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Multicomponent Synthesis of Dihydrofuro-quinolin-4(2*H*)ones Under Conventional and Microwave Irradiation Method in aqueous medium

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ABSTRACT

An aqueous medium multicomponent synthesis of *trans*-2-aroyl-5-methyl-3-aryl-3, 5-dihydrofuro [3, 2-c]-quinolin-4*(2H)*-one in pyridine by conventional and microwave irradiation, easy workup, smaller reaction time and lack of column chromatography are the significant feature of this protocol. Phenacyl bromide with pyridine is first time used as starting with1-methyl-4-hydroxy quinolone, substituted aromatic aldehydes for the biological interest compound (**4a-p**) for this green transformation generating one C-O and two C-C bonds in one operation, Knoevenagel followed by Michael addition and intramolecular cyclisation.

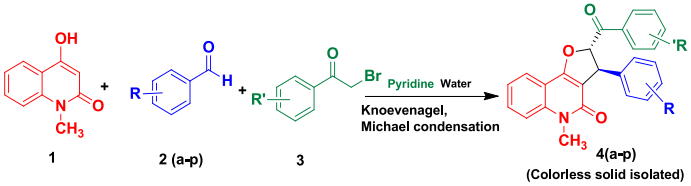
Introduction

Multicomponent reaction (MCRs) plays significant role in organic synthesis which is accepted worldwide as an important method for the synthesis of natural products, medicinal and combinatorial chemistry in recent year [1]. These reactions avoid time consuming and costly processes for the purification of various precursors and isolation of intermediate [2]. MCRs have been proven to be very graceful and rapid way to access complex structures in a single synthetic operation from simple building blocks and show high atom economy and high selectivity [3]. Now a days, many organic transformations have been carried out in water, [4-5]. It is a unique solvent due to being readily available, inexpensive, nontoxic, safer and environmentally benign. The aqueous mediated conditions lead to enhanced reaction rates, higher yields of pure products and easier workup and selectivity of much organic synthesis [6]. In addition to green solvent under the microwave irradiation [7-8].

Furo-quinolinone derivatives widely distributed in nature[9]. They display important biological activities such as anti-malarial, antitumer, anticancer activity in-vitro and were also shown to possess immunosuppressive properties, mitochondrial dysfunction, antimicrobial, insecticidal, antineoplastic, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory, cardiovascular, anti-diuratic, kinase-inhibitors [10]. Similarly their utility as traditional pharmaceuticals in China [11]. in the recent, derivatives of furo-quinolinones has shown promising blocking activities of the voltage-gated potassium channel, KV-3, [12]. Autoimmune disease and inflammation therapy [13]. The previously reported synthetic method for the construction of furo-quinolinone derivatives include: (i) Annulation of N-alkyl furamide by using Palladium catalyzed, [14]. (ii) oxidative cycloaddition by using CAN of 1,3-dicarbonyl with conjugated compound, [15]. (iii) Michael addition of Cyclic 1,3-dicarbonyl compound with nitrostyrene, [16]. (iv) Oxidative cycloaddition of hydroxy quinolinone with olefins by using in silver carbonate/cellite, [17]. another synthetic methods for the same derivatives[18-21]. these synthetic approaches having several disadvantages such as low yield, lack of selectivity, mixture of products or isomers and use of metal catalyst.

In our ongoing efforts, we were interested in the synthesis of di-hydro furo-quinolinones to the best of our knowledge there have been no reports on the expeditious synthesis of di hydro furo-quinolinones via one pot three component reactions using simple starting phenacyl bromide in presence of pyridine in water.

Scheme 1



where R' = H, 4-Cl, 4-F, 4-CH_3 and R= 4-Cl, 4-Me, 4-F, 4-Br, 4-NO_2, 4-OMe, 2-Me, 2-F, 2-4-di-Cl.

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Experimental

General

Aromatic aldehydes, base and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Microwave reactions have been carried out in Biotage microwave synthesizer. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Developed plates were examined with UV lamps (254 nm). Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected. IR spectra were run for KBr disc on Perkin-Elmer 120-000 A apparatus (υ_{max} in cm^{-1}), ^{1}H NMR spectra were recorded on a Bruker spectrometer 300 MHz, ^{13}C NMR 75MHz NMR instrument using TMS as internal standard and $CDCl_3$ as a solvent. Chemical shifts are reported as δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br)

General procedure for the synthesis of dihydrofuro-quinolinone derivatives (4a-4p)

(A) Conventional method

In a round bottom flask an equimolar amount of mixture of 1-methyl-4-hydroxy-2(1*H*)-quinolinone (1 equiv. 1.75gm) **1**, aromatic aldehydes (1 equiv.) **2**, phenacyl bromide (1 equiv.) **3** and pyridine (30 mol %) in water (12 ml) was stirred at room temperature for one minute and then heated to reflux in an oil bath for 3-4 h. Progress the reaction was monitored by thin layer chromatography, After completion of the reaction, extracted with dichloromethane (15 ml ×3), combined organic layer, evaporated in reduced pressure to afford crude product, recrystalised from ethyl alcohol-chloroform, to obtained pure compound **4** yield (78-91%).

