Full Paper

A Microwave-Assisted and Heteropolyacids-Catalysed Cyclocondensation Reaction for the Synthesis of 4(3*H*)-Quinazolinones

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Abstract: We have investigated a microwave–assisted synthesis of 4(3*H*)–quinazolinones by condensation of anthranilic acid, orthoesters (or formic acid) and substituted anilines, using Keggin-type heteropolyacids ($H_3PW_{12}O_{40} \cdot 13H_2O$, $H_4SiW_{12}O_{40} \cdot 13H_2O$, $H_4SiMo_{12}O_{40} \cdot 13H_2O$ or $H_3PMo_{12}O_{40} \cdot 13H_2O$) as catalysts. We found that the the use of $H_3PW_{12}O_{40} \cdot 13H_2O$ acid coupled to microwave irradiation allows a solvent-free, rapid (~13 min) and high-yielding reaction.

Introduction

The quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities. They generally display useful therapeutic and pharmacological properties such as anti-inflammatory, anti-convulsant, anti-hypertensive and antimalarial activity [1-4]. Moreover, the 4(3*H*)–quinazolinone moiety is found in several bioactive natural products [5,6]. For these reasons their synthesis has received considerable attention. Several groups have reported conventional preparation methods which require reflux for several hours and the use of large volumes of solvent [7,8]. Recently, however, more interest has been focused on "dry media" synthesis and particularly on solvent free procedures using microwave irradiation [9-15, reviewed in 13]. Of interest, quinazolinones were recently prepared using various catalysts such as Yb(OTf)$_3$, Bi(TFA)$_3$-FeCl$_4$, silica gel/FeCl$_3$, Nafion-H (a perfluorinated resin-supported sulfonic acid) and La(NO$_3$)$_3$·6H$_2$O [16-21].

The Keggin-type heteropolyacids (HPAs) are believed to have extensive prospects of application in synthesis chemistry since their acidity strength is higher than that of both mineral and Lewis acids. Moreover, they are easy to handle, non-volatile and non-explosive. Heteropolyacids compounds such as H$_3$PW$_{12}$O$_{40}$ are known to be effective catalysts for various kinds of acid-catalyzed reactions [21-24] and we recently reported the first microwave-assisted synthesis of calix[4]resorcinarenes using aldehydes and resorcinol and catalyzed by H$_3$PW$_{12}$O$_{40}$ [25]. However, whether microwave irradiation and the use of HPA as catalysts improves the synthesis of 4(3*H*)-quinazolinones has not been investigated, to the best of our knowledge. We then tested several HPAs (abbreviated henceforth as XM$_{12}$, where X = P or Si and M = W or Mo) in the synthesis of 4(3*H*)–quinazolinones from condensation with anthranilic acid, aniline and ortho esters (or formic acid) at reflux and under microwave irradiation (Scheme 1).

Scheme 1. Synthesis of 4(3*H*)–quinazolinones by cyclocondensation of anthranilic acid (**1**), aniline (**2**) and orthoester (or formic acid) in presence of HPA as catalyst.
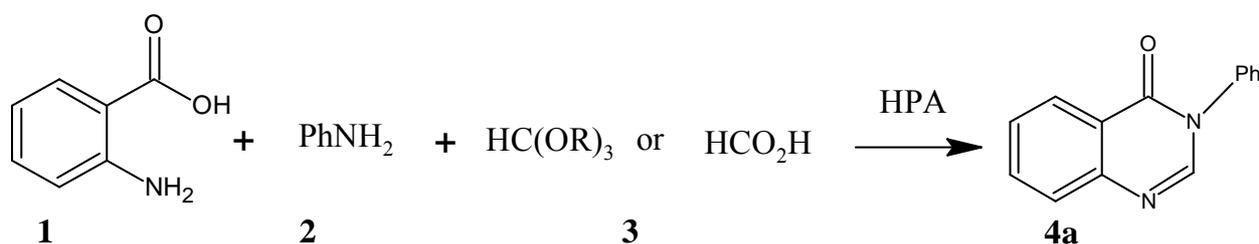
Results and Discussion

4(3*H*)–Quinazolinone synthesis in the presence of orthoesters (R= Me, Et) or formic acid was first carried out at reflux or under microwave irradiation, respectively, with toluene or 2-ethoxyethanol as solvent. As shown in Table 1, yields of 4(3*H*)–quinazolinones depended on the experimental procedure, the nature of reactants as well as that of catalysts.

