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Pentafluorophenylammonium triflate as a suitable and effective metal-free catalyst for the synthesis of quinazoline derivatives via one-pot multicomponent method

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Abstract A simple and facile synthesis of highly functionalized quinazoline derivatives has been successfully developed by treatment of aldehydes, ammonium acetate, and 2-aminoaryl ketones or isatoic anhydride under reflux conditions in the presence of a pentafluorophenylammonium triflate (PFPAT) organocatalyst. These catalytic condensation reactions represent green chemical processes, while the PFPAT organocatalyst is air-stable, cost-effective, easy to handle, and easily removed from the reaction mixtures.

Keywords Organocatalyst · Metal-free · Quinazoline · PFPAT

Introduction

The term 'organocatalysis' describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound [1, 2]. The operational simplicity, ready availability of catalysts, environmental compatibility and low toxicity associated with organocatalysis makes it an attractive method to synthesize complex structures. They can also be applied in less demanding reaction conditions, such as rigorously anhydrous or anaerobic conditions. A lot of catalysts have been designed and applied in this area [3–8]. However, the design and development of new, effective, and easily accessible organic catalysts continues to be a major challenge.

Quinazolines are the important structural motifs that are widely present in numerous natural products, synthetic pharmaceuticals, and functional materials. Since many of these heterocyclic systems exhibit biological activities, such as antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic,

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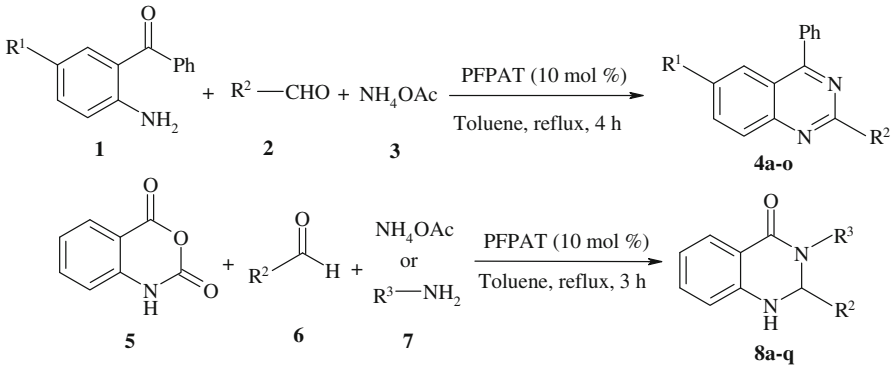
diuretic, antihistamine, antidepressant, and as vasodilating agents, these derivatives have become an integral part of pharmacologically important heterocyclic compounds [9–11]. These derivatives also act as selective JAK2, PDE5, and epidermal growth factor receptor (EGFR) inhibitors of tyrosine kinase activity [12–14]. Furthermore, the quinazoline ring is a core structure of several drug molecules such as gefitinib (Iressa), erlotinib (Tarceva) and actinomycin [15–18]. Considering the above reports, the development of new synthetic methodologies for the construction of quinazoline scaffolds will be a beneficial and interesting challenge. In accordance with the significance of quinazoline, several synthetic methods have been developed for the construction of this kind of fused heterocycles from suitable precursors [19–35]. Very recently, Panja et al. [36] reported I_2 catalyzed reaction between 2-aminobenzophenone, aromatic aldehyde, and ammonium acetate for the preparation of quinazoline derivatives in a one-pot synthesis. Zhang et al. [37] developed a novel catalyst-free synthesis of quinazoline derivatives using a low melting sugar–urea–salt mixture as a solvent. However, some of these procedures have certain limitations such as the use of hazardous organic solvents, strongly acidic conditions, expensive moisture-sensitive catalysts, or tedious work-up conditions, and low yields. In view of these drawbacks, the synthetic protocols utilizing new catalysts devoid of metals are becoming more important due to the growing concern for sustainable chemistry. In recent years, pentafluorophenylammonium triflate (PFPAT) has proved to be very useful as a Brønsted acid catalyst in carrying out various organic transformations [38–44]. PFPAT has received extensive recognitions in organic synthesis due to its unique properties of being readily affordable, water stability, recyclability, operational simplicity, strong tolerance to oxygen, and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts. In a continuation of our interest in developing more efficient and environmentally benign methodologies [45–48], we report a new, convenient, mild, and efficient procedure for the synthesis of quinazoline derivatives, which are obtained through a one-pot three-component condensation reaction of aldehydes, ammonium acetate, and 2-aminoaryl ketones, as well as condensation of aldehydes, ammonium acetate, and isatoic anhydride under reflux conditions using PFPAT as an efficient organocatalyst (Scheme 1).