(B) Microwave irradiation method

A vial containing an equimolar amount of mixture of 1-methyl-4-hydroxy-2(1*H*)-quinolinone (1 equiv., 1.75gm) **1**, arylaldehydes(1 equiv.) **2**, phenacyl bromide (1 equiv.) **3** and pyridine (30 mol %) in water (12 ml) was stirred at room temperature for one minute and then placed in Biotage microwave synthesizer. The vial was subjected to microwave irradiation at 100 °C and 150 W for 8-10 min. The progress reaction was monitored by thin layer chromatography, After completion of the reaction, product were extracted with dichloromethane (15 ml×3), combined organic layer, evaporated in reduced pressure to afford crude product, recrystalized from ethyl alcohol-chloroform, to obtained pure compound **4** yield (82-97%)

All the product are well characterized by the comparison of their spectral data (^{1}H-NMR, ^{13}C-NMR, physical properties-color, melting point etc. with those reported in literature) [22].

Spectral Characterization of synthesized compounds

***Trans*-2-benzoyl-5-methyl-3-phenyl-3, 5-dihydrofuro [3, 2-c]-quinolin-4(2H)-one (4a)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.06gm) of benzaldehyde 2, (1 equiv., 1.99gm) of phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 94% yield of title compound as a colorless solid. m.p.193-195^{0}C, IR (KBr): 1011, 1123, 1690, 1715, 2950, 3051, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s, N–CH_3), 4.87 (1H,d, *J* = 4.5 Hz, 3-CH), 6.12 (1H, d, *J* = 4.5 Hz, 2-CH), 7.26–7.54 (9H, m, Ar-H), 7.61–7.64(2H, m, Ar-H), 7.90–7.98 (3H, m, Ar-H); Anal. calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.66; H, 4.98; N, 3.72.

***Trans*-2-benzoyl-3-(4-chlorophenyl)-5-methyl-3,5-dihydrofuro [3, 2-c]quinolin-4(2H)-one (4b)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.40gm) of 4-chloro benzaldehyde 2, (1 equiv., 1.99gm) of phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 90% yield of title compound as a colorless solid. m.p.190-193^{0}C, IR (KBr): 760, 810, 1011,1125, 1692, 1715, 2955, 3055, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (3H, s, N–CH_3), 4.86 (1H,d, *J* = 4.8 Hz, 3-CH), 6.07 (1H, d, *J* = 4.8 Hz, 2-CH), 7.25–7.40 (6H, m, Ar-H), 7.47–7.53 (2H, m, Ar–H), 7.61–7.66 (2H, m, Ar-H), 7.89–7.95 (3H, m, Ar-H); Anal. calcd for $C_{25}H_{18}ClNO_3$: C, 72.20; H, 4.36; N, 3.37.Found: C, 72.12; H, 4.41; N, 3.42

***Trans*-2-benzoyl-5-methyl-3-(4-methylphenyl)-3,5-dihydrofuro[3,2-c]quinolin-4(2H)-one (4c)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.20gm) of 4-methyl benzaldehyde 2, (1 equiv.1.99gm) of phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 88% yield of title compound as a colorless solid. m.p.194^{0}C, IR (KBr): 1016, 1129, 1692, 1719, 2950, 3053, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (3H, s, CH_3), 3.63 (3H, s,N–CH_3), 4.77 (1H, d, *J* = 4.5 Hz, 3-CH), 6.12 (1H, d, J = 4.5 Hz, 2-CH), 7.17 7.41 (6H, m, Ar–H), 7.47–7.53 (2H, m, Ar-H), 7.61–7.67 (2H, m, Ar-H), 7.89–7.98 (3H, m, Ar-H); Anal. calcd for $C_{26}H_{21}NO_3$: C, 78.93; H, 5.33; N, 3.54. Found: C, 79.01; H, 5.39; N, 3.47.

***Trans*-2-benzoyl-3-(4-fluorophenyl)-5-methyl-3,5-dihydrofuro[3,2-c]quinolin-4(2H)-one (4d)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.24gm) of 4-fluro benzaldehyde 2, (1 equiv., 1.99gm) of phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 87% yield of title compound as a colorless solid. m.p.193^{0}C, IR (KBr): 780, 805, 1110, 1130, 1690, 1715, 2950, 3051, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (3H, s, N–CH_3), 4.87 (1H,d, *J* = 4.8 Hz, 3-CH), 6.07 (1H, d, *J* = 4.8 Hz, 2-CH), 7.02–7.06 (2H, m, Ar-H), 7.27–7.69 (6H, m, Ar-H), 7.91–8.18 (5H, m, Ar-H); Found: C, 75.22; H, 4.57; N, 3.45.

