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Synthesis of quinazolinone analogues using sodium perborate as catalyst

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An environmentally benign approach for the synthesis of 2-aryl-3*H*-quinazolin-4-ones employing sodium perborate (SPB) as catalyst is described. SPB in water and acetone system is proved as selective catalyst of hydration for cyanides. The rate enhancement and high yield is attributed to the coupling of suitable catalyst with the solvent system. The key step is the microwave prompted reaction sequence combining 2-aminobenzonitrile and aromatic/heteroaromatic aldehydes providing efficient access to intermediate for the synthesis of this important class of nitrogen fused heterocycle.

Keywords: Sodium perborate, quinazolin-4-ones, 2-aminobenzonitrile, microwave irradiation (MWI), solvent-system

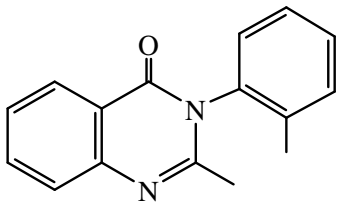
2-Substituted-3*H*-quinazolin-4-one is a privileged structure present in various biologically active compounds such as methaqualone (sedative hypnotic) **1**, chloroqualone (antitussive) **2** and piriqualone (anti-convulsant) **3** (ref. 1-3). Likewise natural alkaloids febrifugine **4** and its stereisomer isofebrifugine **5,** incorporating the quinazoline moiety, have been used for the treatment of *Malaria*[4]. This class of heterocycles also exhibits biological and pharmaceutical activities. For example, researchers from Pfizer have recently discovered a novel potent AMPA receptor antagonist CP-465,022 based on 3-(2-chlorophenyl)-6-fluoroquinazoline-4-one as the template[5]. In literature, few patents delineated this moiety as decanoic acid (2-dimethylamino-ethyl)-{1-[3-(4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-ethyl amide **6 (Figure 1)** has been patented as $CXCR_3$ ligand with micromolar affinity[6].

Moreover reactions in aqueous media are environmentally benign, easy to handle and devoid of any corrosive or carcinogenic effects[7]. In recent years, application of microwave irradiation and recyclable, less expensive mineral supports for organic transformation is emerging significantly. The microwave irradiation in conjunction with the use of mineral-supported reagents under solvent-free condition provide unique chemical processes with special attributes such as enhanced reaction rates, higher yields of pure products, easier work-up and rapid optimization of reactions in parallel and several ecofriendly advantages in the context of Green Chemistry[8].

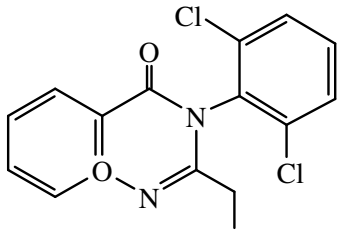
Looking to the other side, a phenomenol growth in the reactions occurring in aqueous media and usage of less expensive catalysts is rising. SPB (sodium perborate, ref. 9), being cheaper and large industrial chemical (over 500,000 tons per annum), is used as a source of "active oxygen" in detergents; means is alternative to peroxides and peroxyacids as safer reagent results in relatively innocuous side products[10,11].

This report highlights the transformation of functional group in microwave and synergism of catalyst (SPB) with particular solvent system. Each sphere of this reporting synthesis falls in the domain of green chemistry which should be welcome in these environmentally conscious days.

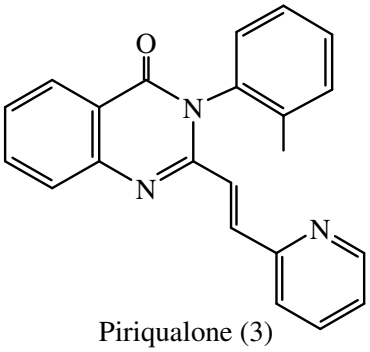
The most common synthetic approach towards quinazolinones involves the amidation of 2-aminobenzonitrile, 2-amino benzoic acid or its derivatives followed by oxidative ring closure under basic conditions[12,13]. This approach, however, is limited by low product yields. Recently, a synthesis of 2-substituted quinazolin-4(3*H*)-ones based on the oxidative cyclization of anthranilamide with aldehydes was reported[14]. But the method suffers from the use of toxic catalyst. Reports on solid phase synthesis of related quinazolinones are an additioal impetus to explore their multifaceted importance[15]. In continuation of our efforts to develop more versatile methodologies for the synthesis of bioactive heterocyclic compounds herein[16], we report a simple and straightforward method for the preparation of 2-aryl-quinazolin-4(3*H*)-ones from readily available



