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Simple and straight forward synthesis of 2,4-disubstituted quinazolines in aqueous medium

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ABSTRACT

Efficient synthesis of diverse quinazolines from readily available starting materials was achieved in aqueous medium *via* one-pot protocol. A number of 2,4-disubstituted quinazolines were prepared in moderate to good yields under mild and catalyst-free conditions. Neutral reaction conditions, easy work-up procedures with wide substrate scope and atom economy are the remarkable features of this method.

1. Introduction

Quinazolines acquired much prominence among N-containing heterocyclic compounds because of their wide range of pharmacological and medicinal properties such as antibacterial [1], antidiabetic [2], antihypertensive [3], antitumor [4,5], anti-inflammatory [6], anticancer[7-13], antiviral [14,15] and antitubercular [16,17]. In addition, this ubiquitous structural motif is present in potent tyrosine kinase and cellular phosphorylation inhibitors [18-20], and also has found applications as ligand for benzodiazepine and neurotransmitter gamma-aminobutyric acid [GABA] receptors in the central nervous system [CNS] [21,22] and as DNA binders [23].

Consequently, diverse approaches have been explored to synthesize various types of quinazolines. 2-Aminobenzonitriles, 2-halophenyl precursors, 2-nitrobenzoic acids or anthranilic acids as well as *N*-arylbenzamides are commonly used starting materials among those methods. The applicability of these methods is restricted due to less availability of these starting materials. Bischler cyclization, Niementowski quinazoline reaction, and the reaction of dicarbonyl compounds with diamines are some of the traditional methods in quinazoline synthesis [24-30]. Bischler reaction requires harsh reaction conditions which are not compatible with many functional and protecting groups. Moreover, syntheses of 2,4-disubstituted quinazolines from anthranilic acids or *o*-fluorobenzoyl derivatives have also been investigated [31].

However, these methods have certain limitations in the substrate generality, availability of starting materials, and reaction procedures. Recently, Walton *et al.* [32] reported the preparation of quinazolines and dihydroquinazolines from 2-aminoarylalkanone *O*-phenyl oximes under microwave conditions at 160 ^{0}C in presence of emimPF_6 in toluene in a two-step process. It also requires anhydrous $ZnCl_2$ for further oxidation of dihydroquinazolines to quinazolines. The preparation of 2-aminoarylalkanone *O*-phenyl oximes is a complicated process which requires pyridine under N_2 atmosphere. Taddei *et al.* [33] synthesized 2,4-disubstituted quinazolines starting from anilides under microwave conditions (heating at 100^0 for 3-6 min, and maintaining the internal pressure at 150 psi). Although this method is efficient, it has limited substrate scope with few examples. Wang and coworkers [34] synthesized various quinazolines from 2-aminocarbonyl compounds and benzyl amines as starting materials using CuO nanoparticles supported on kaolin. The same research group reported quinazoline synthesis using I_2/TBHP as another catalytic system [35]. Very recently, Sarma and Prajapati [36] reported a quinazoline synthesis using urea/$AcONH_4$ as another *N*-source under microwave conditions. Dihydroquinazolines were obtained in relatively high yields in this method. Dabiri *et al.* synthesized quinazolines using acidic ionic liquids under aerobic conditions [37]. The same authors synthesized quinazoline derivatives containing triazole ring systems using cu catalyst via a one-pot four-component reaction [38].

One of the main principles of green chemistry is to develop cost-effective and environmentally benign synthetic protocols which have become one of the main themes of contemporary synthetic chemistry. Herein, we report a mild, catalyst-free single-step procedure for the conversion of readily available 2-aminocarbonyl compounds in water medium to the corresponding substituted quinazolines, as a part of our ongoing research programme in the development of new eco-friendly protocols [39-45]. Even though, different methodologies are reported for this reaction under various

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conditions, to the best of our knowledge this catalyst free reaction was not attempted in aqueous medium.

2. Experimental

2.1. Instrumentation

All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from Fluka and S. D. Fine Chemicals and directly used for the synthesis. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} pre-coated plates. Visualization was accomplished with UV lamp or I_2 stain. ^{1}H NMR and ^{13}C NMR Spectra were recorded on Varian 200, Varian Inova 500 or Avance 300 spectrometer in $CDCl_3$ using TMS as the internal standard; δ in ppm, *J* in Hz. Melting points were determined using Fischer-Johns and Barnstead Electrothermal apparatus and are uncorrected. MS: QSTAR XL, LCQ-Ion Trap spectrometer in *m/z*.

