synthesis in unsealed borosil vessel in presence of potassium carbonate. In this method, isolation is accomplished by just treating the reaction mixture with water, and products were obtained in high yield. Hence, this method was found to be very effective and ecofriendly. The structure of the newly synthesized compounds has been evaluated on the basis of analytical, IR, ^{1}H NMR, and mass spectral data.

Key words: furoquinoline, microwave irradiation, potassium carbonate, solvent-free conditions.

Résumé : On a mis au point une méthode rapide, sans solvant et assistée par les microondes pour la synthèse de nouvelles furoquinoléines. Les synthèses des composés mentionnés dans le titre ont été réalisées en faisant réagir les 2-hydroxy-3-formylquinoléines correspondantes (**1a**–**1c**) avec du chloroacétamide, du chloroacétate d'éthyle et du bromure de phénacylel, en présence de carbonate de potassium, dans un four à microondes spécialement conçu pour les synthèses organiques dans un contenant en borosil non scellé. Dans cette méthode, on isole les produits par un simple traitement du mélange réactionnel avec de l'eau et les rendements en produits obtenus sont élevés. On a donc trouvé que cette méthode est très efficace et écologiquement acceptable. Les structures des nouveaux composés synthétisés ont été déterminées sur la base d'analyses et de données de spectrométrie IR, RMN du ^{1}H et de masse.

Mots-clés : furoquinoléine, irradiation par microondes, carbonate de potassium, conditions sans solvant.

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Introduction

Synthetic organic reactions performed under non-traditional conditions are gaining popularity, primarily to circumvent growing environmental concerns (1). Microwave-assisted heating is an invaluable synthesis technology, since it often dramatically reduces reaction times, typically from days or hours, minutes, or even seconds. It can also provide pure products in quantitative yields. Solvent-free reaction techniques are successfully coupled with microwave (MW) to avoid the use of low boiling point solvents, which may sometimes lead to explosions. Additionally, the use of poisonous and expensive solvents can also be avoided to make manipulations of the reactions much easier. The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be an efficient and safe technique, as it requires shorter reaction times, gives higher yield, and the reactions are easily carried out compared with conventional heating methods (2–3). In addition, the limitations of the microwave-assisted reactions in solvents, namely, the development of high pressure and the need for specialized sealed vessels, are circumvented via the solid-catalyst strategy, which enables organic reactions to occur rapidly at atmospheric pressures and scale up the reactions on a preparative scale (4).

Furo[2,3-*b*]quinoline derivatives constitute an important group of bioactive natural products, such as dictamnine, acrophylline, confusameline, skimmianine, kokusaginine, and aplopine (5–10). They were found to possess a wide-range of biological properties, such as anti-allergic (5), anti-inflammatory (6), cytotoxic (7), antiplatelet aggregation (8–9), and the voltage-gated potassium channel blocking activities (10). Due to their biological importance, several methods have been reported for the synthesis of furoquinoline derivatives (11–15). However, those methods involve multisteps, are time-consuming, produce low yield, and more importantly, the use of more solvents makes those methods less economic. So, there is still need for developing simple, efficient and eco-friendly methods.

Hence, in continuation of our studies on microwave-assisted organic synthesis of linearly condensed quinolines (16–19), by adopting green chemistry, we wish to report microwave-assisted novel synthesis of furo[2,3-*b*]quinoline derivatives using solid base catalyst under solvent-free microwave-irradiation conditions.