***Trans*-2-(4-chlorobenzoyl)-5-methyl-3-phenyl-3,5-dihydrofuro [3, 2-c]quinolin-4(2H)-one (4e)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.06gm) of benzaldehyde 2, (1 equiv.2.33gm) of 4-chloro phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 85% yield of title compound as a colorless solid. m.p.180-182^{0}C, IR (KBr): 730, 805, 1011, 1125, 1690, 1717, 2950, 3055, ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s, N–CH_3), 4.81 (1H, d, *J* = 4.6 Hz, 3-CH), 6.07(1H,d, *J* = 4.6 Hz, 2-CH), 7.29–7.37 (6H, m, Ar-H), 7.44–7.62 (2H,m, Ar-H), 7.63–7.69 (2H, m, Ar-H), 7.91–7.97 (3H, m, ArH); Anal. calcd for $C_{25}H_{18}ClNO_3$: C, 72.20; H, 4.36; N, 3.37. Found: C, 72.12; H, 4.41; N, 3.42.

***Trans*-3-(4-bromophenyl)-2-(4-chlorobenzoyl)-5-methyl-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4f)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.85gm) of 4-bromo benzaldehyde 2, (1 equiv., 2.33gm) of 4-chloro phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 90% yield of title compound as a colorless solid. m.p.218-222^{0}C, IR (KBr): 760, 820,

1011,1130, 1689, 1715, 2950, 3052, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s, N–CH_3), 4.89 (1H,d, *J* = 4.7 Hz, 3-CH), 5.97 (1H, d, *J* = 4.7 Hz, 2-CH), 7.23 (1H,d, *J* = 8.1 Hz, Ar-H), 7.25–7.33 (2H, m, Ar–H), 7.37 (1H, d, *J* = 8.7 Hz, Ar-H), 7.46–7.48 (4H, m, Ar-H), 7.61–7.66 (1H, m,Ar-H), 7.85–7.92 (3H, m, Ar-H); Anal. calcd for $C_{25}H_{17}BrClNO_3$: C, 60.69; H, 3.46; N, 2.83.Found: C, 60.72; H, 3.51; N, 2.88.

***Trans*-2-(4-Chlorobenzoyl)-5-methyl-3-(4-nitrophenyl)-3, 5-dihydrofuro [3,2-c]-quinolin-4(2H)-one (4g)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.51gm) of 4-nitro benzaldehyde 2, (1 equiv., 2.33gm) of 4-chloro phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 87% yield of title compound as a Yellow solid m.p.222-225^{0}C, IR (KBr): 720, 810, 1011, 1130, 1689, 1715, 2950, 3100, 3245, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (3H, s, N–CH_3), 5.17 (1H,d, *J* = 5.1 Hz, 3-CH), 6.01 (1H, d, *J* = 5.2 Hz, 2-CH), 7.31–7.55(5H, m, Ar-H), 7.63–7.71 (2H, m, Ar-H), 7.89–7.94 (3H, m,-Ar-H), 8.21 (2H, d, *J* = 8.7 Hz, Ar-H); Anal. calcd for $C_{25}H_{17}ClN_2O_5$: C, 65.15; H, 3.72; N, 6.08. Found: C, 65.21; H, 3.68; N, 6.13.

***Trans*-2-(4-chlorobenzoyl)-3-(2,4-dichlorophenyl)-5-methyl-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4h)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.75gm) of 2,4-dichloro benzaldehyde 2, (1 equiv., 2.33gm) of 4-chloro phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 88% yield of title compound as a colorless solid. m.p.260-262^{0}C, IR (KBr): 760, 805, 840, 1012, 1130, 1690, 1715, 2950, 3060, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (3H, s, N–CH_3), 5.43 (1H,d, *J* = 5 Hz, 3-CH), 5.90 (1H, d, *J* = 5 Hz, 2-CH), 7.07–7.21 (3H, m, Ar-H), 7.31–7.43 (4H, m, Ar-H), 7.52–7.58 (1H, m, Ar-H), 7.75–7.78 (1H, m, Ar-H), 7.83–7.87 (2H, m, Ar-H); Anal. calcd for $C_{25}H_{16}Cl_3NO_3$: C, 61.94; H, 3.35; N, 2.87.Found: C, 61.99; H, 3.28; N, 2.83.