Experimental

Apparatus and analysis

NMR spectra were determined on an FT-NMR Bruker AV-400 spectrometer in $CDCl_3$ or DMSO-d_6 and are expressed in d values relative to tetramethylsilane; coupling constants (J) are measured in hertz. Melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were recorded on a Rayleigh WQF-510 Fourier transform instrument. Commercially available reagents were used throughout without further purification.



Scheme 1 Synthesis of quinazoline derivatives

General procedure for the synthesis of quinazoline derivatives

A mixture of 2-aminoaryl ketone (1 mmol), an aromatic aldehyde (1 mmol), and ammonium acetate (1.2 mmol) dissolved in 3 mL toluene, and PFPAT (10 mol%) was stirred for 4 h at 110 °C. The reaction was monitored by TLC. The reaction mixture, after being cooled to room temperature, was poured onto crushed ice and stirred for 5–10 min. The crystalline product was collected by filtration under suction (water aspirator), washed with ice-cold water (40 mL), and then recrystallized from hot ethanol to afford pure products.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

A mixture of isatoic anhydride (1 mmol), an aromatic aldehyde (1 mmol) and ammonium acetate (1.2 mmol) dissolved in 3 mL toluene, and PFPAT (10 mol%) was stirred for 3 h at 110 °C. The reaction was monitored by TLC. The reaction mixture, after being cooled to room temperature was poured onto crushed ice and stirred for 5–10 min. The crystalline product was collected by filtration under suction (water aspirator), washed with ice-cold water (40 mL) and then recrystallized from hot ethanol to afford pure products.

Spectroscopic data for selected examples follow:

*2-(4-Methylphenyl)-4-phenylquinazoline (**4b**)* mp: 165–167 °C; IR (KBr, cm^{-1}): 1,075, 1,540, 1,602; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3 H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.50–7.60 (m, 4H), 7.86–7.90 (m, 3H), 8.14 (t, $J = 7.7$, 2H), 8.58 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 121.2, 126.3, 126.5, 127.8, 128.2, 129.2, 129.4, 129.9, 130.2, 130.3, 133.8, 135.2, 137.2, 140.3, 151.6, 159.8, 167.6.

*2-(4-Chloro-phenyl)-4-phenylquinazoline (**4e**)* mp: 188–190 °C; IR (KBr; cm^{-1}): 845, 1,335, 1,520, 1,570; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.65 (m, 6 H), 7.86–7.91 (m, 3 H), 8.11–8.14 (m, 2H), 8.65 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 121.5$, 126.86, 127.2, 128.1, 128.5, 128.7, 129.1, 129.7, 130.4, 133.7, 137.4, 151.5, 159.2, 168.2.

6-Chloro-4-phenyl-2-(p-tolyl)-quinazoline (***4i***) mp: 213–215 °C; IR (KBr, cm^{-1}): 780, 1,340, 1,568, 1,610; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (s, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.61–7.63 (m, 3H), 7.78–7.87 (m, 3H), 8.07–8.09 (m, 2H), 8.56 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 121.8, 125.6, 128.1, 128.5, 129.8, 130.1, 130.3, 130.8, 132.3, 134.3, 135.8, 136.9, 141.1, 150.5, 160.4, 167.3.

6-Chloro-2-(4-nitrophenyl)-4-phenylquinazoline (***4j***) mp: 221–223 °C; IR (KBr, cm^{-1}): 780, 1,350, 1,560, 1,610; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (t, $J = 2.8$ Hz, 3H), 7.83–7.88 (m, 3H), 8.12 (t, $J = 4$ Hz, 3H), 8.36 (d, $J = 9.0$ Hz, 2H), 8.85 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 122.5$, 123.8, 126.1, 128.9, 129.4, 130.5, 130.6, 131.1,133.9, 135.1, 136.8, 143.6, 149.2, 150.3, 158.1, 168.0.