2.2. Synthesis

General procedure for the synthesis of 2,4-Substituted quinazolines in water: To a flask containing the 2-amino acetophenone/2-amino benzophenones (1 mmol) in water (20 mL), aldehydes (1.25 equiv.) and NH_4OAc (0.77 g, 10 mmol) were added. The mixture was magnetically stirred at 75 °C until reaction was complete (as monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (25 mL). The extract was further washed with water and saturated brine solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 2,4-substituted quinazolines in 25-77 % yields (Scheme 1 and 2).

4-Methyl-2-phenylquinazoline (Table 1, Entry 1): Brown. Yield: 62%. M.p.: 72-75 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.61-8.59 (m, 2H, ArH), 8.02 (m, 2H, ArH), 7.53-7.43 (m, 5H, ArH), 2.99 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.3, 160.2, 150.45, 139.7, 138.4, 133.6, 130.5, 129.1, 128.4, 128.3, 126.7, 124.5, 123.6, 122.6, 21.8. MS (ESI, *m/z*): 221 $[M+H]^+$.

6,7-Dimethoxy-4-methyl-2-phenylquinazoline (Table 1, Entry 2): Light yellow. Yield: 59%. M.p.: 132-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.55-8.51 (m, 2H, ArH), 7.46-7.43 (m, 3H, ArH), 7.32 (s, 1H, ArH), 7.12 (s, 1H, ArH), 4.06 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 2.89 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.4, 155.3, 149.7, 149.4, 147.8, 139.0, 138.4, 130.2, 128.7, 128.3, 128.1, 127.9, 107.4, 102.1, 56.1, 55.9, 21.8. MS (ESI, *m/z*): 281 $[M+H]^+$. HR-MS (ESI, *m/z*): 281.1282 $[M+H]^+$. $C_{17}H_{17}N_2O_2^+$; calc. 281.1290.

6-Chloro-2-phenylquinazoline (Table 1, Entry 3): Light yellows. Yield: 60%. M.p.: 200-204 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.36 (s, 1H, ArH), 8.61-8.57 (m, 2H, ArH), 8.0 (m, 1H, ArH), 7.88 (m, 1H, ArH), 7.83-7.79 (m, 1H, ArH), 7.52-7.47 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 159.8, 149.2, 137.5, 135.0, 132.7, 130.8, 130.4, 128.64, 128.60, 125.7, 123.9. MS (ESI): *m/z* 241 $[M+H]^+$.

8-Methyl-6-phenyl-[1, 3] dioxolo [4, 5-g] quinazoline (Table 1, Entry 4): Brown. Yield: 61%. M.p.: 133-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.51 (m, 1H, ArH), 7.49-7.44 (m, 4H, ArH), 7.29 (s, 1H, ArH), 7.22 (s, 1H, ArH), 6.08 (s, 2H, OCH_2O), 2.84 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 165.1, 159.2, 153.4, 149.7, 147.8, 138.3, 129.9, 129.9, 128.4, 128.2, 128.1, 119.5, 105.3, 101.9, 100.1, 22.10. MS (ESI, *m/z*):265 $[M+H]^+$.

2,4-Diphenylquinazoline (Table 1, Entry 5): Yellow. Yield: 63%. M.p.: 117-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.73 (m, 2H, ArH), 8.15-8.16 (m, 2H, ArH), 7.90-7.86 (m, 3H, ArH), 7.60-7.48 (m, 7H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.0, 160.0, 152.2, 138.2, 137.7, 133.3, 130.5, 130.2, 129.7, 129.1, 128.8, 128.2, 126.9, 121.7. MS (ESI, *m/z*): 283 $[M+H]^+$.

6-Chloro-2,4-diphenylquinazoline (Table 1, Entry 6): Yellow. Yield: 67%. M.p.: 201-204 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.68-8.64 (m, 2H, ArH), 8.09-8.06 (m, 2H, ArH), 7.87-7.77 (m, 3H, ArH), 7.62-7.58 (*m*, 3H, ArH) 7.50-7.47 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.6, 160.9, 151.5, 138.2, 137.8, 134.7, 133.0, 131.6, 131.2, 130.6, 129.3, 129.2, 129.0, 126.2. MS (ESI, *m/z*): 317 $[M+H]^+$.