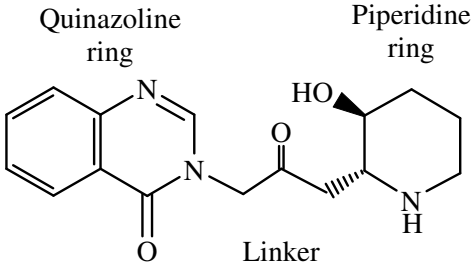
Methaqualone (1)



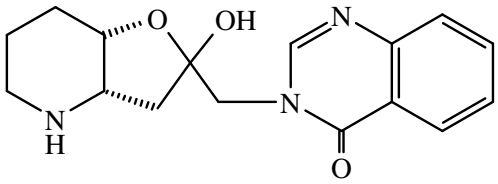
Chloroqualone (2)



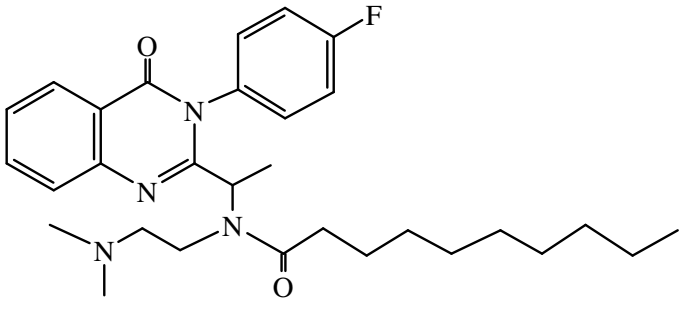
Piriqualone (3)



Febrifugine (4)



Isofebrifugine (5)



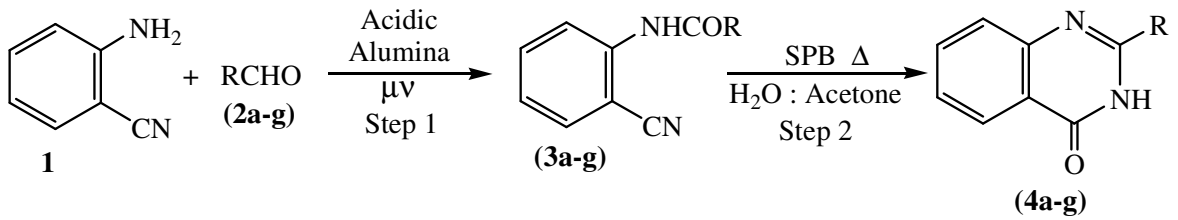
(6)

Figure 1

SPB, 2-aminobenzonitrile and various aromatic/ heteroaromatic aldehydes as starting material with a short reaction sequence.

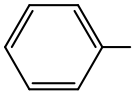
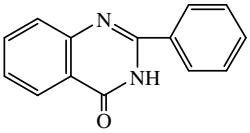
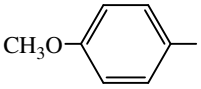
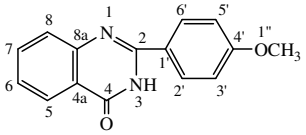
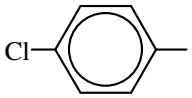
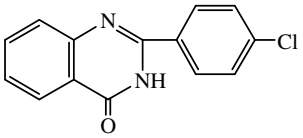
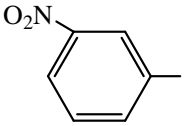
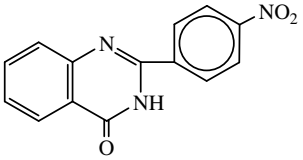
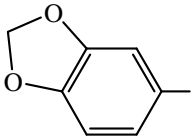
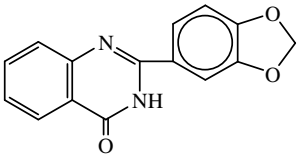
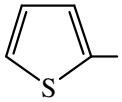
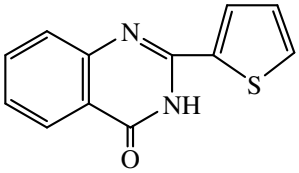
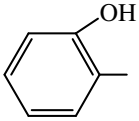
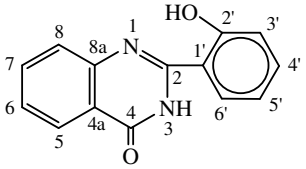
Results and Discussion