Table 1. One–pot synthesis of 3-phenyl-4(3*H*)-quinazolinone from anthranilic acid, aniline and ortho esters (or formic acid) catalysed by various HPA.

Catalyst[a]	Reactant	Conventional Heating[b]	Microwave Irradiation[c]			
			With solvent[d]		Solvent-free	
		Yield (%)[e]	Yield (%)[e]	T(°C)[g]	Yield (%)[e]	T (°C)[g]
PW$_{12}$	HC(OCH$_3$)$_3$	70	57	130	70	163
	HC(OC$_2$H$_5$)$_3$	75	70	126	75	166
	HCO$_2$H	55	-[f]	-	67	165
SiW$_{12}$	HC(OCH$_3$)$_3$	63	48	130	65	160
	HC(OC$_2$H$_5$)$_3$	68	55	125	68	164
	HCO$_2$H	48	-[f]	-	60	165
PMo$_{12}$	HC(OCH$_3$)$_3$	54	43	132	65	156
	HC(OC$_2$H$_5$)$_3$	56	55	127	65	164
	HCO$_2$H	40	-[f]	-	56	163
SiMo$_{12}$	HC(OCH$_3$)$_3$	43	47	135	60	155
	HC(OC$_2$H$_5$)$_3$	49	50	128	60	165
	HCO$_2$H	36	-[f]	-	52	164

[a] catalyst amount: 1.2 mol%
[b] with 25 mL of toluene at reflux [120 min, T(°C)= 110]
[c] microwave irradiation was carried out in two stages: first, activation for 3 min at 300 watts and then, 10 min at 450 watts
[d] 5 mL of 2-ethoxyethanol
[e] isolated yield
[f] invalid result
[g] temperature measurement by IR-thermometer

Compared to the conventional method, microwave activation in the presence of solvent led to lower yields, whereas activation without solvent afforded equivalent or slightly increased yields. It should be noted, however, that, in the latter case, the reaction time was ten-fold shorter (13 min for microwave irradiation *versus* 120 min for conventional heating). Interestingly, when formic acid was used as reactant, the microwave-assisted reactions always gave higher yields than the conventional method. Besides experimental procedure and reactants, the 4(3*H*)–quinazolinone yields also depended on the nature of the heteroatom (P, Si) and the metal atom (W, Mo) of the HPAs (Table 1). Hence, W compounds were more efficient than Mo compounds, whereas P-based HPAs led to better yields than those containing Si. Overall, the yields decreased in the following order: PW$_{12}$>SiW$_{12}$>PMo$_{12}$> SiMo$_{12}$ which is, strikingly, the same order of their acidic strengths [22]. These results suggest that the higher the acidity of the HPA catalysts, the higher the yield of microwave- assisted synthesis of 4(3*H*)–quinazolinones. In subsequent experiments, we choose the PW$_{12}$ catalyst for its better catalytic performance and examined the impact of various orthoesters/anthranilic acid ratios on reaction yields (Scheme 1). Results obtained under solvent–free conditions and microwave irradiation are reported in Table 2. For both HC(OC$_2$H$_5$)$_3$ and HC(OCH$_3$)$_3$, yields increased and reached a peak for ortho esters/anthranilic acid ratios of 1.4:1 before declining. However, with the aforementioned experimental conditions, HC(OC$_2$H$_5$)$_3$ gave higher yields than HC(OCH$_3$)$_3$ (77% versus 63% at the peak).