***Trans*-5-methyl-2-(4-methylbenzoyl)-3-phenyl-3,5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4i)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.06gm) of benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 91% yield of title compound as a colorless solid. m.p.215-218^{0}C, IR (KBr): 1016, 1125, 1694,1718, 2950, 3052, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s, CH_3), 3.63 (3H, s,N–CH_3), 4.84 (1H, d, *J* = 4.5 Hz, 3-CH), 6.13 (1H, d, *J* = 4.5 Hz, 2-CH), 7.25 7.39 (9H, m, Ar-H), 7.60–7.65 (1H, m, Ar-H), 7.83 (2H, d, *J* = 8.4 Hz, Ar-H), 7.97 (1H, d, *J* = 8.1 Hz, Ar-H); Anal. calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54. Found: C, 79.01; H, 5.39; N, 3.47.

***Trans*-3-(4-bromophenyl)-5-methyl-2-(4-methylbenzoyl)-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4j)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.85gm) of 4-bromo benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 90% yield of title compound as a colorless solid. m.p.200-204^{0}C, IR (KBr): 760, 820, 1012, 1123, 1195, 1715, 2953,3051, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (3H, s, CH_3), 3.59 (3H, s,N–CH_3), 4.81 (1H, d, *J* = 4.7 Hz, 3-CH), 6.05 (1H, d, *J* = 4.7 Hz, 2-CH), 7.23 (5H, m, Ar-H), 7.39 (1H, d, *J* = 8.4 Hz, Ar-H), 7.48 (2H, d, *J* = 8.4 Hz, Ar–H), 7.64–7.67 (1H, m, Ar-H), 7.79 (2H, d, *J* = 8.3 Hz, Ar-H), 7.97 (1H, d, *J* = 7.8 Hz, Ar-H); Anal. calcd for $C_{26}H_{20}BrNO_3$: C, 65.83; H, 4.25; N, 2.95.Found: C, 65.78; H, 4.31; N, 2.99.

***Trans*-3-(2,4-dichlorophenyl)-5-methyl-2-(4-methylbenzoyl)-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4k)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.75gm) of 2,4-dichloro benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 85% yield of title compound as a colorless solid. m.p.250^{0}C, IR (KBr): 720, 805-840, 1012, 1130, 1690, 1715, 2935,352, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s, CH_3), 3.63 (3H, s,N–CH_3), 5.47 (1H, d, *J* = 4.8 Hz, 3-CH), 6.02 (1H, d, *J* = 4.8 Hz, 2-CH), 7.19 7.30 (5H, m, Ar-H), 7.37–7.44 (2H, m, Ar-H),7.60–7.66 (1H, m, Ar-H), 7.85–7.89 (3H, m, Ar-H); Anal. calcd for $C_{26}H_{19}Cl_2NO_3$: C, 67.25; H, 4.12; N, 3.02. Found: C, 67.19; H, 4.08; N, 3.07.

***Trans*-3-(4-methoxyphenyl)-5-methyl-2-(4-methylbenzoyl)-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4l):**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.36gm) of 4-methoxy benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 87% yield of title compound as a colorless solid. m.p.162^{0}C, IR (KBr): 705-855, 1005, 1120, 1694, 2930, 3060, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43(3H, s, CH_3), 3.61 (3H, s,N–CH_3), 3.87 (3H, s, O–CH_3), 4.76 (1H, d, *J* = 4.7 Hz, 3-CH), 6.07 (1H, d, *J* = 4.7 Hz, 2-CH), 7.22–8.08 (12H, m, Ar-H); Anal. calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.33; H, 5.39; N, 3.34.

***Trans*-5-methyl-2-(4-methylbenzoyl)-3-(2-methylphenyl)-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4m)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.20gm) of 2-methyl benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 82% yield of title compound as a colorless solid. m.p.166^{0}C, IR (KBr): 760, 1011, 1109, 1692, 1715, 2930, 3060, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (3H, s, CH_3), 2.40 (3H, s,CH_3), 3.61 (3H, s, N–CH3), 4.91 (1H, d, *J* = 4.6 Hz, 3-CH), 6.11 (1H, d, *J* = 4.6 Hz, 2-CH), 7.15–7.83 (12H, m, Ar-H); Anal. calcd for $C_{27}H_{23}NO_3$: C, 73.20; H, 5.66; N, 3.42.Found: C, 79.13; H, 5.72; N, 3.49.

