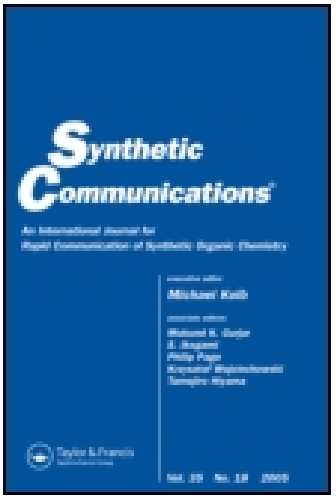

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Ecofriendly and Efficient One-Pot Procedure for the Synthesis of Quinazoline Derivatives Catalyzed by an Acidic Ionic Liquid Under Aerobic Oxidation Conditions

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ECOFRIENDLY AND EFFICIENT ONE-POT PROCEDURE FOR THE SYNTHESIS OF QUINAZOLINE DERIVATIVES CATALYZED BY AN ACIDIC IONIC LIQUID UNDER AEROBIC OXIDATION CONDITIONS

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A three-component condensation reaction between 2-aminobenzophenone derivatives, formaldehyde or aromatic aldehydes, and ammonium acetate efficiently provides substituted quinazolines in a one-pot reaction in the presence of Brönsted acidic ionic liquid, 1-methylimidazolium triflouroacetate ([Hmim]TFA), in conjunction with aerobic oxidation. The ionic liquid was separated from the reaction mixture by simple extraction and was recycled three times without considerable loss in activity.

Keywords: Aerobic oxidation; catalysis; heterocycles; multicomponent; quinazolines

INTRODUCTION

Multicomponent reactions are some of the most efficient methods for the synthesis of organic molecules.[1] The strategy offers significant advantages over classical step-by-step approaches, allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without isolating the intermediates. Over the past decade, the synthesis of heterocycles has become the cornerstone of synthetic organic chemistry. This is because substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents.[2]

Among the nitrogen-containing heterocycles, pyrimidines and quinazolines are useful as fungicides and anticancer, anti-inflammatory, antimicrobial, and antihypertensive agents.[3] In particular, they are potent and highly selective inhibitors of tyrosine kinase.[4] Also, a new series of quinazolines were discovered that function as CC chemokine receptor-4 (CCR4) antagonists. Several CCR4 antagonists with potent inhibitory activity have been reported in the literature (Fig. 1).[5]

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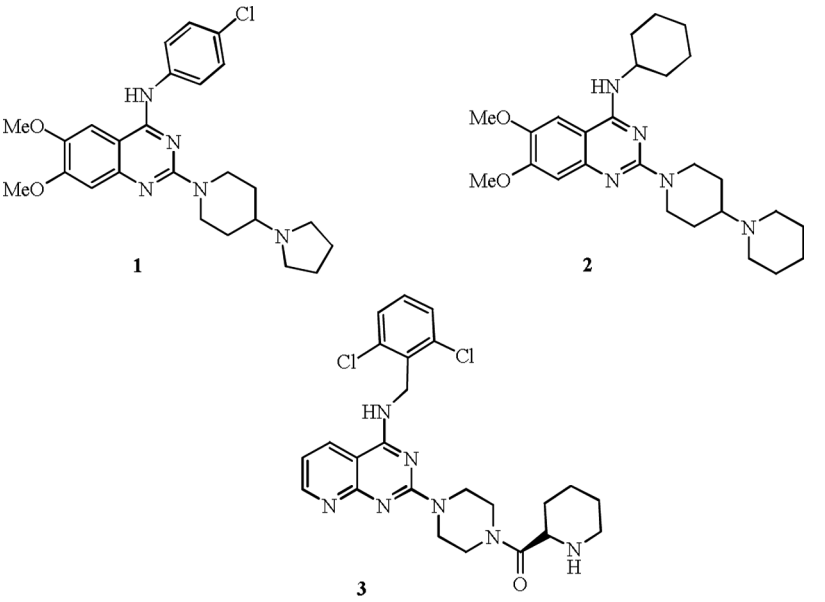


Figure 1. Some 4-substituted quinazoline derivatives with CCR4 inhibitory activities.