6-Chloro-4-(2-chlorophenyl)-2-phenylquinazoline (Table 1, Entry 7): Grey. Yield: 65%. M.p.: 210-212 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.64-8.61 (m, 2H, ArH), 8.06 (m, 1H, ArH), 7.78-7.81 (m, 1H, ArH), 7.62-7.46 (m, 8H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.7, 160.5, 151.2, 138.0, 137.9, 134.5, 133.1, 131.5, 131.4, 130.5, 129.5, 129.1, 128.7, 126.0. MS (ESI, *m/z*): 351 $[M+H]^+$.

7-Bromo-2,4-diphenylquinazoline (Table 1, Entry 8): Yellow. Yield: 62%. M.p.: 136-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.64-8.67 (m, 2H, ArH), 8.14 (m, 1H, ArH), 8.04 (m, 1H, ArH), 7.86-7.88 (m, 1H, ArH), 7.70-7.77 (m, 4H, ArH), 7.47-7.55 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.2, 160.4, 152.3, 138.0, 136.8, 133.7, 131.9, 130.8, 129.5, 128.7, 127.4, 126.6, 124.8, 121.5. MS (ESI, *m/z*): 361 $[M+H]^+$.

6-Nitro-2, 4-diphenylquinazoline (Table 1, Entry 9): Brown. Yield: 25%. M.p.: 214-218 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.03 (*s*, 1H, ArH), 8.71-8.73 (*m*, 2H, ArH), 8.23 (m, 1H, ArH), 7.90-7.91 (*m*, 2H, ArH) 7.65-7.66 (*m*, 3H, ArH), 7.51-7.52 (*m*, 3H, ArH), 7.24 (*s*, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 124.1, 126.9, 167.5, 160.8, 150.8, 132.5, 131.7, 131.1, 130.9, 130.3, 129.3, 129.1, 128.7. MS (ESI, *m/z*): 328 $[M+H]^+$.

4-Methyl-2-p-tolylquinazoline (Table 2, Entry 1): Brown. Yield: 60%. M.p.: 80-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.51 (m, 2H, ArH), 7.99 (m, 2H, ArH), 7.83-7.76 (m, 1H, ArH), 7.52-7.46 (m, 1H, ArH), 7.29-7.23 (m, 2H, ArH), 2.97 (s, 3H, CH_3), 2.43 (s, 3H, CH_3). ESI-MS: 235 $[M+H]^+$.

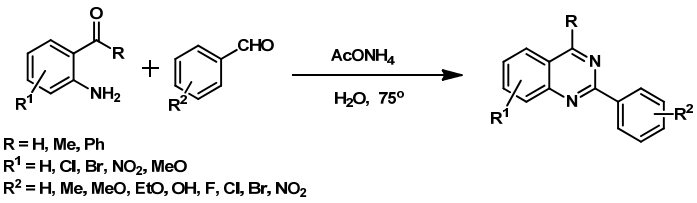
4-Methyl-2-(naphthalen-1-yl) quinazoline (Table 2, Entry 2): Yield: 64%. M.p.: 92-95 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.78 (m, 1H, ArH), 8.09-7.81 (m, 6H, ArH), 7.56-7.47 (m, 4H, ArH), 3.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.5, 159.8, 149.5, 135.1, 134.2, 134.0, 133.0, 129.0, 128.8, 128.6, 128.4, 127.6, 127.4, 127.2, 126.4, 126.3, 125.6, 125.1, 124.5, 122.6, 122.3, 21.6. MS (ESI, *m/z*): 271 $[M+H]^+$. HR-MS (ESI, *m/z*): 271.1239 $[M+H]^+$. $C_{19}H_{15}N_2$; calc. 271.1235.