Table 2. Effect of ortho ester/anthranilic acid ratios on 3-phenyl-4(3*H*)-quinazolinone (**4a**) yield in the presence of PW_{12}.

| Substrate ratio [a]	$HC(OCH_3)_3$		$HC(OC_2H_5)_3$	
	Yield of 4a (%) [b]	T(°C) [c]	Yield of 4a (%) [b]	T (°C) [c]
1.0 / 1	42	163	62	166
1.2 / 1	48	160	66	162
1.4 / 1	63	160	77	168
1.6 / 1	46	157	61	166
1.8 / 1	45	163	72	170
2.0 / 1	44	165	56	176

[a] ortho ester/anthranilic acid ratio
[b] solvent-free conditions and microwave irradiation as described in Table 1
[c] temperature measurement by IR-thermometer

In a third step, a wide range of structurally varied substituted anilines **2**, anthranilic acid (**1**) and triethyl orthoformate (**3**) were used in the presence of a catalytic amount (1,2 mol%) of PW_{12} under microwave irradiation and solvent-free conditions (scheme 2). Results are summarized in Table 3.

Scheme 2. One-pot synthesis of 4(3*H*)–quinazolinones under solvent free conditions, microwave-irradiation and PW_{12} mediated-catalysis with anthranilic acid (**1**), various substituted anilines (**2a-j**) and triethyl orthoformate (**3**).
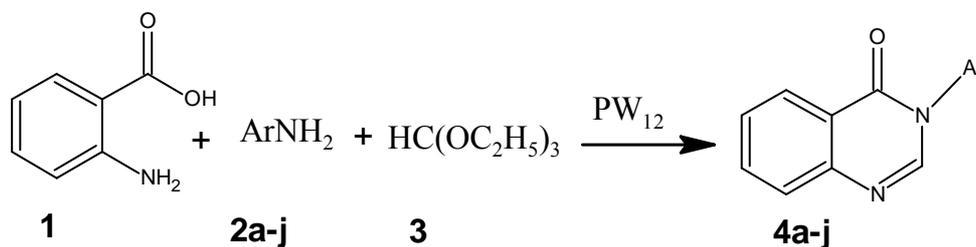
Table 3. Impact of aniline structure on reaction yield.

ArNH₂ (2a-g)	Products	Yield (%)	mp (°C)	lit. mp (°C) [a]	T (°C) [b]
C_6H_5	**4a**	77	139	139	168
4-MeOC_6H_4	**4b**	80	194	194	132
4-MeC_6H_4	**4c**	80	147	147	133
3-MeOC_6H_4	**4d**	65	159	195	130
4-ClC_6H_4	**4e**	55	181	182	142
4-BrC_6H_4	**4f**	60	186	186	140
$2,4\text{-Cl}_2C_6H_3$	**4g**	50	230-236	-	145
$3,4\text{-Cl}_2C_6H_3$	**4h**	45	160-166	-	141
$2,6\text{-Cl}_2C_6H_3$	**4i**	30	252	-	148
$2,5\text{-Cl}_2C_6H_3$	**4j**	35	145	-	146

[a] literature melting points [12, 13, 16]

[b] temperature measurement by IR-thermometer

In all cases, the three components of the reaction proceeded rapidly to afford the corresponding 4(3*H*)-quinazolinones **4a-j** but we noticed a significant difference in reaction yields. Indeed, anilines structure had an obvious impact on the obtained yields since all anilines having electron-donating substituents reacted very well, and gave good yield in a few minutes. It can be inferred from these observations that electron-donating groups (such as methoxy and methyl) are beneficial for the reaction owing to the increased electron density that they induce in the aromatic system. By contrast, electron-withdrawing groups (such as chloro and bromo) are unfavourable for the transformation. Another interesting result is that the reaction with *para*-electron-donating substituted anilines (4-MeO), was more efficient than that with *meta*-electron-donating substituted anilines (3-MeO). Moreover, the condensation yield with dichloroanilines was lower than that with monochloroaniline (Table 3). Thus, the efficiency of the microwave-assisted and solvent-free condensation of anthralinic acid **1** with triethyl ortho formate **3** and aniline derivatives **2a-j** is heavily affected by the electronic nature and the number and the position of substituents on aniline. Analysis of the reaction data (Tables 1 and 2) obtained from model compounds **2** and **3** leads to the following observations:

(a) Comparison between conventional heating and microwave irradiation revealed a specific and strong microwaves effect since, under conventional heating the reaction occurred in a very limited extension. After 60 min, thermal reaction did not allow to produce any quinazolinones **4**, the optimal yields were reached after 120 min of heating. By contrast, quinazolinones **4** were obtained after only 13 min of microwave irradiation.