Therefore, the synthesis of quinazoline derivatives has attracted much attention recently. Introducing the chlorine atom at the 4-position in the quinazolinone skeleton either by using $POCl_3$[6] or thionyl chloride,[7] followed by its substitution with various primary and secondary amines or with palladium-catalyzed intramolecular reductive N-heterocyclization,[8] condensation reactions between amines and carbonyl derivatives, and intramolecular cycloaddition approaches are common to many of these synthetic methodologies.[9] Cross-coupling chemistry has recently enabled the introduction of substituents on existing activated aza-heterocycles.[10] Much effort also has been devoted to the development of the syntheses of these heterocycles by Chilin et al.[11] Ferrini and coworkers have recently reported a synthetic approach to quinazolines by cyclization of acylamides in the presence of ammonium formate under microwave irradiation.[12]

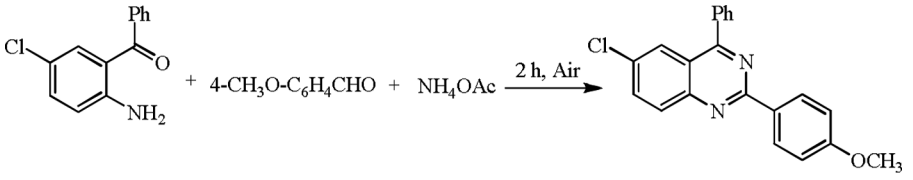
Although some of these methods provide useful strategies for the synthesis of these compounds, they suffer from drawbacks such as multistep syntheses, poor yields, and use of commercially nonviable reagents or expensive catalysts.[13]

Ionic liquids (ILs) have gained wide popularity in recent years. Interest in ILs is brought about by their special properties such as no volatility, thermal stability, no flammability, and the possibility of recycling and reuse.[14] At present, the most extensively studied ILs are salts with imidazolium cations. These ILs have received global attention in various fields of research such as synthesis, catalysis, electrochemistry, and industrial applications.[15–20] Continuing our interest in the progress of a highly expedient methodology for the synthesis of outstanding chemicals and heterocyclic compounds of biological significance,[21–24] in this article, we report an efficient and short route for the synthesis of the quinazoline nucleus from 2-aminobenzophenone derivatives, aldehydes, and

ammonium acetate in the presence of an acidic ionic liquid, 1-methylimidazolium triflouroacetate ([Hmim]TFA).

RESULTS AND DISCUSSION

To develop an environmentally benign process for the synthesis of quinazoline derivatives, we explored the use of different solvents and 0.1 mmol of various Brønsted acids for 2 h. First, we carried out the reaction between 2-amino-5-chloro-benzophenone, 4-methoxy-benzaldehyde, and ammonium acetate as a model reaction (Scheme 1). From Table 1, it is evident that when the reaction was conducted at 80 °C in the presence of 0.1 mmol (0.02 g) [Hmim]TFA without any solvent, the desired product was obtained in 85% yield (Table 1, entry 10). In the absence of a catalyst, the reaction did not yield any significant amount of the product after 2 h (Table 1, entry 11). In the period of our research, we encountered an important point: in the absence of air blowing and under a nitrogen atmosphere, this reaction did not proceed efficiently, and the reaction yielded only a trace after 2 h. Therefore, air has a main role in the preparation of quinazoline derivatives. Also, there were several reports based on aerobic oxidation conditions for the synthesis of various heterocyclic compounds.[25] So, we next turned our attention to the formation of the quinazoline ring systems in these optimal conditions for other substrates. A variety of different substituted aromatic aldehydes and two different types of 2-aminobenzophenones were subjected to this reaction (Scheme 2, Table 2). A variety of substituted aldehydes possessing a wide range of electron-donating and