2-(4-Chlorophenyl)-4-methylquinazoline (Table 2, Entry 3): Brown. Yield: 69%. M.p.: 64-67 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.57 (m, 2H, ArH), 7.94-7.96 (m, 2H, ArH), 7.81-7.78 (m, 1H, ArH), 7.49-7.35 (m, 3H, ArH), 2.86 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.1, 158.8, 150.0, 136.5, 136.3, 133.4, 129.7, 128.9, 128.5, 126.8, 124.8, 123.9, 122.7, 21.7. MS (ESI, *m/z*): 255 $[M+H]^+$.

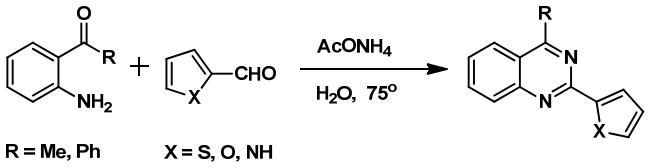
4-Methyl-2-(4-nitrophenyl)quinazoline (Table 2, Entry 4): Brown. Yield: 74%. M.p.: 151-153 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.83 (m, 2H, ArH), 8.34 (m, 2H, ArH), 8.11-8.06 (m, 2H, ArH), 7.92-7.86 (m, 1H, ArH), 7.68-7.60 (m, 1H, ArH), 3.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 133.9, 129.6, 129.4, 127.8, 125.0, 123.5, 22.0. MS (ESI, *m/z*): 266 $[M+H]^+$.

2-(4-Methoxyphenyl)-4-methylquinazoline (Table 2, Entry 5): Brown. Yield: 58%. M.p.: 67-71 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.55 (m, 2H, ArH), 8.02-7.96 (m, 2H, ArH), 7.81-7.75 (m, 2H, ArH), 7.52-7.45 (m, 1H, ArH), 6.96 (m, 1H, ArH), 3.88 (s, 3H, OCH_3), 2.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.4, 161.7, 160.1, 150.6, 133.0, 130.9, 130.3, 129.3, 128.9, 126.0, 124.8, 124.3, 124.0, 122.6, 115.4, 113.7, 55.1, 22.0. MS (ESI): m/z 251 $[M+H]^+$. HR-MS (ESI, *m/z*): 251.1174 $[M+H]^+$. $C_{16}H_{15}N_2O^+$; calc. 251.1184.

2-(4-Ethoxyphenyl)-4-methylquinazoline (Table 2, Entry 6): Grey. Yield: 55%. M.p.: 75-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.53 (m, 2H, ArH), 7.99 (m, 2H, ArH), 7.78 (m, 1H, ArH), 7.48 (m, 1H, ArH), 6.93 (m, 2H, ArH), 4.12 (q, *J* = 6.7, 2H, CH_2), 2.97 (s, 3H, CH_3), 1.46 (t, *J* = 6.7, 3H, CH_3). MS (ESI, *m/z*): 265 $[M+H]^+$.

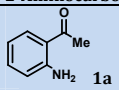
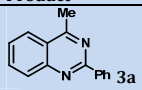
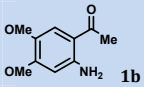
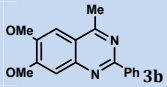
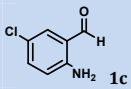
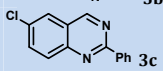
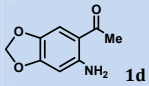
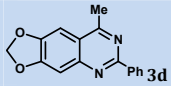
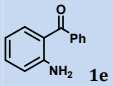
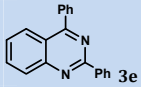
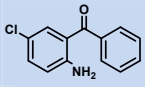
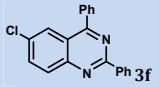
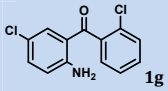
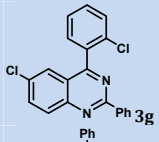
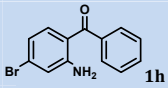
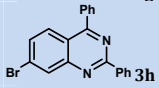
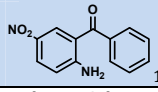
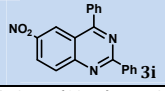


Scheme 1



Scheme 2

Table 1. Synthesis of quinazolines from various 2-aminoarylcarbonyl compounds.[a]

Entry	2-Aminocarbonyl compounds	Benzaldehyde	Product	Yield [b]
1	 1a		 3a	62 [46]
2	 1b		 3b	59*
3	 1c		 3c	60 [46]
4	 1d		 3d	61 *
5	 1e		 3e	63 [46]
6	 1f		 3f	67 [46]
7	 1g		 3g	65 *
8	 1h		 3h	62 *
9	 1i		 3i	25 [47]