(b) In microwave irradiation, thermal energy is generated *in situ* due to the interaction of polar molecules or ionic species with the electric field. So, the power range was set to 450 W, in order to avoid an overheating that may induce products degradation.

(c) A crucial role for acid during the cyclocondensation step cannot be excluded since we obtained very low yields in all reactions carried without acid.

(d) The reactions performed under solvent-free conditions allowed the observation of microwave effects, *i.e.* higher yields and higher measured temperatures.

Besides the efficient energy input that microwaves can provide to the reaction mixtures, a chemical activation effect cannot be discounted. During the irradiation, there is a total or partial alignment of dipolar molecules and/or ionic species with the direction of the electrical field. Such an alignment may then favor interactions between reactants and may lead to shorter and more efficient reactions. Our observation that electron-donating or -withdrawing substituents on anilines have an impact on reaction yields (cf. Table 3) supports the above hypothesis, since these substituents can modify the aniline's dipolar moments and consequently, may affect their behavior in the electrical field.

Finally, regarding the reaction mechanism, we propose that the three–component synthesis of 4(3*H*)-quinazolinones can proceed via three pathways, namely A, B and C (Scheme 3). Pathway A may involve the intermediate imidic ester **5** stabilized by HPA. Then, the imidic ester may be very prone to react with an amine, thus leading to the amidine intermediate **7** (path A). Alternatively, it may form the benzoxazinone **9** through loss of ethanol and cyclocondensation (path C). The benzoxazinone **9** can lead the intermediate **10**, which rapidly cyclizes to yield quinazolones **4**, as previously reported [10]. Path B may first involve the imidic ester **6**, which condenses with anthranilic acid to give the amidine **7**. The latter may then cyclize to form the quinazolinone **4**. The accelerating role of

microwaves on these reaction pathways may also be explained by a thermal effect as well as the chemical activation discussed above. As an example, the polarization of **7** and the supposed formation of **8** (Scheme 3) might be favored by microwave irradiation.

