AN EFFICIENT MICROWAVE-ASSISTED SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES BY A THREE COMPONENT REACTION UNDER CATALYST- AND SOLVENT-FREE CONDITIONS

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Keywords: 2,3-Dihydroquinazolin-4(1*H*)-ones, microwave irradiation, catalyst- and solvent-free synthesis, isatoic anhydride, aldehydes, ketones.

An efficient and green synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by microwave-assisted reaction of isatoic anhydride, ammonium acetate and an aldehyde or a ketone under catalyst- and solvent-free conditions is described.

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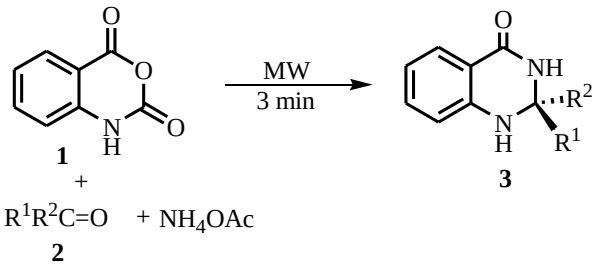
Introduction

2,3-Dihydroquinazolin-4(1*H*)-ones (**3**) are a class of nitrogen heterocycles that have attracted much attention because of their broad range of pharmacological activities such as antibacterial,[1] antifungal,[2] antimalarial,[3] antitumor,[4] anticancer,[2,5] anti-inflammatory,[6] and anticonvulsant[7] activities. Moreover, they are also used as key intermediates for the synthesis of quinazolin-4(3*H*)-ones.[8-10] Two important routes for synthesis of **3** are the reactions of (i) *o*-aminobenzamide and an aldehyde or a ketone and (ii) isatoic anhydride, an amine or ammonia source and an aldehyde or a ketone. Reactions through both these two routes are known to be carried out by use of different catalysts and solvents.[11-19] The current trend towards development of catalyst-free and solvent-free reaction conditions[20-25] encouraged us to synthesize **3** by the above-said routes by avoiding the use of any catalyst or solvent. Very recently, we have reported a catalyst- and solvent-free synthesis of **3** by the first route.[26] It is evident from the literature that in 2007 Gao *et al.*[27] reported a synthesis of **3** by the second route simply by heating a mixture of the reactants at 70 °C. However, in our hands the reactions were incomplete at 70 °C within the stipulated time (10 min) and hence higher temperature and/or longer time were required to complete the reactions. Owing to the fact that microwave (MW) irradiation has a number of beneficial effects in process chemistry, particularly with respect to reaction time; it has become an attractive tool for synthetic organic chemists. In order to carry out the above-said reaction within a short time, we studied the reaction of isatoic anhydride, ammonium acetate (ammonia source) and an aldehyde or a ketone under the influence of microwave (Scheme 1). The results were very much satisfactory and the remarkable success obtained in this endeavor is presented herein.



Scheme 1. Microwave-assisted synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (**3**).

Experimental

Melting points were recorded on a Köfler block. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AV-300 (300 MHz) spectrometer. Analytical samples were routinely dried *in vacuo* at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Mass spectra were measured with a Waters Xevo G2QTof HRMS spectrometer. A mono-mode MW reactor, manufactured by CEM Corporation, USA was used for this study. TLC experiments were performed with silica gel G of SRL Pvt. Ltd make. Petroleum ether had the boiling range of 60-80 °C.

Synthesis of 3 by microwave method

In a typical experiment, an intimate mixture of isatoic anhydride (1 mmol), aldehyde/ketone (1 mmol) and ammonium acetate (2 mmol) was taken in a pyrex beaker (100 mL) and it was subjected to irradiation in the MW reactor at 60 °C (300 W) in an open vessel for 3 min (as monitored by TLC). The reaction mixture was then cooled and crystallized from ethanol, which gave **3** in pure state.

 DOI: 10.17628/ECB.2016.5.185

Synthesis of 3 by thermal method

An intimate mixture of isatoic anhydride (1 mmol), aldehyde/ketone (1 mmol) and ammonium acetate (2 mmol) was taken in a round-bottomed flask fitted with an air condenser, and it was heated in an oil bath at 120°C for 10 min. The reaction mixture was then cooled and crystallized from ethanol in order to obtain **3** in pure state.