The key element in this approach is the novel utilization of 2-aminobenzonitrile **1** as a bifunctional building block whose application to the construction of various benzo-fused nitrogen heterocycles of chemical and biological interest is investigated. The intermediates **3a-g** (**Scheme I**) were obtained in good to excellent yields (75-88%) within 6-9 minutes of irradiation (**Table I**). Here, the oxidation of the reactant is assisted by microwave irradiation on using acidic alumina as solid support. As choosing an optimal solvent for adsorption is the primary need for



Scheme I

Table I — Reaction times and yields for the synthesis of 2-Aryl-3*H*-quinazolin-4-ones **4a-g**

S. No.	Compd	R	Product	Time		Yield[a] (%)
				Step 1 (min)	Step 2 (hr)	
1	**4a**			7.5	10.5	85
2	**4b**			7.0	11.5	88
3	**4c**			8.5	11.5	80
4	**4d**			7.5	11.5	78
5	**4e**			6.5	12.5	82
6	**4f**			7.5	13.0	85
7	**4g**			7.5	13.0	87

[a] Isolated and unoptimized yields.

successful synthesis. So, the various solvents were tried and ethanol was found to be the best in terms of solubility as well as eco-friendly nature. These intermediates **3a-g** were then employed as reactant for

the final step. Moving forward to the consecutive step the intermediate **3a-g** was stirred with aqueous solution of SPB in acetone at 60°C for the required time (**Table I**). SPB is a specific catalyst for the conversion of –CN to $–CONH_2$ in aqueous media. Therefore, after few hr, intermediate **3** started disappearing (TLC examination) with the appearance of new spot which indicates the conversion of cyano group (–CN) of the intermediate into amido ($–CONH_2$). During this transformation, the other functional group on intermediate **3** *i.e.* acetyl substituted amine, remained unchanged as the catalyst, SPB, is selective in nature. By adding SPB in aqueous solution form makes this synthetic procedure mild and catalytic. SPB is not only non-corrosive and specific but its usage also leads to easy work up of the reaction, as removal of catalyst is simply done by adding water and removing the aqueous layer. Upon completion of reaction, the easy removal of catalyst also reduces the chances of contamination of product. Various experimental trials were made to standardize the synthesis of final moiety **4a-g**. When the same synthesis carried out in absence of SPB, it gave product, other than the quinazolinone skeleton **4**, which clears the necessity of SPB in this specific reaction. Moreover, on using less than 5 equivalents of SPB, the yields obtained were lower. While, for more than 5 equivalents of SPB, there was no further improvement in the yields. Therefore, the amount of SPB to be used was optimized to be 5 equivalents. The solvent system chosen for step 2 was on the basis of solubility of intermediate **3** and SPB both simultaneously. Other solvent systems tried were ethanol: water, THF: water, ethanol: chloroform but acetone: water (1:1, v/v) was experimentally proved, the best in respect of high yield and less reaction time. This solvent system (acetone : water, 1 : 1, v/v) promotes the easy formation of final product, *via* cyclization caused by dehydrating gl. acetic acid, with no side products and also requires low temperature (~ 70-80°C) for refluxing.