6-Nitro-2-(2-nitro-phenyl)-4-phenyl-quinazoline (***4m***) mp: 233–235 °C; IR (KBr, cm^{-1}): 1,537, 1,345, 1,095, 695; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (d, $J = 8.7$ Hz, 2H), 7.65 (t, $J = 2.2$ Hz, 3H), 7.86–8.22 (m, 3H), 8.60–8.68 (m, 3H), 9.05 (s, $J = 2.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 121.5$, 124.3, 128.1, 129.1, 129.4, 130.3, 130.8, 131.2, 131.4, 135.6, 136.3, 138.2, 145.8, 154.5, 162.1.

6-Nitro-2-(4-methylphenyl)-4-phenylquinazoline (***4n***) mp: 218–220 °C; IR (KBr, cm^{-1}): 775, 1,540, 1,600, 1,655; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H), 7.35 (d, J = 7.8 Hz, 2H), 7.65–7.88 (m, 5H), 8.24 (d, $J = 9.0$ Hz, 1H), 8.62 (d, $J = 7.8$ Hz, 3H), 9.05 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 120.2, 124.1, 126.8, 129.1, 129.3, 129.5, 130.4, 130.8, 131.1, 134.3, 136.5, 142.2, 145.8, 154.5, 163.5, 169.3.

2,3-Dihydro-2-phenylquinazolin-4(1H)-one (***8a***) mp: 225–227 °C; IR (KBr, cm^{-1}): 1,508, 1,610, 1,653, 3,062, 3,302; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.76$ (s, 1H), 6.68 (t, $J = 7.4$ Hz, 1H), 6.76 (d, $J = 8.09$ Hz, 1H), 7.10 (br s, NH), 7.25 (t, $J = 7.3$ Hz, 1H), 7.33–7.41 (m, 3H), 7.50 (d, $J = 7.44$ Hz, 2H), 7.62 (d, $J = 7.7$ Hz, 1H), 8.28 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 67.4$, 115.2, 115.8, 117.9, 127.7, 128.2, 129.1, 129.3, 134.1, 142.5, 148.7, 164.4.

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (***8b***) mp: 201–203 °C; IR (KBr, cm^{-1}): 1,292, 1,483, 1,650, 1,667, 3,025, 3,307; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.77$ (s, 1H), 6.70 (t, $J = 8.1$ Hz, 1H), 6.95 (d, $J = 6.4$ Hz, 1H), 7.15 (br s, 1H, NH), 7.22–7.47 (m, 3H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.61 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.3$ Hz, 1H), 8.34 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 65.8$, 114.4, 115.1, 117.27, 127.3, 128.3, 128.7, 132.9, 133.3, 140.7, 147.7, 163.4.

2,4-Dichloro-2,3-dihydroquinazolin-4(1H)-one (***8d***) mp: 182–184 °C; IR (KBr, cm^{-1}): 1,661, 3,025, 3,179, 3,337; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.1$ (s, 1 H), 6.71(t, $J = 8.1$ Hz, 1H), 6.93(d, $J = 6.4$ Hz, 1H), 7.04 (br s, 1H, NH), 7.24–7.29 (t, $J = 7.5$ Hz, 1 H), 7.47–7.50 (m, 1 H), 7.65–7.68 (m, 3 H), 8.25 (br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 63.3$, 114.6, 114.7, 117.6, 127.4, 128.6, 128.9, 130.9, 132.9, 133.5, 133.9, 136.9, 147.5, 163.6.

2-(4-Bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (***8g***) mp: 201–203 °C; IR (KBr, cm^{-1}): 1,430, 1,480, 1,651, 1,665, 3,025, 3,188, 3,307; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.76$ (s, 1H), 6.67–6.77 (m, 2H), 7.15 (s, 1H, NH), 7.25 (dt, $J_1 = 7.7$ Hz, $J_2 = 1.5$ Hz, 1H), 7.45 (d, $J = 8.6$ Hz, 2H), 7.58–7.62 (m, 3H), 8.35

(br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.8, 114.4, 114.9, 117.3, 121.5, 127.3, 129.1, 131.2, 133.4, 141.1, 147.6, 163.5.