2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one (3a)

Colorless crystals, yield 92 %, m.p. 217-219 °C (lit.[11] 216-218 °C). IR (KBr): ν/cm^{-1} = 3308, 3188, 3066, 1655, 1610, 1509, 1434. ^{1}H-NMR ($CDCl_3$): δ = 4.39 (br. s, 1H, NH), 5.76 (br. s, 1H, NH), 5.91 (s, 1H, H-2), 6.67 (d, 1H, *J* = 7.9 Hz), 6.91 (t, 1H, *J* = 7.2 Hz), 7.34 (t, 1H, *J* = 7.4 Hz), 7.46 (br. s, 3H), 7.59 (s, 2H), 7.95 (d, 1H, *J* = 7.6 Hz). MS (relative intensity) m/z: 225.2142 (M+1). Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N 12.49. Found: C, 74.72; H, 5.51; N, 12.25.

2,3-Dihydro-2-p-tolylquinazolin-4(1*H*)-one (3b)

Colorless crystals, yield 92 %, m.p. 228-230 °C (lit.[11] 225-227 °C). ^{1}H-NMR ($CDCl_3$): δ = 2.40 (s, 3H, Me), 4.35 (br. s, 1H, NH), 5.72 (br. s, 1H, NH), 5.87 (s, 1H, H-2), 6.66 (d, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.5 Hz), 7.25 (d, 2H, *J* = 7.9 Hz), 7.33 (t, 1H, *J* = 7.1 Hz), 7.48 (d, 2H, *J* = 7.9 Hz), 7.95 (d, 1H, *J* = 7.1 Hz).

2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one (3c)

Colorless crystals, yield 90 %, m.p. 194-196 °C (lit.[12] 197-198 °C), ^{1}H-NMR ($CDCl_3$): δ = 3.84 (s, 3H, OMe), 4.35 (br. s, 1H, NH), 5.73 (br. s, 1H, NH), 5.85 (s, 1H, H-2), 6.66 (d, 1H, *J* = 7.7 Hz), 6.90 (t, 1H, *J* = 7.5 Hz), 6.95 (d, 2H, *J* = 8.6 Hz), 7.33 (br. t, 1H, *J* = 7.8 Hz), 7.52 (d, 2H, *J* = 8.6 Hz), 7.94 (br. d, 1H, *J* = 7.5 Hz). Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.70; H, 5.39; N, 10.84.

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3d)

Colorless crystals, yield 95 %, m.p. 225-227 °C (lit.[28] 225-226 °C). ^{1}H-NMR ($CDCl_3$): δ = 4.62 (br. s, 1H, NH), 6.03 (br. s, 1H, NH), 6.35 (d, 1H, *J* = 1.6 Hz, H-2), 6.67 (d, 1H, *J* = 8.0 Hz), 6.88 (t, 1H, *J* = 7.5 Hz), 7.30-7.43 (m, 4H), 7.73-7.76 (m, 1H), 7.92 (br. d, 1H, *J* = 7.2 Hz).

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3e)

Colorless crystals, yield 95 %, m.p. 206-207 °C (lit.[11] 205-206 °C). ^{1}H-NMR ($CDCl_3$): δ = 4.37 (br. s, 1H, NH), 5.81 (br. s, 1H, NH), 5.89 (s, 1H, H-2), 6.68 (d, 1H, *J* = 8.0 Hz), 6.92 (t, 1H, *J* = 7.5 Hz), 7.35 (t, 1H, *J* = 7.7 Hz), 7.42 (d, 2H, *J* = 8.3 Hz), 7.54 (d, 2H, *J* = 8.3 Hz), 7.94 (d, 1H, *J* = 7.8 Hz)**.** Anal. Calcd. for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 65.17; H, 4.17; N 11.02.

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3f)

Colorless crystals, yield 92 %, m.p. 194-196 °C (lit.[11] 195-197 °C). ^{1}H-NMR ($CDCl_3$): δ = 5.80 (br. s, 1H, NH), 5.89 (s, 1H, H-2), 6.67 (d, 1H, *J* =8.1 Hz), 6.92 (t, 1H, *J* = 7.6 Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.48 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.6 Hz), 7.95 (d, 1H, *J* = 7.5 Hz).