***Trans*-3-(2-fluorophenyl)-5-methyl-2-(4-methylbenzoyl)-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4n)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.24) of 2-fluro benzaldehyde 2, (1 equiv., 2.13gm) of 4-methyl phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 89% yield of title compound as a colorless solid. m.p.230-232^{0}C, IR (KBr): 698, 765, 1011, 1109, 1690, 1715, 2940, 3060, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (3H, s, CH_3), 3.61 (3H,s, N–CH_3), 5.22 (1H, d, *J* = 4.8 Hz, 3-CH), 6.12 (1H, d, *J* =4.8 Hz, 2-CH), 7.01–7.13 (2H, m, Ar-H), 7.22–7.27 (5H, m, Ar-H), 7.36 (1H, d, *J* = 8.7 Hz, Ar-H), 7.59–7.64 (1H, m, Ar-H), 7.84 (2H, d, *J* = 8.1 Hz, Ar-H), 7.92 (1H, d, *J* = 7.8 Hz, Ar-H); Anal. calcd for $C_{26}H_{20}FNO_3$:C, 75.53; H, 4.88; N, 3.39. Found: C, 75.59; H, 4.92; N, 3.44.

***Trans*-3-(4-bromophenyl)-2-(4-fluorobenzoyl)-5-methyl-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4o)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.85gm) of 4-bromo benzaldehyde 2, (1 equiv., 2.17gm) of 4-fluro phenacyl bromide 3 and (30 mole %) of

pyridine in 12 ml of water, 90% yield of title compound as a colorless solid. m.p.233^{0}C, IR (KBr): 695, 734, 885, 1015, 1105, 1690, 1715, 2930, 3049, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s, N–CH_3), 4.86 (1H,d, *J* = 4.7 Hz, 3-CH), 6.01 (1H, d, *J* = 4.8 Hz, 2-CH), 7.13–7.31(5H, m, Ar-H), 7.39 (1H, d, *J* = 8.7 Hz, Ar-H), 7.48 (2H, d, *J* =7.2 Hz, Ar-H), 7.61–7.65 (1H, m, Ar-H), 7.90–7.98 (3H, m, Ar-H); Anal. calcd for $C_{25}H_{17}BrFNO_3$: C, 62.78; H, 3.60;N, 2.93. Found: C, 62.83; H, 3.67; N, 2.89.

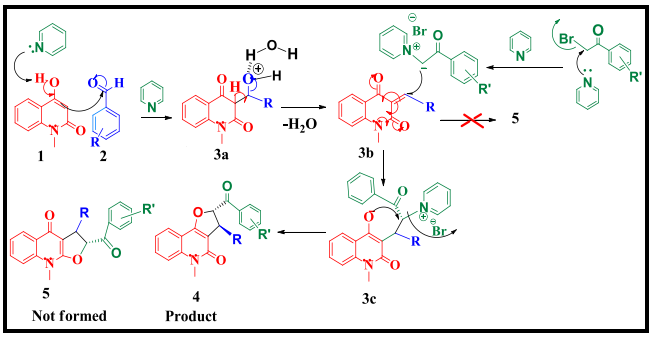
***Trans*-3-(2,4-dichlorophenyl)-2-(4-fluorobenzoyl)-5-methyl-3, 5-dihydrofuro [3,2-c]quinolin-4(2H)-one (4p)**

Using the general procedure starting from (1 equiv. 1.75gm) of 1-methyl-4-hydroxy-2(1*H*)-quinolinone 1, (1 equiv., 1.75gm) of 2,4-dichloro benzaldehyde 2, (1 equiv., 2.17gm) of 4-fluro phenacyl bromide 3 and (30 mole %) of pyridine in 12 ml of water, 97% yield of title compound as a colorless solid. m.p.252-255^{0}C, IR (KBr): 696, 760, 810, 1011, 1120, 1689, 1717, 2956, 3060, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (3H, s, N CH_3), 5.52 (1H,d, *J* = 4.7 Hz, 3-CH), 5.99 (1H, d, *J* = 4.6 Hz, 2-CH), 7.11–7.34 (7H, m, Ar-H), 7.61–7.67 (1H, m, Ar-H), 7.81 (1H, d, *J* =7.8 Hz, Ar-H), 7.97–8.01 (2H, m, Ar-H); Anal. calcd for $C_{25}H_{16}Cl_2FNO_3$: C, 64.12; H, 3.44; N, 2.95. Found: C, 64.17; H, 3. 39 ; N, 3.05.

Result and Discussion

Initially, we optimized reaction condition and performed series of reactions with 30% mole of different catalyst and solvent were tried for the better compatibility to found that 30 mole % of pyridine in 12mLwater under reflux for 3 hr. which afforded 91% yield and under microwave irradiation for 8 min. afforded 97% yield of product (**4**) summarized in (Table1) pyridine water pair emerged was best catalyst-solvent combination gave an excellent yield (Table1. entry 9) due to pyridinium bromide (ionic liquid) was prepared in *situ*. The base was tried in different mole % of catalyst (10%, 15%, 20%, 25%, 30%, 40%). On increasing amount of catalyst more than 30 mole %, no substantial yield of product, while decrease amount of base catalyst less than 30 mole % yields was reduced, we excess amount of pyridine and compare with time of reaction as the decrease the reaction time to 1-2 min had no influence on the yield thus reaction time reduced to 2 min. It may be concluded that the excess of pyridine that act as a catalyst in the Knoevenagel followed Michael condensation reaction. Other bases such as NMP, pyridine, K_2CO_3, tri-ethyl amine were screened. However, the use of NMP, triethyl amine and potassium carbonate gave moderate yield. (Table1, entry 1, 14, 18) In contrast to the above results, without catalyst reaction do not detected. (Table**1**, entry **22**).