Both aromatic and heteroaromatic aldehydes work well with this chosen solvent system whereas other systems did not give satisfactorily results with heteroaromatic aldehyde. To our surprise, this system shows synergism with SPB (catalyst), as SPB becomes highly reactive and attacks promptly to give amido derivatives of intermediate **3** which need not be isolated as it might lead to low yield and more reaction time. As soon as SPB converts – CN group to $CONH_2$, 1-2 mL of gl. acetic acid was added which makes the reaction medium suitable for cyclization and hence leads to final target moiety.

The synthesised derivatives **4a-g** are high melting coloured substances. Their IR spectra contains characteristic absorption bands of stretching vibrations of C=O group at 1660-1675 cm^{-1}. The stretching vibrations of C-H bonds in the aromatic ring appears at 3060-3030 cm^{-1}. In the IR spectra of compound **4e** the bands of the fragment C–O–C are observed in the region 1080-1200 cm^{-1}. Also, the ^1H NMR spectrum of **4a-g** showed NH proton at approximately δ 11.0-12.0. Chemical shifts of ^{13}C NMR spectra is in accordance with the desired synthesised product. Apart from IR and ^1H NMR, elemental analysis and mass spectra also supported the proposed product.

Experimental Section

Microwave irradiation was carried out on a Kenstar-OM 9925E Microwave Oven (800 W, 2450 MHz). The temperature of the reaction-mixture was measured with a non-contact Mini-Gun type IR thermometer (model 8868). IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrometer using KBr pellets. ^1H NMR spectra were obtained on a Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in δ. Elemental analysis was performed on a Heraeus CHN-Rapid analyzer. The melting points (uncorrected) were determined on a Thomas Hoover melting point apparatus. Mass spectra were recorded on a TOF MS. ^{13}C NMR spectra were recorded at 75.6 MHz on a Bruker Topspin spectrometer (300 MHz). All reactants were purchased from Sigma-Aldrich and Lancaster and used as such without further purification. Solvents used in reaction are double distilled using vaccum distillation.

General procedure for the synthesis of 2-substituted-3*H*-quinazolin-4-ones 4a-g

Step 1 (Microwave-assisted synthesis)

To the solution of 2-aminobenzonitrile **1** (0.01 mole), aromatic or heteroaromatic aldehydes (0.01 mole) in EtOH (2-3 mL), acidic alumina (Aldrich: 150 mesh; 58 Å; surface area 55 m^2/g; *p*H of aqueous suspension is 5.5 ± 0.5) (15 g) was added with stirring and air dried. It was then placed in an alumina-bath used as heat sink and subjected to MWI

intermittently. The progress of reaction was monitored by TLC examination (Merck TLC: mean particle size 10-12 µM; particle size distribution 5-20 µM; layer thickness 250 µM; plate height 30 mm). Upon completion of reaction, the product was eluted from acetone. Recovering the solvent under reduced pressure gave required product **3a-g**.

Step 2 (Conventional Method)

To the mixture of N-(2-cyano-phenyl)-acetamide **3a-g** (0.01 mole) and acetone (5-10 mL), SPB (8.3 g, 5 eq.) dissolved in water (5-10 mL) was added and the reaction-mixture was stirred for 3-4 hr at 80°C. Then 1-2 mL of gl. acetic acid was added and the stirring was continued for the mentioned time period. The progress of reaction was monitored through TLC (Merck TLC : mean particle size 10-12 µM; particle size distribution 5-20 µM; layer thickness 250 µM; plate height 30 mm). Upon completion, the reaction-mixture was allowed to cool and then it was filtered. The reaction-mixture was diluted with water (20-30 mL), neutralized under ice cooling with 5% aqueous NaOH and extracted with Et_2O (2 × 20 mL). The ethereal extract was dried with Na_2SO_4 and concentrated using a rotary evaporator to give final product **4a-g** which was further purified by column chromatography [column of silica gel, elution with *n*-hexane : EtOAc :: 6 : 4 (v/v)]

2-Phenyl-3*H*-quinazolin-4-one 4a. m.p. 235-37°C (236 °C, ref. 17) IR (KBr, cm^{-1}): 1660; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.5-8.1 (9H, m, Ar-H), 11.50 (1H, s, NH); HRMS: M^+ 221.8 (222.0); Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.46; H, 4.39; N, 12.41%.

