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Green chemical multi-component one-pot synthesis of fluorinated 2,3-disubstituted quinazolin-4(3*H*)-ones under solvent-free conditions and their anti-fungal activity

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Abstract

A rapid one-pot solvent-free procedure has been developed for the synthesis of fluorinated 2,3-disubstituted quinazolin-4(3*H*)-ones by neat three-component cyclocondensation of anthranilic acid, phenyl acetyl chloride and substituted anilines under microwave irradiation. The experimental methodology and microwave conditions described here are well established, allowing significant rate enhancement and good yields compared to conventional reaction conditions. The reaction is generalized for *o*-, *m*- and *p*-substituted anilines with electron-donating and -withdrawing groups to give quinazolin-4(3*H*)-ones. Synthesized compounds have been screened for their anti-fungal activity.

Keywords: Quinazolines; Three-component system; Microwave irradiation

1. Introduction

Quinazoline compounds are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases like leprosy and mental disorder and also exhibit a wide range of activities [1]. A well known methaquolone [2] having quinazoline nucleus, is a sedative and hypnotic drug and reported to possess anticonvulsant activity.

Recently, several scientists elucidated that quinazoline system possess variable sites at positions 2 and 3 which can be suitably modified by the introduction of different heterocyclic moieties to yield the potential anticonvulsant agents [3].

Incorporation of fluorine atoms or CF_3 group to heterocycles is known to influence the biological activity [4]. Fluorinated quinazoline has been the attraction of pharmacologists and chemists during last several years due to wide variety of activity possessed by them [5]. Number of patents mention the utility of fluorinated quinazolines as important anti-fungal [6], herbicidal [7], pesticidal [8], CNS depressant [9] and AMPA inhibitors [10], etc. Thus, their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds.

Microwave-induced rate enhancement of various reactions is becoming popular with organic chemists [11]. However, recently, more interest has been focussed on 'dry media' synthesis and particularly on solvent-free procedure using various mineral oxides [12] and solvent-less reactions with neat reactants in the absence of a catalyst or solid support [13]. Recently, the diversity generating potential of multi-component reactions (MCRs) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated. Consequently, the design of novel MCRs is an important field of research [14].

Conventional synthesis of disubstituted quinazolin-4(3*H*)-ones involves two steps [15] i.e. (i) cyclodehydration of 2-benzamidobenzoic acid (**I**) with excess of acetic anhydride under anhydrous conditions and removal of excess of acetic anhydride under reduced pressure gave benzoxazin-4-one (**II**) (ii) refluxing the **II** with amines in

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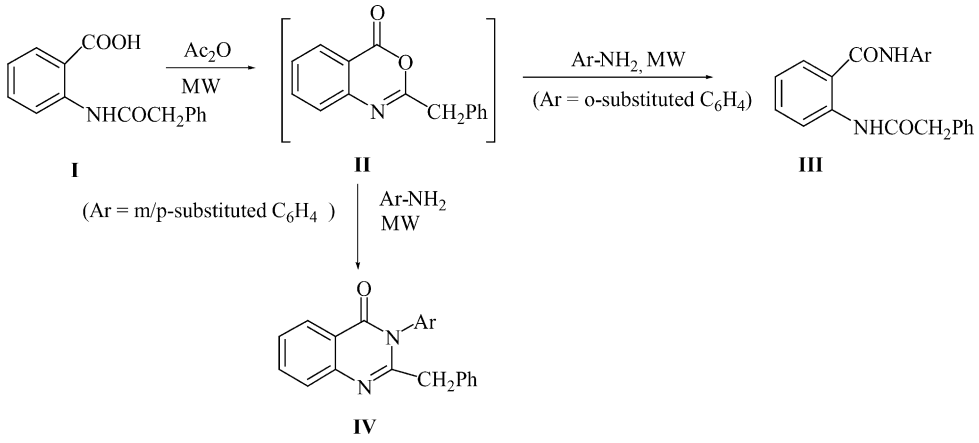
Table 1
Comparative studies for the synthesis of **IVa**

Method	Medium	MW power (W)	Time (min)	Yield (%)	Temperature[a] (°C)
A	(a) Acidic alumina	640	4 + 10	82	132
	(b) Montmorillonite KSF	640	3 + 7	88	141
B	Neat (without solvent and support)	640	5	92	165
C	Neat (path I)	640	4	91	162
	Neat (path II)	640	5	90	164

Time 4 + 10 indicates that first irradiation for 4 min gives compound **II** (detected by TLC) and then further irradiation after adding 3-trifluoromethyl aniline for 10 min yield **IVa**.
[a] Measured immediately after the reaction using a glass thermometer.