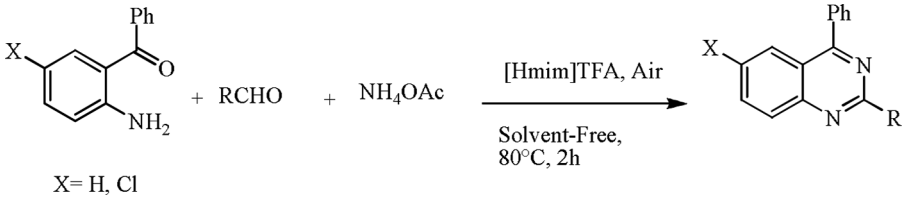


Scheme 1. Optimization reaction.

Table 1. Optimization of the reaction conditions

Entry	Catalyst	Solvent	Temperature (°C)	Yield (%)[a]
1	*p*-TSOH	EtOH	Reflux	17
2	*p*-TSOH	MeOH	Reflux	Trace
3	*p*-TSOH	H_2O	Reflux	Trace
4	*p*-TSOH	CH_3CN	Reflux	Trace
5	*p*-TSOH	PhMe	Reflux	Trace
6	*p*-TSOH	CH_2Cl_2	Reflux	10
7	SSA	EtOH	Reflux	12
8	IL	EtOH	Reflux	Trace
9	IL	H_2O	Reflux	Trace
10	IL	—	80	85
11	—	—	80	Trace

[a]Isolated yield after 2 h.



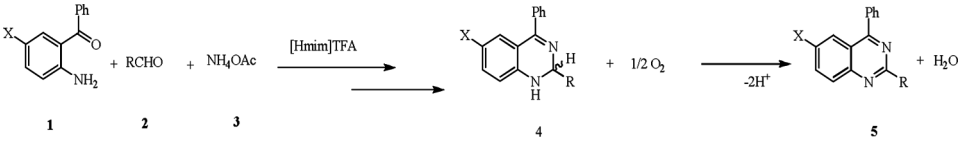
Scheme 2. Synthesis of quinazoline derivatives.

electron-withdrawing functional groups such as methoxy, hydroxy, bromo, chloro, nitro, and fluoro afforded the corresponding products in good yields. Hetero-aromatic aldehydes such as pyridine carbaldehyde derivatives produced the desired products in excellent yields (Table 2, entries 9, 10, 19, and 20). Aliphatic aldehydes were also examined. Among the aliphatic aldehydes, only formaldehyde reacted smoothly to provide the corresponding quinazoline in excellent yield (Table 2, entry 1). It seems that aliphatic aldehydes possessing an α-hydrogen atom undergo aldol condensation under the reaction condition. In general, as indicated in Table 2, in all cases the reactions proceeded efficiently with excellent yields within 2 h at 80 °C under air blowing. The reactions were clean, and no side products could be detected in the NMR spectra of the crude products.

Table 2. Synthesis of quinazolines by the reaction of 2-aminobenzophenones, aldehydes, and ammonium acetate in the presence of [Hmim]TFA at 80 °C under aerobic oxidation conditions

Entry	X	R	Mp (°C)	Yield (%)[a]
1	Cl	H	115	83
2	Cl	3-Br-C_6H_4	178	91
3	Cl	4-CH_3O-C_6H_4	161	85, 87, 82
4	Cl	C_6H_5	185	80
5	Cl	2-OH-C_6H_4	197	87
6	Cl	4-Cl-C_6H_4	187	94
7	Cl	2,4-$(Cl)_2$-C_6H_3	162	92
8	Cl	2-NO_2-C_6H_4	128	88
9	Cl	3-Pyridyl	173	85
10	Cl	4-Pyridyl	192	90
11	Cl	2-F-C_6H_4	130	95
12	Cl	3-F-C_6H_4	173	92
13	Cl	4-F-C_6H_4	193	90
14	H	3-Br-C_6H_4	103	87
15	H	4-CH_3O-C_6H_4	153	92
16	H	4-NO_2-C_6H_4	195	85
17	H	4-Cl-C_6H_4	170	90
18	H	2,4-$(Cl)_2$-C_6H_3	97	82
19	H	3-Pyridyl	142	86
20	H	4-Pyridyl	145	85
21	H	3-F-C_6H_4	160	85
22	H	4-F-C_6H_4	128	90

[a]Isolated yield.