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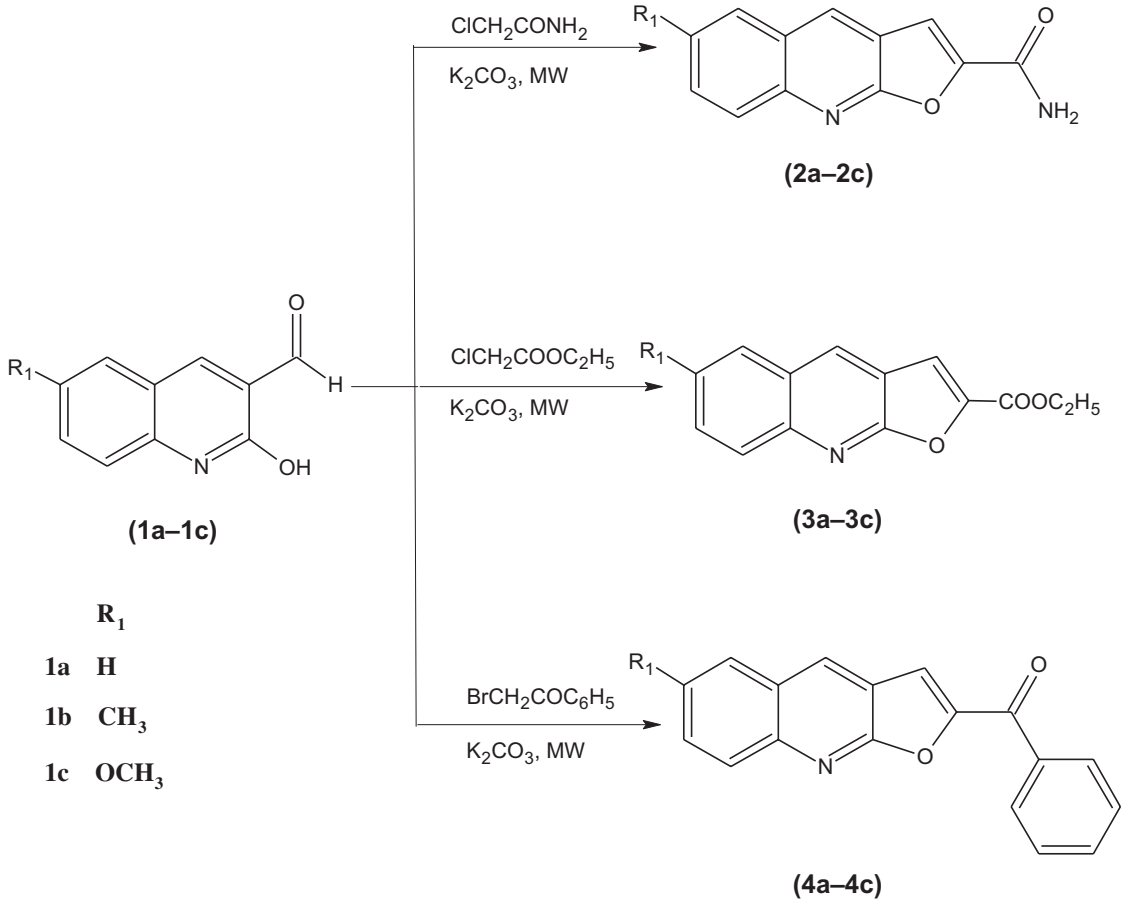
Scheme 1.



Results and discussion

2-Hydoxy-3-formyl quinolines (**1a**–**1c**), were found to be the excellent starting materials for the synthesis of novel furoquinoline derivatives. The starting compounds were prepared according to the literature method (20). In the present study, the cyclization of (**1a**–**1c**) with phenacylbromide, chloroacetamide, and ethylchloroacetate under microwave irradiation in one pot furnished the title compounds (**2a**–**2c**), (**3a**–**3c**), and (**4a**–**4c**) in good yields (Scheme 1).

The reaction proceeds through the nucleophilic substitution of a halogen. Then, the carbanion intermediate results after treatment by a base, which adds on the aldehydic carbon atom with simultaneous elimination of water, resulting in the formation of the cyclized products (21) (Scheme 1). The temperature was measured by introducing the thermometer inside the reaction mixture just at the end of the reaction, and the temperature was found to be 130–135 °C. To see whether these conditions work under non-microwave experiment, reactions were carried out in a pre-heated oil bath. It has been found that although the reaction did take place, the yield was quite low. The acceleration of reactions by microwave exposure results from material–wave interactions leading to thermal effects (which may be easily estimated by temperature measurements) and specific (non-purely thermal) effects. Clearly, a combination of these two contributions can be responsible for the observed effects.

Thermal effects (dielectric heating) can result from dipolar polarization as a consequence of dipole–dipole interactions between polar molecules and the electromagnetic field. They originate in the dissipation of energy into heat as an outcome of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at each alternation of the electric field at a very high frequency.

This energy dissipation in the core of materials allows a much more regular repartition in temperature when compared with classical heating. Classical thermal phenomena (conduction, convention, radiation, and so forth) only play a secondary role in the a posteriori equilibration of temperature, and as a result of this, the rate of the reaction increases in MW method.