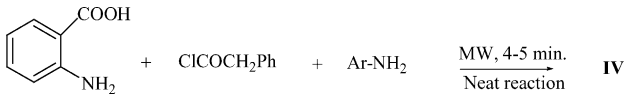


Scheme 1.

glacial acetic acid/pyridine [16]. The products were obtained in moderate yield and require 10–12 h refluxing.

Although the synthesis of 3*H*-quinazolin-4-one core nucleus under microwaves is reported involving the reaction of anthranilic acid with formamide [17]. But to the best of our knowledge no report is available in the literature for fluorinated disubstituted quinazolines involving multi-component reaction for the synthesis of series of compounds to make them available for bioactivity evaluation.

For the afore-mentioned reasons and in view of our general interest in the development of environmentally friendlier synthetic alternatives using microwaves [18], we studied extensively the synthesis of fluorine containing quinazolin-4(3*H*)-ones under microwave irradiation by various methods (Table 1) i.e. (A) using inorganic solid support montmorillonite KSF/acidic alumina (Scheme 1); (B) neat one-pot synthesis without using any dehydrating agent, solvent or support (Schemes 2 and 3). The best results obtained from neat synthesis (method B) have been reported.



Scheme 2.

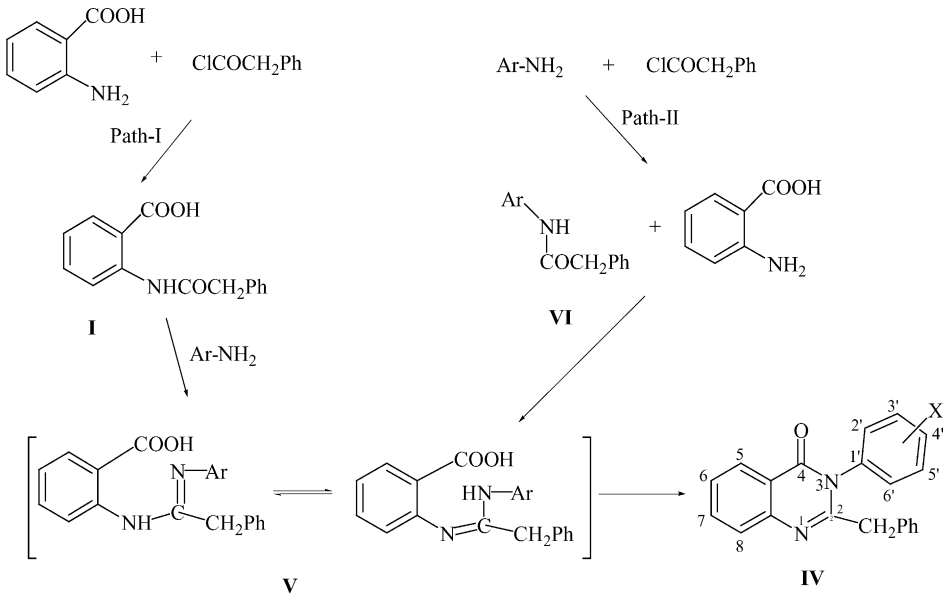
2. Results and discussion

In method A, the intermediate benzoxazin-4-one (**II**) was synthesized 'in situ' by the cyclodehydration of **I** with acetic anhydride using inorganic solid supports. The method is environmentally friendly, as acetic anhydride remains adsorbed over the solid support and there is no evaporation into the atmosphere.