Scheme 3. The plausible mechanism of the reaction.

Finally, to make this method more appropriate, we proved that the catalyst ([Hmim]TFA) could be reused for more cycles with almost consistent activity. For this aim, the reaction in Scheme 1 was selected. After completion of the reaction, water was added, and then the solid was isolated by filtration. The IL in water was recovered easily by evaporation at 80 °C under a vacuum. The recovered IL was washed with diethyl ether. After heating at 80 °C in a vacuum for another 1 h, the IL was used in the following runs without considerable loss of its activity after three runs (Table 2, entry 3).

The possible mechanism of the reaction of 2-aminobenzophenone derivatives **1**, aldehydes **2**, and ammonium acetate **3** in the presence of [Hmim]TFA and air is shown in Scheme 3. [Hmim]TFA acts as an acidic catalyst that promotes the three-component condensation reaction and leads to the generation of 1,2-dihydroquinazolines **4**, which immediately undergo dehydration in conjunction with oxygen from the air. At the end, quinazolines **5** are obtained in good to excellent yields.

EXPERIMENTAL

General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Fourier transform (FT)–IR 10 MB BOMEM spectrometer. Mass spectra (MS) were documented on a Finnigan-MAT8430 mass spectrometer operating at an ionization potential of 70 eV. The elemental analyses were performed with an Elementar Analysensysteme GmbH Vario EL in CHNS mode. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solutions in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as internal standard. The chemicals used in this work were purchased from Merck and Fluka chemical companies.

Typical Procedure for the Synthesis of 2-(3-Bromophenyl)-6-chloro-4-phenylquinazoline (Table 2, Entry 2)

[Hmim]TFA (0.02 g, 0.1 mmol) was added at 80 °C to a magnetically stirred mixture of 5-chloro-2-aminobenzophenone (0.231 g, 1.0 mmol), 3-bromobenzaldehyde (0.185 g, 1.0 mmol), and ammonium acetate (0.07 g, 1.0 mmol), while air was bubbled into the reaction mixture. After 2 h, water was added, and the mixture was filtered. The residue was recrystallized from EtOH to afford the pure product as a yellow powder (0.36 g, 91%): mp 178 °C, IR (KBr) cm^{-1}: 1530, 1475, 1385,

1070, 797. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.37–8.83 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.34, 122.90, 125.84, 127.21, 128.82, 130.06, 130.10, 130.38, 130.89, 131.58, 133.06, 133.62, 134.72, 136.86, 139.83, 150.35, 158.95, 167.71. MS m/z: 395 (M^+, 100), 359 (75), 177 (50), 75 (45), 51 (25). Anal. calcd. for $C_{20}H_{12}BrClN_2$: C, 60.71; H, 3.06; N, 7.08. Found: C, 60.54; H, 3.25; N, 7.25.

Compound Characterization Data

6-Chloro-4-phenylquinazoline (Table 2, Entry 1). White powder (0.19 g, 83%); mp 115 °C. IR (KBr) cm^{-1}: 3029, 1691, 1534, 1480, 1362, 843, 696. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.61–8.12 (6H, m, H-Ar), 9.39 (1H, s). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 123.71, 125.83, 128.88, 129.85, 130.40, 130.69, 133.53, 134.73, 136.53, 149.62, 154.83, 167.66. MS m/z: 240 (M^+, 70), 239 (100), 205 (95), 177 (25), 151 (20), 75 (35), 51 (30). Anal. calcd. for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.60; H, 4.00; N, 11.87.