2-(4-(Dimethylamino)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (3g)

Colorless crystals, yield 93 %, m.p. 208-209 °C (lit.[11] 208-210 °C). ^{1}H-NMR ($CDCl_3$): δ = 2.99 (s, 6H, -NMe_2), 4.33 (br. s, 1H, NH), 5.68 (br. s, 1H, NH), 5.80 (s, 1H, H-2), 6.65 (d, 1H, *J* = 8.0 Hz), 6.73(d, 2H, *J* = 8.6 Hz), 6.88 (t, 1H, *J* = 7.5 Hz), 7.32 (t, 1H, *J* = 7.7 Hz), 7.43 (d, 2H, *J* = 8.6 Hz), 7.94 (d, 1H, *J* = 7.8 Hz).

2-(Benzo[*d*][1,3]dioxol-5-yl)-2,3-dihydroquinazolin-4(1*H*)-one (3h)

Colorless crystals, yield 92 %, m.p. 199-201 °C (lit.[29] 201 °C). ^{1}H-NMR ($CDCl_3$): δ = 4.33 (br. s, 1H, NH), 5.71 (br. s, 1H, NH), 5.82 (s, 1H, H-2), 6.02 (s, 2H, O-CH_2-O), 6.66 (d, 1H, *J* = 8.0 Hz), 6.83 (d, 1H, *J* = 7.9 Hz), 6.90 (t, 1H, *J* = 7.5 Hz), 6.99 (d, 1H, *J* = 7.9 Hz), 7.14 (s, 1H), 7.33 (t, 1H, *J* = 7.5Hz), 7.94 (d, 1H, *J* = 7.4 Hz).

2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)quinazolin-4(1*H*)-one (3i)

Colorless crystals, yield 92 %, m.p. 219-220 °C (lit.[30] 220 °C). ^{1}H-NMR ($CDCl_3$): δ = 3.94 (s, 3H, OMe), 4.33 (br. s, 1H, NH), 5.68 (br. s, 1H, NH), 5.77 (s, 1H, H-2/OH), 5.83 (s, 1H, OH/H-2), 6.67 (d, 1H, *J* = 7.8 Hz), 6.88-7.01 (m, 3H), 7.21-7.30 (m, 1H), 7.34 (t, 1H, *J* = 7.8 Hz), 7.95 (d, 1H, *J* = 8.3 Hz).

2,3-Dihydro-2-(thiophen-2-yl)quinazolin-4(1*H*)-one (3j)

Colorless crystals, yield 96 %, m.p. 214-216 °C (lit.[31] 213-215 °C). ^{1}H-NMR ($CDCl_3$): δ = 4.56 (br. s, 1H, NH), 5.97 (br. s, 1H, NH), 6.20 (*s*, 1H, H-2), 6.70 (1H, *d*, *J* = 7.9 Hz), 6.92 (1H, *t*, *J* = 7.4 Hz), 7.02 (1H, *t*, *J* = 4.3 Hz), 7.22 (1H, *br. d*, *J* = 3.3 Hz), 7.35 (1H, *t*, *J* = 7.9 Hz), 7.40(d, 1H, *J* = 5.0 Hz), 7.95 (d, 1H, *J* = 7.7 Hz).

2,3-Dihydro-2-(pyridin-3-yl)quinazolin-4(1*H*)-one (3k)

Colorless crystals, yield 91 %, m.p. 217-218 °C [lit.[32] 219-221 °C]. ^{1}H-NMR ($CDCl_3$): δ = 4.39 (br. s, 1H, NH), 5.86 (br. s, 1H, NH), 5.99 (s, 1H, H-2), 6.70 (d, 1H, *J* = 8.1 Hz), 6.94 (t, 1H, *J* = 7.6 Hz), 7.34-7.44 (m, 2H), 7.96 (br. d, 1H, *J* = 7.8 Hz), 8.03 (br. d, 1H, *J* = 7.8 Hz), 8.71 (br. d, 1H, *J* = 3.5 Hz), 8.78 (br. s 1H).