Under the above optimized conditions, pyridine-water as good catalyst-solvent combination, which was employed subsequently for all further reactions (Table **2**.) among these electron withdrawing group substituted to aromatic compound gave an excellent yield (Table **2. 4p**.), unsubstituted groups gave good yield. (Table **2. 4a**) These final products could be isolated readily by simple filtration, because of their lower solubility in water. Single recrystallization of the product from chloroform-ethanol mixture afforded analytically pure samples, thus avoiding extraction and chromatographic separations. For comparison purposes, all the reactions leading to a collection of novel trans-dihydrofuro [3,2-c]-quinolin-4(2H)-ones conventional over microwave irradiation method



Scheme 2. Possible Mechanism for the formation of dihydrofuro quinolinone derivatives

Table 1. Effect of catalyst, solvent and time on the yield of dihydrofuro quinolinone derivatives (4)

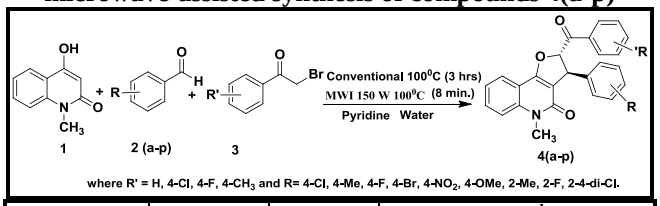
Entry	Base catalyst (30 mole %)	Solvent	Conventional	MW
			Yield/ Time (h.)	Yield /Time(min.)
1.	NMP	Water	63/4	68/10
2.	NMP	AcOH	15/4	20/10
3.	NMP	EtOH	30/4	40/10
4.	NMP	DMF	20/4	30/10
5.	Pipyridine	Water	55/4	60/10
6.	Pipyridine	AcOH	00/4	00/10
7.	Pipyridine	EtOH	30/4	40/10
8.	Pipyridine	DMF	20/4	30/10
9.	**Pyridine***	**Water**	**91/3**	**97/8**
10.	Pyridine	AcOH	40/4	46/10
11.	Pyridine	EtOH	62/3	65/8
12.	Pyridine	DMF	55/4	60/10
13.	Pyridine	CH_3CN	60/4	65/10
14.	Et_3N	Water	59/4	60/10
15.	Et_3N	AcOH	40/4	45/10
16.	Et_3N	EtOH	60/4	66/10
17.	Et_3N	DMF	50/4	53/10
18.	K_2CO_3	Water	59/4	62/10
19.	K_2CO_3	AcOH	40/4	48/10
20.	K_2CO_3	EtOH	57/4	60/10
21.	K_2CO_3	DMF	54/4	58/10
22	-	Water/EtOH	00/5	00/15

[a] Isolated yield * Recycle in different mole % of catalyst (10%, 15%, 20%, 25%, 30%, 40%),NMP = N-Methyl Pyrolidine

The overall yields of both methods, good to excellent, the microwave irradiation can be considered more advantageous because of it required shorter reaction time. The structures of all the products were characterized by ^{1}H NMR, ^{13}C NMR, were recorded on Bruker 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent and CHN analysis.^{1}HNMR spectra of compound 4 shown two different doublet for the methylene proton δ 4.86 ppm (d, 1H) *J*=4.6Hz. and another δ 6.12 ppm (d, 1H) *J*=4.6Hz. at lower field values for the trans isomers. This strongly indicated that compound have trans-isomer. On the basis of experimental results, a plausible mechanism for the formation of quinolinone derivatives 4. is depicted in Scheme **2**. The initial step in this reaction is deprotonation of 1-methyl,4-hydroxy quinolinone **1**, by pyridine, cyclic enolate ion undergoes delocalized and nucleophilic attack to aromatic aldehydes **2**, new C-C bond generated a key intermediate as aldol **3a**, dehydration of intermediate to formed product Knoevenagel condesation **3b**, then Michael addition of pyridinium bromide from generated in *situ* to **3b** afforded cyclic enolate ion as another key intermediate **3c**, which undergo rapid intramolecular cyclisation by eliminating good leaving group to give the

corresponding product **4** An expected minor product **5** did n't formed, there is no α-β cyclisation takes placed because of lone pair of nitrogen atom influence neighboring carbonyl group.