The IR absorption bands observed in the region 3000–3200 cm^{-1}, due to tautomeric form of –NH and –OH stretching frequency, and in ^1H NMR spectrum, a broad singlet due to –NH at δ 11.0 and a singlet at δ 10.5 due to –CHO group found in the starting compound (**1a**–**1c**) were absent in the final compounds.

The IR spectra of **3a** exhibited the typical ester carbonyl group absorption at 1680 cm^{-1}. The ^1H NMR (DMSO-d_6) spectrum of the compound (**3a**) displayed a triplet at δ 1.39 (3H), a quartet at 4.38 (CH_2) characteristic of an ethyl group, singlet at 8.56 (C_3–H), and singlet at δ 8.22 (C_4–H). The aromatic proton signals appeared between 7.35–8.10 ppm, indicating that the reactive partner was attached to

the quinoline moiety. The structure of **3a** was further confirmed by the appearance of the molecular-ion peak at *m*/*z* 241 (M^+).

Material and methods

Melting points were determined in open capillaries and are uncorrected. The FTIR spectra were recorded on NICOLETAVATAR 360-FTIR instrument by using KBr pellets. The ^{1}H NMR were recorded on a BRUKER AMX-400 spectrometer operating at 400 MHz and mass spectra on AGILENT LC-MSD-TRAP-XCT mass spectrometer. Elemental analyses were done on Vario EL CHNOS elemental analyzer. Focused microwave irradiations were performed with specially designed microwave oven (Biotage, Emrys Optimizer operating at 300 W) for organic synthesis.

Experimental

General microwave procedure for the synthesis of furo[2,3-*b*]quinolines

A mixture of **1a** (1.730 g, 10 mmol), phenacylbromide (1.990 g, 10 mmol), and anhyd. potassium carbonate (1.380 g, 20 mmol) was ground for uniform mixing. The mixture was then subjected to microwave irradiation in a microwave oven for 12 min at an interval of 1 min at 160 W to complete the reaction (TLC). The reaction mixture was then poured into water, stirred, and the solid obtained was filtered and dried. The crude product was recrystallized from aq. DMF to give 2.322 g (85%) of **4a**. All other compounds were prepared in a similar way with 85%–90% yield.

Physical and spectral data of the products

Furo[2,3-b]quinoline-2-carboxamide (2a)

Recrystallized from aq. DMF. Yield: 85% (MW). Mp: 226–228 °C. IR (KBr) cm^{-1}: 3330, 3145 ($CONH_2$). ^{1}H NMR (400 MHz, DMSO-d_6): 7.50 (2H, bs, –$CONH_2$), 8.55 (s, C_3–H), 8.20 (s, C_4–H), 7.33–8.12 (m, 4H, Ar–H). MS *m*/*z*: 212 (M^+). Anal. calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.77; N, 13.20. Found: C, 67.90; H, 3.79; N, 13.22

6-Methylfuro[2,3-b]quinoline-2-carboxamide (2b)

Recrystallized from aq. DMF. Yield: 86% (MW). Mp: 237–239 °C. IR (KBr) cm^{-1}: 3340, 3155 ($CONH_2$). ^{1}H NMR (400 MHz, DMSO-d_6): 2.11 (s, 3H, –CH_3), 7.53 (2H, bs, –$CONH_2$), 8.53 (s, C_3–H), 8.24 (s, C_4–H), 7.30–8.14 (m, 3H, Ar–H). MS *m*/*z*: 226 (M^+). Anal. calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.42; N, 12.38. Found: C, 69.04; H, 4.47; N, 12.34.

6-Methoxyfuro[2,3-b]quinoline-2-carboxamide (2c)

Recrystallized from aq. DMF. Yield: 90% (MW). Mp: 250–252 °C. IR (KBr) cm^{-1}: 3350, 3150 ($CONH_2$). ^{1}H NMR (400 MHz, DMSO-d_6): 3.90 (3H, s, Ar–OCH_3), 7.54 (2H, bs, –$CONH_2$), 8.50 (s, C_3–H), 8.18 (s, C_4–H), 7.25–8.12 (m, 3H, Ar–H). MS *m*/*z*: 242 (M^+). Anal. calcd. for $C_{13}H_8N_2O_3$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.42; H, 4.16; N, 11.54.