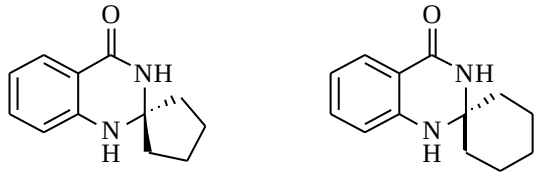
Compound 3l

Colorless crystals, yield 93 %, m.p. 256-258 °C (lit.[29] 257-260 °C). ^{1}H-NMR ($CDCl_3$): δ = 1.81 (s, 4H, 2 × CH_2), 1.97 (s, 4H, 2 × CH_2), 4.25 (br. s, 1H, NH), 5.89 (br. s, 1H, NH), 6.66 (d, 1H, *J* = 7.9Hz), 6.86 (t, 1H, *J* = 7.6 Hz), 7.31(t, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 7.7 Hz).

 DOI: 10.17628/ECB.2016.5.185

Compound 3m

Colorless crystals, yield 95 %, m.p. 219-220 °C (lit.[33] 217-219 °C). ^{1}H-NMR ($CDCl_3$): δ = 1.24-1.82 (m, 10H, $5CH_2$), 4.35 (br. s, 1H, NH), 6.27 (s, 1H, NH), 6.64 (d, 1H, *J* = 8.0 Hz), 6.81 (t, 1H, *J* = 7.5 Hz), 7.28 (br. t, 1H, *J* = 7.5 Hz), 7.86 (br. d, 1H, *J* = 7.8 Hz).



3l **3m**

Figure 1. Structures of compounds **3l** and **3m**.

Results and Discussion

The microwave-assisted reaction being reported involves subjecting of an intimate mixture of isatoic anhydride, ammonium acetate and aldehyde/ketone (1:2:1 mole ratio)

Table1. Optimization of synthesis of **3a** under MW conditions.

Time min	**3**	**5**	**1**	**2**	**3**	**4**	**5**
Temp. °C	45	45	60	60	60	60	60
Yield (%)	0	trace	64	81	92	90	85

directly to microwave irradiation. The time and temperature were first optimized using benzaldehyde (Table 1). The yields of different **3** under the optimized conditions (MW, 3 min, 60 °C) are given in the experimental section with the spectral properties of the individual compounds. The yields of the products were found to be excellent and the reactions were very clean. The crude products of the reactions were pure enough to give analytical samples simply by crystallization from ethanol. This solvent- and catalyst-free methodology is sufficiently mild to tolerate a variety of functionalities. All the synthesized 2,3-dihydroquinazolin-4(1*H*)-ones (**3a-m**) are known in the literature and were identified from their physical and spectral data.[11,12,27-33]

Table 2. Synthesis of **3a** under thermal conditions for 10 min.

Temp. °C	**70**	**80**	**90**	**100**	**110**	**120**	**130**
Unreacted **1** %	30	19	10	5	trace	0	0
Yield %	64	72	80	88	91	92	90

Since in the thermal process reported by Gao *et al.* [27] the reactions were not complete within 10 min at 70 °C, we tried to get an optimized condition using isatoic anhydride, ammonium acetate and benzaldehyde by gradually increasing the reaction temperature for completion of reaction within this time (Table 2). The yields of **3a-m** under the optimized conditions, *i.e.*, at 120 °C and 10 min reaction time, vary between 91 and 96 %.

Conclusions

We have developed a simple microwave-assisted synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (**3**) without the use of any added catalyst, solvent, surfactant or solid support. The method is very efficient and environmentally benign.

Acknowledgments

Financial assistance from the UGC-CAS and DST-PURSE programs, Department of Chemistry is gratefully acknowledged. The authors also acknowledge the DST-FIST program to the Department of Chemistry, Jadavpur University for providing the NMR spectral data. They are grateful to Professor B. C. Ranu, Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata for extending the facility of using a Scientific Microwave Oven for this study. AD and NS are thankful to the CSIR and UGC, New Delhi for their Research Fellowships.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Received: 16.06.2016.
Accepted: 08.07.2016.