The condensation reaction of **II** with *para*-/*meta*-/*ortho*-substituted fluorinated anilines have been studied. *Meta*-/*para*-substituted anilines gave cyclized product quinazoline (**IV**). While the *ortho*-substituted anilines gave an intermediate *o*-acylaminobenzanilide (**III**), which is in contrast to earlier report of Mishra et al. [15] where they reported the formation of cyclized quinazolones in case of *ortho*-substituted anilines also.

Although, the solvent-free procedure using inorganic support under microwaves is an attractive ecofriendly methodology, it requires appreciable amount of solvent for adsorption of reactants and elution of products.

Further, in view of our aim to synthesize a series of fluorinated 2,3-disubstituted quinazolones with pharmacophoric groups and to establish structure activity relationship in quinazolones, we have developed a 'green chemistry procedure' using neat multi-component reaction conditions, which aims at complete elimination of the solvent as well as



X = 2-CF_3 ; 2-F ; 3- CF_3,4Cl ; 3-F ; 3-CF_3.

Scheme 3.

solid support from the reaction. These no-solvent reactions, when coupled with microwave irradiation prove to be advantageous for environmental reasons as well, due to their uniforating effect and shorter reaction time.

Experimentally, anthranilic acid, phenyl acetyl chloride and corresponding amines are admixed and irradiated inside the microwave oven. The formation of final product quinazolone (**IV**) can proceed via two pathways I and II (Scheme 3).

Path I involves first *N*-phenylacetylation of anthranilic acid and condensation of resultant 2-benzamidobenzoic acid (**I**) with the amines and then intramolecular amidation of the intermediate amidine (**V**) afforded the desired final product **IV**. While another path II involves *N*-phenylacetylation of amines instead of anthranilic acid. The possibility of all routes are confirmed by isolation of intermediates in some cases or the reaction of 2-benzamidobenzoic acid (**I**) with 3-trifluoromethylaniline and the condensation of **VI** with anthranilic acid were conducted under microwave irradiation, the desired product **IVa** was obtained in few minutes. Thus, *N*-phenylacetylation step occurs very quickly. Attempts to use $PhCH_2COOH$ instead of $PhCH_2COCl$ were not successful.

In conclusion, we have introduced a simple one-pot multi-component cyclocondensation reaction for the synthesis of disubstituted quinazolin-4(3*H*)-ones without using any dehydrating agent, solvent or support. Reaction occurred in shorter time with easier work-up process and this method was applicable even when *o*-substituted anilines were used, while conventional methods failed to give **IV** in case of *o*-substituted anilines.

The formation of *o*-acyl aminobenzanilide (**III**) and quinazoline 4(3*H*)-ones (**IV**) have been confirmed on the basis of spectral studies. The IR spectra of **IIIa**,**b** (Table 2) showed characteristic absorption bands at 3360–3400 (NH), 1700–1680 (both C=O). The ^{1}H NMR spectra of **IIIa**,**b** showed broad peaks at δ 8.92 and 9.25 ppm due to two NHCO protons (exchangeable with D_2O) and a singlet at δ 4.22–4.26 ppm due to $COCH_2Ph$ protons. ^{13}C NMR spectrum of **IIIa** also showed the presence of two carbonyl signals at δ 169.9 and 169.2 ppm. The remaining signals were obtained at δ 140.8, 133.9, 133.6, 133.4, 130.7, 128.8, 128.3, 127.9, 126.4, 126.3, 125.5, 125.3, 125.3, 121.8, 120.1, 119.2 (aromatic and CF_3 carbon) and 45.0 ($CO–CH_2$) ppm.

IR spectra of quinazolones **IVa–f** (Table 3) showed the only one carbonyl absorption band at 1695–1700 cm^{-1} and 1605–1610 (C=N) cm^{-1} confirms the ring closure in all compounds. It was further confirmed on the basis of ^{13}C NMR spectrum of **IVd** which showed only one signal at δ 169.7 (C=O) ppm along with other peaks at 155.4 (C=N), 139.5, 138.6, 137.5, 135.8, 131.3, 130.9, 129.3, 128.6, 127.3, 126.4, 125.6, 123.3, 122.0, 120.7, 119.5

Table 2
Physical and analytical data of *o*-acylaminobenzanilide (**IIIa**,**b**)

Compound	R	Time (min)	Yield (%)	Temperature[a] (°C)	Melting point (°C)	Molecular formula
IIIa	2-$CF_3C_6H_4$	3 + 7	89	140	160	$C_{22}H_{17}F_3N_2O_2$
IIIb	2-F. C_6H_4	3 + 6	85	139	168	$C_{21}H_{17}FN_2O_2$

[a] Measured immediately after the reaction using a glass thermometer.