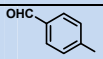
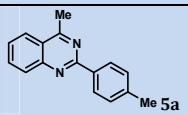
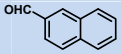
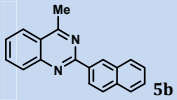
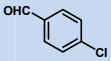
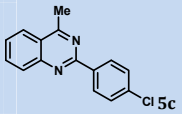
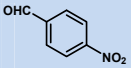
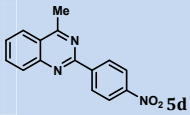
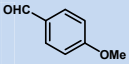
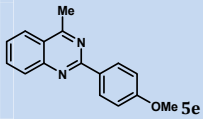
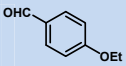
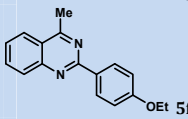
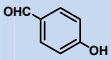
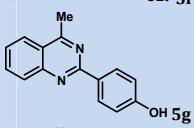
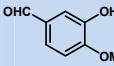
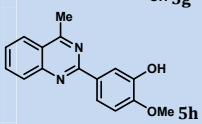
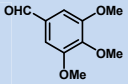
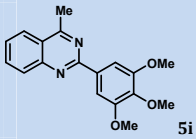
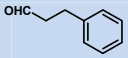
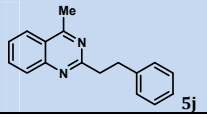
[a] Reaction conditions: Substituted 2-aminoarylcarbonyl compounds (1.00 eq), benzaldehyde (1.25 eq), $AcONH_4$ (10 eq) in H_2O at 75 °C.
[b] Yields in percentage.
* New compounds.

4-(4-Methylquinazolin-2-yl)phenol (Table 2, Entry 7): Brown. Yield: 52%. M.p.: 208-210 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.41 (s, 1H, OH), 8.41 (m, 2H, ArH), 8.05 (m, 1H, ArH), 7.93-7.79 (m, 2H, ArH), 7.52 (m, 1H, ArH), 6.84 (m, 2H, ArH), 2.96 (s, 3H, CH_3). MS (ESI, *m/z*): 237 $[M+H]^+$.

2-Methoxy-5-(4-methylquinazolin-2-yl)phenol (Table 2, Entry 8): Brown. Yield: 58%. M.p.: 198-200 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.23 (m, 1H, ArH), 8.16 (s, 1H, OH), 8.00 (m, 2H, ArH), 7.83-7.76 (m, 1H, ArH), 7.52-7.46 (m, 1H, ArH), 6.98 (m, 1H, ArH), 6.81-6.76 (m, 1H, ArH), 4.07 (*s*, 3H, OCH_3), 2.98 (*s*, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 134.7, 133.3, 130.9, 129.0, 127.6, 126.0, 122.9, 121.0, 117.4, 115.7, 114.5, 110.9, 56.0, 21.9. MS (ESI, *m/z*): 267 $[M+H]^+$. HR-MS (ESI, *m/z*): 267.1135 $[M+H]^+$. $C_{16}H_{15}N_2O_2^+$; calc. 267.1133.

4-Methyl-2-(3,4,5-trimethoxyphenyl)quinazoline (Table 2, Entry 9): Brown. Yield: 57%. M.p.: 140-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.05-8.02 (m, 2H, ArH), 7.90 (s, 2H, ArH), 7.85-7.79 (m, 1H, ArH), 7.55-7.50 (m, 1H, ArH), 4.03 (s, 6H, OCH_3), 3.91 (s, 3H, OCH_3), 3.02 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 153.3, 150.5, 133.3, 129.3, 126.6, 124.9, 105.9, 60.8, 56.2, 22.0. MS (ESI, *m/z*): 311 $[M+H]^+$. HR-MS (ESI, *m/z*): 311.1384 $[M+H]^+$. $C_{18}H_{19}N_2O_3^+$; calc. 311.1395.

Table 2. Synthesis of quinazolines from various benzaldehydes [a].