6-Chloro-2-(4-methoxyphenyl)-4-phenylquinazoline (Table 2, Entry 3). Light yellow powder (0.30 g, 87%); mp 161 °C, IR (KBr) cm^{-1}: 1607, 1527, 1249, 1023, 832, 700. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 3.91 (3H, s, OCH_3), 7.03–8.66 (8H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 55.39, 113.91, 121.88, 125.77, 128.71, 130.01, 130.14, 130.35, 130.49, 130.65, 132.03, 134.38, 137.22, 150.58, 160.28, 161.97, 167.39. MS m/z: 346 (M^+, 100), 345 (80), 311 (50), 77 (20), 51 (20). Anal. calcd. for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.58; H, 4.52; N, 8.25.

6-Chloro-2,4-diphenylquinazoline (Table 2, Entry 4). Yellow powder (0.25 g, 80%); mp 185 °C, IR (KBr) cm^{-1}: 3044, 1531, 1474, 1170, 842, 687. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.53–8.68 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.19, 125.79, 128.59, 128.67, 128.76, 130.06, 130.23, 130.78, 130.88, 132.60, 134.51, 137.09, 137.77, 150.50, 160.47, 167.54. MS m/z: 316 (M^+, 80), 315 (100), 281 (90), 177 (25), 77 (40), 51 (30). Anal. calcd. for $C_{20}H_{13}ClN_2$: C, 75.83; H, 4.14; N, 8.84. Found: C, 75.65; H, 4.34; N, 9.02.

2-(6-Chloro-4-phenylquinazoline-2-yl)phenol (Table 2, Entry 5). Yellow powder (0.29 g, 87%); mp 197 °C, IR (KBr) cm^{-1}: 3055, 1589, 1535, 1247, 841, 753. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 6.99–8.75 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 117.94, 119.25, 121.66, 126.22, 128.99, 129.14, 130.88, 133.16, 133.66, 135.48, 137.12, 140.22, 145.43, 148.91, 151.69, 156.75, 160.97, 164.85. MS m/z: 332 (M^+, 97), 331 (100), 279 (75), 166 (20), 119 (25), 65 (20). Anal. calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.94; N, 8.42. Found: C, 72.00; H, 4.12; N, 8.60.

6-Chloro-2-(4-chlorophenyl)-4-phenylquinazoline (Table 2, Entry 6). Light yellow powder (0.33 g, 94%); mp 187 °C, IR (KBr) cm^{-1}: 1529, 1386, 1081, 702. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.48–8.64 (8H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.19, 125.85, 128.79, 130.04, 130.38, 130.70, 132.89, 134.74, 136.11, 136.89, 137.05, 150.24, 159.37. MS m/z: 351 (M^+, 70), 349 (100), 315 (90), 177 (40), 75 (45), 51 (20). Anal. calcd. for $C_{20}H_{12}Cl_2N_2$: C, 68.39; H, 3.44; N, 7.98. Found: C, 68.22; H, 3.62; N, 8.15.

6-Chloro-2-(2,4-dichlorophenyl)-4-phenylquinazoline (Table 2, Entry 7). Light yellow powder (0.35 g, 92%); mp 162 °C, IR (KBr) cm^{-1}: 3429, 2926, 1555, 1519, 1382, 891, 696. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.39–8.17 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 121.92, 125.86, 127.26, 128.91, 130.09, 130.51, 130.76, 132.89, 133.81, 134.99, 135.86, 136.50, 149.96, 167.67. MS *m/z*: 385 (M^+, 100), 349 (80), 100 (30), 75 (40), 51 (30). Anal. calcd. for $C_{20}H_{11}Cl_3N_2$: C, 62.28; H, 2.87; N, 7.26. Found: C, 62.24; H, 2.93; N, 7.32.