*2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**8j**)* mp: 179–180 °C; IR (KBr, cm^{-1}): 1,240, 1,386, 1,482, 1,608, 1,650, 3,174, 3,296; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3H), 5.79 (s, 1H), 6.76 (t, J = 7.4 Hz, 1H), 6.83(d, J = 7.6 Hz, 1H), 7.04 (dt, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 2H), 7.10 (br s, NH), 7.30–7.35 (m, 1H), 7.51–771 (m, 3H), 8.28 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 66.3, 113.6, 114.4, 115.1, 117.07, 127.3, 128.2, 133.2, 133.4, 148.0, 159.5, 163.6.

*2,3-Dihydro-3-phenyl-2-(4-chlorophenyl)quinazolin-4(1H)-one (**8n**)* m.p: 216–218 °C; IR (KBr, cm^{-1}): 1,088, 1,385, 1,486, 1,613, 1,631, 3,025, 3,294. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (d, J = 2.7 Hz, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 7.18–7.22 (m, 1H), 7.25–7.29 (m, 3H), 7.31–7.42 (m, 6H), 7.67–7.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.1, 114.8, 115.3, 117.7, 126.1, 126.2, 128.1, 128.4, 128.5, 128.6, 132.9, 133.8, 139.6, 140.5, 146.4, 162.1.

Result and discussion

In preliminary experiments, the model reaction of 2-aminobenzophenone (1.0 mmol), benzaldehyde (1.0 mmol), and ammonium acetate (1.2 mmol) catalyzed by PFPAT was conducted to screen the optimal reaction conditions, and the results were listed in Table 1. It is noteworthy that, in the absence of a catalyst, the reaction failed to give the desired product, even after long reaction time (24 h; Table 1, entry 1).

Then, the effect of temperature, the amount of catalyst, and the reaction time on the yield of the product were examined. Reaction at 110 °C in toluene in the presence of 10 mol% PFPAT afforded the product **4a** in 88 % yield (Table 1, entry 4). Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entry 10), while reducing these factors led to a reduction in product yield (Table 1, entry 3). Building upon this result, further studies were conducted and it was found that 10 mol% of PFPAT was optimum for this reaction and gave a product of 88 % yield in just 4 h (Table 1, entry 4). The reaction was also examined in solvents such as H_2O, THF, CH_2Cl_2, ethanol, and diethyl ether. In the presence of solvents, the reaction was sluggish and the formation of byproducts was observed (Table 1, entries 5–9). Moreover, when the reaction was carried out in toluene medium, in most cases a solid product was separated at the end of the reaction.

To establish the scope and generality of this three-component reaction, we extended our studies with a wide range of substrate combinations, and the desired substituted quinazolines were obtained in excellent yields (Table 2).

This protocol well tolerates aromatic aldehydes containing both electron-donating and electron-withdrawing substituents. The electronic effect seemed to have a slight influence on the reaction since either the electron-withdrawing or the electron-donating groups on the different aromatic ring resulted in the scarcely discriminated yields from the reaction, as evidenced by benzaldehydes with either