Entry	2-Aminoaceto phenone	Aldehyde	Product	Yield[b]
1		 4a	 5a	60 *
2		 4b	 5b	64 *
3		 4c	 5c	69 [47]
4		 4d	 5d	74 [48]
5		 4e	 5e	58 *
6		 4f	 5f	55 *
7		 4g	 5g	52 [49]
8		 4h	 5h	58 *
9		 4i	 5i	57*
10		 4j	 5j	60 [50]

[a] Reaction conditions: 2-aminoacetophenone (1.0 eq), substituted benzaldehyde (1.25 eq), $AcONH_4$ (10 eq) in H_2O at 75 °C.
[b] Yields in percentage,
* New compounds.

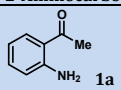
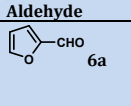
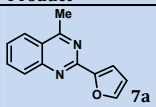
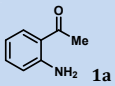
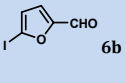
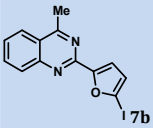
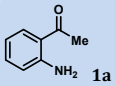
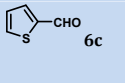
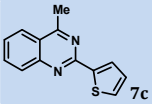
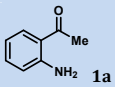
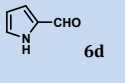
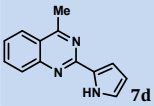
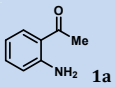
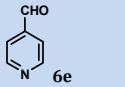
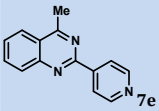
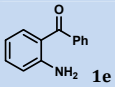
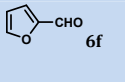
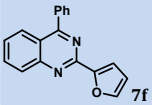
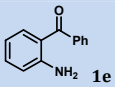
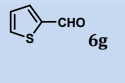
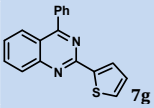
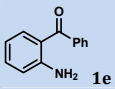
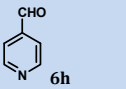
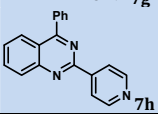
4-Methyl-2-phenethylquinazoline (Table 2, Entry 10): Brown liquid. Yield: 60%. M.p.: 102-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.99 (m, 1H), 7.91 (m, 1H), 7.79-7.77 (*m*, 1H), 7.52-7.49 (*m*, 1H), 7.27-7.20 (*m*, 4H), 7.13-7.10 (*m*, 1H), 3.34-3.31 (*m*, 2H), 3.21-3.18 (*m*, 2H), 2.90 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 167.8, 165.8, 150.2, 141.7, 133.2, 128.7, 128.5, 128.3, 126.5, 125.9, 124.8, 41.5, 34.8, 21.6. MS (ESI, *m*/*z*): 249 $[M+H]^+$.

2-(Furan-2-yl)-4-methylquinazoline (Table 3, Entry 1): Yield: 72%. M.p.: 105-107 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.07-8.02 (m, 1H, ArH, Furan H), 7.84-7.81 (m, 1H, ArH), 7.65 (m, 1H, Furan H), 7.54-7.51 (m, 1H, ArH), 7.42 (m, 1H, ArH), 6.57 (m, 1H, Furan H), 2.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 145.2, 133.7, 129.2, 126.8, 124.9, 113.9, 111.9, 22.1. MS (ESI, *m*/*z*): 211 $[M+H]^+$. HR-MS (ESI, *m*/*z*): 211.0872 $[M+H]^+$. $C_{13}H_{11}N_2O^+$; calc. 211.0871.

2-(5-Iodofuran-2-yl)-4-methylquinazoline (Table 3, Entry 2): Green. Yield: 68%. M.p.: 144-148 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.05-8.00 (m, 2H), 7.85-7.80 (m, 1H), 7.56-7.51 (m, 1H), 7.29 (d, *J* = 3.4, 1H, Furan H), 6.73 (d, *J* = 3.4, 1H, Furan H), 2.96 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.2, 157.6, 149.9, 133.7, 129.1, 126.9, 124.9, 122.9, 116.2, 21.8. MS (ESI, *m*/*z*): 337 $[M+H]^+$. HR-MS (ESI, *m*/*z*): 336.9838 $[M+H]^+$. $C_{13}H_{10}N_2OI^+$; calc. 336.9837.