6-Chloro-2-(2-nitrophenyl)-4-phenylquinazoline (Table 2, Entry 8). Yellow powder (0.32 g, 88%); mp 128 °C, IR (KBr) cm^{-1}: 3420, 1536, 1380, 772, 692. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.60–8.21 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.14, 124.17, 125.95, 128.89, 130.14, 130.30, 130.56, 130.87, 131.76, 132.25, 133.42, 133.87, 134.99, 136.35, 150.19, 159.06, 167.69. MS *m/z*: 361 (M^+, 100), 326 (75), 280 (30), 279 (50), 177 (20), 77 (40), 51 (48). Anal. calcd. for $C_{20}H_{12}ClN_3O_2$: C, 66.40; H, 3.34; N, 11.61. Found: C, 66.19; H, 3.54; N, 11.80.

6-Chloro-4-phenyl-2-(pyridin-3-yl)quinazoline (Table 2, Entry 9). Yellow powder (0.27 g, 85%); mp 173 °C, IR (KBr) cm^{-1}: 3430, 2921, 1529, 1381, 693. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.45–9.87 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.44, 123.50, 125.89, 128.31, 128.85, 129.08, 130.05, 130.48, 130.90, 133.29, 133.45, 134.86, 136.73, 150.07, 150.36, 151.04, 158.51, 167.86. MS *m/z*: 317 (M^+, 80), 316 (100), 282 (80), 75 (30), 51 (40). Anal. calcd. for $C_{19}H_{12}ClN_3$: C, 71.81; H, 3.81; N, 13.22. Found: C, 71.66; H, 3.95; N, 13.37.

6-Chloro-4-phenyl-2-(pyridin-4-yl)quinazoline (Table 2, Entry 10). Yellow powder (0.28 g, 90%); mp 192 °C, IR (KBr) cm^{-1}: 3435, 2911, 1529, 1384, 695. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.63–8.82 (8H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.41, 122.77, 125.90, 128.87, 130.05, 130.54, 131.08, 133.85, 134.95, 136.64, 145.19, 150.28, 150.32, 158.28, 167.96. MS *m/z*: 317 (M^+, 80), 316 (100), 282 (80), 75 (25), 51 (40). Anal. calcd. for $C_{19}H_{12}ClN_3$: C, 71.81; H, 3.81; N, 13.22. Found: C, 71.73; H, 3.95; N, 13.34.

6-Chloro-2-(2-fluorophenyl)-4-phenylquinazoline (Table 2, Entry 11). Yellow powder (0.31 g, 95%); mp 132 °C, IR (KBr) cm^{-1}: 1617, 1527, 1379, 749, 691. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.25–8.24 (12H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 116.77, 117.08, 121.88, 124.22, 125.77, 128.84, 130.08, 130.37, 130.88, 131.71, 131.82, 132.18, 133.34, 134.76, 136.74, 150.20, 159.05, 160.01, 165.75, 167.72. MS *m/z*: 334 (M^+, 70), 333 (100), 299 (95), 257 (20), 75 (60), 51 (35). Anal. calcd. for $C_{20}H_{12}ClFN_2$: C, 71.75; H, 3.61; N, 8.37. Found: C, 71.56; H, 3.83; N, 8.56.

6-Chloro-2-(3-fluorophenyl)-4-phenylquinazoline (Table 2, Entry 12). Yellow powder (0.30 g, 92%); mp 173 °C, IR (KBr) cm^{-1}: 1589, 1534, 1381, 851. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.20–8.45 (12H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 115.25, 115.59, 117.47, 117.73, 122.29, 124.24, 125.79, 128.78, 129.95, 130.34, 130.87, 132.98, 134.65, 136.87, 140.17, 150.34, 159.18, 159.23, 167.59, 167.61. MS *m/z*: 334 (M^+, 70), 333 (100), 299 (95), 257 (20),

75 (60), 51 (35). Anal. calcd. for $C_{20}H_{12}ClFN_2$: C, 71.75; H, 3.61; N, 8.37. Found: C, 71.63; H, 3.75; N, 8.51.