Table 2. Comparison study of conventional and microwave-assisted synthesis of compounds 4(a-p)



Compound	R	R'	Yield of 4[b] (%)	
			Conventional/ Time (h.)	MWI/ Time (min.)
4a	-H	-H	89/3	**94/08**
4b	-4-Cl	-H	86/4	90/10
4c	-4-CH_3	-H	85/4	88/10
4d	-4-F	-H	82/4	87/10
4e	-H	-4-Cl	80/4	85/10
4f	-4-Br	-4-Cl	85/4	90/10
4g	-4-NO_2	-4-Cl	80/4	87/10
4h	-2,4-Cl_2	-4-Cl	85/4	88/10
4i	-H	-4-CH_3	87/3	91/08
4j	-4-Br	-4-CH_3	85/4	90/10
4k	-2,4-Cl_2	-4-CH_3	82/4	85/10
4l	-4-OCH_3	-4-CH_3	78/4	87/10
4m	-2-CH_3	-4-CH_3	80/4	82/10
4n	-2-F	-4- CH_3	85/4	89/10
4o	-4-Br	-4-F	84/4	90/10
4p	-2,4-Cl_2	-4-F	**91/3**	**97/08**

[a] Reaction condition1-methyl-4-hydroxy-2(1H)-quinolinone (1 equiv. 1.75gm) 1, aromatic aldehydes (1 equiv.) 2, phenacyl bromide (1 equiv.) 3 and pyridine (30 mol %) in water (12 ml), MWI.(150 W)
[b] Isolated yield

Conclusions

In conclusion, we have developed multicomponent synthesis of trans-2-benzoyl-5-methyl-3-aryl-3,5 dihydrofuro [3, 2-c] quinolin-4*(2H)*-one derivatives an excellent yield in shorter reaction time by microwave irradiation technique over conventional heating technique in water with an easy workup, purification of final product involved simple filtration of the solid material separated from the reaction mixture followed by its recrystallization using minimum amount of solvent, the first time phenacyl bromide (**3**) instead of its competitors substrate, reagent or ionic liquid to gave better yield in short reaction time, An effort toward the synthesis of other important drug molecules with a quinolinone moiety by microwave irradiation as well as conventional method is ongoing in our laboratory. Also work is in progress to obtain biological activity such as antibacterial, antifungal, and anticancer of these important compounds.

We believe that, this method found to be useful addition to present methodologies for the synthesis of dihydrofuro [3, 2-c] quinolin-4*(2H)*-one derivatives.

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References

[1] (a) Domling, A. "Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry", Chem. Rev., 106, pp. 17–89, 2006. (b) Ramon, D.J.M.; Yus, "Asymmetric Multicomponent Reactions (AMCRs): The New Frontier", Angew. Chem., Int. Ed., 44, pp. 1602–1634, 2005.

[2] (a) Damiano, R.J.; Francisco, G.; Carlos, M. "Microwave-assisted, sequential four-component synthesis of polysubstituted 5,6-dihydroquinazolinones from acyclic precursors and a mild, halogenation-initiated method for their aromatization under focused microwave irradiation", Green Chem., 15, pp. 511-517, 2013. (b) Tietze, L.F. "Domino Reactions in Organic Synthesis", Chem. Rev., 96, pp. 115–136,1996.

[3] (a) Umkeherer, M.; Kalinski, M.; Kolb, J.; Burdack, C. "A new and versatile one-pot synthesis of indol-2-ones by a novel Ugi-four-component-Heck reaction", Tetrahedron Lett., 47, pp. 2391-2393, 2006. (b) Cariou, C.C.A.; Clarkson, G.J., Shipman, M. "Rapid Synthesis of 1,3,4,4-Tetrasubstituted β-Lactams from Methyleneaziridines Using a Four-Component Reaction", J. Org. Chem., 73, pp. 9762-9764, 2008.

[4] Gong, K.; Z.-W. He.; Xu, Y.; Fang, D.; Z.-L. Liu. "Green synthesis of 5-benzylidene rhodanine derivatives catalyzed by 1-butyl-3-methyl imidazolium hydroxide in water", Monatshefte fur Chemie, 139, 8, pp. 913–915, 2008.

[5] Li, C. J. "Organic Reactions in Aqueous Media with a Focus on Carbon−Carbon Bond Formations: A Decade Update", Chem. Rev., 105, pp. 3095, 2005.

[6] Chanda, A.; Fokin, V. V. "Organic Synthesis "On Water", Chem. Rev., 109, pp. 725, 2009.

[7] (a) Mosely, J.D.; Kappe, C.O. "A critical assessment of the greenness and energy efficiency of microwave assisted organic synthesis", Green Chem., 13, pp. 794-804, 2011. (b) Kappe, C.O. "Microwave dielectric heating in synthetic organic chemistry", Chem. Soc. Rev., 37, pp. 1127-1139, 2008.