4-Methyl-2-(thiophen-2-yl)quinazoline (Table 3, Entry 3): Yield: 74%. M.p.: 98-101 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.09 (m, 1H, ArH), 7.96-7.93 (m, 2H, ArH), 7.77-7.74 (m, 1H, ArH), 7.46-7.43(m, 2H, Thiophene H), 7.14-7.12 (m, 1H, Thiophene H), 2.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 133.3, 131.9, 130.1, 129.4, 128.9, 128.6, 127.9, 127.3, 126.2, 124.7, 119.3, 21.6. MS (ESI, *m*/*z*): 227 $[M+H]^+$. HR-MS (ESI, *m*/*z*): 227.0635 $[M+H]^+$. $C_{13}H_{11}N_2S^+$; calc. 227.0642.

Table 3. Synthesis of quinazolines from heterocyclic aldehydes [a].

Entry	2-Aminocarbonyl	Aldehyde	Product	Yield[b]
1	 1a	 6a	 7a	72 [51]
2	 1a	 6b	 7b	68 *
3	 1a	 6c	 7c	74 [52]
4	 1a	 6d	 7d	65 *
5	 1a	 6e	 7e	77 [53]
6	 1e	 6f	 7f	72 [54]
7	 1e	 6g	 7g	70 [49]
8	 1e	 6h	 7h	76 [53]

[a] Reaction conditions: 2-Aminoacetophenone/2-Aminobenzophenone (1.00 eq.), heteroaromatic aldehyde (1.25 eq), $AcONH_4$ (10.00 eq) in H_2O at 75 °C.
[b] Yields in percentage.
* New compounds.

4-Methyl-2-(1H-pyrrol-2-yl)quinazoline (Table 3, Entry 4): Brown. Yield: 65%. M.p.: 122-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.69 (bs, 1H, NH), 7.97 (m, 1H, ArH), 7.83 (m, 1H, ArH), 7.77-7.72 (m, 1H, ArH), 7.44-7.40 (m, 1H, ArH), 7.16 (s, 1H, Pyrrole H), 6.92 (s, 1H, Pyrrole H), 6.31-6.28 (m, 1H, Pyrrole H), 2.94 (*s*, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.3, 154.6, 150.2, 133.6, 131.2, 128.4, 125.8, 124.9, 121.3, 112.1, 110.9, 21.9. MS (ESI, *m/z*): 210 $[M+H]^+$. HR-MS (ESI, *m/z*): 210.1027 $[M+H]^+$. $C_{13}H_{12}N_3^+$; calc. 210.1031.

4-Methyl-2-(pyridin-4-yl)quinazoline (Table 3, Entry 5): Brown. Yield: 77%. M.p.: 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.75 (d, *J* = 6.0, 2H, Pyridine H), 8.47 (d, *J* = 6.0, 2H, Pyridine H), 8.11-8.07 (m, 2H, ArH), 7.91-7.86 (m, 1H, ArH), 7.65-7.59 (m, 1H, ArH), 3.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 168.4, 158.0, 150.0, 145.4, 134.0, 129.7, 127.8, 125.0, 123.6, 122.4, 22.0. MS (ESI, *m/z*): 222 $[M+H]^+$. HR-MS (ESI, *m/z*): 222.1030 $[M+H]^+$. $C_{14}H_{12}N_3^+$; calc. 222.1031.

2-(Furan-2-yl)-4-phenylquinazoline (Table 3, Entry 6): Brown. Yield: 72%. M.p.: 168-170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.12 (m, 1H, Furan H), 8.06 (m, 1H, ArH), 7.87-7.79 (*m*, 3H, ArH), 7.66 (*s*, 1H, Furan H), 7.56-7.45 (*m*, 5H, ArH), 6.57 (*s*, 1H, Furan H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 153.0, 151.8, 145.01, 137.4, 134.0, 130.0, 129.8, 129.0, 128.3, 127.0, 126.7, 121.5, 114.1, 112.0. MS (ESI, *m/z*): 273 $[M+H]^+$. HR-MS (ESI, *m/z*): 273.1025 $[M+H]^+$. $C_{18}H_{13}N_2O^+$; calc. 273.1027.