6-Chloro-2-(4-fluorophenyl)-4-phenylquinazoline (Table 2, Entry 13). Yellow powder (0.30 g, 90%); mp 193 °C, IR (KBr) cm^{-1}: 1597, 1537, 1380, 834. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.17–8.69 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 115.38, 115.67, 122.06, 125.81, 128.77, 130.02, 130.29, 130.75, 130.80, 130.85, 132.62, 133.96, 134.60, 137.00, 150.44, 159.50, 166.43, 167.60. MS m/z: 334 (M^+, 60), 333 (100), 299 (95), 257 (20), 75 (60), 51 (35). Anal. calcd. for $C_{20}H_{12}ClFN_2$: C, 71.75; H, 3.61; N, 8.37. Found: C, 71.62; H, 3.75; N, 8.51.

2-(3-Bromophenyl)-4-phenylquinazoline (Table 2, Entry 14). Yellow powder (0.31 g, 87%); mp 103 °C, IR (KBr) cm^{-1}: 1609, 1535, 1386, 774. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 7.47–8.66 (13H, m, H-Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 121.66, 122.59, 127.31, 127.48, 128.75, 129.11, 129.22, 130.47, 130.66, 130.91, 131.38, 133.88, 135.00, 137.20, 140.21, 151.47, 157.85, 157.87, 168.59, 168.61. MS m/z: 361 (M^+, 100), 279 (30), 177 (40), 76 (60), 50 (65). Anal. calcd. for $C_{20}H_{13}BrN_2$: C, 66.50; H, 3.63; N, 7.75. Found: C, 66.47; H, 3.80; N, 7.93.

2-(4-Methoxyphenyl)-4-phenylquinazoline (Table 2, Entry 15). Yellow powder (0.29 g, 92%); mp 153 °C, IR (KBr) cm^{-1}: 3748, 1598, 1526, 1251, 1022, 771, 536. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 3.91 (3H, s, OCH_3), 7.03–8.68 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 55.39, 113.86, 121.40, 126.56, 127.03, 128.52, 128.88, 129.88, 130.17, 130.32, 130.86, 133.51, 137.76, 152.00, 160.03, 161.77, 168.22. MS m/z: 312 (M^+, 95), 311 (100), 77 (20), 51 (20). Anal. calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.57; H, 5.32; N, 9.17.

2-(4-Nitrophenyl)-4-phenylquinazoline (Table 2, Entry 16). Yellow powder (0.28 g, 85%); mp 195 °C, IR (KBr) cm^{-1}: 1601, 1540, 1348, 1077, 839, 709. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.64–8.90 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 121.97, 123.66, 127.15, 128.07, 128.68, 129.38, 129.44, 130.17, 130.26, 134.02, 137.23, 144.05, 149.13, 151.82, 157.94, 168.71. MS m/z: 327 (M^+, 100), 326 (95), 280 (50), 75 (50), 51 (35). Anal. calcd. for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.15; H, 4.21; N, 13.07.

2-(4-Chlorophenyl)-4-phenylquinazoline (Table 2, Entry 17). Light yellow powder (0.28 g, 90%); mp 170 °C, IR (KBr) cm^{-1}: 3067, 1534, 1334, 1085, 770, 699. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.49–8.68 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 121.71, 127.08, 127.23, 128.59, 128.72, 129.10, 130.01, 130.17, 133.73, 136.69, 137.51, 151.89, 159.20, 168.45. MS m/z: 316 (M^+, 80), 315 (100), 102 (20), 76 (23), 50 (23). Anal. calcd. for $C_{20}H_{13}ClN_2$: C, 75.83; H, 4.14; N, 8.84. Found: C, 75.63; H, 4.36; N, 9.04.

2-(2,4-Dichlorophenyl)-4-phenylquinazoline (Table 2, Entry 18). Yellow powder (0.29 g, 82%); mp 97 °C, IR (KBr) cm^{-1}: 3435, 2923, 1531, 1380, 780, 691. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.42–8.23 (10H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 121.40, 127.11, 127.21, 128.02, 128.69, 129.10, 130.19, 130.39, 132.84, 133.99, 134.03, 135.56, 136.90, 137.08, 151.53, 160.32, 168.42. MS

m/z: 350 (M^+, 60), 349 (100), 177 (25), 76 (30), 50 (25). Anal. calcd. for $C_{20}H_{12}Cl_2N_2$: C, 68.39; H, 3.44; N, 7.98. Found: C, 68.26; H, 3.55; N, 8.11.