Table 3
Physical and analytical data of 2-phenylmethyl-3-(substituted-phenyl)-quinazolin-4(3*H*)-ones (**IVa–f**)

Compound	R	Method A			Method B			Melting point (°C)	Molecular formula
		Time (min)	Yield (%)	Temperature[a] (°C)	Time (min)	Yield (%)	Temperature (°C)		
IVa	3-CF_3·C_6H_4	3 + 7	88	141	5	92	165	101	$C_{22}H_{15}F_3N_2O$
IVb	3-F·C_6H_4	3 + 6	82	142	5	87	165	185	$C_{21}H_{15}FN_2O$
IVc	3-CF_3·4-Cl·C_6H_3	3 + 7	81	137	5	88	164	166	$C_{22}H_{14}ClN_2O$
IVd	2-CF_3·C_6H_4	–	–	–	4	92	159	129	$C_{22}H_{15}F_3N_2O$
IVe	2-F·C_6H_4	–	–	–	6	91	150	182	$C_{21}H_{15}FN_2O$
IVf	4-F·C_6H_4	–	–	–	5	90	155	142	$C_{21}H_{15}FN_2O$

Method A: using inorganic solid support; method B: neat one-pot synthesis. All compounds gave satisfactory elemental analysis (C, H and N) within ±0.25% of theoretical value.
[a] Measured immediately after the reaction using a glass thermometer.

(aromatic and CF_3 carbon) and 24.1 (CH_2Ph) ppm. Further, the disappearance of NH peaks in **IVa–f** peaks at (δ 8.92 and 9.25 ppm) showed the formation of quinazolones (**IV**). The presence of fluorine attached to phenyl ring has been confirmed by ^{19}F NMR. The detailed spectral data of compound **IIIa**,**b** and **IVa–f** are given in Table 6. In the mass spectrum of representative compounds the molecular ion peak at *m/z* 398 and 380 (100%) was corresponding to the molecular weight of compounds **IIIa** and **IVd**, respectively.

2.1. Evaluation of anti-fungal activity

The synthesized compounds were screened for anti-fungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root rot of okra, *Fusarium oxysporum*, causing wilt of mustard and *Colletotrichum capsici* causing leaf spot and fruit rot of chilli. It was done by two methods (Tables 4–6).

2.2. Poison plate technique

The compounds synthesized were dissolved in acetone and compounds were prepared in 1000 and 500 ppm concentrations [19]. Potato–dextrose–agar medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into Petri plates in three replication. A culture of test fungus was grown on PDA for 6–7 days. Small disc (4 mm) of fungus culture was cut with a sterile cork-borer and transferred asceptically, upside-down in the center of petridishes containing the medium and fungicides. Plates were incubated at 25 ± 1 °C for 6 days. Colony diameter was measured and data was statistically analysed (Table 4).

Table 4
Effect of concentrations of different chemicals on the mean radial growth (cms) of different fungi in vitro

Compound	*Rhizoctonia solani*		*Fusarium oxysporum*		*Colletotrichum capsici*	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
IVa	1.08[a]	1.75	1.58	1.83	1.33	2.17
IVb	2.58	1.50[a]	1.60	3.92	2.58	3.67
IVc	1.83	2.58	2.25	4.25	1.75	3.25
IVd	2.08	7.67	2.92	5.00	1.50	3.50
IVe	6.67	8.25	1.08[a]	1.67	0.75[a]	1.25[a]
IVf	1.92	3.83	1.25	1.58[a]	2.50	4.08
Check	9.00	9.00	8.17	8.17	7.33	7.33
CD 1%	1.22	1.02	0.77	1.14	1.03	1.08

At par with minimum value.
[a] Minimum value.