4-Phenyl-2-(thiophen-2-yl)quinazoline (Table 3, Entry 7): Brown. Yield: 70%. M.p.: 139-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.14 (m, 1H, ArH), 8.08 (m, 1H, ArH), 7.86-7.77 (*m*, 3H, ArH), 7.65 (*s*, 1H, Thiophene H), 7.56-7.43 (*m*, 5H, ArH, Thiophene H), 6.57 (*s*, 1H, Thiophene H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 151.8, 138.2, 137.3, 133.5, 130.1, 129.9, 129.7, 129.3, 128.8, 128.5, 128.1, 127.1, 126.5. MS (ESI, *m/z*): 289 $[M+H]^+$. HR-MS (ESI, *m/z*): 289.0789 $[M+H]^+$. $C_{18}H_{13}N_2S^+$; calc. 289.0799.

4-Phenyl-2-(pyridin-4-yl)quinazoline (Table 3, Entry 8): White. Yield: 76%. M.p.: 148-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.76 (*d*, *J* = 5.2, 2H, Pyridine H), 8.51 (*d*, *J* = 6.0, 2H, Pyridine H), 8.15 (m, 2H, ArH), 7.94-7.84 (*m*, 3H, ArH), 7.62-7.58 (*m*, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 157.8, 151.8, 150.3, 145.2, 137.3, 133.6, 130.1, 130.0, 129.5, 128.5, 127.8, 127.0, 122.3. MS (ESI, *m/z*): 284 $[M+H]^+$. HR-MS (ESI, *m/z*): 284.1178 $[M+H]^+$. $C_{19}H_{14}N_3^+$; calc. 284.1187.

3. Results and discussion

While developing a new and catalyst-free method for quinazoline derivatives, a model reaction was carried out in aqueous medium between 2-aminoacetophenone (1), benzaldehyde (2) and $AcONH_4$ as substrates (Scheme 1). Initially, the desired quinazoline was obtained in 62% yield, after heating the reaction mixture for 15 h at 100 °C. Reaction time and temperature were optimized at 4 h and 75 °C. In the investigative studies, reactions were conducted varying the molar quantities of aldehydes (1.0-1.5 eq.) as well as $AcONH_4$ (2.5 to10.0 eq.). The experiments indicated that 10.0 equiv. of $AcONH_4$ resulted in favorable completion of the reaction with 1.25 equiv. of aldehyde.

In order to assess the solvent efficacy the reactions were conducted in different organic solvents such as AcOEt, toluene, MeCN, MeOH, $(Me)_2CHOH$, CH_2Cl_2 and DMSO. However, H_2O

appeared to be the best choice among the solvents examined, whereas no product formation was observed in toluene. Reactions conducted in MeCN, $(Me)_2CHOH$ and MeOH resulted in trace amounts of quinazoline with so many byproducts. Lower yields were obtained in case of AcOEt, CH_2Cl_2 and DMSO. Therefore all the reactions were carried out in H_2O at 75 ^oC under optimized conditions.

Further, the substrate scope was expanded with a variety of 2-amino carbonyl compounds (Scheme 1). Under the optimized reaction conditions, a range of functional group tolerance can be observed (Table 1) among substituted 2-aminocarbonyls. The investigation was also extended to diversely substituted aldehydes. When electron-withdrawing groups, such as Cl and NO_2 were introduced to the phenyl ring of benzaldehyde, reactions resulted in good yields (Table 2, entries 3-4), whereas the introduction of electron-donating groups, such as MeO, EtO as well as OH to the phenyl ring of benzaldehyde, decreased the yields (Table 2, entries 5-9).

Heterocylic aldehydes (Table 3, entries 1-8) were also compatible in this methodology to find wider applicability in synthetic as well as medicinal chemistry. Aliphatic aldehydes such as propanal, butanal, hexanal, octanal and cyclohexane carboxaldehyde were also examined for their reactivity in this protocol. Hexanal, cyclohexane carboxaldehyde resulted in corresponding dihydro quinazolines as products. Rest of the aliphatic aldehydes remained inactive in the present reaction conditions. All the products were identified by comparison of Mass, ^1H and ^{13}C NMR spectra.

4. Conclusion

In summary, a simple, eco-friendly one-pot protocol for the synthesis of various 2, 4 substituted quinazolines is reported. The ready availability of the starting materials and easy reaction conditions add to the utility of this convenient methodology.

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