4-Phenyl-2-(pyridin-3-yl)quinazoline (Table 2, Entry 19). Yellow powder (0.24 g, 86%); mp 142 °C, IR (KBr) cm^{-1}: 1571, 1531, 1336, 767, 693. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.28–9.91 (11H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 121.98, 123.64, 127.15, 127.70, 128.64, 129.22, 130.19, 133.94, 134.16, 136.66, 137.25, 149.50, 150.12, 151.84, 157.97, 168.70. MS *m/z*: 283 (M^+, 70), 282 (100), 76 (25), 51 (25). Anal. calcd. for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.42; H, 4.81; N, 14.97.

4-Phenyl-2-(pyridin-4-yl)quinazoline (Table 2, Entry 20). Yellow powder (0.24 g, 85%); mp 145 °C, IR (KBr) cm^{-1}: 1600, 1528, 1386, 774, 693. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.63–8.83 (9H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 122.32, 122.73, 127.17, 128.24, 128.68, 129.45, 130.19, 130.28, 134.05, 137.17, 146.41, 149.48, 151.79, 157.75, 168.83. MS *m/z*: 283 (M^+, 70), 282 (100), 76 (25), 51 (25). Anal. calcd. for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.36; H, 4.80; N, 15.08.

2-(3-Fluorophenyl)-4-phenylquinazoline (Table 2, Entry 21). Yellow powder (0.25 g, 85%); mp 160 °C, IR (KBr) cm^{-1}: 1589, 1537, 1334, 775. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.21–8.53 (13H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 115.52, 117.32, 121.84, 124.30, 127.07, 127.38, 128.60, 129.19, 129.92, 130.03, 130.08, 130.21, 133.75, 137.47, 140.63, 151.86, 159.04, 161.64, 164.88, 168.47. MS *m/z*: 300 (M^+, 100), 299 (90), 223 (20), 196 (25), 150 (20), 76 (40), 50 (35). Anal. calcd. for $C_{20}H_{13}FN_2$: C, 79.98; H, 4.36; N, 9.33. Found: C, 79.80; H, 4.54; N, 9.53.

2-(4-Fluorophenyl)-4-phenylquinazoline (Table 2, Entry 22). Yellow powder (0.27 g, 90%); mp 128 °C, IR (KBr) cm^{-1}: 1600, 1544, 1334, 771, 697. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 7.19–8.76 (13H, m, H-Ar). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 115.32, 115.61, 120.45, 121.57, 127.09, 128.58, 128.70, 128.94, 130.05, 130.17, 130.76, 130.88, 133.74, 134.22, 137.54, 151.77, 154.15, 159.23, 168.53, 177.78. MS *m/z*: 300 (M^+, 100), 299 (90), 223 (20), 150 (20), 76 (40), 50 (35). Anal. calcd. for $C_{20}H_{13}FN_2$: C, 79.98; H, 4.36; N, 9.33. Found: C, 79.76; H, 4.55; N, 9.56.

CONCLUSION

In conclusion, we have introduced a three-component condensation reaction leading to quinazoline derivatives, which constitute an essential part of many natural products and have antimicrobial, antitumor, or fungicidal activity, from simple and readily available precursors employing [Hmim]TFA as an acidic IL and reusable catalyst under aerobic oxidation conditions. To the best of our knowledge, this is the first report on the synthesis of quinazolines starting from 2-aminobenzophenones, aldehydes, and ammonium acetate. The simplicity, efficiency, excellent yields of products, easy workup procedure, and avoidance of hazardous organic solvents are among the advantages of this new method for the synthesis of different kinds of quinazolines.

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