Scheme 3. Proposed mechanism for the cyclocondensation reaction.
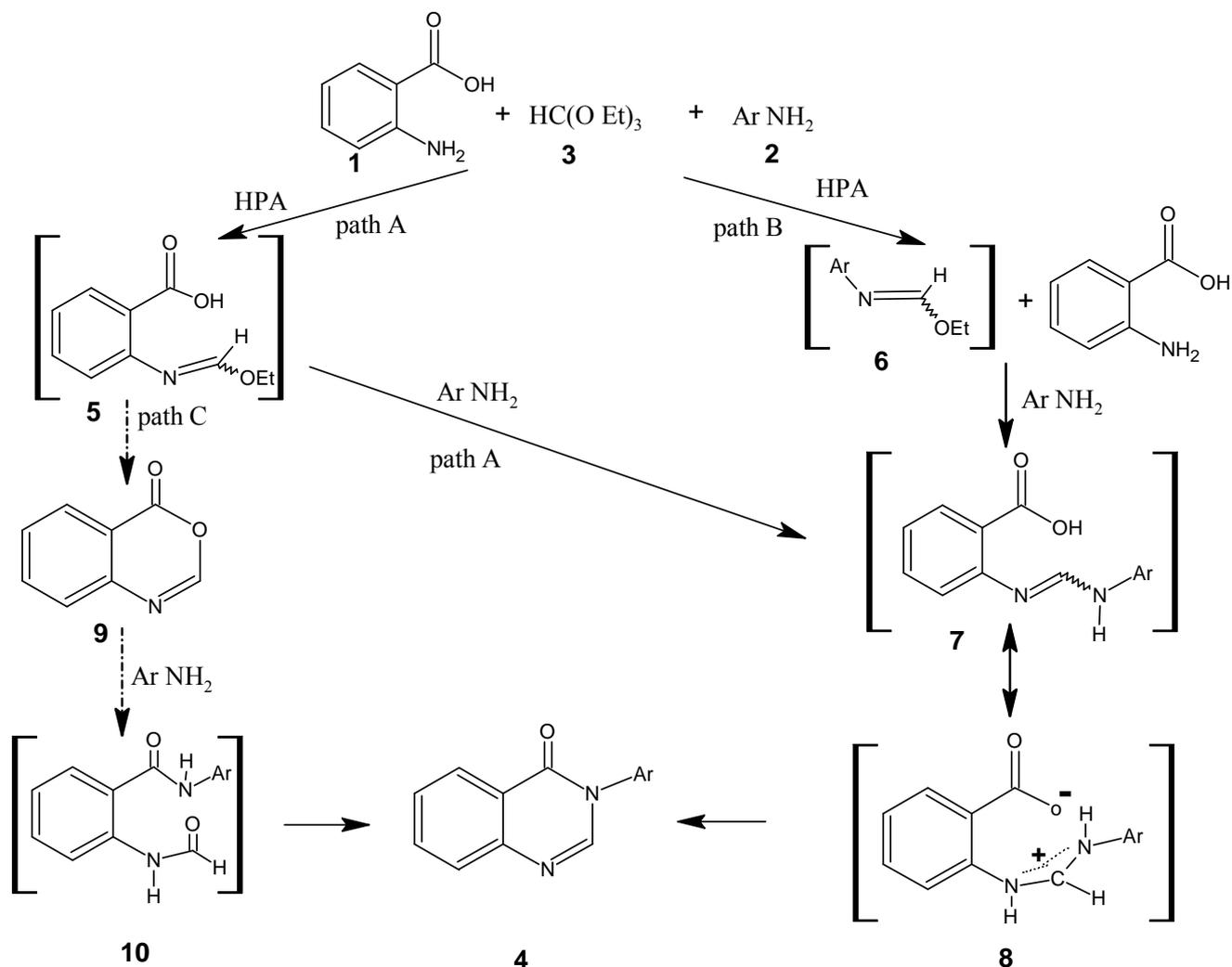
Conclusions

We developed a single-step and efficient synthesis of 4(3*H*)-quinazolinones using anthranilic acid, ortho esters and substituted anilines under PW_{12}-mediated catalysis, microwave irradiation and solvent-free conditions. Mildness of the catalysts, avoidance of solvents, short reaction times (13 min) and good yields (80%) are the outstanding advantages of the present protocol.

Experimental

General

Pure heteropolyacids $H_nXM_{12}O_{40}$ (PM$_{12}$) were prepared by the standard method involving the synthesis of the corresponding sodium salt and the extraction of acid by diethyl ether and its

purification by crystallization in water at 4°C [26]. Anthranilic acid was purchased from Sigma. Amines, toluene and 2-ethoxyethanol were purchased from Aldrich. All melting points were measured on a Stuart Scientific SMP3 apparatus fitted with a microscope and uncorrected. The IR absorption spectra (KBr disks, cm^{-1}) were measured on a Nicolet Magna 550 series II IR Spectrophotometer. ^{1}H-NMR (300.13 MHz) and ^{13}C-NMR (75.47 MHz) spectra were recorded in deuterated chloroform (CDCl$_3$) on a Bruker DRX 300 spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ values (ppm). Mass spectra were recorded on a Nermag R 10-10C quadruple mass spectrometer at 70 eV. All the compounds gave satisfactory elemental analyses.

The multimode microwave reactor (a modified microwave oven Candy MGA 20M) has a single magnetron (2450 MHz) unt with a maximum delivered power of 800W. Experiments were carried out in a Pyrex reactor fitted with a condenser. During experiments, temperature was monitored with an external infra-red thermometer (Flashpoint FZ400). Our modifications to a domestic microwave oven, adopted since 1992, are similar to those described, currently, for microwave chemistry experiments [27]. In a typical design, a hole was drilled for a condenser tube in the oven top. External steel tube of the same diameter (~12 cm long) was welded to the hole in order to eliminate possible microwave leakage. The microwave equipment operates within the safety limits prescribed: accepted limit on the safe stray leakage of the microwave power density is 10mW/cm^2 at 2450 MHz measured at a 50 mm distance from the equipment (Microwave Leakage Detector). The apparatus has been adapted for laboratory applications with an external reflux condenser, multi-limb vacuum receivers and Dean-Stark trap. (Figure 1)

Figure 1. Fractional separations in a modified microwave oven (with a freezing bath and under vacuum).