2.3. Pot trial method

White-seeded sorghum grains were soaked in water for about 12 h [20]. Hundred and sixty grams of the soaked kernels were placed in 500 ml flasks and 20 ml of water was added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask and flasks were kept for 10 days at 25–27 °C. Hundred seeds of okra were taken for one treatment of each compound. Inoculum was added at 2 g/kg of soil, 3 days prior to sowing. Sowing was done after 3 days and germination data were recorded after 7, 15 and 25 days of sowing. Suitable checks were maintained and the data was statistically analysed (Table 5). 'Baynate' and 'Thiram' are standard fungicides used as seed dressers to control this disease. 'Baynate' was found best in reducing the plant mortality.

Table 5
Evaluation of quinazolin-4(3*H*)-ones derivatives as seed dressers against *Rhizoctonia solani* causing root rot of okra (in pot trial)

Compound	Percent germination 7 DAS	Plant stand 25 DAS
IVa	42.00	48.00
IVb	63.00	45.00
IVc	70.00	42.00
IVd	58.00	41.00
Ve	28.00	21.00
Vf	59.00	40.00
Baynate (0.2%)	98.00	64.00
Thiram (0.3%)	79.00	68.00
Check with inoculum	12.00	4.00
Check without inoculum	95.00	90.00

DAS: days after sowing.

Table 6
Spectral data of compounds **IIIa**,**b** and **IVa–f**

Compound	IR (cm^{-1})	^1H NMR (δ, ppm)	^{19}F NMR (δ, ppm)
IIIa	3365–3395 (2× NH), 3060, 2940, 2850 (aromatic and aliphatic C–H), 1700, 1680 (2× C=O), 1490 (NO_2)	δ 4.22 (s, 2H, CH_2Ph), 6.90–8.35 (m, 13H, Ar–H), 8.92 and 9.25 (2× bs, 2× 1H, 2× NH exchangeable with D_2O)	−64.21 (s, CF_3)
IIIb	3360–3400 (2× NH), 3060, 2955, 2860 (aromatic and aliphatic C–H),1700, 1685 (2× C=O), 680, 720.	δ 4.26 (s, 2H, CH_2Ph), 6.98–8.26 (m, 13H, Ar–H), 8.95 and 9.22 (2× bs, 2× 1H, 2× NH exchangeable with D_2O)	−119.90 (s, 2-F)
IVa	3050, 2940, 2840 (aromatic and aliphatic C–H), 1700 (C=O), 1605 (C=N)	δ 3.96 (s, 2H, CH_2Ph), 6.88–7.19 (m, 5H, phenyl ring protons of CH_2Ph), 7.22–8.18 (m, 7H, Ar–H), 8.40 (dd, 1H, 5-H)	−63.38 (s, CF_3)
IVb	3050, 2980, 2860 (aromatic and aliphatic C–H), 1695 (CO), 1605 (C=N)	δ 3.95 (s, 2H, CH_2Ph), 6.84–7.10 (m, 5H, phenyl ring protons of CH_2Ph), 7.19–8.14 (m, 7H, Ar–H), 8.39 (dd, 1H, 5-H)	−119.61 (s, 3-F)
IVc	3040, 2970, 2860 (aromatic and aliphatic C–H), 1705 (C=O), 1608 (C=N)	δ 3.98 (s, 2H, CH_2Ph), 6.86–7.12 (m, 5H, phenyl ring protons of CH_2Ph), 7.25–8.15 (m, 6H, Ar–H), 8.38 (dd, 1H, 5-H)	−63.21 (s, CF_3)
IVd	3040, 2970, 2860 (aromatic and aliphatic C–H), 1700 (C=O), 1608 (C=N)	δ 3.95 (s, 2H, CH_2Ph), 6.82–7.15 (m, 5H, phenyl ring protons of CH_2Ph), 7.31–8.25 (m, 7H, Ar-H), 8.45 (dd, 1H, 5-H)	−64.45 (s, CF_3)
IVe	3050, 2980, 2850 (aromatic and aliphatic C–H), 1700 (C=O), 1610 (C=N)	δ 3.96 (s, 2H, CH_2Ph), 6.85–7.18 (m, 5H, phenyl ring protons of CH_2Ph), 7.21–8.10 (m, 7H, Ar–H), 8.40 (dd, 1H, 5-H)	−119.61 (s, 2-F)
IVf	3060, 2980, 2860 (aromatic and aliphatic C–H), 1700 (C=O), 1615 (C=N)	3.97 (s, 2H, CH_2Ph), 6.88–7.19 (m, 5H, phenyl ring protons of CH_2Ph), 7.10–8.10 (m, 7H, Ar–H), 8.39 (dd, 1H, 5-H)	118.88 (s, 4-F)