Ethyl furo[2,3-b]quinoline-2-carboxylate (3a)

Recrystallized from aq. DMF. Yield: 86% (MW). Mp: 251–253 °C. IR (KBr) cm^{-1}: 1680. ^{1}H NMR (400 MHz, DMSO-d_6): 1.39 (t, 3H, –CH_3), 4.38 (q, 2H, –OCH_2), 8.56 (s, C_3–H), 8.22 (s, C_4–H), 7.35–8.10 (m, 4H, Ar–H). MS *m*/*z*: 241 (M^+). Anal. calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.56; N, 5.80. Found: C, 69.74; H, 4.52; N, 5.84.

Ethyl 6-methylfuro[2,3-b]quinoline-2-carboxylate (3b)

Recrystallized from aq. DMF. Yield: 88% (MW). Mp: 245–247 °C. IR (KBr) cm^{-1}: 1675 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 2.16 (s, 3H, –CH_3), 1.39 (t, 3H, –CH_3), 4.38 (q, 2H, –OCH_2), 8.57 (s, C_3–H), 8.24 (s, C_4–H), 7.40–8.13 (m, 3H, Ar–H). MS *m*/*z*: 255 (M^+). Anal. calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49. Found: C, 70.53; H, 5.06; N, 5.42

Ethyl 6-methoxyfuro[2,3-b]quinoline-2-carboxylate (3c)

Recrystallized from aq. DMF. Yield: 87% (MW). Mp: 220–222 °C. IR (KBr) cm^{-1}: 1670. ^{1}H NMR (400 MHz, DMSO-d_6): 3.95 (3H, s, Ar–OCH_3), 1.39 (t, 3H, –CH_3), 4.38 (q, 2H, –OCH_2), 8.58 (s, C_3–H), 8.28 (s, C_4–H), 7.37–8.12 (m, 3H, Ar–H). MS *m*/*z*: 255 (M^+). Anal. calcd. for $C_{15}H_{13}NO_3$: C, 66.42; H, 4.79; N, 5.16. Found: C, 66.46; H, 4.83; N, 5.19.

Furo[2,3-b]quinolin-2-yl(phenyl)methanone (4a)

Recrystallized from aq. DMF. Yield: 89% (MW). Mp: 236–237 °C. IR (KBr) cm^{-1}: 1660. ^{1}H NMR (400 MHz, DMSO-d_6): 8.60 (s, C_3–H), 8.21 (s, C_4–H), 7.49–8.18 (9H, m, Ar–H). MS *m*/*z*: 273 (M^+). Anal. calcd. for $C_{18}H_{11}NO_2$: C, 79.12; H, 4.03; N, 5.12. Found: C, 79.16; H, 4.06; N, 5.00.

(6-Methylfuro[2,3-b]quinolin-2-yl)(phenyl)methanone (4b)

Recrystallized from aq. DMF. Yield: 90% (MW). Mp: 247–249 °C. IR (KBr) cm^{-1}: 1670 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 2.26 (s, 3H, –CH_3), 8.58 (s, C_3–H), 8.24 (s, C_4–H), 7.45–8.13 (8H, m, Ar–H). MS *m*/*z*: 287 (M^+). Anal. calcd. for $C_{19}H_{13}NO_2$: C, 79.44; H, 4.52; N, 4.87. Found: C, 79.47; H, 4.56; N, 4.83.

(6-Methoxyfuro[2,3-b]quinolin-2-yl)(phenyl)methanone (4c)

Recrystallized from aq. DMF. Yield: 86% (MW). Mp: 260–262 °C. IR (KBr) cm^{-1}: 1665. ^{1}H NMR (400 MHz, DMSO-d_6) 4.10 (3H, s, Ar–OCH_3), 8.56 (s, C_3–H), 8.28 (s, C_4–H), 7.43–8.11 (8H, m, Ar–H). MS *m*/*z*: 303 (M^+). Anal. calcd. for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.29; N, 4.62. Found: C, 75.20; H, 4.24; N, 4.64.

Conclusion

In conclusion, a simple microwave-assisted method has been developed for the synthesis of furo[2,3-*b*]quinolines under solvent-free conditions in presence of K_2CO_3. This microwave-irradiation method is superior from the view of the yield, reaction time, and facial workup compared with the conventional (thermal) method.

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