Table 1 Effect of different PFPAT and solvent on formation of **4**

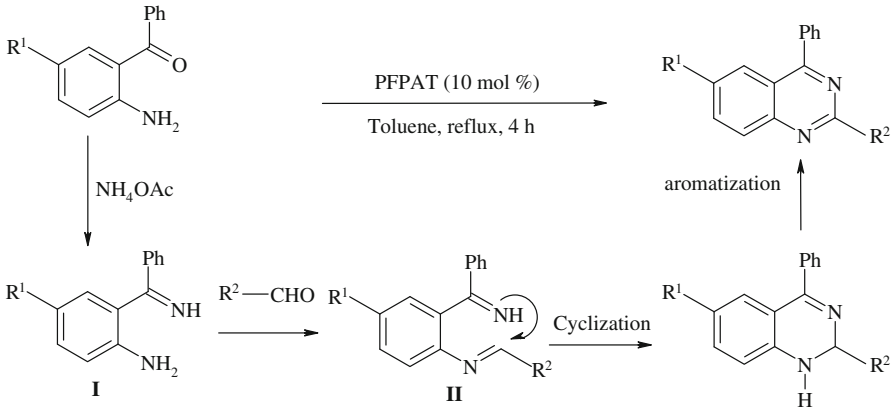
Entries	PFPAT amount (mol%)	Condition/solvent	Time (h)/yield
1	0	RT/toluene	24/0
2	10	RT/toluene	24/30
3	5	110 °C/toluene	8/70
4	10	110 °C/toluene	4/88
5	10	RT/CH_2Cl_2	24/15
6	10	RT/THF	24/10
7	10	RT/ethanol	24/10
8	10	RT/H_2O	24/0
9	10	RT/diethyl ether	24/0
10	15	110 °C/toluene	4/88

RT Room temperature

Table 2 PFPAT-catalyzed synthesis of functionalized quinazolines

Entries	R^1	R^2	Product	Yield (%)	mp (°C)	References
1	H	C_6H_5	**4a**	88	120–122	[36]
2	H	4-Me-C_6H_4	**4b**	92	165–166	[37]
3	H	4-OMe-C_6H_4	**4c**	90	155–157	[36]
4	H	4-OH-C_6H_4	**4d**	90	185–186	[37]
5	H	4-Cl-C_6H_4	**4e**	95	189–190	[37]
6	H	4-Br-C_6H_4	**4f**	92	141–143	[36]
7	H	4-NO_2-C_6H_4	**4g**	95	193–194	[37]
8	Cl	2-Cl-C_6H_4	**4h**	88	99–100	[37]
9	Cl	4-Me-C_6H_4	**4i**	95	213–214	[37]
10	Cl	4-NO_2-C_6H_4	**4j**	90	221–223	[36]
11	Cl	3-Pyridyl	**4k**	90	169–171	[37]
12	Cl	2-Thienyl	**4l**	85	224–225	[37]
13	NO_2	4-Cl-C_6H_4	**4m**	90	233–234	[37]
14	NO_2	4-Me-C_6H_4	**4n**	92	216–218	[37]
15	Me	C_6H_5	**4o**	Trace	–	

an *o*- or a *p*-Cl substituent (Table 2, entries 5, 8), which resulted in the corresponding products (95–92 %). Both 4-methoxybenzaldehyde (Table 2, entry 3) and 4-nitrobenzaldehyde (Table 2, entry 7) were suitable substrates in this reaction. The experimental procedure is very efficient, convenient, and rapid, and has the ability to tolerate a variety of other functional groups, such as alkyl, methoxyl, nitro, and halides under these reaction conditions. Furthermore, acid sensitive aldehydes [49, 50] worked well without any decomposition or polymerization under these reaction conditions (entries 11, 12). However aliphatic aldehydes did not undergo condensation under this reaction condition.



Scheme 2 Proposed mechanism for quinazoline synthesis

The effect of substituent on 2-aminobenzophenone derivatives on the yield and reaction time has also been studied (Table 2, entries 9–15). It was found that the performance of this three-component reaction strongly depends on the electronic property of the substituents on the aniline ring of 2-aminobenzophenone. In general, electron-withdrawing groups worked well, affording good-to-excellent yields in all cases (Table 2, entries 9–14).

Lastly, the very simple reaction workup furnished products of satisfactory purity in most cases without chromatographic purification. The structure of the products (**4a–o**) was established from their IR spectral data and comparison of their melting points with those of authentic samples [36, 37]. Also, the structure of some products was confirmed by ^{1}H NMR and ^{13}C NMR spectral data. A plausible mechanism for the formation of quinazoline is shown in Scheme 2 [36].