3. Experimental

Melting points were determined in open glass capillary and were uncorrected. IR spectra were recorded on a Perkin-Elmer (Model-577) in KBr pellets. ^1H NMR and ^{13}C NMR were recorded on Jeol model FX 90Q and Bruker-DRX-300 using $CDCl_3$ as solvent and TMS as internal reference at 89.55 and 75.47 MHz, respectively. ^{19}F NMR was recorded on Jeol model FX 90Q at 84.25 MHz, using $CDCl_3$ as solvent and/or hexafluorobezene as external reference. Mass spectrum of representative compound was recorded on Kratos 50 mass spectrometer at 70 eV. Purity of all compounds was checked by TLC using silica gel 'G'-coated glass plates and benzene–ethylacetate (8:2) as eluent. The microwave-induced reactions were carried out in BMO-700T modified domestic oven fitted with a condenser and a magnetic stirrer. Montmorillonite KSF and acidic alumina were Aldrich product and used as received. 2-Benzamidobenzoic acid has been synthesized by literature method [21].

2-Phenylmethyl-3-(3-trifluoromethylphenyl)-quinazolin-4(3*H*)-one (**IVa**) was prepared by three different procedures under microwave irradiation.

3.1. Method A: using inorganic solid supports

A mixture of 2-benzamidobenzoic acid (**I**) (2 mmol) and acetic anhydride (2.5 mmol) was adsorbed on acidic alumina/montmorillonite KSF (2 g), mixed thoroughly and irradiated inside the microwave oven at 640 W until the completion of reaction (TLC). After completion of reaction the 3-trifluoromethylaniline (2 mmol) was added to the reaction mixture and irradiated for appropriate time (Table 1). The product was extracted into ethanol and the excess solvent was evaporated on a roto-evaporator to give compound, which was purified by methanol and identified as **IVa** (Scheme 1).

From the comparative results, it has been observed that the montmorillonite KSF is the best solid support as compared to acidic alumina (Table 1). The remaining compounds **IVb**,**c** and **IVf** (in case of *meta-*/*para*-substituted anilines) and **IIIa**,**b** (in case of *ortho*-substituted anilines) were similarly prepared by using montmorillonite KSF.

3.2. Method B: neat three-component cyclocondensation

An equimolar mixture of anthranilic acid (2 mmol), phenyl acetyl chloride (2 mmol) and 3-trifluoromethylaniline (2 mmol) contained in a Erlenmeyer flask fitted with condensor was placed in the microwave oven and irradiated for 5 min (TLC) at 640 W. The reaction mixture was cooled at room temperature to give solid mass, which was crystallized from ethanol (Scheme 2).

3.3. Method C: alternative procedure for preparation of *IVa*

A mixture of **I** (2 mmol) and 3-triflouromethyl aniline (2 mmol) was irradiated for 4 min (TLC) at 640 W. After cooling, the resultant residue was crystallized from methanol yielding 91% of **IVa** (path I) (Scheme 3).

In order to verify the viability of path II under the above conditions, a mixture of phenyl acetyl anilide (**VI**) (2 mmol) and anthranilic acid (2 mmol) was irradiated (5 min, TLC). The resultant residue was crystallized from ethanol to give **IVa** yield of 90%.

The identity of compounds synthesized by various methods was established by their mixed mp, IR and ^{1}H NMR spectral studies.

All compounds **IVb–f** listed in Table 3 were similarly synthesized by neat three-component method comparatively in high yield and reduced time.

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