General Procedure for the preparation of 4(3*H*)-quinazolinones **4a-j**

Method I (conventional heating): The synthesis of 4(3*H*)-quinazolinones from anthranilic acid (10 mmoles), amine (10 mmol) and formic acid or ortho esters (14 mmol) in presence of a catalytic

amount of heteropolyacids (1. 2 mol%) was carried out under reflux in toluene (25 mL) for 2 h. The obtained solid was crystallized in ethanol after washing with water to eliminate any catalyst residue.

Method II (microwave irradiation): The synthesis of 4(3*H*)-quinazolinones from anthranilic acid (10 mmol), amine (10 mmol) and formic acid or orthoesters (14 mmol) in the presence of a catalytic amount of heteropolyacids (1. 2 mol%) and 2-ethoxyethanol (5 mL) was carried out under microwave irradiation. The power was initially set to 300 W for 3 min, then it was increased to 450 W for 10 min. The obtained solid was crystallized in ethanol after washing with water to eliminate any catalyst residue.

Method III (microwave irradiation without solvent): is the solvent-free version of method II.

*3-Phenyl-4(3*H*)-quinazolinones* (**4a**). IR ν_{max}: 1699, 1598 and 1463; ^{1}H-NMR: δ = 8.34 (d, *J* =7.6 Hz, 1H), 8.16 (s, 1H), 7.72-7.78 (m, 2H), 7.51 (t, *J* =7.31 Hz, 1H) and 7.28-7.36 (m, 5H); ^{13}C-NMR: δ = 160.7, 147.1, 147.2, 136.3, 135.2, 134.6, 129.9, 128.6, 128.1, 127.4, 127.0 and 122.6; GC/MS: m/z (%) = 222.2 (M[+], 100), 223.2 (M+1, 15); Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; O, 7.2. Found: C, 75.60; H, 4.44; N, 12.52.

3-(4-Methoxyphenyl)-4(3H)-quinazolinone (**4b**). IR ν_{max}: 1699, 1598, 1463; ^{1}H-NMR: δ = 8.28 (d, *J* = 7.6 Hz, 1H), 8.12 (s, 1H), 7.68-7.72 (m, 2H), 7.42 (t, J =7.3 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H) and 3.71 (s, 3H); ^{13}C-NMR : δ = 161.2, 148.3, 146.2, 134.3, 133.2, 131.5, 128.1, 127.1, 126.2, 125.1, 124.8, 124.2, 122.1 and 55.9; GC/MS : m/z (%) = 252.2 (M[+], 100); 253.2 (M[+]+1, 14); Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; O, 12.68. Found: C, 75.63; H, 4.71; N, 11.03.

3-(4-Methylphenyl)-4(3H)-quinazolinone (**4c**). IR ν_{max}: 1690, 1603, 1457; ^{1}H-NMR: δ = 8.29 (d, J = 7.6 Hz, 1H), 8.11 (s, 1H), 7.69-7.71 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H) and 2.26 (s, 3H); ^{13}C-NMR: δ = 159.9, 147.3, 146.2, 134.3, 133.2, 131.5, 128.1, 127.1, 126.2, 125.1, 124.8, 124.1, 122.1 and 20.5; GC/MS: m/z (%) = 236.2 (M[+], 100); 237.2 (M[+]+1, 14); Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; O, 6.95. Found: C, 76.28; H, 5.18; N, 11.70.

3-(3-Methoxyphenyl)-4(3H)-quinazolinone (**4d**). IR ν_{max}: 1692, 1605, 1456; ^{1}H-NMR: δ = 8.29 (d, *J* = 7.6Hz, 1H), 8.13 (s, 1H), 7.66-7.73 (m, 2H), 7.42 (t, *J* =7.3Hz, 1H), 7.23-7.35 (m, 4H) and 3.71 (s, 3H); ^{13}C-NMR: δ = 162.2, 148.3, 146.2, 134.3, 133.2, 131.4, 128.1, 127.1, 126.2, 125.1, 124.8, 124.2, 122.1 and 56.8; GC/MS: m/z (%) = 252.2 (M[+], 100); 253.2 (M[+]+1, 14); Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; O,12.69. Found: C, 71.46; H, 4.75; N, 11.13.