In this process, PFPAT acts as Brønsted acid and plays a significant role in increasing the electrophilic character of the electrophiles (Scheme 2). First, the keto group of benzophenone moiety is activated by PFPAT followed by the *N*-nucleophilic amine attacks on the carbonyl to form intermediate **I**. Subsequently, the reaction of activated aldehyde with **I** proceeds to afford intermediate **II** that is converted to product **4** via an intramolecular cyclization. The highly hydrophobic pentafluorophenyl moiety effectively repels H_2O produced by the dehydration steps. The present protocol was extended using isatoic anhydride, and the reaction of benzaldehyde, ammonium acetate, and isatoic anhydride was carried out under similar reaction conditions. The desired product **8a** was obtained in 90 % yield. The reaction of other aromatic aldehydes substituted with Cl, Br, F, Me, NO_2, and MeO was also performed with isatoic anhydride and ammonium acetate, and the desired products **8b–j** were isolated in good yields (Table 2, entries 2–10). To expand the scope of amine substrates, ammonium acetate and primary aromatic amines including aniline, *p*-toluidine, and 4-chloroaniline were applied to this protocol. In all cases, the desired reactions took place successfully to afford a series of 2,3-dihydroquinazolin-4(1*H*)-one (**8m–q**) in good yields (Table 3).

Table 3 PFPAT catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

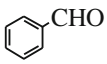
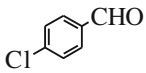
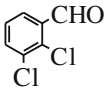
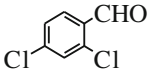
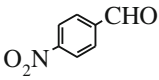
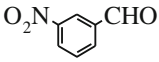
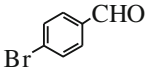
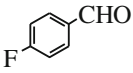
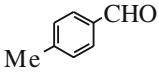
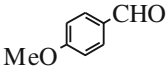
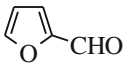
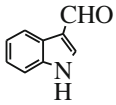
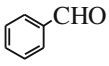
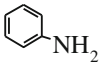
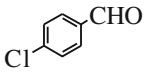
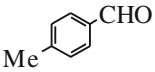
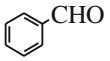
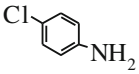
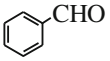
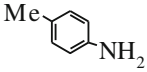
Entries	Aldehyde	Amine	Product	Yield	mp (°C)	References
2		NH_4OAc	**8a**	90	224–225	[31]
2		NH_4OAc	**8b**	95	200–202	[32]
3		NH_4OAc	**8c**	80	229–230	[32]
4		NH_4OAc	**8d**	85	142–184	[32]
5		NH_4OAc	**8e**	90	300–301	[32]
6		NH_4OAc	**8f**	80	180–181	[31]
7		NH_4OAc	**8g**	90	200–202	[32]
8		NH_4OAc	**8h**	95	236–238	[31]
9		NH_4OAc	**8i**	90	227–229	[32]
10		NH_4OAc	**8j**	80	179–180	[31]
11		NH_4OAc	**8k**	90	182–185	[31]
12		NH_4OAc	**8l**	80	218–220	[32]
13			**8m**	85	202–204	[33]

Table 3 continued

Entries	Aldehyde	Amine	Product	Yield	mp (°C)	References
14			**8n**	90	216–218	[33]
15			**8o**	80	216–217	[33]
16			**8p**	85	219–220	[33]
17			**8q**	90	195–196	[33]

The superiority of PFPAT to other arylammonium triflates is ascribed to the lower basicity of the $C_6F_5NH_2$ counter-amine compared to $ArylNH_2$. The use of $C_6F_5NH_2$ raised the acidity of catalyst and the highly hydrophobic pentafluorophenyl moiety effectively repels H_2O produced by the dehydration steps. In addition, $C_6F_5NH_2$ easily separated from the reaction mixture after workup with distillation under reduced pressure ($C_6F_5NH_2$: bp 153 °C at 760 mmHg).

Conclusion

In conclusion, we have developed an efficient synthesis of quinazoline derivatives via the one-pot three-component coupling reaction of aldehydes, ammonium acetate, and 2-aminoaryl ketones or isatoic anhydride under reflux conditions using PFPAT as an efficient organocatalyst. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages: (1) PFPAT is easy to prepare from commercially available pentafluoroaniline and triflic acid, (2) short reaction time, (3) ease of product isolation/purification by non-aqueous work-up, (4) no side reaction, (5) low costs and simplicity in process and handling, and (6) quinazolines are produced by an environmentally benign process.

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