[8] (a) Sarafi, Y.M.; Sadatshahabi, K.; Alimohmmadi and Tasbakshi. "A green and rapid approach for the stereoselective vinylation of phenol, thiol and amine derivatives in water", Green Chem, 13, pp. 2851-2858, 2011. (b) Xhang, X.D.; Ye, H.; Sun, D.; Guo, J.; Wang.; Huang, H.; Zhang, X.; Jiang, H. ; Liu, H. "Microwave-assisted synthesis of quinazolinone derivatives by efficient and rapid iron-catalyzed cyclization in water", Green Chem., 11, pp. 1881-1888, 2009.

[9] (a) M.F. "Grundon, Quinoline, quinazoline, and acridone alkaloids", Natural Prod. Rep., 7, pp. 131-138, 1990. (b) Openshaw, H.T. "Quinoline alkaloide other than those of cinchona", Alkaloids, pp. 223-267, 1967.

[10] Meng-Hsin Chna,; Fitzgeralda, P.; Suresh, B.; Cheryl, D.S.; Thompsonb, M. C.; Stephen, J.; O'Keefeb.; Dennis Zallerb, M.; James, B.; Doherty. "Design and Synthesis of Potent, Orally Bioavailable Dihydroquinazolinone Inhibitors of p38 MAP Kinase", Bioorg. & Med. Chem. Lett., 18, 6, pp. 2222–2226,2008.

[11] Wu, T.; C-Y Li.; Y-L.; Leu and C-Q Hu. "Limonoids and alkaloids of the root bark of Dictamnus angustiflius", Phytochemistry, 50, pp. 509-512, 1999.

[12] Butenschon, I.K.; Hansel, W.M. "Angular Methoxy-Substituted Furo- and Pyranoquinolinones as Blockers of the Voltage-Gated Potassium Channel Kv1.3", J. Med. Chem., 44, pp. 1249-1256, 2001.

[13] Cahalan, M.D.; Chandy, K.G. "Ion channels in the immune system as targets for immunosuppression", Curr. Opin. Biotechnol, 8, pp. 749-756, 1997.
[14] Lindahl.; Fredrik.; Carroll.; Anthony Richard.; Quinn.; Ronald, J.; Justin Anthony. "Synthesis of 5- methyl ro [3,2-c]quinolin-4(5H)-one via palladium-catalysed cyclisation of N-(2-iodophenyl)-N-methyl-furamide", Tetrahedron Lett., 47, pp. 7493-7495, 2006.
[15] Lee, Y.R.; Kim, B.S.; Kim, D.H. "Ceric Ammonium Nitrate (CAN)-Mediated Oxidative Cycloaddition of 1, 3-Dicarbonyls to Conjugated Compounds. Efficient Synthesis of Dihydrofurans, Dihydrofurocoumarins, Dihy dro furoquinolinones, Dihydrofurophenalenones, and Furonaphthoquinone Natural Products", Tetrahedron, 56, 45, pp. 8845-8853, 2000.
[16] Barange, D.K.; Kavla, V.; Kuo, C.W.; Lei, P.M.; Yao, C.F. "Synthesis of C3-nitroalkylated-4- hydroxycoumrin and hydroxyiminodihydrofuroquinolinone derivatives via the Michael addition of cyclic 1,3-dicarbonyl compounds to β-nitrostyrenes", Tetrahedron, 67, pp. 2870-2877, 2011.
[17] Lee, Y.R.; Kim, B. S.; Kweon, H.I. "Efficient Synthesis of Dihydrofuroquinolinones and Furoquinolinones by Silver (I)/Celite Promoted Oxidative Cycloaddition", Tetrahedron , 56, pp. 3867-3874, 2000.
[18] Tanaka, K.; Toda, F. "Solvent-Free Organic Synthesis", Chem. Rev., 100, pp. 1025-1074, 2000.
[19] Ismabert, N.; Lavila, R. "Heterocycles as Key Substrates in Multicomponent Reactions: The Fast Lane towards Molecular Complexity", Chem-Eur. J., 14, pp. 8444, 2008.
[20] Sunderhaus, J.D.; Martin, J.D. "Applications of Multicomponent Reactions to the Synthesis of Diverse Hetercyclic Scaffolds", Chem-Eur. J., 15, pp. 1300-1308, 2009.
[21] Candeias, N.R.; Montalbano, F.; Cal, G. "Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction", Chem. Rev., 110, pp. 6169-6193, 2010.
[22]Sethuraman, I.; Sabbu, P.; Natrajan, A. "A facile eco-friendly three-component protocol for the regio- and stereoselective synthesis of functionalized trans-dihydrofuro[3,2-c]-quinolin-4(2H)-ones", Green Chemistry, 14, pp. 336, 2012.