2-(4-Methoxy-phenyl)-3*H*-quinazolin-4-one 4b. m.p. 244-46°C (247°C) (ref.17) IR (KBr, cm^{-1}): 1655; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.8 (3H, s, OCH_3), 7.1-8.2 (8H, m, Ar-H), 11.05 (1H, s, NH); HRMS: M^+ 252.5 (252.0); Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.02; H, 4.26; N, 10.99%. ^{13}C NMR (75.6 MHz, DMSO-d_6) δ: C_2-159.7, C_4-161.7, C_{4a}-120.4, C_5-127.3, C_6-126.9, C_7-134.2, C_8-124.6, C_{8a}-142.7, $C_{1'}$-118.6, $C_{2'}$-124.5, $C_{3'}$-111.7, $C_{4'}$-163.2, $C_{5'}$-111.7, $C_{6'}$-124.5, $C_{1''}$-55.9.

2-(4-Chloro-phenyl)-3*H*-quinazolin-4-one 4c. m.p. 307-309°C (306°C, ref.18) IR (KBr, cm^{-1}): 1670; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.5-8.3 (8H, m, Ar-H), 11.07 (1H, s, NH); HRMS: M^+ 255.5 (256.0). Anal. Calcd. for $C_{14}H_9N_2OCl$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.55; H, 3.49; N, 10.07%

2-(3-Nitro-phenyl)-3*H*-quinazolin-4-one 4d. m.p. >300°C (Lit. >300°C). IR (KBr, cm^{-1}): 1675. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.7-8.5 (8H, m, Ar-H), 11.05 (1H, s, NH); HRMS: M^+ 267.8 (267.0); Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found: C, 62.88; H, 3.28; N, 15.55%.

2-Benzo[1,3]dioxol-5-yl-3*H*-quinazolin-4-one 4e. m.p. 276-78°C (279°C, ref. 20) IR (KBr, cm^{-1}): 1660. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.15 (s, 2H, CH_2), 7.0-8.2 (m, 7H, Ar-H), 11.77 (s, 1H, NH); HRMS: M^+ 266.0 (266.0); Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.77; H, 3.89; N, 10.57%

2-Thiophen-2-yl-3*H*-quinazolin-4-one 4f. m.p. 286-88°C (287-88°C, ref. 21). IR (KBr, cm^{-1}): 1670. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.1-8.2 (m, 7H, Ar-H + thienyl-H), 11.80 (s, 1H, NH); HRMS: M^+ 229.3 (228.0); Anal. Calcd. for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27; S, 14.05. Found: C, 63.16; H, 3.50; N, 12.25; S, 13.99%.

2-(2-Hydroxy-phenyl)-3*H*-quinazolin-4-one 4g. m.p. 296-98°C (301-02°C, ref. 22) IR (KBr,cm^{-1}): 3250, 1665; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.9-7.8 (m, 8H, Ar-H), 11.08 (broad signals, 2, NH, OH); HRMS: M^+ 238.8 (238.0); Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.45; H, 4.27; N, 11.79%. ^{13}C NMR (75.6 MHz, DMSO-d_6): δ C_2-159.5, C_4-161.7, C_{4a}-120.1, C_5-126.9, C_6-126.9, C_7-135.0, C_8-124.9, C_{8a}-143.1, $C_{1'}$-113.2, $C_{2'}$-152.5, $C_{3'}$-116.9, $C_{4'}$-133.9, $C_{5'}$-118.0, $C_{6'}$-124.6.

Conclusion

In summary, a concise, green and efficient entry to 2-aryl-3*H*-quinazolin-4-ones method is developed which is amenable to access analogues. This route features the short reaction time in step 1 by using microwave irradiation and the specificity of catalyst (SPB) which facilitates step 2. By the reaction of a range of various aldehydes, novel libraries of quinazolinone derivatives could be obtained, which

would make this method a suitable candidate for combinatorial and parallel synthesis in drug discovery. These results also illustrate intermediate **3** as a useful substrate for the generation of an array of nitrogen fused heterocycles with two points of diversity and for synthesis of mentioned target moiety.

Acknowledgement

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