3-(4- Chlorophenyl)-4(3H)-quinazolinone (**4e**). IR ν_{max}: 1696, 1601, 1462; ^{1}H-NMR: δ = 8.33 (d, *J* = 7.5 Hz, 1H), 8.13 (s, 1H), 7.68-7.71 (m, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H) and 7.25 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR: δ= 160.2, 148.8, 146.6, 136.1, 135.2, 134.6, 132.7, 130.5, 128.3, 127.2, 127.8 and 125.1; GC/MS : m/z (%) = 256.0 (M[+], 100); 257.0 (M[+]+2); Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; Cl, 13.81; N, 10.91; O, 6.23. Found: C, 65.50; H, 3.41; N, 11.13.

3-(4-Bromophenyl)-4(3H)-quinazolinone (**4f**). IR ν_{max}: 1692, 1605, 1456; ^{1}H-NMR: δ = 8.43 (d, *J* = 8.6 Hz, 1H), 8.12 (s, 1H) and 7.95-7.21 (m, 7H); ^{13}C-NMR: δ = 160.0, 145.3, 134.6, 133.4, 132.7, 131.4, 130.7, 128.5, 128.1, 127.7, 127.6, 127.6 and 127.1; GC/MS : m/z (%) = 302, 300 (M[+]); Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; Br, 26.53; N, 9.30.

3-(2,4-Dichlorophenyl)-4(3H)-quinazolinone (**4g**). IR ν_{max}: 1679, 1610, 1452; ^{1}H-NMR: δ= 8.13 (d, *J* = 7.6 Hz, 1H), 7.95 (s, 1H), 7.85-7.66 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H) and 7.25 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR: δ= 164.2, 162.8, 147.6, 136.3, 134.2, 132.6, 130.7, 129.5, 128.3, 127.2, 127.8, 124.1 and 123.1; GC/MS : m/z (%) = 291.13 (M[+]); Anal. Calcd. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; , Cl, 24.36; N, 9.62.

3-(2,5-Dichlorophenyl)-4(3H)-quinazolinone (**4h**). IR ν_{max}: 1673, 1604, 1450; ^{1}H-NMR: δ = 8.43 (d, *J* = 7.6 Hz, 1H), 8.13 (s, 1H), 7.69-7.72 (m, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR ($CDCl_3$): δ = 165.2, 163.1, 148.8, 141.6, 134.0, 133.1, 130.2, 129.7, 128.3, 128.2, 126.2, 125.7, 123.1 and 123.1; Anal. Calcd. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; , Cl, 24.36 ; N, 9.62.

3-(2,6-Dichlorophenyl)-4(3H)-quinazolinone (**4i**). IR ν_{max}: 1660, 1618, 1456; ^{1}H-NMR: δ = 8.23 (d, *J* = 7.6 Hz, 1H), 8.13 (s, 1H), 7.69-7.72 (m, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H) ; 7.25 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR: δ= 165.2, 163.3, 148.4, 136.6, 133.2, 128.6, 127.6, 127.5, 127.2, 127.0, 126.9 and 123.1; Anal. Calcd. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77, Cl, 24.36; N, 9.62.

3-(3,4-Dichlorophenyl)-4(3H)-quinazolinone (**4j**). IR ν_{max}: 1687, 1625, 1461; ^{1}H-NMR: δ = 8.23 (d, *J* = 7.6 Hz, 1H), 8.18 (s, 1H), 7.69-7.72 (m, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H) and 7.25 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR: δ = 165.2, 163.3, 147.8, 137.7, 134.4, 133.2, 130.7, 130.0, 128.6, 127.1, 127.0, 122.2, 122.1 and 119.9; Anal. Calcd. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; Cl, 24.36; N, 9.62.

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